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CME

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- Pathogenesis of HIV disease
- Epidemiology of HIV and HIV prevention efforts
- Neurologic disorders in HIV disease and their treatment
- Viral hepatitis
- Antiretroviral therapy
- Complications of HIV disease

Intended Audience

This enduring material is designed for physicians and other health care practitioners who are actively involved in the medical care of people with HIV and HCV infection. This activity is also relevant for other practitioners, including nurse practitioners, nurses, physician assistants, pharmacists, and others.

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Invited Review

CROI 2017: Basic Science Review

Mario Stevenson, PhD

The Conference on Retroviruses and Opportunistic Infections (CROI) continues to be the preeminent gathering for HIV/AIDS researchers. It provides a forum in which investigators involved in all aspects of research on HIV/AIDS and related conditions can present and be updated on the latest scientific developments in the field. In 2017, basic research continued to be strongly represented at the conference. Most of the presentations focused on mechanisms of viral persistence in the face of effective antiretroviral therapy as well as approaches to measuring viral reservoirs and intervening in those reservoirs. The intermix of basic and clinical research presentations provided a dynamic forum for the sharing of knowledge that is crucial to moving the field forward.

Keywords: CROI, 2017, HIV, reservoirs, persistence, cure, lentiviruses, rebound kinetics, Zika

Viral Reservoirs and Mechanisms of Antiretroviral Therapy Persistence Under Antiretroviral Therapy

HIV/AIDS researchers are exploring various approaches aimed at achieving a cure to HIV infection. Cure can be defined as a functional cure in which the virus is still present but is being contained in such a way that control of the virus does not require antiretroviral therapy and that the infected individual is unable to transmit the virus. A sterilizing cure is one in which all vestiges of replication-competent virus have been eliminated. Under the definition of a sterilizing cure, some residual proviral DNA may remain. However, that DNA may be defective and, as such, unable to drive production of infectious virus. Development of approaches that generate a functional or a sterilizing cure will require a better understanding of the mechanisms of HIV-1 persistence under effective antiretroviral therapy. Although there has been great progress in defining the processes that underscore HIV-1 persistence and the cellular reservoirs that sustain this persistence, there is still much to be learned.

In terms of the cells supporting HIV-1 persistence, much of the focus has been on peripheral blood-derived CD4+ T cells where numerous studies have demonstrated the presence of viral genomes in a latent state (one in which there is no virus production unless the cell is stimulated with agents that induce host cell activation). The latent viral reservoir in long-lived memory CD4+ T cells may provide lifelong persistence and is the single biggest obstacle to viral eradication.

As important to the identification of the cellular reservoirs sustaining HIV-1 persistence under effective antiretroviral therapy are the methods employed to measure those reservoirs. This aspect of cure research has been particularly challenging. Methods used to measure the latent reservoir are labor intensive, lack precision, and require a large number of cells.

The limitations to assays currently being used to track reservoir size will complicate attempts to monitor the effectiveness of strategies to eliminate those viral reservoirs. Kaufman and colleagues (Abstract 46) described a highly sensitive approach to simultaneously detect HIV-1 Gag protein and RNA in clinical samples. The method is a variation on RNA flow-fluorescence in situ hybridization (Flow FISH). CD4+ T cells from leukapheresis samples are negatively selected using magnetic beads and then allowed to remain quiescent overnight or stimulated with latency reactivating agents. The cells are subsequently intracellularly stained for HIV-1 Gag and incubated with oligonucleotide pairs that recognize conserved sequences in the HIV-1 genome. The next steps involve amplification (branching) and labeling that amplifies the signal several thousand fold. The dual RNA and protein staining achieved by this approach brings substantial specificity to the detection of reservoir cells and allows detection of as few as 1 infected cell per million CD4+ T cells.

The assay was used to compare the frequency of infected cells in HIV-1 infected, untreated subjects, with subjects on antiretroviral therapy before and after stimulation ex vivo with phorbol[12]myristate[13] acetate (PMA) and ionomycin. For individuals with chronic infection, RNA/Gag-positive cells, in the region of 1 to several hundred or million CD4+ T cells, could be detected. The number increased 3-fold with PMA/ionomycin stimulation. Surprisingly, for individuals on suppressive antiretroviral therapy, in half of the individuals, low numbers of RNA/Gag-positive cells (1-10/million CD4+ T cells) were detectable prior to PMA/ionomycin stimulation. With stimulation with PMA/ionomycin, there was a 10-fold increase in the frequency of RNA/Gag-positive cells from...
avairemic participants. Comparison of RNA/Gag Flow FISH assay with measures of proviral and total DNA indicated that DNA-positive cells were 2 to 3 log₁₀ more abundant than RNA/Gag-positive cells. This is most likely explained by the high frequency of defective proviruses present in infected individuals. Although reservoir measurements of viral DNA are technically straightforward, the fact that most proviruses are defective limits the ability of DNA measurements to inform on the size of the biologically active reservoir; that is, those cells harboring replication-competent virus. For individuals on antiretroviral therapy, there was, as expected, a correlation between the frequency of RNA/Gag-positive cells and integrated DNA copies. The RNA/Gag Flow Fish assay is an important advance in the technologies that can be applied to viral reservoir measurement.

Cells harboring viral RNA and gag are more likely to represent cells harboring functional proviruses as opposed to cells identified on the basis of viral DNA positivity. The high sensitivity and specificity of the approach will allow small changes in viral reservoir size to be tracked, which will be crucial for gauging the efficacy of cure strategies. Still remaining is the limitation that the RNA/Gag Flow FISH assay requires large numbers of cells such that leukapheresis is necessary. In addition, there was a surprisingly poor correlation between the RNA/Gag Flow FISH assay and the quantitative viral outgrowth assay (qVOA) that is considered the “gold standard” approach for measurement of the biologically active viral reservoir. Similarly, there was a poor correlation with the Tat/Rev-induced limiting dilution assay (TILDA). In the post-treatment changes in viral RNA levels are gauged with latency-reversing agents (LRAs). Until reasons for the differences are understood, parallel use of several viral reservoir assays will likely be needed to gauge reservoir size. Nevertheless, the ability to track the frequency of RNA- and gag-positive cells before and after use of LRAs provides a powerful addition to the cure researcher’s toolbox.

Kearney (Abstract 47) provided in-depth insight into the role of expanded clones in viral persistence. The study by Chomont, Sekaly, and colleagues indicated that HIV-1-infected cells may persist through homeostatic proliferation that would allow duplication of proviruses between daughter cells produced at mitosis. Several groups followed up these initial observations by demonstrating the existence of clonally expanded proviruses that arose as a result of numerous proviral duplication events from the proliferation of infected cells. A central question is the extent to which proviral expansion through homeostatic proliferation contributes to the maintenance of a biologically active viral reservoir.

Two factors would work against the ability of homeostatic proliferation to maintain the viral reservoir. First, the vast majority of proviruses in infected individuals contain APOBEC3G-mediated hypermutations as well as premature stop codons and deletions that render the provirus nonfunctional. Second, the process of cell division may drive proviral gene expression, which would lead to destruction of the host cell by viral cytopathicity or host-mediated immune clearance. Kearney examined whether expanded proviruses were replication competent and whether cells harboring those proviruses also harbored viral RNA transcripts. The study focused on previously described individuals in whom expanded clones represented the major population of proviruses. Previous studies from the group of Maldarelli and Hughes identified a clonally expanded provirus (AMBI1) that was highly represented among clonal proviral populations in an infected individual. Viral outgrowth assay (VOA) results indicated that AMBI1 produced replication-competent viruses. Among the cells that harbored clonally expanded proviruses, approximately 4% also expressed viral RNA that was similar to the frequency of RNA-expressing cells harboring defective proviruses. This further indicated that more than 90% of replication-competent proviruses within cells were in a latent state.

The authors next determined whether there were any differences between blood and lymph nodes in the frequency of cells harboring replication-competent, expanded proviruses or in the frequencies of those cells expressing viral RNA frequency. The same expanded clones were found in CD4+ T cells from blood and lymph nodes. Furthermore, a larger proportion of expanded proviruses in lymph node CD4+ T cells expressed viral RNA than in blood CD4+ T cells. These results beg the question as to how cells harboring expressed, clonally expanded proviruses survive over time. Kearney offered the hypothesis that such clonal populations persist because the majority of cells harboring expanded proviruses are in a latent state. Thus, although the subpopulation of RNA-expressing cells are likely to be cleared by viral cytopathicity and immune surveillance, there is a steady state maintained by the continuous expansion of clones through homeostatic proliferation.

There are important implications to these findings. Therapies that promote killing and clearance of RNA-expressing cells would limit the maintenance of the clonally expanded reservoir and, perhaps, of the cells harboring unique proviruses (if the frequency of RNA-expressing cells is a finite property of infected cells). It remains to be determined what dictates the frequency of expanded clones that express viral RNA or what triggers promote proviral expression in infected cells. Those triggers can be thought of as natural latency reactivation processes because they achieve the desired effect of promoting clearance of the infected cell. It is possible that intervals of RNA expression is a consistent feature of all infected cells. As such, the reservoir may be more dynamic and subject to greater degrees of turnover than previously suspected. This, in turn, bodes well for viral cure efforts.

Picker (Abstract 49) discussed the role of therapeutic vaccination in viral cure strategies. Kearney’s earlier talk in the same session raised the possibility that continuous maintenance of a fraction of infected cells that express viral
RNA renders the viral reservoirs susceptible to immune surveillance and cytopathicity. This provides the rationale for the use of therapeutic vaccines that could potentially promote the elimination of reservoir cells actively expressing viral antigens. Picker’s group previously demonstrated that when macaques were vaccinated with Rhesus cytomegalovirus (RhCMV) vectors expressing simian immunodeficiency virus (SIV) antigens and then infected with SIV, the engendered immune responses not only arrested viral spread, but also led to elimination of the viral reservoirs. This surprising result suggests that the RhCMV vector-elicited immune responses were effective in clearing a stable SIV reservoir, or alternatively, that the viral reservoir was unstable and arrest of viral spread by RhCMV vector-driven immune responses led to its decay and clearance.

To distinguish between these possibilities, animals were infected with SIV and placed on early antiretroviral therapy. Animals were then challenged with RhCMV SIV vectors. On discontinuation of antiretroviral therapy, time to rebound correlated with the timing of antiretroviral therapy initiation, with the greatest delay in viral rebound occurring in the animals receiving earliest antiretroviral therapy. In addition, some animals receiving early antiretroviral therapy did not rebound. This was due to elimination of the viral reservoir in those animals as opposed to immune-mediated elite control. Although adoptive transfer from cleared animals to uninfected monkeys failed to transmit infection, low levels of residual viral DNA and RNA could be detected in tissues of monkeys that failed to rebound following discontinuation of antiretroviral therapy. In one monkey receiving antiretroviral therapy 6 days postinfection that had apparently cleared the viral reservoirs (no infection after adoptive transfer), there was a rebound in viral replication 8 months after the antiretroviral therapy. The results indicate that the reservoir established early (within the first 4-5 days) is short lived and if virus spread is blocked by RhCMV SIV immune responses, clearance is achieved within 6 months. However, if the initiation of antiretroviral therapy is delayed by as little as 1 day, the reservoir is more permanent and is not cleared. Taken together, the data argue that immune responses engendered by RhCMV SIV do not enhance reservoir clearance, but rather arrest viral spread prior to establishment of a long-lived reservoir. The results highlight the differences in the control of primary infection versus post—antiretroviral therapy reactivation.

The determinants that dictate viral rebound kinetics after treatment interruption are not well understood. It has been suggested that the time to rebound is an indicator of viral reservoir size. For example, studies from Li and colleagues have demonstrated a direct relationship between time to rebound and levels of cell-associated viral RNA. In one study, Ananworanich and colleagues (Abstract 124) examined whether individuals initiating antiretroviral therapy in Fiebig stage 1 exhibited longer intervals to rebound following treatment interruption. The rationale was that reservoir size would be much smaller in individuals initiating very early antiretroviral therapy and, as a result, exhibit delayed rebound after treatment interruption or perhaps virologic control. The cohort comprised 7 male and 1 female participants who at Fiebig stage 1 initiated antiretroviral therapy and were on effective antiretroviral therapy for a median of 2.8 years. Unfortunately, viral rebound after treatment interruption was similar for individuals in Fiebig stage 1 initiating antiretroviral therapy and for those initiating antiretroviral therapy during chronic infection. Thus, despite early antiretroviral therapy limiting viral reservoir size, it is unable to promote viral remission or control of the viral reservoirs that drive viral recrudescence after treatment interruption. One possibility is that time to rebound is not an accurate gauge of viral reservoir size and that rebound timing is reflected by the magnitude of immune responses levied against the viral reservoir. In such a scenario, the intermittent release of infectious virus from the viral reservoirs would result in rebound intervals that poorly correlate with the size of the reservoir.

Mitchell and colleagues (Abstract 125) examined myeloid and dendritic cell subsets in individuals who initiated antiretroviral therapy in Fiebig stage III or IV (Western blot negative) and underwent treatment interruption. Plasma cytoid (p) dendritic cells (DCs) and inflammatory monocytes sense viral RNA and serve as an early response to acute infection. The authors reported that there was a significant increase in the percentages of pDCs during treatment interruption that preceded appearance of plasma viremia by 1 week. There was also an increase in the frequency of nonclassical monocytes during treatment interruption and before viral recrudescence. No changes were observed in the myeloid DC population. These results are important in that they indicate that viruses are being sensed before the appearance of viremia and, as such, provide a biomarker of posttreatment interruption rebound. It remains to be determined whether the magnitude of the changes in pDC or nonclassical monocytes correlate with viral reservoir size or the interval to viral rebound. The availability of cellular biomarkers will be invaluable in studies aimed at deciphering determinants of posttreatment interruption rebound kinetics.

Kearney and colleagues (Abstract 120) addressed the controversial topic of whether ongoing viral replication might contribute to maintenance of the viral reservoirs. Ongoing viral replication, as defined by numerous cycles of viral replication, would be expected to lead to evolution in viral sequences. The authors examined rates of sequence evolution over a period of the changes in pDC or nonclassical monocytes correlate with viral reservoir size or the interval to viral rebound. The availability of cellular biomarkers will be invaluable in studies aimed at deciphering determinants of posttreatment interruption rebound kinetics.

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of 7 years for 10 children on effective antiretroviral therapy. Viral diversity for 8 of the children whose virus was fully suppressed did not change between samples obtained early and those obtained late in the treatment period. In contrast, there was sequence evolution in 2 children who had partial virus suppression. The authors concluded that there is no evidence of ongoing viral replication in individuals on suppressive antiretroviral therapy, and that there is no role for ongoing virus replication in the maintenance of the reservoir. Unfortunately, the study as conducted cannot exclude contribution of new rounds of infection to reservoir maintenance. Two studies using raltegravir intensification demonstrated de novo infection in the face of suppressive antiretroviral therapy. One way to reconcile the conflicting reports is that de novo infection under effective antiretroviral therapy is single round rather than numerous rounds. In such a scenario of single-round replication, reservoir cells maintain HIV-1 production, and those viruses are able to initiate single-round infection of new cells. However, those newly infected cells do not efficiently drive a new round of infection. Under these conditions, de novo infection would not lead to sequence evolution. The debate on whether reservoir cells can be established by new rounds of infection is not settled.

