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A publication of the IAS–USA

Selected Highlights of the 2022 Conference on Retroviruses and Opportunistic Infections (Part 1)

Invited Reviews

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IAS–USA International Antiviral Society–USA

Topics in Antiviral Medicine™

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On completion of this activity, which contains 4 articles, the learner will be better able to:

- Describe the important new data presented at the 2022 Conference on Retroviruses and Opportunistic Infections and the potential clinical implications for patients in the areas of epidemiologic trends, prevention research, and basic science research in the HIV and SARS-CoV-2 pandemics
- Describe the potential treatment options for depression and bipolar depression disorders and understand how it impacts those with HIV
- Describe the current epidemiology of tuberculosis, shorter regimens for its treatment, and recent advancements in treatment for patients with drug-resistant tuberculosis

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Invited Review

CROI 2022: Summary of Basic Science Research in HIV and SARS-CoV-2

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The Conference on Retroviruses and Opportunistic Infections (CROI) 2022, which was held as a virtual conference, continues to serve as the preeminent forum that features research advances in HIV-1 and its associated coinfections. The conference has extended its area of coverage to include research advances in SARS-CoV-2. As pointed out in the presentation from Hatziioannou in the New Investigators workshop, there has been an explosion in research activity on SARS-CoV-2 that has eclipsed that for HIV-1. In the past 12 months, there were approximately 6600 publications on HIV-1 and approximately 64,000 on SARS-CoV-2. Although these numbers include review articles, they reveal the tremendous response by researchers to the existential threats posed by lentiviruses and coronaviruses. This poses challenges for any conference committee tasked with selecting abstracts for presentation from the large number submitted for consideration. CROI organizers have consistently been able to assemble a program that, through invited presentations, abstract-driven talks, posters, interactive sessions, workshops, and symposia, showcases the most recent research advances.

Keywords: CROI 2022, HIV-1, reservoirs, cure, SARS-CoV-2

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Virology

The structure of SARS-CoV-2 is being revealed in great detail. The viral spike protein, which harbors the receptor-binding domain, may display that domain in an open or closed confirmation. By comparison, the coreceptor-binding region on the HIV-1 envelope remains closed until the virus engages CD4. This triggers a conformational change that exposes the coreceptor-binding domain, which allows the envelope to attach to the coreceptor. This mechanism is designed to minimize the vulnerability of the envelope to antibodies to the coreceptor-binding region. A similar mechanism may be used by SARS-CoV-2 to limit exposure of the receptor-binding domain to neutralizing antibodies. The spike protein was found in 2 main isoforms, a more abundant prefusion and a less abundant postfusion isoform.[1] In the prefusion isoform, the spike trimers were found in 3 classes according to the receptor-binding domain orientation: closed, open, and mobile, mostly closed receptor-binding domain conformations. In the open form, the receptor-binding domain was surface–exposed and able to bind angiotensin-converting enzyme 2 (ACE2). Once bound to the receptor, the prefusion spike underwent a structural transition to a postfusion form in which the prefusion trimers are likely shielded from neutralizing antibodies. Understanding what triggers the conformational change will be important to guide the design of vaccines and small molecule fusion inhibitors that target vulnerable epitopes in the receptor-binding domain.

Zoonotic origins of coronaviruses were also discussed by Hatziioannou (Abstract 1). There have been 7 different coronaviruses known to cross from

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animal hosts into humans: 5 beta coronaviruses and 2 alpha coronaviruses. SARS-CoV-2 is most closely related to coronaviruses circulating in bats and has 79% homology to the SARS-CoV coronavirus detected in humans 18 years ago. Although genetic evidence demonstrates homology to natural viruses circulating in bats, there is no definitive picture on the animal origins of SARS-CoV-2 or when and where the first human transmission occurred. Bats are natural hosts of alphacoronaviruses and betacoronaviruses and RaTG13, a coronavirus isolated from the *Rhinolophus affinis* bat in Yunnan province in China, has 96.2% identity to SARS-CoV-2 and has more than 90% identity with SARS-CoV-2 in all open reading frames (ORFs) throughout the genome including the highly variable S and ORF8. More recently, another bat virus, RmYN02, isolated in Yunnan from a *Rhinolophus malayanus* to RaTG13 bat, was found to have 93% identity to SARS-CoV-2 across the genome and 97% identity in the 1 ab gene.

Although first reported in Wuhan, China, in December 2019, a controversial report claims to have detected SARS-CoV-2 in December 2019 in a patient hospitalized for hemoptysis in a hospital north of Paris, France.[2] This would suggest that the COVID-19 epidemic started earlier in France. This result still needs to be confirmed with retrospective analyses of banked samples from diverse geographic areas. These observations suggest the presence of bat reservoirs of SARS-CoV-2. However, the divergence between SARS-CoV-2 and related bat coronaviruses spans more than 20 years of sequence evolution. Therefore, although these bat coronaviruses are likely to be SARS-CoV-2 precursors, SARS-CoV-2 is unlikely to be their direct descendent.

Pangolins have received attention as possible intermediate hosts for SARS-CoV-2. Palm civets and dromedary camels served as intermediary hosts for SARS-CoV and MERS-CoV, respectively. However, in the case of SARS-CoV and MERS-CoV, viruses in the intermediate hosts and humans exhibited over 99% sequence identity. The fact that, outside of the receptor-binding domain, pangolin coronaviruses have no more than 92% sequence identity with SARS-CoV-2 argues against pangolins being directly involved in the SARS-CoV-2 outbreak. Therefore, the picture remains incomplete as to whether an intermediate host played a role in the introduction of SARS-CoV-2 to humans.

The first half of the retroviral replication cycle, encompassing events from viral fusion with the target cell membrane to integration of viral DNA with host cell DNA, has been a subject of strong interest by numerous research groups and this research continues to turn up surprises. After the virus fuses with the cell membrane, the viral core that contains the genomic viral RNA and reverse transcriptase and integrase enzymes that catalyze cDNA synthesis and integration, respectively, is deposited in the target cell cytoplasm. Once in the cytoplasm, classic models of retroviral biology suggest that the core then dissipates to liberate viral RNA that then undergoes reverse transcription. A theme that continues to prevail in the biology of lentiviruses is that viral genes often have additional functions beyond their classic roles in viral replication. This is to be expected since viruses have to achieve many things with a limited repertoire of viral proteins. Research has revealed, in tremendous detail, the processes governing the integration of viral cDNA with host cell DNA. Abstract 52 presented evidence suggesting that the viral integrase, which catalyzes integration of viral cDNA into host cell DNA, is also involved in viral maturation. Within the virion, integrase is contained within the viral core that is deposited in the cytoplasm together with genomic viral RNA. Integrase needs to remain in tight proximity to viral cDNA as it is being synthesized and transported to the nucleus, where it will catalyze integration of the viral cDNA into host cell DNA. The introduction of mutations in integrase had pleiotropic effects on the virion that included effects on viral replication that were not due to defective integration. Some mutations in integrase impact interaction of integrase with genomic viral RNA, and some cause mislocalization of integrase within the virion that leads to degradation of the viral RNA in target cells. It now appears that integrase mutations that perturb its interaction with genomic viral RNA also impair virion maturation. The interaction of integrase with genomic viral RNA appears to be dependent on a positive electrostatic

potential of the C-terminal domain of integrase. Collectively, these studies reveal activities for the integrase protein that extend beyond its role in proviral formation and that center on the interaction between integrase and genomic viral RNA.

As discussed in the symposium "Navigating to the Nucleus" and the oral abstract session "HIV/simian immunodeficiency virus (SIV) Host and Cellular Interactions," studies suggest that the entire core accesses the nucleus. This would seem unremarkable but for the fact that the ability of lentiviruses to transduce nondividing cells requires that they translocate the core across an intact nuclear envelope. HIV-1 waits until the nuclear compartment has been accessed before uncoating and liberating viral nucleic acids. This appears to be a mechanism to allow evasion of nucleic acid-sensing mechanisms of the host cell that otherwise would trigger an antiviral interferon (IFN) response.

Similar obstacles are faced by coronaviruses as they invade the cell. Presentations in oral abstract session 1 discussed the complex interplay between SARS-CoV-2 and effectors of innate immunity (Abstracts 18-26). Previous studies demonstrated that rare inborn errors in TLR3- and IRF7-dependent type I INF increase the risk of severe COVID-19 pneumonia[3] and individuals with autoantibodies to type I INF were at increased risk of severe COVID-19 pneumonia.[4] Rapamycin analogues increased cellular susceptibility to SARS-CoV-2 infection by facilitating spike-mediated virus entry (Abstract 22). The extent to which rapamycin analogues enhanced virus infection was correlated with their ability to promote lysosomal degradation of the IFN-induced transmembrane proteins (IFITM)2 and IFITM3 that have previously been shown to inhibit entry of a large number of enveloped viruses. Investigators expanded on recently published work that IFITM3 knockdown actually impaired cell infec tion by SARS-CoV-2 (Abstract 23). Knockdown of IFITM2 but not IFITM1 significantly reduced entry and replication of variants of concern including B.1.1.7, (Alpha) B.1.351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta). Furthermore, viral infection was inhibited by an antibody to the N-terminus of IFITM2. Abstract 23 discussed data to suggest that innate immunity is a driver of SARS-CoV-2 evolution. The authors tested the sensitivity of early lineages A, B, B.1, and variants of concern lineages B.1.1.7, B.1.351, P.1, and variants of concern (B.1.1.7 etc) to various IFNs. IFN sensitivity of the volatile organic compounds (VOCs) decreased relative to that of the ancestral B lineage and Alpha and Delta variants were also more resistant to B.1. This suggests that the evolution of SARS-CoV-2 is accompanied by increasing IFN resistance. It remains to be determined whether the reduction in IFN is a contributor to SARS-CoV-2 evolution or whether increased resistance to IFN is a consequence of SARS-CoV-2 evolution. Data were presented to suggest that antagonizing type I IFN inhibits SARS-CoV-2 replication and inflammation (Abstract 25). Macaques were treated with an IFN-I antagonist prior to SARS-CoV-2 infection which led to significant reductions in SARS-CoV-2 viral loads in upper and lower airways as well as reductions in soluble markers of inflammation. There were also decreased levels of IFN-stimulated genes post-infection in macaques treated with an IFN-I antagonist. Therefore, IFN-I appears to play an important role in the progression of COVID-19. As such, this finding could open up new avenues for development of therapeutic approaches to ameliorate COVID-19.

Abstract 26 presented findings that point to a molecular mechanism underscoring clotting disorders in patients with COVID-19. Abnormal clotting occurs in individuals with severe COVID-19 and also in those who are asymptomatic, and the fibrin clots observed in SARS-CoV-2 infection are difficult to manage due to their resistance to fibrinolysis by plasmin. The authors reported that the spike protein of SARS-CoV-2 bound to fibrinogen and fibrin, which accelerated fibrin polymerization. The authors also injected mice with HIV-1 virions that were pseudotyped with spike and observed thombo-inflammatory responses including fibrin deposition in the lung, endothelial activation, and macrophage influx. The proinflammatory effects of spike could be blocked with an antifibrin monoclonal antibody. Collectively, this suggests that clotting is a driver of inflammation during SARS-CoV-2 infection as opposed to inflammation being a driver of clotting.

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Viral Pathogenesis, Reservoirs, and Cure

An understanding of the reservoirs that sustain HIV-1 persistence in the face of effective antiretroviral therapy (ART) is important for the design of strategies to promote the elimination of those reservoirs. There has been a lot of interest in studying how the viral reservoirs are shaped, perhaps by host immune responses under long-term ART. There is good evidence that persistence of replication-competent HIV-1 during long-term ART is caused by a combination of at least 2 mechanisms. The first is maintenance of transcriptionally silent but intact proviral genomes within long lived CD4+ T cells. These latent proviruses are established early in infection and are believed to confer life-long persistence of the virus. The second is homeostatic proliferation of latently infected cells leading to a stable reservoir through self-regeneration. Clonally expanded proviruses are capable of generating infectious virions in vivo and viruses from clonally expanded proviruses populate rebounding viremia following analytic treatment interruption. There is also the possibility that proviral expression within anatomic reservoirs could be driven by innate immune (inflammatory) responses (eg, microbial translocation, concurrent infections, and antigenic stimulation).

Abstract 68 longitudinally examined the proviral landscape in ART-treated volunteers for approximately 20 years and in individuals on shorter durations of ART (median, 9 years). The frequency of intact relative to defective proviruses was assessed. After long-term ART, there was no significant difference in the frequencies of total or intact proviruses compared with individuals on short-term ART. However, the proportion of clonally expanded intact proviruses was higher in individuals on long-term ART. There was also an increased proportion of intact proviruses in nongenic DNA in those on long-term ART relative to those on shorter ART durations. There were no differences in chromosomal integration site locations for defective proviruses between the 2 ART groups. This suggests that under long-term ART, there is an increased proportion of intact proviruses in nongenic regions, suggesting that immune responses might promote selective elimination of proviruses that, due to their location in genic or heterochromatic regions, are more transcriptionally active and more susceptible to antiviral clearance mechanisms. Prior studies from this group on elite controllers (ECs), also suggested that there is a selection for proviruses in non-genic regions over time.[5] In the majority of ECs, proviruses were found to be intact and replication competent, but were concentrated in non-genic or regions of host cell DNA. This was surprising because a number of studies have demonstrated HIV-1 integrates preferentially within gene-rich regions of human chromosomes. These regions have a relaxed chromatin architecture that allows free access of transcription factors that regulate gene expression. Those proviruses also bore epigenetic modifications that limited their transcriptional capacity. Collectively, these studies suggest that there is greater selective pressure on proviruses in heterochromatic regions of the chromosome that eventually shapes the proviral population to become inert or in a state of latency that rarely reactivates (ie, deep latency).

The relationship between drivers of cell proliferation and proviral activity was presented in Abstract 69. Integration of viral DNA within chromosomal DNA of the host cell is essential in the replication cycle of retroviruses. These integrated viral sequences then adopt the dynamics and longevity of the cell they occupy. Therefore, when the host cell undergoes mitosis, the chromosomal DNA, as well as the integrated provirus, is duplicated. If the provirus is located close to a host gene that can influence cell cycle and cell proliferation, promoter elements within the provirus can impact the activity of the host gene and promote the division rate of the host cell. This represents a mechanism by which the proviral population can be maintained and expanded. Clonal expansion of proviruses in this way can result in marked over-representation of proviruses. Furthermore, proviruses in more rapidly dividing host cells might also be more transcriptionally active. Abstract 69 examined HIV expression (cell-associated viral RNA) and T-cell clonal expansion in cytomegalovirus (CMV) and HIV-1 antigen-specific CD4+ T cells from infected subjects. The authors determined that cells harboring HIV-1 RNA were larger in clone size

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and had a higher proportion of cytotoxic CD4+ T cells. This indicates that drivers of T-cell proliferation promote viral persistence. Because the study employed single cell profiling, the biologic competence of the proviruses could not be assessed so viral RNA served as a surrogate for the reservoir. Although the level to which cell-associated viral RNA can inform on the dynamics of the biologically competent viral reservoirs is unknown, there are several reports demonstrating that the level of cell-associated RNA in CD4+ T cells in ART-suppressed individual predicts the rapidity with which HIV-1 will rebound when those individuals interrupt ART. By extension, therefore, antigens driving clonal T-cell proliferation also drive reservoir persistence.

The majority of reservoir studies have been conducted with circulating CD4+ T cells. However, the CD4+ T-cell reservoirs within various anatomic compartments harbor the largest proportion of the viral reservoir. Abstract 67 examined viral reservoirs in several anatomic locations in samples collected immediately postmortem from individuals who donated their bodies for HIV cure research. Tissue was obtained within 6 hours of death from 2 individuals who were on long-term ART. The viral reservoirs in anatomic compartments (including lymph nodes, gut, liver, spleen, brain, and testes) were characterized for near-full-length viral DNA and cell-associated viral RNA. Highest levels of viral DNA and RNA were found in the lymph nodes, liver, lungs, and spleen. Clonally expanded proviruses were found in several tissues. This indicates that cells harboring clonally expanded proviruses recirculate amongst anatomic sites during long-term ART.

Almost all of the attention on reservoirs of HIV-1 persistence has been focused on CD4+ T-cell reservoirs. However, several recent studies indicate that tissue macrophages may support viral persistence in individuals on effective ART. Abstract 19 presented intriguing evidence that virus in semen from acutely infected individuals originates from macrophages. Most infections worldwide involve sexual transmission by virus present in semen. Therefore, the composition of virus in semen and characteristics of the virus that aid in its transmission are of intense interest. Since these questions are difficult to address in human participants, Abstract 19 presented observations on the source of virus in semen in macaques after acute simian immunodeficiency virus (SIV) infection. Six animals were infected intravenously with a barcoded virus that permited tracking of individual viral lineages. Semen and blood were collected over 17 days postinfection. Lymphoid and male genital tract tissue were collected at necropsy. Viral populations in the samples were assessed by next-generation sequencing and tissues were analyzed by DNA and RNA scope to determine the nature of the infected cells in the different tissues. As early as 4 days postinfection, viral RNA and cell-associated viral RNA/DNA was detectable in seminal plasma and seminal cells, respectively. Remarkably, viral RNA levels in seminal plasma approached 109 copies/mL, which exceeds what is typically observed at the peak of plasma viremia in SIV-infected macaques. Based on RNAscope analysis, macrophages in seminal fluid and in male genital tract tissues were the main source of virus in seminal fluids. Analysis of lineages suggested early compartmentalization of viruses between seminal and blood plasma. These results indicate that very high seminal viral load and numbers of infected cells occur during primary infection. These observations now need to be extended to humans to determine what role viruses produced in macrophages might play in sexual transmission of HIV-1.

HIV-associated neurocognitive disorder (HAND) is a well-recognized manifestation of HIV-1 infection, especially in untreated infection. It has been suspected that release of neuronotoxic agents from HIV-1–infected microglia are responsible for the neuronal death observed in HIV-1 infection. However, identification of the mechanisms involved as well as the identity of the neuronotoxic agents themselves has been challenging, mainly due to challenges with in vivo analysis and limitations of animal models. Abstract 18 featured results using a brain organoid microglial model to identify processes underscoring HAND. The authors resorted to induced pluripotent stem cells (IPSCs) to derive cerebral and choroid plexus organoids. In both models, microglia were the most predominantly infected cell type following HIV-1 infection. Infection of microglia led to upregulation of the inflammatory chemokines C-C motif chemokine ligand 2 (CCL2) and C-X-C motif

chemokine ligand 10 (CXCL10) that promote migration of T cells and monocytes across the blood brain barrier. ART inhibited HIV-1 replication within IPSC-derived microglial organoids; it did not block chemokine production. Infected microglia also exhibited inflammatory responses involving several members of the S100 family of genes that have been implicated in several neurologic disorders including HAND. These studies allow detailed interrogation of the processes that drive HAND in HIV-1 infection.

Although there is intense interest in revealing the reservoirs that sustain HIV-1 persistence in the face of ART suppression, there is an equally sustained effort to identify strategies that promote elimination of those reservoirs. Most of the strategies being explored center around approaches that enhance removal of infected cells by the immune surveillance mechanisms of the host. Because most of the viral reservoir is likely to be latent and invisible to the immune system, researchers are exploring numerous ways to reactivate the latent provirus so that infected cells can be recognized by host antiviral clearance forces of the host. Abstract 343 presented a reservoir clearance approach that is distinct to most reservoir clearance strategies currently being pursued. The viral reverse transcriptase and protease proteins are initially contained with a GagPol polyprotein. During virus budding from the plasma membrane of the host cell, the protease self-cleaves the polyprotein to liberate itself and other Gag and Pol subunits from the polyprotein. This sequence of events likely prevents premature activation of the protease and within the infected cell where it might catalytically cleave cytosolic proteins. This would likely impact the health of the infected cell and reduce its capacity to generate progeny virions. Protease inhibitors such as indinavir interrupt this process leading to the production of immature, noninfectious virions. If an nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) binds to a newly translated GagPol polyprotein, this results in homodimerization of the polyprotein and premature protease activation. Previous studies have demonstrated that this then leads to nonspecific cleavage of host cell proteins that ultimately result in apoptosis of the infected cell.[6,7] Furthermore, this cytocidal effect of NNRTIs is also seen after latency reversal.[7] Abstract 343 presented efforts to identify small molecules that target the NNRTI binding site of HIV-1 reverse transcriptase to promote Gag-Pol dimerization and premature protease activation. A total of 6628 compounds from a library of NNRTI-related analogues that target the NNRTI binding site were assessed for their ability to selectively kill HIV-1–infected cells. A small percentage of these compounds (1.7%) were cytotoxic. These compounds were optimized for specific cytotoxicity on infected cells. One of these compounds (Pyr01) had 1000-fold increased killing relative to analogue Pyr02 that had similar antiviral activity. Pyr01 represents a novel bifunctional NNRTI that serves as a reverse transcriptase inhibitor and that has the ability to selectively kill HIV-1 expressing reservoir cells through premature activation of the viral protease. This line of investigation opens up exciting new approaches with which to promote elimination of viral reservoirs in infected individuals.

