

Topics in Antiviral Medicine™

A publication of the IAS-USA

Selected Highlights of the 2026 Conference on Retroviruses and Opportunistic Infections

CROI 2026: Basic Science Highlights From the 2026 Conference on Retroviruses and Opportunistic Infections **CME**

Mario Stevenson, PhD

CROI 2026: Neuro-HIV at the Crossroads of Coinfections, Reservoirs, ART, and Comorbidities **CME**

Michael J. Corley, MA, PhD; Sarah B. Joseph, PhD; Phillip Chan, MBChB, PhD

CROI 2026: Antiretroviral Therapy in Adult, Maternal, and Pediatric Populations With HIV **CME**

Shauna H. Gunaratne, MD, MPH, DTM&H; Timothy J. Wilkin, MD, MPH; Hong-Van Tieu, MD, MS

CROI 2026: Innovations in HIV Care and Service Delivery to Improve Treatment Outcomes **CME**

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CROI 2026: Tuberculosis and Other Infectious Complications in People With HIV **CME**

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CROI 2026: Advances in Epidemiology and Treatment of Viral Hepatitis **CME**

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Sudipa Sarkar, MD; Todd T. Brown, MD, PhD

CROI 2026: Acute and Postacute COVID-19 **CME**

Annukka A. R. Antar, MD, PhD

CROI 2026: Global Epidemiology and Prevention of HIV and Other Sexually Transmitted Diseases **CME**

Susan P. Buchbinder, MD; Albert Y. Liu, MD, MPH

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Learning Objectives

On completion of this activity, which contains 9 articles on important new data presented at the 2026 Conference on Retroviruses and Opportunistic Infections, the learner will be better able to:

- Describe basic science research on HIV, including viral reservoirs and cure
- List neurologic HIV complications, including coinfections and comorbidities
- Describe the latest research on antiretroviral therapy for adult, maternal, and pediatric populations with HIV
- Describe the latest innovations in HIV care and service delivery
- List the current diagnostic and treatment options for tuberculosis and other opportunistic infections in adults and children with HIV
- Describe the recent advances in the epidemiology and treatment of viral hepatitis
- Describe important data on HIV comorbidities
- List the clinical manifestations and treatment options for acute and post-acute COVID-19
- Describe the epidemiologic trends and the latest preventative methods for HIV and other sexually transmitted infections

This enduring material is designed for physicians who are actively involved in the medical care of people with HIV and other viral infections.

This activity is also relevant for other practitioners, including nurse practitioners, nurses, physician assistants, pharmacists, and others.

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*Invited Review***Basic Science Highlights From the 2026 Conference on Retroviruses and Opportunistic Infections****Mario Stevenson, PhD**

University of Miami Miller School of Medicine, Florida

Abstract: *The 2026 Conference on Retroviruses and Opportunistic Infections in Denver, Colorado, showcased major advances in our understanding of HIV replication, viral persistence, host–virus interactions, and innate immune sensing. Basic science presentations emphasized the remarkable complexity of the HIV replication cycle and highlighted how structural virology, systems biology, and genome-wide screening approaches are transforming the field. A consistent highlight of the conference is the Scott M. Hammer workshop for new investigators and trainees in which scientific experts help orient trainees to thematic areas being covered in the conference. This underscores the conference’s dedication to the mentoring and training of early career investigators new to the field of HIV/AIDS research.*

Keywords: antiviral targets, CROI 2026, cure, HIV, pathogenesis, reservoirs, virology

Introduction: Themes in Basic Virology of HIV

An overarching theme across the basic science sessions was the central role of the HIV capsid as a dynamic regulatory structure that coordinates various steps of viral replication. Once thought to function primarily as a structural shell protecting the viral genome, the capsid is now recognized as a molecular hub controlling reverse transcription, nuclear trafficking, immune evasion, and integration targeting. Several presentations examined the architecture of the capsid lattice and the mechanisms with which viral proteins and host cofactors interact with the interior and exterior surfaces of the capsid. These studies

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reveal that the capsid not only organizes viral replication complexes but also helps shield viral nucleic acids from innate immune sensors. Detailed insight was provided on viral RNA organization and packaging inside the capsid. New structural and biochemical studies demonstrated that viral integrase plays an unexpected role in tethering genomic RNA to the interior of the capsid lattice. These findings suggest that the architecture of the viral core is coordinated through intricate interactions between capsid protein, viral RNA, and enzymatic components of the replication complex. Understanding how ribonucleoprotein complexes are assembled within the capsid provides important insight into the earliest stages of infection and may reveal new targets for antiviral drug development.

Important research revealed the interaction between HIV replication and innate immune sensing pathways. Several studies explored how viral RNA and reverse transcription products are detected by host-pattern recognition receptors such as melanoma differentiation–associated protein 5 (MDA5) and cyclic GMP-AMP synthase (cGAS). These findings illustrate how subtle changes in viral RNA structure, capsid stability, or nuclear trafficking can determine whether HIV replication proceeds undetected or triggers potent antiviral responses. Increasing evidence suggests that the virus has evolved sophisticated mechanisms to manipulate these pathways, allowing productive replication and minimizing immune detection.

Several presentations highlighted the power of genome-wide functional screens to identify host factors that regulate HIV infection. Clustered regularly interspaced short palindromic repeats (CRISPR)–based screening approaches now allow investigators to systematically identify antiviral restriction factors and host proteins that facilitate viral replication. These studies are beginning to map the full landscape of HIV–host interactions in primary CD4+ T cells, revealing unexpected cellular pathways that influence viral entry, replication, and immune evasion. Together, the presentations reviewed here highlight the remarkable progress being made in dissecting the molecular and cellular mechanisms that govern HIV replication and persistence. The following sections review selected abstracts that exemplify these themes.

HIV Replication and Persistence

The HIV capsid plays a central role in viral replication by forming a conical core that houses the viral genome and replication enzymes. During infection, the capsid coordinates many early steps of the viral life cycle, including reverse transcription, nuclear trafficking, and integration. Because of these essential functions, the capsid has emerged as a promising target for antiviral drug development. Sundquist (Abstract 14) provided a comprehensive overview of the structural biology of the HIV capsid and described the decades-long research effort that ultimately led to the development of lenacapavir, the first US Food and Drug Administration–approved capsid inhibitor. Structural studies have revealed that the mature HIV capsid is composed of approximately 250 hexamers and 12 pentamers of the capsid protein, arranged in a fullerene-like lattice that forms the characteristic conical core. High-resolution cryoelectron microscopy has provided detailed insight into the interfaces that stabilize this lattice and enable capsid assembly.

Biochemical analyses demonstrate that capsid interactions with host proteins such as cyclophilin A, nucleoporins, and cleavage and polyadenylation specificity factor 6 (CPSF6) regulate capsid stability and intracellular trafficking. These interactions help guide the viral replication complex toward the nucleus and protect viral nucleic acids from innate immune sensors.

Building on this structural understanding, researchers identified small molecules capable of binding specific pockets within the capsid lattice. Optimization of these

Lenacapavir was developed using translational research bridging basic structural biology and clinical drug development

compounds ultimately led to the development of lenacapavir, a long-acting capsid inhibitor that disrupts numerous stages of the viral replication cycle. Lenacapavir binds to the capsid protein at a site involved in host factor interactions, thereby altering capsid stability and interfering with nuclear import.

Clinical trials have demonstrated that lenacapavir provides potent antiviral activity and can be administered as a twice-yearly subcutaneous injection, representing a major advance in long-acting HIV therapy and prevention. The development of lenacapavir represents a remarkable

example of translational research bridging basic structural biology and clinical drug development. Nearly 3 decades of collaborative work between academic laboratories and industry partners helped to fully elucidate capsid structure and exploit it as a therapeutic target.

Importantly, capsid inhibitors may provide new opportunities for long-acting treatment and prevention strategies. By targeting a highly conserved structural component of the virus, these drugs may also retain activity against viruses resistant to other antiretroviral classes. The HIV capsid encloses the viral RNA genome and replication enzymes within a conical core. However, because the mature capsid occupies only a portion of the virion interior, the mechanism by which viral RNA remains confined within the capsid during maturation has been unclear. Previous work suggested that viral integrase might interact with RNA, but the structural basis of this interaction had not been defined. Using cryoelectron microscopy, Cherepanov (Abstract 15) described studies to determine how viral RNA is sequestered within the viral capsid. These studies revealed filamentous assemblies composed of integrase octamers, each formed by 2 asymmetric tetramers associated with RNA molecules. The spacing and orientation of these integrase assemblies closely matched the geometry of the capsid lattice. Imaging of purified HIV cores demonstrated that integrase filaments attach to the luminal surface of the capsid shell, forming a tethering network that anchors viral RNA within the core. Mutations disrupting integrase–RNA interactions produced aberrant virions in which viral RNA was mislocalized outside the capsid, resulting in loss of infectivity. These findings reveal an unexpected structural relationship between integrase and the capsid lattice.

Integrase appears to function as a molecular tether that secures viral RNA to the interior of the capsid, ensuring proper genome encapsidation during viral maturation. This finding also provides a potential explanation for the antiviral effects of allosteric integrase inhibitors, which induce eccentric virion formation by disrupting integrase–RNA interactions. Future work will explore whether targeting this structural interaction could provide new strategies for antiviral therapy.

Innate immune sensors detect viral nucleic acids and trigger antiviral responses. However, HIV replication often proceeds without strong activation of innate immunity. This suggests that the virus has evolved mechanisms to shield its nucleic acids from immune detection. Kutluay (Abstract 16) described studies highlighting that capsid lattice stability is a crucial determinant of innate immune sensing. Destabilizing capsid mutations increased detection of reverse transcription products by

the cGAS-stimulator of interferon genes (STING) pathway. Surprisingly, hyperstable capsids also enhanced immune sensing due to altered nuclear trafficking and reverse transcription dynamics. These results indicate

HIV-1 uncoating, which occurs predominantly within nuclear speckles, is a major determinant of where the virus integrates in the host genome

that HIV replication requires a precise balance between capsid stability, reverse transcription, and nuclear import. Disrupting this balance exposes viral DNA to innate immune sensors. A central question in HIV biology is how the components of the incoming viral core within the nucleus shape the final integration event. Although HIV has long been known to prefer integration into transcriptionally active, gene-rich chromatin, more recent work has shifted attention from integration as a purely biochemical process to integration as a highly spatial one. Intact or largely intact HIV cores can enter the nucleus, interact with host nuclear factors, and traffic to specific subnuclear compartments before uncoating. Nuclear speckles, which are membrane-free compartments enriched in splicing and RNA-processing proteins, have emerged as favored sites for incoming HIV complexes. Because speckle-associated chromatin domains are generally transcriptionally active, they offer an attractive explanation for HIV's integration bias. However, it has remained unclear whether the site of uncoating itself directly determines where integration occurs, or whether uncoating and integration are merely correlated downstream events.

Pathak (Abstract 17) described experiments to assess the position of nuclear HIV cores, the timing and location of uncoating, and the final sites of proviral integration. The investigation further examined whether capsid inhibitors such as PF74 and lenacapavir could perturb this spatial choreography after nuclear entry. Using fluorescently labeled HIV-1 cores together with nuclear speckle markers, Pathak showed that most nuclear viral cores localized to nuclear speckles and that uncoating occurred predominantly within these structures. This finding strengthens the emerging model that uncoating is not a diffuse nuclear event but instead happens in a specialized nuclear microenvironment. The work further showed that binding of CPSF6 to capsid is necessary to retain HIV cores within

nuclear speckles. When infected cells were treated with PF74 or lenacapavir after nuclear entry, viral cores rapidly lost their interactions with CPSF6 and exited nuclear speckles. These data connect capsid integrity, CPSF6-dependent speckle retention, uncoating position, and integration site selection into a unified pathway, and suggest that the interval between uncoating and integration is very short. Once the core was displaced from speckles and disrupted, integration followed in the altered local environment rather than after extensive diffusion of the viral DNA. CPSF6-mediated retention of viral cores in speckles appears essential for normal integration targeting, whereas postentry treatment with capsid inhibitors disrupts this localization, shifts uncoating outside speckles, and redirects integration toward less transcriptionally active chromatin regions. Future studies should determine whether different cell types, particularly macrophages versus activated CD4+ T cells, display the same speckle-centered uncoating pathway. It will also be important to define how altered integration targeting affects long-term proviral expression, latency establishment, and immune visibility.

The mature HIV-1 capsid core is a sophisticated macromolecular assembly. How viral ribonucleoprotein complexes are physically encapsulated within the mature capsid during maturation is an important but not fully understood question. The mature core contains the viral RNA genome, nucleocapsid, reverse transcriptase, and integrase, all arranged inside the capsid shell in a way that preserves infectivity. Since the conical core is assembled during proteolytic maturation and occupies a defined internal volume, there must be an ordered mechanism that couples capsid formation to genome retention. Prior work suggested that integrase plays a noncatalytic role in proper virion morphogenesis and that disruption of integrase-RNA interactions leads to eccentric, noninfectious particles. However, the structural basis for that process and the role of capsid itself in binding viral RNA were incompletely understood.

Briganti (Abstract 100) described attempts to define the architecture of the HIV-1 core and to identify the molecular determinants that allow viral ribonucleoprotein complexes to be packaged inside it. By combining single-particle cryoelectron microscopy, cross-linking and immunoprecipitation (CLIP) assays, and innovative biochemical assays using capsid-like particles, the investigators aimed to establish a mechanistic model of encapsidation. The structural analysis of native HIV-1 cores identified bridging nucleoprotein interactions involving capsid hexamers, viral RNA, and integrase tetramers on the luminal side of the capsid. Biochemical studies further showed that capsid hexamers, but not capsid monomers, specifically

bind viral RNA segments. This indicates that RNA recognition is an emergent property of assembled capsid lattice units rather than of isolated capsid protein, reinforcing the idea that mature capsid architecture generates new functional surfaces.

CLIP experiments confirmed that capsid binds viral RNA within mature virions, and substitutions in capsid residues that impaired interactions with viral RNA produced aberrant noninfectious virions in which viral ribonucleoprotein complexes were mislocalized outside the translucent capsid shell. Thus, capsid–RNA interaction is not incidental but functionally required for proper core organization. These results advance a structural mechanism for one of the least understood steps in HIV maturation: the encapsidation of the viral ribonucleoprotein complex. The finding that capsid hexamers bind viral RNA inside mature virions adds a new functional dimension to the capsid lattice. Rather than acting solely as a shell around preorganized contents, the capsid appears to participate directly in constructing and stabilizing the architecture of the core interior. These results also suggest that noncatalytic integrase functions, especially those related to RNA tethering and encapsidation, are equally fundamental to infectivity and may be pharmacologically targetable.

An intriguing aspect of HIV biology is that viral RNA must retain features needed for genome packaging, translation, dimerization, and export, yet those same unusual features risk recognition by host innate immune sensors. HIV-1 partially solves this by exploiting transcription start site heterogeneity to generate distinct unspliced RNAs with 1 or 3 guanines at the 5' end (cap1G RNA and cap3G RNA, respectively). Hughes (Abstract 101) highlighted previous work from her group and others showing that HIV-1 unspliced RNA exported through the Rev-chromosome region maintenance 1 (Rev-CRM1) pathway can activate MDA5-dependent innate immune responses in macrophages. What had not been clear was why HIV universally conserves heterogeneous transcription start site usage and whether different unspliced RNA species differed intrinsically in immunogenicity. In primary monocyte-derived macrophages, the investigators found that infection with cap1G-only virus induced high levels of type I interferon, whereas infection with cap3G-only virus produced little to no detectable interferon response. The interferon response induced by cap1G virus was blocked by inhibitors of reverse transcription, integrase, and Rev-CRM1-mediated export, indicating that productive early replication and canonical viral RNA export were required.

Knockdown studies showed that MDA5 and mitochondrial antiviral signaling (MAVS) protein, but not retinoic acid-inducible gene-I (RIG-I) protein, were essential for

cap1G-driven interferon secretion. Consistent with this, MDA5 immunoprecipitated HIV-1 unspliced RNAs during wild-type and cap1G-only infection, but not during cap3G-only infection. These results provide direct evidence that cap1G RNA is the immunostimulatory viral

Transmitter-founder and rebound HIV-1 viruses frequently display enhanced replication fitness and relative resistance to type I interferon, yet classical sequence analysis has not explained these phenotypes fully

RNA species recognized by MDA5. The investigators then went further to dissect mechanism. Viruses engineered to express cap1G-like leader structures with exposed caps behaved differently from native cap1G RNAs, showing that cap sequestration versus exposure is a crucial variable. In addition, replacing the Rev-CRM1 export pathway with a constitutive transport element that drives nuclear RNA export factor 1 (NXF1)-dependent export altered immunogenicity, demonstrating that the route of nuclear export is also a determinant of sensing. Together, the data suggest that MDA5 recognition depends on a combination of RNA start site, 5' leader conformation, and export pathway. This is also consistent with published work from the same group showing that MDA5 sensing is tightly governed by transcription start site and 5' leader structure. In summary, these studies demonstrate that cap1G HIV-1 unspliced RNA is the principal driver of MDA5-MAVS-dependent type I interferon responses in infected macrophages, whereas cap3G RNA is largely nonimmunogenic. The immunogenicity of HIV unspliced RNA depends on transcription start site choice, 5' leader structure, cap exposure, and use of the Rev-CRM1 export pathway.

Transmitter-founder and rebound HIV-1 viruses frequently display enhanced replication fitness and relative resistance to type I interferon, yet classical sequence analysis has not explained these phenotypes fully. This has prompted interest in non-sequence-based viral determinants, including epitranscriptomic RNA modifications. N6-methyladenosine, or m6A, is a reversible chemical modification that influences RNA stability, translation, structure, and recognition by host proteins. HIV RNA is known to carry m6A marks, but whether these

modifications directly alter viral fitness and interferon sensitivity has remained uncertain. Ye and colleagues (Abstract 102) tested the hypothesis that m6A-modified HIV RNAs evade cellular RNA sensing and thereby enhance replication fitness and interferon resistance, which might point to a mechanism by which viral phenotype could change without fixed coding mutations. The investigators experimentally altered the m6A status of HIV-1 RNA by treating producer cells with inhibitors of the m6A writer machinery, including methyltransferase-like 3 (METTL3)/METTL14 inhibitors, or with inhibitors of the m6A eraser fat mass and obesity (FTO)-related protein. Virions with reduced or increased m6A modification were then used to infect activated and polarized human T-helper 17 cells in the presence or absence of type I interferon. Viruses with depleted m6A modifications showed lower HIV RNA and p24 expression after infection and were markedly more sensitive to interferon. In contrast, hypermethylated viruses displayed enhanced resistance to type I interferon. These data support the central premise that m6A on viral RNA contributes to replication fitness and interferon escape.

The investigators extended these findings to infected primary cells. In acutely infected Th17 cells and in reactivated memory CD4+ T cells from people with HIV (PWH), type I interferon reduced viral RNA and protein levels and decreased the number of cells containing intact proviruses. These effects were amplified when m6A levels were

HIV can gain phenotypic advantages through chemical decoration of its RNA genome

reduced pharmacologically. Single-cell RNA sequencing and protein analyses showed that lowering m6A enhanced interferon-induced expression of several antiviral genes, including interferon-induced protein with tetratricopeptide repeats 1 (IFIT1), IFIT5, IFITM1, and tripartite motif 13 (TRIM13). The combined treatment also perturbed cell-cycle regulatory pathways, reduced cell viability, and appeared to favor elimination of cells harboring intact proviruses. This study is novel because it reframes interferon resistance as an epitranscriptomic property of HIV, not just a genetic one, and suggests that the virus can gain phenotypic advantages through chemical decoration of its RNA genome, potentially shaping early infection, transmission, rebound, and reservoir persistence. Future studies may

evaluate whether m6A-targeting strategies can be used safely *in vivo*.

A defining feature of HIV pathogenesis is the constant evolutionary contest between viral accessory proteins and host restriction factors. Although many classical restriction factors have already been identified, it is increasingly clear that the known set is incomplete. Standard CRISPR screens have been useful for discovering host factors, but many approaches do not recapitulate the full viral replication cycle or the dynamic selective pressures that shape replication in infected cells. Gosálbez and colleagues (Abstract 104) previously developed an HIV-guided CRISPR platform in which replication-competent HIV itself carries single-guide RNAs targeting host genes. In Cas9-expressing cells, viruses that knock out antiviral genes gain a replication advantage, allowing enriched single-guide RNAs to reveal the targeted restriction factors. Related prior work established the sensitivity of this strategy for discovering physiologically relevant defense factors.

Gosálbez expanded this concept to a genome-wide scale and incorporated a parallel viral protein U (Vpu)-deficient HIV-1 screen to identify factors specifically antagonized by Vpu. The rationale was to build a more complete, unbiased map of antiviral genes across the viral life cycle and to illuminate the immune evasion pathways governed by Vpu. The investigators generated replication-competent HIV-1 constructs encoding more than 77,000 distinct single-guide RNAs for genome-wide targeting and passaged these libraries in Cas9-expressing CEM-M7 cells with or without interferon- β . This yielded a large-scale selection system in which enrichment of specific single-guide RNAs in viral supernatants marked genes whose loss benefited viral replication. The screen identified numerous candidate antiviral factors. Among the strongest signals was a cluster of genes involved in DNA replication and repair, including deoxyribonuclease 1 (DNaseL1), G protein subunit beta 1 like (GNB1L), MPN domain-containing (MPND), Nth like DNA glycosylase 1 (NTHL1), DNA polymerase epsilon subunit 4 (POLE4), and RecQ-mediated genome instability 2 (RMI2). Validation in primary CD4+ T cells showed that knockout of these genes increased viral yield approximately 2- to 3-fold, supporting genuine antiviral activity. This is particularly interesting because it implicates DNA maintenance and genome integrity pathways in the restriction of HIV, areas not usually considered central in canonical HIV defense models. The parallel Vpu-deficient screen yielded more than 50 factors that were specifically enriched when Vpu was absent, including ADAM metalloproteinase with thrombospondin type 1 motif 16 (ADAMTS16), adenosine diphosphate-ribosylation factor interacting protein 1 (ARFIP1), carcinoembryonic

antigen-related cell adhesion molecule 5 (CEACAM5), and RAB7A. Their selective enrichment suggests that these genes encode antiviral activities normally counteracted by Vpu. Validation in primary CD4+ T cells was ongoing, but the design itself provides a powerful route to identify Vpu-sensitive immune evasion targets.

Systematic Discovery of Pro- and Anti-HIV Host Factors in Primary Human CD4+ T Cells

Although HIV research has identified many host proteins required for or restrictive to infection, the landscape remains incomplete, particularly in primary human CD4+ T cells, which are the principal targets of HIV in vivo. Prior work has relied on transformed cell lines or focused on candidate genes, leaving open the possibility that key regulators in authentic primary T cells have been missed. Technical barriers, especially the difficulty of performing genome-wide perturbation screens at scale in primary T cells, have limited progress.

Dugan and colleagues (Abstract 105) addressed that challenge by applying orthogonal genome-wide CRISPR activation and CRISPR knockout screens directly in primary human CD4+ T cells. The investigators also designed the work to dissect whether host factors act at entry, co-receptor expression, T-cell activation, or postentry stages. The screens nominated hundreds of candidate antiviral and proviral factors. Among the most notable antiviral hits identified by CRISPR activation was peptidase inhibitor 16 (PI16). Overexpression of PI16 in CD4+ T cells led to potent inhibition of HIV entry. Mechanistically, PI16 physically interacted with CD4+ and with numerous HIV host factors involved in fusion, indicating that it acts at or near the plasma membrane entry interface.

A second hit was peptidylprolyl isomerase D (PPID), also known as cyclophilin 40 (Cyp40). PPID is a homologue of cyclophilin A, but in contrast with CypA, which helps shield HIV cores from TRIM5 α and facilitates early postentry events, PPID acted as a potent antiviral factor. The study showed that PPID inhibited nuclear import of the viral core. Its antiviral activity depended on residues G89 and P90 in precursor 55 Gag (Pr55Gag) for incorporation into virions, indicating that PPID is packaged into viral particles and exerts its effect from within or immediately after virus entry. The investigators further demonstrated that the tetratricopeptide repeat (TPR) motifs in the PPID C-terminal domain are sufficient to convert CypA into an antiviral factor. In addition, a TPR-domain site required for interaction with translocase of outer mitochondrial membrane 70 (TOM70) was essential for PPID-mediated restriction, suggesting that TOM70 recruitment contributes to the antiviral mechanism. The experimental design

also included challenges with C-X-C chemokine receptor type 4 (CXCR4)- and C-C chemokine receptor type 5 (CCR5)-tropic viruses, as well as VSV-G pseudotyped viruses, allowing the team to infer whether hits were entry related or post entry in function. Secondary pooled and arrayed validation experiments further linked candidate factors to the regulation of receptor expression and T-cell activation states. Future work should determine how broadly these findings generalize across naive, memory, activated, and tissue-resident CD4+ T-cell subsets. It will also be important to define the biochemical mechanism by which PPID blocks nuclear import and how TOM70 participates in that process. For PI16, the next key question will be whether its antiviral activity can be enhanced pharmacologically or mimicked therapeutically.

Viral Reservoir and HIV Cure Research

The viral reservoir and cure sessions highlighted how the HIV cure field is evolving from descriptive studies of persistence toward increasingly mechanistic, quantitative, and intervention-oriented science. A central message across the presentations was that HIV persistence during suppressive antiretroviral therapy (ART) is not explained by a

At the clonal level, long-term ART does not simply “freeze” the reservoir in place; instead, individual infected clones may decay, persist, plateau, or expand over time

single process, cell type, or molecular mechanism. Rather, the reservoir is a dynamic and heterogeneous biologic system composed of infected cell populations that vary in proviral integrity, inducibility, proliferative behavior, anatomic location, transcriptional activity, and susceptibility to immune clearance. This complexity has major implications for cure strategies, because no single intervention is likely to be effective across all reservoir states.

A dominant theme was the need to understand reservoir heterogeneity at many levels. At the molecular level, only a minority of proviruses in treated individuals is intact and replication competent, yet defective proviruses are not biologically silent and can still contribute to chronic immune stimulation and antigen expression. At the cellular level, infected cells differ in phenotype, proliferative

history, differentiation state, and transcriptional responsiveness. At the clonal level, long-term ART does not simply “freeze” the reservoir in place; instead, individual infected clones may decay, persist, plateau, or expand over time, sometimes over decades. At the tissue and systems level, the reservoir behaves as an ecologic population shaped by cell survival, homeostatic proliferation, immune pressure, and therapeutic intervention.

Another major theme was the increasing importance of single-cell and systems approaches for dissecting latency and reservoir behavior. Genome-wide CRISPR screening, perturbation sequencing (Perturb-seq), single-cell RNA sequencing (scRNAseq), and computational modeling are now allowing investigators to move beyond bulk measurements of reservoir size and toward the identification of the regulatory circuits that govern whether a provirus remains silent or becomes transcriptionally active. These approaches are powerful because they capture the fact that genetically similar or even clonally related cells can respond differently to the same latency-reversing perturbation. This has shifted the field away from viewing latency reversal as a simple pharmacologic trigger and toward understanding it as a context-dependent outcome shaped by cell state. The sessions also emphasized that long-term ART profoundly remodels the host immune system, with important implications for cure strategies. Conventional thinking has often assumed that HIV-specific immunity in people treated during chronic infection is irreversibly exhausted or senescent, particularly after decades of infection and aging. However, emerging data suggest that this view may be overly simplistic. Under prolonged viral suppression, HIV-specific CD8⁺ T-cell populations may undergo clonal renewal and regain features of functional competence, including proliferative potential and cytolytic capacity. These observations are highly relevant because most cure strategies ultimately depend, directly or indirectly, on immune-mediated control or clearance of infected cells. A further theme was the increasing convergence between HIV cure research and lessons from cancer immunotherapy. The field is paying growing attention to principles established in oncology, including the importance of durable expansion, persistence, trafficking, and fitness of cytotoxic effector cells. Just as successful cancer immunotherapies require not only target recognition but also robust effector cell persistence and function, effective HIV remission strategies will likely require immune effectors capable of recognizing rare, infected cells across diverse anatomic and transcriptional contexts. Broadly neutralizing antibodies (bNAbs), therapeutic vaccines, engineered T cells, and combinatorial immunotherapies are therefore being evaluated not in

isolation but as part of integrated strategies to reshape the reservoir and the host response. Taken together, the cure-related presentations reinforced several key ideas. First, latency is not a uniform, binary state but a spectrum of proviral and cellular phenotypes. Second, the reservoir is maintained largely through infected cell survival and clonal expansion rather than ongoing rounds of productive replication. Third, immune competence under long-term ART may be more recoverable than previously appreciated. Finally, successful cure strategies will likely need to integrate mechanistic understanding of latency, longitudinal reservoir dynamics, and immune reconstitution into tailored combination approaches. The following abstracts illustrate these emerging themes particularly well.

Spatial Transcriptomic and Proteomic Profiling of HIV Reservoirs in Lymphoid Tissues

Despite the remarkable success of combination antiretroviral therapy, HIV persists in long-lived cellular reservoirs that prevent eradication of infection. Lymphoid tissues, particularly lymph nodes, represent a major anatomical reservoir where infected cells can evade immune surveillance. Previous studies have shown that HIV-infected cells often localize within B-cell follicles where cytotoxic

HIV-infected cells persist within specialized follicular niches in lymph nodes during suppressive ART

T lymphocytes have limited access. However, the precise cellular and spatial organization of these reservoir niches remains incompletely understood.

Ndhlovu (Presentation 2) reviewed efforts to address this knowledge gap by applying integrated spatial transcriptomics and proteomic imaging approaches to lymph node tissues from individuals receiving suppressive ART. By combining spatial gene expression profiling with high-dimensional histocytometry, the investigators aimed to characterize the follicular immune microenvironment that permits persistence of HIV-infected cells. Understanding the structural and cellular factors that limit immune clearance is essential for developing strategies aimed at reservoir elimination. Using spatial transcriptomics platforms, the investigators generated high-resolution maps of gene expression within lymph node sections obtained from ART-suppressed individuals. These analyses

were integrated with multiplex protein imaging and histocytometric analyses that allowed the identification of specific immune cell subsets within the tissue microenvironment. Several important observations emerged.

First, HIV RNA-positive cells were found to be highly enriched within germinal center and follicular regions of lymph nodes. These regions exhibited unique transcriptional signatures characterized by elevated expression of genes associated with T follicular helper (Tfh) cells and follicular dendritic cells. Importantly, and consistent with previously published work,¹ cytotoxic CD8+ T cells were relatively excluded from these regions, suggesting that spatial segregation contributes to immune evasion. Second, the investigators identified distinct cellular networks surrounding HIV-infected cells, including Tfh cells, regulatory T cells, and follicular dendritic cells that collectively formed a specialized microenvironment. These niches exhibited elevated expression of immune checkpoint molecules and antiinflammatory signaling pathways, which may dampen antiviral immune responses. Third, high-dimensional histocytometry revealed that infected cells frequently interacted with follicular helper T cells and dendritic cell populations that produce survival and activation signals. These interactions may support long-term persistence of infected cells despite suppressive therapy. These findings provide further evidence that HIV reservoirs persist within highly structured immunological niches in lymphoid tissues. The spatial segregation of infected cells from cytotoxic effector cells may represent a key barrier to reservoir elimination. Moreover, the presence of regulatory immune networks within these regions suggests that local immunosuppressive signals further protect infected cells from immune clearance.

Latent HIV Reversal Via Functional Genomics and Single-Cell Perturbation Modeling

A major barrier to HIV cure is the persistence of latently infected cells harboring replication-competent proviruses that remain transcriptionally silent during suppressive ART. These latent proviruses evade antiviral drugs, which act only on actively replicating virus, and immune-mediated clearance, which generally depends on antigen expression. For many years, efforts to reverse latency have focused on identifying individual latency-reversing agents capable of broadly inducing proviral transcription. However, clinical and preclinical studies have repeatedly shown that no single perturbation is sufficient to reactivate the full latent reservoir. This has pointed to a deeper biologic problem: latency is not governed by a single dominant block, but by a multilayered network of host pathways,

chromatin states, transcription factor availability, signaling thresholds, and cell-state features.

Li's presentation (Presentation 4) was framed around the idea that successful latency reversal must be understood as a systems problem rather than a single-pathway problem. Genome-wide CRISPR knockout screening can identify host regulators that constrain or enable HIV transcription, and single-cell perturbation approaches such as

HIV latency is maintained through intersecting pathways involving chromatin repression, transcriptional elongation blocks, signaling constraints, and cell-state determinants

Perturb-seq can determine how individual cells respond to those perturbations. The rationale for combining these methods is particularly strong, because bulk reactivation assays often obscure the underlying heterogeneity of response. A treatment that appears modestly effective overall may strongly reactivate a small subset of cells, leaving most of the reservoir unaffected. Thus, to design rational cure strategies, it is necessary not only to identify the pathways controlling latency, but also to understand which reservoir cell states are poised to respond. Using a latent HIV cell-line model, the investigators performed genome-scale CRISPR knockout screens and identified a complex regulatory landscape controlling proviral silencing and reactivation. Rather than pointing to a single dominant suppressive pathway, the screen revealed numerous host networks wherein perturbation affected latency. The results suggested that combinations of targeted interventions, rather than single gene disruptions or single pharmacologic classes, had the greatest potential to induce robust reactivation. This is an important observation because it supports the growing view that latency is maintained redundantly through intersecting pathways involving chromatin repression, transcriptional elongation blocks, signaling constraints, and cell-state determinants.

The investigators then applied Perturb-seq and computational modeling to dissect how individual cells responded to specific perturbations. These analyses showed that genetically identical cells can follow divergent transcriptional trajectories after the same intervention. In other words, the effect of a latency-reversing strategy was

shaped by cell-to-cell heterogeneity. Only particular sub-populations appeared primed for productive reactivation, whereas others remained silent or followed incomplete or abortive transcriptional responses. This may explain why even strongly rational interventions may fail to induce broad reservoir expression when assessed across a heterogeneous cell population. Future studies should extend these findings into primary-cell and ex vivo reservoir models from people on long-term ART, where latency is likely even more heterogeneous than in cell-line systems. It will also be important to identify reproducible biomarkers of the cell states most amenable to reactivation so that interventions can be designed or stratified accordingly.

The HIV Reservoir: Persistence and Expansion Under Long-Term ART

Although ART effectively suppresses plasma viremia, it does not eliminate the reservoir of HIV-infected cells that gives rise to rebound when treatment is stopped. Over the past decade, a broad consensus has emerged that the principal reservoir consists of CD4+ T cells carrying integrated, inducible, replication-competent proviruses, and

The quality of the persisting HIV-specific T-cell pool under long-term ART may be more favorable for remission

the much larger pool of defective proviruses may still contribute to immune activation and viral antigen production. At the same time, the field has increasingly recognized that the reservoir is maintained predominantly through clonal expansion of infected cells, not through sustained cycles of ongoing replication in the face of effective ART. However, many crucial questions remain unresolved: how does the reservoir evolve over decades of suppressive therapy, why do some individuals exhibit continued reservoir decay while others plateau or expand, and which biologic features of infected clones predict long-term persistence?

Mellors (Presentation 26) addressed these fundamental questions by providing an overview of emerging data on the long-term dynamics of the HIV reservoir and linking them to therapeutic efforts aimed at achieving durable remission. He summarized several key issues that now define the modern view of the HIV reservoir. First, intact proviruses account for only a small fraction of infected cells, whereas most proviruses are defective.

Nonetheless, it is the intact, inducible proviruses that principally determine rebound risk after ART interruption. Second, the reservoir is maintained mainly through clonal expansion of infected cells rather than continuous de novo infection. Third, although proviral integration sites do not appear to be the dominant driver of clonal expansion in most cases, intact proviruses are disproportionately found in Krüppel-associated box zinc finger (KRAB-ZNF) genes. This suggests that genomic context may influence persistence, perhaps by favoring low-level expression, immune invisibility, or stable maintenance, although the mechanisms remain unclear. Fourth, proviral expression is highly variable. Even on ART, most reservoir proviruses are latent, but a meaningful degree of expression persists across some clones and some individuals, sufficient in many cases to generate chronic low-level viremia. Whether this residual viremia is infectious or materially contributes to rebound remains uncertain, but it indicates that reservoir silence is not absolute. Longitudinal studies over decades of ART have revealed at least 3 patterns of intact proviral dynamics, ie, continuous decay, decay to a stable plateau, and expansion during the second decade of therapy. Expansion appears least frequent but can be dramatic, including cases in which a single infected clone undergoes pronounced outgrowth. These observations indicate that long-term reservoir behavior is not uniform across individuals and that the reservoir remains biologically active in population terms even when virologically suppressed.

Mellors also reviewed the current therapeutic landscape, including latency reversal or silencing approaches, proviral knockout strategies, therapeutic vaccination, cellular therapies, bNAbs, and combination regimens. Several approaches, especially those involving bNAbs, have shown promising signals, but the field remains limited by small studies and insufficient statistical power. Drawing from cancer immunotherapy, Mellors emphasized that durable remission likely requires highly functional cytotoxic effector cells capable of expansion and persistence, as illustrated by the success of chimeric antigen receptor- and T-cell receptor-engineered approaches in oncology. Future work should define the biologic mechanisms that distinguish reservoirs that continue to decay from those that plateau or expand during long-term ART. Particular attention should be paid to the role of antigen-driven proliferation, homeostatic signals, integration-site context, and immune pressure in shaping these trajectories. It will also be important to determine whether residual proviral expression promotes immune recognition, fuels inflammation, or contributes directly to rebound competence. On the therapeutic side, more rigorously powered

studies are needed to evaluate bNAbs, engineered T-cell therapies, and combination approaches. A particularly important future direction will be to integrate longitudinal reservoir measurements with immune fitness profiling so that remission strategies can be matched to the biology of each individual reservoir.

HIV-Specific T-Cell Responses in PWH on Long-Term ART

CD8+ T cells are central to immune control of HIV infection and are a key component of nearly all immune-based cure strategies. However, in people who initiate ART during chronic HIV infection, HIV-specific CD8+ T cells have traditionally been viewed as dysfunctional, exhausted, and potentially limited in their capacity to mediate durable viral control if treatment is stopped. This concern is further compounded by the fact that many PWH are now aging on long-term ART, raising the possibility that immune senescence and thymic involution could further compromise the quality of HIV-specific cellular immunity. These issues are highly relevant to cure research because strategies such as therapeutic vaccination, latency reversal plus immune clearance, bNAb combinations, and engineered cellular therapies all depend, directly or indirectly, on a host immune system capable of exerting control over infected cells.

Latency is maintained redundantly through intersecting pathways involving chromatin repression, transcriptional elongation blocks, signaling constraints, and cell-state determinants. Appay (Presentation 27) reviewed whether prolonged rates of viral suppression and immune reconstitution under ART might allow the emergence of renewed or replacement clones with improved functional properties. Using flow cytometry and single-cell RNA sequencing in PWH on very long-term ART, including individuals with 25 to 30 years of clinical follow-up, the study aimed to define the phenotypic and transcriptomic characteristics of persistent HIV-specific CD8+ T-cell responses. The key finding of the study was that instead of being dominated by exhaustion and senescence markers, HIV-specific CD8+ T cells in PWH undergoing long-term treatment displayed features of early differentiation and stemness. These cells appeared to retain proliferative and cytolytic potential, suggesting a more rejuvenated and functionally competent phenotype than many would have predicted in people treated during chronic infection and followed for decades.

Single-cell and phenotypic analyses supported a model of clonal succession. According to this model, older, more exhausted clones are progressively replaced over time by newly generated clones with improved functional properties. This concept is important because it suggests that successful ART does not simply preserve a damaged

HIV-specific repertoire; rather, it may permit ongoing immune remodeling and selective renewal of antiviral T-cell populations. This observation is noteworthy given the expected effects of aging and reduced thymic output, implying that the immune system in PWH retains more regenerative capacity than previously assumed. The presentation also linked these findings to cure relevance by noting that similarly stem-like, less terminally differentiated HIV-specific CD8+ T cells have recently been associated with posttreatment control. This raises the possibility that the quality of the persisting HIV-specific T-cell pool under long-term ART may be more favorable for remission strategies than older models of irreversible dysfunction would suggest. Latency is maintained redundantly through intersecting pathways involving chromatin repression, transcriptional elongation blocks, signaling constraints, and cell-state determinants.

In addition to the biologic findings, the presentation emphasized a translational point: immune interventions should be aligned with the physiologic and clinical context of the target population. The optimal strategy for inducing effective CD8+ T-cell responses may differ depending on age, immune reconstitution status, treatment history, and

An unresolved question in HIV cure research is whether the central nervous system contains a true, biologically meaningful reservoir that is distinct from the better-characterized reservoir in CD4+ T cells

baseline T-cell composition. The proposed model of clonal succession suggests that prolonged ART may gradually reshape the HIV-specific repertoire, enabling the replacement of older, exhausted clones with functionally fitter ones. If correct, this has implications for the timing and design of cure interventions. Individuals on stable long-term therapy may in some cases be better candidates for immune-based remission strategies than previously appreciated, provided their HIV-specific responses can be appropriately boosted or redirected.

Future studies should determine how broadly this phenomenon extends across different age groups, treatment histories, and timing of ART initiation, including individuals treated during acute versus chronic infection. It will also be important to establish whether these rejuvenated

HIV-specific CD8+ T-cell populations can directly mediate reservoir control in *ex vivo* or *in vivo* models and whether their presence predicts outcomes in analytic treatment interruption studies.

Characterization of HIV Proviruses in Brain Microglia in PWH on ART

An unresolved question in HIV cure research is whether the central nervous system (CNS) contains a true, biologically meaningful reservoir that is distinct from the better-characterized reservoir in CD4+ T cells. Among candidate CNS reservoir cells, brain microglia have long attracted particular interest because they are long-lived, self-renewing myeloid cells resident in the brain, and are capable of surviving for prolonged periods in an inflammatory environment. If infected microglia harbor intact proviruses, they could represent a uniquely challenging reservoir because of their anatomic location, limited accessibility to immune effectors, and distinct cellular biology compared with circulating T cells. At the same time, interpretation of HIV nucleic acid detected in brain tissues has remained difficult, because signals attributed to microglia may in some cases reflect infiltrating infected T cells, adherent material, or phagocytosed HIV-containing debris rather than authentic myeloid infection.