Murry (Abstract 118) presented an update on studies with the investigational TLR7 agonist GS-9620. At previous CROIs, the group demonstrated that GS-9620 induced transient blips of viremia in SIV-infected macaques and that, remarkably, led to sustained remission in 2 of 9 animals following antiretroviral therapy interruption and no viral rebound even after CD8+ T-cell depletion. The investigational TLR7 agonist also potentiated the activity of an Ad26/MVA vaccine regimen with delayed rebound posttreatment interruption and viral control in 3 of 9 animals. The group further investigated potential mechanisms through which GS-9620 exerted biological activity. GS-9620 was found to induce virus production from patient peripheral blood mononuclear cells (PBMCs). In addition, GS-9620 increased HIV-specific CD8+ T cell activation and proliferation and SIV-specific cytolytic activity. GS-9620 was also found to enhance antibody-mediated targeting of HIV-1-infected cells. These effects were found to require type 1 interferons. These results indicate that GS-9620 enhances immunity to HIV-1 through production of type 1 interferons from pDCs. The resulting responses include an increase in HIV-1 production followed by subsequent increases in cell-mediated immunity to those cells. GS-9620 holds promise in cure strategies aimed at combating viral reservoir persistence.

Basic Research

Despite substantial progress in research on the viral etiology of AIDS, aspects of the virus replication cycle remain relatively obscure. Arguably, the processes that regulate how HIV-1 translocates through the cell to integrate within cellular DNA is one of the most intriguing, yet poorly understood, steps of the viral replication cycle. Once the virus binds to, and fuses with, the target cell, it must liberate its core (which contains the viral genome and reverse transcriptase and integrase enzymes that catalyze the complementary [c] DNA synthesis and integration steps) into the cell cytoplasm. The core itself must then disassemble to liberate the viral genome and enzymes inside the cytoplasm so that the process of reverse transcription can proceed. Once synthesized, the viral cDNA must then somehow find its way to the nucleus of the cell so that it can contact and integrate into cellular DNA. The uncoating of the viral capsid is a mysterious event that must be coordinated with the timing of reverse transcription. A better understanding of the individual steps involved could reveal new targets for intervention.

Mamede and colleagues (Abstract 15) presented findings using live-cell fluorescent imaging to visualize the events that occur when the capsid core disassembles shortly after fusion between viral and cell membranes. In this approach, the HIV-1 Gag protein is fluorescently labeled and incorporated into virion particles as a polypeptide. During virion assembly and maturation, the labeled Gag protein is liberated and some labeled Gag molecules end up inside the viral core and some on the outside of the virus core yet still within the virus particle. This then allows the step of fusion of the viral membrane with the cell membrane (which releases the labeled Gag outside the core) and the breakdown of the capsid core (which releases the labeled gag protein inside the core) to be visualized separately. The authors then challenged cells with a low multiplicity of labeled virions, essentially 1 virion per cell. This is important because at higher multiplicities of infection, many virions enter a nonproductive pathway of infection that complicates interpretation of the data. The authors observed that most labeled gag was released into the cytoplasm within 30 minutes of infection. This suggests that capsid disassembly is rapid and occurs in the cytoplasm as opposed to results from others indicating that capsid disassembly is delayed and occurs closer to the nuclear envelope.

Lentiviruses in general have the remarkable ability to infect nondividing cells and the use of lentivirus-based vectors allows transduction of nondividing targets such as neurons, microglia, and muscle cells. This ability is all the more enigmatic given the constraints placed on the virus to cross the nuclear membrane. During initial infection, the fusogenic nature of the viral envelope permits fusion of viral and cell membranes that are required to allow entry of the viral core into the cytoplasm. Similar events must occur at the nuclear envelope. In this case, a subviral particle known as the reverse transcription complex or preintegration complex,
which comprises nascent viral cDNA and viral proteins, such as integrase, must traverse the nuclear envelope. As the complex approximates the size of a ribosome, it is unlikely that it simply diffuses across the nuclear envelope. There are also no virion proteins that would allow it to fuse with the nuclear envelope. Therefore, facilitated transport is required but the process used by lentiviruses to traverse the nuclear envelope remains a mystery.

Burdiick and colleagues (Abstract 17) presented data on live cell imaging of the events that occur during translocation of the virus across the nuclear envelope. In this case, the authors labeled viral preintegration complexes through a fluorescently tagged APOBEC3F protein that is incorporated in viral cores during virus replication, or with a fluorescently tagged integrase that must remain in association with preintegration complexes to catalyze the integration of viral DNA. The majority of contacts of preintegration complexes with the nuclear envelope were short lived (in the order of a few seconds) and only a minor population of complexes maintained longer contacts (20 minutes or more). The ability of the preintegration complex to form a stable association with the nuclear envelope was compromised by capsid mutations that destabilize the viral core or by knockdown of the nuclear envelope protein Nup358. More detailed analysis of individual preintegration complexes indicated long intervals of association with the nuclear envelope that extended to approximately 1.5 hours. Once the nuclear envelope was crossed, complexes rapidly moved away from the point of nuclear entry. Given the rather rapid intervals for nuclear envelope contact and movement away from it, the long contact time of preintegration complexes with the nuclear envelope is intriguing and perhaps reflects orchestrated rearrangement of preintegration complex components that are required to allow the complex to physically pass through the nuclear envelope.

In the same session, Xue and colleagues (Abstract 18) examined viral and cellular factors involved in passage of the viral preintegration complex across the nuclear envelope. A number of studies have highlighted the role of the capsid in translocation of the viral reverse transcription complex through the cytoplasm. The capsid has interfaces for CPSF6 and cyclophilin A that have important roles in reverse transcription, interaction of the nuclear pore complex, and association with chromatin. How the capsid might be involved in docking of the complex with the nuclear envelope is not clear. The authors conducted a small interfering RNA (siRNA) screen of all known nucleoporins and identified novel cofactors (Nup35 and POM121) as being required for HIV-1 infection. Intriguingly, Nup35 and POM121 are FG-nucleoporins that maintain the nuclear diffusion barrier and serve as docking sites for nuclear transport receptors. The requirement for FG nucleoporins in HIV-1 infection was dependent on the interaction of the capsid with cyclophilin A, and disruption of this interaction reversed the impairment of infectivity created by Nup35 knockdown. The authors proposed that HIV-1 uses cyclophilin A to restrict access to a domain in the capsid until the preintegration complex docks at the nuclear pore complex. This suggests that the HIV-1 core acts as a nuclear transport receptor and achieves nuclear entry through successive FG interactions. This design of small molecules that inhibit capsid binding to CPSF6 could represent a novel class of antivirals that limit nuclear import of viral DNA.

Treatment of permissive cells with interferon induces the expression of genes that potentiate antagonize HIV-1 infection. Although some of these interferon-induced restrictions have been identified, novel interferon-induced antiviral factors were discussed by Ohainle and colleagues (Abstract 19). The authors used clustered regularly interspaced short palindromic repeats (CRISPR) technology to knockout genes in THP-1 cells that normally become nonpermissive to HIV-1 infection upon treatment with interferon. The screen identified known restriction factors including MxB and interferon-stimulating gene (ISG)15 as well as previously unknown restrictions such as the nuclearolar Nedd4-binding protein 1 that is incorporated in promonocytic leukemia (PML) bodies. The next step will be to identify how these antiviral factors antagonize viral replication.

**Zika Virus Research**

For the first time, CROI featured presentations on Zika virus (ZIKV). Of particular interest is the nature of ZIKV persistence in body fluids. Given the tragic consequences of pregnancy during active ZIKV infection and the fact that ZIKV can be sexually transmitted, a full understanding of the duration of ZIKV persistence is necessary to guide reproductive health. The Centers for Disease Control and Prevention (CDC) recommends that women with confirmed ZIKV infection or symptoms of infection should wait at least 8 weeks before trying to get pregnant, and men should wait at least 6 months after the onset of symptoms before engaging in unprotected sex. The true interval of ZIKV RNA persistence is, however, not known. In order to minimize the occurrence of ZIKV infection during pregnancy, it is essential to devise guidelines based on the actual duration of ZIKV persistence as well as assays best designed to reveal persistent ZIKV.

Most information regarding the persistence of viral RNA has been derived from case studies and, as a result, the window for detection in various body fluids is uncertain. Studies from the outbreak in French Polynesia indicated that viremia is of low intensity and is short lived, in the order of several days after onset of symptoms. However, viral RNA could...
be detected up to 60 and 81 days in whole blood, perhaps because of adherence of ZIKV virions to erythrocytes. The time frame over which viral RNA can be detected in saliva did not appear to be much different to that in serum. However, in 2 case reports of individuals infected with ZIKV while traveling to Haiti, ZIKV RNA was detectable in saliva by RT-PCR 47 and at 91 days after resolution of symptoms. Because of the potential for male to female transmission, several reports have examined the duration of ZIKV persistence in semen and reported detectable ZIKV RNA between 60 and 188 days following resolution of symptoms. The most comprehensive analysis on duration of ZIKV RNA in different compartments was conducted in cynomolgus and rhesus macaques infected subcutaneously with ZIKV (Abstract 1055LB). Viremia was resolved by day 10, but viral RNA remained detectable in saliva and semen until the end of the study, 3 weeks after resolution of viremia. Unfortunately, the limited duration of the study did not allow assessment of the full duration of viral RNA in saliva or semen.

Paz-Bailey and colleagues (Abstract 1055LB) presented a detailed evaluation of the persistence of ZIKV in body fluids. A total of 150 study participants with acute infection were enrolled on the basis of ZIKV RNA in urine or blood. Serum, saliva, urine, and semen or vaginal secretions were obtained weekly over the first month, then at 2, 4, and 6 months. ZIKV RNA in body fluids was assessed by RT-PCR. The 50th and 95th percentiles, respectively, for time to loss of ZIKV RNA detectability was 14 and 54 days for serum, 8 and 39 days for urine, and 34 and 81 days for semen. Few subjects had detectable ZIKV RNA in saliva or vaginal secretions. These data suggest revision of guidelines for ZIKV-exposed women planning pregnancy. Unfortunately, whole blood was not monitored in this study and case reports suggest extended persistence of ZIKV RNA for 81 days in whole blood.7,8 Therefore, additional studies are required to define the full extent of ZIKV persistence to more effectively guide reproductive decisions for couples in whom there has been infection with ZIKV.


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Additional References Cited in Text

Invited Review

CROI 2017: HIV Epidemic Trends and Advances in Prevention

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At the 2017 Conference on Retroviruses and Opportunistic Infections (CROI), trends in the HIV epidemic were highlighted, with decreasing HIV incidence reported across several countries, although key groups remain undiagnosed and undertreated. In the United States, men who have sex with men (MSM) continue to comprise the largest number of new and undiagnosed HIV infections, with rising incidence in MSM 25 to 34 years old and Latino MSM. Phylogenetics are being used to identify rapidly growing HIV transmission clusters, which can inform prevention efforts. HIV testing is a crucial first step for accessing HIV prevention and treatment, and several innovative strategies to increase HIV testing show promise. Sexually transmitted infections (STIs) have been on the rise but predate widespread use of HIV pre-exposure prophylaxis (PrEP); enhanced STI screening and treatment coupled with PrEP could substantially reduce STI incidence in the United States. Several studies indicate increasing PrEP awareness and use, although disparities exist in vulnerable populations. PrEP persistence remains a challenge, and practitioner adherence to prescribing guidelines is suboptimal. Novel PrEP delivery models are being developed to increase PrEP knowledge, access, and support.

Keywords: Phylogenetics, epidemiology, HIV, CROI, 2017, incidence, prevalence, trends, PrEP, STIs, syphilis, prevention, viral suppression, testing, sexual networks, MSM, PWID, drug use

Trends in the Epidemic

Singh and colleagues at the Centers for Disease Control and Prevention (CDC) estimated trends in HIV incidence, prevalence, and undiagnosed infections in the United States, using data from the National HIV Surveillance System (NHSS) (Abstract 30). Between 2008 and 2014, HIV incidence overall decreased by 3.6% per year, with approximately 37,600 new infections occurring in 2014. By transmission category, HIV incidence attributed to heterosexual contact and injection drug use declined during this period (7.3% and 13.8% per year, respectively), but remained stable among men who have sex with men (MSM) (0.7% per year). In 2014, MSM had the highest HIV prevalence (615,400) and the highest percentage of undiagnosed HIV infections (17.3%). By race or ethnicity, HIV incidence was relatively stable among black MSM (0.7% per year) and declined among white MSM (3.1% per year), but increased among Latino MSM (2.4% per year). The percentage of undiagnosed infections decreased for all racial or ethnic groups from 2008 to 2014, but remained highest among black and Latino MSM (20%-21%) than with white MSM (13%) in 2014. By age, HIV incidence decreased among MSM aged 15 years to 24 years (3.2% per year), but increased among MSM aged 25 years to 34 years (4.8% per year), and was highest among those aged 25 years to 34 years in 2014. Although the percentage of undiagnosed infections decreased among MSM aged 15 years to 24 years (4.5% per year) and 25 years to 34 years (1.2% per year), MSM aged 13 to 24 years continued to have the highest proportion of undiagnosed infections in 2014 (52%). The researchers called for tailored testing, prevention, and treatment approaches in these groups to address disparities.

Johnson and colleagues at the CDC presented state-level estimates of HIV incidence, prevalence, and undiagnosed infections using the NHSS data (Abstract 899). During 2008 to 2014, overall HIV incidence declines were driven by a decrease in HIV infections in 8 states and the District of Columbia. Five states (California, Georgia, Florida, New York, and Texas) accounted for 52% of new HIV infections. HIV prevalence increased by 2.4% per year during this period, driven by increases in 23 jurisdictions. Undiagnosed infections decreased by 3.4% per year, with decreases observed in 7 states. In 2014, Southern states accounted for 50% of annual HIV infections, 45% of persons living with HIV infection, and 50% of undiagnosed infections. These findings highlight the need for tailored prevention programs in this region and in states with high numbers of undiagnosed infections.
Grabowski and colleagues reported data on the impact of combination HIV prevention on trends in HIV incidence in the population-based Rakai Community Cohort Study in Uganda (Abstract 34LB). Antiretroviral therapy was introduced in 2004, and coverage increased from 12% in 2006 to 69% in 2016. Expanding antiretroviral coverage was associated with a decrease in HIV viral load suppression from 42% in 2009 to 75% by 2016 among all HIV-seropositive persons. Male circumcision scale-up efforts began in 2007, and coverage increased from 15% in 1999 to 59% in 2016. Between 1999 and 2016, the only substantial changes in sexual behaviors occurred in adolescents aged 15 years to 19 years, with the proportion reporting never having sex increasing among men and women. Compared with the preintervention period prior to scale-up of combination prevention efforts (1999-2004), HIV incidence decreased by 42% from 1.16 to 0.66 per 100 person-years of observation in 2016 (adjusted incidence rate ratio [aIRR], 0.58). Declines in HIV incidence were greater in men than women (54% vs 32%, respectively), likely due to the direct beneficial effects of male circumcision. Although these results indicate that combination HIV prevention can have a substantial population-level impact, the authors pointed out that HIV incidence remains above elimination levels and highlighted the need for higher coverage and additional prevention interventions, such as preexposure prophylaxis (PrEP).

Patel and colleagues presented data on the feasibility of using community-based testing to obtain sentinel population estimates of HIV incidence and viral suppression in the high HIV prevalence region of Namibia (Abstract 35). Leveraging routine HIV testing and linkage to care activities of an existing community-based organization (Total Control of the Epidemic), 2218 adults were enrolled into a sentinel surveillance study, 37% of whom were aged 15 years to 24 years. HIV prevalence in the cohort was 21%; 64% of HIV-seropositive persons were diagnosed, with the proportion diagnosed higher in women than men (70% vs 41%, respectively). HIV incidence over 1-year follow-up was 1.32 per 100 person-years, with incidence highest among young women in rural settings (3.52 per 100 person-years). Viral load suppression at follow-up was 75% among individuals who tested HIV seropositive at baseline. There were no HIV seroconversions among the 81 circumcised men or among the 34 participants who had a partner on antiretroviral therapy. The authors highlighted the need to focus prevention interventions on adolescent girls and young women as well as finding and diagnosing men.