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Invited Review

CROI 2022: Epidemiologic Trends and Prevention for HIV and SARS-CoV-2

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At the 2022 Conference on Retroviruses and Opportunistic Infections, several speakers discussed disparities in HIV and COVID-19 infections and outcomes. Although the lifetime risk of HIV infection in the United States is higher overall in males than females, Black females have higher risk than White males. In 12 countries in sub-Saharan Africa, women aged 15 to 34 years accounted for more than half of all infections. Because knowledge of HIV serostatus is important for treatment and for prevention, several novel strategies were evaluated in the distribution of HIV self-test kits to undertested populations in the United States and sub-Saharan Africa. Data were presented on new products in the pre-exposure prophylaxis (PrEP) pipeline, including long-acting injectable cabotegravir, islatravir, vaginal rings, and in-situ forming implants. Challenges remain in the rollout of oral PrEP, and a number of innovative strategies to address barriers were discussed. Models suggest that the greatest impact of novel PrEP agents would be to increase the pool of persons using PrEP, rather than through improved efficacy. COVID-19 caused substantial declines in HIV and sexually transmitted infection prevention and treatment services, which have started to rebound, but are not yet at prepandemic levels in several settings.

Keywords: CROI 2022, PrEP, HIV, COVID-19, SARS-CoV-2, epidemiology, prevention

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HIV Epidemiology

Singh and colleagues presented data on the lifetime risk of a diagnosis of HIV infection in the United States (Abstract 43). Using data from the National HIV Surveillance System, the National Center for Health Statistics, and census data, they found that the lifetime risk for males of an HIV diagnosis was 1 in 76 and for females was 1 in 309, based on data from 2017 to 2019. Risk was highest for Black males (1/27), Hispanic males (1/50), and Black females (1/75). In contrast, rates were substantially lower for White males (1/171), Asian males (1/187), White females (1/874), and Asian females (1/1298). Geographically, risk was highest in Washington, DC, (1/39) and lowest in Wyoming (1/655). The US South accounted for 9 of 10 states with the highest lifetime risk of HIV. The 10-year risk was highest for males aged 20 years (1/195) and for females aged 30 years (1/1152). Most of the risk accumulated before age 50 years, accounting for 85% of the risk for men and 76% of the risk for women. Although these data are modestly improved from 2010 to 2014, they point to the ongoing disparities, by race/ethnicity, sex, and geography, that continue in the United States.

Life expectancy for people with HIV increased by 4.2 years from 2008 to 2018

Siddiqi and colleagues reported on the life expectancy after an HIV diagnosis for people with HIV in the United States from 2008 to 2018 (Abstract 761). They found that there was an average increase in life expectancy of 1.3% per year. From

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a life expectancy of 28.6 years in 2008, life expectancy increased by 4.2 to 32.8 years in 2018. Persons with AIDS at diagnosis had a considerably shorter life expectancy (27.2 years). Life expectancy was highest for Hispanic persons (36.2 years), followed by Black persons (32.0 years), followed by White persons (30.3 years). By transmission category, the longest life expectancy was for men who have sex with men (MSM) (34.1 years), followed by heterosexual women (30.4 years), MSM who inject drugs (29.9 years), women who inject drugs (26.0 years), heterosexual men (25.9 years) and men who inject drugs (24.4 years). Over the 11-year period, life expectancy improved for all persons by age group, sex at birth, race/ethnicity, transmission category, and stage of disease at diagnosis. However, the improvements were not uniform across all groups. Moreover, life expectancy for people diagnosed with HIV was shorter than for the general US population, emphasizing the importance of HIV prevention and of early diagnosis.

Perez and colleagues reported on large clusters of HIV among MSM in the United States (Abstract 44). They used molecular techniques to identify clusters from 2018 to 2019, and then followed those clusters of 5 or more cases forward through September 2021. The largest clusters they identified had more than 25 people and were concentrated in MSM (72%), with fewer among people who inject drugs (PWID, 19%), and no predominant risk group (9%). Large MSM clusters had an average of 23 transmission events per 100 person-years, nearly 6-times higher than the estimated overall average transmission rate of 4 transmission events per 100 person-years. These clusters were racially/ethnically diverse, being made up of nearly equal parts Black, Latino, and White individuals. The authors point out that if these clusters are identified early, interventions may be useful to stop the spread of HIV infection.

Zhou and colleagues reported on new HIV diagnoses in North Carolina from 2018 to 2021 (Abstract 45). They used Primer ID next-generation sequencing with multiplexing to determine viral diversity, an indication of chronic versus recent infection, and to measure drug resistance mutations on 814 new diagnoses at the North Carolina State Laboratory; this accounted for approximately one-third of all new diagnoses in North Carolina over that time. Overall, 40% were recent infections, 47% were chronic infections, and 13% were of indeterminate duration. They noted that in early 2020, the absolute number of infections fell, but the proportion of recent infections rose, likely related to reduced testing due to COVID-19. In late 2020 to 2021, there was a rise in the number of infections, but a lesser proportion were recent infections, signaling a return to broader HIV testing and diagnosis. Factors associated with recent infection included being White (odds ratio [OR], 1.82), being younger than 30 years of age (OR, 1.73), and being diagnosed in 2020 (OR, 1.74); Hispanic persons were less likely to have recent infections (OR, 0.52). The most common drug resistance mutations were against the non-nucleoside reverse transcription inhibitors, although these were declining over time. Resistance to nucleoside reverse transcriptase inhibitors (nRTIs) increased over time, and protease and integrase strand transfer inhibitor (InSTI) mutations remained low and stable. This high-throughput methodology allows for a novel way to track recent infections.

Skaathun and colleagues reported on the high HIV incidence among PWID on the US/Mexico border during the COVID-19 pandemic (Abstract 785). Among 611 persons, overall incidence was 5.2 per 100 person-years, somewhat higher among people located in Tijuana (incidence 11.0/100 person-years). This may reflect a disruption in some harm reduction services and established social networks, and the authors call for mobile harm reduction services with scale-up of antiretroviral therapy (ART) and pre-exposure prophylaxis (PrEP) for susceptible populations. Bonacci and colleagues reported on missed opportunities for prevention and care among PWID in a West Virginia HIV outbreak (Abstract 786). They reviewed medical records from the county's largest medical system and a community clinic serving PWID, before and after HIV diagnosis for 65 individuals. On average, PWID had 3.2 encounters per person-year before HIV diagnosis, during which 62 screening tests were performed, but no one was prescribed PrEP. Only 4 persons (6%) of PWID

received syringe services, 31% were prescribed naloxone, and 45% were prescribed medication for opioid use disorder. The authors identified missed opportunities to prevent HIV transmission with HIV testing and PrEP and missed opportunities to address opioid use. Moallef and colleagues reported on the risk of overdose among people who use unregulated drugs in 9 urban centers in the United States and Canada from May 2020 to April 2021 (Abstract 749). Among 889 participants, 41 (4.6%) reported experiencing a nonfatal overdose in the past month. Persons who had experienced nonfatal overdoses were more likely to be female (adjusted odd ratio [aOR], 2.2), to receive medications for opioid use disorder (aOR, 2.5), to be homeless or unstably housed (aOR, 2.2), and to report being highly impacted by the COVID-19 pandemic (aOR, 2.4). The authors call for multilevel interventions to address vulnerabilities and the main drivers of the poisoning crisis.

Li and colleagues reported on HIV risk behaviors among Black and Latina transgender women in the United States (Abstract 790). They recruited 900 HIV-negative transgender women from 7 US cities using respondent-driven sampling, and found that risk practices were higher among Black and Hispanic transgender women than White or other counterparts. Among Black and Hispanic transgender women, 4 in 5 had a cisgender man as their last sex partner, 1 in 4 had condomless sex at last sex, and 1 in 2 had concurrent sex partners. Fewer than 40% of transgender women reported being on PrEP, although the prevalence of PrEP use was higher among Hispanic than White or other women (adjusted prevalence ratio [aPR], 1.5; 95% confidence interval [CI], 1.14-1.96), suggesting the need to increase access to PrEP programs for transgender women at risk for HIV acquisition.

Rosenberg and colleagues reported on HIV incidence across 12 countries in sub-Saharan Africa (Abstract 787). The data were gathered through Population-Based HIV-1 Impact Assessment (PHIA) household surveys and were pooled across countries. Among persons aged 15 to 59 years old, HIV incidence was 3.8 per 100 person-years for women (95% CI, 3.0-4.5) and 1.9 per 100 person-years for men (95% CI, 1.3-2.5). Rates for women were highest among 15- to 34-year-olds, significantly higher than among men at those ages. Rates for men were highest among 35 to 44 years of age. Overall, 316,270 new annual infections were estimated out of a target population of 121 million people in the 12 countries. Women aged 15 to 34 years accounted for 52.5% of all new infections. These high HIV infection rates highlight the need for HIV prevention strategies to be scaled up in these countries. Guo and colleagues evaluated data from these PHIA surveys in 12 sub-Saharan African countries and found that awareness of HIV serostatus was low, varying from Côte d'Ivoire at 50% to Eswatini at 87%. In multivariable regression models, men overall and young men and women (aged 15 to 24 years) were less likely to be aware of their HIV-positive status across all countries. In addition, male sex, younger age, rural residence, and lower education level were less likely to have ever tested for HIV. Among those who had ever tested, fewer than half had tested in the 12 months prior to the survey. This suggests the need for scale-up of HIV testing, particularly for these undertested populations.

In 12 sub-Saharan African countries, women aged 15 to 34 years accounted for more than half of all new HIV infections

Incident HIV infection during pregnancy contributes up to 25% of mother-to-child transmissions in sub-Saharan Africa. Woldesenbot and colleagues reported on HIV incidence among pregnant women from 2 national surveys in South Africa (Abstract 701). They used data from 2 cross-sectional surveys in 2017 and 2019 in South Africa; each were comprised of more than 36,000 pregnant women receiving antenatal care from 1590 facilities. HIV incidence was calculated using a recency HIV antibody assay. The annual HIV incidence was 1.5% and 1.2% in 2017 and 2019, respectively. Factors associated with a higher odds of recent infection

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included being in a non-marital relationship, residing in a rural area, having a high school education or lower, and having the current pregnancy be unintended. The annual incidence for both years was higher than the UNAIDS (Joint United Nations Programme on HIV/AIDS) target of less than 1%. These data should help in identifying and intervening with prevention interventions for women at increased risk of HIV infection.

Hampshire and colleagues presented data on the association of heavy rainfall with higher HIV prevalence in 21 counties in sub-Saharan Africa (Abstract 789). Using data from Demographic and Health Surveys (DHS) in these 21 countries from 1997 to 2017, they found the odds of having HIV infection to be higher among those with a larger number of years of heavy rainfall in the 10 years prior to the survey (aOR, 1.14; 95% CI, 1.11-1.18), as well as the odds of having a sexually transmitted infection (STI) in the past 12 months (aOR, 1.11; 95% CI, 1.07-1.15), and of reporting a greater number of sexual partners in the past 12 months (aOR, 1.12; 95% CI, 1.06-1.17). The association between heavy rainfall and high HIV prevalence was particularly pronounced in women and in those living in rural settings. They hypothesize that such increased prevalence may arise from flooding and food insecurity leading to transactional sex and migration, and damage to public infrastructure weakening access to health resources for HIV prevention.

Akullian and colleagues presented a mathematical model investigating the contribution of acute or early HIV infection to new HIV infections in young adults in Eswatini (Abstract 794). They found that ART scale-up has had the largest effect in reducing transmission from people with HIV in the latent stage of infection, decreasing from contributing 70% of HIV incidence to 40% of HIV incidence with the onset of universal test-and-treat policies. Although the absolute number of new infections contributed from acutely infected individuals (less than 3 months from acquisition) declined, the proportion of total transmissions increased from 10% to 15% before versus after universal test and treat. In the universal test-and-treat era, most infections (50%-60%) in men and women younger than 25 years of age were from individuals infected for less than 1 year. They found that incidence above 1% could be sustained despite universal test and treat, suggesting that additional measures are needed to eliminate new HIV infections. Gountas and colleagues also created a mathematical model to evaluate whether meeting the 95-95-95 target for Greek MSM would be enough to meet the UNAIDS goal of reducing HIV incidence by 90% by 2030 (Abstract 797). They found that under a status quo scenario, Greek MSM would reach the 95-95-95 target by 2030, but that it would only reduce HIV incidence by 32.4% compared with 2010 levels. Therefore, the authors called for scale-up of PrEP to achieve target reductions in HIV incidence. Cambiano and colleagues created a mathematical model of HIV incidence in MSM in the United Kingdom (Abstract 898). They found that the HIV incidence declined 74% from approximately 2600 new HIV infections in MSM in 2011 to approximately 670 in 2021. In their model, condom use, PrEP, a boost in HIV testing and ART played a key role in reducing new HIV infections. They predicted that continuation of current prevention policies is likely to lead to virtual elimination (defined as less than 1/1000 new person-years of infection) in 25 years' time.

HIV Testing

Drammeh and colleagues presented trends in HIV testing and linkage to HIV treatment in 41 countries from 2016 to 2021 (Abstract 89). These data included 41 of 59 PEPFAR (President's Emergency Plan for AIDS Relief) countries, and 99.3% of PEPFAR's HIV testing and treatment results. Since 2018, HIV tests decreased from approximately 20 million annual tests to 15 million annual tests, as PEPFAR moved from recommending universal testing to testing targeted to those believed to be at increased risk of HIV infection; however, test positivity remained relatively stable over that period of time at approximately 4%. This would suggest that the new testing guidance is not identifying a population enriched for persons with HIV, and that more people with HIV may be missed by this new testing strategy. Since 2016, the proportion of newly diagnosed

persons initiating ART has increased from 60% to 90%, approaching the 95% target set by UNAIDS.

Chavez and colleagues presented data on distribution of 100,000 oral HIV self-test kits throughout the United States and Puerto Rico in 2021 (Abstract 143). Their campaign, run through the TakeMeHome portal, focused its efforts on reaching Black and Hispanic MSM, transgender women of any race/ethnicity, and Black women in areas with high HIV burden. They planned for the campaign to last for up to 18 months, but 100,000 test kits were distributed by 8 months. In total, 52,277 ordered 1 or 2 test kits, 55% of which were ordered in high-HIV-burden areas. Overall, 26% of persons ordering tests had never been previously tested, and an additional 33% had been tested more than 12 months prior. Cisgender MSM placed 47% of the orders, 18.4% of whom had never been tested, substantially higher than the 5% of MSM who report never having tested in the National HIV Behavioral Surveillance study. The program also reached cisgender Black women (11% of all orders, 22% of whom had never tested), and transgender women (1.6% of all orders, 24% of whom had never tested.) The Center for Disease Control and Prevention (CDC) plans to continue its direct-to-consumer marketing and distribution of self-tests, and hopes that state and local health departments and community-based organizations will also promote use of HIV self-testing.

The CDC distributed 100,000 oral HIV self-test kits in 8 months throughout the United States and Puerto Rico

Thakker and colleagues reported on HIV self-testing conducted in 28 states in India from June through December 2021 (Abstract 144). In India, 24% of persons with HIV are unaware of their status, necessitating strategies to increase testing. The team used virtual counselors to approach potential testers through dating Apps and social media platforms. They reached 1959 persons with self-test kits, 73% of whom requested assistance in conducting the self-test. Overall, 79% of testers were MSM, 8% were transgender, 11% were female sex workers, and 2% were PWID. Of these, results were reported in 92% of testers. Overall, 5% of persons were found to be HIV positive, much higher than the overall prevalence of 0.2% in the general Indian population. Of these, 72% were male and the median age was 27 years. Only 41% of those with a positive screening test had confirmatory tests, were linked to care, and received ART. Bell and colleagues reported on another evaluation of virtual HIV testing in 6839 persons in 22 Indian states (Abstract 806). In this study, 7% of persons tested positive, 73% of whom had no prior HIV testing history. Only 51% of those testing positive initiated ART; persons with no prior testing history were less likely to initiate ART than those with previous testing experience (66% versus 75%, respectively). Both studies suggest that these online testing strategies, using a team of virtual outreach workers, are successful in identifying persons unaware of their HIV status, but more work is needed to link newly diagnosed persons to HIV care.

Salvadori and colleagues tested a 3-in-1 rapid blood self-test for HIV, hepatitis B surface antigen, and hepatitis C antibody, collected by fingerstick, in Thailand (Abstract 814). Overall, 2260 persons presented for testing, half of whom were born female, and 59% of whom had never previously tested for HIV. When given the option for health care worker-based or self-testing, 81.6% of clients chose self-testing, with most able to correctly interpret the results. Only 37 (2%) of 1844 self-testers misinterpreted at least 1 result, and 93.3% reported being "very satisfied" with the testing. This suggests that multiplex rapid blood self-testing may be highly acceptable and could contribute to easier access to testing and earlier diagnosis of HIV, hepatitis B, and hepatitis C.

Davey and colleagues presented data on a randomized trial of distribution of self-test kits for the male partners of women with HIV versus clinic referral in South Africa (Abstract 145). In South Africa, 13% of men with HIV are unaware of their status (approximately 1 million men), and clinic-based

testing has numerous barriers for men to attend. In this study, women with HIV with partners of unknown serostatus were randomly assigned to receive home oral self-test kits to distribute to their partners, or to refer their partners for clinic-based testing. In an intention to treat analysis, 78% of women assigned to the self-testing group reported that their partners underwent HIV testing, compared with 55% in the control group (relative risk [RR], 1.4; 95% CI, 1.1-1.8). Seropositivity was similar between the 2 groups of partners (14% versus 12%). There was 1 case of intimate partner violence (partner yelled at the woman) and 1 case in which the partnership broke up. The authors recommend that women with partners of unknown HIV serostatus receive home self-test kits to distribute to their partners. In contrast, Mujugira and colleagues presented data on a partner testing program with self-test distribution by Ugandan pregnant women with HIV (Abstract 897). They enrolled 500 pregnant women with HIV, and randomly assigned them 2:1 to a secondary distribution of HIV self-testing kits or an invitation for fast-track HIV testing. In this study, there was no significant difference in the proportion of male partners who tested (49% versus 45%, respectively), nor in linkage to ART or PrEP for their partners, depending on their HIV status. The authors call for additional strategies to reach men for HIV testing.

Hensen and colleagues presented a cluster randomly assigned trial of an HIV testing intervention for adolescents and young adults, aged 15 to 24 years, in Zambia (Abstract 813). The Yathu Yathu trial randomized 20 zones in 2 communities to an intervention, comprised of a community-based hub providing sexual and reproductive health services staffed by peer support workers or a control condition, comprised of only a health facility. Overall, 1989 youth participated, half of whom were male. After the intervention, knowledge of HIV status by self-report or HIV testing was higher in the intervention arm than the control arm (73.3% versus 48.4%, respectively; aPR, 1.53; $P<0.001$). The authors concluded that delivering a community-based, peer-led, and incentivized sexual and reproductive health services increased knowledge of HIV serostatus and could thus make a substantial contribution to increasing access to HIV prevention and care.

Chirairo and colleagues evaluated the yield of HIV testing of partners (assisted partner services [APS]) of persons newly diagnosed versus persons with established diagnoses in Namibia (Abstract 147). Both sets of persons with HIV were asked about partners within the past 24 months, who were then contacted and, if not known to be HIV positive, were recommended for HIV testing. There was similar acceptance of APS (90% vs 89%, respectively) and of the number of contacts identified per person (1.06 vs 1.0, respectively) in persons with new versus established HIV infection. Persons newly diagnosed had a lower proportion of partners with a previous diagnosis than persons with established diagnoses (13% vs 37%, respectively), and higher HIV case finding (0.14 vs 0.09 positive tests per index case, respectively), but the latter was not statistically significantly different. The authors recommend that APS be offered to persons with new and established HIV infections to uncover previously undiagnosed HIV infections in sexual partners. Golden and colleagues also evaluated APS and the risk of adverse events in Mozambique (Abstract 148). They found the number of contacts per index case (1.03) was similar to that in the Chirairo study, but the case finding was higher (0.36 new HIV positive diagnoses per index case). Only 5 of 211 persons who had a fear of an adverse event actually had an adverse event (2.4%) and the rate overall was even lower (1.2%). Only 0.5% suffered physical violence, 0.9% were pushed, abandoned, or yelled at, and 0.8% lost financial support. The best predictor of having an adverse event was having a partner who was notified but not HIV tested. The authors concluded that APS is a safe intervention.

Sexually Transmitted Infections

Killian and colleagues reported on the prevalence of syphilis in Tanzania, Uganda, Zambia, and Zimbabwe based on PHIA surveys conducted between 2016 and 2019 (Abstract 141). The prevalence of syphilis was higher among people with HIV, ranging from 2.9% in Zimbabwe to 9.6% in Zambia;

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among HIV-negative persons, it ranged from 0.8% in Tanzania to 2.1% in Zambia. However, the majority of individuals with syphilis are HIV-negative,

Although the prevalence of syphilis was higher among people with HIV in 4 African countries, individuals without HIV account for three-fourths of the more than 1 million syphilis cases

accounting for approximately three-fourths of the more than 1 million syphilis cases across the 4 countries. Among people with HIV, syphilis prevalence did not differ by age or other demographics but was higher among those with 2 or more sexual partners in the past 12 months. Among HIV-negative individuals, syphilis prevalence increased with age and was higher among people with less than a secondary education; those who were divorced, widowed, or separated; and individuals with lower socioeconomic status. These findings highlight the need for consistent and frequent screening for syphilis among people with or at-risk for HIV and improved access to effective syphilis treatment.