Thomas and colleagues (Abstract 110) addressed these issues directly using autopsy tissues from PWH on suppressive ART enrolled in the Last Gift rapid autopsy program. The investigators asked 3 central questions: how often does the brain microglia harbor HIV proviruses, what fraction of those proviruses are potentially intact, and where are those proviruses integrated in the human genome? The investigators isolated DNA from several autopsy-derived tissue compartments, including brain microglia, mixed brain tissue, brain T cells, spleen bulk cells, and spleen T cells. Microglial isolates were defined as CD11b+ cells with high transmembrane 119 (TMEM119) positivity, providing strong support for microglial enrichment. DNA was diluted to the proviral endpoint and subjected to multiple displacement amplification, followed by screening for potentially intact proviruses using polymerase chain reaction detection of the long terminal repeat (LTR), packaging signal (Psi), and Rev response element (RRE) regions, which are commonly lost in defective genomes. Integration site sequencing was then used to define host genomic locations and assess clonality. HIV proviruses were detected in brain and spleen compartments, and as expected, the majority were defective. However, in 1 donor, a substantial fraction of proviruses met criteria for being potentially intact, including 27% of microglia-derived proviruses and 48% of spleen-derived proviruses.

This is a notable observation because it indicates that at least some HIV DNA associated with brain microglia is not merely fragmented or grossly defective, but may retain the structural hallmarks of replication competence. Integration site analyses identified large clones with identical integration sites present across brain and spleen tissues, a pattern consistent with a T-cell origin. These shared clones were detected in brain microglia, brain T cells, and spleen, suggesting that some of the proviral signal observed in brain-associated microglial fractions may derive from infected T cells that have trafficked into the CNS, adhered to microglia, or been phagocytosed by them. At the same time, the study identified smaller clones observed only in the microglial compartment, some of which were potentially intact. These microglial-only clones provide evidence that at least part of the CNS proviral burden may reside in a more specific myeloid reservoir.

The overall picture is therefore mixed but informative: the brain compartment contains signals consistent with infiltrating or clonally expanded T-cell-derived proviruses as well as signals supporting the existence of infected microglia with potentially intact proviruses. These results build upon earlier published studies indicating that brain microglia harbor inducible proviruses that exhibit a macrophage-tropic phenotype.²

A major challenge in HIV cure research is the inability to noninvasively track where and when viral rebound begins during analytical treatment interruption. Plasma viremia provides only a delayed and indirect signal of recrudescence infection, reflecting viral production after rebound has already propagated beyond its earliest tissue foci. Yet, the biologic events that determine whether and where rebound emerges likely begin much earlier within discrete anatomic compartments such as lymphoid tissue, gut, bone marrow, or the CNS. Understanding these earliest events is important for cure strategies, because it could reveal the active tissue reservoirs responsible for rebound and identify windows of vulnerability in which host immune responses or therapeutic interventions might still contain infection before it becomes systemic.

Henrich and colleagues (Abstract 113) presented a study that was designed to address that gap using multimodal positron emission tomography (PET) imaging during analytical treatment interruption (ATI). The investigators used one tracer, [⁸⁹Zr]-VRC01, to visualize tissue-associated HIV envelope (Env)/glycoprotein 120 (gp120), and another, [¹⁸F]FAraG, to detect activated or cycling T cells. The investigators first performed longitudinal [⁸⁹Zr]-VRC01 PET imaging in 3 individuals participating in an ATI study. Imaging time points included 2 days prior to first detectable plasma HIV RNA level, during viral rebound, and after ART reinitiation


in a person with subsequently controlled virus. The 2 participants imaged in the pre- or perirebound period showed higher levels of tracer uptake in more various tissues than reported in previous studies on PWH on suppressive ART. These included inguinal lymph nodes, colorectal tissue, femoral bone marrow, and perivascular brain parenchyma, with particularly notable increases in the frontal cortex and cerebellum. In contrast, the controller imaged after ART reinitiation showed VRC01 uptake values that were similar to those seen in ART-suppressed individuals.

The investigators then examined T-cell activation dynamics using [¹⁸F]-FaraG PET-magnetic resonance imaging before ATI and again a median of 9 days after ART interruption. Repeat scanning was performed between 5 and 35 days before detectable plasma HIV RNA level, allowing the assessment of events in a truly prerebound state. In 3 of 4 participants, the investigators observed up to a 2.3-fold increase in tracer uptake in various inguinal lymph nodes compared with pre-ATI baseline. The highest uptake occurred in a participant who subsequently rebounded 35 days after imaging, suggesting that tissue immune activation may precede measurable plasma viremia by a substantial interval. In addition, 1 individual showed an approximately 1.5-fold increase in tracer uptake in several brain regions, including the frontal, temporal, cerebellar, and pontine areas, 17 days before the first detectable plasma viral load.

Together, these findings indicate that HIV-associated signal and immune activation can be visualized in tissues before virus becomes detectable in plasma. The imaging patterns also suggest that rebound may arise from variable focal sites rather than from simultaneous diffuse activation of a uniform systemic reservoir. The study offers direct evidence that HIV recrudescence during ATI is a tissue-first event that can be detected before standard plasma assays show rebound. The identification of focal activity in lymph nodes, gut, bone marrow, and brain supports the view that rebound emerges from anatomically heterogeneous reservoir sites that differ among individuals. The CNS-related findings are noteworthy. Increased uptake in perivascular brain regions and broader brain activation prior to plasma rebound raises the possibility that the brain may participate more actively in rebound dynamics than often appreciated, at least in some individuals. Although the imaging results do not by themselves prove productive infection in specific brain cell types, they do suggest that the CNS can be involved in early viral-host responses during ATI.

Methodologically, the work points toward a powerful new toolkit for cure studies. Noninvasive whole-body imaging could complement reservoir assays, tissue biopsies, and plasma measurements by revealing where

active processes are occurring in vivo. This could be especially valuable in small interventional studies, where identifying the anatomic impact of a therapeutic strategy may be more informative than relying only on time-to-rebound endpoints.

At a broader level, the study underscores that reservoir biology is spatially organized. Cure strategies that succeed in blood may still fail if they do not adequately target anatomically privileged or variably active tissue sites. Future studies should evaluate these imaging approaches in larger ATI cohorts and directly correlate tracer uptake patterns with tissue biopsies, plasma virology, immune phenotyping, and rebound timing. It will be important to determine whether specific anatomic uptake signatures predict rebound kinetics, posttreatment control, or response to cure-directed interventions. 

All abstracts cited in the text appear in the CROI 2026 Abstract eBook, available online at www.CROIconference.org

The IAS–USA has identified and resolved ahead of time any possible conflicts of interest that may influence CME activities with regard to exposition or conclusion. All financial relationships with ineligible companies for the author and planners/reviewers are below.

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*Invited Review***CROI 2026: Neuro-HIV at the Crossroads of Coinfections, Reservoirs, Antiretroviral Therapy, and Comorbidities****Michael J. Corley, MA, PhD¹; Sarah B. Joseph, PhD²; Phillip Chan, MBChB, PhD³**¹University of California San Diego; ²University of North Carolina at Chapel Hill; ³Yale University, New Haven, Connecticut

Abstract: *The 2026 Conference on Retroviruses and Opportunistic Infections (CROI) featured important new and impactful findings relevant to the neurologic HIV (neuro-HIV) field. Reports included new evidence linking herpesvirus coinfections to cognitive heterogeneity; studies on neuroinflammation, neuronal injury, and amyloid-related processes in treated HIV; and studies using advanced technologies to address the HIV-infected cells that persist in the central nervous system during antiretroviral therapy and the mechanisms that may maintain those populations. New therapeutic findings were presented on low-dose hydrocortisone and pregnenolone as potential strategies to improve cognition and reduce inflammatory signaling. Additional studies linked brain health in people with HIV to antiretroviral-associated neuropsychiatric effects and to aging-related comorbidities, including cerebrovascular disease, diabetes, metabolic syndrome, insulin resistance, and metabolic dysfunction-associated steatohepatitis. This review summarizes these findings and highlights new mechanistic and therapeutic directions for the neuro-HIV field.*

Keywords: antiretroviral therapy, ART, brain aging, central nervous system, CNS reservoirs, cognitive heterogeneity, herpesvirus coinfections, microglia, neuro-HIV, neuroinflammation, neuropsychiatric

Introduction

The effects of HIV on the central nervous system (CNS) were the focus of several important presentations at the 2026 Conference on Retroviruses and Opportunistic Infections (CROI). As people with HIV (PWH) are living longer on effective antiretroviral therapy (ART), the neurologic HIV (neuro-HIV) field has increasingly shifted beyond

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the question of whether viral suppression can be achieved in the CNS to the broader challenge of preserving brain health across the lifespan. This includes understanding the biologic basis of cognitive heterogeneity, defining the mechanisms that sustain HIV persistence in the CNS, and identifying modifiable contributors to neuroinflammation, neuronal injury, and neuropsychiatric symptoms. There is growing interest in how contemporary ART regimens may influence brain structure, neuropsychiatric symptoms, and cognitive trajectories, supported by recent studies underscoring that brain health in PWH reflects a complex interplay between ART-specific effects, treatment timing, and cumulative vascular and metabolic risk, reinforcing the need for integrated approaches to optimize neurologic and mental health across the lifespan. This review is organized around 5 themes from CROI 2026: coinfections and cognitive heterogeneity in treated HIV; neuroendocrine interventions for cognition and neuroinflammation; HIV CNS reservoirs; ART and brain health; and neurologic effects of medical comorbidities. Together, these studies advance the understanding of the multifactorial basis of neuropsychiatric complications in PWH and highlight emerging mechanistic and therapeutic targets.

Coinfections, Brain Aging, and Cognitive Heterogeneity in Treated HIV

In aging PWH, chronic coinfections may represent an underrecognized contributor to accelerated brain aging and cognitive heterogeneity by sustaining neuroinflammation, neuronal injury, and altered antiviral immune responses beyond the effects of HIV alone. Riggs and colleagues (Abstract 481) examined relationships between herpesvirus measures and cerebrospinal fluid (CSF) biomarkers of neuronal injury, neuroinflammation, and amyloid pathology in 107 virally suppressed PWH from the CHARTER (CNS HIV Anti-Retroviral Therapy Effects Research) and HNRC (HIV Neurobehavioral Research Center) cohorts (mean patient age, 55 years; 83% male; 41% Black and 51% White). The

median CD4+ count was 577 cells/ μ L and median duration of HIV infection was 22 years; 94% were cytomegalovirus (CMV) immunoglobulin G (IgG) seropositive and 100% were Epstein-Barr virus (EBV) IgG seropositive. Cell-associated CMV, EBV, and HIV DNA levels were quantified in peripheral blood mononuclear cells (PBMCs) by digital droplet polymerase chain reaction (ddPCR) and plasma IgG titers were measured by immunoassay.

Eleven CSF biomarkers were assessed, including neurofilament light (NFL), soluble tumor necrosis factor receptor-II (sTNFR-II), total tau, amyloid- β 1-42 (A β 42), and monocyte chemoattractant protein-1 (MCP-1).

In multivariable models, 6 CSF biomarkers remained associated with viral measures after adjustment for age, sex, race, ethnicity, CD4+ cell count, CD4+ cell nadir, and CSF/serum protein ratio. EBV (IgG and DNA) was associated with neuronal injury markers (NFL and tau), whereas CMV (IgG and DNA) was associated with neuroinflammation (sTNFR-II) and complex effects on amyloid processing and

and HNRC cohorts. Total antibody reactivity burden did not differ by cognitive impairment status, arguing against global immune senescence and in favor of virus-specific immune phenotypes as determinants of cognitive heterogeneity. After correction for false discovery rate (FDR), working memory and executive function showed the strongest association compared with other cognitive domains. In CSF and plasma, herpes simplex virus (HSV-1) antibody responses were associated with intact working memory ($P=.009$) and executive function ($P=.034$). HSV-2 and EBV antibody responses were associated with better working memory. In contrast, HIV-1 envelope antibody responses consistently tracked with worse cognitive performance across numerous domains. These associations remained after adjustment for age, sex, and CD4+ cell count, supporting the conclusion that the antiviral immune repertoire may shape cognitive outcomes in PWH.

These observations underscore the need for methods capable of detecting low-level, compartment-specific herpesvirus activity at single-cell resolution, particularly for EBV, CMV, and HSV, which may contribute to neuroinflammation, neuronal injury, and cognitive heterogeneity in treated HIV. Addressing this gap, Duchon and colleagues (Abstract 465) developed the primary and opportunistic pathogen recovery via quasi-mapping and single-cell transcriptomics (POP-ROQS), a computational workflow designed to jointly capture human and viral transcripts from single-cell RNA (scRNA) sequencing data, including CSF cells. Standard scRNA pipelines are largely host-centric and routinely exclude low-abundance viral transcripts during barcode filtering and quality-control steps, causing pathogen-associated droplets to be missed. POP-ROQS overcomes this limitation by aligning reads to a joint human-viral reference genome that includes representative HIV-1, HIV-2, simian immunodeficiency virus, CMV, EBV, HSV-1, and HSV-2 genomes, and by applying postalignment FASTQ parsing to classify droplets as containing intracellular (infected host cell) or extracellular/ambient viral RNA. In paired CSF and peripheral blood sample analyses, 7 participants who were virally suppressed and 1 participant who was ART naive were sampled longitudinally after ART initiation. POP-ROQS substantially outperformed the standard Cell Ranger pipeline for viral detection. Although the most striking gains were observed for HIV, the platform concurrently detected EBV, CMV, and HSV transcripts, providing an important proof of concept for studying various neurotropic and immunomodulatory viruses in parallel within scarce CSF samples. Performance improved further when reference indexes incorporated diverse representative viral genomes rather than single or redundant genomes, an important consideration

Herpesvirus coinfection may modify the profile of neurologic injury in virally suppressed individuals with HIV

clearance (A β 42 and soluble amyloid precursor protein α [sAPP α]). HIV DNA level was not significantly associated with any CSF biomarker. A clustering analysis confirmed a significant association between viral cluster measures (EBV IgG, EBV DNA, CMV IgG, CMV DNA) and CSF biomarker clusters (NFL, sTNFR-II; $\beta=0.230$; $R^2=0.394$; $P<.0001$). These exploratory, cross-sectional findings suggest that CMV- and EBV-related mechanisms, rather than residual HIV, may drive ongoing neurologic injury in virally suppressed PWH, and raise the possibility that antiviral interventions targeting herpesviruses could benefit brain health in aging PWH.

Riggs and colleagues presented complementary data using a high-resolution virome-wide antibody profiling approach (Abstract 470). Using the VirSIGHT molecular indexing of proteins by self-assembly (MIPSA) platform, which characterizes antibody reactivity against 286,793 DNA-barcoded viral peptides from more than 500 human viruses, the investigators profiled antiviral antibody responses in paired CSF and plasma samples from 88 PWH on suppressive ART (81% male; mean age, 52 years; median CD4+ count, 680 cells/ μ L) from the CHARTER

for sensitively capturing herpesvirus diversity. By enabling simultaneous detection of EBV, CMV, HSV, and HIV transcripts at single-cell resolution across compartments, POP-ROQS provides a valuable new tool for defining the cellular sources and tissue context of chronic viral activity that may shape brain aging and cognitive outcomes in PWH.

Targeting Neuroendocrine Pathways to Improve Cognition and Neuroinflammation

Women with HIV experience high rates of trauma, chronic stress, and depression, all of which are linked to cognitive impairment. Candidate mechanisms include dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, glucocorticoid (GC) receptor function, neuroinflammation, and HIV persistence, yet no existing interventions directly target these pathways. Rubin and colleagues (Abstract 112) conducted a phase II clinical trial at Johns Hopkins University (2018–2024) to determine whether low-dose hydrocortisone (LDH), a pharmacologic modulator of HPA axis function, could improve cognition in virally suppressed women with HIV and to examine neuroendocrine, immune, and HIV-related mechanisms underlying treatment effects. Eligible participants (aged 18–65 years) had self-reported stress or a mood or anxiety disorder and objective impairment in at least 1 cognitive domain. The primary outcome was the Hopkins Verbal Learning Test–Revised (HVLT-R). The initial study was a double-blind, placebo-controlled, crossover trial testing the immediate (30-minute) and delayed (4-hour) cognitive effects of a single 10 mg LDH dose; 81 participants were randomly assigned (mean age, 55.2 years [standard deviation, 8.0 years]; 81% Black). LDH produced a robust cortisol increase (5.14-fold) peaking 75 minutes post dose ($P < .001$). At 4 hours, LDH significantly improved HVLT-R total learning compared with placebo ($P = .03$; Cohen $d = 0.27$) and showed a trend toward improved delayed recall ($P = .08$; Cohen $d = 0.21$). Attention improved at the 30-minute and 4-hour timepoints ($P < .05$ for each).

A follow-up study was a randomized, double-blind, placebo-controlled trial of daily LDH for 4 weeks. LDH significantly improved delayed recall ($P = .005$; Cohen $d = 0.34$) and prevented decline on an attentional measure compared with placebo ($P = .016$), although the effect on treatment-time interaction did not reach significance ($P = .14$). LDH was well tolerated, with no serious adverse events (AEs). Notably, there were no significant associations between changes in peripheral biomarkers including cortisol, inflammatory markers, GC receptor expression, and HIV reservoir measures, and LDH-related cognitive

improvements, suggesting that other biologic mechanisms, potentially including direct CNS effects, may underlie the observed benefits.

Complementing this clinical evidence, Daly and colleagues (Abstract 476) investigated the immunomodulatory properties of pregnenolone, an endogenous neuroactive steroid (NAS) synthesized in the mitochondria of adrenal, gonadal, and brain cells, in 33 PWH (all on ART; plasma HIV-1 RNA level < 200 copies/mL) and 20 people without HIV (PWoH). Endogenous plasma NAS levels were measured by mass spectrometry. Although pregnenolone levels did not differ significantly between groups, higher endogenous pregnenolone levels were inversely correlated with levels of interleukin-6 (IL-6; $r = -0.52$; $P < .01$) and monocyte chemoattractant protein-1 (MCP-1; $r = -0.39$; $P = .03$) in the full cohort. Among PWH, the correlation with IL-6 remained significant ($r = -0.52$; $P = .03$). Soluble CD163, a marker of monocyte/macrophage activation, was significantly higher in PWH than in PWoH ($P < .01$). In vitro experiments using PBMCs from PWH and PWoH stimulated with the toll-like receptor 4 (TLR4) agonist lipopolysaccharide (LPS) or the TLR1/2 agonist PAM3CSK4 demonstrated that pregnenolone dose-dependently reduced IL-6 production ($P < .001$) in CD14+CD16– classical monocytes and increased regulatory cytokines interleukin-10 (IL-10; $P < .001$) and transforming growth factor- β (TGF- β ; $P < .001$). This immunomodulatory effect, mediated primarily through innate immune pathways, suggests that pregnenolone shifts monocytes toward a regulatory phenotype. These preclinical data support the ongoing phase II SOOTHE (Neuroactive Steroid to Treat Depressed Mood: A Trial for People With HIV) trial, which is evaluating pregnenolone in PWH who have major depressive disorders.

HIV CNS Reservoirs

Despite intense investigation in recent years, fundamental questions about the nature and significance of HIV reservoirs in the CNS remain unresolved. At CROI 2026, several presentations addressed key issues, including determining which HIV-infected cells persist in the CNS during ART, how CNS reservoirs are maintained, and whether CNS reservoirs contribute to viral rebound during treatment interruption.

One study presented by Kincer (Abstract 458) analyzed HIV RNA sequences in CSF and plasma collected from untreated individuals to infer which CNS cell types are infected during untreated infection—and thus, which cells may seed long-lived CNS reservoirs. Genetically distinct (ie, compartmentalized) viral lineages in the CSF were found

in 32% of participants, indicating that they had virus populations independently replicating in the CNS. Importantly, CNS replication was associated with neurologic symptoms, elevated CSF-to-plasma viral load ratios, and evidence of inflammation. To further investigate the cellular origins of these CNS-derived viral populations, they examined the cellular tropism of *env* genes cloned from the CSF in a subset of these individuals and determined that 58% had HIV

The nature and significance of HIV reservoirs in the CNS, along with the mechanisms underlying viral persistence, remain to be fully elucidated

populations in their CSF that were adapted to replication in myeloid cells (macrophage/microglia). This phenotype (M tropism) is rarely observed in the periphery, suggesting that these lineages were likely produced by HIV-infected myeloid cells. The remaining 42% of individuals had HIV in their CSF that was adapted to replication in CD4+ cells (ie, T tropic) and was likely produced by sustained replication in CD4+ cells in the CNS. These results suggest that HIV-1 replication in the CNS can occur in CD4+ cells or myeloid cells (macrophage/microglia), emphasizing the possibility that each cell type may contribute to CNS reservoirs. In addition, they observed that replication in each cell type is associated with neurologic symptoms, raising questions about whether replication in CD4+ cells and myeloid cells generates brain injury through different mechanisms.

Studies of CD4+ cells in the periphery have clearly shown that clonal expansion is fundamental to the persistence of HIV-infected cells during ART. To better understand the contribution that clonal expansion makes to the maintenance of HIV reservoirs in the CNS, Thomas and colleagues (Abstract 110) performed HIV integration site analyses on brain and spleen cells isolated from 3 PWH who were virologically suppressed at death and donated their bodies to the Last Gift Project. Surprisingly, for 1 participant, the same integration site was observed in CD4+ cells in the brain and spleen as well as in microglia in the brain. Observing the same integration site in CD4+ cells isolated from different compartments is easily explained by the migration of HIV-infected, clonally expanding CD4+ cells, but it is difficult to understand how the same integration site can be observed in different cell types (eg, microglia and CD4+ cells). To better understand this result, the

investigators performed T-cell receptor (TCR) sequencing and inferred that more than 1.8% of cellular DNA in the microglia population was derived from T cells. These results are consistent with phagocytosis of HIV-infected CD4+ cells by microglia or contamination of microglia populations with HIV-infected CD4+ cells. Although this work clearly illustrates that HIV-infected cells can be detected in the CNS during ART and suggests that proliferation is a mechanism that maintains CNS reservoirs, additional studies are needed to understand whether the microglia population contains phagocytosed HIV-infected CD4+ cells.

Although many studies have identified HIV-infected cells in the CNS during ART, it remains unclear whether these cells contribute to viremia when ART is stopped. Henrich and colleagues (Abstract 113) utilized advanced imaging approaches to assess HIV expression and CD4+ cell activation during analytic treatment interruption (ATI) in humans. Addressing these issues in the CNS involves many challenges, including the need for markers that can penetrate the CNS and the challenges of timing 2 complex protocols (ATI and imaging) to detect the early stages of viral rebound. In their first study, ⁸⁹Zr-labeled VRC01 antibody with positron emission tomography/magnetic resonance imaging was used to visualize cells expressing HIV Env during ATI (before viral RNA was detectable in the blood). They observed increased uptake of ⁸⁹Zr-labeled VRC01 in inguinal lymph nodes (mean tissue-blood ratio of the maximum standardized uptake value, 0.33 vs 0.15), colorectal tissue (0.5 vs 0.21 in PWH on ART) and femoral bone marrow (1.09 vs 0.4 in PWH on ART). Surprisingly, elevated uptake signals of ⁸⁹Zr-labeled VRC01 were also detected in the perivascular brain parenchyma during ATI. However, it is unclear how to interpret this result, given the poor penetration of ⁸⁹Zr-labeled VRC01 into the CNS and the lack of signal in the brain parenchyma.

Henrich and colleagues (Abstract 113) also performed a longitudinal imaging study to assess whether ATI increased cellular activation, using a tracer (¹⁸F-AraG) that penetrates the CNS efficiently and accumulates in activated cells (particularly in CD4+ cells, but it may also accumulate in myeloid cells). They did not observe a substantial change in tracer uptake during ATI, suggesting that ATI did not have a major impact on cell activation in the brain. Overall, these studies illustrated the power of longitudinal imaging analyses and the challenges of observing HIV and HIV-associated inflammation in the brain.

Suzuki and colleagues (Abstract 459) explored whether HIV expression in the periphery during ART is associated with CNS injury. Expression of long translation-competent

HIV-1 transcripts in peripheral CD4+ cells was associated with lower N-acetyl aspartate (NAA; a marker of neuronal integrity) levels in frontal white matter as measured by magnetic resonance spectroscopy ($P=.003$). In contrast, transcripts edited by apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (APOBEC)-3, ie, translationally incompetent transcripts, were not associated with worse neuronal integrity. Although the study was unable to show causation, it raises questions about whether the specific HIV transcripts expressed in CD4+ cells in the periphery are a marker of expression in cells trafficking through the CNS, ie, the cells directly contributing to brain injury, or whether there is a systemic phenomenon that could increase APOBEC-mediated hypermutation and reduce brain injury (eg, by blocking CCL2 signaling).

These studies are consistent with the idea that HIV can persist in the CNS before and during ART, but many questions remain about the mechanisms that facilitate HIV persistence in that compartment and the impact that HIV may have on brain health during ART. Although the technologies highlighted in these studies provide new opportunities for understanding CNS reservoirs, they illustrate that there is no single approach that can comprehensively profile CNS reservoirs.

Antiretroviral Agents and Brain Health

As ART continues to extend life expectancy for PWH, attention has increasingly shifted beyond viral suppression to the long-term health of organ systems that are vulnerable to aging and chronic disease, particularly the brain. Notably, Makinson and colleagues (Abstract 454) conducted a 5-year study comparing cognitive changes between PWH aged 55 to 70 years receiving ART and matched PWH. This multisite French study of 117 PWH and 585 PWH assessed cognitive changes using a 5-test cognitive battery screening tool. PWH demonstrated worse global neuropsychologic (NP) Z-scores at baseline and experienced greater declines in NP Z-scores during the 5-year study period, with a pronounced decrease in verbal semantic fluency. These findings highlight the need to identify and address risk factors that may negatively affect brain health in PWH.

During the past decade, integrase strand transfer inhibitors (INSTIs), particularly dolutegravir (DTG), have become widely used as components of the initial ART regimens. However, DTG use has been increasingly reported to be associated with the onset or worsening of neuropsychiatric AEs, including insomnia, sleep disturbances, anxiety, and depression. Rodriguez-Evaristo and colleagues (Abstract 464) conducted a randomized,

open-label trial at the Hospital de Infectología, Centro Médico Nacional “La Raza” between June 2023 and December 2024 to evaluate changes in depressive and anxiety symptoms, insomnia, and sleep quality among PWH initiating DTG or boosted darunavir (DRV/c) in combination with TDF/FTC. In this study, DTG was associated with higher rates of ART discontinuation due to worsening

Dolutegravir was associated with higher rates of ART discontinuation due to worsening neuropsychiatric symptoms, including new-onset suicidality and an increased need for psychiatric interventions

neuropsychiatric symptoms, including new-onset suicidality and an increased need for psychiatric interventions such as antidepressant therapy. These findings highlight the importance of screening for neuropsychiatric changes after initiating or switching ART regimens.

Foster and colleagues (Abstract 463) examined whether DTG inhibits acetylcholinesterase (AChE), a mechanism that could potentially contribute to neuropsychiatric AEs following DTG usage. Using 3-dimensional docking analyses, they demonstrated that DTG interacts with the active site of AChE with high binding affinity, suggesting inhibitory potential. Furthermore, postmortem human brain analyses revealed significantly less AChE activity in the frontal cortex of PWH on DTG-based regimens than in those not on DTG-based regimens. In addition, among PWH who switched from a DTG-based to a non-DTG-based regimen, AChE activity in plasma was significantly reduced. These observations underscore the need for further investigation into DTG-associated modulation of AChE activity and its potential role in neuropsychiatric AEs.

Cooley and colleagues (Abstract 462) examined whether regional brain volume changes differed with lamivudine (3TC) use in middle-aged PWH. Individuals receiving 3TC demonstrated larger brain volumes in the basal ganglia and regions throughout the frontal lobe (eg, orbitofrontal and superior frontal cortices), but significantly smaller parahippocampal volumes, than those on non-3TC-based regimens. The 3TC users exhibited a steeper age-related decline in parahippocampal volume, alongside a lesser decline in regions of the basal ganglia, than those on

non-3TC-based regimens. However, there were no group differences in cognitive performance cross-sectionally or longitudinally. Given that parahippocampal atrophy is associated with mild cognitive impairment and Alzheimer's disease in the general population, these findings underscore the need for longer-term follow-up studies incorporating neuroimaging and Alzheimer's disease biomarker outcomes.

In addition to neuropsychiatric AEs, previous research suggested an increased risk of stroke among PWH during ART initiation or reinitiation following treatment interruption. Smuts and colleagues (Abstract 442) estimated the

Several abstracts reported associations between antiretroviral drugs and CNS outcomes, including neuropsychiatric adverse events, brain volume changes, and stroke incidence

annual incidence of stroke and examined the association between stroke occurrence and the timing of ART initiation in a large prospective cohort of PWH in South Africa. They identified 688 PWH with acute or subacute stroke confirmed by neuroimaging, corresponding to an annual incidence rate of 171 per 100,000 adult PWH. More than 85% of strokes were ischemic, most commonly involving the middle cerebral artery territory. Notably, nearly one-quarter of affected individuals had initiated or reinitiated ART within 6 months preceding the stroke event. These findings are consistent with previous studies suggesting an increased risk of stroke during the early months following ART initiation, potentially reflecting an immune reconstitution-like phenomenon. Collectively, these studies reinforce the concept that brain health in PWH is shaped by sustained virologic suppression and by potential ART-related mechanisms.

Potential Neurologic Impacts of Concurrent Medical Conditions

Beyond the elevated risk of stroke observed in the early months following ART initiation, stroke is more prevalent among PWH than among PWOH, even during the maintenance phase of virologically suppressive ART. Farrell and colleagues (Abstract 448) examined the burden of

subclinical cerebrovascular injury among PWH receiving ART in the MACS (Multicenter AIDS Cohort Study)/WIHS (Women's Interagency HIV Study)-CCS (Combined Cohort Study), stratifying findings by cerebral vessel size (small vessel disease [SVD] vs large artery disease [LAD]) and by sex-specific effects of modifiable risk factors. Neuroimaging assessments included brain magnetic resonance imaging, magnetic resonance angiography with vessel wall imaging, and phase-contrast 4-dimensional flow imaging of the intracranial arteries. In the study, female participants exhibited a higher prevalence of hypertension, elevated body mass index, greater depressive symptom burden, lower levels of physical activity, and higher rates of current smoking than male participants. These differences were accompanied by a significantly greater burden of SVD, but not LAD, among women, independent of age, race, cardiovascular disease, and other traditional risk factors. Interventions targeting these modifiable factors may help reduce the observed sex-based disparities in cerebrovascular risk among women with HIV.


Many studies at CROI 2026 explored the association between cognitive changes and metabolic conditions, including diabetes, metabolic dysfunction-associated steatohepatitis (MASH), and metabolic syndrome. Vance and colleagues (Abstract 445) examined cognitive intraindividual variability (IIV), the dispersion in cognitive performance across numerous test results within the same individual, among women with and without HIV in the WIHS and evaluated associated risk factors. A comprehensive cognitive battery of tests spanning 7 cognitive domains demonstrated that women with HIV exhibited greater cognitive IIV across the lifespan than women without HIV. In addition to older age and depressive symptoms, diabetes was identified as a factor associated with increased cognitive IIV, suggesting a potential link between diabetes and neuropathology in women with HIV.

Hockney and colleagues (Abstract 451) investigated whether metabolic syndrome was associated with cognitive impairment in the MACS. The study included 1588 men with or at risk of HIV. A cognitive global deficit score was derived from 6 cognitive domain scores generated by a comprehensive cognitive battery of tests. The findings revealed that older age (≥ 65 years) was the dominant predictor of cognitive impairment, particularly among PWH. Moreover, the presence of metabolic syndrome among older PWH further increased the risk of cognitive impairment.

In a Thailand-based study, Porkaew and colleagues (Abstract 453) examined longitudinal changes in performance on the Montreal Cognitive Assessment (MoCA) test among 291 PWH aged 50 years or older, stratified by

the presence of MASH as assessed by transient elastography (FibroScan). Over a median follow-up period of 5.9 years, PWH with MASH experienced a greater decline in MoCA performance than those without MASH. In adjusted models, the association between MASH and MoCA performance decline remained independent of age, sex, body mass index, education level, employment status, smoking, alcohol use, diabetes, hypertension, duration of HIV infection, and ART regimen. These findings underscore the need for prospective studies to determine whether early identification and management of MASH in PWH would reduce the risk of cognitive decline.

Tavasoli and colleagues (Abstract 473) examined the association between cognitive performance and markers of metabolic dysfunction, including glycosylated acetyl

regimens used in PWH may play a role in brain health. Given the expanding literature on weight change and metabolic effects of ART drugs, future studies may benefit from investigating whether ART-associated metabolic alterations mediate or modify neurologic outcomes in PWH. These findings underscore the importance of individualized ART selection, vigilant monitoring for neuropsychiatric and cognitive changes, and appropriate screening and management of modifiable metabolic conditions in clinical settings. 

All abstracts cited in the text appear in the CROI 2026 Abstract eBook, available online at www.CROIconference.org

Clinical studies have linked metabolic disorders, including diabetes, metabolic syndrome, and MASH, to adverse neurovascular and cognitive outcomes

groups, the diabetes risk index (DRI), the lipoprotein insulin resistance index (LP-IR), branched-chain amino acids, and gut metabolites. The study included 200 participants equally stratified by HIV status and diabetes mellitus status. Higher DRI and LP-IR levels were associated with worse cognitive performance among PWH, but not among PWH. These findings suggest that insulin resistance, a key pathophysiologic feature of diabetes, metabolic syndrome, and MASH, may contribute to cognitive vulnerability in PWH, and that HIV infection may confer a unique metabolic susceptibility affecting brain function.

Conclusion

The studies presented at CROI 2026 suggest that metabolic comorbidities that accompany aging and some ART

The IAS–USA has identified and resolved ahead of time any possible conflicts of interest that may influence CME activities with regard to exposition or conclusion. All financial relationships with ineligible companies for the authors and planners/reviewers are below.

Financial relationships with ineligible companies within the past 24 months: Dr Corley reported no relevant financial relationships with ineligible companies. (Updated March 26, 2026) Dr Chan reported no relevant financial relationships with ineligible companies. (Updated March 26, 2026) Dr Joseph reported no relevant financial relationships with ineligible companies. (Updated March 26, 2026)

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*Invited Review***CROI 2026: Antiretroviral Therapy in Adult, Maternal, and Pediatric Populations With HIV****Shauna H. Gunaratne, MD, MPH, DTM&H¹; Timothy J. Wilkin, MD, MPH²; Hong-Van Tieu, MD, MS³**¹Columbia University Irving Medical Center, New York, New York; ²University of California San Diego; ³New York Blood Center, New York

Abstract: *The 2026 Conference on Retroviruses and Opportunistic Infections provided data on several investigational antiretroviral compounds with the potential for twice-yearly dosing. A complete yearly regimen seems likely to be available in the coming years. Data on doravirine/islatravir showed that this regimen is an effective 2-drug regimen in those initiating antiretroviral therapy (ART) and in those switching from a suppressive regimen. Several abstracts on ART resistance were presented, focusing on the emergence of resistance to integrase strand transfer inhibitors and to lenacapavir. Recent data highlighted new strategies for the empiric treatment of severe pneumonia in infants with HIV, the potential for long-term ART-free remission using broadly neutralizing antibodies and very early initiation of ART, the evaluation of simplified and long-acting ART regimens, and optimizing transition services for adolescents with perinatally acquired HIV to adult care.*

Keywords: ART, CAB, cabotegravir, DOR, doravirine, HIV, integrase strand transfer inhibitors, ISL, islatravir, LEN, lenacapavir, long-acting antiretroviral therapy, maternal health, pediatric health, pharmacokinetics, resistance, rilpivirine

Novel Long-Acting Anti-HIV Compounds

At the 2026 Conference on Retroviruses and Opportunistic Infections (CROI), there was a strong emphasis on long-acting (LA) antiretroviral therapy (ART) formulations. Moreover, several compounds showed promise for twice-yearly dosing, suggesting that a complete

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twice-yearly ART regimen is viable in the near future. Gupta and colleagues (Abstract 174) presented data on GS-3242, an investigational LA integrase strand transfer inhibitor (InSTI). They investigated the pharmacokinetic (PK) parameters associated with 3 different doses of intramuscular administration of GS-3242 in people without HIV. The results supported a possible dosing schedule of every 4 months, potentially as infrequently as every 6

GS-3242 and VH-184 are investigational InSTIs with the potential for twice-yearly dosing

months. They investigated the antiviral activity of GS-3242 monotherapy in people with HIV (PWH) not on ART using an oral formulation dosed on day 1 and day 2. They found a mean plasma HIV-1 RNA level reduction of 2.31 log₁₀ copies/mL through day 11, which is comparable to other InSTIs. Future studies will investigate this compound in novel combinations of LA regimens.

Back and colleagues (Abstract 176) presented data on LA formulations of VH-184, an investigational InSTI with antiviral activity against HIV-1 isolates resistant to second-generation InSTIs such as dolutegravir (DTG) and bictegravir (BIC). They evaluated several formulations with subcutaneous and intramuscular administration. Only mild injection-site reactions were noted. They concluded based on available PK data that twice-yearly dosing is feasible, which is being pursued in ongoing studies.

Thakkar and colleagues (Abstract 175) presented PK data on LA formulations of VH499, an investigational HIV-1 capsid inhibitor, in people without HIV. They investigated various formulations including subcutaneous and intramuscular administration. Injection-site reactions were common and occurred more frequently with subcutaneous formulations; however, these adverse events

were generally mild or moderate. Based on the population PK models generated from these data, future studies will investigate twice-daily dosing of VH-499.

Rolle and colleagues (Abstract 178) presented data on monthly intramuscular long-acting cabotegravir (LA CAB) given with every 6-month N6LS, an investigational broadly neutralizing antibody (bNAb) targeting HIV-1, in people with stable virologic suppression with documented susceptibility to N6LS. A total of 125 participants were randomly assigned 2:2:1 to intravenous N6LS plus LA CAB, N6LS subcutaneously plus LA CAB, or continued oral ART, respectively. The 12-month results presented were consistent with prior 6-month results, ie, the intravenous formulation was better tolerated than the subcutaneous formulation, and virologic suppression was generally sustained from month 6, with 94% achieving plasma HIV-1 RNA level below 50 copies/mL in the intravenous group. No additional participants in the intravenous group experienced confirmed virologic failure (VF) from month 6 to month 12.

Single-Tablet Oral Regimens

Single-tablet regimens have generally been studied in those initiating ART or in those who are stably suppressed on ART without a history of VF. Orim and colleagues (Abstract 181) presented data on the use of a BIC/LEN single-tablet regimen in those virally suppressed on a complex regimen and with a history of VF. Participants with stable virologic suppression on a complex regimen (median, 3 tablets/d)

Switching to BIC/LEN is an effective strategy for those on complex ART regimens

were randomly assigned 2:1 to switch to BIC/LEN or remain on a complex regimen. Both arms did well through 48 weeks, with high rates of virologic suppression, very low rates of confirmed VF, and no emergence of resistance. Participants switching to BIC/LEN reported greater treatment satisfaction than those remaining on a complex regimen.

Messner and colleagues (Abstract 513) presented data on switching to BIC/LEN in people who were stably suppressed on BIC/emtricitabine (FTC)/tenofovir alafenamide (TAF) without history of VF. They conducted a randomized, double-blinded clinical trial and found that switching to BIC/LEN resulted in virologic outcomes that were noninferior to staying on BIC/FTC/TAF.

Rockstroh and colleagues (Abstract 177) compared doravirine (DOR)/islatravir (ISL) with BIC/FTC/TAF in those initiating ART for the first time. This randomized, double-blind trial enrolled 536 participants. The rates of viral suppression were high in each group, and DOR/ISL achieved noninferiority vs BIC/FTC/TAF (91.8% vs 90.6%, respectively; difference, 1.2%; 95% CI, -3.7 to 6.2). The

DOR/ISL was noninferior to comparator regimens for those initiating ART and as switch therapy for suppressed individuals

rates of confirmed VF were similar in both arms; 2 participants in the DOR/ISL arm and zero participants in the BIC/FTC/TAF arm had treatment-emergent resistance mutations. Suppression rates in the DOR/ISL arm were similar among those with a plasma HIV-1 RNA level above 100,000 copies/mL and those above 500,000 copies/mL. Weight gain did not differ between arms. These data suggest that DOR/ISL is an additional viable 2-drug regimen for those initiating ART.

Two presentations reported on 96-week outcomes in clinical trials that compared switching those with virologic suppression on BIC/FTC/TAF (Abstract 514) or other oral ART (Abstract 515) to DOR/ISL. The studies found that switching to DOR/ISL resulted in noninferior virologic outcomes vs continuing the baseline ART regimen. Post and colleagues (Abstract 519) performed a subgroup analysis of these trials to describe the renal outcomes of those with mild or moderate renal impairment at the study baseline. They found similar virologic outcomes in those with and without renal impairment and found that DOR/ISL did not adversely affect renal outcomes.

Real-World Data on LA CAB/RPV

There were several presentations on the use of long-acting cabotegravir/rilpivirine (LA CAB/RPV) in real-world settings. Rolle and colleagues (Abstract 525) investigated an early switch to LA CAB/RPV among people initiating ART with oral DTG/lamivudine (3TC). Participants were offered the option of switching to LA CAB/RPV as soon as their plasma HIV-1 RNA level was below 50 copies/mL. They found low rates of viral nonsuppression through month 11 (approximately 5%); 1 of 129 (<1%) experienced emergence of resistance to LA CAB/RPV. This suggests

that switching from oral induction ART to LA CAB/RPV as soon as plasma HIV-1 RNA suppression is achieved is a reasonable strategy.

Abstracts 527 to 529 compared virologic outcomes among those initiating LA CAB/RPV without viral suppression and those with viral suppression. These studies were consistent in finding that low-level detection of HIV-1 RNA was more common among people initiating LA CAB/RPV with viremia; however, these rates were low

Additional real-world evidence and a small clinical trial support the use of LA CAB/RPV in those with viremia, although those with preexisting DRMs and low CD4+ cell counts were not studied

in both groups. Similarly, confirmed VF was very low in both groups. Data on median CD4+ counts of the study populations were limited and only mentioned in Abstract 527, where the median CD4+ count was above 500 cells/ μ L. Baseline drug resistance mutations (DRMs) among the study participants were not mentioned. These data support the use of LA CAB/RPV in those without virologic suppression, but caution remains in its use in those with preexisting DRMs or low CD4+ cell counts, as these groups were not studied.