**Risk Factors for HIV Infection**

Kerani and colleagues described the epidemiology of HIV among foreign-born people living in the United States, using data from the NHSS (Abstract 851). Among 210,888 people diagnosed with HIV infection between 2010 and 2014, 17% were estimated to be foreign born. Compared with US-born people diagnosed with HIV infection, those who were foreign born were more likely to be female (27% vs 20%), to have acquired HIV through heterosexual transmission (men, 18% vs 10%; women, 91% vs 83%), and to have an AIDS classification within 3 months of HIV diagnosis (55% vs 26%). Migrants from Africa and the Caribbean were disproportionately affected by HIV infection, accounting for 39% of foreign-born HIV cases, but only 13% of the foreign-born population in the United States. Geographic distribution of foreign-born people with HIV infection varied by region of birth, with approximately two-thirds of migrants from South America and the Caribbean living in 1 of 5 metropolitan areas with the largest number of cases.

Ivy and colleagues evaluated whether changes in risk behaviors and access to care among men who have sex with men and women (MSMW) could help explain a reduction in new HIV diagnoses among black women in the United States (46% decline between 2008 and 2014) (Abstract 852). Based on cross-sectional data from the National HIV Behavioral Surveillance System (NHBSS) collected in 2008, 2011, and 2014, several high-risk sexual behaviors increased during this period. Among 1173 black MSMW who reported being HIV seronegative, vaginal sex without condoms (58%, 57%, and 67%, respectively; \( P = .02 \)) or anal sex without condoms (17%, 24%, and 27%, respectively; \( P = .02 \)) with a woman increased statistically significantly over time, as did the percentage who reported anal sex without condoms with a man in the past 12 months (45%, 39%, and 51%, respectively; \( P = .04 \)). HIV testing, HIV serostatus awareness, early linkage to care, and receiving antiretroviral therapy increased substantially between 2008 and 2014. Increases in awareness of serostatus and being on antiretroviral therapy may have helped drive down HIV infections among black women.

Holz and colleagues assessed trends in HIV incidence and associated risk factors among MSM and transgender women in the Bangkok MSM Cohort Study (Abstract 854). Among 1744 participants followed up in this cohort between 2006 and 2015, 271 seroconversions were detected, for an overall HIV incidence density of 5.6 per 100 person-years. HIV incidence rose over time to a high of 8.2 per 100 person-years in 2008, and subsequently declined. Multivariable risk factors for incident HIV infection included being 21 years of age and younger (adjusted relative risk [aRR] 2.18; 95% confidence interval [CI], 1.49-3.19), use of drugs to enhance sex (aRR 2.59; 95% CI, 1.83-3.65), having group sex (aRR 1.60; 95% CI, 1.20-2.14), inconsistent condom use (aRR 1.73; 95% CI, 1.35-2.21), and history of syphilis infection (aRR 1.86; 95% CI, 1.12-3.06). From the same cohort, Wimonsate and colleagues reported on changes in risk behaviors among MSM after HIV seroconversion (Abstract 855). Among 183 participants followed up...
before and after seroconversion, there was a 64% reduction in group sex, an 82% reduction in anal sex without a condom with a steady male partner, and a 79% reduction in anal sex without a condom with a casual partner. These decreases in high-risk sexual behaviors were sustained for at least 12 months after seroconversion.

Mobility can disrupt individuals from HIV prevention and care systems and intensify transmission. Oalwore and colleagues presented data on the relationship between migration and HIV incidence in the Rakai Community Cohort Study (Abstract 1015). Among 16,165 seronegative participants included in this study, 28% were migrants, of whom 68% were women. There were 849 HIV incidence events between 1999 and 2015, 28% of which occurred in migrants. HIV incidence was higher in the first 2 years following migration, and has not declined in recent migrants despite scale-up of combination HIV prevention: aIRR for HIV seroconversion was 1.97 for women and 2.42 for men. These findings highlight the need for timely prevention interventions prioritized for migrants in sub-Saharan Africa. Camlin and colleagues evaluated the relationship between mobility and HIV prevalence in Uganda and Kenya in the SEARCH (Sustainable East Africa Research in Community Health) study (Abstract 860). Mobility in the past month or past year was associated with higher HIV prevalence, with stronger effects for women.

Stigma is an important structural factor that may contribute to transmission and acquisition of HIV. Rodriguez-Hart evaluated the association between sexual stigma and the acquisition of HIV or other sexually transmitted infections (STIs) in a prospective cohort study among 1480 MSM in Nigeria (Abstract 918). Participants were classified into low- (43%), medium- (45%), and high-stigma (12%) subgroups, using a latent class analysis of 9 stigma indicators. As stigma increased in severity, STI incidence increased in a statistically significant dose-response relationship (8.1% in the low-stigma group, 12.2% in the medium-stigma group, and 16.3% in the high-stigma group; \( P = .003 \)). Incident HIV infections were less common and did not increase statistically significantly with increasing stigma severity (2.8%, 3.2%, and 5.8%; \( P = .798 \)). The authors demonstrated that the association between stigma and HIV and STI incidence was partially mediated by suicidal ideation and sex without condoms.

Several investigators presented data evaluating the use of risk scores to identify appropriate candidates for PrEP. Washington and colleagues developed an empiric risk score to guide PrEP uptake among MSM in coastal Kenya (Abstract 856). In a cohort of 757 HIV-seronegative MSM followed up for a median of 14 months, HIV incidence was 6.9 per 100 person-years. Independent predictors (each worth 1 point in the risk score) included having sex exclusively with men, receptive anal sex, any unprotected sex, and group sex, and being 18 years to 24 years of age. A risk score of 1 or greater corresponded to an incidence rate of 3.6% or higher per year, and would identify 4 of every 5 MSM in the cohort for PrEP initiation. Burgess and colleagues sought to validate a previously developed risk score in women to predict HIV acquisition in young women in South Africa (Abstract 857). They assessed a 7-item risk score derived from women who participated in the VOICE (Vaginal and Oral Interventions to Control the Epidemic) trial and applied this risk score to young South African women aged 18 years to 30 years enrolled in the FACTS (Follow-on African Consortium for Tenofovir Studies) 001 study. Scores of 5 or higher identified 84% of incident infections in 77% of the cohort. The area under the curve (AUC) was 0.56, indicating poor discriminative accuracy. The authors posited that the poor performance may be due to the younger age of the cohort, in which risk was uniformly high, and other factors, such as intimate partner violence, may need to be incorporated to improve score performance. Ayieko and colleagues developed an HIV risk score based on the SEARCH HIV test-and-treat trial in Kenya and compared it with self-assessed risk (Abstract 858). An 8-item risk score was developed using machine learning and included age, sex, marital status, polygamy, education, circumcision, occupation, and alcohol use. Among 3973 HIV-uninfected adults, only 17% perceived themselves to be at risk for HIV acquisition. Among the 810 individuals identified to be high risk by the risk score, only 23% perceived themselves to be at risk. These data suggest that strategies to improve accurate risk perception may be needed to optimize the uptake of empirically targeted PrEP.

**Recent migration or mobility is associated with higher HIV incidence and prevalence in East Africa.**

**Networks of HIV Risk**

Two studies at this year’s conference explored the role of risk networks in explaining racial disparities in HIV prevalence. Momplaisir and colleagues evaluated individual and network factors associated with HIV prevalence among people who inject drugs (PWID) in the HPTN (HIV Prevention Trials Network) 057 study (Abstract 842). In an analysis of 252 index participants and 464 network members, racial consistency (all members of a network sharing the same race) was high among blacks (79%) and whites (70%) and lower among Hispanics (31%). HIV prevalence was 27% within all-black networks, 14% in all-white networks, and 23% in mixed networks. Sexual risk was similar across networks, but needle-sharing behaviors were significantly lower in all-black networks (23%) than in all-white (48%) and racially mixed networks (46%) (\( P < .05 \)). In a multivariable model, being in an all-black network (adjusted odds ratio [aOR], 3.6) or racially mixed network (aOR, 2.0) were associated with being in an HIV-seropositive network; other associated factors included homelessness (aOR, 2.0), recent incarceration (aOR, 0.4), and cocaine injection (aOR, 1.7), although individual risk behaviors were not associated with being in an HIV-seropositive network. The investigators call for interventions at the network level, including offering treatment to HIV-seropositive individuals and PrEP to at-risk individuals.
Janulis and colleagues explored the role of concurrency (i.e., sexual partnerships overlapping in time) in explaining racial disparities among young black MSM (Abstract 843). In an analysis of data from 659 young MSM participating in a longitudinal cohort study in Chicago, concurrency was uncommon, and there was little difference in concurrency rates by race or ethnicity. However, higher levels of racial homophily were observed among young black MSM than among young white MSM ($P = .001$). Additionally, in simulated models, black participants were more likely to be at greater levels of HIV-specific network risk (they were more likely to be connected with an HIV-seropositive partner and closer to these individuals within the network), whereas white participants were more likely to be in larger networks, and more central in these components. These results suggest that concurrency is unlikely to explain racial disparities in HIV infection, whereas racial homophily and higher HIV prevalence in sexual networks of young black MSM may explain some of these disparities.

Several investigators described the role of phylogenetics in identifying rapidly growing HIV transmission clusters in HIV outbreaks. Mehta and colleagues presented data on real-time identification of a new transmission cluster in Tijuana, Mexico (Abstract 844). Among 2759 participants in 8 research studies in Tijuana between 2004 and 2016, 288 sequences from seroconverters were obtained and analyzed to identify phylogenetic clusters; 42% of sequences were linked to one or more sequences, forming 57 transmission clusters. In one of the study cohorts of people who inject drugs, 12 seroconversions occurred between January 2015 and July 2016, including 8 between April 2016 and July 2016. These seroconversions coincided with the implementation of a public safety policy to “clean” the homeless population from the region, leading to the displacement of these individuals. Qualitative interviews with these seroconverters revealed that all had encounters with police and many needed to change their location of residence and injection drug use. These findings highlight that changes in public safety policy can disrupt HIV prevention efforts and impact HIV transmission dynamics.

Monterosso and colleagues described efforts to identify and investigate a rapidly growing HIV transmission cluster in Texas (Abstract 845LB). Using data collected through the NHSS, the CDC identified a molecular cluster in Texas that grew rapidly between July 2015 and June 2016. From 27 confirmed cluster cases and other cluster cases, 112 additional ones were identified through review of interview records from partner services. Among 76 confirmed cluster cases and other cluster cases with records available, all were born male; 79% were aged 17 years to 29 years; 87% were Hispanic; and 90% reported having sex with men. The median lifetime number of sex partners was 45 (range, 2-300); 72% indicated they had anonymous sex partners; only 7% reported always using condoms; and 18% had an STI within 12 months before HIV diagnosis. Although many cases had encounters with medical care, none were on PrEP, 50% had evidence of treatment interruptions or poor adherence, and 24% were not currently virally suppressed. Rapid growth of this cluster was likely a result of high-risk behaviors, limited PrEP access, and delayed viral suppression in some cases; these findings highlight the need to prioritize linkage to care and PrEP referral for individuals associated with this cluster.

McVea and colleagues developed a framework for predicting HIV phylogenetic clusters at high risk for growth (Abstract 848). Using sequences from 9091 individuals in the British Columbia, Canada, drug treatment program, 47 distinct clusters were classified as large (≥ 20 members) and small (> 20 members) clusters and rapid (≥ 5 new members in the past year) versus slow (> 5 new members in the past year) growth. Growth of 1.8 members or more over 3 months characterized clusters that would become large, and a proportion of more than 50% MSM in the cluster categorized clusters that were growing rapidly.

Zheng and colleagues presented data on a cross-sectional analysis using social network information to predict HIV serostatus in 3 rural communities in Kenya in the SEARCH “Test and Treat” study (Abstract 36). During the census, 15,028 adults named social contacts in 5 social domains (health, emotional support, money, free time, and food), which were matched to enumerated residents to create community-wide social networks. Overall, testing coverage was 85%, and HIV prevalence was 16%. After adjusting for individual risk factors, men with an HIV-seropositive female contact in any domain were more likely to be HIV seropositive (aRR, 1.5), and women with an HIV-seropositive male contact in any domain were more likely to be HIV seropositive (aRR, 1.4), with higher risk if the HIV-seropositive contact was 10 years older or more (aRR, 1.6). Women with an HIV-seropositive female contact in the health domain were also more likely to be HIV seropositive (aRR, 1.6). Among young women aged 15 years to 24 years, higher risk was associated with having an older HIV-seropositive contact in the food domain (aRR, 4.1), free time (aRR, 7.9), health (aRR, 3.5), or any domain (aRR, 3.4). The authors suggest that social network information may be useful in informing targeted testing and prevention efforts and enhancing the HIV care cascade through peer-support networks.

### Youth

Hader presented an overview of the HIV epidemic in youth (Abstract 58). She pointed out that several countries in sub-Saharan Africa are projected to have substantial population growth over the next 35 years, and described the “youth bulge” in which a larger number of African youth will age into young adulthood, resulting from reductions in childhood mortality and slower accompanying declines in fertility. In Africa, the population of youth aged 15 years to 24 years is expected to grow from an estimated 200 million in 2016 to more than 300 million in 2030. Even with similar or declining
HIV infection rates, this growing population of sexually active young people will result in a greater number of new HIV infections, or epidemic growth. To reverse these trends, an understanding of HIV transmission dynamics is crucial. Hader reviewed data from South Africa showing cycles of HIV transmission in which women aged 25 years and under become infected from men 25 years to 40 years old, who are largely unaware of their HIV serostatus. As these women age, they form relationships with similarly aged men and then may transmit HIV infection to these partners, continuing the cycle. She also presented data from a population-based survey in Zimbabwe showing that young people were much less likely to know they were HIV-infected, and women more likely to be aware of their HIV serostatus than men. Although young people who knew their HIV serostatus had high rates of being on treatment and achieving viral suppression, overall rates of viral suppression among youth under 30 years of age were low (37%), much lower than levels needed to interrupt transmission in social networks.

Hader also described trends in urbanization in Africa, with the urban population projected to increase from 40% in 2016 to 58% in 2050. For young people who migrate from rural to urban areas, this may result in youth being disconnected from family and community support networks. Hader also emphasized the importance of providing quality education and employment opportunities for youth, which have been linked to decreased risk behaviors and better health. Sexual and physical violence are common in both girls and boys under the age of 18 years, and boys who experience violence are more likely to grow up and be a perpetrator of violence, highlighting the importance of interventions to address violence in both girls and boys. She pointed to data among adolescent girls in South Africa showing that structural factors such as hunger, community violence, and informal settlements lead to abuse, victimization, and school dropout, which all contribute to various HIV risk behaviors.

Although the growing youth population has often been characterized as a pending disaster, others have viewed the “youth bulge” as an asset or dividend, bringing a stronger workforce, economic growth, and decreased dependency as more young adults are able to care for children and the elderly. Hader expressed optimism that a number of HIV prevention tools are now available or under investigation for youth; however, she highlighted that these interventions must fit into the lives of these youth. She emphasized that young people are not a single, unified population but represent diverse, overlapping identities and are constantly in transition. Youth expect instant communication, transparency, and collaboration, and are facile at web-based self-learning; these expectations can be harnessed in developing prevention interventions for youth; however, she highlighted that these interventions must fit into the lives of these youth. She identified the need for context-specific data disaggregated by age and gender to understand the needs of youth and to guide targeting efforts to maximize reach and impact of interventions. She also pointed to the need for youth leaders to help design and deliver high quality interventions; for community and faith-based leadership to promote health and wellness social norms and eliminate violence and stigma; and for political leaders to address policy and structural barriers to service delivery, education, and employment. She ended by highlighting the PEPFAR DREAMS (President’s Emergency Plan for AIDS Relief Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe) initiative, a comprehensive program addressing a number of structural barriers faced by African youth that aims to decrease HIV infections by 40% in adolescent girls and young women by 2017.