Patel and colleagues reported on HIV risk among patients with discordant syphilis antibody profiles within the Montefiore Health System (Abstract 873). They defined a discordant profile as having a positive initial treponemal test, negative nontreponemal test, and positive confirmatory treponemal test. Among 28,274 patients with syphilis testing between January and June 2018, 960 (3.4%) had a discordant syphilis antibody profile: 798 had previously treated syphilis, 97 had untreated late latent syphilis, 5 had early primary syphilis with prozone phenomenon, and 60 were inadequately assessed. Among 522 HIV-negative patients with a discordant syphilis profile, 15% had active HIV risk, including 11% on PrEP, 6% with gonorrhea or chlamydia within the past 3 years, and 0.38% had early syphilis. These findings suggest that clinicians should counsel individuals with discordant syphilis testing about HIV risk and consider PrEP.

Several studies reported on STIs in pregnancy and associated pregnancy outcomes. Castilho and colleagues presented data on prenatal syphilis risk among 2,169 pregnant women with HIV in Brazil (Abstract 885). Overall, 166 (7.7%) had prenatal syphilis, of whom 91% had documented treatment. The median gestational age at syphilis diagnosis was 14.6 weeks. Compared with those without prenatal syphilis, women with HIV with prenatal syphilis were younger, more likely to be Black or mixed race, more likely to have less than 8 years of education, were diagnosed with HIV in later calendar years, and were more likely to have ever used tobacco, alcohol, and crack or cocaine. Adverse pregnancy outcomes (stillbirth, spontaneous abortion) were rare and did not differ in those with or without prenatal syphilis.

Oluoch and colleagues reported on the risk of bacterial vaginosis (BV) before and during first pregnancy among Kenyan adolescent girls and young women (AGYW) at risk for HIV (Abstract 878). Among 400 AGYW aged 16 to 20 years, 42% had a positive pregnancy test during study follow-up. Overall, 38% of participants had BV before pregnancy and 23% had BV during pregnancy. The adjusted relative risk (aRR) of BV during pregnancy among AGYW who had experienced BV pre-pregnancy was 0.66 (95% CI, 0.48-0.92), indicating that pregnancy in this cohort was associated with a 34% reduction in BV diagnosis. A history of chlamydia infection was associated with BV during pregnancy (RR, 4.13; 95% CI, 1.73-9.90). The authors hypothesize that changes in the hormonal milieu during pregnancy may explain the protective effect from BV during pregnancy.

Nyemba and colleagues evaluated the impact of diagnosing and treating curable STIs during pregnancy on adverse pregnancy and birth outcomes (Abstract 886). Among 619 pregnant women (79% with HIV) attending antenatal clinics in South Africa, the prevalence of any STI was 37%: 26% with chlamydia, 18% with trichomonas, and 6% with gonorrhea. Overall, there were 93% singleton live births, 5% miscarriages, and 2% stillbirths, and among live births, there were 1% neonatal deaths,

7% low birthweight in full-term babies, and 10% preterm delivery, resulting in a composite adverse pregnancy outcome in 24%. Diagnosis and treatment of any STI at the first antenatal care visit was not associated with adverse pregnancy or birth outcomes. However, in women with HIV, diagnosis and treatment of chlamydia (aRR, 1.57; 95% CI, 1.04-2.39) and gonorrhea (aRR, 1.69; 95% CI, 1.09-3.08) were independently associated with the composite adverse pregnancy outcome. The researchers highlight the urgent need for STI testing and treatment in antenatal clinics to reduce the high burden of STIs in pregnant women in South Africa.

Rossotti and colleagues evaluated the impact of the nonavalent human papillomavirus (HPV) vaccination on oral HPV infection (Abstract 876). Among 211 MSM and transgender women (65% with HIV, mean CD4+ count 788 cells/μL) assessed before and after nonavalent vaccination, 14% tested positive for oral HPV infection at baseline, with higher rates in people with HIV (18.8% vs 5.4% in PrEP users and 5.9% in other individuals being screened for STIs). The positivity rate did not change over time after vaccination, and recreational drug use was the only factor associated with HPV acquisition (adjusted hazard ratio [aHR], 3.52; 95% CI, 1.22-10.10). Although viral clearance was observed in the large majority of those with oral HPV at baseline, a significant proportion acquired a new infection over time; these trends did not differ by HIV status.

Omollo and colleagues evaluated the use of a risk score to facilitate targeted STI diagnostic testing in young Kenyan women (Abstract 877). Using data from the POWER (Prevention Options for Women Evaluation Research) cohort, a PrEP implementation science project for AGYW in family planning clinics in Kenya, they developed a risk score to identify youth at increased risk for chlamydia or gonorrhea infection, which included parameters for age, marital status, living situation, breastfeeding status, and use of family planning methods. Among 996 women with test results, 12% presented with STI symptoms; the overall prevalence of chlamydia or gonorrhea was 21%. The area-under-the-receiver operating curve (AUC) for the risk score was 0.71, and having a risk score of 4 or higher (occurring in 52% of women), had 78% sensitivity and 57% specificity for detection of chlamydia or gonorrhea infection. Using the syndromic approach, symptoms had only 15% sensitivity and 88% specificity, missing 85% of all infections, highlighting the inadequacy of syndromic management and the need for improved screening algorithms and high-quality diagnostic tests in this population.

Hazra and colleagues presented data on a novel delivery model of linking emergency department patients to a Sexual Wellness Clinic for STI services and PrEP (Abstract 872). Patients presenting to the emergency department with STI complaints were screened by a triage physician and transported to the Sexual Wellness Clinic for medical evaluation, comprehensive STI testing and treatment, and same-day PrEP initiation. From February 2019 to September 2021, 560 patients were seen in the clinic; median age was 30 years, half were cisgender female patients, and 72% had public (Medicaid/Medicare) insurance. STI positivity rates were 24% for syphilis, 15% for gonorrhea, 13% for chlamydia, 0.89% for herpes simplex virus (HSV), and 0.54% for HIV. There were 90 same-day PrEP starts (16%), of which 57% were cisgender female patients. All new PrEP starts had follow-up appointments scheduled, with 20% continuing to take PrEP at 3 months and 11% at 6 months. This study demonstrates that transferring emergency department patients to a specialized sexual health clinic is feasible and can identify unique target populations, including cisgender women. However, additional efforts are needed to improve adherence to PrEP.

Preexposure Prophylaxis

Novel PrEP Agents and Formulations

Landovitz and colleagues presented updated efficacy data from the ongoing HPTN (HIV Prevention Trials Network) 083 study, a phase IIb/III randomized trial comparing long-acting injectable cabotegravir (CAB-LA) administered every 8 weeks with daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) in cisgender men and transgender women who have sex with men (Abstract 96). At last year's CROI,

data from the blinded phase of the trial through May 2020 showed 51 incident HIV infections (12 assigned to CAB-LA, 39 assigned to TDF/FTC) with a hazard ratio (HR) of 0.32 (95% CI, 0.16-0.58), supporting approval of CAB-LA for PrEP by the US Food and Drug Administration (FDA) in December 2021. In this updated analysis, 4 additional infections were detected in the blinded phase (2 CAB-LA, 2 TDF/FTC) and 42 infections (11 CAB-LA, 31 TDF/FTC) were identified in the 1-year period after unblinding (May 2020-May 2021) in which participants continued their original randomized study treatment until the protocol was amended to offer eligible participants open-label CAB-LA. Reduction in risk for CAB-LA versus TDF/FTC remained similar in the unblinded phase (HR, 0.33; 95% CI, 0.17-0.66) and when blinded and unblinded periods were combined (HR, 0.34; 95% CI, 0.22-0.54). HIV incidence was higher in both arms in the unblinded phase (0.76/100 person-years in the CAB-LA arm vs 2.20/100 person-years in TDF/FTC arm), which was attributed to a decline in adherence in both groups and increased contributions of person-years from high incidence regions in Latin America during the unblinded period. The 2 newly identified blinded CAB-LA arm infections occurred in the setting of on-time CAB-LA injections. Of the 11 newly identified unblinded CAB-LA arm infections, 1 had on-time injections, 3 had delayed injections, and 7 occurred more than 6 months after the last CAB-LA exposure (2 of these 7 never received a CAB-LA injection). Six additional new CAB-LA arm infections were identified after 3 years on study (after the prespecified analysis period), all of which occurred more than 6 months after the last injection. No new safety concerns were identified with the additional year of follow-up visits.

Eshleman and colleagues reported on the timing of emergence of InSTI resistance among CAB-LA–arm breakthrough infections in HPTN 083 (Abstract 95). The authors used a single genome sequencing assay to assess for InSTI resistance at low viral loads and whether earlier detection of these infections using a sensitive RNA assay for screening would reduce InSTI resistance risk. In all 7 participants with InSTI resistance mutations, detection of infection at study sites using rapid tests and antigen/antibody tests was delayed (median, 60 days). In 5 of the 7 cases, major InSTI resistance mutations were first detected in samples from individuals with low viral loads. Use of a qualitative RNA assay for HIV screening would have detected HIV infection before a major InSTI resistance mutation was detected in 4 cases or before additional major InSTI resistance mutations accumulated in 2 cases. Given the high efficacy of this injectable PrEP regimen, the authors recommend that CAB-LA be considered in settings where HIV RNA screening is not readily available.

As the efficacy trials of CAB-LA used TDF/FTC as an active comparator, Donnell and colleagues constructed counterfactual estimates of CAB-LA efficacy against placebo (Abstract 86). The HPTN 084 study conducted among 3224 women in sub-Saharan Africa demonstrated an 89% reduction in HIV acquisition in participants who received injectable CAB-LA versus oral TDF/FTC. Using data from 3 contemporaneous randomized HIV prevention trials taking place in similar locations (AMP [Antibody Mediated Prevention] trial, ECHO [Evidence for Contraceptive Options and HIV Outcomes] trial, and HVTN [HIV Vaccine Trials Network] 702), the researchers constructed estimates of counterfactual placebo incidence rates of 2.62, 4.47, and 4.21 per 100 person-years, respectively, resulting in CAB-LA versus placebo estimates of 93%, 95%, and 93%, respectively. These findings illustrate a potential approach for estimating efficacy in future prevention trials with no placebo arm.

Young and colleagues presented on preclinical work to develop a long-acting injectable for prevention of HIV and unplanned pregnancy (Abstract 80). They developed an in situ forming implant (ISFI) that is injectable, long acting for more than 3 months, administered subcutaneously, biodegradable, and removable, and loaded them with dolutegravir (DTG) or CAB and etonogestrel (ENG) or medroxyprogesterone acetate (MPA). The optimized formulations of these combinations were then evaluated in a 90-day pharmacokinetic (PK) and safety study in female mice (12 in each group). In vivo plasma concentrations of CAB and DTG were above the previously established threshold of 4

times the protein-adjusted inhibitory concentration (4× PA-IC_{90}) for 90 days. There were no significant differences in antiretroviral drug release when formulated with either hormone. DTG, CAB, and MPA demonstrated zero-order release kinetics, and ENG elicited first-order release. Drug depots retrieved after 90 days showed 41% to 65% degradation of the polymer and substantial residual drug remaining, respectively, particularly for CAB and MPA, suggesting that these multipurpose technology ISFIs have the potential to release for longer than 90 days in vivo. All formulations were safe and well tolerated.

Massud and colleagues evaluated the PK and efficacy of biodegradable ISFIs with CAB in macaques (Abstract 855). Two 1-mL injections of CAB ISFI were administered to 6 rhesus macaques who were then challenged with simian HIV $(SHIV)_{162p3}$. Median plasma CAB levels were high at week 4 and remained about 1.9-fold above the 4× PA-IC_{90} for up to 6 months after administration, and median CAB levels in vaginal and rectal tissues increased more than 2-fold by week 12. Four CAB-treated animals exposed to SHIV twice weekly starting at week 4 or week 12 postadministration were fully protected after 8 SHIV exposures for up to 6 months, compared with 2 untreated animals that were infected with SHIV after 1 rectal challenge. Implant removal in 2 macaques at week 12 resulted in a rapid decline in plasma CAB levels within 3 days, and CAB levels fell below the limit of detection by week 3 postremoval. No skin reactions or safety concerns were observed at the implant sites in any of the CAB-treated animals.

Macdonald and colleagues reported on metabolic and renal outcomes of monthly oral islatravir, a nucleoside analogue reverse transcriptase translocation inhibitor, in a phase IIa trial for HIV PrEP (Abstract 85). In this study, 224 participants (68% female, 41% Black) at low risk for HIV were randomly assigned to islatravir 60 mg, 120 mg, or placebo taken once monthly. At 24 weeks, median percent changes from baseline in weight, total hip bone mineral density (BMD), lumbar spine BMD, peripheral fat, and trunk fat were small and comparable for the islatravir 60 mg and placebo groups. There were slight median percent increases in weight (+1.8%), peripheral fat (+2.5%), and trunk fat (+3.4%) in the islatravir 120-mg arm compared with baseline. No changes in serum creatinine level or estimated glomerular filtration rate (eGFR) were observed across treatment groups, and small and similar decreases in urinary retinol-binding protein to creatinine ratios were observed across groups, indicating no significant proximal renal tubular dysfunction. Based on declines in lymphocytes seen in clinical trials of islatravir, the PrEP program has been placed on a clinical hold by the US FDA, and all participants enrolled in phase III efficacy trials are being offered open-label daily PrEP.

Hendrix and colleagues presented on the PK distribution of islatravir 60 mg and 120 mg in blood and mucosal tissues among 44 participants enrolled in the tissue PK substudy of the same trial (Abstract 83). Drug concentrations in rectal, vaginal, and cervical tissue and rectal cells, and peripheral blood nuclear cells (PBMCs) showed parallel declines between weeks 1 and 4, with similar trough levels across tissue types and cells observed at week 24. For both doses, islatravir levels in rectal cells and PBMCs remained above the PBMC PK threshold established in prior PK/pharmacodynamic (PD) studies. Drug concentrations were generally similar across tissue types in women and men for islatravir and its active form (islatravir triphosphate [ISL-TP]), and drug penetration was similar in rectal and vaginal tissue. Based on these findings, the authors suggest that plasma islatravir levels may be useful as a surrogate for drug exposure in cervical and rectal tissue.

Two-thirds of young African women chose the dapivirine vaginal ring over daily oral PrEP in the REACH study

Ngure and colleagues presented results on choice and adherence to the dapivirine vaginal ring or oral PrEP among 247 young African women in the REACH (Reversing the Epidemic in Africa with Choices in HIV Prevention) study (Abstract 88). In

this 18-month crossover trial, participants were randomly assigned to the monthly ring or daily oral TDF/FTC for the first 6-month period, switched to the other product for the second 6-month period, then were given a choice of ring, oral PrEP, or neither in the third 6-month choice period. The mean age of participants was 18 years, 87% were not married, and 40% had ever been pregnant. Of the 227 (92%) participants who reached the choice period, more than two-thirds (67%) chose the ring, 31% chose oral PrEP, and 2% chose neither product. Residual dapivirine levels in used rings and tenofovir diphosphate (TFV-DP) levels in dried blood spots indicated that participants used both the ring and oral PrEP consistently in the crossover and choice periods with some to high adherence; less than 5% of visits were categorized as no or low adherence to study product. High adherence to oral PrEP in the crossover period was strongly associated with choice of oral PrEP; however, this relationship was not observed for ring choice. These findings demonstrate that AGYW can make informed choices about HIV prevention products and can use products effectively with proper support.

There were no differences in tenofovir diphosphate levels in dried blood spots among transgender men and women taking versus not taking gender-affirming hormones

Liu and colleagues presented data on the safety, PK, and acceptability of a 90-day tenofovir vaginal ring in 49 participants assigned female sex at birth (Abstract 82). An extended-duration vaginal ring containing tenofovir could increase adherence and effectiveness, reduce cost and clinic/user burden, and may also help prevent herpes simplex virus 2 acquisition. Participants in this phase I trial were randomly assigned 2:1 to receive a polyurethane ring loaded with 1.4 grams of tenofovir or a placebo ring used continuously for 91 days. The tenofovir ring was well tolerated with no statistically significant differences in reported adverse events across arms. Geometric mean tenofovir concentrations in cervicovaginal fluid and cervical tissue remained high through day 56 but declined at day 91 in a subset of participants. Similarly, geometric mean TFV-DP tissue concentrations exceeded the 1000 femtomole per mg target based on macaque challenge studies through day 56 but fell at day 91. Returned rings were analyzed for residual TFV-DP, and 13 of 32 tenofovir rings had low or no residual tenofovir, consistent with most the tenofovir being released from the ring, with no significant differences by sociodemographics or sexual activity. Acceptability of the ring was high, with most participants reporting a high likelihood of using the ring in the future, if effective. Additional studies are needed to better characterize the higher drug release from the ring in some participants and to determine the optimal duration of use.

PrEP in Pregnancy

Delany-Moretlwe evaluated the safety and PK of CAB-LA in pregnant women in the blinded phase of the HPTN 084 trial (Abstract 700). In this study, which demonstrated CAB-LA was superior to TDF/FTC in preventing HIV in women in sub-Saharan Africa, participants with a positive pregnancy test stopped the blinded study product (CAB-LA or TDF/FTC) and were started on open-label TDF/FTC. Among 3224 women enrolled, there were 49 confirmed pregnancies (29 in the CAB-LA arm, 20 in the TDF/FTC arm) for an overall pregnancy incidence of 1.3 per 100 person-year. Although CAB-LA participants (n=6) experienced more pregnancy-associated adverse events than TDF/FTC participants (n=1), all pregnancy-associated adverse events were assessed as unrelated to study product, and no congenital

Residual CAB-LA was generally well tolerated in pregnant women

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abnormalities were observed. Of the 43 participants with confirmed pregnancy who received at least 1 injection, the incidence of grade 2 or higher adverse events was 113 per 100 person-years in the CAB-LA arm and 166 per 100 person-years in the TDF/FTC arm (P=.064). The CAB-LA geometric mean apparent terminal phase half-life was similar in pregnant women in HPTN 084 to that in nonpregnant women in HPTN 077 (62 days vs 64.3 days, respectively). These findings suggest that residual CAB-LA was generally well tolerated in pregnant women. Ongoing studies will examine the safety and PK of CAB-LA in women who choose to continue CAB-LA during pregnancy.

Davey and colleagues reported on pregnancy and birth outcomes in oral PrEP-exposed and -unexposed pregnant women in South Africa (Abstract 705). Among 997 pregnancy outcomes ascertained in the PrEP-PP (PrEP in Pregnancy and Postpartum) study, 93% were PrEP exposed. Overall, 94% had singleton live births; 5% had miscarriages or stillbirths in the PrEP-exposed group vs 9% in the PrEP-unexposed group (P=.06). Birth outcomes did not differ between the PrEP-exposed versus PrEP-unexposed groups (P=.99), and among the PrEP exposed, there was no association with duration of antenatal PrEP exposure and birth outcomes (P=.84). These findings support the integration of PrEP into the prevention of mother-to-child transmission and antenatal care programs in communities with high HIV incidence.

In the same study, Davey and colleagues evaluated PrEP continuation and adherence during pregnancy and the postpartum period (Abstract 704). Among 1201 pregnant women in the study, 84% started PrEP during their first antenatal visit. At 1 month and 3 months, 66% and 58% received a repeat prescription, respectively. Among 179 participants who reported any PrEP use at their 3-month visit and had dried blood spots analyzed, two-thirds (65%) had TFV-DP present in their sample (62% in pregnancy and 73% postpartum). Overall, 13% of samples were consistent with approximately 7 doses per week, 17% indicated 2 to 6 doses per week, and 35% indicated fewer than 2 doses per week. Correlates of having detectable TFV-DP included older maternal age, early gestational age at first antenatal clinic visit, single relationship status, and high baseline HIV risk perception. As many women demonstrated intermittent PrEP use in this study, interventions are needed to improve peripartum PrEP continuation and adherence.

Larsen and colleagues presented findings on PrEP use persistence among Kenyan women who initiated PrEP during pregnancy in the PrIMA (PrEP Implementation for Mothers in Antenatal Care) study (Abstract 845). Among 361 women who initiated PrEP and were analyzed in this cohort, 58% persisted with PrEP use at 9 months postpartum. Among those, 53% reported not missing any PrEP pills in the past 30 days. Participants with partners with HIV and those 24 years or older were more likely to persist with PrEP. These findings suggest that adherence interventions should prioritize younger pregnant women and those who may not know their partner's HIV status.

Matthews and colleagues reported on PrEP use among South African women with plans for pregnancy in the next year (Abstract 846). Among 327 women completing safer conception counseling, of whom most (96%) did know their partners' HIV status, 195 initiated PrEP. The median adherence during periconception follow-up was 63% as measured using electronic pill caps, with adherence declining over time (73% during the first 3 months and 62% at 12 months). Approximately 32% to 36% of women had high levels of plasma tenofovir through 6 months, but only 14% at month 12. HIV incidence was high in this cohort: 4.04 per 100 person-years overall, 3.66 per 100 person-years among PrEP initiators, and 4.62 per 100 person-years among those who did not initiate PrEP. These results highlight the need for additional PrEP support strategies for young women during the periconception period.