These results were supported by Chen and colleagues (Abstract 530), who presented data from a small clinical trial that randomly assigned 45 individuals with ongoing viremia despite oral ART with no DRMs associated with CAB or RPV. Participants were randomly assigned to continue oral ART or change to LA CAB/RPV. Median CD4+ count was 319 cells/ μ L. They found more superior virologic suppression among those randomly assigned to LA CAB/RPV than in those who continued oral ART (19/25 [76%] vs 8/20 [40%], respectively; $P=.03$).

Dietrich and colleagues (Abstract 534) examined the relationship between body mass index (BMI) at the time of LA CAB/RPV initiation and subsequent virologic outcomes in the OPERA (Observational Pharmaco-Epidemiology Research and Analysis) cohort. The rates of viral suppression among BMI strata (<30 kg/m², 30 to <40 kg/m², 40 kg/m² and higher) were similar at approximately 95%. The rates of confirmed VF through a median of 16 months of follow up were low in all groups. These data support the use of LA CAB/RPV in PWH with obesity.

Spinelli and colleagues (Abstract 484) evaluated the relationship between low-level viremia and plasma trough concentrations of CAB and RPV. They found that low-level viremia occurred more commonly among those receiving every 2-month dosing of CAB/RPV than in those receiving monthly dosing, and that low-level viremia was related to lower CAB concentrations, suggesting that dose adjustment based on drug concentrations may be needed in a subset of individuals.

Resistance to InSTIs

A themed discussion focusing on noncanonical mutations leading to InSTI resistance highlighted Abstracts 550, 551, 553, and 585, which showed that envelope (*env*) mutations were associated with InSTI resistance. Kengni and colleagues (Abstract 550) examined mutations in PWH in Cameroon who had VF on DTG-based ART. They observed 17 new noncanonical mutations, the majority in *env* and a few in group-specific antigen (*gag*) that conferred InSTI

Noncanonical mutations outside integrase, particularly in env, can lead to InSTI resistance

resistance. They found mutations frequently occurring outside integrase, with 100% of these mutations occurring in *env*.

Hikichi and colleagues (Abstract 551) presented bench data on HIV-1 mutations acquired in the presence of raltegravir or DTG. HIV-1, in the presence of raltegravir, caused the emergence of mostly integrase resistance mutations known to confer resistance to InSTIs. By contrast, HIV-1 exposed to DTG first showed the emergence of *env* mutations that permitted ongoing viral replication in the presence of DTG. Subsequently, the virus acquired mutations in the nucleocapsid (NC) and integrase. These experiments demonstrated that HIV-1 can use noncanonical resistance pathways in *env* to continue replicating, which thereby allows it to acquire mutations in integrase and NC.

Coetzee and colleagues (Abstract 553) presented real-world data on these noncanonical mutations in PWH with VF on DTG in South Africa, where they observed mutations in *gag* and *env* leading to InSTI resistance. Charpentier presented data (Abstract 585) from a cohort of 145 PWH who had VF while taking an InSTI regimen. In the cohort for whom they had NC sequence data, 10.8% had mutations

in the NC that confer resistance to InSTIs. However, these individuals did not have mutations in integrase.

Swaine and colleagues (Abstract 566) presented data from the United Kingdom about the efficacy of BIC/FTC/TAF in a cohort of 238 individuals who had prior nucleoside reverse transcriptase inhibitor (nRTI) resistance-associated mutations (RAMs) but no InSTI RAMs. None of the individuals with K65R/N had VF on BIC/FTC/TAF. VF or low-level viremia was rare in their cohort, occurring in 3.4% of their participants, with nonadherence contributing to half of those cases. No major InSTI emergent resistance was observed in those with VF. These data are similar to previously reported results such as the NADIA (Nucleosides and Darunavir/Dolutegravir In Africa) trial, where the use of DTG paired with an nRTI backbone containing tenofovir was effective in achieving virologic suppression despite high background nRTI resistance.¹

Santoro and colleagues (Abstract 568) presented resistance data from an Italian cohort on LA CAB/RPV. They defined VF as 2 consecutive viral loads above 50 copies/mL or 1 viral load above 50 copies/mL with a change in ART. In

Lenacapavir can be added to achieve viral suppression even in individuals with background resistance and can be done in combination with a fully injectable regimen

all, 2.1% of participants on LA CAB/RPV met their endpoint of VF, with a median time of 6.6 months to VF. They found that 74.4% of those with VF had nonnucleoside reverse transcriptase inhibitor (NNRTI) or InSTI resistance, and 43.9% had substantial resistance to second-generation InSTIs. Reassuringly, 92.9% of their participants with VF were able to suppress on an alternative regimen.

Jeffrey presented data (Abstract 554) from experiments evaluating the resistance profile of VH-184 (previously mentioned above), a new third-generation InSTI that is being developed as an LA injectable. When testing the activity of VH-184 against pseudotyped viruses from participants who had VF in prior trials, they found that VH-184 was able to retain more potent activity in the presence of InSTI mutations than BIC. This holds promise for VH-184 as a treatment for individuals in whom second-generation InSTIs have failed.

Resistance to Lenacapavir

Bekerman and colleagues (Abstract 586) presented resistance data from a phase II, randomized, open-label trial examining the efficacy of once-weekly oral ISL and oral LEN (ISL/LEN) as switch therapy. From baseline genotyping, 5 participants who had reverse transcriptase (RT) RAMs (including M184V) maintained virologic suppression on ISL/LEN at week 96. In 2 participants who had viremia on ISL/LEN and had posttreatment genotyping performed, no treatment-emergent resistance was seen.

Gistand (Abstract 582) presented real-world data from a cohort of 50 PWH with baseline resistance in San Francisco, California, who started on LA LEN. A total of 92% of these individuals were on injectable therapy only, 70% of the individuals had baseline NNRTI resistance, and 10% had baseline InSTI resistance. A total of 44% of individuals were virally suppressed before starting LEN, but this increased to 100% by week 15 after LEN was added. At week 140, 95.7% of the cohort had sustained viral suppression. These data support using LEN to achieve viral suppression even in individuals with background resistance and demonstrate that it can be done in combination with a fully injectable regimen.

Two abstracts from Begovic and colleagues (Abstract 579) and Margot and colleagues (Abstract 581) showed that capsid polymorphisms at T107 do not confer resistance to LEN except for the T107N mutation.

VanderVeen and colleagues (Abstract 567) presented resistance data from a phase II, open-label study for a combination of 2 bNAbs, teropavimab and zinlirvimab, administered with LEN twice yearly for the treatment of HIV-1. Emergent resistance of LEN was rare, occurring in only 1 of 80 participants.

Empiric Treatment Strategies for Pneumonia in Infants With HIV

Globally, infants with HIV face a high mortality rate, with pneumonia as the leading cause of death.² In Abstract 151, the EMPIRICAL (Empirical Treatment Against Cytomegalovirus and Tuberculosis in HIV-infected Infants With Severe Pneumonia) trial evaluated whether empiric cytomegalovirus treatment with valganciclovir improved survival in 558 infants with HIV aged 28 to 365 days who were hospitalized for severe pneumonia. EMPIRICAL was a phase II-III, randomized, open-label, 2×2 factorial study conducted in 19 hospitals across 6 African countries.³ Participants were randomly assigned to receive standard of care alone (empiric antibiotics plus *Pneumocystis jirovecii* treatment), or in combination with valganciclovir,

tuberculosis treatment, or both,, with ART initiated on day 15 (± 7 days) if the child was not already taking prescribed ART. The groups were recategorized and analyzed according to the receipt of valganciclovir. The primary outcome was all-cause mortality at day 15 and through 1 year of follow up. The median age was 4.4 months, 49% were female, and 25% had severe malnutrition. A total of 71% of the children were newly diagnosed with HIV; median CD4+ cell percentage was 15.3% and median HIV-1 RNA level was $6.3 \log_{10}$ copies/mL. Analysis revealed that 51% of infants with available results had cytomegalovirus viremia attributable to pneumonia. All-cause mortality at day 15

Empiric valganciclovir improves early survival in infants with HIV with severe pneumonia

was significantly lower in the valganciclovir group than in the no-valganciclovir group (23.2% vs 27.0%, respectively; hazard ratio [HR], 0.60; 95% CI, 0.41–0.87). Although the survival benefit was most pronounced in the first month of follow up, the overall 1-year mortality rate was 43.1% with valganciclovir and 47.5% without (adjusted HR [aHR], 0.79; 95% CI, 0.62–1.02). No evidence of interaction between empiric valganciclovir and empiric tuberculosis treatment was noted. Valganciclovir was not associated with more adverse events, neutropenia, or anemia during the 1-year follow-up period. The authors concluded that empiric valganciclovir improves early survival in infants with HIV with severe pneumonia, suggesting that its inclusion in care guidelines may be warranted.

Advancing ART-Free Remission in Children

One strategy under investigation for advancing ART-free remission in children is the use of bNABs to limit the HIV reservoir size and sustain viral suppression, with the long-term goal of achieving ART-free remission. Earlier results from the Tatelo study suggested that this approach could potentially work in children.⁴ The IMPAACT (International Maternal Pediatric Adolescent AIDS Clinical Trials Network) 2042 Tatelo Plus study (Abstract 152) extends this work by testing 3 broader and more potent LA bNABs (VRC07-523LS, PGDM1400LS, and PGT121.414.LS) for treatment. Tatelo Plus is a single-arm, open-label, phase I/II trial in Botswana that enrolled children who started ART near birth. In step 1, the children received combination bNABs and ART for 32 weeks. In step 2, children who remained virally

suppressed and met prespecified eligibility criteria for ART interruption then stopped ART for a 24-week bNAB-only period. Study sizes were small: 12 children completed Step 1, and all maintained viral suppression (<40 HIV RNA copies/mL) during the 32-week period. Ten children entered step 2 to receive bNAB-only treatment. During the ART interruption phase of step 2, seven of the 10 children (70%) received all 3 bNABs, and 3 (30%) received 2 bNABs upon the detection of resistance to the third antibody. Among the 10 children who entered step 2, 80% were female, median age at ART initiation was 3 days, and median age at step 2 entry was 9 years. All 10 children had negative HIV DNA polymerase chain reaction testing, and 9 children (90%) had negative HIV enzyme immunoassay testing at step 2 entry. All 10 children maintained viral suppression, with HIV-1 RNA level below 40 copies/mL throughout the entire 24-week bNAB-only period. The bNAB regimen was well tolerated, with no grade 3 or 4 adverse events reported. The study findings support the use of combination bNABs, guided by phenotypic susceptibility testing and biomarker criteria, as a strategy for ART interruption. These results represent an initial step toward future bNAB trials aimed at achieving ART-free remission in children.

In the nonrandomized, open-label, IMPAACT P1115 trial, infants with in utero HIV-1 infection were initiated on ART (2 nRTIs + nevirapine + raltegravir) within 48 hours of birth. A subset of these children received the monoclonal antibody VRC01 within 72 hours. Abstract 839 reported on 22 infants with confirmed in utero HIV-1 infection: 11 received ART alone and 11 received a combination of ART and VRC01. By week 96, 81% of these infants achieved virologic control, with a cumulative incidence of first confirmed viral suppression increasing from 52% at week 24 to 81% at week 96. Furthermore, 27% of these infants had sustained virologic control through week 96. In addition to these findings, Abstract 840 demonstrated that VRC01 was safe and well tolerated among 222 neonates in the IMPAACT P1115 trial, with 98% of doses administered within 48 hours of birth. Local injection-site reactions were rare (1.1%) and mild, and no systemic injection reactions were reported. Median VRC01 levels at 1-week postbirth dose were similar for infants with HIV and without HIV. However, for repeated doses, VRC01 clearance was faster among infants with HIV than predicted from data for HIV-exposed but uninfected children, particularly among those with concurrent viremia after 10 weeks. These data highlight the importance of accounting for HIV status and viremia when determining the optimal dosing of bNABs for infants.

Very early initiation of ART in infants may limit the formation of the latent HIV reservoir and increase the

likelihood of ART-free remission. Cromhout and colleagues (Abstract 153) characterized the variation in time to viral rebound after stopping ART in children in a prospective analytic treatment interruption (ATI) study in KwaZulu-Natal, South Africa. Nineteen infants were enrolled in this study from an initial birth-treatment cohort of 330 mother-child pairs with HIV, where all infants were started on ART at birth and initiated on 3-drug ART within 21 days of birth. Children eligible to enroll were older than 36 months of age and virally suppressed (plasma viral load <30 copies/mL) for more than 24 months and met stringent immune and reservoir criteria for ATI. The children stopped ART and underwent close safety monitoring, and ART was restarted if

DTG/3TC was found to be an effective switch therapy for the maintenance of viral suppression in children based on data from the D3/Penta21 trial

plasma viral load increased to more than 30 copies/mL. A total of 42% of the study children were male and median age was 59 months. Thirteen of 19 children (68%) experienced viral rebound within 6 weeks and 6/19 (32%) remained virally suppressed beyond 12 weeks. Among these 6 children, 3 later had viral rebound at 4.8, 18, and 24 months, and 3 remained off ART with sustained viral suppression for 52, 30, and 10 months. The authors noted that males undergoing ATI were more likely to remain virally suppressed longer than females in the cohort, suggesting that innate immune sex differences may contribute to this disparity in ART-free remission dynamics. This was suggested by prior research from the investigators, who reported on 5 children, all male, who had maintained ART-free aviremia following unscheduled ATI.⁵ The authors noted that the proportion of very-early treated children (32%) who maintained viral suppression beyond 12 weeks post ATI in this study was higher than has been previously reported in adults. The findings suggest greater potential for ART-free remission in children who initiate ART early, underscoring the need for additional studies combining ATI with bNABs and other cure strategies.

Advances in Pediatric ART

Two-drug ART is increasingly under investigation as an alternative to 3-drug regimens for HIV treatment,

but evidence in children remains limited. D3/Penta 21 (DTG/3TC Fixed-Dose Formulations For the Maintenance of Virological Suppression in Children With HIV Infection Aged 2 to <15 Years Old) (Abstract 154) was a 96-week, open-label, non-inferiority trial that evaluated the efficacy and safety of a 2-drug regimen (DTG/3TC) compared with a 3-drug control regimen (DTG-based + 2 nRTIs) in children. The study enrolled children with HIV who were virally suppressed for at least 6 months, had no prior treatment failure, were aged 2 years to less than 15 years, and weighed at least 10 kg. A total of 386 children were enrolled globally and randomly assigned to DTG/3TC or DTG-based 3-drug ART. The median age was 8.3 years and 54% were female. The median CD4+ cell percentage was 38%. In the intention-to-treat analysis, confirmed viral rebound (viral load, ≥ 50 copies/mL) by week 96 occurred in 11 of 193 (5.9%) in the DTG/3TC arm and 13 of 193 (6.6%) in the 3-drug ART arm, meeting criteria for noninferiority. Most children with confirmed viral rebound of 50 copies/mL or higher were resuppressed by week 96. Safety was similar between groups, with similar serious adverse events and grade 3 or higher events; there were no ART-modifying adverse events. The proportion of children with emergent InSTI (DTG) or nRTI DRMs at confirmed viral load of 50 copies/mL or higher was similar between the 2 groups. Across 96 weeks, health care resource utilization was comparable between the 2 arms; however, drug costs were \$145 less per child per year in the DTG/3TC arm than in the DTG-based 3-drug ART arm. These findings support DTG/3TC as a simpler maintenance option for children, with efficacy and safety comparable to DTG-based 3-drug ART.

IMPAACT 2017 (MOCHA; More Options for Children and Adolescents) was a phase I/II, noncomparative study that evaluated the safety, tolerability, and PKs of LA CAB/RPV

LA CAB/RPV appeared to achieve therapeutic drug concentrations in children with no concerning safety signals

among adolescents. Results through week 96 (and end-of-study follow up) were reported in Abstract 155. The study enrolled 144 virally suppressed adolescents with HIV who were aged 12 years to younger than 18 years and weighed 35 kg or more, across 18 sites in 5 countries. The median age was 15 years; 51% were female, and 92% had perinatally acquired HIV. Participants switched from oral ART

and received a 4-week oral CAB/RPV lead in, followed by injectable CAB/RPV. A total of 95% of participants completed follow up through week 96, and 137 of 144 (95%) received at least 13 injections. Drug-related adverse events through week 96 occurred in 60 of 144 (42%) of participants. Injection-site reactions were the most common (37%) and were typically mild and short in duration (≤ 7 days), with pain reported more often after LA RPV than after LA CAB injections (31% vs 16%, respectively). There were 2 grade 3 drug-related adverse events (abscess and pain/abscess) and 1 grade 4 anaphylaxis-like postinjection reaction that resolved but led to discontinuation of the study drug. At week 96, a total of 94.4% of participants maintained viral suppression (HIV-1 RNA level, < 50 copies/mL). No confirmed VF events occurred. At week 96, RPV and CAB trough concentrations were similar to those observed in adults and remained above efficacy targets, supporting an acceptable PK profile. Among those assessed at week 96, all participants preferred injections over daily pills.

Abstract 854 presented safety and PK data on CAB/RPV from the IMPAACT 2036 CRAYON (Cabotegravir and Rilpivirine Long-Acting Injections in Young Children) study. The trial evaluated 61 children with HIV aged 2 years to 12 years and weighing between 10 and below 40 kg. Following a 4-week oral lead-in period, participants transitioned to monthly intramuscular injections of LA CAB/RPV using weight-band dosing. Children achieved plasma concentrations and drug exposure levels comparable to those observed in adults and adolescents. The most common adverse event was grade 1 or 2 injection-site pain. No children discontinued treatment due to safety concerns.

Children who are on DTG-containing ART regimens and tuberculosis prophylaxis with 12 weeks of once-weekly rifapentine and isoniazid (3HP) present a unique challenge, as children clear DTG more rapidly and rifapentine may further decrease drug exposure. Salazar-Austin and colleagues (Abstract 150) presented results from the DOLPHIN-KIDS (Rifapentine and Isoniazid TB Preventive Therapy [3HP] for Children Taking Dolutegravir-Based Antiretroviral Treatment) trial, a 2-stage, phase I/II study evaluating DTG PK, safety, and virologic suppression in children with HIV receiving DTG with 3HP. In stage 1, the children received twice-daily DTG with 3HP for 12 weeks. Subsequent PK modeling predicted that once-daily DTG would produce therapeutic concentrations in children weighing at least 10 kg, which was tested in stage 2. In this second stage, children with HIV weighing at least 10 kg with established viral suppression (< 50 copies/mL) received ART consisting of once-daily DTG plus 2 nRTIs, which was initiated at least 4 weeks before starting 3HP.

The participants completed 3HP for 12 weeks concurrent with their ART, followed by an 8-week follow-up period. The children underwent semi-intensive and sparse DTG PK sampling in addition to HIV-1 RNA viral load monitoring. DTG PK sampling results were considered acceptable if the lower 95% CI of the observed trough concentration was more than 158 ng/mL and all trough values remained

Once-daily DTG and 2 nRTIs are effective in achieving virologic suppression in children with HIV when coadministered with 3HP for tuberculosis prophylaxis, paired with adherence counseling

above the protein-adjusted (PA) IC_{90} (64 ng/mL). Of the 41 enrolled children (median age, 5.5 years; range, 1.5–16.9 years; 46% female, all Black African), 22% had less than 90% adherence by pill count during 3HP treatment. The lower 95% CI for DTG trough concentrations with once-daily DTG was 200 ng/mL overall and 75 ng/mL at 3 days post dose. However, 2 participants did not meet the PK criteria and had predose trough levels below 64 ng/mL at the 3-day postdose timepoint, although none fell below the limit of quantification. No treatment-related grade 3 or higher adverse events occurred. The regimen was well tolerated, with no participants discontinuing once-daily DTG-based ART while on 3HP. Most participants (95%) remained virally suppressed at study completion and 2 participants developed transient HIV-1 RNA blips that later became undetectable following adherence counseling. The authors noted that although the minimum effective DTG trough concentration is not yet firmly established, the PA IC_{90} of 64 ng/mL serves as the current target. The authors raised the question of whether infrequent, time-limited decreases in DTG concentration are clinically relevant, given that all children on daily DTG-based ART achieved viral suppression at study completion. They concluded that 3HP as tuberculosis prophylaxis may be coadministered with once-daily DTG and 2 nRTIs in children with HIV who weigh at least 10 kg without the need for DTG dose adjustment, provided it is combined with effective adherence counseling.

In Abstract 850, the authors showed that children weighing 3 to 20 kg with HIV and tuberculosis coinfection and being treated with ART and rifampicin-based TB treatment achieved effective drug levels with twice-daily DTG

that were comparable to standard once-daily DTG without rifampicin, with the dosing strategy considered safe.

Abstract 851 presented findings from the UNIVERSAL1 (Pharmacokinetic Study of a Novel DTG/FTC/TAF Dose Ratio for Children) study, which evaluated a new, simplified DTG/FTC/TAF dose ratio designed to improve ease of use and treatment adherence for children in African settings. The study showed that once-daily administration of

An ongoing randomized, open-label trial suggests that DOR may be safe and effective for use during pregnancy, although further studies are needed

5 mg/15 mg/1.88 mg dispersible tablets (for children weighing 3 kg to <20 kg) and 50 mg/200 mg/25 mg film-coated tablets (for children weighing 20 to <25 kg) achieved DTG and FTC exposure levels similar to those observed in adults. Although TAF and tenofovir disoproxil fumarate (TDF) exposures varied across weight bands, the levels remained within established ranges that were considered safe and effective.

Pregnancy, Maternal Health, and Infant Exposure


The DoraDO (Doravirine Dose Optimization in Pregnancy) study (Abstract 797) is an ongoing, randomized, open-label trial investigating the safety and PKs of DOR, a second-generation NNRTI, among 76 pregnant South African women initiating ART between 8 and 26 weeks of gestation. Participants were randomly assigned to receive DOR (100 mg once daily) in combination with TDF/3TC or the standard of care ART (TDF/3TC/DTG). The study found that although maternal DOR exposure was reduced during the second and third trimesters, trough concentrations remained consistently above the therapeutic target (>3 ng/mL). Safety data from 46 women showed no significant differences in serious adverse events between the DOR and standard-of-care arms, with no HIV transmissions or birth defects reported. Furthermore, despite a moderate transfer of DOR into breast milk (~30%), infant drug levels remained low postpartum. These results suggest that DOR is a promising option for use during pregnancy; however, follow-up studies are needed to inform clinical guidelines for DOR use during pregnancy and breastfeeding.

In an ongoing observational cohort of 261 pregnant women with HIV in Kenya receiving DTG-based ART (Abstract 787), Marwa and colleagues evaluated the association between timing of isoniazid initiation by trimester for tuberculosis prevention and adverse pregnancy outcomes. The study found that those who initiated isoniazid in the first trimester experienced a significantly higher frequency of any adverse outcome than those starting in the second trimester (43.2% vs 27.6%, respectively; risk ratio, 1.56; 95% CI, 1.06–2.31; $P=.024$). Specifically, first-trimester initiation was associated with a higher incidence of stillbirth (7.7% vs 4.0%; RR, 2.50; 95% CI, 1.02–6.08; $P=.043$) and preterm birth (21.2% vs 7.7%; RR, 2.73; 95% CI, 1.36–5.00; $P=.005$). Although these results suggest that the timing of isoniazid initiation is an important safety consideration, the authors noted that larger studies are needed to confirm these findings.

Findings from the Pediatric HIV/AIDS Cohort Study (Abstract 830), which enrolled children in the US and Puerto Rico, showed that children who are HIV exposed but uninfected have a substantial risk of developing cardiometabolic complications. In an analysis of 1669 participants, the incidence of meeting a metabolic trigger (defined as BMI >95th percentile) was 98.5 cases per 1000 person-years (421 participants over 4273 person-years of follow up). Among the subset of children undergoing fasting metabolic testing, the weighted prevalence was 18.6% for dyslipidemia and 16.8% for insulin resistance. These data suggest that HIV-exposed but uninfected children who exhibit a high BMI have substantial cardiometabolic risk factors. In addition, the findings underscore the need for further investigation into how in utero HIV and ART exposure and early life factors influence cardiometabolic health in the long term.

Supporting Adolescent Transitions in HIV Care

Adolescents with perinatally acquired HIV transitioning to adult services are a vulnerable group, with loss of viral suppression and decreases in retention in care frequently observed during this transition period. InT-SHA-VIP (Interactive Transition Support for Adolescents With HIV Comparing Virtual and In-Person Delivery) (Abstract 156) was a hybrid implementation-effectiveness, stepped-wedge, cluster-randomized trial evaluating an adolescent-friendly transition support intervention conducted at 16 clinics in KwaZulu-Natal, South Africa. Eligibility criteria included adolescents aged 15 to 19 years with perinatally acquired HIV who had been receiving ART for at least 6 months, who were aware of their HIV status,

and had scored low to intermediate on a transition readiness assessment. The intervention consisted of facilitated peer discussion groups, delivered virtually or via monthly in-person sessions. Of the 372 adolescents enrolled, 178 were assigned to the immediate-intervention arm and 146 to delayed standard of care. Within the immediate-intervention arm, 53% attended in-person sessions and 47% attended virtual sessions. At 9 months, the in-person delivery significantly increased viral suppression (HIV-1 RNA <200 copies/mL) compared with delayed standard of care (93% vs 84%, respectively; adjusted odds ratio [aOR], 2.9; $P = .035$). In contrast, virtual delivery did not significantly impact viral suppression (87% vs 84%, respectively; aOR, 0.9; $P = .9$). Retention in care (a composite outcome based on pharmacy refills and clinic attendance) improved relative to delayed care for in-person delivery (27% vs 13%; aOR, 2.7; $P = .004$) and virtual delivery (57% vs 13%; aOR, 7.7; $P < .001$). Overall, the InTSHA-VIP model improved transition outcomes by boosting viral suppression through in-person delivery and enhancing retention with in-person and virtual delivery modes, showing that structured, adolescent-centered support can improve transition to adult HIV care. 

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*Invited Review***CROI 2026: Innovations in HIV Care and Service Delivery to Improve Treatment Outcomes****Barbara S. Taylor, MD, MS**

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Abstract: *At the 2026 Conference on Retroviruses and Opportunistic Infections (CROI), investigators presented new findings and innovative interventions that may impact HIV service delivery and care cascade metrics. CROI 2026 focused on challenges faced by specific populations and novel interventions that address those challenges. These include the use of machine learning to predict virologic failure or missed clinic visits; individual-level interventions, such as in-person or virtual training and adherence support; clinic-based person-centered care and optimized clinic practices interventions; and a system-wide opt-out HIV screening and linkage program across federally qualified health centers that led to 100% linkage to care for those newly diagnosed with HIV. Point-of-care testing for HIV-1 RNA viral load and tenofovir adherence were well received by participants but not associated with improved outcomes. Researchers discussed the impact of disruptions in funding for HIV care and research, particularly among countries receiving support from the US Agency for International Development and the President's Emergency Plan for AIDS Relief. Although data continue to emerge on the profound impact of funding cuts, the collaboration of researchers, care delivery experts, and community members led to the restoration of some programs and continued support for National Institutes of Health-funded research.*

Keywords: care cascade, CROI 2026, funding, HIV, PEPFAR, USAID

The HIV Care Cascade and the Use of Machine Learning to Predict Cascade Elements

At the 2026 Conference on Retroviruses and Opportunistic Infections (CROI), investigators offered novel data on HIV

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care cascade metrics, with 2 presentations demonstrating challenges faced by younger people with HIV (PWH). Heck and colleagues (Abstract 182) used population-based HIV impact assessment (PHIA) surveys conducted after 2019 in Eswatini, Lesotho, Malawi, Mozambique, Tanzania, Uganda, and Zimbabwe, to explore subgroups of men with HIV facing challenges in diagnosis, treatment, and viral suppression. They concluded that most men who were unaware of their HIV status or who were virally unsuppressed belonged to 1 or more of the following subgroups: sero-different couples, those with recent mobility, adolescent boys and young men, older adults, sex workers, and gay or bisexual men. The overall care cascade for men with HIV was 85% status aware, 82% on treatment, and 76% virally suppressed, but those with recent mobility, those aged 18 to 29 years, and those in serodifferent couples faced the most challenges in care cascade metric attainment. Adolescent boys and young men who had recent mobility experienced higher rates of all 3 suboptimal cascade outcomes: 31% were undiagnosed, 4.8% were untreated, and 11.9% were unsuppressed.

A longitudinal study of men who have sex with men (MSM) and people who inject drugs (PWID) in India (Abstract 922) found disparities in outcomes for men aged 18 to 29 years between surveys conducted in 2012 to 2013 and 2022 to 2024. Prevalence increased from 6% to 16% (MSM aged 18-29 years) and 15% to 27% (PWID aged 18-29 years). Viral suppression was lowest for those aged 18 to 29 years (21% of PWID aged 18-29 years vs 68% of PWID aged >40 years; 65% of MSM aged 18-29 years vs 85% of MSM aged >40 years) from 2023 to 2024. These presentations underscore the need for support for young adults, particularly men, in achieving viral suppression.

Many investigators at CROI used machine learning and artificial intelligence-driven models to support HIV prevention and treatment. Christian and colleagues (Abstract 1077) used data from 158,134 PWH with longitudinal viral load records in Rwanda to develop a machine learning model to predict unsuppressed viral load. Virologic failure often followed signals of instability, including frequent clinic visits and referrals to enhanced counseling. They tested 4 learning models, and the best performing model, LightGBM, predicted unsuppressed viral load with

an accuracy of 81.2%, a specificity of 91.4%, and a recall of 75.3%. Similarly, investigators used data from 8 clinical sites in Kenya to build a machine learning-based model to predict the probability of a patient missing their next scheduled clinic visit (Abstract 1076). They conducted a pilot study that included previsit outreach to those patients identified to be at risk for missing their next visit

Individual counseling and training interventions led to improved virologic suppression for adolescents transitioning to adult HIV care clinics, men with HIV and stimulant use disorders, and women with HIV and prior sexual trauma

and found that men and older patients were more likely to be flagged as at risk. Outreach led to higher odds of returning to the clinic.

Innovative HIV Care Delivery Interventions

CROI 2026 featured numerous successful, innovative HIV care delivery interventions targeting HIV care cascade metrics. Three notable examples described individual-level training or counseling programs that improved virologic suppression. The first, a training program for adolescents transitioning to adult HIV care environments from Zanoni and colleagues (Abstract 156), compared an existing, in-person training intervention for adolescents with HIV with a modified version that offers virtual training via WhatsApp, with a control group receiving standard care. Unfortunately, the cluster randomized trial was halted after 9 months because of funding cessation. At that time, the in-person intervention was associated with a significant increase in virologic suppression (93%; $P = .035$) compared with the standard of care group (87%), but virologic suppression did not differ between the virtual intervention (84%) and standard care ($P = .9$). Retention in care was higher in the in-person and virtual intervention groups than in the standard of care group. Funding has now been restored for this project and investigators will continue with the second phase, expanding the 2 interventions to 8 additional clinics.

A second study of an individual-level virtual intervention tested the efficacy of the Supporting Treatment

Adherence for Resilience and Thriving (START) mHealth App in 286 sexual minority men with HIV and stimulant use disorder in the US (Abstract 184). All participants had a recent history of nonadherence to antiretroviral therapy (ART) and 46% had a detectable viral load at baseline. They were randomly assigned to the START intervention, which integrates positive affect skills with self-monitoring of mood and ART adherence, or a website-based control condition with referrals to additional practitioners. At 6 months, the adjusted odds ratio (aOR) for virologic suppression, defined as below 300 copies/mL based on the cutoff threshold for the mail-in dried blood spot test used in the study, was 0.42 in the START intervention arm (95% CI, 0.19-0.93) compared with the website-based controls. The difference was driven by a 2-fold greater incidence of virologic rebound in the control group, and the number needed to treat was 5. There was no effect on the reported severity of the individual's stimulant use disorder. Investigators noted that recruitment was very challenging; only 1 in 5 individuals screened for the study enrolled. Despite this, cost for this mHealth intervention was feasible and the potential impact for the growing population of men with HIV using stimulants is encouraging.

Finally, Sikkema and colleagues (Abstract 185) designed a task-shared trauma-focused coping intervention, Improving AIDS Care after Trauma (ImpACT), for women with HIV and sexual trauma in South Africa. In a hybrid type I effectiveness trial, they compared 4 or more sessions of the ImpACT intervention to problem-solving therapy (PST) in 349 women with HIV. Retention was low (70%) over 12 months in each study arm, but 94% of participants in the ImpACT intervention arm achieved viral suppression to below 50 copies/mL compared with 84% in the PST arm ($P = .049$). Investigators measured psychologic metrics and determined that the interventions led to improvement in coping skills; however, social/spiritual coping was significantly higher in the ImpACT group than in the PST group. These 3 investigations shed light on how subgroups impacted by HIV can benefit from individual-level training or counseling interventions tailored to their specific circumstances.

CROI 2026 also included innovative interventions occurring at the clinic or health system level. A cluster randomized trial in Zambia investigated a person-centered care (PCC) intervention that included training and coaching of health care workers, evaluation of client experience with feedback to clinic staff, and performance-based facility incentives (Abstract 183). Overall, virologic suppression was more common during the intervention condition than during the control condition (61% vs 53%, respectively; adjusted hazard ratio, 1.18; 95% CI, 1.05-1.33).

The PCC intervention was associated with reduced treatment interruptions, shorter time to documented virologic resuppression, and improved patient-clinician communication.

A sequential multiple-assignment randomized clinical trial in South Africa tested the impact of optimized clinical practices, which included welcome back services, 6-month refills, outreach to long-term follow-up care, chronic medicine dispensing, and smart locker pickup at the clinic, on viral suppression (Abstract 186). The first phase of the study comparing optimized clinic practices with and without a conditional lottery incentive found no differences between the 2 groups. In the second phase, those with a detectable viral load, not engaged in care, or with more than 2 barriers to care were randomly assigned 2:1:1 to continue in their original assignment group, to smart locker ART pickup and monitoring, or to home ART delivery and monitoring. There was no significant difference between these groups, with high levels of viral suppression (88%) across all 3 arms. However, there was a difference for those aged younger than 30 years. The adjusted relative risk for virologic suppression for those younger than 30 years of age in the smart locker compared with the optimized clinic practices group was 1.24 (95% CI, 1.01-1.52; $P = .04$) and home delivery was noninferior to the optimized clinic practices group. These data suggest that optimized clinic practices are associated with high levels of viral suppression across all age groups, and that younger PWH may benefit from alternative strategies for ART delivery.

A study of more than 216,000 patients receiving care at 13 clinics from a network of federally qualified health centers (FQHCs) provided a powerful proof of concept for enhanced opt-out HIV screening and linkage to care in a primary care setting (Abstract 159). The program identified 218 newly diagnosed people with HIV and 1667 who were out of care. They successfully linked 100% of these clients to care, with 90% of linkage to care events occurring within 30 days of testing. Overall, the network of FQHCs supports more than 30 clinics and nearly 5 million patients in the US, making them well positioned to scale up the program across their network. In summary, CROI 2026 highlighted numerous novel individual- and system-level interventions that support virologic suppression, often tailored to specific communities or contexts.

Point-of-Care and Virtual Laboratory Testing to Improve HIV Care

Several CROI 2026 presentations focused on new uses of point-of-care (POC) testing to improve HIV care outcomes.

Gorbach and colleagues (Abstract 977) described supporting the virtual submission of HIV viral load results to an app-based digital cohort, EPI-LoVE (Exploring, Predicting, and Intervening on Long-term Viral Suppression Electronically). Participants chose 1 of 4 modalities to send their data to the platform, including uploading a personal copy

People with HIV welcomed point-of-care and remote monitoring for virologic suppression and adherence

of their test (41%), using a self-collection blood kit (24%), testing at an external laboratory site (12%), or testing at an affiliated clinic (22%). Of those who submitted viral load data, 37% were not virologically suppressed and 56% were suboptimally engaged in HIV care, demonstrating high uptake even for those with challenges for virologic suppression.

Project Bright, a study of virologic suppression among gay men with HIV experiencing intimate partner violence, piloted a strategy of using self-collected blood in micro-container tubes (Abstract 165). Specimen return rates were 75.4% to 76.9% over 12 months and sample viability was more than 91%. Investigators concluded that participants were willing to participate in this type of remote monitoring and achieved high levels of virologic suppression, with only 7% having quantifiable virus at any time. Finally, Drain and colleagues used monthly urine tenofovir testing and every-6-month POC viral load testing to support adherence among South Africans initiating first-line ART. Among the 72% of participants retained in care at 72 weeks, there was no significant difference in viral suppression rates between those assigned to POC testing (93%) and controls (90.3%). These 3 presentations demonstrate that POC testing is feasible and sometimes the preferred modality for testing, even if not associated with improved viral suppression.

International Impact of Disruptions to Funding for HIV Service Delivery and Care

The impact of federal funding disruptions on HIV service delivery and research was a theme running throughout CROI this year. The cluster randomized trial by Zanoni and colleagues (Abstract 156) mentioned above was just one of many projects placed on hold or discontinued because

of changes in the President's Emergency Plan for AIDS Relief (PEPFAR), US Agency for International Development (USAID), or other funding structures. In an interactive symposium, Garnett (Abstract 21) explained that substantial reductions in funding for PEPFAR were predicted, but the abrupt nature of the change was not. Current projections show PEPFAR funding will decrease by 40%, from \$4.85 billion in fiscal year 2025 to \$2.9 billion in 2026. The programmatic goal is to continue service delivery but


Funding changes often led to interruptions in services aside from direct care that remain integral to successfully functioning clinics

reduce expenditures on technical assistance, prevention, and health systems. Garnett emphasized the extreme challenge of maintaining HIV prevention programs and support structures for HIV care in most countries receiving support from PEPFAR.

These assertions were underscored by a rapid cross-sectional survey of a global cohort of HIV clinics by Brazier and colleagues (Abstract 1051) in June and July of 2025, shortly after the changes in funding. Of 76 clinics responding, 47% reported disruptions in services, particularly for HIV counseling and testing and for preexposure prophylaxis (PrEP). Care services were impacted, with 22% reporting disruptions of ART availability, 24% reporting absence of viral load testing, and 24% noting inability to conduct early infant diagnostic testing. There were stark geographic variations, with no Latin America-based clinics reporting disruptions in care and widespread disruptions in Eastern and Southern Africa.

Similarly, a facility audit across a population-based sample of clinics in KwaZulu-Natal, South Africa (Abstract 1054) determined that 42% of clinics reported disruptions in services. Although these were more common in PEPFAR-supported clinics, disruptions were seen in some nonsupported clinics. Layoffs of nonclinical staff were common, particularly lay health workers, file clerks, and data entry technicians. The authors noted that many interruptions were in what they call "silent" services, ie, those not in direct patient care but integral to a successfully functioning clinic, such as clinical mentoring, technical support, and patient tracing.

Batiste emphasized the community impact of these service disruptions in her talk (Abstract 22) using qualitative data from community members to underscore the erosion of trust and confusion that followed the funding cuts. She proposed the use of community-led monitoring, now a part of the Joint United Nations Program on HIV/AIDS standards,¹ to support community resilience and local control of HIV prevention and treatment programs.

Kambugu described the numerous changes in National Institutes of Health (NIH) policy over the past year and their impact on HIV research in Africa (Abstract 23). He noted that most NIH awards in Africa are held by the US-based institutions, and funds flow to African institutions through subawards. The indirect cost cap of 15% in February 2025 led to hiring slowdowns or freezes, reversals of program expansion plans, and reductions in funds available for compliance, monitoring, and data systems. When foreign subawards were prohibited in May 2025, clinical trials were curtailed, enrollment was paused across numerous research studies, and the administrative burden of contracts, subaward renewals, and reporting increased. Although the NIH enacted a replacement structure for international collaboration in May 2025, the complex award architecture and increased reporting and compliance burden continue to impact collaborative research between the US and African countries. As Staley reminded us in his plenary (Abstract 11), there is reason to hope, as bipartisan support for continued NIH funding grows and many funding streams have been restored. Staley called for continued collaboration between clinicians, researchers, and advocates to call out the importance of HIV care delivery and research, and the human impact of current funding trajectories. 

All abstracts cited in the text appear in the CROI 2026 Abstract eBook, available online at www.CROIconference.org

The IAS–USA has identified and resolved ahead of time any possible conflicts of interest that may influence CME activities with regard to exposition or conclusion. All financial relationships with ineligible companies for the author and planners/reviewers are below.

Financial affiliations in the past 24 months: Dr Taylor reported serving as an advisor or consultant to Gilead Sciences, Inc. (Updated April 15, 2026)

Reviewer/Planner 1 reported consulting or advisor fees from Generate Biomedicines and Gilead Sciences, Inc.

(Updated April 10, 2026) *Reviewers/Planners 2 and 3 reported no relevant financial relationships with ineligible companies.* (Updated April 29, 2026)

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*Invited Review***CROI 2026: Tuberculosis and Other Infectious Complications in People With HIV****Andrew D. Kerkhoff, MD, PhD¹; Jason Zucker, MD²; Diane V. Havlir, MD¹**¹University of California San Francisco; ²Columbia University, New York, New York

Abstract: *The 2026 Conference on Retroviruses and Opportunistic Infections (CROI) featured numerous studies on tuberculosis and other opportunistic infections in people with HIV. High mortality rate among people with HIV hospitalized with disseminated tuberculosis (TB) and among those treated for drug-resistant TB represents a major clinical challenge. Intensified TB treatment in one trial and adjunctive prednisone in another failed to reduce mortality in hospitalized people with HIV with disseminated TB. In addition, a novel higher-dose linezolid dosing strategy did not improve culture conversion in drug-resistant TB. Recommended options for TB prevention are increasing, and include 1-month daily (1HP) and 3-month weekly (3HP) isoniazid-rifampentine regimens. Two head-to-head trials comparing 1HP and 3HP found comparable efficacy, although 1HP was associated with lower treatment completion rate and greater treatment intolerance. These and other key findings from TB, mpox, and other opportunistic infection-related studies are summarized herein.*

Keywords: coinfection, CROI, cryptococcal meningitis, cytomegalovirus, HIV, Kaposi sarcoma, opportunistic infection, TB, tuberculosis

Tuberculosis**Treatment**

There is an urgent need to reduce the unacceptably high mortality rate among people with HIV (PWH) hospitalized with tuberculosis (TB), particularly those with advanced HIV disease and disseminated TB. Two large, randomized clinical trials presented at *the 2026 Conference*

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on *Retroviruses and Opportunistic Infections (CROI)* addressed this crucial gap.