Substance Use

Hoots and colleagues presented data on changes in prescription opioid, methamphetamine, and cocaine use among MSM in 20 US cities, based on data from 2008, 2011, and 2014 cycles of the NHBS in MSM (Abstract 871). Overall use of each of the 5 drugs was relatively stable over that period, with 8% of MSM each reporting opioid or methamphetamine use in 2014, and 19% reporting cocaine use. Although rates of opioid use were lowest in black MSM than in other racial and ethnic groups, rates increased statistically significantly only in this subgroup over time, with 4.2% of black MSM reporting opioid use in 2008 and 5.9% reporting this in 2014. Opioid use also increased statistically significantly in persons with less than a high school education (from 7.1% to 10.1%) and among persons with incomes under $20,000 per year (from 5.7% to 9.3%). The authors recommended early assessment and treatment of drug dependence for those using opioids to prevent transition to injection drug use.

Two studies reported on city-specific substance use patterns in NHBS surveys. Kuo and colleagues presented data from the same NHBS surveys in MSM that were completed in Washington, DC, from 2008 to 2014 to evaluate changes in patterns of substance use over that time (Abstract 872). They found an increase in crystal methamphetamine use among black MSM (from 4.4% to 9.9%) simultaneous with a decrease in crystal methamphetamine use in white MSM (from 9.5% to 4.7%). For white and black MSM, having 4 or more sex partners (aOR, 3.2 and 2.7, respectively) and being HIV seropositive (aOR, 10.6 and 4.2, respectively) were associated with crystal methamphetamine use. For white MSM, being 30 years or older (aOR, 2.5) and having an annual income of less than $20,000 (aOR, 8.5) were also associated with crystal methamphetamine use in the prior year. These authors urged the development of effective prevention interventions for crystal methamphetamine users.

Glick and colleagues presented data from the NHBS survey conducted in 2005, 2009, 2012, and 2015 in PWID in King County, Washington (Abstract 873). Of 1713 men and women participating in any of the 4 cross-sectional surveys,
Sexually Transmitted Infections

Golden provided an overview of syphilis epidemiology and implications for public health (Abstract 56). He began by showing the substantial increase in cases of primary and secondary syphilis in the United States from 1996 to 2015 (Figure), with the initial increase beginning in 2000, but with a further marked increase coincident with the Department of Health and Human Services (DHHS) guidelines for universal antiretroviral treatment in 2012. In 2015, 90% of syphilis in the United States occurred in men, with 82% of these cases occurring in MSM. Similar trends in syphilis have been seen globally. He notes that coincident with this increase have been increases in other STIs, including urethral gonorrhea, which is most often symptomatic and therefore not subject to the same biases seen in screening for asymptomatic STIs. However, as STIs have been increasing from 2007 to 2015 in King County (syphilis by 74%, urethral gonorrhea by 146%, and urethral chlamydia by 61%), rates of new HIV diagnoses have declined by 36%, likely the successful result of HIV treatment as prevention. Golden showed data from 4 US cities showing a decline of the proportion of syphilis cases occurring in HIV-seropositive MSM from approximately 60% to 40% in all 4 cities. Using data from King County, he made a compelling case that incident syphilis cases have moved from being concentrated in high-risk HIV-seropositive MSM to being seen in what he described as a lower-risk population of HIV-seronegative MSM who do not have a history of syphilis or methamphetamine use. This coincided with a decrease in condom use and serosorting among HIV-seropositive MSM and an increase in the number of sex partners in HIV-seronegative MSM. He hypothesized that syphilis has spread from the HIV-seropositive population into the HIV-seronegative population of MSM. He noted, however, that the increase in syphilis rates predates PrEP, as do increases in other STIs. He raised concern for the possibility of a bridge from MSM with syphilis into the increasing rates of congenital syphilis, as a substantial minority of MSM also report having female partners.

Golden closed with 4 public health recommendations arising from these trends in syphilis. First, he emphasized the importance of increasing syphilis screening. He gave an example of the Australian effort to order a syphilis test along with all viral load tests in their HIV-infected population, and showed that from 2007 to 2014, syphilis testing concomitant with viral load testing has increased from 27% to 73% of all tests. This has also been associated with an increase in the proportion of cases of syphilis in people who were diagnosed while asymptomatic from 21% to 85%. However, he warned that in the setting of frequent syphilis testing, clinicians should be aware that 28% of primary syphilis and 44% of secondary syphilis cases will continue to have
positive syphilis titers at 36 months. He recommended that any 2-fold increase in titer be repeated to rule out a false-positive diagnosis of incident syphilis in those previously diagnosed and treated.

His second point was that although ocular syphilis has been getting increasing attention of late, including in the lay media, ocular syphilis has been detected in 2.5% to 4.5% of all syphilis diagnoses and appears to be stable over time. He noted that 7.9% of syphilis diagnoses will be complicated with ocular, otic, or symptomatic neurosyphilis, and recommended screening for symptoms routinely at diagnosis. Screening tools can be found on the King County Department of Health website (http://www.kingcounty.gov/depts/health.aspx).

He recommended using a syphilis diagnosis as an opportunity for conducting HIV prevention, including provision of PrEP. Further details of the King County program are described later in the discussion about new PrEP implementation strategies. Golden closed by pointing to the importance of integrating condom messages into general sexual health messages, noting that the vast majority of MSM use condoms some of the time, and that using them less than all of the time should not be considered a failure.

Several studies presented at CROI 2017 documented increased rates of STIs over time. Ungsedhapand and colleagues reported on data from more than 10,000 clients who underwent HIV and syphilis testing at the Silom Community Clinic in Bangkok, Thailand (Abstract 862). HIV and syphilis coinfection increased from 1.3% of clients in 2006 to 9.5% of clients in 2015. Risk factors for coinfection included being older than 21 years (aOR, 1.8), having been born outside of Bangkok (aOR, 1.5), and being of Thai descent (aOR, 2.0). Hiransuthikul and colleagues reported on recurrent STIs among MSM and transgender women enrolled in the Thai Test and Treat Cohort (Abstract 863). Among 448 participants, they reported STI rates of 2.2 per 100 person-months, with statistically significantly higher recurrent STIs among those who were HIV seropositive at baseline (aOR, 1.8).

Novak and colleagues reported on the incidence and risk factors for incident syphilis in 6888 HIV-infected persons in the HIV Outpatient Study from 1999 to 2015 (Abstract 864). Overall, 9.3% of participants acquired 1 or more syphilis diagnoses during a median follow-up of 5.2 years. In multivariable analysis, incident syphilis was associated with being 50 years of age or younger (aOR, 1.53) and non-Hispanic black (aOR, 1.6). MSM were statistically significantly more likely (aOR, 3.1) and heterosexual women statistically significantly less likely (aOR, 0.35) than heterosexual men to acquire syphilis. Syphilis incidence increased with each 5-year period compared with 1999 (aOR, 1.5 for 2000-2004; aOR, 2.1 for 2005-2009; aOR, 4.2 for 2010-2015).

In contrast, Ganesan and colleagues reported that among 2719 men and women enrolled in the US Military HIV Natural History Study, syphilis rates have been decreasing, with the highest incidence in 2004 to 2007 (3.2/100 person-years), and the lowest rates in 2012 to 2015 (2.4/100 person-years) (Abstract 865). Although blacks in the United States have experienced the largest declines over time, in a multivariable model being black (aOR, 2.4) and reporting anal sex (aOR, 3.0) were independent risk factors for acquiring syphilis infection.

Jenness and colleagues presented a modeling study that suggests that regular STI testing and treatment offered to PrEP users could substantially reduce STI incidence at a population level (Abstract 1054). In their network-based mathematical model that takes into account transmission between different types of partners (main, casual, one-off), they found that with 40% PrEP coverage of a high-risk population, 42% of gonorrhea and 40% of chlamydia infections could be averted over the next 10 years, even with a 40% increase in risky sexual practices. Even a doubling of risk compensation would result in net STI prevention benefits relative to no PrEP, because of the 17% and 24% increases, respectively, in the detection of asymptomatic and rectal cases. They state that quarterly STI testing could result in a further 50% decrease in STI incidence over biannual screening intervals. However, these benefits would be realized only with the inclusion of routine STI screening and treatment as part of PrEP provision.

Molina presented an overview of antibiotic prophylaxis strategies for prevention of bacterial STIs (Abstract 55). He pointed out that more than 1 million bacterial STIs (such as
syphilis, gonorrhea, chlamydia, and trichomonas) are acquired each day in the world, the majority of which have no or mild symptoms. In 2015, the United States reported the second year in a row of increases in new cases of gonorrhea, chlamydia, and syphilis. Molina pointed out that antibiotic prophylaxis is not a new strategy, with the first reported study from 1943 of a single dose of sulfathiazole given to 450 US military men to prevent STIs following sex. Although this strategy was successful, with no cases of chancre and 1 single case of gonorrhea seen in the treated men, the 1 breakthrough gonorrhea infection was caused by an antibiotic-resistant strain, a theme that recurred in Molina’s reporting of this approach to preventing bacterial STIs. Of the various approaches outlined (postexposure prophylaxis, treatment of incubating STIs in sex partners, periodic presumptive treatment, mass drug administration, and daily prophylaxis), only treatment of incubating STIs is currently recommended, such as the treatment with penicillin of sexual contacts of persons diagnosed with syphilis, as recommended by the CDC.

In an oral abstract session, Molina and colleagues presented data from a randomized controlled trial (RCT) of postexposure prophylaxis of bacterial STIs in MSM enrolled in the open-label component of the IPERGAY study (Abstract 91LB). In this study, 232 MSM were randomly assigned to take 200mg doxycycline or placebo 24 to 72 hours after each sexual episode, with a maximum of 6 pills in a 1-week period. Follow-up was 91% in each arm of the study through a median follow-up period of 9 months. They noted a statistically significant decrease in incident chlamydia and syphilis infections (hazard ratio, 0.30 and 0.27, respectively), but without a statistically significant decrease in gonorrhea rates. Men took an average of 7 pills per month and 21% discontinued use because of adverse effects or for other reasons. Testing for antibiotic resistance, a major concern with postexposure prophylaxis strategies, is currently underway. Molina cautioned that antibiotic prophylaxis for STIs is still not recommended because more data are needed, and the risk of development of antibiotic resistance is of great concern.

HIV Testing

Knowledge of one’s HIV serostatus is a crucial first step to accessing HIV prevention and treatment services, and several presentations at CROI 2017 focused on innovative strategies to increase HIV testing in different settings.

HIV Self-Testing

In a themed discussion on HIV self-testing, Stekler provided an overview of this testing strategy. In the United States, an HIV home collection kit was approved in 1996, and a home self-test was approved by the US Food and Drug Administration (FDA) in 2012. Although these and other HIV tests are available globally, approximately 40% of HIV-seropositive persons worldwide remain unaware of their HIV infection in 2016. Home tests can offer more timely HIV diagnosis; however, they may be subject to test misinterpretation, have longer window periods associated with lower sensitivity in high-incidence populations, and limit the opportunity for posttest counseling, which may delay linkage to care or PrEP as indicated. Prior research has shown that home HIV testing is acceptable, with preference for and greater ease of use with oral fluid testing. Studies have also demonstrated that home testing can increase testing among high-risk MSM, and in some settings can identify new cases and improve linkage to care. However, modeling studies have also shown that replacing clinic tests with home tests may increase HIV prevalence. Stekler pointed out several gaps in our knowledge of self-testing, including the best ways to implement this strategy, how to reach persons who would not otherwise test, how to link testers to HIV care or PrEP services, how to test for STIs, and the overall impact of home HIV testing on the epidemic.

Salcuni, Edelstein, and colleagues presented results of an HIV Self-Test Giveaway program to distribute free HIV self-tests online in New York City (Abstracts 891 and 898). Men and transgender people who have sex with men were recruited through dating mobile applications and websites over a 23-day period, and eligible participants were provided a code to have an HIV self-test kit mailed at no cost. Among 2497 eligible participants, 71% redeemed the code and 48% took a follow-up survey, of whom 92% reported receiving the HIV self-test and 80% reported using it. Among survey respondents, 85% were previously aware of the home HIV test, 57% had seen the home HIV test at a pharmacy, and 23% had used at least 1 home HIV test. Higher income and recent HIV testing were associated with awareness, pharmacy exposure, and use of the HIV self-test, and recent anal sex without condoms was associated with use of the HIV self-test. Having health insurance or not was not associated with any of the outcomes along this continuum, suggesting that self-testing can provide an alternative to those without adequate access to health care. Among 884 HIV self-test users, 72% were under 35 years of age, 41% identified as black or Hispanic, and 42% had never tested or had not tested in the prior year. Although only 5 individuals (0.6%) received reactive results with no prior HIV-seropositive results, 80% of these individuals reported a confirmatory test and had an HIV care appointment. Most (71%) of the self-test users reported testing sooner than usual or for the first time, and almost all (98%) reported being likely to recommend the HIV Self-Test Giveaway to a friend.

Sanders and colleagues presented results on a peer-led HIV–self-testing program among gay and bisexual MSM (GBMSM) in coastal Kenya (Abstract 893). Six GBMSM were trained in basic counseling skills, use of the oral HIV self-test, and the importance of confirmatory testing, and each
lay counselor distributed 4 to 5 kits per week with instructions to report for confirmatory testing at the clinic regardless of HIV test result. Over a 3-month period, 337 kits were extended to GBMSM with a median age of 26; 99% of GBMSM returned for confirmatory testing, with 29 (8.7%) confirmed HIV seropositive; 24 (82.8%) of these individuals started antiretroviral therapy on the day of HIV confirmation. These results were compared with traditional HIV testing and counseling done by peers in the clinic over a 6-month period, in which 690 GBMSM were mobilized and tested, and 24 (3.5%) were newly diagnosed, of whom 20 (83%) started antiretroviral therapy after a median of 5 days. The researchers concluded that peer-led oral self-testing followed by clinic-based confirmatory testing and immediate antiretroviral therapy initiation was feasible and acceptable in coastal Kenya and resulted in a higher proportion of undiagnosed HIV infection ($P < .001$) than with clinic-based testing.

Providing HIV self-tests to women attending antenatal and postpartum clinics for distribution to their male partners is a novel strategy to increase HIV testing rates among men and couples in sub-Saharan Africa. Schaffer and colleagues evaluated the role of partner violence in women’s ability to distribute self-tests to their male partners in Kisumu, Kenya (Abstract 894). Among 176 HIV-seronegative women with a primary partner, 21% reported a history of intimate partner violence in the 12 months prior to enrollment. Although there were high rates of couples self-testing (55%) and partner self-testing (34%) in 3 months, couples (aOR, 0.13; 95% CI, 0.03-0.54) and partner (aOR, 0.10; 95% CI, 0.02-0.46) self-testing were statistically significantly less likely to occur if a woman reported a history of recent intimate partner violence. The authors concluded that the benefits of secondary distribution of HIV self-tests by women to their male partners may not be fully realized in relationships in which partner violence occurs.