PrEP in Transgender People

Blumenthal and colleagues evaluated the bidirectional effects of hormone therapy and TDF/FTC PrEP in a large cohort of transgender individuals in the ImPrEPT (iTAB plus Motivational Interviewing for PrEP Adherence in Transgender Individuals)

study (Abstract 84). Among 172 participants enrolled in the hormone substudy, 114 had paired samples available for analysis, with a mean age of 33 years, 14% were Black participants, and 31% were Latinx participants. Among 49 transgender women on stable estrogen, estradiol concentrations did not change significantly between weeks 0 and 12 in those taking PrEP (185 vs 222 pg/mL; *P*=.53). Among 39 transgender men on stable testosterone, testosterone concentrations decreased marginally from week 0 to week 12 in individuals taking PrEP (373 vs 274 ng/dL; *P*=.052); however, the effect size was small. At week 12, there were no differences in TFV-DP levels in dried blood spots in transgender women not taking hormones versus those taking hormones (1886 vs 1589 fmol/punch, *P*=.26) and transgender men not taking hormones versus those taking hormones (1682 vs 1962 fmol/punch, *P*=.49), after adjusting for age, creatinine clearance, and weight. Additionally, there were no changes in body image satisfaction or satisfaction with hormone therapy on gender transition.

From the same study, Morris and colleagues reported results of a randomized controlled trial of a text messaging support intervention with or without brief motivational interviewing (bMI) in transgender individuals (Abstract 990). In this study, 265 participants were randomly assigned 1:1 to receive individualized Texting for Adherence Building (iTAB) with or without bMI. Adherence for the primary outcome (TFV-DP concentrations in dried blood spots ≥1246 fmol/punch [≥7 doses/week] at weeks 12 and 48) was 49% for 57 transgender men, 37% for 19 nonbinary individuals, and 31% for 145 transgender women. Adherence for the secondary outcome (TFV-DP ≥719 fmol/punch [≥4 doses/week] at weeks 12 and 48) was 58% for transgender men, 47% for nonbinary individuals, and 44% for transgender women. Adherence was not statistically different between the iTAB+bMI and iTAB alone groups for either outcome; however, participants in the iTAB+bMI arm showed an increase in self-reported adherence compared with iTAB alone (daily dose taken 59.8% of days vs 48.7% of days, respectively, *P*=.011); this improvement was primarily seen in transgender women.

Zhu and colleagues reported on PrEP need and services provided to transgender persons in the THRIVE (Targeted Highly Effective Interventions to Reverse the Epidemic) project (Abstract 853). Among 1413 Black and Hispanic transgender women and men enrolled, 83% of transgender women without HIV and 63% to 67% of transgender men without HIV were eligible for PrEP. Nearly 90% of PrEP-eligible participants were referred for PrEP, but less than half were linked to a practitioner or were prescribed PrEP. These findings highlight the importance of addressing barriers to PrEP linkage and prescription among Black and Latinx transgender men and women.

Hoover and colleagues assessed the extent to which HIV prevention services are provided to transgender people prescribed gender-affirming hormone therapy (GAHT) (Abstract 852). Based on data in the 2012 to 2019 MarketScan database, the estimated number of people with transgender-related International Classification of Diseases (ICD)-9/10 codes increased from 7993 in 2012 to 94,168 in 2019, and the estimated number of transgender people prescribed GAHT increased from 1,961 (24.5%) to 38,110 (41%) during this period. Although HIV testing and PrEP prescriptions increased among transgender women and men using GAHT during this period, provision of these prevention services was still low. In 2019, only 23% of transgender women were tested for HIV, and 18% were prescribed PrEP; only 18% of transgender men were tested for HIV, and 12% were prescribed PrEP. The authors recommend holistic service models that provide HIV prevention services in addition to GAHT.

Although PrEP awareness has increased among Latinx MSM in the United States, PrEP use has remained low at 11% to 12%

Trends in the PrEP Continuum

Several studies evaluated trends in the PrEP continuum in priority populations globally. Barry and

colleagues characterized the PrEP continuum among 9011 Latinx MSM participating in the annual American Men's Internet Survey (Abstract 841). Although PrEP awareness increased from 52% to 84% from 2014 to 2020, only one-third of those aware reported discussing PrEP with a health care clinician in the last 12 months, and current PrEP use remained low and relatively stable at 11% to 12% from 2016 to 2020. In a multivariate model, older age, identifying as gay, having health insurance, and meeting CDC PrEP eligibility criteria were most strongly associated with current PrEP use. These findings highlight the need for tailored strategies that take into account the diverse characteristics and contexts of Latinx MSM that can present barriers to PrEP use.

In Ending the HIV Epidemic rural states, nurse practitioners and physician assistants accounted for 42% of PrEP prescribers but served more than two-thirds of PrEP patients in 2020

Bennett reported on the spatial distribution and clustering of PrEP uptake among women in the United States (Abstract 847). Using PrEP utilization data from AIDSVu.org, county-level clustering of PrEP utilization was found primarily in major metropolitan areas in California, Florida, southern Louisiana, Georgia, Washington state, and the Northeast, many of which were in Ending the HIV Epidemic (EHE) focus counties. In an analysis of estimated annual percent change in PrEP use from 2012 to 2019, the largest region-specific increase for PrEP utilization was in the Midwest (13.3%) and the smallest in the Northeast (3.8%). The largest state increase was seen in Louisiana (31.2%) and the largest decrease was seen in Massachusetts (–10.4%). The researchers conclude that understanding where PrEP utilization is increasing relative to surrounding areas and identifying gaps, along with improved education about PrEP, is needed to address the HIV epidemic among women.

Irie and colleagues evaluated PrEP discontinuations among women prescribed PrEP from 2012 to 2019 in a national network of community health centers (Abstract 925). Among 9741 people prescribed PrEP, 669 (7%) were cisgender women. Among these women, the mean age was 36 years, 33% were Black, 20% Latina, most were on Medicaid (46%) or uninsured (27%), and 87% had incomes below 138% the federal poverty level. Among women prescribed PrEP, 56% discontinued PrEP use within 1 year, with higher discontinuation observed among women who were uninsured or at a lower income. The authors call for responsive implementation strategies to improve not only PrEP uptake, but also PrEP continuation in this population.

Zhu and colleagues estimated the number of PrEP users and prescribers in rural areas in the United States (Abstract 834). Based on data from a national longitudinal prescriptions database, the number of rural PrEP users in the United States increased from 605 to 10,997 and the number of rural PrEP prescribers increased from 456 to 4935 from 2014 to 2020. The estimated annual percent change was higher in EHE rural states than in non-EHE rural states. In EHE states, although 55% of rural PrEP prescribers were physicians and 42% were nurse practitioners or physician assistants (NP/PAs), NP/PAs served more than 66% of rural PrEP patients in 2020.

Using the same prescription database, Islek and colleagues reported on prescription patterns for brand and generic PrEP medications in the United States (Abstract 833). Among 240,409 persons prescribed PrEP between October 2020 and March 2021, 44% were prescribed brand tenofovir alafenamide/emtricitabine (TAF/FTC), 33% generic TDF/FTC, and 22% brand TDF/FTC. The proportion of PrEP users prescribed brand TDF/FTC decreased from 37% to 19% and those prescribed generic TDF/FTC increased from 17% to 33% during this period. Women were less likely to be prescribed TAF/FTC or generic TDF/FTC vs brand TDF/FTC than men. Black and Hispanic individuals were less likely to be prescribed generic TDF/FTC versus brand TDF/FTC; however, they were more likely to be prescribed TAF/FTC versus brand TDF/FTC than White individuals. Additionally, compared with the privately insured,

those with public insurance or who paid cash were less likely to be prescribed TAF/FTC versus brand TDF/FTC, or generic TDF/FTC versus brand TDF/FTC. Also using the IMS Health Quintiles VIA (IQVIA) database, Huang and colleagues reported on trends in out-of-pocket payments for PrEP drugs in the United States from 2019 to 2021 (Abstract 832). Under the Patient Protection and Affordable Care Act, most health plans were required to offer PrEP to beneficiaries without copays beginning in January 2021. The mean total payments per 30 tablets of PrEP decreased from $1687 in 2020 to $1365 in Quarter 1 to Quarter 3 2021 due to more use of generic TDF/FTC. Similarly, the mean payment per month among cash payers decreased from $1725 in 2020 to $839 in 2021.

Neilan and colleagues evaluated use of sexual health clinic services among adolescents and young adults in metropolitan Boston, Massachusetts (Abstract 829). Between January 2019 and June 2021, there were nearly 8000 visits seen, of which 78% were among male patients, 50% were among White patients, and 20% were among uninsured patients. Current PrEP use was lower among Black patients (RR, 0.88; 95% CI, 0.81-0.96), those with 1 to 5 sexual partners (RR, 0.67; 95% CI, 0.63-0.72), and 6 to 10 partners (RR, 0.83; 95% CI, 0.78-0.89) than among those with more than 10 partners in the past year. Among female individuals, age 26 years or younger versus older than 26 years was associated with a 76% decrease in current PrEP use among those with an indication. Using the 2021 PrEP guidelines, which broadened PrEP indications led to a 28% increase in visits with PrEP indications overall, with 33% of visits indicated under 2017 PrEP guidelines versus 61% of visits under 2021 guidelines, which increased similarly across age groups. Although use of sexual health clinical resources (eg, HIV or STI testing, preventive vaccines, or PrEP) did not differ by age, preventive vaccinations (hepatitis A and B virus, human papillomavirus) were lower among the uninsured.

Hill and colleagues evaluated PrEP indications and PrEP knowledge, access, and interest among 314 individuals with hepatitis C virus (HCV) infection in Washington, DC, and Baltimore (Abstract 837). Overall, 109 (35%) had an indication for PrEP, of whom 45% had a drug use indication, 36% had a sexual indication, and 19% had both a drug use and sexual indication. Only 27% were aware of PrEP, 10% had ever been offered PrEP, and 2% were taking PrEP. Interest in PrEP was reported in 38% of participants and was associated with self-perception of HIV risk and study site. PrEP awareness was associated with study site, race, age, and sexual PrEP indication on bivariate analyses; however, only study site remained significant in the multivariable regression analysis. Additionally, past offer of PrEP by a clinician was associated with study site, highlighting the substantial variability in PrEP access by location of health care utilization.

Veloso and colleagues reported on long-term PrEP engagement among MSM and transgender women in Latin America (Abstract 838). Among 9509 participants enrolled in the ImPrEP Study, a large PrEP implementation study in Brazil, Mexico, and Peru, 87% completed 52 weeks of follow-up at the time of analysis. Of these 8279 participants, 69.8% showed long-term PrEP engagement, defined as attending the week 4 visit and 2 quarterly visits within the first year of follow-up visits. Engagement was higher in Brazil (81%) than in Mexico (68%) and Peru (51%), and lower among transgender women, participants younger than 35 years old, and those with lower educational attainment. Participants reporting more than 10 sexual partners and those who self-reported complete PrEP adherence at the week 4 visit had higher long-term PrEP engagement. The HIV incidence rate was 0.85 per 100 person-years in the overall cohort and was higher among participants from Peru (2.62/100 person-years), transgender women (1.97/100 person-years), and those aged 18 to 24 (1.94/100 person-years).

Zeballos and colleagues presented data on PrEP discontinuation among adolescent PrEP users in Brazil (Abstract 843). Among 1146 participants who started PrEP in PrEP1519, the first PrEP demonstration study among adolescent MSM and transgender women in Latin America, 22% were 15 to 17 years old, 92% were MSM, and 70% self-identified as Black or Brown. Over the study period, 54% were persistent PrEP users, and almost half discontinued

PrEP (47%). In a multivariate analysis, the risk of PrEP discontinuation was higher among adolescent transgender women than in MSM (aHR, 1.64) and among those with medium (aHR, 1.68) and low-risk (aHR, 1.31) perception for HIV infection, than in those with high-risk perception.

Strategies to Improve PrEP Linkage, Uptake, and Delivery

Kimball and colleagues evaluated the effects of PrEP navigation on linkage to a PrEP prescriber among US MSM in the THRIVE demonstration project (Abstract 835). Among 1355 PrEP-eligible MSM who used PrEP navigation from 3 THRIVE sites, 48% linked to a PrEP prescriber, compared with only 3% linked to PrEP among MSM who did not use navigation. Overall, MSM who used PrEP navigation were

> ***MSM who used PrEP navigation were 16.7 times more likely to link to a PrEP prescriber than those who did not use navigation***

16.7 times more likely to link to a PrEP prescriber than those who did not use navigation; Black MSM, Latinx MSM, and White MSM who used navigation were 18.4 times, 8.8 times, and 18.9 times more likely to link to a PrEP prescriber, respectively.

Zucker and colleagues presented results of the Get2PrEP3 randomized controlled trial of clinician messaging to improve linkage to PrEP services (Abstract 917). Within a university medical center in New York, 191 patient visits with a positive STI test were randomly assigned to a clinician message sent via email, clinician message sent via the electronic medical record, or standard of care (no message). Messages highlighted the patient's recent STI, PrEP candidacy, and local PrEP resources, including information for referrals. Patients whose clinicians received any message were 7% (95% CI, 1.01-1.14) more likely to have a PrEP discussion or referral documented 1 to 4 weeks after the patient's visit. Future studies will evaluate whether sending an electronic medical record message directly to the patient can increase the provision of HIV prevention services among patients with a positive STI test.

Ngure and colleagues presented results from a randomized trial of 6-month PrEP dispensing supported by interim HIV self-testing (HIVST) to improve PrEP delivery in Kenya (Abstract 146). Participants were randomly assigned 1:1:1 to receive 6-month PrEP dispensing with blood-based HIVST and biannual clinic visits; 6-month PrEP dispensing with oral-fluid HIVST and biannual visits; or 3-month PrEP dispensing with clinic-based testing at quarterly visits. Among 495 participants enrolled, 165 men and 130 women were in serodifferent relationships, and 200 women were not in a known serodifferent relationship. At 6 months, the combined 6-month PrEP and HIVST arms were noninferior to the 3-month PrEP and clinic-based testing arm for HIV testing (83% vs 84%, respectively; risk difference [RD] –1.2%), PrEP refills (78% vs 81%, respectively; RD, –2.6%), and PrEP adherence defined as having any TFV-DP detected (61% vs 57%, respectively; RD, 2.4%). In subgroup analyses, findings were similar across groups; however, women not in known serodifferent couples had higher PrEP adherence in the 6-month PrEP and HIVST arm than those in the 3-month PrEP and clinic-based testing arm (51% vs 31%, respectively; RD, 20%). These findings suggest that HIVST to support PrEP continuation can enable new models of community-based PrEP delivery requiring less frequent contact with the health care system. In the same study, Mogere and colleagues evaluated the ability of PrEP users to interpret HIVST results (Abstract 817). Participants received HIVST training with a clinician at enrollment and were asked to interpret preprinted colored images of blood-based or oral fluid HIVST results at the 6-month visit. Correct interpretation of blood-based and oral fluid results was 92% and 88%, respectively, for strong HIV-positive results, 77% and 96%, respectively, for strong HIV-negative results, 87% and 88%, respectively, for invalid test results, and 50% and 55%, respectively, for weak HIV-positive results. The researchers recommend additional research to understand strategies to support accurate interpretation of HIVST results in the setting of community-delivered PrEP.

Ortblad reported findings from a pilot study of pharmacy-based PrEP initiation and refills in Kenya (Abstract 928). In this model, trained pharmacists asked clients purchasing services that indicated potential HIV risk (eg, emergency contraception, STI treatment) if they had ever considered taking PrEP, screened interested clients for HIV risk, counseled them on PrEP safety, and prescribed and dispensed PrEP with support from a remote clinician. From November 2020 to October 2021, pharmacists screened 575 clients and started 287 (50%) on PrEP. Among those who initiated PrEP, median age was 26 years, 43% were female, 38% were married, 84% had a partner of unknown HIV status, 72% reported inconsistent condom use, and 53% reported numerous sexual partners. PrEP continuation, defined as returning to their follow-up visit and refilling PrEP, was 53%, 36%, and 21% at months 1, 4, and 7, respectively. These findings suggest that populations at HIV risk frequently visit retail pharmacies and that PrEP initiation and continuation at pharmacies is similar to or exceeds that observed at public clinics in Kenya.

Heffron and colleagues evaluated PrEP uptake in a stepped-wedge cluster randomized trial of integrating PrEP into 12 public ART clinics in Uganda (Abstract 927). Among 1381 HIV serodifferent couples enrolled, median age was 28 years, 78% of couples were married, and 62% of partners with HIV were women. Among partners without HIV enrolled after PrEP launch in their clinic, 81% initiated PrEP within 90 days of enrolling. Of partners with HIV, there was no statistically significant difference in the frequency of viral suppression at 6 months during the control and intervention periods (81.9% vs 76.7%, respectively; RR, 0.94; 95% CI, 0.82-1.07).

Beauchamp and colleagues developed and evaluated a tool to assess HIV prevention readiness among AGYW in South Africa and Zimbabwe (Abstract 842). In the HPTN 082 open-label oral PrEP demonstration study, 451 AGYW were administered the HIV Prevention Readiness Measure (HPRM), a 25-item tool to assess PrEP readiness with components on connection with care, medication beliefs, disclosure, and support. The HPRM score and individual factors (self-efficacy, PrEP disclosure, and social support) demonstrated good reliability and predicted higher TFV-DP concentrations in dried blood spot tests. Additionally, PrEP disclosure predicted higher odds of persistent adherence at 3 and 6 months (OR, 1.53; 95% CI, 1.04-2.23; P=.03), suggesting that interventions that support disclosure to trusted others may increase adherence.

To facilitate immediate oral PrEP initiation, Heck and colleagues evaluated the frequency of renal dysfunction among young women initiating PrEP in South Africa (Abstract 922). Among 319 young women screened for an oral PrEP demonstration project in KwaZulu-Natal, South Africa, no cases of abnormal renal dysfunction were detected, and 229 enrolled. Of the 90 women who did not enroll, 60% did not return to the study, possibility indicating a loss of motivation. Among 31 women who had detectable drug levels at month 3, the mean creatinine clearance level declined 7.5% from 158 to 145 mL/min between screening and month 3, which was not considered clinically significant. These findings highlight that immediate oral PrEP initiation prior to creatinine clearance level confirmation is a safe option for young women.

Kohler and colleagues presented results of a randomized trial of patient actor training to improve PrEP services for AGYW in Kenya (Abstract 915). In this cluster randomized trial at 24 PrEP sites, 94 health care clinicians participated in a 2-day training that included role-play encounters with standardized patient actors, and the quality of PrEP counseling was measured using unannounced patient actors among 232 consenting clinicians. The mean quality score was 74% at intervention sites and 58% at control sites; mean adherence to PrEP guidelines was 57% at intervention sites and 36% at control sites, and mean communication scores were 90% at intervention sites and 81% at control sites (all P<.001).

An Interactive Session focused on what it will take to increase PrEP and postexposure prophylaxis (PEP) use in AGYW (Interactive Session 5). Despite a slow start to PrEP scale-up, Baggaley highlighted that PrEP recommendations are now included in the guidelines for most countries in Africa. Despite the

challenges with COVID-19, data suggest there were 1.5 million PrEP users in 2021 across 9 African countries, and in Eastern and Southern Africa, more than 70% of PrEP users were women. Although most countries have not reported age and sex of PrEP users, Global AIDS Monitoring data indicate that there were more than 12,000 PrEP users aged 15 to 19 years across 14 countries in Africa. To increase PrEP use for AGYW, she emphasized the need for positive messaging designed by women in their communities to increase awareness; understanding and adapting to AGYW's PrEP journey (including stopping and restarting PrEP and switching regimens); and offering differentiated and simplified PrEP services, including reducing the burden of laboratory monitoring, using HIV self-testing, and providing virtual support. Additionally, she recommended integrating PrEP delivery into sexual reproductive health services, including family planning clinics and antenatal and postnatal services. Baggaley discussed that new PrEP products providing increased choice could increase acceptability and demand for PrEP, but that implementation science research is crucially needed to optimize delivery and support choice among AGYW. The dapivirine ring is a safe product that offers the potential for community-based delivery outside of clinical settings, including through pharmacies, and CAB-LA could help address adherence challenges with oral PrEP among youth. Finally, she pointed to the low community and clinician awareness and limited availability of PEP, and called for a "rethink" of how to make PEP more accessible in the community, such as through the use of HIV self-testing before starting PEP, virtual support platforms, and facilitating transitions from PEP to PrEP.

Aieko shared experiences implementing a patient-centered PEP program across 5 rural communities in Kenya and Uganda (Interactive Session 5). He highlighted the need for prevention options for individuals with unanticipated, periodic, high-risk exposures. Following community sensitization and training for health care leaders and clinicians, they launched a PEP package available 7 days per week and included a client hotline and options for out-of-facility medication delivery. In a pilot study conducted between December 2018 and May 2019, 124 people sought PEP; one-third were male, one-fourth were under 25 years of age, and 41% were fisherfolk. Additionally, 20% of participants reported an exposure with a serodifferent partner, 72% were with a new or existing partner, and 7% were from transactional sex. Overall, 12% of visits were conducted at out-of-facility sites, and 35% of participants had at least 1 out-of-facility visit. At the 4-week visit, 97% were retained, 88% were adherent, and 95% were tested for HIV, with no serious adverse events or seroconversions reported in the study. These findings suggest that patient-centered approaches with flexibility to enhance convenience can improve engagement in PEP services.