Blanc and colleagues (Abstract 123) presented results from the DATURA ANRS 12424 (Determination of Adequate Tuberculosis Regimen in Patients Hospitalized With HIV-Associated Severe Immune Suppression) trial, a phase III, randomized, open-label superiority trial conducted in Cambodia, Cameroon, Guinea, Mozambique, Uganda, and

Intensification of TB treatment with high-dose rifampicin and isoniazid did not improve outcomes in hospitalized people with HIV with disseminated TB

Zambia. PWH aged 15 years and older who were hospitalized for TB with a CD4+ count of 100 cells/ μ L or less were randomly assigned to receive intensified TB treatment of high-dose rifampicin (RIF; 35 mg/kg/d) and isoniazid (INH; 10 mg/kg/d) with standard-dose ethambutol and pyrazinamide (PZA) for the first 8 weeks, along with oral corticosteroids for 6 weeks and albendazole 400 mg daily for 3 days, or standard TB treatment. Antiretroviral therapy (ART) with tenofovir/lamivudine plus twice-daily dolutegravir (DTG) was initiated at week 2 in both arms. Among 908 participants in the modified intention-to-treat (mITT) group (44% women; median age, 37 years; median CD4+ count, 44 cells/ μ L; 88% with disseminated TB; 70% ART naive), the cumulative mortality rate at 48 weeks was 29.4% in the intensified arm and 26.8% in the standard arm (adjusted hazard ratio [aHR], 1.13; 95% CI, 0.88-1.45; $P=0.4$), with a similar trend among those with a CD4+ count of 50 cells/ μ L or less (aHR, 1.28; 95% CI, 0.94-1.75). Overall, grade 3 or 4 adverse event (AE) rates were similar between arms (adjusted relative risk [aRR], 0.98; 95% CI, 0.90-1.06), although drug-induced liver injury was significantly more common in the intensified arm (13.4% vs 5.3%; aRR, 2.7; 95% CI, 1.8-4.2), and paradoxical

TB-associated immune reconstitution inflammatory syndrome (IRIS) was lower (2.8% vs 6.4%; aRR, 0.5; 95% CI, 0.3-0.8). Intensification of TB treatment did not improve survival among hospitalized people with advanced HIV.

Namale and colleagues (Abstract 124) reported results from the prednisone vs placebo comparison of the NEW-STRAT TB (Testing New Strategies for Patients Hospitalised With HIV-associated Disseminated Tuberculosis) trial, a 2x2 factorial randomized clinical trial at 3 hospitals in Cape

Adjunctive prednisone did not reduce mortality in hospitalized people with HIV with disseminated TB

Town, South Africa. This trial also evaluated intensified TB treatment (high-dose RIF + levofloxacin). The intensified arm was stopped early after the 14-day mortality rate was significantly higher (10.9% vs 5.0%; $P=.008$), as previously reported at CROI 2025.¹ In the prednisone comparison, eligible adults had HIV-associated disseminated TB (positive blood Xpert Ultra, urine Xpert Ultra, or urine lipoarabomannan [LAM] testing) and were randomly assigned to prednisone 1.5 mg/kg/d or placebo for 14 days. Among 712 participants in the mITT population (55% female; median age, 36 years; median CD4+ count, 43 cells/ μ L; median HIV viral load, log 5.4 copies/mL), 12-week mortality rate was 17.6% (95% CI, 14.0-22.0) in the prednisone arm and 19.2% (95% CI, 15.5-23.7) in the placebo arm (difference, -1.6%; 95% CI, -7.5 to 4.2; $P=.6$). At 14 days, the mortality rate was 6.8% vs 9.5% (difference, -2.8%; 95% CI, -6.9 to 1.3; $P=.2$). Grade 3 and grade 4 AEs and nonfatal serious AEs occurred at similar frequencies in the study arms. Subgroup analyses suggested possible heterogeneity by hemoglobin level (≤ 7 g/dL vs >7 g/dL; interaction $P=.01$) and creatinine clearance rate (≤ 50 mL/min vs >50 mL/min; interaction $P=.045$), with a trend toward harm among those with lower hemoglobin level and renal impairment. There was no statistically significant interaction between the prednisone and intensified TB treatment factorial randomizations. Although well tolerated, a 14-day course of adjunctive prednisone did not reduce the mortality rate in patients hospitalized with disseminated HIV-associated TB. Together with the DATURA trial findings, these results underscore that TB treatment intensification and adjunctive corticosteroids fail to improve outcomes in this severely ill population, reinforcing the need for novel

approaches to address the persistently high mortality rate among hospitalized people with advanced HIV and TB.

Four-month rifapentine (RPT)-based TB regimens are now a US Food and Drug Administration (FDA)-approved shortened treatment option, but their pharmacokinetic (PK) interactions with DTG-based ART are not well characterized. Wasserman and colleagues (Abstract 146) presented results from A5406 (Pharmacokinetics and Safety of Double-Dose Dolutegravir When Used With Rifapentine for HIV-Associated Tuberculosis), a phase II, open-label, single-arm PK study conducted at 4 sites in South Africa and Thailand that evaluated the safety and adequacy of DTG exposure during coadministration with RPT. Adults with HIV not currently on ART with drug-susceptible TB received twice-daily DTG 50 mg plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) with a 4-month RPT-based TB treatment regimen (2 months of daily RPT 1200 mg, INH, PZA, and moxifloxacin [MFX] followed by 2 months of daily RPT, INH, and MFX), switching to once-daily DTG 2 weeks after RPT discontinuation. Among 30 participants enrolled (43% female; median age, 35 years; median CD4+ count, 185 cells/ μ L), DTG area under the curve from 0 to 24 hours (AUC_{0-24}) was 34.2 μ g·h/mL with twice-daily dosing during RPT coadministration and 48.8 μ g·h/mL with once-daily dosing after RPT discontinuation (geometric mean ratio, 0.70; 90% CI, 0.61-0.80), with DTG clearance increasing 2.2-fold (95% CI, 1.9-2.5). In simulations, 98.8% of individuals were predicted to remain above the efficacy threshold of 0.158 μ g/mL with twice-daily DTG during RPT compared with only 29.8% with once-daily dosing. All participants on treatment achieved virologic suppression by week 21, with no hepatotoxicity attributed to the study regimen. These findings provide reassurance that twice-daily DTG achieves adequate drug exposures during RPT coadministration and support the use of DTG-based ART during shorter RPT-based TB regimens.

Diabetes is an important TB risk factor, but the PK impact of metformin, a commonly used diabetes treatment, on first-line TB drugs has not been well characterized. Rossouw and colleagues (Abstract 785) conducted a PK substudy nested within the METHOD (Safety and Tolerability of Metformin in People With Tuberculosis [TB] and Human Immunodeficiency Virus [HIV]) trial, a phase IIa randomized clinical trial of adjunctive metformin (500 mg once daily for 1 week, then 500 mg twice daily through week 12) in 78 adults with HIV-associated pulmonary TB, performing population PK modeling from samples collected at week 5. Metformin coadministration reduced modeled INH bioavailability by 15.6% (95% CI, 4.45-26.4%; $P=.009$) and RIF bioavailability by 24.1% (95% CI, 7.83-36.3%; $P<.001$); PZA exposure was unaffected. It is unclear

whether these represent clinically significant reductions, but given the crucial role of RIF and INH in TB treatment and existing concerns about subtherapeutic drug concentrations, these findings may warrant further investigation.

Drug-Resistant Tuberculosis

Optimizing linezolid (LZD) dosing in drug-resistant TB regimens remains a high priority, as LZD toxicity — particularly myelosuppression and peripheral neuropathy — substantially limits tolerability and treatment completion. Benson and colleagues (Abstract 149) presented results from ACTG (AIDS Clinical Trials Group) A5356 (A Phase II, Prospective, Randomized, Multicenter Trial to Evaluate the Efficacy and Safety/Tolerability of 2 Linezolid Dosing Strategies in Combination With a Short Course

A novel higher-dose linezolid strategy did not improve outcomes in drug-resistant TB

Regimen for the Treatment of Drug-Resistant Tuberculosis), a phase IIb, randomized, open-label, multicenter trial in 7 countries comparing 26 weeks of standard-dose LZD 600 mg daily with an investigational higher-dose strategy of LZD 1200 mg daily for 4 weeks followed by 1200 mg thrice weekly, each combined with bedaquiline (BDQ), delamanid (DLM), and clofazimine (CFZ). Among 138 adults with newly diagnosed pulmonary drug-resistant TB (median age, 36 years; 37% female; 20% PWH; 66% multidrug-resistant TB), sputum liquid culture conversion by week 26 was similar in both arms (97% vs 94%), although time to conversion was longer in the higher-dose arm (aHR, 0.63; 95% CI, 0.42-0.95; $P = .03$). Favorable TB outcomes at week 26 were higher with standard-dose LZD than higher-dose LZD (65% vs 53%, respectively), with lower premature treatment discontinuation (8% vs 16%, respectively). Although overall rates of grade 2 or higher AEs were similar between arms, the profiles differed, ie, Fridericia-corrected QT interval prolongation was more common with higher-dose LZD than standard-dose LZD (41% vs 23%, respectively), whereas peripheral neuropathy (16% vs 9%, respectively) and increased alanine aminotransferase levels (14% vs 4%, respectively) were more frequent with standard-dose LZD than higher-dose LZD, possibly reflecting higher cumulative exposure with uninterrupted daily dosing over 26 weeks. Dose reductions for toxicity occurred in approximately one-quarter

of participants (26% in the standard-dose arm vs 29% in the higher-dose arm), although time to first dose reduction was earlier in the higher-dose arm.

Companion PK analyses (Abstract 788) confirmed that at week 4, 80% to 100% of participants achieved pharmacodynamic targets for LZD (80% in the standard-dose arm vs 100% in the higher-dose arm) and 90% for DLM across both arms, with LZD exposure 2.5-fold higher in the higher-dose arm and DLM exposure similar between arms. These data support the continued use of the currently recommended LZD 600 mg daily dose in DR-TB regimens, as a novel higher LZD dosing strategy did not improve outcomes and was associated with more treatment discontinuations.

Surveillance of drug resistance in the era of BDQ-based and pretomanid (PTM)-based regimens is essential to ensure their long-term durability. Cardenas-Alvarez and colleagues (Abstract 780) evaluated baseline and emergent resistance among 129 PWH with culture-positive RIF-resistant or multi-DR (MDR)-TB enrolled in the ADAPTIV (An Adaptive Randomized Controlled Trial) study in KwaZulu-Natal, South Africa. Baseline phenotypic resistance to BDQ and PTM was observed in 5.5% and 2.7%, respectively, including in 1 participant with resistance to both agents. Emergent resistance to BDQ and PTM occurred in 2.7% and 0.9%, respectively, with no emergent LZD resistance detected. These findings highlight a concerning prevalence of baseline and emergent resistance to the core components of BDQ, PTM, and LZD (BPAL)-based regimens in this high-burden setting, potentially raising important questions about their long-term durability as these regimens are scaled more broadly.

Prevention

Shorter TB preventive therapy (TPT) regimens improve treatment completion and reduce the burden of HIV-associated TB compared with longer INH-based regimens. Regimens comprising 12 weekly doses of INH plus weight-based RPT (3HP) or 28 daily doses of INH plus weight-based RPT (1HP) are recommended by the World Health Organization (WHO) for PWH. The 3HP regimen is also recommended in US guidelines, whereas 1HP has not been universally adopted. Despite both regimens being available options, they had not previously been directly compared. Two randomized clinical trials presented at CROI 2026 addressed this important gap.

Avihingsanon and colleagues (Abstract 145) conducted a randomized, open-label, phase III, noninferiority trial comparing 1HP and 3HP in 1500 PWH on efavirenz-based (58%) or once-daily DTG-based ART (42%) across 14 sites in Thailand. Most participants were male (82%), with

a median age of 32 years and a median CD4+ count of 348 cells/ μ L. Over a median follow-up time of 3.7 years, there were 3 confirmed active TB cases (2 of 748 participants in the 1HP arm [0.27%] vs 1 of 752 in the 3HP arm [0.13%]), with a corresponding incidence difference of

Although 1HP and 3HP appear similarly effective and safe for TB prevention in people with HIV, 1HP may have higher treatment intolerance and lower completion rates than 3HP

0.13% (95% CI, -0.32 to 0.58) that met the prespecified noninferiority criterion (upper 95% CI, below 2.5%). Notably, all TB cases occurred after 3 years of follow-up. Grade 2 to 4 hepatotoxicity was similar between arms (7.7% vs 6.9%; $P = .18$) and grade 3 to 4 AEs (<3% across arms) and treatment discontinuations due to AEs (<3% across arms) were low and did not differ by arm or ART backbone. HIV-1 RNA suppression at 144 weeks exceeded 93% in each arm regardless of ART backbone.

The One-to-Three trial, presented by Moodley and colleagues (Abstract 148), was a phase IV randomized clinical trial comparing 1HP and 3HP in virally suppressed PWH on DTG-based or efavirenz-based ART in South Africa and India. The primary endpoint was treatment completion, assessed by a prespecified composite endpoint that required concordance across self-report, pill count, and electronic monitoring device (EMD) data. Among 500 participants (median age, 42 years; 68% female; median CD4+ count, ~800 cells/ μ L), treatment completion was significantly lower in the 1HP arm than in the 3HP arm (75.6% vs 87.6%, respectively; difference, 12.1%; 95% CI, 5.7–18.5; $P < .001$), driven largely by lower EMD-confirmed adherence (79.2% vs 96.4%, respectively; $P < .001$), although self-reported and pill count adherence exceeded 90% in each arm. The investigators noted that EMD box openings may have underestimated true adherence in the daily 1HP arm. Notably, treatment-limiting AEs were more frequent with 1HP (3.2% vs 0% with 3HP; $P = .002$), although targeted grade 2 or higher AEs and virologic failure rates were similar between arms.

Collectively, these data support both regimens as safe and effective options for TB prevention in PWH, with 3HP demonstrating more favorable completion and tolerability

in the One-to-Three trial, an important finding to monitor if 1HP is scaled up in real-world settings.

Pregnant women with HIV face heightened TB risk but have been largely excluded from TPT trials. The DOLPHIN-Moms (Safety and Tolerability of 1 Month Daily [1HP] and 3 Months Weekly [3HP] Isoniazid and Rifapentine With Pharmacokinetics of Dolutegravir [DTG] in Pregnant People With HIV) trial (Abstract 147) is a phase II, randomized clinical trial evaluating the safety and PK data of DTG-based ART with 1HP or 3HP in pregnant women at 20 to 34 weeks' gestation in South Africa. At CROI 2025, data demonstrated that twice-daily DTG maintained adequate trough concentrations and viral suppression with either 1HP or 3HP; however, simulation models of once-daily DTG suggested that trough levels would fall below the acceptable threshold with 1HP but remain adequate with 3HP — a finding that required confirmation with observed data.² At CROI 2026, Mathad and colleagues reported new PK data from 38 participants receiving 3HP with an ART regimen that included standard once-daily DTG. Median DTG trough concentrations remained above the 158 ng/mL target threshold at 97% to 100% of assessments across all timepoints, consistent with data from nonpregnant adults, and viral suppression exceeded 90% during TPT. These findings provide PK data and clinical evidence for the use of 3HP in pregnant women with HIV on standard once-daily DTG-based ART.

Prior data have confirmed that 3HP can be coadministered with once-daily DTG-based ART in adults without dose adjustment, but because RPT is a potent inducer of the primary enzymes responsible for DTG metabolism and children clear DTG more rapidly than adults, standard DTG dosing may not achieve adequate exposure during 3HP coadministration. Salazar-Austin and colleagues (Abstract 150) presented results from the DOLPHIN-Kids (Rifapentine and Isoniazid TB Preventive Therapy [3HP] for Children Taking Dolutegravir-Based Antiretroviral Treatment) trial, a phase I/II PK and safety study evaluating once-daily DTG-based ART coadministered with 3HP in 41 children with HIV weighing 10 kg or more who were virally suppressed at entry (median age, 5.5 years; 46% female; all Black African). DTG trough concentrations were significantly reduced during 3HP coadministration and formal PK criteria were not met, ie, the fifth percentile fell below the 158 ng/mL threshold and 2 participants had trough levels below the protein-adjusted 90% inhibitory concentration of 64 ng/mL — 1 individual remained virally suppressed throughout and the other resuppressed with adherence counseling. No grade 3 or higher drug-related AEs occurred, no participants discontinued due to AEs, and 95% were virally suppressed at study

completion. Although formal PK criteria were not met, the absence of drug-related AEs and high rates of viral suppression at study completion suggest that 3HP may be coadministered with once-daily DTG-based ART in children weighing 10 kg or more, with strong adherence support and close monitoring.

Large-scale real-world effectiveness data on TPT across diverse programmatic settings remain limited. Shah and colleagues (Abstract 771) used a target trial emulation framework applied to individual-level electronic health records from Haiti, Kenya, Nigeria, Uganda, Ukraine, and Zimbabwe to estimate the programmatic effectiveness of TPT among 235,424 PWH initiating ART from 2018 to 2021. Initiating TPT within 8 weeks of HIV care entry was associated with a 61% reduction in TB incidence (pooled HR, 0.39; 95% CI, 0.34–0.43) and a 45% reduction in mortality (pooled HR, 0.55; 95% CI, 0.51–0.58) across the 6 countries. These findings provide large-scale real-world evidence reinforcing the effectiveness of TPT in reducing TB incidence and mortality among PWH, further supporting TPT as an essential component of HIV care in high TB burden settings.

Kalema and colleagues (Abstract 770) evaluated TB incidence among 130,954 adult PWH enrolled in HIV care across Kenya, Uganda, and Tanzania before (2012–2016) and after (2017–2020) implementation of the WHO test and treat strategy (TTS), using data from the East Africa International Epidemiology Databases to Evaluate AIDS (IeDEA) consortium. TB incidence declined significantly following TTS implementation, from 19.3 to 12.9 per 1000 person-years (aHR, 0.55; 95% CI, 0.42–0.73), but disparities persisted. Males experienced higher TB incidence than females (HR, 1.74; 95% CI, 1.61–1.87) and adults aged 25 to 34 years (HR, 1.31; 95% CI, 1.14–1.51) and 35 to 44 years (HR, 1.39; 95% CI, 1.19–1.61) had higher TB hazard than the reference group comprising individuals aged 18 to 24 years. Notably, the frequency of TPT use was not reported, limiting the ability to disentangle the effects during the post-TTS period. These findings add further real-world evidence of the importance of expanding access to timely HIV diagnosis and ART, highlighting the need for targeted interventions in higher-risk subgroups, including men.

Diagnosis and Case Finding

Asymptomatic TB is an increasingly recognized challenge in high-burden settings, but its prevalence among PWH enrolled in clinical trials has not been well characterized. Tapley and colleagues (Abstract 774) conducted a cross-sectional TB substudy nested within CoVPN 3008 (Multicenter, Randomized, Efficacy Study of COVID-19

mRNA Vaccine in Regions With SARS-CoV-2 Variants of Concern), a COVID-19 vaccine trial among predominantly PWH in Botswana, Kenya, Malawi, South Africa, Uganda, and Zambia. All participants underwent comprehensive TB screening regardless of symptoms, including chest radiography, sputum smear, Xpert Ultra, and culture; asymptomatic TB was defined as microbiologically confirmed TB in the absence of a current cough, fever, night sweats, or unintentional weight loss. Among 5694 participants, 88% were PWH (median CD4+ count, 724 cells/ μ L) and microbiologically confirmed TB was identified in 108 participants (1.9%), of whom 82 (76%) were asymptomatic. TB prevalence did not differ significantly by HIV status (2.1% in PWH vs 3.3% in people without HIV [PWoH]; $P=0.4$) and was significantly higher in males (4.0% vs 1.7% in females), those with prior TB (4.2% vs 1.7% in those without prior TB), smokers (3.4% vs 1.8% in nonsmokers), and in those with at-risk drinking (3.0% vs 1.7% in those without at-risk drinking). These findings underscore the limitations of symptom-based TB screening and highlight the need for improved screening approaches to detect all forms of HIV-associated TB in clinical trials and in other contexts in high TB burden settings.

TB meningitis remains a frequently missed diagnosis associated with poor outcomes in high TB and HIV prevalence settings. Milburn and colleagues (Abstract 775) integrated routine cerebrospinal fluid (CSF) Xpert MTB/RIF Ultra testing into the evaluation of adults (defined as age >16 years) with a suspected central nervous system infection at hospitals in Botswana and Zimbabwe, identifying microbiologically confirmed TB meningitis in 7.1% of 1131 patients undergoing lumbar puncture (LP), with inpatient mortality of 56% among confirmed cases. Only 21 (39%) received empiric anti-TB treatment prior to microbiologic confirmation. These findings suggest that empiric anti-TB treatment is likely underutilized while awaiting microbiologic confirmation, and routine rather than targeted CSF Xpert testing may be warranted in high TB burden settings where feasible.

Diagnosing TB in children remains challenging due to the paucibacillary nature of pediatric TB and the difficulty of obtaining respiratory samples. Bollore and colleagues (Abstract 776) compared the diagnostic performance of 3 urine-based assays (PathFast LAM, Determine LAM, and IS6110 polymerase chain reaction [PCR]) in 591 hospitalized children with suspected TB in Zambia. Overall, 53 had microbiologically confirmed TB, and the overall sensitivity of PathFast LAM was 76%, increasing to 83% (95% CI, 0.65–0.94) among children with HIV, outperforming both Determine LAM and IS6110 PCR in sensitivity and

exceeding the 75% minimum performance target set by the WHO for a near point of care (POC) test. Specificity exceeded 89% across all subgroups, which is likely an underestimate based on clinical data. Although these initial data are promising for the PathFast LAM test using urine samples, prospective validation in larger and more diverse pediatric populations is needed.

Tuberculosis Pathogenesis and Outcomes

Early mortality in HIV-associated TB remains poorly understood. Boloko and colleagues (Abstract 778) investigated whether inflammasome activation and secondary hemophagocytic lymphohistiocytosis (HLH) contribute to the high early mortality rate seen in hospitalized PWH with TB. Among 355 adults with confirmed HIV-associated TB (median CD4+ count, 57 cells/ μ L), 22% had died by 12 weeks. HLH prevalence ranged from 19% to 50% depending on the criteria used and was associated with mortality by all criteria. Mycobacterial load correlated with ferritin ($R=0.61$; $P<.001$) and caspase-1 ($R=0.43$; $P<.001$), and caspase-1 was independently associated with increased mortality risk (HR, 4.9/ \log_{10} increase; 95% CI, 2.5–9.6; $P<.001$). These findings suggest that inflammasome-driven hyperinflammation along the HLH spectrum plays a prominent role in HIV-associated TB pathogenesis and mortality, and may represent a target for adjunctive therapeutic strategies.

Mpox

Epidemiology and Outbreak Dynamics

Silent and unrecognized transmission emerged as a consistent theme across various settings. Abdullahi and colleagues (Abstract 325) found 13.6% baseline mpox seropositivity among healthy Nigerian adults, with 3% showing evidence of recent asymptomatic exposure over 9 months, suggesting substantial unrecognized transmission. Co and colleagues (Abstract 500) similarly identified 24.8% mpox virus (MPXV) immunoglobulin G (IgG) seropositivity among men who have sex with men (MSM) with sexual risk factors in the Philippines, with serologic evidence of transmission predating the first official case by approximately 3 months. Together, these studies suggest that case counts substantially underestimate true infection burden, especially in settings without robust surveillance, highlighting the need for expanded genomic and serologic monitoring.

Additional studies underscored the importance of genomic surveillance and health system preparedness to detect and contain spread before it escalates. Lautner

and colleagues (Abstract 208) reported that clade IIb lineages E and F dominated MPXV samples in Berlin from 2022 through 2025, with emerging clade Ib detections increasing since late 2025. Phylogenetic analysis indicated that these represent numerous independent introductions rather than local viral evolution or vaccine evasion, suggesting that the virus is repeatedly imported across

Mpox case counts substantially underestimate true infection burden, especially in settings without robust surveillance, highlighting the need for expanded genomic and serologic monitoring

borders. This kind of genomic surveillance can be useful when health systems are able to respond rapidly, as illustrated by Eleeza and colleagues (Abstract 957), who found that facilities supported by the Epidemic-Ready Primary Health Care initiative in Sierra Leone substantially outperformed standard facilities on case-detection speed and infection prevention and control measures, demonstrating that structured investment in facility-level preparedness can meaningfully improve outbreak response in resource-limited settings.

Diagnostics

As mpox cases become less frequent and clinical suspicion wanes, the risk of missed diagnosis grows, making syndromic molecular testing increasingly important. Da Silva and colleagues (Abstract 497) developed a multiplex PCR test that simultaneously detects MPXV, herpes simplex virus (HSV)-1, HSV-2, and *Treponema pallidum* from a single swab. Rizzo and colleagues (Abstract 1034) extended this approach to a broader genital ulcer panel, adding *Chlamydia trachomatis* lymphogranuloma venereum (LGV) serovars, *Haemophilus ducreyi*, and varicella zoster virus (VZV), achieving concordance with routine diagnostics and potentially identifying coinfections missed by single-pathogen testing.

Nsawotebba and colleagues (Abstract 498) further showed that using saliva achieved diagnostic performance similar to lesion swabs during a 2025 outbreak in Uganda. Anal swabs showed high sensitivity, whereas urine, although highly specific, had the lowest sensitivity and should not be used as a primary specimen.

Clinical Manifestations and Impact of Treatment

When MPXV infection occurs, HIV coinfection and structural vulnerabilities consistently amplify its severity and mortality rate. Banai and colleagues (Abstract 499) demonstrated that integrated HIV, syphilis, and mpox screening across 11 high-burden health zones in Kinshasa is feasible and has high impact; 80.5% of suspected mpox cases received dual HIV/syphilis rapid testing alongside MPXV PCR evaluation, identifying HIV coinfection in 12.3% of confirmed cases (more than 12 times the national prevalence) and syphilis in 9.0%, underscoring that mpox response programs represent a crucial and often missed opportunity for HIV and sexually transmitted infection detection. The consequences of missed coinfection were stark, with a case fatality rate of 28% among individuals with HIV/MPXV-coinfection at tertiary hospitals. This was further supported by Namusoosa and colleagues (Abstract 955), who reported that HIV coinfection was present in 50% of the 46 deaths across the national outbreak in Uganda.

The central role of HIV immune status in mpox outcomes is further illustrated by treatment response data. Grinsztejn and colleagues (Abstract 501) analyzed predictors of lesion resolution in 106 participants with severe mpox in the UNITY (Assessment of the Efficacy and Safety of Tecovirimat in Patients With Monkeypox Virus Disease) open-label arm. Faster lesion resolution was associated with younger age, earlier presentation, and controlled or absent HIV infection, with uncontrolled HIV viremia being the strongest predictor of prolonged healing.

Greninger and colleagues (Abstract 502) reported that acquired tecovirimat resistance emerged in 6.5% of participants in the ACTG A5418/STOMP (A Randomized, Placebo-Controlled, Double-Blinded Trial of the Safety and Efficacy of Tecovirimat for the Treatment of Human Mpox Disease) open-label arm, predominantly in those with advanced HIV and CD4+ counts below 80 cells/ μ L. This finding suggests that profound immunosuppression permits sustained viral replication, which, in turn, creates selective pressure for resistance mutations to emerge under drug exposure. Clinical resolution by day 57 occurred in only 28.6% of resistant cases and 94.7% of nonresistant cases, underscoring that in the most immunocompromised patients, prolonged viral replication drives resistance and limits the prospects for recovery.

At a mechanistic level, Yazici and colleagues (Abstract 496) used human *in vitro* models to characterize cell-type-dependent MPXV replication, finding that THP-1 macrophages support progressively increasing viral replication, peaking at 4 days post infection, whereas epithelial cells are least permissive. This is particularly relevant in

the context of advanced HIV, where macrophage function is impaired, and their susceptibility to MPXV replication may help explain the sustained viral loads observed by Greninger and colleagues.

Bbosa and colleagues (Abstract 954) applied deep metagenomic sequencing to samples from 22 fatal mpox cases in Uganda and found VZV coinfection in the majority of fatalities among PWH and PWOH. *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii* were also identified among these fatal cases, suggesting that coinfections may have contributed to mortality.

Alongside coinfections, structural barriers present a challenge to the management of mpox; in New York, New York, Castellano and colleagues (Abstract 956) demonstrated that being uninsured or on Medicaid was independently associated with greater mpox severity, as was HIV with CD4+ count below 200 cells/ μ L, underscoring that biologic and structural factors impact outcomes.

Vaccination and Immunity

Vaccine coverage remains inadequate in many populations. Atkins and colleagues (Abstract 1124) identified a striking gap: among transfeminine persons in the US with a clear vaccination indication, only 25% had received at least 1 dose despite 83% having recently seen a clinician, underscoring that closing immunization gaps remains the most urgent priority.

Among those who are vaccinated, questions about durability persist, and the data are inconsistent. Liu and colleagues (Abstract 319) found that mpox-specific antibodies waned substantially by 2 years post vaccination in smallpox-naïve MSM; notably, most breakthrough infections occurred in those who had not mounted an initial antibody response, suggesting that clinical risk is concentrated in primary vaccine nonresponders and raising the question of whether postvaccination serology has a role in identifying this population.

The Mazzotta group confirmed and extended this picture across 3 abstracts. By 3 years post vaccination, antibody titers were largely undetectable in smallpox-naïve individuals (Abstract 323), T-cell responses were significantly reduced in PWH with CD4+ count below 350 cells/ μ L despite similar antibody levels (Abstract 322), and a booster dose administered at least 2 years after the primary cycle rapidly restored humoral and cellular immunity, with intradermal administration eliciting higher neutralizing antibody titers than subcutaneous administration and supporting a dose-sparing strategy (Abstract 324).

The key tension in these data is between immunologic waning and clinical protection. Despite the serologic

decline documented above, Zucker and colleagues (Abstract 320) reported that prior immunity continued to confer meaningful protection against severe disease and hospitalization in a 2025 multicenter cohort, even years after vaccination, suggesting that antibody titers alone do not fully capture immune response. Meana and colleagues (Abstract 321) add a counterpoint, finding that those vaccinated more than 2 years prior in Washington state showed a trend toward higher severity scores using a modified severity scoring tool, a finding more consistent with the immunologic waning data. Overall, these studies do not yet resolve whether or when boosters are warranted for the general vaccinated population, but converge on PWH with low CD4+ cell counts as being at greatest risk and most likely to benefit.

Other Opportunistic Infections

Cryptococcal Meningitis

In 2022, the WHO recommended a single high-dose liposomal amphotericin B (L-AmB) regimen with fluconazole and flucytosine as induction therapy for cryptococcal meningitis (CM), based on the AMBITION (AMBITION-cm: AMBIsome Therapy Induction OptimizatioN - Intermittent High-Dose AmBisome on a High Dose Fluconazole Backbone for Cryptococcal Meningitis Induction Therapy in Sub-Saharan Africa) trial results. Falconer and colleagues (Abstract 769) conducted a prospective cohort study (2023–2025) evaluating this regimen as part of routine care in Médecins Sans Frontières-supported hospitals in the Democratic Republic of Congo, Guinea, and Mozambique. Among 174 adult PWH with CM (median CD4+ count, 50 cells/ μ L), 2-week and 10-week mortality rates were 22% (95% CI, 17–30) and 43% (95% CI, 36–51), respectively, with a favorable safety profile including grade III/IV renal impairment in only 2% and hypokalemia in 3%. Notably, 37% of survivors were discharged before day 7. Fidelity to recommended care was variable, eg, 85% received L-AmB within 4 hours of admission, 79% had at least 1 follow-up LP, and only 34% completed WHO-recommended laboratory monitoring. These data suggest that although single-dose L-AmB is largely feasible in low-resource settings, a persistently high mortality rate shows that current regimens and strategies are inadequate.

POC diagnostics are central to the WHO advanced HIV disease care package and detection of CM, but cascading implementation gaps can substantially reduce their effectiveness. Falconer and colleagues (Abstract 1097) leveraged pre- and postimplementation programmatic data

from 3 Médecins Sans Frontières-supported programs in Guinea, Democratic Republic of Congo, and Mozambique, using sequential loss modeling to estimate that the cumulative effects of suboptimal performance across POC CD4+ cell count testing, POC serum cryptococcal antigen screening, and LP linkage could result in up to 66% of true CM cases being missed, but that this could be reduced to 25% with optimized implementation support. These findings underscore that novel POC diagnostics must be accompanied by robust implementation strategies, including structured supervision and quality assurance, to realize their potential in advanced HIV disease care in resource-limited settings.

Histoplasmosis

TB and histoplasmosis are leading opportunistic infections among people with advanced HIV disease in Latin America and the Caribbean, but the prevalence and outcomes associated with coinfection are not well described. To address this, Camiro-Zuñiga and colleagues (Abstract 768) pooled data from 4 prospective implementation studies evaluating rapid opportunistic infection diagnostics in 1282 individuals with advanced HIV disease. Among these, 325 (25.3%) had TB, 108 (8.4%) had histoplasmosis, and 46 of the 325 TB cases (14.1%) had histoplasmosis coinfection. Mortality rate was dramatically higher among patients with coinfection than in those with TB alone (34.6% vs 7.8%, respectively, at 90 days and 41.9% vs 9.3%, respectively, at 365 days; $P < .001$). These data highlight that TB-histoplasmosis coinfection is common in endemic settings and carries a markedly higher mortality rate than TB alone, underscoring the importance of maintaining a low threshold for histoplasmosis testing in PWH presenting with TB in compatible clinical settings.

Cytomegalovirus

Cytomegalovirus (CMV) pneumonia is a major but often unrecognized cause of death in infants with HIV, yet empiric treatment is not currently the standard of care. Rojo

Empiric valganciclovir reduced early mortality in infants with HIV and severe pneumonia

and colleagues (Abstract 151) presented results from EMPIRICAL (Empirical Treatment Against Cytomegalovirus and Tuberculosis in HIV-Infected Infants With Severe Pneumonia), a phase II/III, randomized, open-label

factorial trial evaluating empiric valganciclovir and empiric TB treatment independently in 558 infants with HIV aged 28 to 365 days hospitalized with severe pneumonia across 19 hospitals in 6 African countries; the TB treatment arm results are reported separately. CMV viremia was detected in 84.3% of participants at baseline and 51.3% had viral loads above 4.1 log copies/mL, consistent with CMV-attributable pneumonia. Valganciclovir was associated with a significant reduction in early mortality (23.2% vs 27.0% at 15 days; HR, 0.60; 95% CI, 0.41–0.87), but this benefit diminished over time. Overall 1-year mortality rate, although lower in the valganciclovir arm, remained high in the trial arms (43.1% vs 47.5%; HR, 0.79; 95% CI, 0.62–1.01; $P=.07$). Valganciclovir was associated with higher rates of neutropenia (16.7% vs 9.2%; $P=.013$) and anemia (36.6% vs 27.7%; $P=.030$) during the first 15 days, although grade 3 or 4 neutropenia did not differ significantly. The high burden of CMV-attributable pneumonia in this population, combined with a modest but borderline significant mortality benefit and largely reassuring safety profile, suggest that empiric valganciclovir warrants serious consideration as a strategy to reduce early mortality in infants with HIV and severe pneumonia.

Kaposi Sarcoma

Understanding why Kaposi sarcoma (KS) persists requires a clearer picture of human herpesvirus-8 (HHV-8) biology and immune control. Kibanga and colleagues (Abstract 627) found HHV-8 DNA in various organs in 30% of serologically negative individuals at autopsy, demonstrating that standard serology substantially underestimates true HHV-8 prevalence, a finding with direct implications for transplant safety. Isnard and colleagues (Abstract 628) found that higher anti-HHV-8 IgG binding capacity was inversely correlated with circulating HHV-8 viremia in PWH and in MSM who are HIV negative, a relationship not observed for CMV or Epstein-Barr virus, suggesting a specific and potentially protective role for humoral immunity in controlling HHV-8 replication.

These biologic insights point to the need for better clinical tools to identify who is at risk and to monitor KS. Dittmer and colleagues (Abstract 122) demonstrated in 169 participants from the ACTG A5264/AMC067 REACT-KS (Antiretroviral Therapy (ART) Alone or With Delayed Chemo Versus ART With Immediate Chemo for Limited AIDS-Related Kaposi Sarcoma) trial that detectable plasma HHV-8 DNA at entry was the strongest predictor of treatment failure at 48 weeks, outperforming interleukin-6, tumor necrosis factor receptor type 2, and c-reactive protein, and was associated with worse progression-free survival and higher rates of KS-IRIS. Flores-Andrade and colleagues (Abstract 630) provided additional insight,

showing that an HHV-8 viral load above 3.0 log₁₀ copies/mL independently predicted visceral KS involvement with high specificity, suggesting a decisive rule to identify which patients with cutaneous KS warrant aggressive visceral work-up, which is particularly relevant given that more than 40% of KS cases develop visceral disease.

Borok and colleagues (Abstract 629) showed that HHV-8 DNA concentrations were similar in paired oral and cutaneous KS tumors within the same individual, with intraindividual variability substantially lower than interindividual variability, raising questions about the biologic and clinical significance of between-person differences in tumor viral load that warrant further investigation. Together, these studies make a case for routine HHV-8 viral load measurement as a standard part of KS clinical assessment.

Clinical data from CROI 2026 help to define those at greatest risk once KS is established. Volkow-Fernández and colleagues (Abstract 625) compared 218 PWH with disseminated KS, finding that those with pulmonary involvement had higher rates of IRIS, more chemotherapy cycles, and a substantially greater burden of concurrent AIDS infectious events including CMV end-organ disease and syphilis. Importantly, after adjustment, the mortality rate did not differ between pulmonary and nonpulmonary groups, and nearly 75% of the cohort was alive and in complete remission at 4 years. This underscores the importance of aggressive evaluation and treatment of coinfections alongside chemotherapy, which is central to improved outcomes regardless of disease extent.

Mercado Matos and colleagues (Abstract 626) found that among patients with HHV-8-associated diseases, survival was driven by disease phenotype rather than viral subtype, with concurrent primary effusion lymphoma conferring the worst prognosis. KS and multicentric Castleman disease alone were not independently associated with mortality; however, HHV-8 subtype A was associated with worse outcomes in the setting of primary effusion lymphoma, a finding that warrants confirmation in larger cohorts.

Human Papillomavirus and Associated Malignancies

High-risk strains of human papillomavirus (HR-HPV) are prevalent among key populations at risk for anal cancer, yet vaccination coverage remains low. Füllekrug and colleagues (Abstract 1007) found anal HR-HPV in 68% of MSM using HIV preexposure prophylaxis (PrEP) and in 34% of PrEP-naïve peers in a German-Austrian cohort, with HPV-16 and HPV-18 more prevalent among PrEP users. Despite this elevated burden, vaccination rates were low in each group (22% and 15%, respectively), underscoring a primary prevention gap that is addressable through the

integration of HPV vaccination into PrEP programs. In the ANRS PrevHPV-TG (HPV Infection, Sexually Transmitted Infections and Anal Dysplasia in the Transgender Population) cohort of transgender women, Ferré and colleagues (Abstract 1012) found anal HR-HPV in 70%, with concomitant oral and anal infections occurring together in 12% of cases. Modeling indicated that 9-valent vaccination

Two-dose 9-valent HPV vaccination had noninferior immunogenicity in PWH compared with 3-dose — but only in those with viral suppression

would have prevented infection in at least 1 anatomic site in 72% of participants, with low vaccination coverage and high rates of engagement in transactional sex highlighting the magnitude of unmet prevention need in this high-risk population.

Across populations with HIV, HPV persistence after treatment and through cooccurring infections represents a central challenge for cancer prevention. Diwan and colleagues (Abstract 1008) followed 400 women with HIV in Kenya for a decade after random assignment to cryotherapy or loop electrosurgical excision procedure for grade 2 cervical intraepithelial neoplasia, finding that HPV prevalence remained at 54% after 10 years with no difference between treatment arms, and that nearly half of genotypes detected were already present in the first 2 years, highlighting that ablative and excisional treatments remove lesions but do not reliably clear underlying infection. Harfouch and colleagues (Abstract 1009) conducted a longitudinal cohort study in transgender women and MSM and found that baseline HPV-16 and abnormal anal cytology both tended to persist at 1 year, with HIV status and sex-hormone levels not significantly associated with persistence, suggesting that anal cancer screening remains a priority for all transgender women regardless of HIV status.

Euzen and colleagues (Abstract 1011) examined anal microbiome dynamics in MSM from the DEPIST-H (Prevalence and Longitudinal Follow-up of Anal Lesions, HPV Infection, and Associated Sexually Transmitted Infections Among Men Who Have Sex With Men in Togo) cohort and determined that primary HSV infection was associated with shifts in microbial composition over time, whereas

HR-HPV persistence aligned with proinflammatory dysbiosis signatures characterized by the depletion of protective genera and enrichment of inflammation-linked taxa. This study points to a potential role for virus-microbiome interactions in sustaining HPV persistence.

Immune status shapes not only susceptibility to HPV but the response to vaccination against it, as 2 studies from CROI 2026 demonstrated. Nuwagaba-Biribonwoha and colleagues (Abstract 157) compared 2-dose 9-valent HPV vaccine regimens in children, adolescents, and young women with HIV against the standard 3-dose regimen in adolescent girls and young women without HIV in Eswatini, finding noninferior immunogenicity for nearly all subtypes across cohorts with HIV, with the exception of HPV-45 in older adolescent girls and young women. Crucially, those with unsuppressed viral load had lower titers and did not meet noninferiority thresholds, supporting 2-dose regimens for PWH only in the context of maintained viral suppression. Supporting those findings, Ansaldo and colleagues (Abstract 1010) found that a baseline CD4+ count above 500 cells/ μ L was associated with stronger early cellular immune responses to HPV vaccination, including larger increases in CD4+ and CD8+ polyfunctional T cells, suggesting that tailored vaccination schedules may be warranted for those with lower CD4+ cell counts to ensure durable protection.

Implementation of anal cancer screening programs revealed their feasibility in real-world settings and persistent challenges. Andrews and colleagues (Abstract 638) analyzed 2223 anal cytology samples at a large Ryan White HIV/AIDS Program-funded clinic in Dallas, Texas, and found that 79% of patients opted for self-collection, with no difference in unsatisfactory rates or cytology results compared with clinician collection. However, a 24% unsatisfactory rate overall highlighted the crucial importance of the collection technique as programs scale up.