Indravudh and colleagues evaluated preferences for HIV self-testing services and linkage to care using Discrete Choice Experiments as part of baseline household surveys within a cluster randomized trial of HIV self-testing in rural Malawi (Abstract 895). Respondents preferred home delivery of HIV self-test kits to distribution through health facilities or mobile clinics, particularly among those never tested. There was also a preference for lay distributors of test kits rather than healthcare workers and intimate partners. Participants were indifferent to pretest assistance, but were averse to instruction leaflets as the only form of posttest support. Importantly, never testers preferred more extensive support. Cost, even at a low price, was a strong disincentive for testing, although men and those who had never tested were less averse to price. For linkage to care, participants preferred services at home or at the home of a health care worker, with short waiting times and a separate waiting room at health facilities.

In the same session, Indravudh presented data on providing user support for HIV self-testing in Malawi (Abstract 896). In the first phase of this study, cognitive interviews were conducted in 20 literate adults asked to use the HIV self-test without any additional assistance. Although most participants were able to self-test accurately with only the instructions for use, many experienced difficulties affecting timeliness and confidence of use of the kit, including trouble using the equipment (15/20), not knowing how to interpret symbols and illustrations (8/20), not knowing how to open the package (7/20), and not understanding next steps after self-testing (15/20). This was followed by a feasibility evaluation of the HIV self-test in 2 rural villages in which participants were offered the option of self-testing (confirmed by standard testing), standard testing, or no testing; self-testers were provided a brief kit demonstration prior to use. Among 540 participants in this cross-sectional feasibility study, 86% chose to use the self-test, 4% tested through standard methods, and 11% declined to test. Self-read tests agreed with the reference standard for 12 of 13 HIV-seropositive participants (93% sensitivity) and 276 of 277 HIV-seronegative participants (99.6% specificity). Almost all participants (95%) reported the self-test was very easy to use, although the most common error was reading results before the specified time (which occurred in 5 participants).

### Additional Strategies to Increase HIV Testing

To address lower HIV testing rates among men in sub-Saharan Africa, Chamie and colleagues evaluated the comparative effectiveness of several novel incentive strategies to increase HIV testing uptake among 2530 men in rural Uganda (Abstract 33). Participants were randomized to 1 of 3 incentive types informed by behavioral economics: 1) gain-framed incentive, in which participants were told they would receive a prize for HIV testing; 2) loss-framed incentive, in which participants were told they had won a small prize at enrollment, asked to choose their prize, and told they would lose the prize if they did not come in for testing; and 3) lottery incentive, in which those who tested for HIV would be entered into a lottery to instantly win a large prize; each incentive type had a low and high amount (US $1 vs $5 per participant). Overall, 76% tested for HIV at the campaign, with a prevalence of 7.6%. HIV testing uptake did not differ across the groups overall: compared with the gain-framed control groups (74%), HIV testing uptake was 77% in the loss-framed groups ($P = .24$) and 78% in the lottery groups ($P = .08$). However, among participants in the low-cost groups, testing uptake was statistically significantly higher in the lottery group than in the gain-framed group (80% vs 72%, $P < .01$), this finding was not seen in the high-cost groups. Testing uptake did not differ by low versus high cost amounts (75% vs 77%, $P = .42$). Furthermore, rates of HIV seropositivity and the proportion of participants newly diagnosed with HIV infection did not differ between the lottery and the gain-framed groups. The researchers suggest that lottery-based incentives with low-incentive amounts may be more cost-effective than higher amounts.

Shanaube and colleagues presented data on the acceptability and uptake of a community intervention to increase HIV serostatus knowledge among adolescents in Zambia (Abstract 834). In the PopART (Population Effects of Antiretroviral
Therapy to Reduce HIV Transmission) for Youth study, adolescents were contacted in their homes by community HIV care practitioners during annual rounds of outreach and offered participation in the PopART intervention, which included home-based HIV counseling, testing, linkage to prevention such as voluntary medical male circumcision and prevention of mother-to-child transmission (PMTCM). Treatment included immediate antiretroviral therapy irrespective of CD4+ cell count as well as sexual health and tuberculosis services. Between October 2015 and September 2016, 15,456 adolescents aged 15 years to 19 years were enumerated, of which 72% agreed to participate; 1.6% refused, and 26% were not found at home. More men (33%) than women (20%) were not found at home, and younger adolescents (aged 15 years) were more difficult to contact. HIV prevalence was 1.3% and varied by sex (0.6% in men, 1.9% in women). Knowledge of HIV serostatus increased from about 27% to 88% among adolescents who consented to participate in the intervention. The authors conclude that delivering a community-level, door-to-door combination HIV prevention package is acceptable, but complementary strategies to reach more men are needed.

Besa and colleagues presented results on the impact of home-based testing among pregnant women in the same PopART study (Abstract 959). Among 55,291 women who had health data recorded in this study, 7.7% were pregnant. Of these, 7.8% self-reported they were HIV seropositive, and the remaining were offered HIV counseling and testing. The HIV prevalence among those tested by the community HIV care providers was higher for women who had not attended antenatal clinics (12.3%) than for those who had (6.3%). Knowledge of HIV serostatus among pregnant women increased from 60% before the intervention to 95% after.

Medley and colleagues reported on strategies to increase male-partner testing in antenatal care in South Africa (Abstract 958). This program promoted both facility-based and home-based testing through training of health care workers and lay counselors in couples’ HIV testing and counseling, providing education to couples on the importance of partner HIV testing, and sending invitation letters to male partners. Among 1453 women who completed the postpartum assessment, 27% tested HIV seropositive. The proportion of women who reported their male partner tested for HIV infection increased from 20% to 43% (P < .0001). Based on clinic records, 690 couples tested at one of the facilities, with 14% testing concordant positive and 9% serodiscordant, and 176 couples tested at home, with 5% concordant positive and 14% serodiscordant. In multivariable analyses, statistically significant correlates of partner testing included being married, being known to be HIV seropositive on treatment, and being in the postintervention cohort (OR 3.1). Focus group data suggested that the partner invitation letters were the most useful component of the intervention.

Haukoos and colleagues compared the effectiveness of several screening strategies in a pragmatic randomized trial of rapid HIV testing in emergency departments (Abstract 956). Across 4 urban emergency departments, 76,561 participants were randomized to 1) nontargeted, rapid opt-out HIV screening; 2) enhanced targeted HIV screening, using the Denver HIV Risk Score as a validated HIV risk prediction tool; or 3) traditional targeted HIV screening, using conventional risk behaviors as defined by the CDC. A total of 14,405 HIV tests were completed across arms, with 25 (0.2%) confirmed new HIV infections. Enhanced targeted HIV screening (P = .37) and traditional targeted HIV screening (P = .11) were not superior to nontargeted HIV screening, with all 3 strategies identifying comparable numbers of new HIV diagnoses.

De la Flor and colleagues presented data on HIV and HCV testing among jail inmates (Abstract 957). Opt-out HIV and HCV testing was offered to individuals entering the Dallas County jail between October 2015 and July 2016. Of 3155 inmates tested for HIV infection, 41 (1.3%) had a positive HIV fourth-generation Ag/Ab screening test, of which 24% were false-positive results. Among the 30 participants with confirmed HIV infection, 6 were new diagnoses, all of whom were linked to care. Among those previously known to be HIV seropositive, one-third were not engaged in HIV care before incarceration, and 75% were linked to HIV care while in jail. For HCV testing, 16% (500/3042) had a positive antibody screening test; the mean age was 49, 80% were men, and one-third had a previously documented positive HCV antibody test. Only 52% of HCV infections were born in the “baby boomer” cohort (between 1945 and 1965), with some racial differences noted in this cohort (60% black vs 35% white). These data highlight that routine opt-out HIV/HCV testing among jail inmates can identify multiple HIV and HCV infections. Although new HIV diagnoses were rare, this testing provided an opportunity to link individuals to HIV care.

Two groups of investigators evaluated HIV testing motivations and patterns in MSM. Katz and colleagues evaluated HIV testing motivations in a national online survey of US MSM (Abstract 901). Among 1419 MSM, 78% reported prior HIV testing, of whom 9% had tested positive. Younger and non-gay/bi-identified men were more likely to have never been tested (P < .001 for both). Among those who tested negative or did not know their test result, 51% tested on a regular schedule, of whom 33% tested quarterly, 38% tested every 6 months, and 22% tested annually. Regular testers had tested more recently than nonregular testers (median of 3 vs 10 months since the last test, P < .001). Among those who had tested, reasons for the last test included regular testing (51%), having a potential exposure (28%), starting a new relationship (8%), and being recommended by a practitioner (7%); also, 24% reported ever having tested in response to symptoms they believed may be acute HIV infection. Men who had ever tested were more likely to think they should test on a regular schedule (86% for testers vs 63% for never testers, P < .0001) and less likely to test after being exposed to HIV infection (22% for testers vs 49% for never testers, P < .0001). The authors conclude that although messages regarding frequent, regular testing have reached most MSM, additional strategies are needed to help MSM translate this knowledge into practice.

An and colleagues evaluated trends in HIV testing frequency among US MSM in the NHBSS (Abstract 902). From
2008 to 2014, the mean inter-test interval between 2 successive tests decreased from 8.6 to 6.5 months among those aged 18 years to 29 years, from 11.3 to 7.7 among those aged 30 years to 39 years, and from 14.0 to 10.8 among those aged 40 years or older. Within each age group, the inter-test interval decreased among black, Hispanic, and white MSM. Among MSM aged 18 years to 29 years and those 40 years and older, Hispanic MSM had higher mean inter-test intervals than black and white MSM in 2011 and 2014. Although most MSM surveyed adhered to CDC recommendations of annual testing, these results suggest that strategies to increase testing frequency among older and Hispanic MSM may be needed.

**Cost Effectiveness of HIV Screening Strategies**

Several investigators provided data on the cost-effectiveness of different HIV testing approaches at this year’s conference. Mabileau and colleagues evaluated the clinical impact, cost, and cost-effectiveness of different testing strategies in 5 European countries (Estonia, France, and Spain) (Abstract 1028). Testing strategies, in addition to current HIV testing practices, were evaluated for different transmission groups, and incremental cost-effectiveness ratios (ICERs) were calculated and considered cost-effective if the ICER was less than the annual per capita gross domestic product. Modeling results indicated that frequent HIV testing among high-risk groups increased life expectancy in people living with HIV infection. In France and Estonia, investigators recommended that MSM should have additional HIV testing every 12 months (ICERs, €16,200 and €18,600/year of life saved [YLS], respectively), and every 36 months in Spain (ICER €25,300/YLS). PWID should be tested every 3, 6, and 36 months in Estonia, Spain, and France, respectively (ICERs, €7000, €18,300, €19,700/YLS, respectively). For the overall population, one additional lifetime test was cost-effective for incidence below 0.009 per 100 person-years, and an additional test every 10 years was cost-effective for higher incidence levels.

Hutchinson and colleagues evaluated the cost-effectiveness of HIV screening for heterosexuals in the United States using a dynamic, compartmental model of the HIV epidemic (Abstract 1029). For high-risk heterosexuals, defined as those living in urban, high-poverty, white-minority areas with high HIV prevalence, annual screening was found to be cost-effective (ICER, $70,579), and could be considered economically attractive at 6-month intervals (ICER, $129,411). For the general heterosexual population, HIV screening was considered beyond the accepted threshold of cost-effectiveness when done more frequently than every 20 years (ICER, $70,579).

Cambiano and colleagues evaluated the population level impact and cost-effectiveness of different delivery models for HIV self-testing using a dynamic model of the HIV epidemic in Zimbabwe (Abstract 1030). Five different delivery approaches were evaluated, including secondary distribution of HIV self-tests to partners of pregnant women; pharmacy-based distribution of HIV self-tests to people who had sex without a condom since the last test; and community-based distribution (CBD) to young people, female sex workers, or adult men between the ages of 25 and 49. Based on an estimated 85% of people living with HIV infection in Zimbabwe knowing their HIV serostatus in 2016, several of the HIV self-testing strategies could increase rates of HIV serostatus knowledge to allow the first UNAIDS 90 goal to be reached. Furthermore, CBD could avert between 1200 (if introduced only in female sex workers) and 4500 (if introduced in all populations with 20% linkage to voluntary medical male circumcision) new HIV infections per year. However, due to high levels of HIV serostatus awareness, these strategies were unlikely to be cost-effective. The authors suggest that introduction of HIV self-testing into regions with lower testing coverage, more effective linkage of HIV prevention strategies (eg, PrEP and voluntary medical male circumcision), and lower kit costs could increase cost-effectiveness.

Sharma and colleagues evaluated the cost-effectiveness of assisted partner services to increase HIV testing and linkage in sub-Saharan Africa (Abstract 1032). Randomized clinical trial data in Kenya previously demonstrated higher rates of HIV testing of sexual partners in individuals who received assisted partner services compared with controls (41% vs 9%). In a dynamic HIV transmission model, it was projected that the population receiving partner services would increase to 11% and reduce HIV infections by 2.7% over the next 10 years. The ICER for implementing partner services was $1,568/disability-adjusted life year (DALY) averted, and this decreased to $1,156/DALY averted with task-shifting of intervention delivery from health care professionals to community health workers. This ICER falls below Kenya’s gross domestic product per capita and is considered very cost-effective.

**Detecting Acute and Early Infection**

Identifying individuals with acute HIV infection (AHI) is important to facilitate the immediate initiation of antiretroviral therapy and to reduce the likelihood of onward transmission. Dijkstra and colleagues developed and validated a risk score to assist in the detection of acute HIV infection among MSM (Abstract 886). Using data from 1562 HIV-seronegative MSM enrolled in the ACS (Amsterdam Cohort Study), an AHI risk score was developed that included 4 symptoms (fever, lymphadenopathy, oral thrush, and weight loss) and 3 risk factors (>5 sexual partners, gonorrhea, and receptive anal sex without a condom). This risk score identified 24% of MSM who would be indicated for AHI testing in the ACS, with a sensitivity and specificity of 76%. The risk score was then validated in the MACS (Multicenter AIDS Cohort Study) and showed comparative specificity of 89% but lower sensitivity (56%). The authors suggest that screening with this AHI risk score could increase efficiency of HIV-I RNA testing and potentially facilitate early diagnosis and immediate treatment.

Dijkstra and colleagues also presented data on incorporating a point-of-care HIV-I RNA test into a rapid diagnostic and referral strategy to identify acute HIV infections in the ACS (Abstract 887). MSM were referred to the study by an online media campaign, by their medical practitioner, or during
routine STI screening. Among 206 eligible men enrolled in the study with potential AHI symptoms, 19 (9.2%) MSM were newly diagnosed with HIV infection. Two participants had a positive point-of-care RNA and negative fourth-generation test (Fiebig I), 8 participants had a positive RNA and positive antigen but negative antibody on the fourth-generation test (Fiebig II), and 7 were recently infected with a positive RNA and a positive antigen/antibody fourth-generation test but negative HIV rapid test (Fiebig III-V). Additionally, 2 were diagnosed with established HIV infection (positive HIV rapid test). The median time from intake to delivery of results was 3.2 hours. All participants were referred to an HIV treatment center for immediate initiation of antiretroviral therapy. The authors concluded that their AHI strategy yielded a high proportion (8.3%) of those selected for testing having acute or recent HIV infection, and point-of-care RNA testing detected an additional 2 diagnoses of AHI.

Linley and colleagues evaluated the utility of HIV testing history in identifying AHI infection (Abstract 889). Using data from NHSS, they defined AHI cases as HIV infection in which the last reported date of negative test was 60 days or less before diagnosis, and compared cases based on a laboratory report with those from other sources (eg, individual self-reported or practitioner-reported). Among 220,195 diagnoses, 6% had a last negative test by laboratory report, of which 18% had AHI; 23% had a last negative report from other sources, and 6% had AHI. The proportion of AHI cases with a viral load of 100,000 copies/mL or more was higher for laboratory report–based AHI (65%) than for other source-based AHI (50%, P < .001), and the proportion of AHI cases with incidence assay results indicating recent infection was higher for laboratory report–based AHI (85%) than for other source-based AHI (58%, P < .001). From 2008 to 2014, the proportion of AHI among those with a laboratory-based report of last negative test date increased 145%. The researchers concluded that last negative test results based on laboratory reports are more accurate than those from other sources, and efforts to improve the collection of laboratory reports could increase the ability of HIV surveillance programs to identify AHI.