Naidoo presented on experiences with PrEP implementation in AGYW as part of the DREAMS (Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe) program in South Africa (Interactive Session 5). She highlighted the importance of using a variety of strategies to drive demand and uptake of PrEP among AGYW, including mobile van outreach, HIV prevention ambassadors in the community, learner support agents within schools who advocate for PrEP and sexual reproductive health implementation, collaboration with community-based organizations, and leveraging community radio and social media. She described collateral benefits of integrating PrEP with sexual reproductive health services, including addressing the numerous burdens of disease among young people, including STIs, violence, unplanned pregnancy, and poor mental health through a holistic service delivery approach. They have implemented a school-based model in South Africa that has increased access to HIV prevention and sexual reproductive health services in this setting, leading to significant uptake of contraception and PrEP, high rates of STI screening, and better PrEP continuation. PEP provision has been limited based on supply chain issues, particularly for community-based models of service delivery.

Matambanadzo described experiences implementing PrEP among young women who sell sex in Zimbabwe (Interactive Session 5). She pointed to the rapid rise in HIV prevalence among young female sex workers, increasing from 2% at age 16

years to 27% by age 19 years and 52% by age 24 years. Common barriers to PrEP uptake and continuation in this population include the burden and cost of frequent clinic visits, daily pill burden, stigma from health workers and messaging for PrEP as only for "certain high-risk groups," confusion between PrEP and ART, associated HIV stigma, and low HIV risk perception. Additionally, programming and messaging have not accommodated transitions in and out of PrEP, and there has been a lack of support within the community for PrEP adherence and continuation. Despite COVID-19 disruptions, efforts to scale up PrEP in this population through differentiated service delivery have led to a 4-fold increase in PrEP initiations among female sex workers ages 16 to 24 years in Zimbabwe in 2020, and 70% of PrEP initiations in 2021 were among those under the age of 29 years. Several strategies that have increased motivation and use of PrEP include having sex workers lead PrEP education efforts; increasing the number of PrEP access points, including drop-in centers and home-based PrEP services; engaging PrEP champions and ambassadors to support demand creation and adherence through PrEP refill groups; linking mobile sex workers to PrEP; scaling up telehealth and virtual peer support; and integrating PrEP as part of a one-stop shop with family planning and STI services. Future efforts will include exploring pharmacy-based PrEP distribution, intensifying sexual gender-based violence prevention and support, and exploring PrEP dispensation by non-clinical microplanners.

Modeling the Impact and Cost-effectiveness of PrEP

Balasubramanian and colleagues projected the impact of expanded long-acting injectable PrEP use among MSM on local HIV epidemics in the United States (Abstract 916). Using the Johns Hopkins HIV Economic Epidemiological Model (JHEEM) in 32 high-priority urban areas in the United States, they projected HIV incidence among MSM from 2020 to 2030 under a range of interventions that increase PrEP uptake by 10% or 25% above baseline levels with either long-acting injectable PrEP or oral PrEP. In the absence of any intervention, baseline levels of oral PrEP use led to a projected reduction in HIV incidence of 19% (95% CI, 1%-36%). At 10% additional PrEP uptake, the reduction in HIV incidence ranged from 33% with all oral PrEP to 36% with all long-acting injectable PrEP. At 25% additional uptake, incidence reductions ranged from 50% with all oral PrEP to 55% with all long-acting injectable PrEP. A greater reduction in HIV incidence was observed between uptake levels rather than between oral and long-acting injectable PrEP, suggesting that the greatest potential impact of long-acting injectable PrEP is in expanding total PrEP uptake in conjunction with oral PrEP. As potential effects varied by city, strategies to expand PrEP use should account for local dynamics.

Also using the JHEEM model, Schnure and colleagues compared the benefits of prevention and care continuum interventions on HIV incidence in Baltimore (Abstract 830). The investigators projected the impact of 4 interventions scaled up from 2023 to 2027: increased PrEP use, improved linkage to care for newly diagnosed people with HIV, increased retention among people living with HIV in care, and improved viral suppression among unsuppressed people with HIV in care. Overall, HIV incidence can be reduced by 73% in Baltimore by combining PrEP (25% coverage) with 95% levels of linkage, retention, and viral suppression. About one-third of this effect was achieved when targeting young Black and Hispanic MSM, one-third by expanding to all MSM and PWID, and one-third by expanding to the full population. Overall, improvements in PrEP coverage and retention in HIV care had the largest individual effects.

Stansfield and colleagues modeled the benefits from using on-demand oral PrEP by MSM in the United States and Thailand (Abstract 836). Using data from the HPTN 067 study, the investigators simulated HIV risk reduction in 2 synthetic cohorts of 10,000 MSM prescribed PrEP in Harlem and Bangkok. They assigned PrEP either using a trial-based analysis, in which on-demand PrEP was assigned if determined to be optimal based on higher effectiveness and fewer pills, and an implementation analysis, in which on-demand PrEP was assigned if daily PrEP adherence was fewer than 3.5

pills per week. On-demand PrEP was assigned for 36% (Harlem) and 30% (Bangkok) of individuals in the trial-based analysis and 30% (Harlem) and 11% (Bangkok) in the implementation analysis. Mean effectiveness increased by 18% (Harlem) and 7% (Bangkok) in the trial-based analysis, and 20% (Harlem) and 34% (Bangkok) in the implementation analysis. Overall, on-demand PrEP was optimal mainly for MSM with low adherence to daily PrEP, with little advantage to assigning on-demand PrEP based on sex frequency.

Amick and colleagues reported on the cost-effectiveness of oral PrEP among young MSM in the United States (Abstract 831). They used the Cost-Effectiveness of Preventing AIDS Complications model to simulate the ATN (Adolescent Trials Network) 110/113 PrEP study populations and compare annual HIV screening alone and generic or branded PrEP with quarterly screening. Compared with annual screening, generic PrEP would increase the Quality Adjusted Life Years (QALYs) from 8.37 to 8.42, reduce HIV infections from 40% to 35%, and decrease costs by $14,000 over 10 years. Generic PrEP would be cost-saving at HIV incidences off PrEP of 2 or greater per 100 person-years over 10 years and 0.5 or greater per 100 person-years over a lifetime. With branded PrEP, costs would increase by $15,000 over 10 years resulting in an incremental cost-effectiveness ratio of $318,000/QALY over 10 years, but would be cost-saving over a lifetime. Despite low retention and adherence observed in ATN 110/113, these findings suggest that PrEP would be cost-saving compared with annual HIV screening alone when implemented in a population of young MSM at high risk of HIV infection.

Postexposure Prophylaxis

Fox and colleagues presented the results of a randomized controlled trial of a self-start home PEP program among 139 MSM in the United Kingdom (Abstract 849). Participants were randomly assigned to immediate or deferred (after 48 weeks) provision of a 5-day PEP starter pack of TDF/FTC/maraviroc to keep at home and self-initiate if required. During the first 48 weeks of the study, the median time from exposure to the first dose was 7.6 hours for the immediate arm versus 28.5 hours for the deferred arm ($P<.01$). The most common reason for taking PEP was receptive anal sex with a man of unknown HIV status, reported in 81% of cases. Uptake of PEP was appropriate in 29/33 cases. The deferred arm had almost double the number of missed opportunities for PEP uptake compared with the immediate arm (474 vs 268, respectively; $P=.625$). Home PEP was well tolerated, and there was no change in the number of condomless anal sex acts in the prior 3 months in either arm. One participant in the deferred arm acquired HIV; this participant had ongoing HIV exposure and had been advised to start PrEP. These findings suggest that providing home PEP starter packs may be a valuable HIV prevention tool and could be incorporated into HIV prevention guidelines.

Coleman and colleagues evaluated the implementation of a PEP hotline in Washington, DC (Abstract 850). In collaboration with an academic physician group, the DC Department of Health launched a 24-hour, 7-days-a-week clinician-staffed PEP hotline, in which eligible callers received 5- to 7-day PEP starter packs through 4 strategically located pharmacies and had follow-up appointment at a government-run sexual health care clinic. In the first 6 months of the program, there were 201 eligible PEP callers, of whom 70% received a starter prescription, and 84% attended an initial PEP clinic consultation within 72 hours of exposure. Of those who started PEP, 38% transitioned to PrEP after completing the PEP regimen. Compared with individuals diagnosed with HIV in DC in 2019, PEP users in this study were more likely to be White than Latinx (OR, 0.38; 95% CI, 0.19-0.75) or Black (OR, 0.12; 95% CI, 0.06-0.21).

Male Circumcision

Zewdie and colleagues evaluated the HIV protective effects of traditional and medical circumcision in the HPTN 071/PopART (Population Effects of Antiretroviral Therapy to Reduce HIV Transmission) study (Abstract 87). In this cluster randomized trial, study communities were randomly assigned to the

full PopART intervention including immediate ART, the PopART intervention with ART initiation according to current national guidelines, or standard of care, with referral for medical male circumcision included in the 2 PopART intervention arms. Among 10,803 HIV-negative men with self-reported circumcision status included in this analysis, 56% were uncircumcised, 26% were traditionally circumcised, and 18% were medically circumcised. Overall, 83% of men who reported being medically circumcised were from Zambia, and 90% of men who reported traditional circumcision lived in South Africa. HIV incidence among those who were medically circumcised was 0.31 per 100 person-years, among those traditionally circumcised was 0.94 per 100 person-years, and among the uncircumcised was 0.97 per 100 person-years. Although the risk of HIV for medically circumcised men was 70% lower than those uncircumcised (aHR, 0.30; 95% CI, 0.16-0.55), there was no difference in the risk of HIV acquisition for traditionally circumcised versus uncircumcised men (aHR, 0.84; 95% CI, 0.54-1.31). Uptake of medical male circumcision was 11% in PopART communities, with an adjusted rate ratio in the PopART communities compared with standard of care of 1.10 (95% CI, 0.82-1.50; P=.48), indicating a nonsignificant 10% higher uptake of medical circumcision in communities randomly assigned to the PopART intervention. Although traditional circumcision is practiced as a rite of passage to adulthood in many South African communities, these results suggest that medical male circumcision may offer increased HIV prevention in men who are traditionally circumcised.

HIV Monoclonal Antibodies and Vaccines

Sobieszczyk and colleagues presented data from the HVTN 130/HPTN 089 study of broadly neutralizing antibodies (Abstract 81). This study evaluated intravenously administered VRC07-523 coadministered with PGDM1400, PGT121, or 10-1074 in HIV uninfected adults; 1 arm of this 27-person study included 3 antibodies (VRC07-523, PGDM1400, and PGT121). The antibodies were well tolerated, with no serious adverse events and no unexpected reactions. The antibodies maintained their neutralization in serum after administration, with no evidence of PK interactions between antibodies. The greatest neutralization breadth was achieved with the triple combination administration. Mahomed and colleagues presented data on a phase I trial of subcutaneously administered VRC07-523LS and PGT121 (Abstract 856). The 2 antibodies were administered alone and in combination, compared with a placebo injection in 45 women, aged 18 to 40 years, in South Africa. The most common reactogenicity events were injection site tenderness and headaches, and of the 9 adverse events designated as related (proteinuria, elevated alanine aminotransferase and aspartate aminotransferase) were mild and transient. Both antibodies retained neutralizing activity postadministration and no antidrug antibodies were detected. The PK data suggest that the subcutaneous administration of VRC07-523LS is appropriate at 16 weeks to 24 weeks, while shorter intervals (less than 8 weeks) are appropriate for PGT121. These antibodies continue to be assessed for their HIV prevention potential.

Feinberg gave an excellent plenary talk on the past, present, and future of HIV vaccines (Abstract 117). He pointed out that although we have highly effective prevention and therapy with antiretroviral drugs, we did not meet the UNAIDS 2020 goal of having fewer than 500,000 new HIV infections globally; instead, there were 1.5 million new infections worldwide in that year. There is a risk that the number of new infections could actually worsen over time because of issues like the youth bulge in sub-Saharan Africa (raising the absolute number of new infections, if incidence remains stable), service interruption due to COVID-19, an increased number of people needing therapy, and the risk of increasing ART resistance. An HIV vaccine could be a major contributor to reducing new HIV infections. He also pointed out why the features of HIV make developing an HIV vaccine so much more difficult than developing a COVID-19 vaccine, including much greater viral diversity, more glycosylation shielding immunologic targets, and the difficulties in generating broadly neutralizing antibodies against HIV. He

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pointed out that we are moving from an era in which an empirical approach was taken to developing a vaccine (testing approaches and only determining correlates of protection after demonstrating efficacy), to a rational design approach (identifying a correlate and then working backwards to develop the vaccine that generates that immune response). He noted that of 6 HIV vaccine efficacy trials to date, only 1 vaccine showed marginal protection, and the most recent completed efficacy trial (HVTN 705, described below), failed to find significant efficacy. He pointed out that the AMP trials of broadly neutralizing antibodies showed substantial protection for the subset of participants exposed to virus sensitive to the antibody, proving the principle that broadly neutralizing antibodies are a mechanistic immune correlate of protection, and should be the target of future HIV vaccine efforts. He went on to describe a number of approaches to developing such a vaccine through reverse engineering.

Gray and colleagues presented data from the HVTN 705 Imbokodo vaccine phase IIb trial (Abstract 121). They pointed out that in 2020, 25% of new infections in sub-Saharan Africa occurred in women 15 to 24 years of age, pointing to tremendous HIV prevention need for this population. The Imbokodo study enrolled 2637 women aged 18 to 35 years in 5 sub-Saharan African countries; participants were randomly assigned 1:1 to either a combination of an adenovirus type 26 (Ad26) vectored mosaic vaccine with a clade C gp140 vaccine or a placebo injection, administered at 4 different time points over 12 months. The vaccines were relatively well tolerated, and there were no serious adverse events related to study product and no cases of thrombocytopenic thrombosis, as has been described in Ad26 COVID-19 vaccines using the same vaccine backbone. Overall efficacy was 25.2% (95% CI, –10.5% to 49.4%; P=.14). As the lower bound of the 95% CI was less than zero, this trial was not continued. However, the HIV incidence in both the vaccine (3.6/100 person-years) and placebo (4.3/100 person-years) groups shows the tremendous need for highly effective prevention strategies for this population of young women in sub-Saharan Africa.

COVID-19 Epidemiology

Justman and colleagues presented data from the COMPASS (Community Prevalence of SARS-CoV-2 Study) investigation, a SARS-CoV-2 seroprevalence survey conducted in the first half of 2021 of 22,667 adults and children in 15 sites throughout the United States (Abstract 46). They found overall SARS-CoV-2 seroprevalence of 2.4%, and polymerase chain reaction (PCR) positivity on a nasal swab of 0.8%. Seropositivity was similar for adults and children. Overall, 55.8% of persons who were PCR positive stated they were asymptomatic, and 51.3% of seropositives reported that they had not had previous symptoms of COVID-19, pointing out the limitations of case-based reporting for identifying SARS-CoV-2 infections. COVID-19 vaccine willingness was 78% overall, and did not differ by sex or race/ethnicity, but persons over 60 years of age were significantly more likely to report willingness to receive a COVID-19 vaccine.

Simbayi and colleagues reported the results of a national household SARS-CoV-2 seroprevalence survey in people ages 12 years and older in South Africa from November 2020 to June 2021 (Abstract 753). Overall seroprevalence was 19.6%, which translates to an estimated 8.7 million persons previously infected, 5.1 times higher than the number of cases reported. Seropositivity was higher among females (aOR, 1.44) and persons with hypertension (aOR, 1.28) and was lower among persons 18 to 35 years of age (aOR, 0.69) than among those 12 to 17 years of age. There was substantial geographic variability, with particularly high rates in rural areas. These data emphasize the need to get vaccines to the broader population, including adolescents.

Momplaisir and colleagues reported on racial/ethnic and neighborhood social vulnerability disparities in COVID-19 outcomes in the University of Pennsylvania Health System from March 2020 to March 2021 (Abstract 751). Overall, 225,129 unique individuals were entered into their system, of whom 7% had a positive test, and 20% of these were hospitalized. Across the study period, they found that racial/ethnic minorities and residents of medium or high social vulnerability areas had significantly higher

odds of testing positive for and hospitalizations with COVID-19 than non-Hispanic White individuals. These disparities were particularly acute in the first wave of the pandemic (March 1, 2020, through June 30, 2020), when the odds ratios for testing positive were 2.8 for Black individuals, 4.2 for Hispanic individuals, 1.6 for Asian individuals, 2.3 for high social vulnerability index individuals, and 1.1 for medium vulnerability index individuals. The odds ratios for hospitalizations during the first wave were 1.7 for Black individuals, 1.8 for Hispanic individuals, 1.6 for Asian individuals, and 1.3 for high social vulnerability index individuals. Although there were no significant disparities in 30-day in-hospital mortality among racial/ethnic groups during the first wave, there was higher mortality among Hispanic persons (OR, 1.7) and Asian persons (1.6) during the subsequent wave (July 1, 2020, through March 1, 2021). Rowan and colleagues evaluated the association between environmental factors and COVID-19 hospitalizations in the Metro Denver area (Abstract 752). They found that living in an apartment (aOR, 1.2), in areas with higher levels of fine particulate matter (PM, 2.5) (aOR, 1.35), percent overcrowding (aOR, 30.18), percent housing burdened (aOR, 1.4), and higher transit scores (aOR, 1.01) were independent risk factors for hospitalization when controlling for race/ethnicity, income, sex, age, social vulnerability index, and medical risk factors. The authors concluded that COVID-19 disease severity may be worsened by environmental features around a person's home.

Kronfli and colleagues presented data on SARS-CoV-2 seroprevalence and risk factors among incarcerated adult men in 3 provincial prisons in 2021 (Abstract 750). Overall, 22% tested positive, with differences by prison (ranging from 15% to 27%). In a Poisson regression model, independent risk factors for SARS-CoV-2 seroprevalence were being incarcerated most (50%-99%) or all of the time since March 2020 (aPR, 1.47 and 2.17, respectively), being employed during incarceration (aPR, 1.64), consuming meals with cellmates or in a sector (aPR, 1.46 and 1.34, respectively), and having been screened postprison outbreak (aPR, 2.32). The authors call for decarceration and occupational safety measures, individual meal consumption, and enhanced infection prevention and control measures, including vaccination during incarceration.

Akelo and colleagues reported on adverse pregnancy outcomes associated with COVID-19 infection in western Kenya (Abstract 671). Between August 2020 and August 2021, they enrolled 1688 pregnant women, and had pregnancy follow-up appointments for 998 women. Over follow-up appointments, 169 (22%) tested positive for SARS-CoV-2. Very low birthweight (under 1500 grams) was more common among women diagnosed with COVID-19 (aRR, 4.78; 95% CI, 1.11-20.49), as was very preterm birth (under 34 weeks; aRR, 2.57; 95% CI, 1.34-4.90), and preterm birth (under 37 weeks; aRR, 1.54; 95% CI, 1.03-2.29). There was no association of COVID-19 diagnosis and hypertensive disorders of pregnancy, pre-eclampsia, stillbirth, and perinatal deaths. Nachega and colleagues presented data on the impact of SARS-CoV-2 infection on outcomes in pregnant women compared with nonpregnant women in 22 health facilities in 6 sub-Saharan African countries from March 1, 2020, to March 31, 2021 (Abstract 672). In this study, pregnancy was associated with an increased risk for intensive care unit (ICU) admission (aRR, 2.38; 95% CI, 1.42-4.01), oxygen supplementation (aRR, 1.86; 95% CI, 1.2-3.35), and in-hospital death (adjusted sub-hazard ratio 2.0; 95% CI, 1.08-3.70). These studies point to the hazards for mothers and infants of SARS-CoV-2 infection during pregnancy, and to the need to reach women of childbearing potential with COVID-19 vaccines.

Begnel and colleagues presented data on the risk of SARS-CoV-2 infection among postpartum Kenyan women and their infants (Abstract 670). SARS-CoV-2 incidence in 205 mothers was 3.0 cases per person-days with no significant difference between those with and without HIV infection, and 1.2 cases per person-days among 178 infants, with no difference between those exposed and unexposed to HIV. Antibody responses waned over 6 months in mothers and infants, suggesting continued preventive measures are needed while vaccine coverage expands in Kenya.

Overton and colleagues presented data on the proportion of SARS-CoV-2 infections that were asymptomatic among people with HIV in the REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) trial (Abstract 746). Among 2464 participants who had samples available for SARS-CoV-2 serology testing from May 2020 to February 2021, the investigators found the cumulative incidence increased from zero cases in May 2020 (0%) to 318 cases (12.9%) by February 2021. Of these, they estimated that 60% were asymptomatic, higher than has been previously reported among people with HIV and the general population. The relative risk of symptomatic infection was higher for persons with obesity (aRR, 1.59), metabolic syndrome (aRR, 1.3), and reduced HDL-C values (aRR, 1.3), and was lower for persons who were Black than those who were White (aRR 0.72), persons older than 60 years of age than persons ages 40 to 49 years (aRR, 0.79), and persons with higher atherosclerotic cardiovascular risk scores (scores 5 to less than 7.5 aRR, 0.64; scores 7.5-10 aRR, 0.46; compared with scores 0 to less than 2.5). They used these data to remind clinicians to educate patients about the risk of asymptomatic disease and appropriate mitigation strategies.