Hessamfar and colleagues (Abstract 641) reported 2-year outcomes following the implementation of French national screening recommendations at Bordeaux University Hospital, where self-sampling for HPV-16 during routine HIV visits identified positivity in 23% of MSM, with severe dysplasia in 36% of those undergoing high-resolution anoscopy (HRA) and biopsy. However, it also identified key implementation gaps, including underreferral of women, high invalid sample rates, and markedly limited HRA access, with only 1 capable center serving a region of 6 million people. Geba and Thomas (Abstract 640) mapped HRA clinics and practitioners nationally, finding that 23 US states lacked a single HRA clinic and that PWH in the South and Midwest face the greatest barriers to access, which is an important reminder that any guideline


recommendations will not be realized without investment in infrastructure.

Refining who should be screened, and how intensively, is a central challenge as anal and oropharyngeal cancer prevention programs expand. Bandala-Jacques and colleagues (Abstract 121) analyzed oropharyngeal squamous cell carcinoma incidence across 21 NA-ACCORD (The

Oropharyngeal squamous cell carcinoma incidence in PWH tripled between 2000 and 2020, with heterosexual men unexpectedly at highest risk

North American AIDS Cohort Collaboration on Research and Design) cohorts spanning from 2000 to 2020, finding that rates tripled over this period and that risk was independently higher in men, in those aged 50 years and older, in those who have ever smoked, and in those with a CD4+ count nadir below 200 cells/ μ L. Notably, heterosexual men had the highest incidence, a finding that challenges screening frameworks focused primarily on MSM and suggests that immunosuppression and smoking history need to inform broader surveillance. Aradan and colleagues (Abstract 639) developed and validated an artificial intelligence (AI) model using immune parameters including the CD4+/CD8+ cell ratio and immune health grade to predict anal dysplasia among PWH. Multivariable models outperformed CD4+ cell count alone and the nadir CD4+/CD8+ cell ratio was the strongest individual predictor, with the approach offering the potential to reduce unnecessary HRAs and better identifying individuals who could benefit.

Aceiton and colleagues (Abstract 642) developed a machine-learning-based risk stratification score using routine clinical variables from 157,725 PWH across the ART-CC (Antiretroviral Therapy Cohort Collaboration) cohort, finding that an extreme gradient boosting model achieved higher sensitivity than current clinical guidelines and reduced the proportion classified as screening eligible, with nadir CD4+ cell count, age, and years in HIV care emerging

as the strongest predictors; this provides a potential approach to improve screening efficiency in settings where HRA capacity remains severely constrained. 

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All relevant financial relationships with ineligible companies have been mitigated.

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Invited Review

CROI 2026: Advances in Epidemiology and Treatment of Viral Hepatitis

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Abstract: *The 2026 Conference on Retroviruses and Opportunistic Infections (CROI) highlighted hepatitis B outcomes in people with HIV on non-hepatitis B-active regimens. Advances in hepatitis B treatment were covered, with some abstracts highlighting novel investigational agents such as antivirals or immune modulators. Data were presented from a phase III trial examining the safety and efficacy of bulevirtide, an investigational agent for hepatitis D treatment. Pharmacokinetic data in animal models from a long-acting injectable intraparticle coformulation of glecaprevir/pibrentasvir were presented for the treatment of hepatitis C. Several abstracts highlighted interventions to increase hepatitis C virus infection detection rates, such as rapid or point-of-care testing, and others focused on improving linkage to care to increase hepatitis C treatment and sustained virologic response rates. Finally, a single abstract showed 2 investigational agents with antiviral activity for hepatitis E virus infection.*

Keywords: HBV, HCV, HDV, hepatitis B, hepatitis C, hepatitis D, hepatitis E, HEV, HIV, pharmacokinetics

Advances in Hepatitis B Epidemiology and Treatment

Hepatitis B epidemiology and treatment were the focus of several important presentations at the 2026 Conference on Retroviruses and Opportunistic Infections (CROI). Haser and colleagues (Abstract 142) presented data on hepatitis B virus (HBV) reactivation or infection rates in people with HIV (PWH) on tenofovir-sparing antiretroviral therapy (ART). They studied 5779 PWH in the CNICS (Center for AIDS Research [CFAR] Network of Integrated Clinical

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Systems) cohort who were on non-tenofovir-containing ART, had baseline hepatitis B surface antigen (HBsAg) and surface antibody (HBsAb) testing, and did not have active HBV infection. They used a composite outcome of HBV reactivation or infection, defined as a positive HBsAg or HBV DNA level of 10 IU/L or higher. The median CD4+ count in their cohort was 603 cells/ μ L and 26% had an unsuppressed HIV viral load (>200 copies/mL). Eighty percent were on ART containing emtricitabine (FTC) or lamivudine (3TC), hereafter referred to as XTC. Fifteen percent of patients had evidence of prior HBV infection with a positive core antibody, 57% had no prior HBV infection, and 29% had an unknown HBV infection status with unknown core antibody values. They observed HBV reactivation or infection in 21 of 5779 patients (0.4%). Most

HBV reactivation or infection is rare in PWH on tenofovir-sparing antiretroviral regimens, but a CD4+ count below 200 cells/ μ L is a risk factor

of these events were new HBV infections, with 13 of 21 events occurring in patients with no prior HBV infection (although interestingly, 4 had a positive HBsAb at baseline). Rates of HBV reactivation or infection were lower in those who were on an XTC-containing regimen (0.3%) than in those on ART without HBV activity (0.8%; P =unavailable). Fourteen percent of those with HBV reactivation or infection had liver inflammation with an alanine transaminase (ALT) level of 100 U/L or higher. In a multivariable regression analysis, they found Black race (adjusted odds ratio [aOR], 6.3; 95% CI, 1.5-25.9), Asian race (aOR, 13.7; 95% CI, 1.8-104.6) and CD4+ count below 200 cells/ μ L (aOR, 3.2; 95% CI, 1.3-7.5) were significantly associated with an increased risk of HBV reactivation or infection. The study authors conclude that HBV reactivation or infection is rare on a tenofovir-sparing ART regimen. Interestingly, HBV

reactivation or infection occurred in groups with prior positive HBsAb, suggesting that levels may have waned over time, leading patients to become at risk for HBV acquisition or reactivation. These data suggest some utility in checking hepatitis B serologies periodically, eg, annually, as suggested by the National Institutes of Health HIV/AIDS Clinical Guidelines,¹ for patients on tenofovir-sparing ART, as well as identifying candidates for hepatitis B vaccination. Moreover, all PWH without active HBV infection but with a negative HBsAb (including those with isolated positive or unknown hepatitis B core antibody [HBcAb]) should be offered adjuvanted hepatitis B vaccine (HepB-CpG) to prevent HBV infection.

Brunet (Abstract 593) presented HIV/HBV coinfection outcomes from the OPERA (Observational Pharmaco-Epidemiology Research and Analysis) cohort of patients on long-acting cabotegravir and rilpivirine (LA CAB/RPV). In their cohort of 5275 participants on LA CAB/RPV, 12% had

HBV reactivation rates are low in PWH on LA CAB/RPV overall, but those with prior hepatitis B without immunity remain an important group for which to monitor closely for reactivation and for whom hepatitis B vaccination should be offered

evidence of previous HBV infection with immunity, 1% of participants had previous HBV infection without immunity, and fewer than 1% had active HBV infection. Overall, follow-up data were limited in those with prior or active HBV infection. In participants with active HBV infection and follow-up data, 52% had reactivation of HBV on LA CAB/RPV; most of these participants were then started on a hepatitis B antiviral drug. HBV reactivation occurred in fewer than 1% of those with prior HBV infection with evidence of immunity and in 3% of those with prior HBV infection but without immunity. They did not find a significant difference in HIV viral suppression among the different HBV infection groups.

Real-world data from the OPERA cohort suggest that HIV/HBV coinfecting patients should be monitored closely, and that although LA injectables are an effective treatment for HIV, those with active HBV infection are likely to have reactivation and should be on an antihepatitis

B agent at the start of LA CAB/RPV. It is reassuring that HBV reactivation is rare in those demonstrating immunity, but the reactivation rate of 3% in those with prior HBV infection without immunity suggests a rare but important complication for which to monitor. These individuals should be offered an adjuvanted hepatitis B vaccine. Those without prior hepatitis B infection but who are switching to LA CAB/RPV should be prioritized for a HepB-CpG vaccine series to prevent HBV infection.

Wang (Abstract 588) presented hepatitis B outcome data in chronic hepatitis B patients taking pevifoscorvir sodium, an investigational antiviral drug with a dual mechanism of action of inhibition of HBV pregenomic RNA encapsulation and blockage of HBV covalently closed circular DNA (cccDNA) establishment. Twenty-one patients with chronic hepatitis B were given once-daily pevifoscorvir sodium for 96 weeks, then taken off the agent for 8 weeks and switched to a nucleoside or nucleotide analogue. By week 96, they found 100% of patients with hepatitis B e-antigen (HBeAg) positivity had suppressed HBV viral loads (target detected under the lower quantification limit or not detected). At week 96, 89% of the participants with a negative HBeAg had a suppressed HBV viral load. They observed sustained decreases in hepatitis B antigens and HBV RNA levels during the 8-week period off pevifoscorvir, suggesting that the antiviral agent may decrease HBV cccDNA levels. A phase II study of pevifoscorvir compared with nucleoside/nucleotide analogue monotherapy in hepatitis B patients is currently underway.

Currie and colleagues (Abstract 587) demonstrated the safety and efficacy of VRON-0200, an investigational immunomodulator that targets HBV core and polymerase (Pol) proteins but not the HBsAg. They administered VRON-0200 alone or VRON-0200 plus investigational antiviral drugs to a cohort of adults with ongoing active HBV infection (with a positive HBsAg). They observed a decline in the HBsAg level around day 28 after receipt of VRON-0200, with 85% of participants having sustained or continued declines at the end of the study (360 days). They observed a similar decline in the combination treatment cohort, with continued declines for 1 month after receipt of the investigational antiviral drug. A phase IIB study is underway to continue studying the use of VRON-0200 to prime the anti-HBV immune response followed by an antiviral drug to boost the response, with the goal of a functional cure for hepatitis B.

Marks and colleagues (Abstract 591) presented data from regional analyses from the ACTG (Advancing Clinical Therapeutic Globally for HIV/AIDS and Other Infections; formerly AIDS Clinical Trials Group) 5379 BEE-HIVE (B-Enhancement of HBV Vaccination in Persons With HIV)

study. BEE-HIVE is a phase III randomized clinical trial comparing the seroprotective response from the HepB-CpG vaccine with the response from a standard 3-dose aluminum hydroxide adjuvant (HepB-alum) vaccine in PWH who had previously not responded to the Hep-B alum vaccine. This trial previously showed superior seroprotection with the HepB-CpG vaccine over the Hep-B alum vaccine.² In analyses across Africa, Asia, Brazil, and the US, they observed higher rates of seroprotection with the HepB-CpG vaccine than the Hep-B alum vaccine in all regions except Brazil (due to the low sample size). They observed variations in age at first hepatitis B vaccination, which likely contributed to some of the differences in seroprotection rates seen by region.

Advances in Hepatitis D Epidemiology and Treatment

Wyles and colleagues (Abstract 141) presented data from the MYR301 trial, a multicenter randomized phase III trial looking at safety and efficacy of bulevirtide (BLV), an investigational drug for the treatment of hepatitis D in PWH

Bulevirtide is shown to be safe and effective for the treatment of hepatitis D

or without HIV. They enrolled adults with chronic hepatitis D virus (HDV) infection with detectable HDV RNA level with or without cirrhosis (Child-Turcotte-Pugh score, ≤ 7), with an ALT level below 10 times the upper limit of normal. A total of 150 participants were enrolled across 3 treatment arms: 2 mg BLV; 10 mg BLV; or delayed treatment until week 48, followed by initiation of 10 mg BLV. Efficacy was defined as virologic response with an undetectable HDV viral load or a decline of $2\log^{10}$ or more from baseline HDV viral load, a biochemical response with normalized ALT, or a combined virologic and biochemical response. There were no significant differences in baseline characteristics among the treatment arms, with nearly 50% of participants enrolled with cirrhosis at baseline, similar baseline mean HDV RNA levels, and about 53% to 65% of participants on antiviral treatment for hepatitis B. Two participants had triple infection with HIV, HBV, and HDV. Through week 144, virologic response rates were 73% in the 2 mg BLV arm, 76% in the 10 mg BLV arm, and 92% in the delayed treatment arm. Fifty-nine percent of

participants in the 2 mg BLV arm reached the ALT normalization endpoint compared with 60% in the 10 mg BLV arm and 58% in the delayed treatment arm. Combined response rates (viral and biochemical response) ranged from 54% to 58% among the 3 treatment arms (P -values and CIs not provided). When looking at undetectable HDV RNA level as an endpoint by week 144, about 50% of the participants receiving 10 mg BLV (at enrollment or delayed) had undetectable HDV RNA level compared with 29% in the 2mg BLV group. At week-96 follow-up (after BLV had been stopped), about 20% of the participants across treatment groups had sustained undetectable HDV RNA level.

No serious adverse events related to BLV were reported in this study, and the most common adverse events observed were injection-site reactions, vitamin D deficiency, and headache. Most notably, ALT flares related to HDV rebound were observed after coming off BLV, and most occurred within the 6-month period after stopping BLV. The 2 participants with HIV, HBV, and HDV infection responded to BLV, ie, they achieved the combined virologic and biochemical response endpoint and had HDV RNA suppression to below 50 IU/mL at week 144. Ultimately, this study showed that BLV use for HDV infection was safe and effective, particularly with regard to virologic response.

Alberola and colleagues (Abstract 590) conducted a nationwide cohort study examining characteristics of people with hepatitis D in Spain. Of the 589 individuals who tested positive for HDV, 19% had HIV and 20% had concomitant hepatitis C. The individuals with hepatitis D in the cohort who underwent transient elastography had a mean liver stiffness of 10.4 kPa. In general, the cohort had evidence of advanced fibrosis; 26% had a fibrosis-4 (FIB-4) score above 2.67. Rates of active HDV infection were significantly higher in PWH than in those without HIV ($P < .05$).

Advances in Hepatitis C Epidemiology and Treatment

Haders (Abstract 589) presented pharmacokinetic data in animal models of a novel investigational oral direct-acting nonnucleoside inhibitor, MDL-001, with in vitro activity against HBV and hepatitis C virus (HCV). One dose of oral MDL-001 was able to reduce HCV RNA viral load for up to 28 days, equivalent to daily sofosbuvir 50 mg/kg. MDL-001 levels in liver tissue exceeded the 90% effective concentration (EC_{90}) range. The investigators did not observe any toxicity in the 400 animals receiving MDL-001. This study showed promising preclinical data of a novel single-dose oral agent showing efficacy against hepatitis C and safety in animal models.

Arshad and colleagues (Abstract 610) presented pharmacokinetic data from an LA formulation of glecaprevir (GLE)/pibrentasvir (PIB) administered via intraparticle coformulations, interparticle mixing (discrete particles) in a single injection, or discrete injections in an animal model. They observed improved pharmacokinetics in the group receiving GLE/PIB intraparticle coformulations, with concentrations of the drugs remaining at the therapeutic level in plasma measurements for 8 weeks after

Intraparticle coformulation of glecaprevir/pibrentasvir shows therapeutic plasma concentrations of the drugs for 8 weeks after 1 dose

administration. The pharmacokinetics of the intraparticle formulation did not vary by route of administration (intramuscularly or subcutaneously). The interparticle mixing group did not demonstrate an extended half-life of GLE or increased PIB exposure as seen in the coformulated group and a previous study.³ The study authors concluded that with intraparticle coformulation, the decreased solubility of PIB impairs GLE release, leading to an improved half-life of GLE. GLE is hypothesized to increase the bioavailability of PIB. Overall, the synergistic effect seen in this study holds promise for coformulations of LA GLE/PIB that can be given in 1 dose.

Abstracts 612 through 617 presented various studies attempting to improve HCV infection testing and linkage to care. Several studies showed that rapid or point-of-care testing improved HCV infection testing rates, and at times, hepatitis C diagnoses. Blair and colleagues (Abstract 615) examined time to treatment initiation based on point-of-care HCV infection testing compared with standard laboratory testing in American Indian populations in Oklahoma. In the point-of-care group (with test results available in 1 hour), the mean time to treatment initiation was significantly shorter (18.2 days) than the laboratory standard-of-care group (92.4 days; $P < .0001$), with a 4-fold decrease in time to initiation of treatment in the point-of-care group compared with the laboratory standard-of-care group (hazard ratio [HR], 4.22; $P < .0001$). Overall treatment initiation rates did not differ among the 2 groups ($P = .5$). In this vulnerable population, rapid testing led to a faster time to treatment, which can aid HCV elimination efforts.

Perez Elias (Abstract 612) presented data from a cluster-randomized trial of rapid HCV testing at primary care centers in Spain. They observed HCV infection rates over a 4-month period, then observed HCV infection rates over a 4-month intervention period with a control arm, a rapid HCV testing arm, and a self-administered risk questionnaire followed by rapid testing arm. They observed significantly higher increases in HCV infection testing in the rapid testing arm (incidence rate ratio [IRR], 2.07; 95% CI, 1.47-2.92; $P < .001$) and in the rapid testing plus self-administered questionnaire arm (IRR, 2.36; 95% CI, 2.12-2.62; $P < .001$) than in the observation phase. Although not significant, the study authors observed increased rates of new hepatitis C diagnoses in the rapid testing arm (IRR, 2.98; 95% CI, 0.97-9.13; $P = .055$) and in the rapid testing plus questionnaire arm (IRR, 2.75; 95% CI, 0.94-7.99; $P = .063$). Rapid testing for HCV infection paired with self-administered questionnaires appears to increase HCV screening rates and may lead to the recognition of new hepatitis C diagnoses.


Vue and colleagues (Abstract 613) examined HCV infection testing rates in emergency departments in California with an opt-out testing system compared with the previous opt-in approach. They observed large increases in number of patients tested, rates of positive hepatitis C antibody, and rates of positive HCV RNA level (P -values and CIs not provided). The trends in this study show that opt-out HCV infection testing in emergency rooms can be an effective approach in improving HCV infection testing rates.

Gallo and colleagues (Abstract 617) examined HCV infection testing turnaround times and linkage to care with a point-of-care HCV infection test administered in the emergency room in Miami, Florida. This point-of-care test decreased turnaround time of a hepatitis C diagnosis by 92% compared with standard laboratory-based testing, which led to increased same-visit linkage to care rates (P -values and CIs not provided). These results, in addition to those from Vue and colleagues, suggest that point-of-care opt-out strategies in emergency departments can greatly improve linkage to care outcomes.

Silver and colleagues (Abstract 616) showed that a volunteer-based linkage-to-care program in Los Angeles, California, was able to link 52% of study participants to care (P -values and CIs not provided), suggesting that community-based volunteer programs could be an effective outreach method. A pharmacist-led approach was presented by Bhattacharya (Abstract 614) in an emergency department in a Veterans Affairs hospital in Los Angeles, California. They observed improved rates of linkage to care after pharmacist-led intervention, along with improved

rates of sustained virologic response (SVR) and decreased rates of HCV viremia. Creative approaches to linkage to care programs may be key in HCV elimination efforts.

Advances in Hepatitis E Treatment

Hepatitis E treatment remains a challenge because there are no antiviral drugs for hepatitis E virus (HEV) infection available. Huang and colleagues (Abstract 596) presented in vitro data from 2 investigational antiviral drugs for HEV infection. They observed high levels of active metabolite in hepatocytes of 2 prodrugs, AT-2490 and AT-587. These drugs were shown to have increased potency over sofosbuvir and ribavirin against HEV. They did not observe any toxicity in vitro. These 2 drugs may remain promising candidates for future study for hepatitis E treatment. 

All abstracts cited in the text appear in the CROI 2026 Abstract eBook, available online at www.CROIconference.org

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All relevant financial relationships with ineligible companies have been mitigated.

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Invited Review

CROI 2026: HIV Comorbidities

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Abstract: *Aging-related comorbid conditions have major effects on the health, quality of life, and survival of people with HIV (PWH). The 2026 Conference on Retroviruses and Opportunistic Infections (CROI) featured a number of studies about various comorbid diseases in PWH. Cardiovascular diseases and hypertension were important topics at CROI, with ancillary analyses from the REPRIEVE (Pitavastatin to Prevent Cardiovascular Disease in HIV Infection) trial and studies from lower- and middle-income countries. Metabolic dysfunction-associated fatty liver disease was highlighted in a themed discussion and studies on glucagon-like protein-1 receptor agonists in PWH and antiretroviral-related weight gain were featured prominently in other sessions. Research focusing on aging in PWH was presented, including numerous studies examining the effects of exercise and physical activity and important studies documenting the high prevalence of osteoporosis and frailty in PWH in sub-Saharan Africa. This review focuses on the abstracts presented at CROI 2026 in these areas, highlighting those with the most clinical impact.*

Keywords: aging, antiretroviral therapy, cardiovascular, complications, comorbidities, CROI 2026, frailty, GLP-1 RA, glucagon-like peptide-1 receptor agonist, HIV

Cardiovascular Disease

Investigation into cardiovascular disease (CVD) was featured prominently at the 2026 Conference on Retroviruses and Opportunistic Infections (CROI), including studies about subclinical cardiac dysfunction and its potential drivers. Perez-Blazquez and colleagues (Abstract 646) examined the association of HIV with CVD, in particular, early subclinical cardiovascular disease. Forty-two people with HIV (PWH) and 26 people without HIV (PWoH) underwent speckle tracking echocardiography, a sensitive method of

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detecting subclinical cardiovascular dysfunction. Parameters including left ventricular (LV) ejection fraction (EF), global myocardial work index (GWI), global myocardial work efficiency (GWE), and absolute value of left ventricular global longitudinal strain (GLS_{vi}) were measured. Although no difference in LVEF was detected between PWH and PWoH, other parameters of LV function, including GWI ($P=.001$), GWE ($P=.013$), and GLS_{vi} ($P<.001$), were lower in PWH than in PWoH. Greater viral reservoir size was associated with lower GWE. This study contributes to an improved understanding of adverse subclinical changes in myocardial function in PWH and the potential role of reservoir size in its pathogenesis. It is consistent with other studies that demonstrate an association between HIV reservoir size and comorbidities, including CVD in the 2000HIV (2000 HIV Human Functional Genomics Partnership Program) study (Abstract 326).

In another study investigating cardiac dysfunction, Omar and colleagues (Abstract 116) sought to characterize CVD in PWH in South Africa, particularly heart failure (HF), in the current antiretroviral therapy (ART) era. The investigators conducted an observational, cross-sectional study of 1008 PWH and 500 PWoH who were matched by age, sex, and presence of hypertension. The participants underwent laboratory testing and an echocardiogram. Covariates in logistic regression analyses included diabetes, smoking, and obesity. Most of the participants were female (795 PWH, 370 PWoH), and 95.3% of the PWH were on a dolutegravir (DTG)-containing regimen. Diastolic dysfunction was more prevalent in PWH than in PWoH ($P=.03$). HF with preserved EF (HFpEF) was more common among PWH and PWoH (8.4% and 6.6%, respectively), whereas HF with reduced EF was infrequently observed. Female sex was associated with HFpEF. For PWH, the odds ratio for HFpEF was 1.49 (95% CI, 0.96-2.35). This study provides insight into CVD phenotypes in PWH in South Africa, and its results are consistent with other studies undertaken around the world, showing a higher burden of diastolic dysfunction in PWH.

Several studies at CROI focused on atherosclerosis and myocardial infarction. In an analysis from the REPRIEVE (Pitavastatin to Prevent Cardiovascular Disease in HIV Infection) study, a large randomized controlled trial of

pitavastatin vs placebo in PWH, Grinspoon and colleagues (Abstract 117) determined whether associations were present among inflammatory markers and other biomarkers at baseline and incident CVD in PWH, and whether pitavastatin use influenced these associations. A substantial percentage of participants had high levels of the following markers: high-sensitivity C-reactive protein (hsCRP; 49%), interleukin-6 (IL-6; 33%), and high-sensitivity cardiac troponin T (hs-cTnT; 35%). IL-6 ($P < .001$) and hs-cTnT ($P = .008$)

IL-6 and hs-cTnT were associated with major adverse cardiovascular events even after adjusting for traditional CVD risk factors

were associated with major adverse cardiovascular events (MACEs), even after adjusting for traditional CVD risk factors (using the Pooled Cohort Equations [PCE] score) and statin treatment. When IL-6 and hsCRP were elevated, the risk of MACEs was greater than the risk seen when IL-6 alone or hsCRP alone was elevated. The predictive ability of the PCE score was increased with the addition of inflammatory-, cardiac-, and lipid-related biomarkers to the model. The investigators also noted that the effect of pitavastatin on incident MACEs was not affected by baseline biomarker levels. Several studies are ongoing, including analyses that will determine the effect of treatment on changes in biomarkers over time in REPRIEVE.

Hypertension

Hypertension is an established factor that contributes to CVD in PWH. Hoffman and colleagues (Abstract 676) studied the baseline prevalence and control of hypertension in the REPRIEVE study population. Hypertension was defined as having been previously diagnosed with hypertension or not having been previously diagnosed with hypertension but having a systolic blood pressure of 140 mm Hg or higher or a diastolic blood pressure of 90 mm Hg or higher. Of the 7769 study participants, 36% (95% CI, 35-37) had baseline hypertension, of whom 31% had not previously been diagnosed with hypertension. Baseline hypertension was more prevalent among participants with obesity, female sex, and Black race. Of study participants who had previously been diagnosed with hypertension, 39%

had uncontrolled hypertension, defined as systolic blood pressure of 140 mm Hg or higher with or without diastolic blood pressure of 90 mm Hg or higher. Using the American Heart Association criteria for stages of hypertension, 77% of participants with preexisting hypertension had stage 1 hypertension (systolic blood pressure of 130-139 mm Hg or diastolic blood pressure of 80-89 mm Hg) or greater. This study underscores that there is room for improvement in the treatment of hypertension in PWH.

Building upon this work, Martinez and colleagues (Abstract 118) studied hypertension incidence and its association with MACEs in REPRIEVE. The incident rate of hypertension was higher in the placebo arm (29.6/1000 person-years) than in the pitavastatin arm (24.7/1000 person-years). Pitavastatin significantly reduced the incidence of hypertension by 17% ($P = .017$). Risk factors for incident hypertension included older age, Black race in high-income countries, fasting glucose, obesity, and elevated blood pressure below the level of hypertension. Incident hypertension was associated with the first primary MACE, after adjusting for baseline atherosclerotic

A REPRIEVE analysis underscored the relationship between incident hypertension and MACEs and demonstrated that pitavastatin reduced incident hypertension in PWH

CVD risk (hazard ratio [HR], 2.16; 95% CI, 1.32-3.52). This study underscored the relationship between incident hypertension and MACEs and demonstrated that pitavastatin reduced incident hypertension in PWH.

Hypertension may also be related to specific ART drugs. Odongpiny and colleagues (Abstract 677) investigated the association between DTG and hypertension in a group of PWH in Uganda, most of whom (62%) were female. Before switching to DTG, the majority of the PWH were taking efavirenz (60%) or nevirapine (25%). Median systolic blood pressure and diastolic blood pressure increased by 5 mm Hg (interquartile range [IQR], -5 to 17 mm Hg for systolic blood pressure and -3 to 13 mm Hg for diastolic blood pressure) at 24 months after switching to taking dolutegravir. Switching to DTG (HR, 1.30; 95% CI, 1.02-1.64), body mass index (HR, 1.97; 95% CI, 1.27-3.05), and aged 45 years or older (HR, 1.84 for those aged 45-54 years [95%

CI, 1.33-2.55] and 2.28 for those aged 55 years or older [95% CI, 1.55-3.30]) were independently associated with incident hypertension. A weight gain of more than 10% post switch was associated with a higher incidence of hypertension (HR, 1.96; 95% CI, 1.42-2.69) than a weight gain of between 5% and 10% post switch (HR, 1.73; 95% CI, 1.30-2.32). Given the high prevalence of DTG use in low- and middle-income countries, this study highlights the importance of addressing weight gain to decrease the risk of hypertension.

Metabolic Dysfunction–Associated Steatotic Liver Disease

Metabolic dysfunction–associated steatotic liver disease (MASLD) is highly prevalent in PWH and is associated with CVD. As such, there is a strong interest in identifying therapies that can improve MASLD. Using data from the REPRIEVE study, Fichtenbaum and colleagues (Abstract 597) investigated the effect of pitavastatin on hepatic

Simple, clinically available measures are associated with hepatic steatosis and could be used to develop risk scores to help identify this condition in PWH

steatosis, as measured by noncontrast computed tomography. MASLD was considered present in the setting of hepatic steatosis with 1 or more elements of metabolic syndrome. The baseline prevalence of hepatic steatosis was similar in participants in the placebo arm (20%) and the pitavastatin arm (24%). No significant difference between the 2 treatment arms was noted in hepatic steatosis resolution or progression ($P = .76$). In addition, at 72 months, no difference was seen in the incidence of MACEs in participants with baseline hepatic steatosis and those without baseline hepatic steatosis, although the incidence of diabetes was higher if baseline hepatic steatosis was present ($P < .001$). This study underscores the association of hepatic steatosis with diabetes and the need for additional therapies to address hepatic steatosis in PWH.

Wegermann and colleagues (Abstract 599) addressed the importance of screening for hepatic steatosis in PWH. Given that elevated transaminase levels are not always seen in PWH with MASLD, Wegermann and colleagues

studied whether measures of adiposity, including waist-to-height ratio and body roundness index (which can be easily obtained in a clinical setting) were associated with MASLD. In the HIV NASH CRN (Nonalcoholic Steatohepatitis Clinical Research Network) cohort, waist circumference had a higher discrimination ability than other adiposity measures in the overall cohort (area under the receiver operator characteristic [AUROC] curve, 0.79), and in Black PWH (AUROC curve, 0.81) and White PWH (AUROC curve, 0.74). In Hispanic PWH, waist circumference, waist-to-height ratio, and body roundness index had the same AUROC curve of 0.81. This study highlights that simple, clinically available measures are associated with hepatic steatosis and could be used to develop risk scores to identify those PWH most likely to have hepatic steatosis.

Hiranburana and colleagues (Abstract 600) also examined the need for accessible tools to identify steatotic liver disease in PWH. In a cohort of Thai PWH on integrase strand transfer inhibitor (InSTI)–based ART for 6 months or longer, they studied the associations of steatotic liver disease, as determined by transient elastography or liver ultrasound, with lipid accumulation product, hepatic steatosis index, and triglyceride-glucose index, which can be calculated using the following variables: fasting glucose, fasting triglyceride level, transaminase level, waist circumference, and body mass index. The measures had high discriminatory ability, with an AUROC curve of 0.794 (95% CI, 0.768-0.820) for the lipid accumulation product and an AUROC curve of 0.792 (95% CI, 0.765-0.819) for hepatic steatosis index. The measures were also studied separately in PWH with and without hepatitis B virus or hepatitis C virus coinfection. In PWH with hepatitis B virus or hepatitis C virus coinfection, the lipid accumulation product had the highest discriminatory ability, with an AUROC curve of 0.799. This work contributes to the development of ways to improve the detection of steatotic liver disease in PWH, especially in resource-limited settings.

Weight Gain in PWH

Although InSTI use has been associated with weight gain and incident diabetes in ART-naive PWH, less is known about the effect of InSTI use on glycemia in ART-naive PWH with preexisting diabetes. Using data from NA-ACCORD (The North American AIDS Cohort Collaboration on Research and Design), Hwang and colleagues (Abstract 685) investigated the effects of starting an InSTI-based regimen on weight and glycemia in ART-naive PWH with preexisting diabetes, compared with starting a nonnucleoside reverse transcriptase inhibitor

(NNRTI)- or protease inhibitor (PI)-based regimen. Compared with an NNRTI-based regimen, InSTI-based and PI-based regimens resulted in significantly higher incidences of worsening glycemia, as defined by a hemoglobin A_{1c} (HbA_{1c}) increase of 0.5% or more or requiring an increase in glucose-lowering therapy. Similarly, the incidence of weight gain of 5% or more was highest in PWH on an InSTI-based or a PI-based regimen, compared with those on an NNRTI-based regimen. The results of this study could help inform the management of PWH with diabetes, in terms of understanding the potential effect of an InSTI-based regimen on glycemia.

Although the effect of the InSTI DTG on weight in PWH has been well studied, limited information exists on the effect of DTG on weight in PWOH, since DTG is not used for preexposure prophylaxis (PrEP) for HIV. Marconi and colleagues (Abstract 688) conducted a pilot study to investigate the effect of 96 weeks of DTG use on weight in 83 PWOH with human T-lymphotropic virus 1 (HTLV-1) infection, which, like HIV, causes a proinflammatory state. Study participants were randomly assigned to take daily vitamin C or DTG. After 48 weeks, participants in the vitamin C arm with symptomatic HTLV-1 infection switched to the DTG arm. No significant difference in weight from baseline to 96 weeks was noted between the 2 arms. The investigators also studied the effects of DTG on other indices, including total cholesterol level, triglyceride level, low-density lipoprotein level, high-density lipoprotein level, fat percentage, and lean tissue index, and no significant differences were noted among these indices between the 2 treatment groups. Future larger studies are needed to understand the differential effects of DTG on weight in PWH vs PWOH with other inflammatory states.

Although obesity is increasing worldwide, the literature is sparse on trends in weight change among rural populations. Kakande and colleagues (Abstract 119) studied weight changes in rural populations in Kenya and Uganda after a change in first-line ART from efavirenz to DTG. Data from 2 different studies (SEARCH [Sustainable East Africa Research in Community Health] 1.0 population-level study from 2013 to 2014 and SEARCH 2.0 population-level study from 2025) including PWH and PWOH were used. The median age was 35 years in both study populations and 14.3% of the 2013 study population and 12.8% of the 2025 study population were PWH. People on ART regimens made up 52% of the 2013 study population and 87% of the 2025 study population. Obesity was more prevalent in the 2025 study population (12.3% of women and 2.9% of men) than in the 2013 study population (4.3% of women and 0.6% of men). In addition, obesity was more prevalent in PWOH than in PWH, with the greatest prevalence values among

middle-aged females with and without HIV. The change in mean body mass index from 2013 to 2025 was 0.53 kg/m² less in PWH than in PWOH (95% CI, -0.92 to -0.13) after adjusting for age, sex, and HIV status and accounting for the interaction between HIV status and time. Kakande and colleagues provided much-needed work describing weight and body mass index trends in rural East Africa, contributing to the understanding of the association of changes in first-line ART on weight in different world populations.

GLP-1 Receptor Agonists

Glucagon-like protein-1 receptor agonists (GLP-1 RAs) have transformed the management of diabetes, obesity, CVD, and numerous other obesity-related conditions. CROI 2026 highlighted these medications in PWH, including a plenary session entitled “GLP-1 Receptor Agonists: Are They a Cure for Everything?” This review sought to address the question of whether the exuberance that has been expressed about GLP-1 RAs by medical practitioners, patients, social media influencers, and the press is rational or irrational. GLP-1 RAs have been available for more than 20 years, first for the treatment of diabetes and then for the treatment of obesity and its associated conditions as the weight loss effects became clear (without the risk of hypoglycemia). These medications have become more potent over time, with impressive effects on glycemia (~2% reduction in HbA_{1c} level) and weight (~15% reduction) for semaglutide, the most widely used GLP-1 RA, and tirzepatide, a dual-RA for GLP-1 and glucose-dependent insulinotropic peptide (GIP), another gut hormone. In addition, these medications have been shown to have impressive effects on HF, MASLD, sleep apnea, chronic kidney disease, and osteoarthritis in the general population. Importantly, GLP-1 RAs have been shown to reduce the risk of cardiovascular events in people with and without diabetes, an effect that is independent of weight loss or improvements in traditional CVD risk factors, such as lipid levels, glycemia levels, and hypertension.

There are numerous other GLP-1 RA effects that could be particularly relevant for PWH. In studies that have examined the effects of these medications on markers of systemic inflammation, hsCRP has been shown to decrease by approximately 50%, even before any weight loss. The mechanisms underlying this effect are unclear but are of crucial importance for understanding the potential use of these medications in the setting of HIV. Tobacco, alcohol, and substance use disorders disproportionately affect PWH, and emerging data suggest that GLP-1 RAs at relatively low doses may decrease cravings for these

substances in short-term studies in the general population. Numerous randomized trials in PWH with substance use disorders are underway. These medications do have adverse effects, with the most common being gastrointestinal upset. An emerging concern, particularly among older patients, is the impact of these medications on muscle and bone mass, which may be of particular importance in PWH, who have a high burden of frailty and osteoporosis.

GLP-1 RAs reduce the risk of cardiovascular events in people with and without diabetes, an effect that is independent of weight loss or improvements in traditional CVD risk factors

Access to these medications is their Achilles' heel. More than 25% of the world's population is potentially eligible for these medications, but cost and availability remain major challenges. With more than 60 other GLP-1–based medications in the pipeline, semaglutide becoming generic, and new, easier-to-produce formulations, the landscape will rapidly evolve over the next 10 years. There is an urgent need to understand these medications for various indications in PWH, to elucidate their risk profiles, and to implement strategies to improve access.

CROI 2026 highlighted various original studies to help close the data gaps in GLP-1 RAs in PWH. Analyses from 3 different cohorts focused on the effects of semaglutide and tirzepatide on weight and glycemic control. The DC Cohort (DC Cohort Longitudinal HIV Status Neutral Study) study (Abstract 695) examined the weight trajectories of 362 PWH who took GLP-1 RAs for at least 6 months and determined that 30% had weight loss of more than 5%, with 11% having weight loss of more than 10%. As has been observed in PWOH, weight loss was greater in those without diabetes than in those with diabetes. The reason for this heterogeneity is unclear and deserves more research.

In the general population, semaglutide and tirzepatide are the most commonly used incretin agents. In an analysis from the CNICS (Centers for AIDS Research [CFAR] Network of Integrated Clinical Systems) cohort (Abstract 697), weight loss and HbA_{1c} reductions were compared in people initiating semaglutide or tirzepatide. Similar to clinical trials in the general population, the effect of tirzepatide was greater than semaglutide for body weight (–6.2% vs –3.1%, respectively) and HbA_{1c} level (–0.25% vs –0.64%,

respectively). Dosage information was not reported. Finally, in an analysis of the clinic population at the University of California San Diego using tirzepatide (Abstract 696), the mean weight loss was 32 lb over 12 months with an average dose of 10.8 mg weekly (maximum dose, 15 mg weekly). As noted in the DC Cohort study, the effect on weight was greater in those without diabetes than in those with diabetes (37 lb vs 22 lb, respectively). More than a quarter (26%) of people who initiated tirzepatide stopped within 1 year, with adverse effects and access problems being the most common reasons for discontinuation. Taken together, these findings suggest that GLP-1 RA–based medications are efficacious for weight reduction in PWH.

CROI 2026 featured presentations assessing the effects of GLP-1 RAs on other outcomes, with several excellent analyses from the CNICS cohort. In one analysis (Abstract 601), semaglutide use in PWH was associated with reductions in liver fibrosis as measured by the fibrosis-4 (FIB-4) index, especially in those with more advanced liver disease. These findings add to the potential benefits for these medications for various end-organ diseases. Another CNICS analysis (Abstract 447) examined the association of semaglutide and change in depressive symptoms. Concerns about the effects of these medications on mental health have been raised, as some users have reported mood impairment and a decrease in motivation. In this analysis, depressive symptoms were assessed by the Patient Health Questionnaire-9 (PHQ-9) in 354 PWH before and after initiating semaglutide. Overall, PHQ-9 scores did not change after semaglutide initiation, providing some evidence of the safety of semaglutide for mental health outcomes. A CNICS study (Abstract 698) also examined the effect of semaglutide on tobacco use. GLP-1 RAs are currently being investigated for their effects on various substance use disorders, such as those associated with alcohol, opiate, and stimulant use. Some data from the general population suggest that these medications may also decrease tobacco use by decreasing craving. In a population of PWH who reported smoking (mean, 10.5 cigarettes/d) semaglutide was associated with a mean decrease of 2.7 cigarettes per day (a 26% decrease). Due to sample size, effect modification could not be adequately assessed, but effects were seen regardless of semaglutide dose, baseline body mass index, sex, and varenicline use.

Increased systemic inflammation and immune activation are thought to be major drivers of comorbidities in PWH, some of which may be due to impaired gut immune function, leading to microbial translocation. In a randomized controlled trial of liraglutide in PWH from South Africa (Abstract 115), paired duodenal and colonic biopsies

were taken in 5 participants initiating liraglutide at 4 time points (pretreatment, 10 weeks after liraglutide initiation, at 4 months, and at 8 months). There was strong modulation of gut immune and epithelial cells with liraglutide treatment, with increases in duodenal CD4+ cells, reductions in CD69 expression in resident CD4+ cells, and

GLP-1 RAs may have potential benefits on gut immune function, which may be especially impaired in PWH

downregulation of CD8a receptor expression. Transcriptomic analysis showed upregulation for genes related to epithelial differentiation and genes related to epithelial structure. These findings suggest that GLP-1 RAs may have potential benefits for gut immune function, which may be especially impaired in PWH. The clinical consequences of these changes need closer examination, as do dose-response effects and investigation of other GLP-1-based therapies.

Antiretroviral Adherence and HIV Comorbidities

Uncontrolled HIV replication leads to systemic inflammation and immune activation. Less well known is that imperfect ART adherence, even when HIV RNA level is suppressed, is associated with increased markers of systemic inflammation. In a prospective, observational cohort study in the ACTG (Advancing Clinical Therapeutics Globally; formerly AIDS Clinical Trials Group) network (Abstract 657), the relationship between self-reported ART adherence and serious non-AIDS events (SNAEs) was investigated over 24 years among those with HIV viral suppression (<200 copies/mL). Among 2940 participants, 260 SNAEs (126 deaths and 134 nonfatal CVD events) occurred over a median follow-up period of 6.2 years. The mean self-reported adherence rate was 97% (defined as the proportion of prescribed doses taken in the 4 days before the study visit) with approximately 2 reports of adherence per year. The median HIV RNA level was below 50 copies/mL. In the primary analysis, which used inverse probability of censor weights modeling to address potential bias, a 9% reduction in the risk of SNAEs was observed for each 10% increase in adherence. Age and

the degree of HIV RNA level elevation were independently associated with SNAE. These data underscore the importance of ART adherence, even in patients who have HIV RNA suppression.