**Pre-Exposure Prophylaxis: What’s New?**

**Do Vaginal Microbiota Affect PrEP Efficacy?**

Three presentations provided updated data addressing the impact of vaginal dysbiosis and inflammation on tenofovir levels in vaginal tissue and efficacy as a PrEP agent. At IAS 2016, Burgener and Klatt presented a secondary analysis of data from the CAPRISA (Centre for AIDS Programme of Research in South Africa) 004 study that found that tenofovir 1% vaginal gel was efficacious in women with a Lactobacillus-dominated vaginal microbiome (efficacy 61%, P = .01), but not in women with lactobacillus-deficient vaginal microbiome (efficacy 18%, P = .6). Hillier and colleagues explored this relationship between the vaginal microbiota and topical tenofovir administration by evaluating data from a phase I study of 41 noninfected, nonpregnant women administering 7 days of vaginal tenofovir gel or film (Abstract 86LB). They found an association of higher levels of dysbiosis (as measured by Gardnerella vaginalis on polymerase chain reaction [PCR] or Nugent score on gram stain) and lower tenofovir levels in vaginal fluid, cervicovaginal biopsy tissue, and plasma. Conversely, women with high levels of 3 subtypes of Lactobacillus, a measure of healthy vaginal microbiota, had higher levels of tenofovir in vaginal fluid, cervicovaginal biopsy tissue, and plasma. These results confirm the findings of the CAPRISA 004 study and suggest that vaginal dysbiosis could potentially reduce topical PrEP efficacy.

McKinnon and colleagues reported on the effect of genital tract inflammation on the efficacy of topical tenofovir gel among 774 women enrolled in the CAPRISA 004 trial (Abstract 949). Among women without inflammatory cervicovaginal lavage fluid, defined as having 3 or less elevated inflammatory cytokines, tenofovir gel was 57% effective (95% CI, 10%-80%); this estimate increased to 75% effectiveness (95% CI, 25%-92%) among women using gel for 50% or more of their sex acts. Women with inflammatory cytokines, on the other hand, had no effectiveness from tenofovir gel, regardless of whether or not they reported high levels of drug adherence.

Heffron and colleagues presented data suggesting that oral PrEP efficacy is not substantially altered by vaginal dysbiosis (Abstract 85). In the Partners PrEP study conducted in East Africa, women were randomized 1:1:1 to daily tenofovir disoproxil fumarate (TDF) alone, coformulated with emtricitabine (TDF/FTC), or placebo, and underwent monthly HIV testing and baseline and annual vaginal swabs for gram stain. The PrEP efficacy measurement was combined for the 2 active arms, and compared between women with and without bacterial vaginosis (BV), as determined by a Nugent score of 7 to 10 versus 0 to 3, respectively. Daily TDF-based PrEP was efficacious in both the BV (77%) and non-BV subgroups (73%), with no statistically significant difference in efficacy by BV status (P = .9 for interaction). Similar levels of efficacy were seen when vaginal dysbiosis was measured by the presence versus absence of BV morphotypes and Lactobacillus morphotypes. Heffron concluded that because oral PrEP undergoes metabolism through systemic processes, local mediators may not influence the protective benefits of PrEP. She urged that future oral PrEP studies focus on improved adherence among women in sub-Saharan Africa, a population in whom HIV infection rates are high.

**Breakthrough HIV-1 Infections on PrEP**

Previously, the only reports of breakthrough infections in persons believed to be highly adherent to PrEP occurred when TDF was administered alone in the treatment of hepatitis B virus infection or with multidrug resistant HIV-1 infection. At CROI 2017, Hoornenberg and colleagues presented data on a man who appeared to acquire wild-type HIV-1 infection from high levels of sexual activity with men despite high adherence to daily TDF/FTC (Abstract 953). A 50-year-old man...
who was HIV seronegative on HIV RNA and antigen/antibody testing at enrollment began daily TDF/FTC in a demonstration PrEP study in Amsterdam. The participant reported high levels of sexual activity, including an average of 38 to 75 anal sex partners per month through the first 7 months of follow-up, with anal sex without using a condom 12 to 21 days per month. At month 8, he reported an episode of fever and dysuria and was found to be HIV-1 antibody positive, but antigen and HIV-1 RNA negative, at that time. PrEP drugs were stopped, and HIV-1 was detected in his blood 3 weeks later. Tenofovir diphosphate (TFV-DP) levels were measured in dried blood spot (DBS) specimens at 6 and 8 months, and were commensurate with daily PrEP (>2200 femtomoles/punch). Resistance testing revealed wild-type virus, making this the first reported case of an apparently highly adherent participant acquiring wild-type HIV-1 infection. The investigators questioned whether PrEP efficacy may have been reduced in this case because of the high level of sexual activity or whether high blood levels were not reflective of tissue drug levels in this individual. They also commented on the abnormal seroconversion pattern seen in this participant, with an HIV-1 antibody-positive, antigen-negative response. Sivay and colleagues also presented data that explored abnormal HIV-testing results among seroconverters on PrEP (Abstract 955). In HPTN 067, an RCT of daily versus event-driven versus time-driven TDF/FTC for PrEP in 622 participants, 2 simultaneous rapid HIV tests were negative in 9 of 12 seroconverters, all of whom had infrequent PrEP dosing or inadequate adherence. In 4 persons, follow-up rapid tests were also negative, including one person who continued to have negative rapid tests through 8 weeks after a positive fourth-generation HIV test turned positive. The investigators suggested that HIV-1 rapid tests may be insufficiently sensitive during early HIV infection, leading to rapid development of resistance if persons who are HIV-infected continue on PrEP.

Council and colleagues reported on breakthrough infections in participants in the Bangkok Tenofovir Study (Abstract 954). In the parent study, PWID were administered daily directly observed therapy (DOT) with TDF alone. Of 11 seroconverters evaluated in this study, 5 appeared to have high levels of adherence, as determined by DOT and plasma drug-level testing at the first HIV-1 positive blood draw. No drug resistance testing results were reported, so it is unclear whether these breakthrough infections occurred because the route of exposure was likely through injection practices, which may present a higher barrier to protection, or whether TDF alone is inadequate as PrEP, particularly for parenteral exposure. An analysis of data from the Bangkok Tenofovir Study suggested that even with adherence levels in excess of 97.5% as measured by DOT, PrEP effectiveness of TDF in PWID was only 84%.5 suggesting very high levels of adherence are required for protection in this group.

Cabotegravir, an investigational long-acting integrase strand transfer inhibitor (InSTI) is being evaluated for PrEP as a bimonthly intramuscular injection. Garcia-Lerma and colleagues presented data from a study assessing the development of drug resistance when cabotegravir was administered as 3 monthly injections to rhesus macaques acutely infected with simian immunodeficiency virus (SIV) (Abstract 84). Five of the 6 animals developed InSTI-resistant SIV variants in blood, vaginal, or rectal tissues, including the E92Q and E92G mutations at days 81 and 143, respectively, mutations known to confer resistance to InSTIs against HIV infection. Of particular concern was detection of mutations in vaginal and rectal fluid, suggesting that InSTI-resistant virus could theoretically be transmitted sexually. This reinforces the importance of ensuring that persons are HIV uninfected when initiating PrEP, particularly when administering long-acting PrEP agents, which may lead to suboptimal treatment for an extended period of time.

**PrEP Sustained Delivery Technologies Under Development**

Because daily adherence to medication is quite challenging, new technologies are under development that would provide sustained delivery of antiretroviral medications, including for PrEP. Durham and colleagues presented data on a biodegradable implant containing tenofovir alafenamide (TAF) that can be implanted using existing trocar applications (Abstract 420). The investigators described prototype implants that range from 2 mm to 2.5 mm in diameter and 40 mm in length. Preliminary studies using these devices have achieved sustained plasma levels for 14 to 21 days, with rapid tapering and disappearance from the plasma, a favorable quality that avoids the long subeffective pharmacokinetic tail seen in some long-acting formulations of PrEP drugs. However, manufacturing has been challenging, and automated fabrication of these devices is under development, along with plans to evaluate tissue drug levels and animal study data. Ying and colleagues presented initial data on a refillable nonfluidic implant for constant delivery of PrEP medication (Abstract 422LB). They microfabricated silicon nanochannel membranes in compliance with FDA requirements for implantable devices, which were incorporated into medical grade titanium implants. Separate reservoirs contained TAF and FTC. Although TFV-DP levels remained above protective levels in peripheral blood mononuclear cells (PBMCs) over 83 days, FTC-triphosphate levels were sustained only for 28 days, followed by a gradual decline resulting from drug depletion. Transcutaneous refilling was successful and the implants appeared to be well tolerated. The investigators plan future SIV challenge studies to evaluate the potential for these devices to deliver PrEP without requiring daily pill taking.

**Novel PrEP Implementation Strategies**

Katz presented data from a novel program using STI partner services to identify HIV-seronegative men who may benefit from PrEP in King County, Washington (Abstract 89). Of 3936
HIV-seronegative MSM with a newly diagnosed STI, 956 received partner services and had PrEP use assessed. The proportion of MSM diagnosed with a rectal STI or early syphilis who reported that they were already on PrEP at the time of the partner services interview increased from 30% in 2014 to 58% in 2016. Racial and ethnic disparities were seen, with statistically significantly lower proportions of black and Latino MSM reporting prior PrEP use, even after adjusting for year, age, STI type, and substance use. Of men not on PrEP who were referred to PrEP programs, 21% were seen for a first intake visit at a public health site; this number does not include persons who may have sought care with private practitioners. The investigators suggest that identifying high-risk persons through such programs may improve PrEP uptake among those at highest risk, and they have now prioritized inclusion of all black and Latino MSM identified through STI partner services.

Two investigators explored the possibility of having pharmacists deliver PrEP directly to patients. Tung and colleagues reported on the first year of operation of a pharmacist-run HIV PrEP clinic in a community pharmacy setting in Seattle (Abstract 961). Of 375 individuals initially contacting the clinic, 40% were linked with primary care and 245 were started on PrEP. Overall, 75% were retained on PrEP, with the main reasons for discontinuation being insurance restriction, transfer of care elsewhere, or being lost to follow-up. Virtually all of the individuals (97%) had no copay for medication, and the clinic costs were met at 9 months of operation. Broekuis and colleagues reported on Midwest pharmacists’ interest in prescribing PrEP (Abstract 963). Of 140 pharmacists returning an email-based survey, only 42% were familiar with TDF/FTC PrEP, but 54% stated they were fairly or very likely to provide PrEP after additional training as part of a collaborative practice agreement.

Khosropor and colleagues reported on the successful use of text messaging to improve retention in a clinic-based PrEP program (Abstract 964). Their program had 3 components: 1) regular (weekly to monthly) check-in messages, 2) automated appointment reminders, and 3) bidirectional communication with disease intervention specialists. Of 275 individuals who filled their PrEP prescriptions, 79% opted into this optional program. Clinic retention was 76% in those opting to use the program versus 53% among those opting not to use the program. Although this was not a randomized trial and, therefore, improved retention cannot be definitively attributed to the program, the high degree of desirability among participants is promising, and suggests further evaluation of this tool is warranted.

Golub and colleagues reported modest, short-term improvement in PrEP adherence from a brief behavioral intervention among 300 PrEP users in New York City (Abstract 965). Participants were randomized to a brief sexual health intervention, a brief adherence intervention, both interventions, or neither. At 3 months, participants receiving either intervention were statistically significantly more likely to be adherent to PrEP, defined as having a TDF-DP level in DBS consistent with 4 or more doses per week, than individuals randomized to neither intervention (94% vs 85%, P = .005). No statistically significant difference was seen at 6 months (92% vs 86%). The investigators suggest that brief counseling interventions should be explored and that ongoing counseling may be required.

**PrEP Awareness, Targeting and Uptake**

Several presentations documented the increase in PrEP awareness and use among MSM. Khaketla and colleagues presented data on 528 HIV-seronegative MSM enrolled in the longitudinal Momentum Health Study in Vancouver, Canada (Abstract 966). PrEP awareness increased from 18% in 2012 to 80% in 2016. PrEP awareness was statistically significantly higher in men with an annual income of $60,000 or greater (aOR, 0.24), in men with more than a high school education (aOR, 2.1), in men who practiced viral load sorting for prevention in the past 6 months (aOR, 2.56), in men with some markers of sexual risk (2 or more sexually transmitted infection diagnoses [aOR, 1.97]); and in those who used ecstasy in the past 6 months (aOR, 1.46). However, PrEP knowledge was lower in MSM who were Aboriginal (aOR, 0.36) or Latino (aOR, 0.40), and men who had previously received drugs for sex (aOR, 0.22). Despite high PrEP knowledge overall and the fact that 73% of men reported medical prescription insurance coverage, only 8 men reported PrEP use in any 6-month period. In fact, TDF/FTC PrEP was only licensed in Canada in February 2016 and is not currently publicly funded in British Columbia, suggesting that insurance coverage issues may be severely restricting PrEP access in British Columbia.

Buskin and colleagues compared several different methods for measuring PrEP uptake from 2014 to 2016 among MSM in Seattle (Abstract 973). Comparing an annual survey of health care practitioners about PrEP prescriptions with estimates from surveys of PrEP users (Seattle Pride surveys, the NHBS survey in MSM conducted in 2014, STI partner services, and the Seattle STI clinic) yielded similar results. These investigators estimate that 10% to 11% of MSM overall and 30% to 40% of high-risk MSM have used PrEP. As with other reported studies, PrEP use appears to be higher among white MSM than men of color, with the fewest disparities seen in the STI clinic patients (PrEP use 40% among white MSM, 31% among black MSM, 34% among Latino MSM, 33% among Asian/Pacific Islander MSM). The investigators report that their city-wide goal is to be administering PrEP to 50% of high-risk MSM by 2020, and suggest that they are on target to achieve that goal.

McMahan and colleagues focused on PrEP knowledge and uptake among 216 MSM and 5 transgender women who used methamphetamine in Seattle (Abstract 967). Although 97% of participants had heard of PrEP and 93% stated they...
knew where to get it, only 7 participants (3%) stated they had used PrEP. Insurance did not appear to be a barrier, as 97% reported having insurance. In qualitative interviews and focus groups, issues around stigma of PrEP use, challenges with keeping clinic appointments, and self-perception of low risk appear to contribute to low uptake in this vulnerable population.

Raifman and colleagues reported on the impact of a 5-minute PrEP education session on PrEP awareness and uptake among HIV-seronegative STI clinic patients in Rhode Island (Abstract 968). They compared knowledge and uptake with a control group of men who have sex with women who also attended the clinic more than once during that time to account for temporal trends. PrEP awareness increased by 19% in the MSM compared with the control group, and uptake increased by 4%. Although PrEP awareness was high in 2015, they found that non-Hispanic black MSM had 0.35 the odds of being aware of PrEP compared with white MSM. They also point to the importance of translating knowledge of PrEP into PrEP uptake in high-risk populations.