Möller and colleagues reported on clinical outcomes of all persons hospitalized in Sweden with COVID-19, comparing those with and without HIV infection (Abstract 760). Of 121 persons with HIV and 64,764 persons without HIV hospitalized for COVID-19 from February 1, 2020, to August 31, 2021, there was no significant difference in the likelihood of severe infection (admission to an ICU or 90-day mortality) between people with or without HIV infection after adjusting for age and sex. Neither level of HIV RNA nor current or nadir CD4+ cell count was associated with worse outcomes; however, 93% of the population was virally suppressed, and median CD4+ count was 560 cells/μL. Among persons with HIV, those with at least 1 comorbidity had a 4.3-fold increased odds of severe COVID-19 compared with persons with HIV without comorbidities. These data would suggest no increased risk of severe COVID-19 among hospitalized persons with well-controlled HIV infection.

Del Amo and colleagues evaluated the association of use of TDF and COVID-19 severity among people with HIV at 69 HIV clinics in Spain (Abstract 867). Of more than 51,000 eligible individuals, they saw 2402 documented SARS-CoV-2 infections from February 1 to December 31, 2020. The median CD4+ count of the cohort was over 700 cells/μL. Compared with persons on TAF/FTC, the relative risk of hospitalization, ICU admission, and death for persons on TDF/FTC was 0.66 (95% CI, 0.43-0.91), 0.28 (95% CI, 0.11-0.90), and 0.37 (95% CI, 0.23-1.90), respectively. The relative risks for persons on abacavir/lamivudine was 1.29 (95% CI, 1.02-1.58), 1.39 (95% CI, 0.70-2.80), and 2.02 (95% CI, 0.88-6.12), respectively. This expands on their previously published work[1] that suggests that TDF/FTC lowers COVID-19 severity among people with HIV and virologic control, although in the current study this effect was limited to persons aged 50 years and older. However, a systematic review and meta-analysis has found mixed results for the association of tenofovir with COVID-19 diagnosis and disease severity.[2] The authors call for confirmatory randomized trials of TDF/FTC for prophylaxis and early treatment of COVID-19.

Abu-Raddad and colleagues reported on the efficacy of natural immunity against reinfection with the Alpha and Beta variants in Qatar (Abstract 759). They used 2 retrospective matched cohort studies and found protection against reinfection was 96.4% to 97.6% against the Alpha variant and 86.4% to 92.3% against the Beta variant, even a year after primary infection.

Impact of COVID-19 on HIV and STI Services and Outcomes

Wu and colleagues presented data on HIV testing, diagnoses, and PEP prescriptions before, during, and after lockdown in 7 provincial and municipal centers for disease control and 8 major infectious disease hospitals specialized in HIV care in various regions of China (Abstract 947). They found that lockdown was associated with a 32.8% decrease in HIV testing in January 2020, the first month after lockdown (incidence rate ratio [IRR], 0.67), but increased

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with the ease of restrictions. Daily HIV diagnoses decreased from a median of 50 before lockdown to 23 during lockdown, and to 48 after lockdown. The number of monthly PEP prescriptions decreased significantly during lockdown (IRR, 0.36) and had not recovered by the end of December 2020 (IRR, 0.46). The authors point to the dramatic declines in HIV testing, diagnoses, and PEP prescriptions in the first month of COVID lockdown, which have all gradually rebounded as restrictions eased.

De la Court and colleagues presented data on changes in PrEP uptake and STI incidence in a PrEP demonstration project in Amsterdam during 3 periods post-COVID-19: 1) lockdown (March 15, 2020–June 15, 2020), 2) reopened public spaces (June 16, 2020-September 15, 2020), and 3) restricted public spaces and curfew (September 16, 2020-December 31, 2020) (Abstract 919). They reported the following factors as being associated with increased or unchanged PrEP use compared with decreased or stopped PrEP use: first period, belonging to a COVID-19 risk group (aOR, 0.44; *P*=.014) and chemsex (aOR, 2.79; *P*=.001); second period, having increased or unchanged number of sex partners (aOR, 3.84; *P*=.01); and third period, being worried about COVID-19 infection (aOR, 0.46; *P*=.02) and chemsex (aOR, 2.19; *P*=.02). STI incidence was significantly lower in 2020 than 2019 during the first period (IRR, 0.43; 95% CI, 0.28-0.68); there was a nonsignificant increase in STIs in the second and third periods. There were no new HIV infections diagnosed throughout this time. The authors found that changes in PrEP largely paralleled risk behaviors and needs, but that focus should be on stimulating PrEP reuptake and to restore regular STI testing. Toy and colleagues also reported on declines in PrEP program engagement early in the COVID-19 pandemic in British Columbia, Canada (Abstract 948). Compared with prepandemic (January 2019-March 2020), they found in the pandemic period (April 2020–June 2021) that HIV testing among clients declined (87% to 82%; *P*<.001), PrEP dispensing declined (72% to 67%; *P*<.001), and PrEP initiations declined (12% to 6.8%; *P*<.001). The authors called for continued program evaluation.

Chang and colleagues presented on HIV and STI testing rates among patients in the Kaiser Permanente Southern California system, serving 15 community hospital catchment areas across 9 counties (Abstract 142). This evaluation included 4.7 million patients with similar racial/ethnic diversity as the surrounding Southern California population. Using electronic health records and comparing postpandemic (March 2020–December 2020) to prepandemic (January 2017–February 2020) periods of time, they found a 26% decline in HIV tests, a 31% decline in chlamydia and gonorrhea tests, and a 17% decline in syphilis tests. Although they found similar declines in HIV and chlamydia diagnoses (25% and 29%, respectively), they saw only a 7% decline in gonorrhea diagnoses and a 32% increase in syphilis diagnoses. The authors hypothesize that gonorrhea and syphilis may be more likely to be symptomatic and hence prompt testing; however, HIV and chlamydia are often asymptomatic and may have been substantially underdiagnosed during that time period. They call for novel strategies to incentivize HIV and STI testing to reduce morbidity from undiagnosed STIs and in efforts to end the HIV epidemic.

Mayer and colleagues reported on HIV, PrEP, and STI trends during the COVID-19 pandemic in a Boston community health center (Abstract 939). Compared with levels in the prepandemic quarter (December 2019–February 2020), they report significant declines in monthly HIV antibody testing (*P*=.017), new PrEP starts (*P*=.014), gonorrhea and chlamydia testing (*P*=.012), and syphilis testing (*P*=.01), with an increase in gonorrhea and chlamydia test positivity (3.1% to 4.4%) during that time (*P*<.001). By the time of the Delta surge (June 2021–August 2021), compared with prepandemic levels, the number of new monthly HIV diagnoses had increased (17.3 versus 7.0; *P*=.02), with continued but improved reductions in new PrEP starts (*P*=.047), gonorrhea and chlamydia testing (*P*=.045), and syphilis testing (*P*=.038). Bonett and colleagues reported on trends in STI screening during COVID-19 and missed cases among adolescents in Philadelphia (Abstract 869). At the Children's Hospital of Philadelphia, monthly STI testing declined

during the pandemic (from 479 to 329), but test positivity increased from a baseline of 12.5% to a peak of 27.5%. They report the proportion of tests performed as asymptomatic testing decreased from a baseline of 72.5% to a nadir of 54.5%, and calculated that they would likely miss diagnosing 23.8% of STI cases.

Fojo and colleagues modeled the potential impact of COVID-19 on the HIV epidemic in 32 US cities (Abstract 943). They assumed that disruptions began on March 1, 2020, with sexual transmission reduced to March 8, 2021, and then rebounded by July 4, 2021. They also assumed that HIV services remained reduced until September 8, 2021, and then normalized by February 4, 2022. Across all cities, simulations projected a decline in HIV incidence and diagnoses, followed by a rebound that lagged 1 to 2 years behind HIV incidence. The projections varied by city, ranging from a median of 3% fewer incident cases in Las Vegas to 9% more HIV infections in Boston post-COVID-19 through 2025. The authors point out that the effects of COVID-19 on HIV transmission are likely to differ substantially at a local level, but that HIV incidence rose more in cities where prepandemic levels of viral suppression were higher.

COVID-19 Vaccines

Gray and colleagues presented safety and real world effectiveness data from the Sisonke study of the Janssen Ad26.CoV2.S vaccine, given as a single dose or with a homologous boost at 4 to 6 months among health care workers in South Africa (Abstract 47). Overall, 496,424 health care workers received 1 dose, and 237,981 received a booster dose; 39,386 of the vaccinees were persons with HIV, the largest cohort reported to date. The vaccines appeared safe, although there were 2 episodes of thrombocytopenic thrombosis and 4 cases of Guillain-Barré syndrome seen after 1 dose; these participants did not receive a second dose. Overall vaccine effectiveness after a single dose was 67% against hospitalization, 75% against hospitalization requiring critical care or intensive care, and 83% against death, and these levels were maintained through the Delta variant period. Although effectiveness against hospitalization, with or without requiring critical care or intensive care was maintained among people with HIV, effectiveness against death was lower among people with HIV at only 65%. One to 2 months after 2 doses, the effectiveness against Omicron-related hospitalization was 85%. These results largely confirm what has been reported from the randomized controlled trials of this vaccine, although these are the first effectiveness data on a large cohort of people with HIV.

Sun and colleagues compared the real-world effectiveness of booster doses of vaccine with a primary regimen among persons with and without immune dysfunction in the N3C (National COVID Cohort Collaborative) (Abstract 48). Pulling data from more than 60 clinical centers in the United States, the investigators used data from 784,555 persons who had received full vaccination, among whom 174,042 had also received a booster dose. Among persons without immune dysfunction, the vaccine effectiveness of boosted persons compared with unboosted persons peaked 7 months after full vaccination at 77.4%, waning to 52.1% by 9 months after full vaccination. Persons with immune dysfunction (HIV, solid organ or bone marrow transplant, autoimmune disease, or cancer) who had received a booster had slightly lower vaccine effectiveness, with a peak of 60.2% 7 months after full vaccination, waning to 39.5% by 9 months after full vaccination. Booster doses were also effective against hospitalization (87%), invasive ventilation (91%), and COVID-19–related death (87%). Protection levels were somewhat lower for persons with immune dysfunction: 79% against hospitalization, 75% against invasive ventilation, and 83% against death. Nonetheless, booster doses appeared to be highly effective, particularly against severe disease, for persons with and without immune dysfunction.

Abu-Raddad and colleagues presented data on the infectiousness of breakthrough infections after vaccination and after natural infection among persons in Qatar (Abstract 49). They measured SARS-CoV-2 real-time quantitative reverse transcription cycle threshold, which measures the inverse of viral load and correlates strongly with culturable virus.

They found that the highest cycle threshold values occurred in persons with reinfection, followed by persons who were vaccinated with the Moderna COVID-19 vaccine, followed by persons who were vaccinated with the Pfizer-BioNTech vaccine, followed by persons who had a primary infection. This suggests that natural infection may reduce the viral load by the greatest amount when breakthrough infections occur, followed by Moderna and then Pfizer vaccination, and suggests that vaccination helps not only by preventing infection but may also reduce infectiousness when breakthrough infections do occur.

Fulda and colleagues presented data on the prevalence of COVID-19 vaccination among people with HIV enrolled in the global REPRIEVE trial (Abstract 50). They tracked the proportion of participants with any COVID-19 vaccination from December 2020 through December 2021, and found that 74% of participants had received a COVID-19 vaccine by December 2021. At that time, vaccination rates were highest among Southeast and East Asian participants at 93%, and lowest among sub-Saharan African participants at 48%. Additional disparities were also seen, with higher proportions of White than Black participants receiving COVID-19 vaccines in high-income and Latin American/Caribbean countries, and higher rates of vaccination in men than women. In addition, older participants, participants with a higher body mass index, and participants on ART for a longer period of time were more likely to have received a COVID-19 vaccine. The authors point to the importance of making COVID-19 vaccines accessible to all populations of people with HIV, and suggest using these data to identify those populations with low rates of COVID-19 vaccination. Tavelli and colleagues also reported on COVID-19 vaccination rates among people with HIV in Italy (Abstract 865). They used medical records to evaluate the vaccination status of more than 3700 people with HIV seen at 1 of 18 clinical centers in Italy from September 19, 2021, to October 8, 2021. Overall, 90.4% had received at least 1 dose and 85.1% had received a full vaccination course. In adjusted logistic regression, factors associated with not being vaccinated were being younger (aOR, 1.26 for every 10 years) and being non-Italian native (aOR, 1.39), while being virally suppressed (aOR 0.65), not having previously had COVID-19 (aOR, 0.68), and being MSM (vs heterosexual; aOR, 0.68) were less likely to be unvaccinated. This study identifies persons who may benefit from increased outreach.

Fedeli and colleagues reported on the impact of SARS-CoV-2 vaccination on HIV-1 RNA levels and antibody response among 31 people with HIV (Abstract 941). They found no significant change in HIV-1 RNA levels after mRNA vaccination. They report somewhat lower anti-receptor-binding domain antibody titers up to 6 months after 2 doses of SARS-CoV-2 mRNA vaccination compared with HIV uninfected healthy controls (month 1 P=.001; month 2 P=.012; month 6 P=.037), but no significant difference after a booster dose. They concluded that the vaccines were safe, and elicited good anti-receptor-binding domain antibodies after 2 doses. Wittkop and colleagues presented data on the humoral immune response after COVID-19 vaccination in people with HIV in the ANRS0001S COV-POPART (COVID-19 Vaccine Cohort in Specific Populations) cohort study (Abstract 868). After excluding persons with previous SARS-CoV-2 infection by self-report or serology, they compared 754 people with HIV to 720 controls; 78% of the people with HIV had an undetectable viral load, and 70% had CD4+ counts above 500 cells/μL. Overall, 22 people with HIV were nonresponders to the vaccine (2.9%). Binding (1151 BAU/mL versus 1337 BAU/mL; P<.01) and neutralizing antibody titers (159.3 versus 271.8; P<.01) were lower in people with HIV than in controls. It is unclear whether this has any clinical implications.

COVID-19 Testing

Moraleda and colleagues presented on the use of oral saliva swab reverse transcript-polymerase chain reaction (RT-PCR) as a diagnostic test for COVID-19 in children (Abstract 822). They studied 1174 children with a median age of 3.8 years (interquartile range 1.7 years-9.0 years), who presented with fever for 5 or fewer days to an emergency department. Of these, 73 (6.2%) tested positive for COVID-19 by either oral or nasopharyngeal RT-PCR or nasal

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RT antigen testing. Using the nasopharyngeal RT-PCR test as the gold standard, the oral saliva RT-PCR swab was more sensitive than the nasopharyngeal antigen rapid test, with sensitivities of 84.8 versus 72.5, respectively. The authors conclude that RT-PCR performed on oral saliva swabs is an accurate option for SARS-CoV-2 testing in children.

Collins and colleagues reported on an evaluation of the case investigation and contact tracing (CI/CT) program in King County, Washington (Abstract 861). Between June 2020 and July 2021, the CI/CT team attempted to contact 87% of COVID-19 cases, and reached 81% of these a mean of 6.1 days after symptom onset and 3.4 days after SARS-CoV-2 testing. In all, the teams interviewed nearly 42,000 cases, helped arrange testing for 5650 contacts, facilitated grocery delivery for more than 7200 households, and referred more than 9100 households for financial assistance. Most survey respondents (81%) stated that they had stayed home during the isolation period, and 69% said that the information and referrals provided by the CI/CT team helped them stay in isolation. The authors concluded that, although many people received their CI/CT outreach after their period of greatest infectiousness, services provided likely helped with adherence to isolation guidelines.

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Invited Review

Addressing Depressive Disorders Among People With HIV

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Depressive disorders are the most common psychiatric disorders among people with HIV. Depressive disorders cause great suffering and disability and, among people with HIV, are associated with numerous negative HIV outcomes, including nonadherence to antiretroviral medication and increased morbidity and mortality. This article is focused on the detection, differential diagnosis, and management of depressive disorders among adults in HIV primary care settings in the United States. Because of the siloed nature of HIV primary health care and behavioral health care in the United States, this paper is geared toward clinicians who are not behavioral health specialists and who are working in HIV care settings that have limited access to behavioral health services and still seek to treat depressive disorders. In clinical settings that are fortunate enough to have well-integrated behavioral health services, HIV primary care clinicians may be able to depend on this specialist workforce, but these settings tend to be the exception and not the rule.

Keywords: HIV, depression, treatment, primary care

Epidemiology of Depression Among People with HIV and Steps to Care

Depressive disorders are the most common psychiatric disorders among people with HIV infection.[1] The lifetime rates of depressive disorders among people with HIV who are seen in HIV care settings in the United States are much higher than rates in the general US population. In 2019, it was estimated that 7.8% of adults in the general US population have had at least 1 major depressive episode,[2] whereas these rates hover around 30% to 40% among people with HIV. Moreover, among people with HIV in the United States, depressive disorders have high rates of comorbidity with other psychiatric illnesses, such as alcohol and substance use disorders, anxiety disorders, and posttraumatic stress disorder (PTSD). Worldwide, estimates of depressive disorders among people with HIV vary widely from 6% to 67%,[3] depending on the population surveyed, the approach to diagnosis, and other factors.

Major depression among people with HIV is associated with increased morbidity, mortality, and worse outcomes along the entire HIV care continuum

The World Health Organization (WHO) classifies major depression as the second most common cause of disability worldwide.[4] Depressive disorders are strongly linked to mortality, through suicide and as a result of suboptimal outcomes in the care and treatment of other medical conditions. Major depression among people with HIV is associated with increased morbidity, mortality, and worse outcomes along the entire HIV care continuum. In all countries, the number of behavioral health practitioners is insufficient to treat the number of people with depressive disorders. This has led to a strong focus

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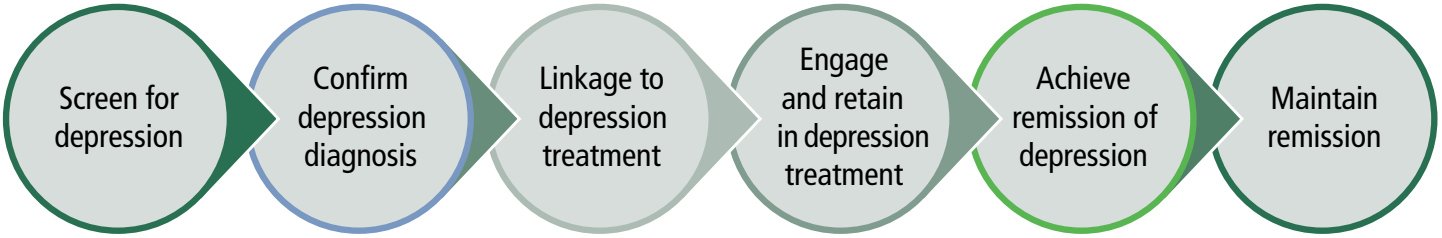

Figure 1. Model of health care continuum care for depressive disorders.

on detecting and treating depressive disorders in primary/HIV care settings. The continuum we use for HIV detection, care, and treatment can be readily adopted to depressive disorders (Figure 1).

Screening for Depression

The US Preventive Services Task Force reports that depression is undetected in up to 50% of all cases in primary care,[3] which has led to a recommendation for depression screening. In primary care settings, the Patient Health Questionnaire-2 (PHQ-2) and the Patient Health Questionnaire-9 (PHQ-9) are the most commonly used tools to screen for major depression, and in some settings, these tools are built into the electronic medical record. The PHQ-2 assesses for the 2 primary affective symptoms of depression: depressed mood and loss of interest or pleasure for at least 2 weeks. Sensitivity and specificity of the PHQ-2 for diagnosing major depression is best estimated at 91% and 67%, respectively, with a score of 2 or higher, and 72% and 85%, respectively, with a score of 3 or higher.[5] The PHQ-9 begins with the same 2 questions as the PHQ-2, but it adds 7 other questions that parallel the symptoms of major depression as described in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*. At a score of 10 or higher, the sensitivity and specificity of the PHQ-9 for major depression are best estimated at 85% and 85%, respectively.[6] The PHQ-2 is sometimes used as the initial screen and, if positive, is then followed by the PHQ-9.

The PHQ-2 and PHQ-9 can be conveniently accessed via the National HIV Curriculum[7] and scored at its website using automatic calculators. This website also offers information about the sensitivity and specificity of these tools.

The PHQ-2 and PHQ-9 have gained wide acceptance because they are briefer than many other depression rating scales; they can be administered in person by a clinician, by telephone, or self-administered by the patient; they can provide an assessment of symptom severity and be used to track symptom improvement; and they are quick to complete, free of charge, available in a variety of languages, and well-validated worldwide.