Cancer

Cancer is one of the leading causes of morbidity and mortality among PWH. Over time, the types of cancer that have been experienced by PWH have shifted, with decreases in AIDS-defining cancers and increases in non-HIV-related cancers. The REPRIEVE study examined cancer incidence in 7507 PWH from around the world (Abstract 620). The highest incident cancers were unrelated to HIV, with prostate cancer being the most common in men and breast cancer being the most common in women. Cancer risk was associated with age and cigarette smoking and was most common in high-income regions.

In an analysis from Italy (Abstract 622), cancer mortality was compared in PWH from the ICONA (Italian Cohort Naive Antiretrovirals) cohort with the general population. Over the study period (2008-2023), the cancer-related mortality rate declined among PWH, but remained higher

Among PWH, those randomly assigned to the physical activity intervention had significantly greater improvements in the chair stand test, handgrip strength test, and muscle mass parameters than the control group

than in the general population. These declines were most attributable to AIDS-defining cancers. However, non-AIDS-defining virus-related and non-virus-related cancer mortality rates remained high. Among virus-related cancers, human papillomavirus-related cancers (anal and cervical), lymphoma (Hodgkins and non-Hodgkins), and Kaposi sarcoma had the highest mortality rates compared with the general population. Among non-virus-related cancers, laryngeal, lung, and bladder cancers and leukemia had the highest mortality rates compared with the general population. These findings underscore the importance of cancer screening in PWH and the identification of risk factors that may drive cancer burden and mortality in PWH.

HIV and Aging

Aging in PWH was a major theme at CROI 2026, given the shifting demographics of the HIV epidemic around the world. Exercise and physical activity are established interventions to improve the health span of older people, including PWH. Although physical exercise can help to delay aging-related conditions, it can also have an impact in people with preexisting aging-related syndromes. In the GYM (Grow Your Muscle) study (Abstract 722), investigators randomly assigned PWH and PWOH with sarcopenia (as measured by bioelectrical impedance analysis) to a home-based, structured physical activity program delivered by a digital platform or to no program and examined changes in muscle mass and muscle strength over 48 weeks. Of the 196 participants who were recruited, 72% (69 PWH and 73 PWOH) completed the study. Among PWH, those randomly assigned to the physical activity intervention had significantly greater improvements in the chair stand test at 12 weeks and handgrip strength at 48 weeks, as well as improvements in muscle mass parameters, than the control group. Among PWOH, larger improvements in the chair stand test (12 and 48 weeks), handgrip strength (48 weeks), and leg extension (48 weeks) were seen in the physical activity intervention group than in the control group, but no differences were seen in the muscle mass parameters. When people who received the physical activity intervention were compared by HIV status, no differences were observed in the changes in strength parameters, but PWH had greater improvements in the muscle mass parameters than PWOH. These findings demonstrate that a home-based physical activity intervention can improve muscle mass and strength measurements in PWH. This home-delivered program using a digital platform was particularly notable for its ease of accessibility. Larger implementation studies are needed to understand the scalability of this intervention.

In addition to physical function, physical activity may improve other aspects of health, including symptoms. In the PROSPER-HIV (Impact of Physical Activity and Diet on Symptom Experience in People Living With HIV) study (Abstract 721), a CNICS-based cohort in the US, 704 older PWH had objective measurements of physical activity (7- to 10-day actigraphy) and diet (24-hour diet recall) once yearly for 3 years. Symptoms were common and did not change over the study interval, with the most bothersome and common being muscle aches (47%), insomnia (46%), fatigue (40%), neuropathy (38%), and anxiety (34%). In multivariable models, increased steps per day, decreased sedentary time, and better diet were independently associated with fewer bothersome symptoms, suggesting the possibility that increased physical activity and better


diet may be crucial factors to promote healthy aging. Cellular senescence is one of the hallmarks of aging and may drive the development of aging-related diseases. Cellular senescence markers were measured in 3 groups of PWH (primary infection, chronic infection, and advanced HIV [defined as CD4+ count <100 cells/ μ L]) before and 1 year after ART initiation, and compared with markers in sex- and age-matched PWOH. Cellular senescence markers remained elevated in PWH with chronic or advanced infection compared with PWOH, but normalized in those with primary infection, suggesting that early treatment

Dual-energy X-ray absorptiometry screening and osteoporosis treatment protocols will be essential to decrease fracture risk in older women with HIV in Africa

may be important to prevent cellular senescence in PWH. The investigators then examined the effect of the senolytic drugs dasatinib and quercetin ex vivo using a 3-day culture of peripheral blood mononuclear cells (PBMCs). Treatment with dasatinib and quercetin decreased cellular senescence biomarkers and induced senolytic activity. Whether this treatment would have similar effects in PWH in vivo and can improve physical function is not clear, but it is being evaluated in an ACTG-sponsored clinical trial (NCT07144293).

As PWH age throughout the world, conditions such as osteoporosis and frailty are increasingly recognized in settings with a high burden of HIV, such as in sub-Saharan Africa. In a study of 179 older women with HIV in Kenya (Abstract 732), 56% had osteoporosis based on spine and hip dual-energy X-ray absorptiometry using the NHANES (National Health and Nutrition Examination Survey) Black female reference database. Higher body mass index and type 2 diabetes were associated with a lower prevalence of osteoporosis, whereas longer duration of ART tended to be associated with an increased osteoporosis prevalence. Tenofovir disoproxil fumarate-based regimens tended to be associated with lower bone-mineral density, but given that 73% were receiving this type of regimen, this factor could not be adequately evaluated. Additional studies are needed to understand whether this high prevalence of osteoporosis will translate into a higher risk of fracture. Nonetheless, given the very high prevalence of osteoporosis in this population, and interventions that can reduce

fracture risk, dual-energy X-ray absorptiometry screening and osteoporosis treatment protocols will be essential to decrease fracture risk in older women with HIV in Africa.

Frailty is an important aging-related condition that will affect an increasing number of PWH in Africa. In a cross-sectional study in urban Tanzania that enrolled 197 women and 196 men with HIV (Abstract 717), the majority of whom were in their 50s, the overall prevalence of frailty was 14% and prefrailty was 49%. Factors associated with frailty or prefrailty were female sex, shorter ART duration, hypertension, lower weight and overweight/obesity, less social support, and increased depressive symptoms. Additional work is needed to understand whether interventions can improve physical function in this population. 

All abstracts cited in the text appear in the CROI 2026 Abstract eBook, available online at www.CROIconference.org

The IAS–USA has identified and resolved ahead of time any possible conflicts of interest that may influence CME

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Invited Review

CROI 2026: Acute and Postacute COVID-19

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Abstract: *The 2026 Conference on Retroviruses and Opportunistic Infections (CROI) furthered our understanding of acute COVID-19, long COVID, postacute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), viral immunity, and SARS-CoV-2 therapeutics. Results of a first-in-human validation study of DNA-encoded monoclonal antibody (DMAb) technology demonstrated safety and robust and durable monoclonal antibody (mAb) production, giving the green light to further develop the DMAB platform. Pemivibart administration to people with advanced HIV was well tolerated and associated with good levels of neutralizing antibodies. A new pan-coronavirus 3C-like protease inhibitor was shown to have similar pharmacokinetics and a similar safety profile in people with renal impairment and people with hepatic impairment. A study of SARS-CoV-2 infections in 2023 demonstrated continued risk for new incident diagnoses and worsening of prior comorbidities in the year after infection. SARS-CoV-2 infection in people with HIV is associated with discernible decline in estimated glomerular filtration rate in the 2 years after infection. A blinded study of circulating SARS-CoV-2 antigen found no association between the presence of antigen and the likelihood of having long COVID. Most people with long COVID in a cohort study have experienced stigma or feeling dismissed in interactions with their clinicians.*

Keywords: COVID-19, HIV, long COVID, monoclonal antibody, PASC, postacute sequelae of SARS-CoV-2, SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Introduction

The 2026 Conference on Retroviruses and Opportunistic Infections (CROI) showcased several high-quality abstracts, covering exciting work in the areas of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-focused

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therapeutics, long COVID, SARS-CoV-2 immunity, and the impact of HIV on SARS-CoV-2 outcomes.

SARS-CoV-2 Therapeutics

Monoclonal Antibodies

In an oral abstract session focused on long-acting antivirals and novel delivery platforms, Tebas (Abstract 180) presented data from a first-in-human study of DNA-encoded monoclonal antibody (DMAB) technology.¹ Although this particular study evaluated a SARS-CoV-2-specific monoclonal antibody (mAb) that is no longer effective against current circulating strains, the potential uses for DMAB technology are much broader. Just 1 or 2 injections of DNA in an individual could result in 2 or more years of steady delivery of mAbs to the circulation, targeting HIV, cancer antigens, autoimmune diseases, or neurologic conditions. DMAB technology could circumvent the current

An exciting proof-of-concept study examined DMAB technology in humans and demonstrated the safety and durability of DMAB-elicited production of a functional monoclonal antibody cocktail

limitations of mAb infusions such as the facilities and time needed to manufacture mAbs, the logistics of transporting and storing mAbs at cold temperatures, the expense and time required to administer an intravenous medication, and the need for repeat infusions.

This was a phase I, dose-escalation study of the electroporation of synthetic plasmid DNA-encoding mAbs that are modified versions of tixagevimab and cilgavimab, which bind distinct sites on the SARS-CoV-2 spike protein. Tixagevimab/cilgavimab was granted emergency use authorization (EUA) by the US Food and Drug Administration

(FDA) in December 2021 for COVID-19 preexposure prophylaxis for vulnerable individuals. Its EUA was revoked in January 2023, at which time more than 90% of circulating SARS-CoV-2 variants in the US were resistant to it. In this study, 2 separate plasmid DNA constructs (one of tixagevimab, one of cilgavimab) were codelivered intramuscularly via localized electroporation 1, 2, or 4 times over the course of 4 weeks at doses ranging from 0.5 mg to 2 mg in 44 healthy individuals. In the 39 individuals who completed the study, blood was sampled monthly for 8 months and then every 1 to 6 months for 96 weeks. More than 90% of participants reported local pain and scabbing and more than 40% reported local erythema, although the pain was reported to resolve within 5 to 10 minutes. Systemic adverse events (AEs) were rare, with myalgia reported in approximately 10% and headache reported in fewer than 10%.

Pharmacokinetic profiling was favorable. The 2 mAbs originating from the separate electroporations of the 2 DNA constructs were coexpressed in the circulation at similar levels. There was rapid production of mAbs by muscle cells, peaking at 6 to 8 weeks after administration. Levels of these antibodies remained stable at biologically relevant levels during the 2-year follow-up period presented here. No antidrug Abs were detected in any participant during the follow-up period. Binding assays demonstrated that mAbs elicited by this platform bound well to several strains of SARS-CoV-2, including ancestral SARS-CoV-2, Delta, and Omicron strain BA.2, although binding to BA.4/5 was decreased, as expected. Neutralization assays of resulting mAbs demonstrated half-maximal inhibitory concentration (IC₅₀) levels similar to tixagevimab/cilgavimab. Although this particular SARS-CoV-2 mAb therapeutic no longer has activity against current strains and will not be further developed, this was a successful proof-of-concept study examining DMAB technology in humans and demonstrating the safety and durability of DMAB-elicited production of a functional mAb cocktail.

Although EUAs for almost all other SARS-CoV-2 mAbs have been revoked due to their loss of efficacy as a result of viral evolution and escape, pemivibart has retained its EUA for COVID-19 preexposure prophylaxis (PrEP) in individuals who are immunocompromised. Pemivibart is an mAb that targets the SARS-CoV-2 spike receptor binding domain and competes with binding of spike to its receptor, human angiotensin-converting enzyme 2 (ACE2). Narayan (Abstract 740) presented a posthoc analysis of pemivibart efficacy for COVID-19 PrEP in people with advanced HIV infection from the phase III CANOPY (A Study to Evaluate the Efficacy and Safety of VYD222 for Prevention of COVID-19) trial of pemivibart administered twice,

3 months apart.² In the study, 27 individuals had advanced HIV, defined as baseline CD4+ T count below 350 cells/ μ L. Although this subgroup had a higher rate of serious AEs in the study than the study group as a whole, they had similar rates of treatment-associated AEs. Neutralizing Ab titers were elevated to levels associated with effective protection by pemivibart and no cases of reverse transcription polymerase chain reaction (RT-PCR)-confirmed symptomatic COVID-19 were reported through month 6. These data suggest that pemivibart is a viable PrEP agent against symptomatic COVID-19 in people with HIV (PWH) with CD4+ counts below 350 cells/ μ L.

Of note, the most recent Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines recommend that pemivibart be considered for a more narrow population of PWH, ie, those with CD4+ counts below 200 cells/ μ L who are at risk of progression to severe COVID-19, and only when the predominant SARS-CoV-2 strains are susceptible to pemivibart.³ Although one can infer that PWH with CD4+ counts below 200 cells/ μ L had no RT-PCR-confirmed symptomatic COVID-19 since none from the broader HIV group did, it was difficult to determine from Narayan's presentation whether the neutralizing Ab titers in those with CD4+ counts below 200 cells/ μ L were elevated to levels associated with protection against COVID-19. It was also difficult to determine whether the rates of serious AEs or treatment-related AEs are different in this narrower group that would be more likely to receive pemivibart in clinical practice.

Small-Molecule Antivirals

Unlike most mAbs developed to date, SARS-CoV-2-targeted small-molecule antiviral drugs such as nirmatrelvir/ritonavir, remdesivir, and molnupiravir have remained effective against all strains of SARS-CoV-2. However, each has their limitations. Nirmatrelvir/ritonavir is an effective

Pemivibart is a viable preexposure prophylactic agent against symptomatic COVID-19 in people with HIV with CD4+ counts below 350 cells/ μ L

oral medication, but it must be taken twice daily, has bothersome taste and gastrointestinal AEs, and has drug-drug interactions. Molnupiravir is also an oral medication, but studies suggest it may be less effective in preventing

hospitalization and death from COVID-19,^{4,6} and given its mutagenic mechanism of action, some fear it may induce host mutations.⁷ In addition, in immunocompromised individuals or in other rarer cases, molnupiravir use can result in mutated SARS-CoV-2 that could be transmitted onward.^{8,9} Remdesivir use currently requires intravenous infusion, although oral prodrugs are currently in development. In this environment, advancements in the SARS-CoV-2 oral antiviral space are of great interest.

Okamoto (Abstract 738) presented preclinical work developing investigational quinazoline derivatives targeting SARS-CoV-2. They started with amodiaquine, an antimalarial drug with antiviral activity against ebolavirus and SARS-CoV-2 that may also inhibit interleukin-6 (IL-6) production from macrophages in an animal model.¹⁰ Its AEs, including hepatotoxicity and agranulocytosis, can be severe so the group replaced its quinoline core with a quinazoline backbone and synthesized and screened hundreds of derivatives to identify candidates with improved SARS-CoV-2 activity with reduced toxic effects. They identified YMSA-0958, a compound with a half-maximal effective concentration (EC₅₀) in cell culture virus infection experiments similar to remdesivir and nirmatrelvir, although with a lower 50% cytotoxic concentration (CC₅₀). The compound also performed as effectively as remdesivir in cell culture experiments

YMSA-0958 is a promising investigational drug targeting SARS-CoV-2, but given its potential for higher toxicity than remdesivir, preclinical toxicity data will be needed to advance this compound

when introduced 2 hours before or simultaneously with SARS-CoV-2 infection. YMSA-0958, like remdesivir, inhibited the SARS-CoV-2 RNA-dependent RNA polymerase. It was effective in decreasing viral RNA in the lung in a BALB/C mouse model of SARS-CoV-2 infection. Given YMSA-0958's potential for higher toxicity than remdesivir, a more detailed description of these preclinical mouse infection experiments and preclinical toxicity data will be needed to advance this compound. It will be interesting to see whether decreased viral replication in the lung is accompanied by decreased levels of IL-6 in the mouse model, given the effects of its precursor molecule

and given that elevated IL-6 is an important biomarker of human COVID-19 severity.¹¹

Nirmatrelvir/ritonavir is an inhibitor of the SARS-CoV-2 3C-like protease (3CL^{pro}), also known as main protease (M^{pro}). 3CL^{pro} is a cysteine protease and is required for the cleavage and maturation of proteins involved in viral replication. 3CL^{pro} sequences from SARS-CoV, SARS-CoV-2, and MERS-CoV share a high degree of similarity, so

The data support dosing of ALG-097558 in individuals with mild-to-moderate hepatic impairment or mild-to-severe renal impairment and advancing its investigation to phase II trials

it is an attractive target for antiviral development. Bardiot et al reported on the discovery and successful preclinical profiling, including animal model testing, of ALG-097558, an oral 3CL^{pro} inhibitor with pan-coronavirus activity and no need for concomitant administration of ritonavir.¹² Phase I studies indicated good safety and pharmacokinetics with 7 or fewer days of treatment. At CROI 2026, Fitzgerald (Abstract 737) presented safety and pharmacokinetic data from a phase I study of ALG-097558 administration to people with moderate hepatic impairment (Child-Pugh class B, n=8) or severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min, n=6), and healthy participants with normal renal and hepatic function. Safety data indicated that ALG-097558 was generally well tolerated, with only 1 treatment-emergent AE of epigastric pain in the hepatic impairment study. Pharmacokinetic data indicated that moderate hepatic impairment or severe renal impairment do not result in a more than 2-fold increase in mean plasma exposures of the study drug and its metabolite compared with healthy controls. The data support the dosing of ALG-097558 in individuals with mild-to-moderate hepatic impairment or mild-to-severe renal impairment and advancing this investigation to phase II trials.

Long COVID and Postacute Sequelae

Long COVID continues to affect millions of people worldwide. Purpura and colleagues (Abstract 752) surveyed people in the C-PIC (COVID-19 Persistence and Immunology Cohort) study of Columbia University. Of 159

individuals who received long COVID-specific health care who answered the survey, 108 (68%) reported having experienced stigma or having felt dismissed by clinicians regarding their long COVID symptoms. People with more severe long COVID were more likely to report stigma or dismissal. This should be a wake-up call to clinicians to work harder to help people with long COVID feel seen, validated, and supported.

Various population-based and electronic health record (EHR)-based studies have demonstrated that SARS-CoV-2 infection is associated with increased incidence of new medical diagnoses and worsening of prior conditions.¹³ Now that virtually every person has immunity to SARS-CoV-2, whether via vaccine or infection or both, it remains unknown to what extent COVID-19 in the current era is associated with postacute sequelae at a population scale. Sax and colleagues (Abstract 748) used the US-based Veradigm Network EHR to identify approximately 250,000 adults with a COVID-19 diagnosis or medical claim in 2023 with 12 months of data available before and after the index diagnosis. A total of 73% of these individuals had evidence of at least 1 COVID-19 vaccination. Documentation of a neurologic condition in the follow-up period that was not documented in the preinfection period was found in 13% of these individuals. Similarly, 9%, 8%, and 4% of the individuals had documentation of cardiovascular, respiratory, and chronic kidney disease (CKD) that was not in the records in the preinfection period. Increases of 3% to 17% in neurologic-, cardiovascular-, respiratory-, and CKD-specific health care utilization rates were found in this population. Even in the post-Omicron era of widespread SARS-CoV-2 immunity, this work provides evidence to suggest that COVID-19 is still associated with increased incidence of new diagnoses and worsening of prior diagnoses in the postacute period.

Byrne and colleagues (Abstract 749) utilized data from the DC Cohort (DC Cohort Longitudinal HIV Status Neutral Study) of PWH and determined rates of incident CKD and change in eGFR in the 2 years after COVID-19 diagnosis. The investigators propensity score-matched 463 PWH with COVID-19 2-to-1 with 855 control PWH. COVID-19 in PWH was associated with eGFR loss of 5.3 mL/min/1.73 m² over 2 years of follow-up compared with PWH without COVID-19. A total of 7.3% of PWH with COVID-19 developed CKD during the follow-up period. An eGFR decline was more likely to occur in people with higher preCOVID-19 creatinine level, prior hepatitis B, and lower albumin levels. A decline in eGFR of more than 25% was associated with female sex, diabetes, and higher creatinine at COVID-19 diagnosis, whereas CD4+ count more than 500 cells/μL was protective. These data

suggest that PWH who have COVID-19 might benefit from the monitoring of kidney function in the months after diagnosis.

Opsteen and colleagues (Abstract 753) examined immune signatures of long COVID in PWH and people without HIV (PWoH), ultimately showing that the immune dysregulation associated with HIV infection overshadows

Long COVID was associated with a higher frequency of circulating classical monocytes, and an increased frequency of classical monocytes correlated negatively with MRI measures of microvascular perfusion

that associated with long COVID. In this study, 73 PWH and 197 PWoH were surveyed and sampled a median of 2.5 years after initial SARS-CoV-2 infection. Long COVID was defined as self-reporting 5 or more new symptoms post COVID or self-reporting 1 or more new symptom together with moderate-to-extreme symptoms or meeting the RECOVER (Researching COVID to Enhance Recovery) 2023/2024 Research Index. In this study, PWH were more likely to be male, be black, have hypertension, use tobacco, and to have had a COVID-19 vaccine prior to first SARS-CoV-2 infection, and were less likely to have been hospitalized for COVID-19, than PWoH. All PWH were virally suppressed on antiretroviral therapy (ART) for a median of 20 years and had a median CD4+ count of 740 cells/mL. The group first analyzed which symptoms associated with each other. Regardless of HIV status, obesity was associated with a greater number of correlated symptom pairs, largely defined by sleep problems, gastrointestinal issues, weakness, dyspnea, and cough. Flow cytometry was performed on blood samples, but significant differences in cell type frequency were associated with HIV status rather than long COVID status. An evaluation of the association of cell frequency with individual symptoms determined that elevated CD16+ nonclassical monocytes were associated with new-onset malaise, which concurs with a prior study demonstrating the significance of monocytes in the immune dysregulation associated with long COVID.¹⁴

The mechanisms underlying long COVID remain unknown, but one hypothesis is that persisting viral antigen or viral replication may cause long COVID. Mateu

and colleagues (Abstract 747) presented data on levels of SARS-CoV-2 antigen detected in the blood in people with and without long COVID. In this study, 425 adults were followed for 2 years, including 167 people with long COVID, 148 people with full recovery from COVID-19, and 110 people without SARS-CoV-2 infection (uninfected). Blood samples were collected at 6 to 12 months post infection and 18 to 24 months post infection. The Simoa platform was used to quantify SARS-CoV-2 spike protein, spike S1 subunit, and nucleocapsid antigen from plasma.

At 6 to 12 months post infection, 31% of people with long COVID, 20% of those with full recovery, and 1 uninfected individual had detectable levels of any antigen. At 18 to 24 months post infection, only 3% of people with long COVID and no recovered or uninfected people had detectable SARS-CoV-2 antigen. Spike protein was detected in plasma in 20% of participants with long COVID, 16% of those with full recovery, and 4% of uninfected individuals. Spike S1 subunit was detected in 4%, 2%, and 2% and nucleocapsid was detected in 7%, 3%, and 2% of people in the long COVID, full recovery, and uninfected groups, respectively. Importantly, there was no significant association between long COVID and detectable antigen, whether examined separately or combined. The *P*-value of this test was not reported, so it is unclear whether there is a nonsignificant trend toward antigen persistence and long COVID. This adds to an uncertain evidence base in which few studies associate the presence of circulating SARS-CoV-2 antigen with long COVID and more studies find no association.

Long COVID and the Brain

One of the hallmarks of long COVID is brain fog and many research groups are working to uncover the mechanisms behind this neurocognitive dysfunction. Singh (Abstract 108) presented a talk during a session on neuropathogenesis about her group's preliminary work to uncover the link between long COVID, myeloid-compartment immune dysfunction, and cerebral vascular dysfunction. This work builds on earlier findings that severe COVID-19 is associated with epigenetic changes in hematopoietic stem and progenitor cells that affect progeny innate immune cells that persist for months to years.¹⁵ This earlier work determined that long COVID was associated with persistent epigenetic changes in monocytes and their precursors as well as increased expression of the calgranulins S100A8/A9 (which together form calprotectin) in monocytes. S100A8/A9 are expressed in neutrophils and monocytes and are released during inflammation to stimulate leukocyte recruitment and cytokine secretion.

To test the hypothesis that monocyte activation and S100A8/A9 expression/secretion exacerbates neurologic dysfunction in people with long COVID, the group examined brain imaging and blood samples from 138 individuals without long COVID and 105 individuals who had

Two or more years post infection, people with neurologic long COVID were no more likely to have evidence of herpesvirus reactivation or higher levels of herpesvirus T-cell responses than those who were recovered or were never infected by SARS-CoV-2

experienced long COVID (90% of whom had current long COVID at the time of the study). Cerebral microvascular perfusion, glymphatic function, and blood-brain barrier function were assessed with different magnetic resonance imaging (MRI) protocols. Using subsets of participants, long COVID was associated with a higher frequency of circulating classical monocytes and an increased frequency of classical monocytes correlated negatively with MRI measures of microvascular perfusion. Long COVID was also associated with increased plasma levels of S100A8/A9, and plasma S100A8/A9 levels are inversely associated with MRI measures of glymphatics. Monocytes from 3 to 5 people with long COVID exhibited increased excretion of IL-6 and CC motif chemokine ligand 2 from endothelial cells after monocytes were stimulated with inflammatory stimuli compared with 4 or 5 people with recovery. More participants are needed to see if these associations are significant, and the study is ongoing.

In a separate study of neurologic long COVID, Bernad and colleagues (Abstract 754) studied symptoms and blood samples in 131 individuals, 43 of whom were a median of 2 or more years post infection with neurologic long COVID, 29 of whom had long COVID, 28 of whom had full recovery after SARS-CoV-2, and 32 of whom were not infected. Assays quantifying herpesvirus viral load and serology were performed alongside flow cytometry for immunophenotyping and functional characterizations of SARS-CoV-2 and herpesvirus-specific T-cell responses. Levels of immunoglobulin G (IgG) against Epstein-Barr virus, cytomegalovirus, and human herpesvirus 6 did not differ across groups. Flow cytometry analyses

demonstrated that CD8+ terminally differentiated effector memory T cells reexpressing CD45RA were elevated in long COVID (but not neurologic long COVID) compared with people with full recovery. People with neurologic long COVID had stronger CD4+ T-cell responses to SARS-CoV-2 antigens than to herpesviruses. The investigators concluded that at 2 or more years post infection, people with neurologic long COVID were no more likely to have evidence of herpesvirus reactivation or higher levels of herpesvirus T-cell responses than those who were recovered or never infected by SARS-CoV-2. The take-home message on long COVID from CROI 2026 is that its biomarkers remain elusive.


Immunity and Acute COVID-19

There were fewer studies on acute COVID-19 and SARS-CoV-2 immunity after acute infection at CROI 2026 than in prior years, reflecting waning interest in acute COVID-19 in immunocompetent individuals. Kapira and colleagues (Abstract 316) examined upper and lower respiratory tract immune responses in PWOH living in Malawi. Bronchoalveolar lavage (BAL), nasal swab, and peripheral blood sampling were performed on 43 individuals after COVID-19 and levels of SARS-CoV-2-specific immunoglobulin A (IgA) and IgG were quantified. Higher levels of spike-specific IgA than nucleocapsid-specific IgA were found in all 3 sampled sites, whereas this was not seen when examining spike and nucleocapsid IgG. Higher frequencies of spike- and nucleocapsid-specific CD4+ cells were observed in BAL than in blood. Circulating spike and nucleocapsid IgG correlated more strongly with BAL/lower respiratory tract Abs than nasal/upper respiratory tract Abs. This suggests that serum levels of SARS-CoV-2 Abs may be viewed as a rough indicator of the level of Abs in the lower respiratory tract and they may not be correlated with protection against infection in the upper respiratory tract.

Nanayakkara and colleagues (Abstract 744) examined whether prior infection or vaccination or both (hybrid immunity) played a role in preventing infection or time to symptom resolution in a prospective observational cohort study of adults with acute COVID-19 in North Carolina. A total of 2731 participants were enrolled beginning in October 2022 with follow-up through August 2025. Studies of this kind are not as common as they were at the beginning of the pandemic, and this work provides an idea of whether vaccination and hybrid immunity still provide benefit to people with mild-to-moderate COVID-19 in the post-Omicron era. Symptoms were assessed daily for 14 days via an online survey. Time of symptom resolution was defined as the first of 2 consecutive days reporting

no symptoms. Hybrid immunity was associated with a 2.7-day faster time to symptom resolution than no prior vaccination/infection. Unvaccinated adults, with or without prior infection, had the slowest symptom resolution. People aged 65 years or older experienced faster resolution of symptoms, perhaps in part due to higher vaccine uptake in this group. These results provide evidence that COVID-19 vaccination is associated with a faster time to symptom resolution in the post-Omicron era.

Conclusion

CROI 2026 showcased a variety of interesting studies pertaining to acute COVID-19, long COVID and postacute sequelae, and SARS-CoV-2 therapeutic agents. These studies offer crucial insights into the therapeutic drugs, pathophysiology, epidemiology, and lived experiences associated with SARS-CoV-2 infection. 

All abstracts cited in the text appear in the CROI 2026 Abstract eBook, available online at www.CROIconference.org

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All relevant financial relationships with ineligible companies have been mitigated.

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*Invited Review***CROI 2026: Global Epidemiology and Prevention of HIV and Other Sexually Transmitted Diseases****Susan P. Buchbinder, MD; Albert Y. Liu, MD, MPH**

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Abstract: *At the 2026 Conference on Retroviruses and Opportunistic Infections (CROI), investigators presented updates on the global HIV epidemic. HIV incidence remains high among key populations, including female sex workers, men who have sex with men, people who inject drugs, and transgender women. Testing for recent infections can guide targeted HIV prevention services to interrupt ongoing transmission. In a cohort study of serodifferent couples in Africa, low-level viremia was associated with reduced but nonnegligible risk of HIV transmission. Sociostructural risk factors play a substantial role in driving new HIV transmissions. Several studies described the use of molecular epidemiology to characterize HIV transmission patterns and identify hot spots. Innovative strategies to increase HIV testing are being evaluated. In an oral preexposure prophylaxis (PrEP) study offering choice between daily and on-demand PrEP, HIV incidence was very low with either regimen. Follow-up data from 2 injectable lenacapavir PrEP trials demonstrated continued high efficacy with very rare breakthrough infections. Although awareness of long-acting PrEP is increasing, use remains low across various cohorts. Several studies reported on the use of PrEP in pregnancy, including a pharmacokinetic study showing no dose adjustment needed for long-acting injectable cabotegravir. Interventions to increase PrEP uptake and persistence show promise. A randomized clinical trial of the meningococcal vaccine did not show efficacy in preventing gonorrhea acquisition. Although doxycycline postexposure prophylaxis (doxy-PEP) use is increasing, it remained low among male veterans with a history of a sexually transmitted infection. Several studies reported on the impact of doxy-PEP on antibiotic use.*

Keywords: CAB, CAB-LA, cabotegravir, CROI, doxycycline, doxy-PEP, HIV, LEN, lenacapavir, long-acting CAB, PEP postexposure prophylaxis, preexposure prophylaxis, PrEP, prevention, STI

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Global Trends in HIV Acquisition and Transmission

At the 2026 Conference on Retroviruses and Opportunistic Infections (CROI), several studies reported on trends in new HIV infections in sub-Saharan Africa. Kosgei and colleagues (Abstract 893) assessed HIV incidence in a cohort of female sex workers and men who have sex with men (MSM) in Kenya. From December 2021 to September 2024, they followed 407 people without HIV with quarterly clinic-based HIV testing and monthly Oraquick

HIV incidence was 3.27/100 person-years among female sex workers in Kenya

self-testing for up to 72 weeks. Among 374 participants analyzed, the median age was 22 years, and 79% were female (88% were involved in transactional sex) and 22% were male (37% were involved in transactional sex). HIV incidence was 2.53 per 100 person-years overall and 3.27 per 100 person-years among female participants, in whom all 12 seroconversions occurred. Among incident cases, 80% had depressive symptoms and 50% had concurrent bacterial sexually transmitted infections (STIs), but only 17% were on preexposure prophylaxis (PrEP) at enrollment and subsequently discontinued.

Kuchukhidze and colleagues (Abstract 888) identified high HIV burden geographic areas to prioritize scale-up of lenacapavir (LEN) PrEP in South Africa. Using routine service delivery data, they identified reliable proxies of HIV incidence. They found that HIV positivity at first antenatal care visit and HIV positivity in the population that was HIV negative (proportion of people with HIV among 1000 people without HIV) were most correlated with district HIV incidence, with the highest incidence rates seen in KwaZulu-Natal, Eastern Cape, and Mpumalanga subdistricts. When LEN rollout is focused on subdistricts with 30% of the population, they estimated that geographic prioritization of LEN could avert one-third more new infections than

uniform geographic allocation. John and colleagues (Abstract 895) assessed recent HIV infections among newly diagnosed people in Tanzania. Between September 2023 and October 2024, they offered people newly diagnosed with HIV a rapid test for recent infection (RTRI), and those with a recent test result and an HIV viral load of 1000 copies/mL or higher were defined as having a recent infection

From 2012 to 2024, HIV incidence among MSM and PWID in India has remained high, and HIV prevalence has increased substantially in these populations during this period

testing algorithm (RITA)-recent infection. Among 20,020 people with a new HIV diagnosis and a valid RTRI test (68% female; median age, 34 years), 3.9% had a RITA-recent infection. RITA-recent infections were higher among females than males (4.5% vs 2.9%, respectively; $P < .001$) and higher in those who engaged in commercial sex in the past year than in those who did not (5.5% vs 3.8%, respectively; $P < .001$). In an adjusted model, younger people aged 15 to 19 years (adjusted odds ratio [aOR], 2.0) and 20 to 24 years (aOR, 1.5) had higher odds of a RITA-recent infection than those aged 30 to 34 years, and those who reported sex with a partner who was HIV positive in the past year were more likely to have a RITA-recent infection (aOR, 1.35) than those who did not. These findings can be used to guide targeted, population-specific HIV prevention services to reduce incident infections.

Tasaneeyapan and colleagues (Abstract 894) assessed demographic and regional patterns of recent HIV infections among MSM in Thailand. Thailand has integrated RTRI with HIV case surveillance data within their routine testing services, using RITA to identify people who likely acquired HIV within the past 12 months (defined as having RTRI-recent test and baseline CD4+ count >200 cells/ μ L). Between September 2022 and March 2024, a total of 2475 individuals were newly diagnosed with HIV, of whom 1209 (49%) were MSM. Among the newly diagnosed MSM, 103 individuals (8.5%) were classified as RITA-case surveillance recent. In multivariable analyses, MSM aged 15 to 24 years were more than twice as likely to have a recent infection than those aged 35 to 44 years (aOR, 2.28), and living in the Northern, Northeastern, Southern, or Bangkok metropolitan areas was associated

with higher adjusted odds of having a recent infection than living in the Central region (aOR, 3.84-6.89). They recommend tailoring resources to these priority populations and geographic regions to promote early diagnosis and interrupt ongoing transmission.

Patel and colleagues (Abstract 922) reported on trends in HIV prevalence and incidence among MSM and people who inject drugs (PWID) in India. They conducted 3 cross-sectional surveys (2012-2013, 2016-2017, and 2022-2024) among 8245 MSM across 3 cities and 16,496 PWID across 6 cities recruited through respondent-driven sampling. HIV incidence remained persistently high between 2012 and 2013 and between 2022 and 2024 among MSM (1.3% vs 1.9%, respectively; $P = .35$) and PWID (4.9% vs 5.9%, respectively; $P = .25$), and HIV prevalence increased from 7% to 20% (adjusted prevalence ratio [aPR], 2.0) among MSM and from 19% to 40% (aPR, 2.0) among PWID during this period. These trends were similar across age groups and occurred in the setting of increasing HIV viral suppression rates from between the periods of 2012 to 2013 and 2022 to 2024 (aPR, 3.2 for MSM; aPR, 2.2 for PWID), although viral suppression rates were lowest among young key populations with HIV (ie, <30 years of age). These findings highlight the importance of scaling up combination prevention services, including PrEP, to achieve HIV epidemic control in India.

Solomon and colleagues (Abstract 901) presented on HIV and hepatitis C virus (HCV) infection incidences in a spatially targeted person-centered clinic in India. In New Delhi, prior data suggested that 70% of all new infections among PWID were attributed to a single venue. In October 2023, through a public-private collaboration, they established “The Blue Shed,” a person-centered facility providing medical services, harm reduction, and social services. Between October 2023 and August 2025, a total of 1276 people (median age, 27 years; 98% assigned male sex at birth) registered for services at this facility. Overall, 88% were unemployed/daily wage earners; 87% reported injecting drugs in the past month, and 60% had a history of sharing injection paraphernalia. The prevalence of HIV, HCV infection, and hepatitis B surface antigen positivity was 45.2%, 74.1%, and 7.5%, respectively. HIV and HCV infection incidences were very high (35.1/100 person-years and 44.3/100 person-years, respectively). Most people visited the facility for food, showers, and harm-reduction services, and per service used at each visit was associated with reduced HIV incidence (adjusted incident rate ratio [aIRR], 0.43; 95% CI, 0.28-0.67). The researchers suggest that additional tools (eg, long-acting [LA] prevention and treatment) will be needed to reduce HIV incidence in this population.

Figueroa and colleagues (Abstract 893) reported on HIV incidence and associated risk factors in a transgender and nonbinary (TNB) cohort in Argentina. They enrolled 499 TNB individuals into TransCITAR (Trans-Specific Co-

In a nationwide cohort of TGW in the US, structural vulnerabilities (being unhoused, engaging in sex work, poverty, and being publicly insured or uninsured) were associated with HIV seroconversion

hort in Argentina), a prospective cohort in Buenos Aires, of which 219 were HIV negative, and tested participants every 6 months during a 60-month period. There were 19 seroconversions during a median 42.3 months of follow-up (most occurring in the first 18 months), resulting in an HIV incidence of 2.75 per 100 person-years. In a multivariable model, sex work (hazard ratio [HR], 6.26) and sexualized drug use (HR, 5.08) were associated with HIV seroconversion, and PrEP use was protective (HR, 0.04). The researchers call for early and tailored prevention strategies for TNB individuals in this region, including timely PrEP, gender-affirming care, harm reduction, and structural interventions to address social vulnerabilities.

Reisner and colleagues (Abstract 192) reported on HIV incidence in a nationwide cohort of transgender women in the US and Puerto Rico. Recent structural and policy shifts have reduced gender identity data collection, and transgender women have faced increased political and structural barriers to care. Between March 2023 and December 2024, they enrolled 2504 transgender women without HIV into the Enhanced Cohort Methods for HIV Research and Epidemiology (ENCORE), a hybrid digital hub-supported community cohort. The median age was 32 years, 28% were non-White, 30% experienced poverty, and 49% had public insurance or were uninsured; 16% had a PrEP indication and 18% reported PrEP use (mostly oral PrEP) in the last 6 months. Overall, there were 39 new HIV diagnoses (25 at baseline, 14 during follow-up). HIV incidence was 3.95 per 1000 person-years overall, 15.45 per 1000 person-years in Black participants, 7.46 per 1000 person-years in Latino participants, 5.65 per 1000 person-years in Asian participants, and 16.27 per 1000 person-years in PrEP-indicated participants.

Baseline structural vulnerabilities were associated with HIV seroconversion, including being unhoused (risk ratio [RR], 4.06), engaging in sex work (RR, 4.88), poverty (RR, 5.83), and having public insurance or being uninsured (RR, 13.60). Additionally, baseline stimulant use (RR, 6.43), having a PrEP indication (RR, 9.55), and PrEP use (RR, 4.73) were associated with HIV seroconversion. The researchers call for tailored interventions and safe, gender-affirming prevention services for transgender women, along with continued gender-inclusive research infrastructure.

Balkus and colleagues (Abstract 900) reported on trends in HIV diagnoses among cisgender women in 3 West Coast counties in the US. Using data from the National HIV Surveillance System for King County, Washington (including Seattle), Los Angeles County, and San Francisco County between 2015 and 2024, they showed that rates of new HIV diagnoses declined among cisgender women from 2015 to 2020 but began rising in 2021, with 40%, 15%, and 63% higher rates for King County, Los Angeles County, and San Francisco County, respectively, in 2024 than in

Rates of new HIV diagnoses in cisgender women in the West Coast of the US have increased substantially from 2021 to 2024

2019. In 2024, the proportion of cisgender women who reported being homeless or unhoused at diagnosis was higher than for the overall population of newly diagnosed individuals (28% vs 20% for King County, 27% vs 14% for Los Angeles County, and 39% vs 16% for San Francisco County), and 1% of cisgender women across all 3 counties were diagnosed with syphilis in the 12 months prior to HIV diagnoses. The researchers call for improved access to stigma-free HIV screening, prevention, and treatment for cisgender women.

Shintani and colleagues (Abstract 902) reported on HIV and STI trends with rising PrEP and doxycycline post-exposure prophylaxis (doxy-PEP) use among MSM in Tokyo. They analyzed data from the Sexual Health Clinic cohort of 2355 MSM between 2017 and 2025. HIV incidence declined from 2.8 per 100 person-years in 2018 to 0.2 per 100 person-years in 2022 and has remained low through 2025. PrEP use increased substantially during this period, with 55% of participants using PrEP by June 2025. STI incidence remained stable during this period despite

increasing uptake of PrEP and doxy-PEP; 30% of participants reported using doxy-PEP in 2025 (including 8% using doxy-PEP without PrEP). Although the reductions in HIV incidence demonstrate the prevention potential of PrEP scale-up even without a national prevention program, the emerging use of doxy-PEP without PrEP underscores the need for integrated and equitable guidance to maximize preventive impact.