Lancki and colleagues pointed to limitations in following the CDC guidelines6 for identifying young black MSM who may benefit from PrEP (Abstract 969). They followed a cohort of 300 HIV-uninfected black MSM aged 16 years to 29 years during PrEP rollout in Chicago from 2013 to 2016. HIV-1 incidence was 85 per 100 person-years. The investigators report that following CDC guidelines for PrEP initiation, based on enrollment data, would have missed 48% of the seroconverters, while the HIV Incidence Risk Index for MSM7 and the manufacturer’s PrEP package insert8 would have missed 15% and 6%, respectively. This speaks to the importance of being more inclusive of persons who may benefit from PrEP, particularly youth, who may underreport or change risk practices over time.

Mayer and colleagues reported on disparities in PrEP uptake in a national online sample of 4638 MSM adults recruited through 2 sexual networking mobile apps. Overall, 8% of men reported ever having used postexposure prophylaxis (PEP) and 15% ever having used PrEP. In a multivariable model, ever having used PrEP was associated with being 25 years of age or older (aOR, 1.9), having private (aOR, 3.8) or public (aOR, 2.0) health insurance compared with no health insurance on PrEP persistence. Individuals with private or public insurance were 4 times more likely to attend the 3-month visit than those who were uninsured, pointing to the crucial importance of health insurance on PrEP persistence.

Scott and colleagues reported on racial and ethnic disparities in persistence among PrEP users in San Francisco (Abstract 974). Of 148 persons receiving PrEP at the San Francisco Department of Public Health Primary Care Clinics from March 2015 through February 2016, 67% remained on PrEP through April 1, 2016. The median duration on PrEP was substantially shorter for black (116 days) and Latino (183 days) individuals than for white (347 days) and Asian (279 days) individuals, indicating either earlier discontinuation or later initiation. They plan further studies to understand reasons for discontinuation among this user population.

Racial and ethnic disparities are seen in PrEP awareness, use, and persistence; insurance barriers are associated with decreased PrEP uptake and persistence.
levels, with levels over 1000 ng/mL, indicating use in the past 48 hours. Although this suggests that fewer than half of the participants initially recruited sustained high PrEP adherence through 1 year, they concluded that PrEP can be successfully delivered to a young, high-risk population. They also reported ongoing high rates of STIs in the population, pointing to the ongoing need for PrEP.

Hoenigl and colleagues reported that substance-using MSM on PrEP had better adherence than those without ongoing substance use in the CCTG 595 PrEP trial (Abstract 977). Among 394 participants enrolled in an RCT to promote adherence through texting via telephone versus standard of care, no difference between intervention and control arms in high PrEP adherence was seen as measured by TFV-DP levels in DBS consistent with taking 4 or more doses per week at week 48. However, participants reporting ongoing “heavy” substance use (5 or more times in the past 3 months at more than half of visits) were statistically significantly more likely to be highly adherent (OR, 2.1), as was ongoing “some” (1-4 times) or “heavy” (5 or more times) alcohol use (OR, 3.2 and 3.4, respectively). Because 59% of substance users were diagnosed with incident STIs during the study, they speculated that this subgroup may have been aware of their high risk, which may have motivated their high levels of adherence.

Gandhi and colleagues evaluated predictors of good adherence in a hair sample subsample of 280 participants enrolled in a PrEP demonstration project in San Francisco, Miami, and Washington, DC (Abstract 978). Hair samples were collected every 12 weeks and good adherence was indicated by tenofovir levels consistent with 4 or more doses of TDF/FTC PrEP per week. Factors associated with good adherence in 876 person-visits were age (OR, 1.42 per decade of age at baseline) and receptive anal sex without using a condom with an HIV-seropositive partner in the past 3 months (OR, 2.35). In support of the Hoenigl study, mentioned above, these investigators also found that amphetamine use in the past 5 months was marginally associated with high adherence (OR, 2.46, P = .07). However, both older participants (those over 45 years at entry) and having high adherence on hair measures were associated with an increased risk of experiencing a drop in estimated glomerular filtration rate (eGFR) to 70 or lower (OR, 3.4 and 1.3, respectively); higher starting GFR was associated with a reduced risk (OR, 0.85 per unit of GFR > 70). This suggests that older participants and those with lower GFRs at PrEP initiation may require more frequent renal monitoring to avoid renal adverse events from TDF/FTC PrEP.

Safety data on PrEP use during pregnancy are limited, but 2 presentations at CROI 2017 addressed birth outcomes in women using PrEP at the time of conception. Heffron and colleagues presented data on 30 pregnancies that occurred in women on PrEP in the Partners Demonstration Project, and compared birth outcomes with 85 pregnancies occurring in 79 women receiving placebo tablets during the Partners PrEP RCT (Abstract 934). The investigators found no differences in pregnancy outcomes in women on PrEP compared with women not on PrEP, including preterm delivery (0% vs 8%), pregnancy loss (17% vs 24%), or congenital anomalies (0% vs 8%). Although infant length and head circumference were marginally lower in the PrEP-exposed group than in the PrEP-unexposed group at month 3, infant growth characteristics were similar at 12 months. These data suggest that TDF/FTC PrEP taken during pregnancy did not adversely affect pregnancy- or birth-related outcomes. Makani and colleagues presented pregnancy incidence and outcome data among women using the dapivirine vaginal ring (Abstract 935). In the ASPIRE RCT, 2629 women were randomly assigned to a monthly dapivirine or placebo vaginal ring; 179 pregnancies occurred in 169 women. No differences were seen in pregnancy incidence (4.0 vs 4.3/100 person-years, respectively) or pregnancy outcomes between the 2 arms (preterm birth, 0% vs 10%; stillbirth, 2% vs 2%; spontaneous abortion, 21% vs 22%; birth anomaly, 8% vs 7%, respectively). These data are also reassuring that dapivirine use in the periconception period does not appear to be associated with adverse effects on pregnancy.


Financial affiliations in the past 12 months: Dr Liu and Dr Buchbinder have participated in research trials that have received provision of medicines from Gilead Sciences, Inc.

Additional References Cited in Text
Invited Review

CROI 2017: Advances in Antiretroviral Therapy

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The 2017 Conference on Retroviruses and Opportunistic Infections (CROI) featured exciting preclinical data on investigational antiretroviral agents with good in vitro efficacy and long half-lives. Investigational medications, including bictegravir, demonstrated excellent efficacy and tolerability, as did dual-agent therapy with dolutegravir paired with rilpivirine or with lamivudine. Dolutegravir monotherapy proved inadvisable due to virologic failure and resistance. The gap between high- and low-income settings along the HIV care continuum is narrowing, with Zimbabwe, Malawi, and Zambia approaching the 90-90-90 targets established by the joint United Nations Programme on HIV/AIDS (UNAIDS), whereas communities in the Southern United States are falling behind. Innovative strategies to improve outcomes include 2-way text messaging, home-based HIV testing, peer navigation, and New York City’s realignment of services into comprehensive sexual health programs. A high prevalence of resistance was documented in low- and middle-income settings and policy considerations were modeled to address increasing resistance rates. Novel resistance mutations to integrate strand transfer inhibitors and nucleoside analogue reverse transcriptase inhibitors were identified, but the clinical implications are unclear and require further investigation. Several studies provided insights on dosing and safety of antiretroviral therapy to prevent mother-to-child transmission through pharmacokinetic analysis. A special session devoted to Zika virus included a study of its effects on the central nervous system and a promising animal study of a Zika vaccine.

Keywords: CROI, HIV, AIDS, Zika, antiretroviral, therapy, treatment strategies, investigational drugs

Investigational Antiretroviral Drugs: Early Studies

HIV-1 Capsid Inhibitors

Tse and colleagues presented data on HIV capsid inhibitors that have potential for slow-release administration for use as a long-acting treatment (Abstract 38). The HIV p24 capsid protein self-assembles into hexamers that combine to form the conical capsid structure surrounding the inner viral core. GS-CA1 is a small molecule with a 50% effective concentration (EC₅₀) of 140 picomoles. During the maturation phase of the viral replication cycle, GS-CA1 interferes with the assembly and eventual disassembly of the viral capsid. It also prevents the nuclear translocation of the preintegration complex without affecting reverse transcriptase function. The binding site appears highly conserved in viral isolates. The GS-CA1 compound appears more potent in vitro than current classes of antiretroviral drugs and is active against highly resistant HIV strains. It has been formulated as a long-acting compound.

Other Classes

GS-PS1. Link and colleagues presented preclinical data on a novel once-daily protease inhibitor that does not require pharmacologic boosting (Abstract 433). The drug appears to have potent activity against HIV strains resistant to darunavir and atazanavir, and has a low propensity to generate resistance in vitro. The long half-life suggests its possible use as part of a once-daily single-tablet regimen for HIV treatment.

GS-9131. GS-9131 is a novel nucleoside analogue reverse transcriptase inhibitor (nRTI) with activity in vitro against HIV strains resistant to currently available nRTIs (Abstract 436). Resistance to GS-9131 emerges through a complex pathway distinct from other nRTIs. GS-9131 is a candidate for once-daily dosing and will likely be studied in individuals with limited treatment options.

UB-421. Wang and colleagues presented a phase II trial of UB-421, a monoclonal antibody that binds the CD4 receptor to prevent HIV-1 entry (Abstract 450LB). In the trial, HIV-infected adults with viral suppression were enrolled into 1 of 2 cohorts: 8 weekly doses of UB-421 10 mg/kg or 8 biweekly doses of 25 mg/kg. All participants interrupted antiretroviral therapy during the infusion period. UB-421 appeared relatively safe in this short-term trial with no emergence of anti-UB-421 antibodies. Grade 1 or 2 rash was noted in half of the participants. Participants remained virally suppressed throughout the

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Sax and colleagues presented a randomized, placebo-controlled phase II trial of bictegravir or dolutegravir with TAF/emtricitabine for initial antiretroviral therapy (Abstract 41). The trial randomly assigned 98 participants to bictegravir (65) or to dolutegravir (33). At week 48, 97% of participants in the bictegravir arm and 91% in the dolutegravir arm had viral suppression according to the US Food and Drug Administration’s (FDA) snapshot algorithm. No resistance to study medication was detected in either arm and no safety concerns were identified. Bictegravir is currently in phase III clinical development as a single-tablet regimen with TAF and emtricitabine.

Ibalizumab

Lewis and colleagues presented a single-arm clinical trial of ibalizumab, an investigational CD4 attachment inhibitor, with an optimized background regimen in highly treatment-experienced HIV-infected adults (Abstract 449LB). Eligible participants had to have resistance to at least 1 agent from each of 3 drug classes, and sensitivity to at least 1 antiretroviral drug to be used in an optimized background regimen. Forty participants were enrolled: the median age was 51 years; 85% were men; the mean viral load was 100,287 copies/mL; 85% were men; the mean viral load was 100,287 copies/mL; the mean CD4+ cell count was 140/µL; and baseline resistance to antiretroviral therapy was extensive. Participants received a single intravenous infusion of 2000 mg ibalizumab without changing baseline antiretroviral therapy. After 14 days, participants began an optimized background regimen and ibalizumab 800 mg administered intravenously every 2 weeks. Plasma HIV RNA levels decreased more than 1 log10 copies/mL at day 14 in 60% of participants. At week 24, 43% of participants had a viral load below 50 copies/mL and 50% of participants had a viral load below 200 copies/mL. Serious adverse events were common, but only 1 drug-related adverse event (immune reconstitution inflammatory syndrome) led to treatment discontinuation.

Lin and colleagues reported on the safety, tolerability, and pharmacokinetics for novel dosing regimens of ibalizumab (Abstract 438). The investigators found that 800 mg every 2 weeks or 2000 mg given intramuscularly or intravenously monthly resulted in sustained antibody concentrations in the therapeutic range. These dosing regimens led to reductions in plasma HIV RNA levels similar to those seen in prior studies that used weekly subcutaneous administration.

New Antiretroviral Strategies

Dolutegravir Plus Rilpivirine

Llibre and colleagues presented 2 phase III open-label, randomized clinical trials comparing dolutegravir plus rilpivirine
with continued antiretroviral therapy in HIV-infected participants who were virally suppressed (Abstract 44LB). Enrolled participants had no history of virologic failure, no chronic hepatitis B virus infection, and no history of viral failure. Dolutegravir plus ritonavir was noninferior to continued antiretroviral therapy (-0.2%; 95% CI, -3.0%-2.5%). Those in the dolutegravir plus ritonavir arm experienced a higher rate of adverse events leading to treatment discontinuation, but the overall rates of treatment success were high in both arms.

**Dolutegravir Plus Lamivudine**

Several trials are investigating a 2-drug regimen of dolutegravir and lamivudine. Joly and colleagues presented a single-arm trial of this regimen as maintenance antiretroviral therapy in HIV-infected adults (Abstract 458). Participants changed existing antiretroviral therapy to dolutegravir and 2 nRTIs for 8 weeks followed by dolutegravir and lamivudine. Participants had to have had a genotype prior to antiretroviral therapy that showed no resistance, no history of virologic failure with resistance, and no chronic hepatitis B virus infection. A total of 104 participants received dolutegravir and lamivudine alone: the median age was 45; 86% were men; the median CD4+ cell count was 743/µL; and the median nadir CD4+ cell count was 399/µL. At week 48, 97% of participants in each treatment arm were virologically suppressed. The virologic suppression with dolutegravir plus ritonavir was noninferior to continued antiretroviral therapy (-0.2%; 95% CI, -3.0%-2.5%). Those in the dolutegravir plus ritonavir arm experienced a higher rate of adverse events leading to treatment discontinuation, but the overall rates of treatment success were high in both arms.

**Dolutegravir Monotherapy**

Dolutegravir appears to have a high barrier to the emergence of resistance. Wijting and colleagues reported on a randomized clinical trial comparing dolutegravir monotherapy with continued antiretroviral therapy in HIV-infected adults with virologic suppression (Abstract 451LB). The 104 participants were randomly assigned to either of the concurrent studies. At week 48, 95% of participants in each treatment arm were virologically suppressed. The virologic suppression with dolutegravir alone was noninferior to continued antiretroviral therapy. After week 24, the participants receiving antiretroviral therapy were allowed to change to dolutegravir alone. After 24 weeks to 48 weeks of receiving dolutegravir alone, 8 participants experienced virologic failure, including 3 who developed InSTI resistance. This suggests that this strategy may not be ready for use in clinical practice and should not be pursued in further clinical trials.

**PRO140**

PRO140 is an investigational monoclonal antibody that binds to human CC chemokine receptor R5 (CCR5) to prevent HIV entry (Abstract 437). Lalezari and colleagues presented findings from a study of 16 participants with CCR5-tropic HIV infection who received PRO140 in the form of 350 mg weekly subcutaneous injections alone as maintenance antiretroviral therapy. Five participants experienced virologic rebound and resumed combination antiretroviral therapy. One participant discontinued the study. Nine participants who received PRO140 alone remained virologically suppressed after 2 years of follow-up. There was no emergence of C-X-C chemokine receptor type 4 (CXCR4) using HIV-1 variants. The strategy is being investigated in other ongoing studies.

**Pharmacokinetic Considerations**

**Tenofovir.** Castillo-Mancilla and colleagues presented data on quantifying tenofovir diphosphate in dried blood spots from individuals receiving TAF as a measure of adherence over a period of several weeks to months (Abstract 405). The red blood cell concentrations were quantifiable, but at lower levels than seen in those who receive TDF. Presumably this is related to the lower tenofovir plasma concentrations observed in individuals receiving TAF as opposed to those receiving TDF.

Dumond and colleagues examined concentrations of tenofovir in the semen of individuals receiving TAF (Abstract 406) or TDF. Tenofovir concentrations were similar in the seminal plasma for those receiving either TAF or TDF. This finding was unexpected because TAF achieves much lower blood plasma concentrations than TDF.