Unfortunately, screening tools for major depression cannot be used to establish a definitive diagnosis of this disorder by themselves, because there are too many false negative and false positive results. Nor are there currently available biologic tests for major depression that can be used to confirm the diagnosis. There are research tools used to assess for major depression that are more accurate than clinical screening tools, but these are too time-consuming to be used in a busy clinical practice. Moreover, a positive screen for major depression requires a differential diagnosis to rule out other conditions.

Differential Diagnosis of Depressive Symptoms

Depressive symptoms can occur as part of almost any serious medical, neurologic, or psychiatric illness. Among people with HIV, depressive symptoms may occur as part of a large variety of common comorbid medical conditions; as a result of the adverse effects of antiretroviral drugs and other prescribed medications; from the use of alcohol and recreational drugs; and in response to various social determinants of health, including loneliness and loss, homelessness, food insecurity, and the experience of interpersonal violence. It is always essential

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to assess depressive symptoms with an awareness of this complex differential diagnosis and the many contributing factors, and to plan a response that takes into account as many of these variables as possible.

Symptoms of depression have become ubiquitous components of stress and distress during the SARS-CoV-2 pandemic among the general population worldwide

Complicating matters further, symptoms of depression have become ubiquitous components of stress and distress during the SARS-CoV-2 pandemic among the general population worldwide.[8] The number of available behavioral health care practitioners is always limited when compared with the number of people in distress. To best utilize these limited resources, it is essential to distinguish people in distress from those who meet the criteria for mental disorders (Table 1).

Table 1. Key Elements That Distinguish Mental Distress and Mental Disorders

Mental disorder	Mental distress
• Usually cause either persistent severe subjective distress • Meet recognized diagnostic criteria (ie, International Classification of Disease, Diagnosis and Statistical Manual of Mental Disorders • Call for evidence-informed mental health interventions such as medication or psychotherapy	• Can occur in response to any adversity • Often does not meet the criteria for a psychiatric diagnosis or require specialized mental health interventions • Often responds well to supportive strategies

A General Approach to Depressive Symptoms

The WHO has outlined an excellent general approach to mental health care, including the management of depressive symptoms, through its pyramid of mental health services. The pyramid captures all of the levels of care that are needed to manage mental health problems, and offers a helpful way of conceptualizing a response to the increased incidence of major depression and other mental disorders during the SARS-CoV-2 pandemic[8] worldwide (Figure 2).[9] The base of the pyramid is the key role of self-care, which has been widely promoted for patients and their health care practitioners. This includes implementing personal strategies such as maintaining social connections through virtual means, carving out time for rest and pleasurable activities, ensuring adequate sleep, and engaging in mindfulness and meditation. Self-care is an essential ongoing component in the prevention and management of all medical and psychiatric illnesses.

The next level up in the pyramid is the key role of informal care. This can include reaching out to social supports in the community including family, friends, neighbors, houses of worship, and community-based organizations. As the use of technology has expanded, the availability of support through virtual means has increased. Informal care is another essential element of mental illness prevention and treatment.

The middle level of the WHO pyramid is primary care. It is at this level that most people with mental health symptoms will first appear within the medical system. Moreover, a recent US study found that 45.7% of antidepressants are prescribed in primary care.[10] Primary care, including HIV primary care, is in a crucial position with regard to the recognition of mental health problems, hence the importance of depression screening in this setting. It is also at the primary care level that decisions are often made regarding who warrants referral to specialty mental health care (Figure 2).[9]

Considerable emphasis has been given to integrating the treatment of uncomplicated major depression into primary care, but numerous educational and health system barriers make achieving this goal difficult. HIV primary care settings that

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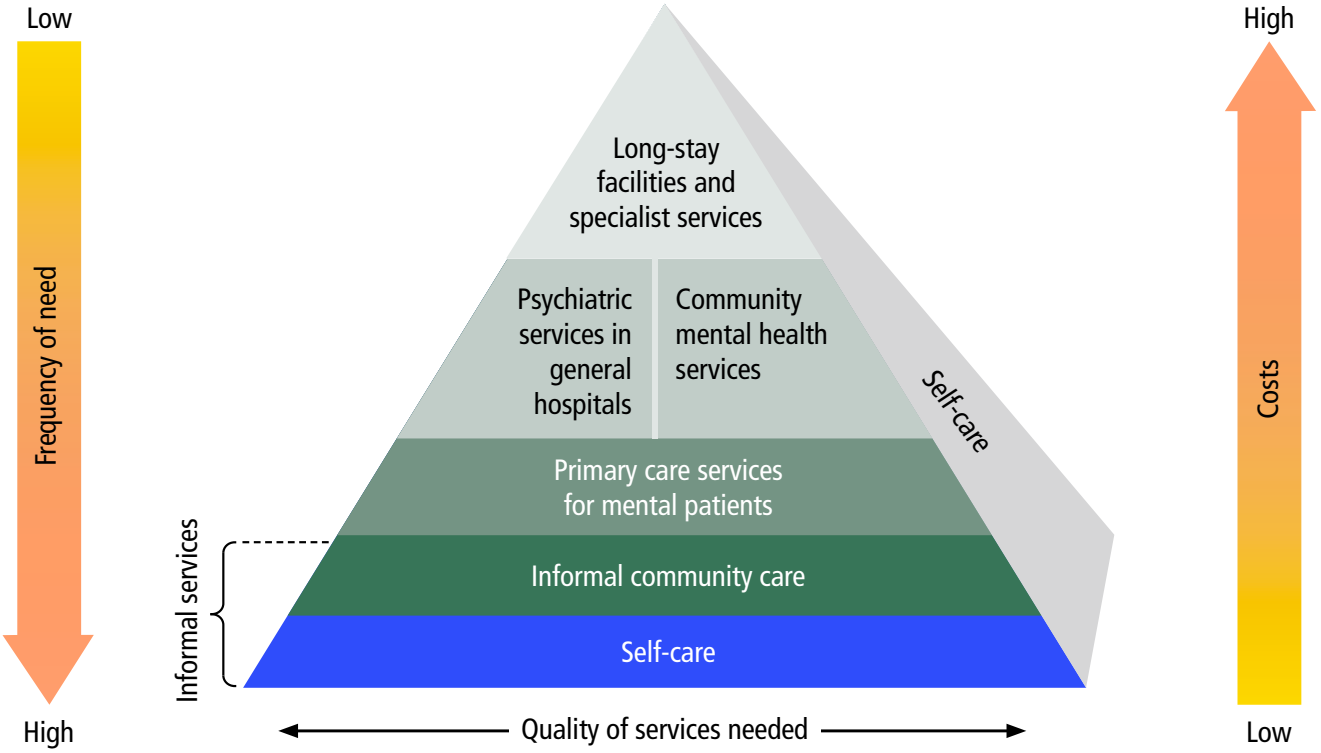

Figure 2. Model for improving health systems and services for mental health. Adapted from the World Health Organization.[9]

have no behavioral health practitioners often consider prescribing antidepressants as the only realistic option for treating depression. This approach is safest and most effective when the prescribing clinicians assess and address contributing medical and psychosocial problems. Moreover, the overuse and the underuse of antidepressants are common problems in the United States. Although a PHQ-9 score of 10 or higher is suggestive of major depression, ruling out bipolar depression is important before prescribing any antidepressant medication.

Depressive Disorders versus Bipolar Disorders

In the most recent version of the *Diagnostic and Statistical Manual of Mental Disorders*, the *DSM-5*,[11] a decision was made to create separate categories for depressive disorders and bipolar disorders. Symptoms of depression are prominent in both conditions.

The most common depressive disorder is major depressive disorder, and the PHQ-2 and the PHQ-9 screen for this condition. Major depression can be conceptualized as a medical comorbidity of HIV infection, with affective symptoms (such as depressed mood, loss of interest, guilt, worthlessness, and suicidal ideation) and somatic symptoms (such as appetite/weight loss, sleep disturbance, motor agitation/retardation, fatigue, and loss of concentration). Persistent depressive disorder shares similar symptomatology with major depressive disorder but can vary in the severity of symptoms and has a longer duration of at least 2 years.[11] The previous diagnosis of dysthymia is now subsumed in this category.

Bipolar disorders are characterized by switching between depressive and elevated moods. The distinguishing feature of bipolar disorders is periods of abnormal and persistently elevated, expansive, or irritable moods and high amounts of energy, referred to as the (hypo)manic phase of the illness, lasting at least 1 week and alternating with periods of depression. The severity of these elevated states determines whether the illness is called bipolar 1 (full mania) or bipolar 2 (hypomania). Cyclothymia is

defined as at least 2 years (1 year in youth) of numerous periods of hypomania and depression that do not fully meet the requirements for mania, hypomania, or major depressive episodes.[11]

Episodes of depression or (hypo)mania that are induced by substance use or medications are specifically listed as "substance/medication-induced" in the *DSM-5*. The screening instruments recommended in this article are based on *DSM-5* diagnoses, and readers are encouraged to review the full criteria for these disorders.

A 2019 systematic review and meta-analysis of studies concluded that more than 3 in 20 patients managed in primary care settings for depression have unrecognized bipolar disorder

Accurately distinguishing between bipolar disorders and depressive disorders can be challenging, and bipolar disorders are often underdetected. A 2019 systematic review and meta-analysis of studies concluded that more than 3 in 20 patients managed in primary care settings for depression have unrecognized bipolar disorder.[12] This occurs in part because people with bipolar disorders spend most of their unwell time in a depressed state and are more likely to seek help when depressed. Evidence suggests that the treatment of bipolar depression with antidepressant monotherapy is not effective, and it may precipitate mania, especially in people with bipolar 1 diagnoses.[13] Mood stabilizers, including atypical antipsychotics, specific anticonvulsants, and lithium, are the psychotropic medications of choice to treat bipolar depression.

What is Known About Effective Treatment for Depression Among People With HIV?

There are some studies that specifically focus on the treatment of depressive disorders in people with HIV, but it is important to look for guidance from more general evidence on the treatment of depressive disorders. Current guidelines for the treatment of depression in adults from the American Psychiatric Association describe effective psychotherapies and medication treatments for depressive disorders.[14] Strong evidence suggests that specific psychotherapies, especially cognitive behavioral therapy and interpersonal therapy, are effective treatments for mild to moderate depression.[14]

However, in HIV primary care settings that do not have access to clinicians who are trained to provide psychotherapy to patients with depressive disorders, prescribing antidepressant medication is often the most immediately available option. However, it is important to bear in mind that although primary care physicians often initiate pharmacologic interventions more frequently than any other treatment option in their patients with newly diagnosed depression,[15] current research and treatment recommendations indicate that psychotherapy is often a patient preference.[16] Primary care programs that have on-site staff who can offer brief evidence-based psychotherapies for depression are at a distinct advantage for engaging patients in depression treatment.

Primary care physicians often initiate pharmacologic interventions more frequently than any other treatment option in their patients with newly diagnosed depression… psychotherapy is often a patient preference

Aim to Achieve Remission of Depression Using a Stepped Care Approach

Outcomes in the treatment of episodes of major depression are often referred to as either response, defined by at least a 50% reduction in symptoms,

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or remission, defined as few or no symptoms. Remission is a much more desirable outcome than response because it is associated with better functioning and prognosis.[17] Moreover, depressive symptoms that persist pose a risk for relapse of major depression.

It helps to understand the trial-and-error nature of prescribing antidepressants. Unlike the treatment of HIV and other infectious diseases, there are no biologic markers that allow matching an antidepressant medication to whether a specific person will improve on that particular medication. Liver enzyme levels can be measured to assess whether a person will be a slow or rapid metabolizer of a specific antidepressant, but this is currently not a part of routine clinical practice. As a result, giving an antidepressant involves monitoring the patient's degree of improvement and the tolerability of its adverse effects. Of course, it is always useful to obtain the patient's past history of successes and failures on previous antidepressant trials and use that as a guide.

Using suboptimal doses of antidepressant medication is one of the common reasons for failure of antidepressant trials in primary care

Starting at a low dose reduces adverse effects, which can be important for people with HIV, especially those who are older or medically complicated. At the same time, it is important to escalate the dose as needed to achieve remission if the patient requires a higher dose and can tolerate the adverse effects. Using suboptimal doses of antidepressant medication is one of the common reasons for failure of antidepressant trials in primary care.[18] An antidepressant may need to be stopped quickly if a patient cannot tolerate it. When this is not the case, a typical antidepressant trial requires 6 to 8 weeks to determine efficacy.

There are many antidepressant studies that illustrate the above points in the treatment of major depression. Of special interest is the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study. This large study of stepped care for the treatment of nonpsychotic major depressive disorder evaluated patients with comorbid medical conditions and was conducted with funding from the National Institute of Mental Health (NIMH) rather than with funding from pharmaceutical companies. The study involved a series of randomized controlled trials that examined the acute and longer-term treatment outcomes associated with the steps needed to achieve an adequate benefit using a measurement-based stepped care approach (Table 2). The study enrolled adult patients who were candidates for the first treatment step. Patients who did not achieve remission or could not tolerate a treatment step were encouraged to proceed to the next step.[19]

There were 2 endpoints: response (>50% reduction of symptoms) and remission (few or no symptoms). There were 4 sequenced treatment steps in the algorithm. The first step for everyone was treatment with the selective serotonin reuptake inhibitor (SSRI) antidepressant citalopram. If citalopram treatment was not successful, step 2 contained 7 switch or add-on options as follows: switch to sertraline; to bupropion-slow release (SR); to venlafaxine-extended release (XR); to cognitive psychotherapy; or use an add-on option: add bupropion-SR, add cognitive psychotherapy, or add buspirone. If step 2 failed, steps 3 and 4 involved other switching and add-on options, including using classes of less-frequently prescribed antidepressants, lithium, tri-iodothyronine (T3), and various antidepressant combinations. These latter steps are unlikely to be used in the primary care setting.

The STAR*D study illustrates the importance for prescribers in HIV primary care to learn to use several antidepressants and to be willing to switch patients from one to another depending on patient outcomes (symptom improvement and ability to tolerate adverse effects). In the STAR*D study, steps 1 and 2 each had about a one-third chance of achieving acute remission. This may sound disappointing, but given the suffering and disability caused by major depression, the value of persistence in finding an effective treatment cannot be underestimated.

The low rates of success in steps 3 and 4 suggest that after the failure of 2 adequate antidepressant trials, patients should be referred to mental health specialty care for further treatment. Other reasons to refer to specialty care include bipolar depression, psychotic depression, risk for suicide or violence, and diagnostic uncertainty.

Selecting an Antidepressant Medication

As the STAR*D study indicates, many different antidepressant medications are available for treating major depression and are variably successful in terms of efficacy and tolerability for any particular person. The literature about antidepressants is too extensive to be summarized here, but some general principles are helpful. It is always important to consider overlapping toxicities and drug interactions with prescribed medications the patient is already taking, and this information can be readily accessed using online resources. Primary care prescribers can select a few of the common SSRIs and serotonin and norepinephrine reuptake inhibitor antidepressants and learn enough about their profiles to become comfortable prescribing them. It is also helpful to know that antidepressants work as antianxiety medications, and may improve the symptoms of anxiety disorders and PTSD. For people with depressive illness and comorbid alcohol or other substance use disorders, it is best to presume that these 2 disorders require separate treatments, and to know that treatments for depression and alcohol or substance use disorders can be administered simultaneously depending on the patient's motivation and the resources available.

Referring Patients to Behavioral Health Care

Although treating uncomplicated major depression in HIV primary care is essential to reaching all people with HIV who suffer from this condition, it is important to identify people with HIV who need referral to specialty care. Common reasons for referral include the failure of 2 adequate trials of antidepressant treatment, suspicion of bipolar disorder, psychotic symptoms, suicide risk, and diagnostic uncertainty. There is a growing literature on the relationship between depression and medical conditions that increase inflammation, such as HIV infection. Studies concerning the potential use of anti-inflammatory agents to treat depression or enhance the therapeutic effects of antidepressants are underway, but the evidence is not yet strong enough to make specific clinical recommendations. Novel agents such as ketamine are also being studied and may be available in some specialty behavioral health care settings.[20]

Common reasons for referral to behavioral health specialty care include the failure of 2 adequate trials of antidepressant treatment, suspicion of bipolar disorder, psychotic symptoms, suicide risk, and diagnostic uncertainty

People with HIV who are on a stable medication regimen for depression that was originally prescribed in a psychiatric setting can often be followed up for maintenance in a HIV primary care setting.

Outcomes of the Treatment of Depression in People With HIV

The key outcomes of successfully treating depressive disorders among people with HIV are relief from suffering, improvement in quality of life, and restoration of function. Depression is a remarkably painful state that robs people of a sense of being fully alive. Dante offers a succinct summary of this state in *Inferno*: "I did not die, but yet I lost life's breath. Imagine for yourself what I became, deprived at once of both my life and death."[21]

Although depressive disorders are associated with increased mortality among people with HIV, it is not known if successful depression treatment reverses this shortened lifespan. Interestingly, there is some evidence that successful treatment of

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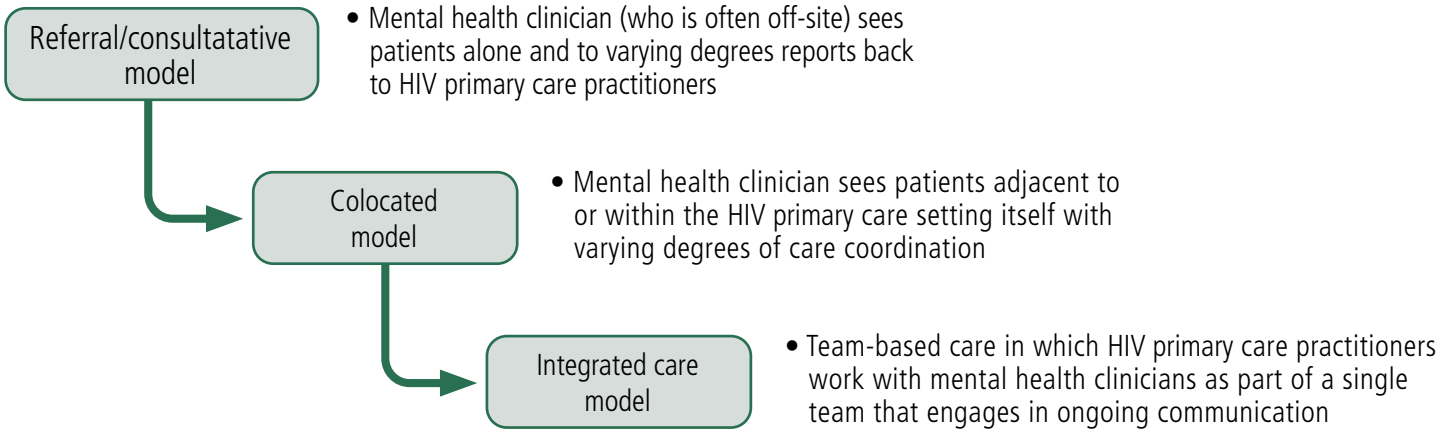

Figure 3. Overall model for linkage to care.

depression prolongs life in a number of other medical conditions.[21,22]

Linkage to Depression Treatment

For HIV primary care practitioners who refer some or all of their patients with depression to behavioral health care practitioners for treatment, there are many models for conceptualizing this collaboration. The schematic in Figure 3 offers a simple summary of these models.

One integrated care model that has received particular attention is the collaborative care model.[23] In this model, a team within the primary care setting manages patients with depression, and a psychiatrist is available as a consultant to the team rather than as someone who directly assesses and treats the patients. Although many excellent models exist for integrating depression treatment into primary care, implementing these models has often proven difficult.[23] Most HIV primary care programs use an approach that seems realistic for their particular circumstances.

Taking antidepressants is associated with adherence to antiretroviral therapy

Engagement and Retention in Depression Treatment

Adherence to medication over time is very difficult for all patients and for all conditions, and adherence to antidepressants is no exception.[24] A recent review of studies suggests that patients taking antidepressants are more likely to adhere to antiretroviral therapy,[25] but it is difficult to know if this simply reflects that these patients are more generally adherent to treatment, or if the treatment of depression directly influences adherence to antiretroviral therapy.

Maintaining Remission

Depression tends to be a recurrent disorder, and taking antidepressant medication continuously is often recommended for chronic and recurrent episodes of major depression. Usually, attempts are made to use the lowest possible doses of medication that keep people well. The literature on the success of discontinuing antidepressants in chronic or recurrent depression is limited and is plagued with confusion between the withdrawal effects of discontinuing antidepressants and actual relapse.[26] At present, patients and their clinicians do best when they engage in joint decision making about which course of action to take.

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Conclusion

Depressive disorders are common among people with HIV. HIV primary care settings have a critical role to play in detecting and treating these conditions, because doing so is critical to the quality of life and functioning of people with HIV. Therefore, it is well worth the time and effort required to conduct the needed differential diagnosis and to persist in seeking treatments that achieve remission from depression. Because the brain and the body form a single integrated system, it is essential to overcome treatment silos and achieve care integration in the long run.

This article is based on a presentation given at the Ryan White HIV/AIDS Program CLINICAL CONFERENCE by Dr Cournos on October 5, 2021: https://youtu.be/N4M2Y-qHx39M. This article was prepared by Dr Fuenmayor and Dr Cournos in January 2022.