Risk and Protective Factors for HIV and STIs

Martin and colleagues (Abstract 903) reported on HIV transmission risk among individuals with low-level viremia. The World Health Organization guidance states that

In the Rakai Community Cohort, they estimated 2.9 HIV transmissions per 100 person-years at a viral load of 1000 copies

individuals with low-level viremia (200-1000 copies/mL) have “almost zero or negligible” risk of transmitting HIV to their sexual partners. The researchers therefore sought to quantify this transmission risk in settings with infrequent monitoring. Among 415 monogamous, serodifferent couples in the Rakai Community Cohort (1995-2022), there were 93 seroconversions among 940 couple-years of follow-up. They estimated 2.9 (95% CI, 1.1-7.5) and 0.6 (95% CI, 0.2-2.1) transmissions per 100 person-years at a viral load of 1000 and 200 copies/mL, respectively. Among people reporting antiretroviral therapy (ART) use and low-level viremia, 28% experienced viral rebound to more than 1000 copies/mL within 16 to 28 months. After accounting for viral rebound, they estimated 1.3 (95% CI, 0.8-2.0) transmissions per 100 person-years from individuals with low-level viremia. This risk could be reduced by 94% with 90-day vs annual monitoring. These findings suggest that transmission risk from low-level viremia is reduced but may not be nonnegligible, especially in the setting of infrequent monitoring. The researchers emphasized that their study findings do not call into question “undetectable = untransmittable” (U=U), which still holds true for viral loads below 200 copies/mL. It is important to note that much of this research was performed prior to the availability of integrase strand transfer inhibitors and that phylogenetic testing was not performed on paired samples.

Ssempijja and colleagues (Abstract 193) reported on the association between awareness of sex partner HIV status and population-level HIV incidence in the Rakai Community Cohort Study in Uganda. Between February 2010 and November 2020, awareness of sex partner HIV status increased from 44% to 73%, whereas HIV incidence declined over time during this period (overall, 0.72/100 person-years). In an adjusted model, an awareness of the HIV status of all partners was associated with a 49% reduction in HIV incidence (50% reduction in female participants and 54% reduction in male participants). Although the number of sex partners and marital status of never or previously married were associated with higher HIV incidence, the observed HIV incidence reduction was independent of number of sex partners and marital status. These findings highlight that serostatus awareness is a key protective factor and a crucial component of HIV prevention strategies.

Carlson and colleagues (Abstract 913) examined the influence of rurality on rates of new HIV and hepatitis C diagnoses in Tennessee, a largely rural state. They estimated that for each 10% increase in rurality, there was a 17.7% decrease in HIV infection rates, a 0.9% increase in HCV infection rates, and a 7.9% reduction in HIV/HCV infection rates. After accounting for modifiable mediating factors (eg, primary care physician density, chlamydia rate, and social vulnerability index), the effect of rurality on HIV risk was attenuated, and the effect on hepatitis C risk was nullified. These results suggest that HIV and possibly hepatitis C prevention should be strengthened in areas with poor health care access or high socioeconomic vulnerability to reduce rural-urban disparities.

LeCates and colleagues (Abstract 941) assessed the impact of behavioral and sociostructural risk factors on HIV risk among women in the urban South. In this retrospective cohort study of 333,263 cisgender women seen in the Grady Health System in Atlanta, Georgia, between 2012 and 2022, there were 617 women (0.19%) newly diagnosed with HIV. People with HIV were mostly Black (89%), with a mean age of 41 years. In a multivariable model, living in a high-incidence zip code (aOR, 4.5) and having a diagnosis of schizophrenia (aOR, 4.1), substance use disorder (aOR, 3.8), bipolar disorder (aOR, 3.4), or syphilis (aOR, 8.7) were associated with HIV. Population-attributable fractions were calculated and were highest for the sociostructural factors that were most prevalent: living in a high-incidence zip code accounted for 63% of HIV risk and elevated social vulnerability index accounted for 21%, compared with 13% for substance use disorder and 5% for bacterial STI diagnoses, which were uncommon. These findings suggest that incorporating sociostructural context into individual

PrEP decision-making could help identify women who could benefit from prevention, particularly in high-incidence settings.

Javanbakht and colleagues (Abstract 899) examined the prevalence and correlates of transactional sex among men in Los Angeles, California. Between August 2014 and January 2025, they enrolled and followed 685 men in a prospective cohort study. At baseline, median age was 31 years, 43% were Black and 38% were Hispanic/Latino, and 53% were people with HIV (PWH). Across all study visits, 62% reported never engaging in transactional sex, 30% reported transactional sex at some but not all visits, and 8% reported it at every visit. Compared with those who reported transactional sex intermittently or not at all, participants who reported transactional sex at all visits had higher levels of unstable housing (63% vs 49% vs 27%, respectively; $P < .001$), methamphetamine use (75% vs 61% vs 37%, respectively; $P < .001$), and giving money, drugs, or other goods in exchange for sex (58% vs 26% vs 2%, respectively; $P < .001$). These findings support ongoing screening and integrating HIV prevention and care services with housing support and stimulant-focused treatment.

In an interactive symposium, Baral (Abstract 31) presented on the topic of structural determinants of HIV and STIs among gender-diverse communities. He began by pointing out that federal funding for surveillance, epidemiologic research, and structural intervention research and programs in gender-diverse individuals has been cut dramatically, despite these communities being disproportionately impacted by HIV. He shared data from the TWIST (Transgender Women's Internet Survey and Testing) study, an online behavioral survey of transgender women and transfeminine individuals undertaken annually in the US since 2019. Among a subset of 3057 TWIST participants, only one-third reported STI testing annually, with screening more common in those who reported condomless anal sex, those who disclosed their gender identity to a health care clinician, and those who were on current gender-affirming hormone therapy. Testing was less likely in younger individuals and those with severe depression. Among those tested for STIs, 16% reported having 1 or more bacterial STIs, with transgender women with HIV being 4.5-times more likely to report an STI diagnosis. Black and Hispanic participants were 2.3- and 1.6-times more likely to report an STI than White individuals, whereas those on gender-affirming hormone therapy were half as likely to report an STI diagnosis.

Regarding intersectional stigma, 63% of transgender women reported lifetime exposure to violence and harassment and 37% experienced social systems exclusion, which was significantly higher for transgender

participants of color (prevalence ratio [PR], 1.71) and PWH (PR, 2.29). Furthermore, transgender women of color who reported social exclusion were nearly 4-times more likely to have HIV (PR, 3.82) and nearly twice as likely to have a bacterial STI (PR, 1.91). They determined that in states with more harmful health care policies, individuals who experienced health care stigma were less likely to report PrEP use (aOR, 0.7). They also examined the relationship between housing status and PrEP use, and concluded that those experiencing sheltered homelessness (eg, living in an emergency shelter or transitional housing) were more likely to be on PrEP than those who were stably housed (aOR, 1.78), suggesting successful PrEP outreach efforts in shelter settings; however, this relationship was seen only in transgender women aged 25 years and older.

Baral also reported results from a 2025 study of 496 transgender women (median age, 27 years) in Liberia. They determined that the weighted HIV prevalence was 23% and STI prevalence was 11%, with only 52% of participants ever undergoing testing for HIV. There was a high burden of gender-identity stigma, including family exclusion (25%), family gossip (34%), and friend rejection (20%). Importantly, structural determinants were predictors of HIV

Cross-border transmission is an expanding component of the European HIV-1 A6 epidemic

diagnosis among transgender women, including being criminalized (aPR, 1.92), having police refuse protection (aPR, 2.37), being scared in public spaces (aPR, 1.63), and experiencing physical violence (aPR, 1.41); and individual risk behaviors (eg, condomless sex, numerous sexual partners) were not predictive of HIV diagnosis. These findings point to the powerful role of structural determinants in driving disparities in HIV and STI outcomes in transgender women.

Several studies described the use of molecular epidemiology to characterize local HIV transmission chains and identify HIV transmission clusters. Dennis and colleagues (Abstract 890) examined whether network bridges can predict emerging HIV transmission hot spots in North Carolina. She explained that molecular clusters often contain embedded recent subclusters, which are focal areas of rapid transmission within established networks. They defined "bridging individuals" as those who connect distinct subclusters within larger clusters. Using HIV

surveillance data in North Carolina from 2010 to 2025, they determined that viremic bridge members occupy highly central network positions that were highly connected (median degree, 9 vs 2 for nonbridges). Baseline viremic bridging predicted subcluster growth, even after adjusting for structural position and cluster size. Additionally, among clusters with recent and rapid subclusters, 78% of viremic-bridging ties span counties, suggesting that bridging positions can link focal growth across jurisdictions and serve as high-impact intervention points to prioritize responses before subclusters accelerate.

Serwin and colleagues (Abstract 877) reported on HIV-1 sub-subtype A6 international transmission patterns across several European countries. HIV-1 sub-subtype A6 is important to recognize because it confers increased likelihood of treatment failure with resistance during the administration of cabotegravir/rilpivirine. They analyzed publicly available HIV-1 sequences along with migration-related metadata from Poland, Czechia, Israel, and Germany from 2011 to 2023 and identified 4093 sequences (26%) forming broad transmission clusters. Over time, migrant inclusion in transmission links increased significantly from 6.3% in 2021 to 14.6% in 2023, as did transmission links involving female individuals, which increased from 2.2% to 5.8% during the study period. Although within-country transmission was most common, they noted substantial cross-border links between Germany and Poland and between Czechia and Poland. These findings suggest that cross-border transmission is an expanding component of the European HIV-1 A6 epidemic, likely a result of migration and recent war-related displacement, highlighting the need for coordinated, cross-jurisdictional prevention strategies focused on mobile populations to limit further HIV transmission.

Adams and colleagues (Abstract 876) compared 2 HIV cluster-detection methods in rural Washington state. They analyzed HIV surveillance data in this region from 2020 to 2024 to identify HIV transmission clusters employing (1) time-space methods that use spatiotemporal proximity, and (2) molecular HIV surveillance methods that use genetic distance. Each method identified 7 clusters, with molecular surveillance capturing mainly urban clusters and time-space identifying urban and rural clusters. In rural areas, 20% of new HIV diagnoses were included in clusters (time-space, 95%; molecular surveillance, 5%), compared with 40% in urban areas (time-space, 87%; molecular surveillance, 13%). Only 2% of people identified in a time-space cluster were also identified in a molecular cluster and only 3% identified in a molecular cluster were also found in time-space clusters. The researchers suggest that jurisdictions should use both methods to detect HIV

transmission clusters, particularly in areas with increasing rural HIV diagnoses.

Bridges and colleagues (Abstract 882) explored heterogeneity in community priorities for HIV molecular epidemiology among 747 MSM (134 with HIV) participating in the American Men's Internet Survey. In aggregate, "ensuring privacy" was given the highest priority (17%) and community engagement was considered the least important (2%). Using latent class analysis, they identified 2 groups with distinct priorities. The "Use the Data" group (63%) prioritized the use of HIV molecular epidemiology to identify and respond to HIV clusters, study HIV evolution, and evaluate HIV prevention, and the "Protect the Data" group (37%) wanted to ensure data privacy, obtain permission to use it, provide disclosure about its use, and prevent law enforcement access to the data. These priorities did not differ by HIV status.

Hall and colleagues (Abstract 1055) examined how national and state HIV prevention funding trends influenced HIV diagnosis rates in the US. Using retrospective time-series regression modeling and funding and HIV diagnosis

For each \$1-million increase in annual federal funding to state health departments, there was an associated 0.015 decrease in new HIV diagnoses per 100,000 people

rate data collected from 2008 to 2023, they estimated that for each \$1-million increase in annual federal funding to state health departments, there was an associated 0.015 decrease in new HIV diagnoses per 100,000 people ($P=.066$). Decreases were greater for males than for females ($P=.029$) and in Black people ($P<.001$) and Hispanic ($P=.006$) populations, and those aged between 13 and 24 years experienced the greatest effect over time. Additionally, the effect of HIV prevention funding was significantly different in Medicaid expansion vs nonexpansion states ($P<.001$), suggesting that concurrent policy solutions are needed to bolster federal funding reach for HIV prevention.

Glaubius and colleagues (Abstract 1091) modeled the potential impact of reaching Ending the HIV Epidemic (EHE) Targets in Missouri. Using an established HIV epidemic model, they analyzed 3 scenarios: (1) business as usual, in which service coverages remained constant at 2023 levels through 2030; (2) EHE targets reached including 95% people aware of their status, 95% linked to care,

95% viral suppression, and 50% PrEP coverage by 2030; and (3) Medicaid disruptions resulting in loss of ART or PrEP coverage among Medicaid recipients. In the business as usual scenario, new infections in 2030 increased 9% over 2020 levels, with 3453 new infections projected to occur cumulatively from 2024 to 2030. In contrast, reaching EHE targets reduced new infections by 35% during the 2024 to 2030 period. In the Medicaid disruption scenario, coverage of ART fell by up to 9% and PrEP by 7%, which could increase new infections by up to 10% in this period. These results highlight the importance of reaching EHE targets and preserving access to ART and PrEP in Missouri.

McGreevy and colleagues (Abstract 993) modeled Scotland and Ireland's progress toward 2030 Joint United Nations Program on HIV/AIDS (UNAIDS) HIV transmission elimination goals. Using a Markov HIV transmission model, they demonstrated that Scotland and Ireland have already achieved the UNAIDS HIV elimination target for their total population, and for heterosexual men, women, and PWID. In contrast, MSM are not expected to meet the 2030 UNAIDS target under current intervention conditions. However, with moderate increases in HIV testing, treatment, and PrEP utilization rates among MSM, they estimate that Scotland could achieve HIV transmission elimination targets by 2030 and Ireland by 2035.

HIV Testing

Perez Elias and colleagues (Abstract 158) presented results from a cluster randomized clinical trial of HIV rapid testing and digital risk assessment in primary care centers in Spain. From July 2023 to February 2025, they conducted a stepped wedge trial in which 8 primary care centers were randomly assigned sequentially to control, rapid HIV testing, and rapid testing plus a digital risk-assessment questionnaire, in which an automatic email was sent to the participant and their practitioner to perform an HIV test and refer to the PrEP clinic if risk was identified. Overall, 14,644 HIV tests were performed, including 692 HIV rapid tests, and 63 participants had positive HIV tests, including 23 new HIV diagnoses (5 by rapid test). Compared with the observation period, HIV screening rates increased in the rapid testing phase (IRR, 1.67; 95% CI, 1.30-2.14) and the rapid testing plus questionnaire phase (IRR, 1.83; 95% CI, 1.60-2.10), with no significant change observed in the control phase (IRR, 1.26; 95% CI, 0.80-1.63). Total HIV diagnoses increased significantly in all rapid testing plus questionnaire (IRR, 2.50) and control groups (IRR, 3.59) compared with the observation period; however, there were no significant increases in new HIV diagnoses

observed in any group, suggesting the need for improved risk stratification to reach undiagnosed individuals.

Long and colleagues (Abstract 159) reported on enhanced opt-out HIV screening and linkage to care across 13 community health centers in the US. From 2021 to 2024, they implemented universal opt-out HIV screening that was integrated into electronic health record workflows, coupled with supported linkage to care services. Across 13 federally qualified health centers in Florida, New

Remnant blood screening in emergency departments identified a third of new HIV diagnoses within a medical system

Mexico, and Puerto Rico in which data were collected, they screened 216,157 individuals for HIV and identified 1948 positive cases (0.9%) including 281 new diagnoses and 1667 who were previously diagnosed but out of care. Overall, 100% of positively diagnosed cases were successfully linked to care, 91% of whom were linked within 30 days of diagnosis. Having a positive HIV screen was associated with being assigned male sex at birth (aOR, 2.32), being non-Hispanic Black (aOR, 2.90), being uninsured (aOR, 1.84), being a current tobacco smoker (aOR, 1.38), having a mental health disorder (aOR, 1.35), and being Creole-speaking (aOR, 2.32), the latter of which was also associated with timely linkage to care (aOR, 4.35). These findings highlight the role of opt-out HIV screening in federally qualified health centers to identify new and previous out-of-care people with HIV and offer a scalable blueprint for nationwide adoption.

Hudon and colleagues (Abstract 160) presented on electronic health record-driven HIV screening in emergency departments (EDs) in the Southeastern US. Beginning in January 2022, they launched a universal HIV screening protocol using remnant blood from standard of care visits across 4 EDs in South Carolina in individuals who had not been tested for HIV in the past year. They created daily electronic health record (EHR) reports of all positive HIV tests in the region (from remnant blood or traditional clinician workup). From January 2022 to December 2023, there were 127 new HIV diagnoses identified, 32 of which were through the remnant blood screening protocol, accounting for 35% of diagnoses within their medical system. New diagnoses via remnant blood screening were more likely

to be among females (31.3% vs 14.7%) and those who reported exclusive heterosexual (50% vs 32.6%) or bisexual activity (28.3% vs 10.5%) than clinician diagnoses. Diagnoses via clinicians were more likely among those who reported exclusive MSM activity (42.2% vs 6.3%) than those via remnant blood diagnoses. Among the 117 individuals with nonacute HIV diagnoses, there were on average 3.8 missed opportunities for HIV screening at prior visits within the past year; among the 10 individuals with acute HIV diagnoses, there were 3.4 missed opportunities for PrEP discussions in the past year. Within their medical system, 97% of new diagnoses were notified of the results, 86% of those aware were linked to care, and 86% of those achieved viral suppression. Based on the success of this program, the researchers recommend expanding remnant blood screening beyond EDs.

Guardiola and colleagues (Abstract 964) reported on HIV detection in EDs using a targeted screening protocol. Between 2021 and 2025, a total of 25 EDs in Catalonia, Spain, implemented an opt-in strategy to test every patient with targeted conditions as recommended by their national Consensus Document (CD). During this period, 47,198 HIV tests were performed, of which 45% were conducted under the CD-defined indications. Overall, 427 new HIV diagnoses were made, for an overall prevalence of 0.90%, with 51% occurring in CD-identified risk conditions, ie, STI (0.8%), chemsex (4.6%), PEP (0.4%), mononucleosis-like syndrome (1.6%), pneumonia (1.2%), and herpes zoster infection (1.4%). At one participating hospital, 58% of patients were linked to HIV care within 1 month, and all patients retained in care achieved virologic suppression.

Sizemore and colleagues (Abstract 965) reported on HIV testing and positivity rates among patients tested for STIs in 2 urban EDs in the US South. From September 2024 to August 2025, a total of 3674 ED patients were tested for STIs. STI positivity rates were higher in the community than in an academic ED setting (23.6% vs 14.3%, respectively; $P < .0001$); however, HIV testing rates were lower in the community than in an academic ED setting (18.3% vs 30.7%, respectively; $P < .0001$). The HIV positivity rate among patients tested for STIs was 12.2% for the academic ED and 7.1% for the community ED. They estimated 10 missed HIV infections in the academic ED and 40 missed HIV infections in the community ED among STI-tested patients who were not tested for HIV. Given the inconsistencies in HIV testing across sites, they recommend universal ED-based routine HIV screening with expanded linkage to care and prevention services.

Bye and colleagues (Abstract 966) assessed the impact of 2 novel clinical decision support tools on rates of HIV

screening in EDs among patients tested for STIs. In January 2024, 11 freestanding EDs in Colorado implemented a comprehensive STI order panel including HIV antigen/antibody testing, syphilis screening, gonorrhea and chlamydia testing, and optional vaginal trichomoniasis testing, and in January 2025, they implemented the Comprehensive STI Agile MD Pathway, which included an STI screening algorithm, the STI Order Panel, guidelines for treatment, and linkage to the infectious diseases clinic for STI, PrEP, and HIV care. HIV cotesting increased from 3% prior to the interventions (2022-2023) to 11.7% after the introduction of the first tool (2024) and to 16.3% after the introduction of the second tool (2025). These improvements were larger in the Denver metropolitan region (increased from 3.4% to 23%) than in the outlying areas (increased from 2.0% to 8.6%). Rates of positive screens in the metro region EDs increased from a baseline of 0.07% to 0.23% in 2025, whereas the rates of positive screens in the outlying EDs were lower and did not increase consistently.

Kyalo (Abstract 161) presented on the use of machine learning to optimize HIV risk prediction and case identification in Eastern Kenya. They applied a machine-learning algorithm with inputs including demographics, STI history, prior HIV testing, and partner characteristics to classify the risk of individuals as low, moderate, high, and very high risk for HIV. In a retrospective analysis of EHR data from 58 health facilities from January 2024 to March 2025, a total of 39,995 individuals were tested for HIV, with an HIV positivity rate of 1.6% ($n=620$). In an adjusted model, individuals in the moderate, high, and very high-risk groups had 2.62, 5.21, and 16.59 higher odds, respectively, of testing positive than in the low-risk group. Patients tested in prevention of mother-to-child transmission service delivery points (aOR, 0.48) and repeat testers (aOR, 0.77) had lower odds of testing positive.

Raji and colleagues (Abstract 1122) reported on the effectiveness of integrated community testing campaigns to increase testing coverage and case detection among pregnant women in Nigeria. In 2024, they implemented community-based HIV and syphilis testing in nonfacility settings (eg, traditional birth attendants, faith homes, and other community settings). In 2023 (baseline), 2,810,560 pregnant women were tested in facilities, with a 0.29% HIV positivity rate and 0.17% syphilis positivity rate. In 2024, community testing reached 407,302 pregnant women, with an HIV yield of 0.21% and syphilis yield of 0.49%, contributing an additional 11% of cases that were HIV positive, and in 2025, a total of 640,917 pregnant women were tested, with an HIV yield of 0.23% and syphilis yield of 0.28%, contributing an additional 18% of cases that were HIV positive. Detection of coinfections also

increased from 43 to 158 for HIV/hepatitis B virus (HBV) coinfections and 29 to 99 for HIV/HCV coinfections. These findings suggest that scaling community-based HIV and syphilis testing could facilitate dual HIV/syphilis elimination in Nigeria.

In a themed discussion, several researchers investigated the use of HIV self-testing to increase testing, identify new diagnoses, and reach untested individuals. De Nooy and colleagues (Abstract 975) used routine data to identify where HIV self-screening would have the biggest impact in

Motorcycle-taxi drivers successfully delivered HIV self-tests in their social networks and identified 177 new positive cases in Kampala, Uganda

South Africa. HIV self-test distribution was associated with 2.3 additional positive results per 100 tests, compared with 3 additional positive results per 100 tests for facility-based tests. The largest impact was observed through community distribution of HIV self-tests, in lower- and middle-prevalence districts, and in those with high treatment gaps. Namulema and colleagues (Abstract 974) reported on the use of HIV self-testing distributed by motorcycle-taxi drivers in Kampala, Uganda. They trained 6 motorcycle-taxi drivers to distribute HIV self-tests and provided testing education and support to fellow drivers, passengers, night food vendors, sex workers, and other community contacts. Individuals who tested negative were provided information about PrEP and male circumcision, and individuals who tested positive were escorted to the facility for confirmatory testing, partner notification, and linkage to care. Over a 12-month period, 2409 kits were distributed by the drivers and 97% of kits were utilized. There were 177 individuals (8%) with positive results, and upon facility testing, 25 were false positives, 13 declined confirmation, and 139 (6%) were confirmed positives. Through assisted partner notification, 147 partners were tested, of whom 32 (22%) were identified as new positive partners. These findings highlight the power of leveraging community and social networks to increase the reach of testing.

Closs and colleagues (Abstract 976) presented on the use of vending machines as stigma-free access points for HIV and syphilis testing and condoms in Memphis, Tennessee, which ranks second in the US for new HIV diagnoses. From May to August 2025, they deployed 3 stigma-free

safer sex vending machines in a public library; a lesbian, gay, bisexual, transgender, queer, and other gender identities and sexual orientations (LGBTQ+) bar; and a university setting. Participants completed an online questionnaire, received free access to HIV/syphilis tests and condoms, and had follow-up with a case manager 1 week later. In the first 100 days of deployment, they reached 326 unique individuals from 62 zip codes; 49% were Black females, 42% were between the ages of 25 and 34 years, and 29% had not tested in the past year. There were 2 new diagnoses that were linked to care and 17 PrEP appointments were scheduled. These findings suggest that vending machines are a scalable, community-centered strategy to promote HIV prevention and sexual health.

Knights and colleagues (Abstract 910) reported on new HIV diagnoses in a county jail in Dallas, Texas. In a retrospective review of EHR data, there were 200 individuals newly diagnosed with HIV at the jail from 2015 to 2023, and rates significantly increased after a systematic, opt-out HIV testing program was implemented in 2020. Among people newly diagnosed with HIV in the jail, 43% reported heterosexual sex as their HIV risk factor, 66% reported active substance use, 44% had a bacterial STI, and 26% had unstable housing. Rates of new HIV diagnosis in the jail were 3-times the county rate and 9-times the national rate. The median CD4+ count at diagnosis was 529 cells/ μL , suggesting that most diagnoses were made early in the disease course. These findings highlight the urgent need for comprehensive HIV testing in correctional settings.

Balasubramanian and colleagues (Abstract 886) reported on the potential impact of ending funding by the US Centers for Disease Control and Prevention (CDC) for HIV tests. Using the Johns Hopkins Epidemiologic and Economic model, they projected incidence forward under 2 scenarios where all CDC-funded HIV testing ends in February 2026, and (1) never resumes, and (2) returns to

Barbershop-based HIV interventions can increase HIV testing and reduce HIV stigma

previous levels from January to December 2029. Across 25 states, they projected 12,714 additional infections by 2030, 10% more infections than if testing had continued. If testing resumed in January 2029, they estimated 10,397 excess infections, or 8% more infections than if testing had continued. They predicted more excess infections

in states that perform more CDC-funded tests and have more rural HIV epidemics. Additionally, the proportion of people who can find an alternative means of testing impacted protected excess incidence; they projected 5% more infections if more than two-thirds found alternative testing, and 16% more infections if fewer than one-third were able to find an alternate test. These findings highlight the value of CDC testing activities in reducing HIV transmission in the US.

Novel Interventions

Two presentations reported on the feasibility and early outcomes of barbershop-based HIV interventions. Lukyamuzi and colleagues (Abstract 1064) implemented a barbershop-based HIV prevention intervention in fishing communities in Uganda in the HIV Prevention Trials Network (HPTN) 111 study. Barbershops were randomly assigned 2:1 to the intervention or standard of care (referral to routine HIV prevention at HIV care centers). Intervention barbers were trained to deliver status-neutral HIV education, distribute HIV self-test kits, and facilitate peer support discussions. From March to June 2024, barbers recruited 250 male clients (median age, 29 years; 75% reported transactional sex in the past 3 months), and barber delivery of the intervention components was high, with 100% of participants in the intervention arm receiving HIV education, 92% taking a self-test kit, and 99% attending a peer group discussion. Feasibility and acceptability of the barber intervention were high, and participants in the intervention arm were more likely to report self-initiated HIV testing (81% in the intervention vs 33% in the standard of care arms; $P < .001$).

Perkins and colleagues (Abstract 1065) presented on Cutting Out Stigma, a barbershop-based education and multimedia intervention in Tennessee. In a 6-month pilot trial, they trained 50 barbers as men's health ambassadors to provide sexual health education, refer clients to HIV services, and share social media posts to reduce HIV stigma. There was broad reach within barbershops (733 patrons/month) and on social media (25,670 people/month), and a substantial number of resource referrals (533 referrals/month). HIV and PrEP knowledge of barbers increased after the intervention. In a mixed-methods analysis, barbers expressed high enthusiasm and reported personal and community benefits. These results suggest that barbershops can be scalable, community-based settings to reduce stigma and promote sexual health in Black communities in the South.

Mancuso and colleagues (Abstract 1072) assessed the impact of school-based HIV prevention for adolescent

mothers across 8 countries in East and South Africa. In a pooled analysis of 2810 adolescent mothers aged 15 to 19 years in the Population-Based HIV Impact Assessment surveys from 2019 to 2022, 10% of adolescent mothers reported receiving school-based HIV prevention programs in the past year. Increasing exposure to these programs was estimated to reduce condomless sex overall, but had minimal impact on PrEP interest, possibly due to variation in PrEP availability and high baseline interest in PrEP.

Agbaje and colleagues (Abstract 973) reported on the impact of peer-led microplanning for HIV prevention among adolescent girls and young women (AGYW) in Nigeria. Through a Global Fund grant, they implemented structured microplanning strategies, which included risk-stratified outreach, safe-space sessions, and participatory accountability with voices from support group sessions. Services provided included PrEP eligibility screening, HIV testing, referrals for gender-based violence, and ART initiation. From December 2024 to August 2025, they reached more than 1.6 million AGYWs with the peer-led microplanning intervention. Community-based testing achieved high coverage with a 0.13% HIV positivity rate, whereas facility testing had a 5-fold higher yield with a 0.65% positivity rate. Young women aged 20 to 24 years accounted for 77% of the 434 AGYWs who tested positive, and all were successfully linked to care.

Beloumou and colleagues (Abstract 1067) assessed the impact of an HIV prevention "social vaccine" on HIV testing in Cameroon. They used the Risk Communication and Community Engagement framework to implement HIV education and testing focused on students, teachers, tutors, and community leaders in high-prevalence regions, and 24 multimedia centers were established in participating communities to support these efforts. Between 2019 and 2023, they enrolled 1203 participants (median age, 18 years) across 45 localities. Overall, the HIV test acceptance rate was 98% and the HIV positivity rate was 1.4%. Individuals with positive tests were older, with the highest rates in those aged 30 to 39 years. Participants in rural areas had the highest positivity rates.

Heise and colleagues (Abstract 1073) examined the impact of state legislation allowing pharmacist dispensation of PrEP in California. In October 2019, California State Bill 159 (SB159) was introduced and broadened the authority for pharmacists to prescribe PrEP without physician approval. Using a claims-based dataset of PrEP prescriptions in an interrupted time series analysis, they observed a significant increase in pharmacist-prescribed PrEP from a median of 4.5 to 12 pharmacists per quarter from before to after SB159 implementation. However, PrEP prescriptions plateaued following SB159 implementation, with the

growth rate decreasing from 7% to 1% per quarter among males. The researchers posit that this limited impact may have been due to inadequate pharmacist training, restrictions preventing prescription continuation, barriers to laboratory testing, difficult reimbursement pathways, and COVID-19 health care disruptions. Although shelter-in-place orders were associated with an initial 33% reduction in HIV diagnoses, these rebounded to 13% above prepandemic levels by late 2021. In 2024, new legislation (SB339) was enacted to address barriers identified in SB159, including authorizing follow-up PrEP prescribing by pharmacists and ensuring insurer coverage of pharmacist-furnished PrEP.

Haberer and colleagues (Abstract 1079) described the use of natural language processing of WhatsApp messages to identify unrecognized HIV prevention needs among young women in Kenya. They used this artificial intelligence method, which can extract meaning and subjective information from text, to analyze deidentified WhatsApp messages from 413 young women (median age, 22 years) from 4 clinical sites in Kenya. They calculated the VOICE (Vaginal and Oral Interventions to Control the Epidemic) HIV risk score based on questionnaire responses and determined that the median VOICE risk score was 7 for women who most often messaged a sex partner vs 5 for those who most often messaged a friend. Topics discussed correlated with the VOICE risk score, which was highest for romance/affection topics and lowest for faith/positivity and transactions/family topics. The researchers suggest that future app development with natural language processing could alert people to their risk and guide them to seek HIV prevention services.

Green and colleagues (Abstract 1099) reported on the impact of an EHR intervention to improve linkage to comprehensive HIV prevention services in Arkansas. Within a multisite, federally qualified health center serving rural populations, they implemented an optimized EHR workflow that included standardized eligibility identification criteria, reporting tools to identify eligible patients, and workflow integration involving pharmacists to support referrals to prescribing services. In the year prior to implementation, 10,894 individuals tested negative for HIV and were assessed for eligibility for linkage to comprehensive HIV prevention services, but only 561 (5.1%) were identified as eligible; of those, 29 (5.2%) were linked to prescribing services. After implementation, 10,735 tested negative and 8778 (81.8%) were identified as eligible; of those, 6934 (79%) were linked to prevention services. These findings suggest that EHR-driven workflows and pharmacist-integrated care models can help expand access to comprehensive HIV prevention services.

Preexposure Prophylaxis

Oral PrEP

Molina and colleagues (Abstract 127) reported on the final results of the ANRS PREVENIR (Prevention of HIV in “Île-de-France”) study of daily vs on-demand coformulated tenofovir disoproxil fumarate (TDF) and emtricitabine

HIV incidence was very low and similar whether MSM chose daily or on-demand TDF/FTC

(FTC) PrEP for MSM and transgender women (TGW) in Paris, which took place from May 2017 to May 2025. The main goal of the study was to evaluate the impact on the number of new diagnoses among MSM and TGW in the Paris region; secondary outcomes were uptake of the 2 regimens and safety and tolerability. They enrolled 3209 individuals, of whom 99% were MSM and only 14 were TGW; 82% were French-born. Although they reported a median of 10 partners in the prior 3 months at baseline, they reported a median of only 2 condomless sex acts in the prior 4 weeks. Participants were allowed to choose daily vs on-demand PrEP and to switch between regimens. At baseline, approximately half chose on-demand PrEP, and that number remained relatively constant over time. By 3 years, more than half of either group had switched to the other regimen at least once. They measured 13 breakthrough infections: 7 taking predominantly on-demand dosing, 3 taking predominantly daily dosing, and 3 spending approximately half of the time on either regimen. Overall incidence was 0.1% per year, with no significant difference between groups. Gastrointestinal adverse effects in the on-demand group were almost twice as frequent as those in the daily group (4.5% vs 2.3%, respectively), but discontinuation due to drug-related adverse effects was low (0.3%/year). During that time, there was a steady increase in the number of people taking PrEP in the Paris region, peaking at more than 25,000 by 2025. Although the number of new HIV infections in the Paris region decreased significantly among MSM born in France (–33%), there was a significant increase in the number of new infections among MSM born outside of France (+73%) and among TGW (+95%). This suggests a focused need for PrEP delivery to these populations.

Injectable PrEP

Ndlovu and colleagues (Abstract 128) presented data from the end of the randomized blinded phase of PURPOSE 1

(Preexposure Prophylaxis Study of Lenacapavir and Emtricitabine/Tenofovir Alafenamide in Adolescent Girls and Young Women at Risk of HIV Infection), a phase III randomized clinical trial of injectable LEN vs oral PrEP in cisgender women aged 16 to 25 years in sub-Saharan Africa. Among 2134 participants receiving LEN, there were 2 new HIV acquisitions compared with a total of 77 HIV

Breakthrough infections were exceedingly rare in all genders receiving lenacapavir

acquisitions in the 2 oral PrEP arms (FTC/TAF and FTC/tenofovir disoproxil fumarate [TDF]), a 96% reduction in HIV acquisition compared with FTC/TDF. Of the 2 participants acquiring HIV, 1 was positive for HIV at week 65, but the week 52 stored sample showed a very low level of HIV-1 RNA, despite on-time injections and LEN blood levels in the expected range and above the predicted protective threshold. The other participant had discontinued LEN injections and switched to open-label FTC/TDF; she had a high viral load (134,000 copies/mL) at week 95, 16 months after her last LEN injection, and a very low levels of LEN in her blood. There were no new safety concerns and no additional discontinuations due to injection-site reactions (ISRs) compared with the previously reported results. These data reinforce the very high levels of efficacy of LEN used as PrEP in this population.

Cantos and colleagues (Abstract 129) presented data from PURPOSE 2 (Study of Lenacapavir for HIV Pre-Exposure Prophylaxis in People Who Are at Risk for HIV Infection), a phase III randomized clinical trial of injectable LEN vs oral FTC/TDF in MSM and transgender and nonbinary participants globally. There was 1 new HIV acquisition to add to the 2 previously reported, resulting in an overall efficacy of 88% compared with FTC/TDF. This 1 new acquisition occurred despite on-time injections and LEN levels on par with levels seen in other participants. The acquisition was diagnosed at week 52 with a positive antigen/antibody test and a viral load of greater than 2 million copies/mL. There was no delay in diagnosis. In this study, there were no new safety concerns and no additional study discontinuations due to ISRs. Similar to PURPOSE 1, this study reinforces the high efficacy of LEN in this population.

Cox and colleagues (Abstract 130) presented data on resistance among breakthrough infections from participants randomly assigned to LEN in PURPOSE 1 and 2. Of

the 5 total infections between the 2 studies, 3 participants had the N74D mutation and 1 participant had Q67H and K70R mutations. The fifth participant was on FTC/TDF at the time of HIV acquisition and had no resistance mutations detected. The authors postulated that the capsid mutations seen were due to ongoing monotherapy with LEN rather than from transmitted drug resistance. To support this hypothesis, they presented data from more than 24,000 samples in the Los Alamos database, of which only 4 had N74D. There were no N74D mutations in another database of nearly 1500 samples across various clades. Among the 89 infections acquired in the 2 studies on FTC/TAF or FTC/TDF, only 5 had resistance mutations to these agents, with the majority from suboptimal adherence. The authors reinforced that HIV acquisition was rare among those on LEN and posited that the resistance mutations seen were from monotherapy on LEN.

Tao and colleagues (Abstract 1062) presented data on real-world medication use and potential interactions with LEN for PrEP. Using a national US database of prescription drugs, they concluded that 83% of PrEP users were taking concomitant prescription medications in 2024. Among

Isolated false-positive RNA testing may occur with long-acting cabotegravir

those, only 0.5% of PrEP users had concomitant use of a strong or moderate CYP3A inducer that would require a LEN dose modification. Fewer than 13% of users had concomitant use of a sensitive CYP3A and a P-glycoprotein substrate that would require monitoring for adverse effects or dose modification when taken with LEN. The most common drug was erectile dysfunction medication (11%). The authors found it reassuring that drug-drug interactions may affect only a minority of PrEP users.

Parikh and colleagues (Abstract 986) presented data on diagnostic outcomes after detectable HIV-1 RNA level in persons on long-acting cabotegravir (CAB-LA) from the SeroPrEP (Seroconversion on PrEP) study. Those on CAB-LA were referred to the study from US clinics if they had a reactive HIV-1 RNA test with a nonreactive antigen/antibody test. Of 9 male participants in this analysis, 8 participants had a single detectable HIV-1 RNA level on clinical testing. Subsequent HIV-1 RNA testing was negative, indicating that these individuals had not acquired HIV. One participant had 2 positive HIV-1 RNA tests and was subsequently determined to have acquired HIV. The

authors suggest that more than 1 positive HIV-1 RNA test may indicate HIV acquisition, but that larger studies are needed.

Parikh and colleagues (Abstract 987) also reported on characterization of HIV acquisition on CAB-LA from the ImPrepCab Brazil (Implementation of Preexposure Prophylaxis of Injectable Cabotegravir) study. They diagnosed 4 HIV acquisitions among 1220 participants on CAB-LA. Of the 4 newly acquired infections, 3 had HIV-1 RNA level below 1000 copies/mL at diagnosis and delayed antibody detection (2-9 months after the first detectable HIV-1 RNA level). Major integrase strand transfer inhibitor (InSTI) mutations were observed in only 1 participant despite ongoing use of CAB-LA prior to HIV confirmation. The authors reiterated the high effectiveness of CAB-LA in preventing HIV acquisition but underscored the need for sensitive point-of-care diagnostics and additional data on responses to InSTI-based treatment in these clinical scenarios.

Fox and colleagues (Abstract 988) reported on a randomized crossover design trial comparing the acceptability and objective measures of ISRs of 1 CAB-LA dose vs 1 LEN dose among 63 participants. They report that participants experienced fewer ISR events after CAB-LA than after LEN injections (nodules, 57% vs 100%, respectively; induration, 20% vs 87%, respectively; and swelling, 36% vs 60%, respectively). ISRs also resolved more quickly after CAB-LA than after LEN injections (6% vs 82%, respectively, had nodules >180 days). Participants were queried at day 190 about the acceptability of local reactions and pain and CAB-LA was more likely to be considered “very or totally acceptable” (70% vs 37% with LEN). Overall, 85% of participants indicated a preference for CAB-LA over LEN at day 190. However, there are several caveats to this study. This ViiV-funded study did not provide information on methods of LEN administration, such as whether or not ice was used to reduce the pain associated with injections. Also, the regimen was a single injection and did not therefore replicate ISRs and acceptability of the different regimens in real-world practice.

Caruso and colleagues (Abstract 1003) presented data on weight change after CAB-LA initiation among PrEP-native users and those switching to CAB-LA from daily TDF/FTC. They followed 171 participants receiving CAB-LA for PrEP (86% of whom were taking daily TDF/FTC at CAB-LA initiation) through 4 injections. Mean weight change was +0.3 kg (range, -9 to +12 kg) among switchers and -0.3 kg (range, -10 to +5 kg) among those new to CAB-LA, with a median weight change across both groups of 0.0 kg. It is reassuring that neither group appeared to have weight change as a result of CAB-LA initiation.

PrEP Awareness, Willingness, and Uptake

Jones and colleagues (Abstract 939) presented data from the American Men’s Internet Survey (AMIS) from the 2021, 2022, and 2023 cycles. Of the nearly 16,000 men who participated across the 3 cycles, almost all were aware of daily oral PrEP, and although awareness of on-demand and CAB-LA PrEP increased, it remained below 50% for both. Oral options were most preferred. Among those who had used PrEP in the past 12 months, only 1.4% and 3.5% reported CAB-LA use in 2022 and 2023, respectively. Black MSM were more likely than White MSM to report CAB-LA PrEP use (OR, 2.3) and rural MSM were less likely than urban MSM to use CAB-LA (OR, 0.4). The authors stated that previous studies indicated a strong preference for CAB-LA among rural MSM, so the lower use may represent access, delivery, clinician, or information barriers that disproportionately affect rural communities.

Mi and colleagues (Abstract 942) presented data on the interaction of health care stigma with state-level health care policies related to sexual orientation and gender identity among more than 5500 TGW participating in the TWIST study. Half of the participants reported experiencing health care stigma, which they defined as the perception, anticipation, or experience of sexual behavior or gender identity stigma in the context of health care in the prior 12 months. Only 9% of the participants were on PrEP in the previous 12 months. In states with more

PrEP awareness and uptake remain low among PWID

protective policy environments, there was no association of health care stigma with PrEP use. However, among states with more harmful policy environments, health care stigma was associated with a decreased likelihood of PrEP use (aOR, 0.70). The authors suggested that interventions to reduce stigma are likely to be most effective when implemented at a state-specific policy level.

Traver and colleagues (Abstract 1115) reported on baseline data from an ongoing randomized clinical trial comparing integrated infectious diseases and substance use disorder outpatient care vs treatment as usual at 4 sites in the US South. They noted that of 142 PWID hospitalized with acute bacterial or fungal infection, 38% met criteria for initiating PrEP, but none were on PrEP. PrEP awareness was below 50% and PrEP interest was just above 50%. Of all 47 persons interested in PrEP, common reasons for not using PrEP included not feeling at risk (40%), lack of prior PrEP

awareness (28%), and lack of health care clinicians offering it (13%). The authors suggested that health care clinicians offer PrEP during and after hospitalization for PWID.

Hull and colleagues (Abstract 1002) presented data on awareness and preferences for PrEP among PWID in Vancouver, Canada. They recruited 359 participants from 6 addiction and primary care clinics, of whom 293 reported drug use in the past 6 months. In this study, PrEP awareness was only 24% among PWID, despite the existence of a public PrEP program for 6 years in British Columbia that includes indicators for use in PWID. Despite low knowledge, willingness to use PrEP was 67% and approximately 63% expressed a preference for every-6-month and every-2-month injectable PrEP over oral PrEP. Preference for every-6-month PrEP was higher among those with unstable vs stable housing (aOR, 1.76), but surprisingly was lower among persons injecting numerous times per day than in those injecting daily or less often (aOR, 0.55). The investigators called for advertisements for injectable medications to be tailored for persons with unstable housing and advertising for oral PrEP to be tailored for those with more frequent drug use.

Lukyamuzi (Abstract 984) presented data on the interest in LA PrEP among men in the Kalangala Islands in Uganda, a setting with high heterosexual HIV transmission. Of 239 participants queried at the end of a 52-week

Dose adjustments are not needed for CAB-LA in pregnancy

study, 94% expressed interest in LA injectable (LAI) PrEP. LEN was more preferred than CAB-LA (47% vs 18%, respectively), although 28% stated they liked both options equally. When asked about interest in taking a monthly pill for prevention, 93% also stated they were interested. Preference for LAI PrEP was higher than for a monthly pill (43% vs 17%, respectively), although 38% stated that they liked both options equally. The authors suggest that implementation and future PrEP trials should prioritize this population and examine actual uptake and sustained use.

PrEP in Pregnancy

Marzinke and colleagues (Abstract 789) and Ford and colleagues (Abstract 790) presented a pharmacokinetic analysis that indicated that dose adjustments for CAB-LA are not required for pregnant women. Both groups evaluated data from 75 women in the HPTN 084 (A Phase 3

Double Blind Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Preexposure Prophylaxis in HIV-Uninfected Women) trial who continued CAB-LA during pregnancy. They reported that from the prepregnant period through the third trimester, there was a median 26% reduction (IQR, 2-40) in total CAB C_{trough} concentrations. However, 98% of unbound CAB concentrations remained above the unbound pharmacologic threshold for protection. Therefore, no dose adjustment is needed for pregnant persons at initiation or follow-up of CAB-LA injections.

Hannan and colleagues (Abstract 810) reported on HIV incidence and oral PrEP effectiveness in pregnant and postpartum South African women. Of the 1920 pregnant women enrolled, only 14% were on oral PrEP and only 23% ever used PrEP during follow-up, despite having oral PrEP routinely offered during antenatal care. They recorded 24 incident infections (incidence rate [IR], 1.61/100 person-years) and the incidence was highest in women aged younger than 24 years (IR, 2.36). Only 1 of these infections occurred in a woman on PrEP, indicating a 76% reduction in HIV incidence among women on PrEP. Incidence was highest in the prenatal period. This suggests that more intensive programs are needed to provide pregnant women with PrEP during the prenatal and postpartum periods.

Namale and colleagues (Abstract 811) reported on PrEP uptake among pregnant and breastfeeding women in 6 high-volume facilities in Kampala, Uganda. Among 3258 women, 87% accessed PrEP. Uptake was significantly lower among women reporting partner violence than in those without partner violence (17% vs 89%, respectively; $P < .001$). Uptake was also lower among women with partners with HIV than in those with partners without HIV or with unknown serostatus (48% vs 74% vs 88%, respectively; $P < .001$). In adjusted analyses, those who were married/cohabiting (aPR, 1.34), single/never married (aPR, 1.36), and separated/divorced (aPR, 1.36) were more likely to use PrEP than other categories. However, PrEP uptake was less likely among women who reported partner violence (aPR, 0.24) than in those who did not. The authors suggested that these data support the integration of violence screening and referral within antenatal and postnatal care.

Ngumbau and colleagues (Abstract 812) presented data on PrEP use trajectories among women initiating PrEP in pregnancy. Among 600 pregnant women vulnerable to HIV who were initiating daily oral PrEP as part of a randomized clinical trial in Western Kenya, 52% discontinued PrEP at least once before 9 months postpartum; median time to first discontinuation was 5.8 months. Women were more likely to discontinue PrEP if they experienced stillbirth or

neonatal loss (RR, 2.56), started antenatal care in their second trimester (HR, 1.61), were primigravida (HR, 1.40), or experienced adverse effects (HR, 1.66). They were less likely to discontinue PrEP if they had high pill-taking self-efficacy (HR, 0.28) or if they had self-perceived HIV risk that was moderate (HR, 0.45) or great (HR, 0.08). The authors called for interventions that enhance self-efficacy and refine risk perception for pregnant women.

Oguttu and colleagues (Abstract 815) evaluated the uptake of CAB-LA PrEP when offered to postpartum women in Botswana immediately after delivery. Of 951 women who met epidemiologic HIV risk criteria (aged 18-30 years, or older than 30 years with fewer than 3 pregnancies) and had no contraindications to participating in the study, 500 (approximately half) chose to initiate CAB-LA and enroll in the study. Of these, only 14% had taken PrEP previously, 52% had any history of condom use, 62% had at least 1 partner 5 or more years older than them, 71% thought they had at least some risk of getting HIV in their lifetime, and 32% stated that their baby had at least some risk of getting HIV. The authors concluded that maternity wards are a practical and strategic entry point for initiating CAB-LA PrEP in young women, based on epidemiologic criteria and not individual risk factors.

From the same study, Shava and colleagues (Abstract 814) conducted a substudy in 20 CAB-LA acceptors and 20 decliners among 40 postpartum women. Acceptors and decliners had similar perceptions of HIV risk and reported sexual behavior. However, despite acknowledging that injectable PrEP can be more private than oral PrEP, there were differences in self-perceived family support (95% of acceptors vs 30% of decliners), friend support (90% of acceptors vs 70% of decliners), and concerns about partner problems due to PrEP disclosure (35% of acceptors vs 95% of decliners). They concluded that anticipated support from partners and family remains crucial for the uptake of PrEP, despite the increased privacy of an injection. They called for shifts in policy and culture, addressing stigma, and increasing PrEP knowledge.

PrEP Rollout

Hill and colleagues (Abstract 162) presented global data on the PrEP-to-need ratio (eg, the number of persons on PrEP for every new HIV infection in that country). He pointed out that with a background HIV incidence of 2.4 per 100 person-years, which describes many key populations globally and was seen in the PURPOSE I and II trials of LEN, 41 people given LEN were needed for each infection averted. However, with the cut in US aid, he pointed out substantial reductions in PrEP use from the beginning through the end of 2025, ranging from a 7% reduction in

Kenya to a 98% reduction in Nigeria. UNAIDS modeling suggests that there will be an increase from the current 1.3 million new HIV infections per year to 1.45 million new infections by 2030, given these cuts. Hill then went on to calculate the PrEP-to-need ratio for countries around the world. Only 4 countries achieved a PrEP-to-need ratio of

PrEP is having no-to-low effect on HIV incidence in low- and middle-income countries

more than 40: Norway, Australia, Denmark, and the UK. An additional 10 countries achieved 10 to 40 people on PrEP per HIV acquisition, including the US, Canada, and several European countries. He stated that 42 countries had 1 to 10 people on PrEP for every HIV acquisition, including Mexico, Brazil, other countries in Europe, and South and East Africa. Finally, 126 countries distributed fewer than 1 PrEP prescription for each acquisition, and these countries were widespread throughout the world. There are only 2.3 million people estimated to be on PrEP, whereas the UNAIDS target is 21.2 million. Of the 2.3 million, he estimated that 96.3% were on oral PrEP, with only 2.9% on CAB-LA and 0.9% on LEN. Therefore, he stated that PrEP is having no-to-low impact on HIV incidence in low- and middle-income countries (LMICs). However, ART has been broadly distributed throughout the world, so the same should be able to be done for PrEP. He called for the following: \$500 million for the first 10 million doses of LEN for LMICs; bringing the price down to less than \$1000 per year for injectable PrEP for countries outside the voluntary licensing agreement; task shifting, HIV self-testing, and same-day PrEP initiations for implementation; and re-opening clinics for key populations globally.

In a related poster, Cross and colleagues (Abstract 943) conducted mathematic modeling to estimate how many people would need to be on LA PrEP to achieve a substantial impact on the worldwide epidemic. They estimated that 2025 CAB-LA uptake was preventing only approximately 1700 new infections per year, and 2025 LEN uptake averted approximately 85 infections. They estimated that we would need 10 million persons in LMICs to take LA PrEP to reduce HIV acquisitions by 250,000 per year, but that will not happen unless it becomes affordable, including a cost of less than \$1000 per year in high-income countries.

In a different model, Gelderblom and colleagues (Abstract 991) projected that we would need 10 million

more people with HIV on treatment (to achieve “undetectable=untransmissible,” or U=U) or 100 million people on PrEP or a combination of both to reduce new infections by 1 million annually. They stated that nearly half of new infections globally occur in people not typically targeted for PrEP programs, and thus we would need numerous LA PrEP options and ultimately a vaccine to stop the HIV pandemic.

Moore and colleagues (Abstract 1087) presented modeling data on the impact of scaling up LEN use in the US. They looked at 2 scenarios: (1) status quo without changes in PrEP use from 2025; and (2) an increase in LEN use by 37%. In comparing 2017 with 2030, they found that the status quo would lead to a reduction in new infections by 15%, but with increased LEN, there would be an estimated reduction in new infections by 25% or an additional 13,700 infections averted. However, neither scenario would achieve the EHE goal of reaching a 90% reduction by 2030. Moreover, progress toward the EHE goals was lowest among those who were heterosexual, uninsured, aged 13 to 24 years, or living in the Northeast or South. The best modeling scenario they presented was if PrEP use increased and all PrEP users were on LEN, which would lead to a 38% reduction by 2030. The authors called on prioritizing those at greatest need to achieve the greatest

Only 4% of all PrEP prescriptions were for CAB-LA from its licensure through 2024

impact on new HIV infections in the US.

Preer and colleagues (Abstract 978) presented US data on PrEP uptake using EHR data from almost 820,000 persons using PrEP in the US from 2012 to 2025. TDF/FTC was most commonly used (77%), followed by TAF/FTC (21%), CAB-LA (1.4%), and LEN (0.1%). The average age at PrEP initiation was 36 years. Geographically, 93% of PrEP users resided in urban areas and less than 6% in rural areas, despite the fact that 13% to 20% of the US population resides in rural areas. By Social Vulnerability Index (SVI), 41% of PrEP users were in the highest quartile and only 12% were in the lowest quartile. This suggests that more interventions are needed to increase PrEP uptake among persons residing in rural and low SVI areas.

Koh and colleagues (Abstract 1059) evaluated different types of PrEP uptake in more recent years (January 2022–December 2024) using pharmacy and medical claims

from a US national claims database. During this more recent period (after CAB-LA was licensed in the US), only 4% of all 361,000 PrEP users were CAB-LA users. Medicaid coverage was higher among CAB-LA users than oral PrEP users (26% vs 14%, respectively). They also found that CAB-LA retention in care was only 56% at 1 year of follow-up and 26% at 2 years of follow-up. The authors suggested that as new LAI-PrEP modalities are rolled out, barriers should be proactively identified and addressed.

Krakower and colleagues (Abstract 885) presented modeling data on the potential impact of over-the-counter (OTC) TDF/FTC PrEP for MSM in the Atlanta metropolitan area. They concluded that if OTC PrEP resulted in a 10% increase in PrEP coverage, it would avert 3.2% of HIV infections over 10 years; a 50% increase would avert 15.4% of new infections. This would be accompanied by an increase from 2.5% (if PrEP were available by prescription only) to 4.8% (50% coverage) in the proportion of PrEP users with glomerular filtration rates below 60 mL/min; an increase in HBV reactivations from zero to 2.27 per 100 person-years among people with HBV infection, and an increase in FTC resistance from 0.68 to 8.4 events per 100 incident infections. The authors concluded that OTC PrEP could produce meaningful population-level HIV prevention benefits if it expanded beyond clinic-based care but suggested that HIV testing at PrEP initiation and targeted renal monitoring should be promoted.

Cannon and colleagues (Abstract 190) evaluated the population-level effectiveness of PrEP among cisgender men and transgender and nonbinary persons who have sex with men with a prior STI in King County, Washington. They evaluated HIV infection rates among persons diagnosed with gonorrhea or syphilis from January 2014 through June 2024 who were HIV negative and followed them for HIV seroconversion over time. There was an overall reduction in new HIV diagnoses over that time of 7% per year. They also found that HIV infection rates were higher among those aged 15 to 19 years and some people of color (American Indian/Alaska Native, Black, Native Hawaiian/Pacific Islander, multiracial). However, after adjusting for age, race, STI diagnosis, and calendar year, those who reported having taken PrEP had a 50% lower rate of HIV infection than those who had not taken PrEP (0.46/100 person-years vs 1.14/100 person-years, respectively). However, Black persons on PrEP did not have a substantial decline in incidence compared with those not on PrEP (1.2/100 person-years vs 1.4/100 person-years, respectively), although there were only 26 Black persons in the study, so these results must be interpreted with caution. Nonetheless, the authors point out that PrEP access alone is insufficient, and that other

support tools may be needed to increase PrEP effectiveness in populations.

Hsu and colleagues (Abstract 979) presented data on CAB-LA use in the OPERA (Observational Pharmacoepidemiology Research and Analysis) cohort, an extraction of EHRs from 101 clinics in 23 US states and territories. During the first 3 years of CAB-LA PrEP use in the US, 1748 people received at least 1 CAB-LA injection. CAB-LA recipients had a median age of 33 years, 11% were women, and 9% were transgender. Race/ethnicity was 27% Black, 29% Latino, and 51% White. Of those receiving CAB-LA injections, 88% completed initiation but one-third discontinued CAB-LA during the study period, of whom 28% reinitiated CAB-LA after a median gap of 7 months. Of those receiving maintenance injections, 59% adhered to the recommended dosing schedule, and most injection delays were short. The team reported only 2 cases of HIV acquisition on CAB-LA, each of whom had received on-time injections. One of these was diagnosed 3 months after initiating CAB-LA, without a baseline HIV test. The second was diagnosed 21 months after initiation. An additional 2 patients acquired HIV after CAB-LA discontinuation. The authors concluded that breakthrough infections are rare on CAB-LA in real-world settings, and that discontinuation and reinitiation patterns suggest continued interest in CAB-LA PrEP.

Another presentation by Barnett and colleagues (Abstract 980) from the OPERA cohort compared PrEP coverage and HIV acquisition between CAB-LA users (1664) and oral PrEP users (38,329). PrEP coverage, defined as continuous use of CAB-LA or oral PrEP, was substantially higher among CAB-LA users (median, 93%) than in oral PrEP users (median, 58%). In this analysis, they reported an incidence rate of 0.09 per 100 person-years in persons on CAB-LA vs 4.9 per 1000 person-years in persons on oral PrEP (IRR, 5.4). However, the authors emphasized the importance of choice, as there were switches between the 2 regimens.

Elion and colleagues (Abstract 981) presented real-world data on CAB-LA use from the Trio Health Cohort, also drawn from EHRs from many clinics. Of nearly 1700 adults who initiated CAB-LA from December 2021 through February 2025, 89% completed initiation and 36% discontinued, of whom 14% reinitiated within 6 months. They reported 3 infections among those in this cohort. One was diagnosed after 7 on-time injections. A second person missed their second injection but otherwise received on-time injections and was found to have acquired HIV at their tenth injection. The third individual was diagnosed at their second injection and did not have HIV testing at initiation; therefore, this person could have already been infected when initiating CAB-LA. The first 2 patients did not have any resistance mutations; the third person was

not tested. This again reinforces the high effectiveness of CAB-LA as well as the idea that a number of reasons could account for the discontinuation rates.

Corma-Gomez and colleagues (Abstract 1060) evaluated oral PrEP persistence and discontinuation among a multicenter cohort of 3200 men and women in Spain. Although PrEP is publicly funded and provided free of charge in Spain through the national health system, the investigators determined that the probability of continuing oral PrEP at 1 year was 77% and at 3 years was 55%. Discontinuation was higher among those aged younger than 39 years (aHR, 1.64; $P < .001$), among women engaged in transactional sex (aHR, 3.19; $P < .001$), and among those with adherence of fewer than 4 pills per week (aHR, 4.53; $P < .001$). The authors pointed out that underserved subpopulations remain underrepresented among those taking PrEP, and that universal access does not ensure equitable use.

Black women make up half of all new diagnoses in women. Cook and colleagues (Abstract 1081) presented data from the EBONI (Engaging Black Women on Cabotegravir LA for PrEP by Optimizing Novel Implementation Strategies) study of CAB-LA delivery to Black women from 20 sites in the US. Of 163 women enrolled, 25% were transgender. Overall, 44% started CAB-LA without having first taken oral PrEP. Persistence on CAB-LA was 74% at month 6 and 57% at month 12; 69% to 89% received on-time injections through month 12. Only 2% discontinued due to adverse events. At 12 months, 71% reported that in-person visits for CAB-LA provided more opportunities to discuss CAB-LA concerns and 55% reported that it provided more opportunities to discuss sexual health care concerns. None of the women acquired HIV during follow-up.

Liu presented data (Abstract 1128) on CAB-LA uptake and retention in a low-barrier clinic for people who use drugs in San Francisco. This health access point is a nurse-led drop-in clinic for PWID and people experiencing homelessness, integrating sexual health and infectious diseases services with substance use treatment and harm-reduction services. Of 425 clients without HIV, 20% were prescribed CAB-LA. Of these, 92% completed their second loading dose on time and 86% persisted on CAB-LA at 6 months after initiation. In multivariable analyses, factors associated with PrEP persistence included being gay or bisexual (aOR, 15.8; $P = .007$) and having a substance use disorder (aOR, 11.1; $P = .04$). The investigators concluded that integration of sexual health, infectious diseases, and substance use services facilitated CAB-LA initiations and that persistence was substantially higher than what has been historically reported for oral PrEP.

Buchbinder and colleagues (Abstract 1125) reported on the rollout of CAB-LA and doxy-PEP at 3 clinics in San Francisco from October 2022 through September 2025. Although doxy-PEP rollout was high (>7000 patients newly prescribed doxy-PEP, which was 20% of MSM and TGW clients at those clinics), CAB-LA rollout was modest (only 462 prescriptions) and level over time. CAB-LA was more likely to be prescribed for TGW than for cisgender

The proportion of substance use treatment facilities in the US offering PrEP increased from 6% to just 11% from 2021 to 2024

men (OR, 3.1) and more likely to be prescribed to Latino clients than White clients (OR, 2.2). Doxy-PEP rollout was lower among Black patients than White patients (OR, 0.7) and lower among TGW than cisgender men (OR, 0.55). Reasons for these disparities are being explored and will guide citywide efforts to increase awareness and access for populations most affected by HIV and STIs.

Rosen (Abstract 1127) presented data on limited PrEP availability in substance use treatment programs across the US. Using data from the National Substance Use and Mental Health Surveillance System, an annual survey of substance use treatment facilities in the US from 2021 to 2024, approximately 13,000 to 14,000 programs were surveyed per year. The percentage of programs offering PrEP increased from 6% in 2021 to 10.6% in 2024 ($P < .0001$). Although there was an increase in all setting types, offers remained lower in residential and outpatient settings than in inpatient settings. Factors that correlated with programs offering PrEP included those that had programs for LGBTQ+ clients (aOR, 1.75), programs for PWH (aOR, 2.32), those that were affiliated with a hospital (aOR, 2.34), and large- vs small-sized programs (aOR, 1.69). This calls for more substance use treatment programs to develop strategies to offer PrEP services to clients who qualify.

PrEP Delivery Models

Chamie and colleagues (Abstract 163) reported on the results of a randomized clinical trial of community precision health vs standard of care among 16 villages in Kenya and Uganda. The intervention consisted of training community health workers to conduct HIV testing and linkage to prevention and treatment services. Clinicians in the intervention communities were also trained to provide dynamic

choice prevention and Life Event Assessment and Planning (LEAP) interventions for PWH. Community health workers were trained to use a smartphone application that allowed them to communicate bidirectionally with clinics, allowing for linkage from referrals and attempts to bring people back for retention if they missed appointments. After 2 years, more than 84,000 people split evenly across intervention and control communities underwent a RITA to measure HIV seroincidence. Seroincidence was 0.06 per 100 person-years in the intervention group and 0.19 per 100 person-years in the control group, a reduction of 70% ($P < .001$). Findings were consistent across country, age group, and sex. Biomedical prevention was undertaken by 1.67% of the population in the intervention group and 0.4% in the control group, which is a 4-fold greater uptake in the intervention arm ($P < .001$). Although the care cascade trended to being better in the intervention arm, there were no significant differences between arms. Thus, the authors posited that biomedical HIV prevention likely contributed to the reduction in HIV seroincidence in intervention communities, and proposed that this scalable, sustainable intervention be rolled out.

Davey and colleagues (Abstract 131) presented data on a dynamic choice model of oral PrEP delivery and testing methods among postpartum women who had discontinued or poor adherence to oral PrEP after birth. They enrolled 266 women with a median age of 25 years, of whom 38% were married or cohabitating, 62% reported their partner was HIV negative, and 60% reported no sexual activity in the past month. Women were allowed to choose their method of PrEP delivery: 49% chose rapid clinic pickup, 46% chose home delivery, and 5% chose community delivery. Over time, 45% switched delivery method, although community delivery remained exceedingly low. Women were also allowed to choose the method of HIV testing; 57% chose clinic-based rapid testing and 43% chose self-testing. At the end of an approximately 6-month period (funding was cut and the study was terminated early), adherence was better in the dynamic choice arm than in the arm with counseling based on urine tenofovir feedback as measured by self-report and picking up PrEP pills (47% vs 34%, respectively; aOR, 1.7; $P = .03$). Prevention effective adherence (coverage when reporting sexual practices) was also better in the dynamic choice arm (72% vs 58%; aOR, 1.7; $P = .1$), but the difference did not achieve statistical significance. The study was also underpowered to assess objective adherence using urine levels, as only approximately half in each arm had urine tenofovir levels available. This suggests that offering dynamic choice of location of pickup and type of HIV testing may help postpartum women to adhere to PrEP.

Buchbinder and colleagues (Abstract 990) presented data on an online pharmacist–delivery model of oral PrEP for persons assigned male sex at birth under a collaborative practice agreement in California. Participants were randomly assigned 2:1 to receive online pharmacy–delivered PrEP with same-day courier delivery (PrEP-3D) or enhanced standard of care with active PrEP navigation. Of 107 enrolled participants, 70 received the PrEP-3D intervention and 37 received enhanced standard of care. PrEP uptake and persistence through 12 months of follow-up were significantly better among the PrEP-3D arm than the enhanced standard of care arm (79.2% vs 52.5%, respectively; OR, 3.5). Participants rated the PrEP-3D intervention as excellent. The authors concluded that pharmacist-prescribed and delivered PrEP holds promise for improving PrEP uptake and adherence among persons assigned male sex at birth.

Koch (Abstract 1068) presented data on pharmacy-initiated PrEP in 2 nonurban Southern California EHE jurisdictions using 12 pharmacies. Pharmacies had iPad self-intake, HIV testing, and PrEP counseling with same-day initiation and follow-up support. Using community health worker and geotargeted social media outreach, they were able to reach 102 persons, 90% of whom were Latino and 15% of whom were Black; 40% reported low income and 55% were uninsured or publicly insured. They achieved same-day PrEP initiations in all participants; visits averaged less than 60 minutes and the 3-month retention rate was 78%. Two of the persons had reactive HIV rapid tests and were linked to confirmatory testing and treatment. The study demonstrated that community pharmacies can rapidly initiate persons on PrEP and support short-term retention, including in lower-income men, who are often underserved in traditional health care settings.

Rutstein and colleagues (Abstract 1063) presented data on the use of peer navigators to increase PrEP uptake and persistence among heterosexual men recruited from STI clinics in Malawi (HPTN 112; Improving HIV Prevention Among Heterosexual Men Seeking STI Services in Malawi [NJIRA]). In this study, men aged 15 years or older who were initiating PrEP services were randomly assigned 2:1 to receive peer navigation (counseling, community tracing for missed PrEP visits, point-of-care STI testing, and PrEP “restart kits”) vs standard of care. They enrolled 200 men from March to November 2024, of whom 155 chose daily oral PrEP, 13 chose event-driven oral PrEP, and 16% chose CAB-LA. Three participants had acute HIV at enrollment, indicating that this was a high-risk group. Unfortunately, at week 26, PrEP persistence was extremely low and not statistically different between the arms (7% in the peer navigation arm vs 12% in the standard of care

arm). Attendance at the PrEP visit was better in the peer navigation arm (81% vs 53% in the standard of care arm). However, a large drop-off in PrEP care occurred immediately after initiation. The authors called for additional strategies to promote PrEP persistence in this population.

Springer and colleagues (Abstract 1071) presented data on a randomized clinical trial of mobile health unit use vs patient navigation to increase PrEP in criminal legal-system-involved people who use drugs in Texas and Connecticut. They enrolled 568 participants, randomly assigned 1:1 to the 2 arms. Although PrEP uptake was faster in the mobile health unit than in the peer navigator arm, only 22 persons (7.6%) recruited from the mobile health unit initiated PrEP compared with 7 persons (2.5%) in the peer navigator arm (HR, 3.1; $P=.009$). Despite this overall low uptake, the authors suggest that bringing services to where people are might lead to an increase in PrEP initiation and reduction in HIV incidence.

Novel PrEP Agents

Dobard and colleagues (Abstract 125) presented data on the efficacy of an islatravir implant on protection against M184V simian HIV (SHIV) rectal challenge in rhesus macaques. Islatravir, a nucleoside reverse transcriptase

A pharmacokinetic modeling study of MK-8527 found that potentially protective levels are achieved within 1 hour of oral dosing and are expected to last for 1 month

translocation inhibitor (NRTTI), is closely related to MK-8527, another NRTTI currently being tested in 2 phase III clinical trials. They asked whether the M184V mutation would lower the efficacy of islatravir when delivered via implant. They determined that an M184V SHIV mutation reduced sensitivity to islatravir 12-fold and to MK-8527 24-fold in vitro. They altered the M184V SHIV mutation to make it stable and used a 4-fold higher dose for rectal challenge, because the M184V SHIV is less transmissible than wild type. Of 6 macaques treated with an islatravir implant, none became infected with numerous rectal challenges with wild-type SHIV. However, 4 of 5 rhesus macaques became infected when rectally challenged with M184V SHIV. Thus, they raised concerns that a single-drug PrEP regimen with an NRTTI may not confer protection against M184V, which is the most common

resistance-associated mutation, but is estimated to be present in fewer than 1% of human transmissions. In the discussion session after the presentation, questions were raised about whether stabilization of the M184V mutation and the 4-fold higher challenge dose might not reflect physiologic parameters in this challenge model. Data on actual infections are awaited from the phase III clinical trials of MK-8527, a sister compound to islatravir.

Kapoor and colleagues (Abstract 126) presented population pharmacokinetic modeling data from phase II studies of MK-8527. Based on these data, they selected the 11-mg oral dose per month as an appropriate dose for 2 phase III studies, one in cisgender women and the other in cisgender men and transgender and nonbinary persons having sex with men. The onset of action appears to occur within 1 hour of oral dosing, with a forgiveness window of ± 7 days between doses. Although pregnancy is expected to lower drug levels by 10% to 30%, this is still expected to maintain efficacious dosing, so no dose adjustment is needed in pregnancy, and women who become pregnant in the phase III trial will be allowed to continue with dosing after undergoing informed consent. For every 10 kg lower weight, they expect a 10% increase in blood levels; however, they anticipate that there would not need to be dose adjustment for adolescents weighing at least 35 kg; adolescents as young as age 16 years will be recruited for the phase III trials.

Le (Abstract 997) reported preclinical data on a subcutaneous ultra-LAI and removable in situ forming implant (ISFI) with dolutegravir alone and in combination with levonorgestrel as a once-yearly injectable for PrEP and as a multipurpose prevention technology for HIV PrEP and contraception. They studied their products in mouse and macaque models. They stated that the dolutegravir ISFI was well tolerated, with minimal systemic inflammation response and mild-to-moderate local inflammatory responses. It stayed above the protective target level for more than 2 years after a single injection in mice, and they stated from modeling work in the macaque model that it would be projected to last for 116 to 350 days. The multipurpose technology ISFI elicited plasma concentrations at target levels for 180 days after a single injection in mice.

Postexposure Prophylaxis

Sapin and colleagues (Abstract 999) presented data from a real-world evaluation of HIV PEP in pocket (PIP), proactively providing a 28-day supply of PEP and instructing users to initiate PEP as soon as possible and within 72 hours of a potential HIV exposure. The team prospectively

recruited PIP users who were matched 1:2 with daily PrEP users from the Ontario PrEP Cohort Study based on age, HIV risk score, and city of residence. They then compared health care costs in US dollars associated with PIP vs PrEP along with quality-of-life outcomes. There were no HIV seroconversions in the groups during follow-up. PIP was associated with direct annual health care cost savings of up to \$1488 per person. The PIP and PrEP groups had comparable self-reported HIV-related anxiety and sexual satisfaction. The study demonstrates that a practical, on-demand HIV prevention approach can be cost-saving for individuals at lower HIV risk.

Fusco and colleagues (Abstract 998) presented data on the single-tablet regimen bicitegravir/FTC/TAF for PEP in an ED in Naples, Italy. Of 405 individuals referred to the ED in the study period, bicitegravir/TAF/FTC was started in 381 persons and confirmed in 273 persons (72%) referred to the infectious diseases service. Participants who continued with PEP were more likely to have reported high-risk sexual exposures than occupational or low-risk contacts. Among those who continued, the 28-day course was completed in 96%. Among those who completed, 9% reported self-limited adverse effects. No HIV seroconversions were documented. Early syphilis was diagnosed in 15 persons. PrEP was recommended to 161 persons, 63% of whom initiated. The authors concluded that PEP with bicitegravir/FTC/TAF is a valuable and effective option for PEP, combining high efficacy with excellent tolerability.

Sexually Transmitted Infections

Marrazzo (Abstract 25) gave a plenary about global STIs. She noted that in 2024, there were 2.2 million STIs diagnosed in the US. That represents a decrease from 2014 in

In the past 10 years, syphilis has increased by 155% and congenital syphilis by 700%

chlamydia of 1% but an increase in gonorrhea of 37%, an increase in syphilis of 155%, and an increase in congenital syphilis of nearly 700%. The rise of syphilis in women is mirrored in the rise in congenital syphilis. She reminded the audience of a recent publication of a randomized clinical trial that demonstrated that 1 dose of benzathine penicillin G was noninferior to 3 doses in serologic response at 6 months in the treatment of early syphilis. She

also discussed the global rise in gonorrhea antimicrobial resistance, including to ciprofloxacin and to azithromycin. Although cases of reported ceftriaxone resistance remain low globally, this is a concern. Two new oral treatments for gonorrhea, zoliflodacin and gepotidacin, have recently received US Food and Drug Administration (FDA) approval. Marrazzo ended by calling for innovation in the

The 4CMenB vaccine did not provide protection against gonorrhea acquisition in the GoGoVax trial

development and delivery of STI diagnostic tests, new antimicrobial agents, new STI vaccines, and better approaches to the prevention of congenital syphilis.

Seib and colleagues (Abstract 197) reported on the GoGoVax (Efficacy Study of 4CMenB [Bexsero] to Prevent Gonorrhea Infection in Gay and Bisexual Men) trial, a randomized clinical trial of the 4CMenB vaccine to prevent gonorrhea acquisition in persons assigned male sex at birth. There have been several observational studies suggesting that this vaccine might offer 33% to 47% protection against acquisition of gonorrhea. GoGoVax was conducted in Australia in 7 clinics in 3 Australian states. To be eligible, participants had to meet the following criteria: assigned male sex at birth; had sex with a man in the last 6 months; aged 18 to 50 years; diagnosis of gonorrhea or infectious syphilis in the past 18 months; HIV negative and on PrEP, or HIV positive and virally suppressed with a CD4+ count higher than 350 cells/ μ L. Participants were randomly assigned 1:1 to receive 2 doses of 4CMenB vaccine 3 months apart or placebo. All participants were followed quarterly for 2 years. The mean age of the participants was 34 years, 90% were HIV negative, and 60% reported 10 or more partners in the previous 6 months. Unfortunately, the 4CMenB vaccine did not confer protection (IRR, 1.01; $P = .97$). This was despite high rates of gonorrhea in both study arms (48/100 person-years for the first episode, 60/100 person-years for all episodes), so this lack of effect was not an issue of statistical power. There were also no differences in various subgroup analyses, including by HIV status, sexual identity, age, history of gonorrhea, history of syphilis, number of sex partners, condom use, group sex, or length of follow-up. This reinforces the results from the DOXYVAC (Doxycycline Prophylaxis and Meningococcal Group B Vaccine to Prevent Bacterial

Sexually Transmitted Infections in France) study,¹ but there are 3 ongoing randomized clinical trials in the field that include women, a population that has not yet been studied.

Chen and colleagues (Abstract 194) presented data on a retrospective analysis of the addition of doxycycline with or without ceftriaxone in addition to benzathine penicillin to treat early syphilis in PWH. Their analysis was conducted using EHRs from their hospital in Taiwan, where some clinicians are adding a 7-day course of doxycycline to benzathine penicillin with or without a single dose of ceftriaxone in the treatment of early syphilis. Their data spanned January 2018 through December 2024. Of 1077 early syphilis episodes among 762 PWH, 42% were treated with benzathine penicillin alone, 53% with the addition of doxycycline, and 5% with all 3 antibiotics. In Cox proportional hazard analysis, a 4-fold reduction in syphilis titers at 12 months was associated with age (per 10 years, aHR, 0.9; $P = .005$), baseline rapid plasma reagin titer (aHR, 1.17; $P < .001$), initial vs repeat episode of early syphilis (aHR, 1.42; $P < .001$), and doxycycline-containing regimens (aHR, 1.45; $P < .001$). Despite study limitations, ie, that it is retrospective in design and did not take into account concomitant doxy-PEP use, the authors concluded that the addition of a 7-day course of doxycycline leads to faster resolution of syphilis titers in PWH.

Rivera-Villegas (Abstract 1015) presented data on 529 cases of syphilis among PWH in their cohort. Approximately 25 (5%) met criteria for ocular syphilis, with the most frequent presentation being optic neuritis (44%), followed by posterior uveitis (32%). Of the 72% of these patients who underwent cerebrospinal fluid venereal disease research laboratory (VDRL) testing, 12% were reactive consistent with neurosyphilis and 8% had otosyphilis. Patients with ocular syphilis had higher VDRL titers (median, 1:128) than those without ocular syphilis (median, 1:16; $P < .001$).

Mogaka and colleagues (Abstract 1017) reported on missed syphilis screening opportunities for pregnant women in Kenya. They conducted chart abstraction from January 2025 to February 2026 for women enrolled in the PrIMI (Improving Perinatal Outcomes Among Kenyan Pregnant Women with an Integrated STI Testing Model) study. Of 2684 women attending antenatal clinic visits with a median gestation of 23 weeks, 87% had been screened for syphilis at the time of data abstraction. Women with HIV were more likely to have missing syphilis testing than women without HIV (33% vs 10%, respectively; $P < .001$). Other factors associated with missing a syphilis test were age older than 24 years (13.8% vs 10.7% in those 24 years or younger; $P = .02$) and multiparous women (14.3% vs 9.1% in primigravidas women; $P = .001$). Syphilis positivity

was nonsignificantly higher in women with HIV than in those without HIV (1.5% vs 0.7%, respectively). These gaps occurred despite the availability of point-of-care testing options. The authors called for identifying barriers and optimizing implementation strategies for pregnant women.

Molina (Abstract 196) presented data from a randomized open-label trial of pritelivir vs investigator choice of treatment for refractory mucosal herpes simplex virus (HSV)-1 or HSV-2 among immunocompromised persons. He noted that 6% to 7% of the US population is immunocompromised from factors such as HIV, posttransplant status, malignancy, or immunosuppressive drugs. Acyclovir resistance is present in up to 27% of immunocompromised patients, including 5% of PWH. Pritelivir is a small molecule with a novel mechanism of action that is active against HIV-1 and HIV-2. They randomly assigned 23 participants to the pritelivir arm and 15 to the investigator choice arm (intravenous foscarnet, intravenous or topical cidofovir, and topical imiquimod). At the end of a 28-day course of treatment, 63% of lesions in the pritelivir arm and 34% in the investigator choice arm were completely healed ($P < .005$). He noted that pritelivir has now received breakthrough designation by the US FDA and may be approved by the FDA in the future.

Doxy-PEP

Forster and colleagues (Abstract 1020) presented data on the modeled impact of doxy-PEP on syphilis incidence among MSM in 4 US cities. They projected that without doxy-PEP, syphilis infections among MSM are projected to rise by 1.71-fold across the 4 locations by 2030. However, if doxy-PEP coverage was 10%, it could avert 37% of infections at the lowest amount (Atlanta, Georgia), and 46% of infections at the highest amount (Miami, Florida). If coverage increased to 25%, doxy-PEP would avert 57% of syphilis cases in Atlanta to 68% in Miami. These data suggest that doxy-PEP could have a substantial impact on the growing rate of syphilis among MSM.

Barry and colleagues (Abstract 1038) reported on the impact of doxy-PEP on bacterial STIs among clients seen at the Magnet Sexual Health Clinic in San Francisco, California. They divided clients into those who reported always using doxy-PEP within 72 hours of sex since their last visit (high adherence) with those who reported often, sometimes, rarely, or never using doxy-PEP since their last visit (inconsistent adherence). Persons with high adherence had significant decreases in chlamydia and gonorrhea; there were too few cases of syphilis to see an impact on this STI, although they did see a significant

decline in syphilis among persons reporting any doxy-PEP use.

Menza and colleagues (Abstract 1037) reported on the etiology of nongonococcal urethritis (NGU) at a sexual health clinic in Seattle and King County, Washington. From 2019 to 2025, the proportion of NGU cases caused by chlamydia decreased from 18% to 3% among MSM. Most NGU cases in MSM (77%) and men who have sex with women (70%) is idiopathic. It is unclear whether persons with idiopathic NGU benefit from antibiotic therapy.

Golden and colleagues (Abstract 1111) modeled the potential impact of decreased STI screening and partner treatment and doxy-PEP on antibiotic use in MSM in King County, Washington. They noted that some public health authorities are advocating for the discontinuation of gonorrhea/chlamydia screening and empiric treatment of sex partners of persons with these 2 STIs to decrease antimicrobial use, a practice they called antimicrobial stewardship. They modeled 4 scenarios in MSM: (1) current practice without doxy-PEP but continued gonorrhea/chlamydia screening; (2) antimicrobial stewardship without doxy-PEP; (3) current practice with 30% doxy-PEP use; and (4) antimicrobial stewardship with 30% doxy-PEP use. They found that antimicrobial stewardship changes could decrease the use of ceftriaxone and doxycycline for STIs by 56% relative to current practices in the absence of doxy-PEP. However, doxy-PEP is estimated to lead to a 27-fold increase in doxycycline use for STI prevention and treatment. Their model suggests that MSM of King County receive approximately 290,000 days of antimicrobials annually and that doxy-PEP increases the total number of days of antimicrobials in this population by approximately 190%. They acknowledge that doxy-PEP is a highly effective intervention for preventing syphilis.

Mittelstaedt and colleagues (Abstract 1047) also evaluated the impact of doxy-PEP prescribing on antibiotic use among MSM and TGW at a Boston sexual health clinic. They evaluated more than 1300 patients, of whom 855 started doxy-PEP from September 2022 through April 2025. Although non-doxy-PEP doxycycline prescriptions decreased by 60%, likely due to fewer chlamydia and syphilis diagnoses, doxy-PEP users received nearly 4-times as many weekly antibiotic prescriptions after starting doxy-PEP. Ceftriaxone prescriptions were unchanged, likely due to the limited efficacy of doxy-PEP in preventing gonorrhea. They did find that total prescriptions decreased by 20% among non-doxy-PEP users, which could have been from decreased transmission of STIs in sexual networks or other factors.


Gomez-Ayerbe (Abstract 1018) presented a case series of 9 syphilis cases among 313 participants on doxy-PEP.

The mean time from start of doxy-PEP to syphilis diagnosis was 37 weeks, and the overall rate (1.92 episodes/100 person-years) was substantially lower than expected. Most of the cases had minimal increases in rapid plasma reagin (although all were at least 1:4 except the 1 case with primary syphilis, which was 1:2). All responded to benzathine penicillin G. The authors note that diagnosis and interpretation of posttreatment rapid plasma reagin titers may be altered by doxy-PEP.

Raccagni and colleagues (Abstract 1036) reported on antimicrobial susceptibility among MSM in Milan, Italy. Of 318 individuals positive for gonorrhoea with 376 culture-positive gonorrhoea episodes, 96% had tetracycline resistance, regardless of doxy-PEP use. However, doxy-PEP

Only 8% of male US veterans with a history of at least 1 bacterial STI had been prescribed doxy-PEP

users were significantly more likely to have high-level resistance to doxycycline (OR, 1.87). There were no ceftriaxone-resistant isolates. The authors called for enhanced resistance surveillance.

Bien-Gund and colleagues (Abstract 1035) reported on doxy-PEP uptake among male US veterans diagnosed with bacterial STIs. Using national Veterans Administration EHRs of the more than 29,000 male veterans diagnosed with at least 1 bacterial STI from January 2022 through September 2025, they found that only 8.4% were prescribed doxy-PEP. Factors associated with being more likely to get a doxy-PEP prescription included being on HIV PrEP (aOR, 23.8; $P < .001$); having HIV (aOR, 7.2; $P < .001$); having recurrent STIs (aOR, 2.5; $P < .001$); having gonorrhoea (aOR, 2.5; $P < .001$) or syphilis (aOR, 1.9; $P < .001$) or several STIs (aOR, 1.8; $P < .001$) compared with chlamydia; or living in the West (aOR, 2.3; $P < .001$) or the Northeast (aOR, 1.5; $P < .001$) compared with the South. Men older than 50 years were significantly less likely to get a prescription than men aged 18 to 30 years (aOR, 0.54; $P < .001$) and White men were less likely to get a prescription than Black men (aOR, 0.87; $P = .02$). This would suggest that a larger proportion of male veterans could benefit from doxy-PEP. 

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