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Invited Review

Update on Tuberculosis/HIV Coinfections: Across the Spectrum From Latent Infection Through Drug-Susceptible and Drug-Resistant Disease

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Tuberculosis (TB) remains the leading cause of death among people with HIV, and annual risk of progression from latent TB infection to active disease in this population is 10%. Diagnostic tests for latent and active TB remain suboptimal for people with HIV who have a CD4+ count below 200 cells/μL, and there is an urgent need for assays that predict progression from latent to active disease, monitor treatment response, and test for cure after latent and active TB treatment. Traditional treatment duration for latent infection and active TB disease has been onerous for patients; however, shorter-course regimens are increasingly available across the spectrum of TB, including for drug-resistant TB. Simultaneous treatment of HIV and TB is complicated by drug-drug interactions, although trials are ongoing to better understand the magnitude of these interactions and guide clinicians in how to use short-course regimens, particularly for people with HIV.

Keywords: HIV, TB, treatment, short-course

Background

Tuberculosis (TB) remains a global threat to public health, with 10 million new cases and 1.2 million deaths attributed to TB in 2019. Despite the dramatic improvement in global access to antiretroviral therapy (ART), TB is still the leading cause of death among people with HIV.[1] Additionally, 1 in 4 people in the world have latent TB infection (LTBI).[2]

TB is spread from person to person via airborne droplet nuclei; recent data also suggest that aerosolization via passive breaths may contribute to onward spread of TB, including in individuals with asymptomatic infection.[3] As with other respiratory infections, the risk of TB transmission is determined by the infectiousness of the index case, host susceptibility, and duration as well as proximity of exposure. Although TB is largely a pulmonary disease, it can infect any area of the body; TB meningitis, one form of extra-pulmonary disease, is the most lethal manifestation of TB.

Despite the massive global burden of TB and the morbidity and mortality risks it confers, resources to diagnose, treat, cure, and prevent TB are still inadequate. In 2019, global funding for research and development of TB therapeutics reached an all-time high of US $906.4 million, a triumph that still falls far short of the US $2 billion recommended by the 2018 United Nations General Assembly High-Level Meeting on Tuberculosis,[4] and of the US $10 billion over 2 years recommended by the Stop TB Partnership.[5] Prevention efforts have also been hampered by the lack of an effective vaccine. Currently, the bacille Calmette-Guérin (BCG) vaccine is the only available tool to prevent infection and, at best, reduces TB infection by 50%.[6] Because of its variable efficacy as well as injection-site reactions and risk of local or systemic infection, BCG vaccine is now only used in high–TB-burden countries where the benefits outweigh the potential risks. Finally,

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TB remains a heavily stigmatized disease and is inextricably linked to poverty and poor living conditions. Stigmatization is a major barrier to seeking care among persons with TB, and this has worsened during the SARS-CoV-2 pandemic. The Global Fund estimates that about 1 million fewer patients were treated for TB in 2020; the COVID-19 pandemic is likely to adversely affect TB control worldwide for decades to come.

Although HIV was only identified in the last 40 years, patients and clinicians have access to a variety of fully active, well-tolerated regimens, many of which are available in 1-pill-per-day combinations or in long-acting injectable formulations. In contrast, the TB bacterium was identified more than 140 years ago, and there is only one regimen considered the standard of care for drug-susceptible (DS) TB. There has been little incentive for pharmaceutical companies to participate in the TB drug development process, given the limitations of existing animal models for preclinical drug testing, the challenges posed by the pharmacokinetic (PK)–pharmacodynamic relationship between mycobacterial agents and TB, and the low expected financial returns. Thankfully, after decades of limited options, the TB pipeline is now increasingly accumulating promising candidates in preclinical and clinical testing (Table 1).

Spectrum of TB Disease

TB has historically been categorized as latent or active, but infection and disease exist on a spectrum. On one end of that spectrum, exposed individuals may immediately eliminate the bacteria from the body via an innate or an acquired immune response without memory T-cell response. These individuals would not develop symptoms or evidence of TB infection based on tuberculin skin test (TST) or interferon gamma release assay (IGRA). There are others who eliminate TB after exposure but do have a memory T-cell response, and therefore would have positive TST and IGRA test results. A third group acquires TB, but the bacteria remain in a quiescent (or latent) form, conferring future risk of activation to TB disease. For the 23% of the world population that is infected with TB, their lifetime risk of developing active disease is 10%. However, among those with HIV who are latently infected, the risk of developing TB disease is 10% per year. Subclinical TB disease is a more recently described condition in which individuals do not develop symptoms but nonetheless have low-level active disease with intermittently positive mycobacterial cultures. Among people who develop symptomatic TB disease, there is a range of severity from minimally ill to severely and critically ill; some of the latter cases are further complicated by the development of pulmonary cavitation and dissemination of disease outside of the lungs.

Diagnosis of Latent TB

Among those individuals who are exposed to TB and develop a memory immune response but who do not immediately progress to active disease, testing for latent disease with TST or IGRA is likely to yield positive results. A TB skin test is performed by injecting tuberculin purified protein derivative (PPD) intradermally in the forearm. If a patient is infected with TB, this injection will induce an immune response and induration at the injection site. What constitutes a positive result on TST depends on the pretest probability for TB, as well as the likelihood of a robust immune response. For patients with HIV, other immunosuppressed individuals, and those who are close contacts of people with TB, a lower threshold of 5 mm induration at the injection site is considered positive. A diameter of 10 mm is considered positive for people born in countries where TB is common, those with certain medical conditions that increase risk of TB, and those who work or reside in settings where TB exposure would be likely. A higher threshold of 15 mm is used for those with no known risk factors for TB infection. IGRA testing measures the immune response to TB in whole blood. Sensitivity of all LTBI testing is about 80% in the general population and 64% to 70% among those with HIV. Anergy, or lack of response, on TST or an indeterminate result on an IGRA test is more likely among people with HIV who have a low CD4+ count, generally defined as less than 200 cells/μL. Positive testing using any of these assays is likely to persist; therefore, there is rarely any value

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Table 1. 2021 Global New Tuberculosis Drug Pipeline by Stage and Development.[a]

Discovery	Preclinical development		Clinical development			Regulatory market approval
Lead optimization	Early-stage development	Good manufacturing practice / good laboratory practice toxicology	Phase I	Phase II	Phase III	
PanD inhibitors	JSF-3285[b]	FNDR-20081[b]	BVL-GSK098[b]	Delpazolid	Pretomanid[b]/moxifloxacin/bedaquiline[b]/pyrazinamide (4-month regimen)	Bedaquiline[b]
Indazole sulfonamides	MPL-446, 447[b]	TB-47[b]	GSK-286[b]	BTZ-043[b]	Truncate TB (2-month regimens)	Delamanid[b]
Diarylthiazoles	CPZEN-45[b]	GSK-839[b]	TBAJ-587		Rifapentine/moxifloxacin/isoniazid/pyrazinamide (4-month regimen)	Pretomanid[b]
DprE1 inhibitors	NTB-3119[b]	OTB-658	TBAJ-876	TBA-7371[b]		
Direct InhA inhibitors	TZY-5-84	Sanfetrinem	TBI-223	OPC-167832[b]		
Mtb energy metabolism	MBX-4888A (1810)[b]		Macozinone[b] (PBTZ-169)	GSK-656[b] (070)		
Macrolides	FNDR-10045[b]		Pyrifazimine (TBI-166)	SQ-109[b]		
Mycobacterial gyrase inhibitors	FNDR-20364[b]			Telacebec[b]		
Arylsulfonamides				SPR720[b]		
Inhibitors of MmpL3, Translocase-1, Clp, PKS13, F-ATP synthase, Oxazolidinones						

Reproduced with permission from Barbara Laughon, PhD.[31]

[a]New molecular entities are not yet approved, are being developed for tuberculosis, or are only conditionally approved for tuberculosis. This table lists the most advanced stage reported for each drug as as of October 2021, except for highlighted drug names, which are current as of March 2021.

[b]New chemical class. Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, and beta-lactam.

in repeat testing once a positive result is observed. These are also indirect tests, as it is not possible to grow the TB bacterium from an infected person or to test for drug susceptibility of the infecting strain.

Diagnosis of Active TB

For over a century, the mainstay of diagnosis for active TB disease has been smear microscopy and culture on solid media. In the last decade, rapid molecular diagnostic tests have entered clinical practice and have considerably shortened the time to TB diagnosis. The Xpert mycobacterium tuberculosis/rifampicin (Mtb/RIF) platform generates results in 2 hours, is more sensitive than smear microscopy for acid-fast bacilli (AFB), and can identify rifampicin resistance.[7] Xpert Ultra has further increased sensitivity and reduced time to result.[8] Genotype Mtb drug resistant (MtbDR) plus gives results in 5 hours and is able to identify isoniazid (INH) and rifampicin resistance. Numerous other platforms using line-probe assays, liquid culture, nucleic acid amplification testing (NAAT), and next-generation sequencing (NGS) are in various stages of development and may hold promise for future diagnostic speed, accuracy, and access. Despite these innovations, smear microscopy and culture conversion are still the only standard tests used to monitor treatment response. There remain crucial needs in the TB diagnostic landscape, including a highly accurate test for TB infection, a test of cure after TB preventative therapy (TPT) of latent infection, biomarkers to predict progression from latent to active disease and monitor treatment response over time, nonsputum-based diagnostics, and proof of cure from active disease.

TB Preventive Therapy

Treatment of latent TB infection can be effective in preventing progression to active disease. A Cochrane review of 11 randomized trials examining 8130 participants with HIV found that the overall reduction in TB disease was 36%, with an even greater reduction of 62% among those participants with positive TST at study entry.[9] Although TPT was effective, uptake was poor. A meta-analysis of 58 studies of TPT found that each step in the care cascade resulted in a considerable drop in the proportion of patients receiving that recommended intervention. These points of attrition included initial testing (71.9% completion), receiving a positive test result (66.7%), referral for positive test (56.0%), completion of medical evaluation (43.7%), recommendation for treatment (35.0%), acceptance and commencement of treatment (30.7%), and treatment completion (18.8%).[10] The main barriers to TPT uptake included length of treatment, concern about adverse effects, unfounded fear of selection for resistance, and for those with HIV, prioritization of ART over TPT.

In response to concerns about the burden of TPT duration, there are now numerous short-course options from which practitioners and patients may choose. The first regimen to treat LTBI was 9 months of INH (9H); this is still included in World Health Organization (WHO) recommendations, as is 6 months of INH (6H). However, the Centers for Disease Control and Prevention (CDC) currently recommends only the shorter course regimens, which include 3 months of daily INH plus rifampicin (3HR), 4 months of daily rifampicin (4R), or 3 months of once-weekly INH plus rifapentine (3HP). Rifapentine (RPT) is a rifamycin, like rifampicin and rifabutin, and has the benefits of a longer half-life and increased potency against TB.[11] Rifapentine has a similar adverse-effect profile to other rifamycins but has potentially more drug-drug interactions, including with nevirapine.[12] Given its potency, it was recently tested in an ultra-short course regimen of 1 month (4 weeks) of daily rifapentine plus INH (1HP) and was found to be noninferior to 9H for preventing TB disease and TB-associated death, or death from unknown cause among adults and adolescents with HIV. Completion rates were also higher (97%) than for 9H (89.5%) ($P<.01$).[13] This regimen can be coadministered with efavirenz-based ART,[14] and a recent study has demonstrated acceptable dolutegravir exposures when dosed twice daily with daily rifapentine plus INH for TPT.[15]

Given that exposure to drug-resistant TB can result in latent infection (rather than active disease), some of the traditional TPT regimens may not

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provide sufficient treatment for LTBI caused by a drug-resistant strain of TB. The optimal treatment for drug-resistant latent TB is currently unknown. For high-risk contacts of persons with drug-resistant TB, a fluoroquinolone is often recommended. Various studies are ongoing to better guide the clinical approach to drug-resistant latent TB (TB-CHAMP, VQUIN MDR, PHOENIx MDR-TB).

Treatment of Drug-Susceptible TB

Although treatment-shortening regimens have been a scientific priority for years,[16] there was until recently only a single recommended regimen for the treatment of drug-susceptible TB: 2 months of INH, rifampicin, pyrazinamide, and ethambutol (HRZE) followed by 4 months of INH and rifampicin (2HRZE/4HR). With this one-size-fits-all approach to the treatment of TB, adverse effects are common and treatment completion rates are suboptimal. For people with HIV, treatment for TB limits or alters ART (Table 1) and can increase monitoring requirements. Treatment duration for drug-susceptible TB was initially 24 months in the 1950s, then shortened to 18 months in the 1960s, 9 months in the 1970s, and finally 6 months in the 1980s. Duration remained stuck at 6 months for the next 40 years, until preclinical data began to emerge that rifapentine could shorten time to culture conversion in a murine model of TB. The TBTC (Tuberculosis Trials Consortium) study 29X demonstrated the treatment-shortening potential of rifapentine, and Study 31/A5349 (S31/A5349) has now demonstrated that a 4-month regimen containing rifapentine and moxifloxacin (2 months of INH, rifapentine, pyrazinamide, and moxifloxacin [2HPZM]/2 months of INH, rifapentine, and moxifloxacin [2HPM]) is noninferior to standard 2HRZE/4HR. The third regimen used in the study without moxifloxacin (2 months of INH, rifapentine, pyrazinamide, and ethambutol [2HPZE]/2 months of INH and rifapentine [2HP]) did not meet noninferiority criteria for efficacy. All-cause mortality during treatment was slightly lower in participants in both of the RPT-containing arms than those in the control arm. Safety was similar between the arms.

Table 2. Antiretroviral Drugs That Are Compatible With Tuberculosis Medications

Tuberculosis drug(s)	Compatible antiretroviral drug(s)
Isoniazid, pyrazinamide, ethambutol	Any antiretroviral drugs
Rifampicin	Any nRTI Efavirenz 600 mg daily Efavirenz 400 mg daily Dolutegravir 50 mg twice daily Raltegravir 800 mg twice daily
Rifapentine 900 mg weekly	Any nRTI Efavirenz 600 mg daily Lopinavir/ritonavir 400 mg/100 mg twice daily Dolutegravir 50 mg daily Raltegravir 400 mg twice daily
Rifapentine 450 mg or 600 mg daily	Efavirenz 600 mg daily Dolutegravir 50 mg twice daily
Rifapentine 1200 mg daily	Efavirenz 600 mg daily
Bedaquiline	Any nRTI Doravirine 100 mg daily Nevirapine 200 mg daily followed by twice daily Efavirenz 600 mg daily Bictegravir/emtricitabine /tenofovir alafenamide Cabotegravir 30 mg oral, cabotegravir 400 mg/rilpivirine 600 mg injection monthly Dolutegravir 50 mg daily Raltegravir 400 mg twice daily
Pretomanid 200 mg daily	Efavirenz 600 mg daily Lopinavir/ritonavir 400 mg/100 mg twice daily
Moxifloxacin 400 mg daily	Any nRTI Doravirine 100 mg daily Nevirapine 200 mg daily followed by twice daily Rilpivirine 25 mg daily Darunavir/cobicistat 800 mg/150 mg daily Any integrase strand transfer inhibitor
Delamanid 100 mg twice daily	Any antiretroviral drug(s)

For additional details, please see the Liverpool Anti-tuberculosis Treatment Selector. Adapted from Liverpool Drug Interactions Group and Imperial et al.[15,30]

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In the rifapentine-moxifloxacin arm, there was 1 instance of QT corrected (QTc) prolongation to 460 milliseconds and 1 instance of knee tendonitis. The WHO now supports the use of this regimen as an acceptable alternative to the current standard 6-month regimen,[17] without reference to people with HIV. The CDC recommends the 4-month rifapentine-moxifloxacin regimen, including for use in people with HIV who have CD4+ counts of 100 cells/μL or more and who are receiving or planning to initiate efavirenz as part of their ART.[18] There are ongoing studies to better understand how to prospectively stratify patients based on severity risk factors in order to shorten TB treatment duration for certain low-risk groups.

Treatment of Drug-Susceptible TB Among People With HIV

There was also uncertainty for many years about the optimal timing of ART initiation and TB treatment. Numerous studies across different countries have now demonstrated that earlier commencement of ART is associated with improved outcomes.[19-21] Though earlier start does increase the risk of immune reconstitution inflammatory syndrome (IRIS), there is still a clear benefit; therefore, ART should not be delayed in persons with pulmonary TB. Major guidelines groups, including the American Thoracic Society (ATS), the Department of Health and Human Services (DHHS), and the International Antiviral Society–USA (IAS–USA),[22] currently recommend early initiation of ART, defined as within 2 weeks for CD4+ count less than 50 cells/μL, and within 8 weeks for CD4+ count greater than 50 cells/μL. The exception to this recommendation is for people with TB meningitis, given that early ART initiation has been associated with increased adverse events and death.[23]

Though there were relatively few participants with HIV enrolled in S31/A5349, efficacy data are so far encouraging for 2HPZM/2HPM. Results were similar among the 194 (8.3%) participants with HIV, with the rifapentine-moxifloxacin arm showing more favorable outcomes than the control arm. An embedded PK substudy within S31/A5349 also demonstrated that efavirenz (EFV) concentrations were not significantly affected by rifapentine and can be coadministered without dose adjustment.[24,25] An upcoming ACTG (AIDS Clinical Trial Group) study will evaluate the effect of this rifapentine-moxifloxacin–containing regimen on dolutegravir PK (A5406).

Antiretroviral Drug-Drug Interactions With TB Medications

As mentioned, potent drug-drug interactions between rifamycins and components of ART complicate TB/HIV cotreatment. Current ART regimens that are compatible with concurrent TB treatment are summarized in Table 2. To varying degrees, all rifamycins are potent inducers of numerous metabolizing enzymes via pregnane X receptor (PXR)–mediated pathways. Rifamycins bind PXR, thereby increasing gene expression of cytochrome P450 enzymes and drug transporters such as P-glycoprotein and multidrug-resistance protein 1, among others.[26] The elucidation of rifamycin drug-drug interactions is particularly crucial for the many millions of people coinfected with HIV and TB who require simultaneous treatment of both diseases.

Immune Reconstitution Inflammatory Syndrome

IRIS occurs as the immune system rebounds with successful virologic control of HIV. TB-related IRIS is more commonly seen with early ART initiation and with a low (ie, <100 cells/μL) baseline CD4+ count. Rarely is TB IRIS severe or fatal, but it can be in certain extrapulmonary manifestations of TB, such as TB meningitis. Management of IRIS requires establishing the diagnosis (often a diagnosis of exclusion after other opportunistic infections are ruled out), performing surgical drainage if necessary, and at times prescribing steroids such as prednisone.[27] There is evidence from a randomized clinical trial that prescribing prophylactic prednisone at 40 mg per day for 2 weeks, followed by 20 mg per day for 2 weeks, may reduce the risk of IRIS in patients with CD4+ count below 100 cells/μL.[28]

Drug-Resistant TB

Drug-resistant TB is a widely observed occurence, with 465,000 incident cases in 2019. Multidrug-resistant (MDR) TB is resistant to rifampicin and INH; pre-extensively drug-resistant (pre-XDR) TB is resistant to rifampicin, INH, and any fluoroquinolone; and XDR TB is resistant to INH, rifampicin, any fluoroquinolone, and either bedaquiline or linezolid. Historically, treatment for any degree of drug-resistant TB substantially increased the duration, complexity, and toxicity of the regimen. A common regimen would contain at least 5 drugs for 18 to 24 months, although these regimens and durations were largely based on observational data and few of the recommended drugs were ever tested in a randomized controlled trial for MDR TB. In 2017, the WHO endorsed a 9-month short course regimen for select patients; the regimen consisted of kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, INH, and ethambutol. Expert consultation was still recommended for these drug-resistant cases. Data from the Nix-TB (Bedaquiline, Pretomanid, and Linezolid for Treatment of Extensively Drug Resistant, Intolerant or Non-responsive Multidrug Resistant Pulmonary Tuberculosis) study have demonstrated that a combination regimen of pretomanid, bedaquiline, and linezolid results in high cure rates for patients with treatment-refractory MDR and XDR TB. Although the efficacy results were impressive, myelosuppression and neuropathy were seen in the majority of participants; therefore, the ZeNIX (Safety and Efficacy of Various Doses and Treatment Durations of Linezolid Plus Bedaquiline and Pretomanid in Participants With Pulmonary, XDR-TB, Pre- XDR-TB or Non-responsive/Intolerant MDR-TB) trial and others are ongoing to determine the optimal linezolid dose to mitigate these toxicities. Additionally, recent data from TB-PRACTECAL has demonstrated that three different 24-week regimens for rifampicin-resistant TB were safe, well tolerated, and efficacious: bedaquiline, pretomanid, linezolid, with or without either clofazimine or moxifloxacin.[29]

Conclusion

Although progress in the treatment of HIV-associated TB has been slow, achievements are steadily being made, including an ultra-short course for TB preventive therapy, a comparably effective 4-month treatment regimen, and monumental improvements in the treatment regimens for MDR and XDR TB. Remaining urgent challenges include finding an effective vaccine, better diagnostics that can be used longitudinally to monitor treatment response, additional short-course regimens for treatment of TB disease, and more studies in children and pregnant women.

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All relevant financial relationships with ineligible companies have been mitigated.

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