**Older HIV-Infected Adults.** Several abstracts evaluated the pharmacokinetic profile of antiretroviral drugs in aging populations. Ahlgren and colleagues studied 99 HIV-infected adults aged 65 years and older and found they had elevated darunavir concentrations (48% higher) compared with younger controls. Concentrations of atazanavir or efavirenz, however, were similar in both groups (Abstract 431). Elliott and colleagues performed intensive dolutegravir pharmacokinetic sampling by comparing 28 HIV-infected adults aged 60 years and older with 16 HIV-infected adults younger than 60 years and found that drug exposure was not affected by age (Abstract 432).

**Crushing Tablets.** Roksam-Kwit and colleagues evaluated the effect on plasma concentrations of crushed fixed-dose dolutegravir/abacavir/lamivudine tablets in 22 HIV-uninfected adults (Abstract 429). The dolutegravir exposure, as measured by area under the curve (AUC), increased by 26% when the crushed tablet was given in an oral suspension, and
increased by 18% when the crushed tablet was coadministered with enteral nutrition. No appreciable difference was noted for exposure when abacavir or lamivudine crushed tablets were taken. The authors concluded that fixed-dose dolutegravir/abacavir/lamivudine could be crushed for individuals who had difficulty swallowing or with the use of an enteral feeding tube.

The HIV Care Continuum

Global Progress Toward Reaching UNAIDS 90-90-90 Targets

Exciting data about progress made on the HIV care continuum and toward reaching the UNAIDS 90-90-90 treatment goals were a highlight at this year’s CROI. In the plenary session, Dr Hakim, from the University of Zimbabwe, gave the N’Galy-Mann lecture in which he detailed the history of HIV/AIDS research in Zimbabwe. Zimbabwe identified its first person living with HIV infection in 1985 and the country’s initial response to the epidemic was impeded by public denial of the existence of HIV. Since 1999, Zimbabwe has developed a national AIDS policy and strategic multisectoral response, supported by a 3% tax on individual and corporate income. As a result, HIV prevalence peaked at 29% in 1986 and is now at 14%, with substantial geographic variation. Based on the Zimbabwe Population-based HIV Impact Assessment (ZIMPHIA), part of the PHIA project, a 5-year initiative to collect information related to HIV infection in approximately 15 to 20 African countries, progress toward achieving 90-90-90 targets in Zimbabwe is being made. ZIMPHIA was conducted between October 2016 and August 2016 by ICAP-Columbia with local partners and the Zimbabwe Ministry of Health, the US President’s Emergency Plan for AIDS Relief (PEPFAR), and the Centers for Disease Control and Prevention (CDC). The UNAIDS 90-90-90 goals are that 90% of all HIV-infected individuals will be aware of their HIV serostatus, 90% of those who are aware of their serostatus will be receiving antiretroviral therapy, and 90% of those receiving antiretroviral therapy will have viral suppression by 2020.

To date in Zimbabwe, 74.2% of HIV-infected individuals have been diagnosed, 86.8% of those diagnosed are on treatment, and 86.5% of those on treatment are virologically suppressed. These achievements are particularly impressive in light of the country’s political climate and economic conditions. Hakim emphasized Zimbabwe’s multifaceted research program, which includes studies with the HIV Prevention Trials Network and the AIDS Clinical Trials Group, and ongoing work to expand medical education and research capacity in the country.

Zimbabwe, Malawi, and Namibia have all made substantial progress toward reaching UNAIDS 90-90-90 targets, but population mobility and limited availability of HIV-1 plasma RNA testing impede progress in many countries.

Justman and colleagues (Abstract 114LB) presented additional data from Zimbabwe, Malawi, and Zambia, collected by PHIA. Representative HIV-focused households were surveyed to estimate HIV incidence and the prevalence of virologic suppression, defined as a plasma HIV-1 RNA level below 1000 copies/mL. In a survey of 76,662 adults and children, the overall response rate was 69.1%, and HIV prevalence among adults (aged 15 years to 59 years) varied dramatically by sex (9.8% of men and 14.4% of women) and by geographic location. Prevalence in the pediatric population was much lower, at 1.4% of those aged 0 years to 14 years. Most striking were the data on progress in achieving the 90-90-90 goals. In all 3 countries, 70.4% of individuals were aware of their serostatus, 87% of those individuals were on antiretroviral treatment, and 88.6% of those were virologically suppressed, with the successes largely driven by older populations. The investigators concluded that the HIV epidemic is stabilizing, or even declining in some circumstances, in the populations surveyed, and that young adults, particularly those who are unaware of their HIV serostatus, should receive targeted testing and treatment interventions to achieve the 90-90-90 goals and maintain current successes.

Olney and colleagues (Abstract 115) used data from ZIMPHIA in a mathematical model of various HIV infection care stages. The investigators predicted that Zimbabwe will achieve 2 of the 3 90-90-90 treatment goals: 90% of diagnosed individuals with HIV infection will receive antiretroviral therapy by 2020, and 90% of those individuals receiving antiretroviral therapy will become virologically suppressed by 2020. However, the goal that 90% of HIV-infected individuals will become aware of their HIV serostatus by 2020 will not be met by a substantial margin. They predicted that only 72% of HIV-infected persons in Zimbabwe would be diagnosed, and the diagnosis and linkage of an additional 11,244 individuals per year would be needed to achieve all 3 goals simultaneously; this would also require a 5% increase in overall funding.

Nguyen and colleagues (Abstract 116) also created a mathematical model to examine the clinical outcomes and cost-effectiveness of 4 strategies in Southwest Kenya. The strategies were to expand voluntary counseling and testing (VCT) to 90% of the community; to offer VCT and linkage to care to 90% of those diagnosed with HIV infection; to provide retention interventions to ensure 90% antiretroviral treatment and 90% virologic suppression for those on treatment; and to offer all 3 interventions combined. The model, using 2012 HIV care continuum data from Médecins Sans Frontières (MSF), showed that 62% of the population was tested, 57% were linked to HIV care, and 40% were virologically suppressed. The time-discrete, dynamic microsimulation model showed that if implemented in 2014, after 15 years the baseline care continuum outcomes would increase from 73% to 94% tested, from 66% to 95% linked, and from 56% to 56% suppressed, respectively, depending on the strategy implemented. Incidence would drop from 1.93 per 100 person-years without intervention to 1.10 per 100 person-years with the combined intervention. The incremental cost-effectiveness ratio was $180 per year of life saved, although this was
dependent on regional HIV prevalence estimates. Results from this model suggest that the combined strategy would be cost-effective in Southwest Kenya and other areas in Kenya where HIV prevalence is more than 3%, but might still fall short of the UNAIDS 90-90-90 treatment targets.

Data from the French National Agency for AIDS Research (ANRS) 12249 cluster randomized trial of a universal test-and-treat approach on HIV incidence in rural South Africa were used to assess 90-90-90 targets in 564 individuals for 1 year after HIV diagnosis (Abstract 1018). Twenty-two percent had migrated out of the study catchment area, 57% were diagnosed, 27% were engaged in HIV care, 12% were receiving antiretroviral treatment, and 10% were virologically suppressed. The investigators highlight that only 17% of this newly diagnosed cohort initiated antiretroviral therapy within 12 months of seroconversion in a setting where linkage to care and treatment was facilitated. These findings are concerning and highlight the challenges of reaching 90-90-90 targets in regions of high population mobility and to support those recently diagnosed as they engage in care.

Patel presented data in the SISTER (Sentinel Incidence Survey to Evaluate the Response), a novel mechanism for assessing 90-90-90 targets by embedding an incidence and virologic suppression survey into an existing, community-based HIV prevention and care management program in Namibia (Abstract 35; also see “HIV Epidemic Trends and Advances in Prevention” by Drs Liu and Buchbinder). At baseline, 64% of 461 people living with HIV infection were aware of their diagnosis, 53% were receiving antiretroviral therapy, and 43% were virologically suppressed. After 1 year, 92% of the cohort was retained, although retention for those living with HIV infection was lower (89%) than for those uninfected (93%, \( P < 0.05 \)). However, achievement toward 90-90-90 targets within the cohort had improved: 99% of the 423 individuals living with HIV infection were aware of their diagnosis, 92% were receiving antiretroviral therapy, and 75% achieved virologic suppression. The investigators concluded that this type of community-based program can be used in other countries to assess progress toward achieving the 90-90-90 targets, and to promote HIV testing and linkage to care and treatment adherence.

**Reaching the Last 90: Challenges of Measuring and Achieving Virologic Suppression**

Several presenters addressed strategies to improve virologic monitoring in low- and middle-income countries in order to meet the 90-90-90 target of 90% virologic suppression. Peeling (Abstract 105) described innovations in plasma HIV-1 RNA measurement and scale-up, emphasizing the dramatic variation in scale-up of viral load testing. In Namibia, 91% of individuals on antiretroviral therapy have had at least 1 plasma HIV-1 RNA test and the turnaround time for results is 5 working days or less. In contrast, in Tanzania only 5% of individuals on antiretroviral therapy have ever had their plasma HIV-1 RNA level measured, and turnaround time for testing is 28 to 50 working days. Two point-of-care platforms for plasma HIV-1 RNA testing are currently available, although they are expensive and have lower throughput than the fully automated laboratory assays. More point-of-care tests are in development. Assays that use dried blood spots are useful, particularly in rural settings, but still have problems with false-positive results associated with measuring cell-associated viral RNA and proviral DNA. Peeling highlighted Uganda’s plasma HIV-1 RNA testing expansion, which uses a 5-tiered laboratory network forming a hub-and-spoke model. The 100 hubs provide analysis of dried blood spots received from 50 spokes each, and monthly tests have increased from 10,000 to more than 70,000 in slightly over a year. Zimbabwe is pursuing a similar model, but with a focus on connectivity. All of Zimbabwe’s point-of-care instruments upload data into the cloud, or Internet servers, which the Ministry of Health then accesses. The data can be used for patient care, but also to ensure quality control and stock management for individual machines. These innovative approaches can be applied in other low- and middle-income countries to expand access to plasma HIV-1 RNA level measurement.

Reynolds (Abstract 104) reviewed the limitations of immunologic monitoring, and emphasized the need for access to plasma HIV-1 RNA testing. He also highlighted the need to address the “viral load cascade,” which means not just providing access to the test but ensuring that the results are acted on and alternate antiretroviral regimens are initiated as indicated. Data from the Rakai fishing communities in Uganda in 2015 showed that only 42% of the HIV-infected population had plasma HIV-1 RNA levels measured, in a setting where testing is routinely available. Reynolds estimates that only 2% to 4% of individuals in low- and middle-income countries are receiving second or third antiretroviral regimens, and reviewed data showing long delays in transitioning individuals to second regimens, even in the setting of demonstrable virologic failure. Delays in switching to second antiretroviral regimens have been associated with the development of drug resistance and mortality, and have clear implications for treatment as prevention strategies.

Three presentations focused on viremia patterns in large cohorts. Crepaz and colleagues (Abstract 31) used data from the CDC HIV National Surveillance System to expand the traditional definition of virological suppression of plasma HIV-1 RNA less than 200 copies/mL to understand virologic dynamics over time. They compared individuals whose last plasma HIV-1 RNA level in 2014 was below 200 copies/mL to those having all their measurements in 2014 be below 200 copies/mL and to those who never achieved a level below 200 copies/mL in 2014. Among the 630,965 people living with HIV infection in the United States in 2014, 57% had a last plasma HIV-1 RNA level measurement below 200 copies/mL, but only 48% achieved durable virologic suppression, with all measures below 200 copies/mL. Eight percent never achieved plasma HIV-1 RNA levels below 200 copies/mL and 32% did not have their plasma HIV-1 RNA levels assessed in 2014. Women, African-Americans, Hispanics, and those between the ages of 13 years and 24 years were less likely to achieve durable
virologic suppression than men, non-Hispanic whites, and those aged 55 years and older, respectively. These data suggest that the current continuum of care outcome measure, which relies on a single plasma HIV-1 RNA assessment, overestimates durable viral suppression by approximately 20%.

Data from 9 clinics participating in the CDC HOPS (HIV Outpatient Study) examined the opposite side of virologic dynamics (Abstract 32). Because most cases of HIV-1 transmission occur when the plasma HIV-1 RNA level is greater than 1500 copies/mL, time spent with plasma HIV-1 RNA levels greater than 1500 copies/mL represents a period of transmission risk and failure of treatment as prevention goals. Among 5873 persons followed up for a median of 5.4 years between 2000 and 2014, the percentage of person-time with plasma HIV-1 RNA greater than 1500 copies/mL decreased from 37% in 2000 to 10% in 2014 (P < .01). A percentage of person-time above 1500 copies/mL was also statistically significant when associated with persons aged 35 years and under and those between 35 years and 49 years than with those people aged 50 years and older, those having public insurance, and those of non-Hispanic black race compared with white. These results show encouraging trends in rates of virologic suppression over time in the United States, which may decrease the risk of HIV transmission.

Hermans and colleagues (Abstract 113) explored the risk of antiretroviral treatment failure after low-level viremia in an observational cohort of 132,782 South African people living with HIV infection and receiving treatment in 57 clinics in urban and rural settings. The researchers found that among 69,454 individuals on an initial NNRTI-based antiretroviral therapy, low-level viremia, defined as plasma HIV-1 RNA levels between 51 and 999 copies/mL, occurred in 12% of persons per year, or approximately 20% overall. The presence of low-level viremia had a statistically significant association with virologic failure, defined as 2 plasma HIV-1 RNA level measurements above 1000 copies/mL. In a stratified analysis, higher degrees of low-level viremia were associated with a greater hazard of virologic failure: those with 400 to 999 copies/mL had a hazard ratio (HR) of 5.7 (95% CI, 5.1-6.4); 200 to 399 copies/mL was associated with an HR of 3.8 (95% CI, 3.4-4.2), and 51 to 199 copies/mL was associated with an HR of 2.2 (95% CI, 2.0-2.4), compared with those whose HIV-1 RNA levels were continuously below 50 copies/mL. Even those who had low-level viremia but then had resuppression to below 50 copies/mL were still at a statistically significant increased risk of virologic failure. The investigators concluded that ongoing viral replication is a predictor of future virologic failure, and that the World Health Organization (WHO) threshold of 1000 copies/mL likely fails to identify those at high risk for virologic failure.

**Strategies to Improve the HIV Care Continuum for Key Populations**

Barnabas (Abstract 107) addressed the challenges of achieving engagement in all stages of the care continuum for priority populations. She first reminded the audience that vulnerability is highly context specific, and that priority populations should be defined by high regional HIV prevalence or incidence rather than by specific behavioral characteristics. For example, individuals who use injection drugs who use safe injection practices are not considered vulnerable. Achieving 90-90-90 targets is more difficult in marginalized populations because they face additional barriers of criminalization, stigma, and discrimination. These barriers are reflected in disparities in antiretroviral therapy coverage for individuals who use injection drugs, sex workers, and men who have sex with men (MSM), and in virologic suppression for postpartum women and youth. Barnabas suggested that strategies to improve the HIV care continuum for these populations must begin with involving members of the key populations and decentralizing services, simplifying treatment protocols, and integrating them with other services, such as safe injection, opioid substitution treatment, and tuberculosis treatment. The following abstracts highlight some of these successful strategies.

**Postpartum Women and Infants.** Two abstracts described successful strategies for engaging postpartum women and infants in care. Myer and colleagues (Abstract 24) randomly assigned 472 consecutive HIV-infected mother-infant pairs to an integrated maternal and child health service offering antiretroviral therapy for the duration of breastfeeding (intervention), or to separate adult antiretroviral treatment services and routine well baby services (local standard of care; control). Among 234 mothers in the control arm, 56% met the criteria for the combined primary outcome of maternal retention in care and viral suppression to plasma HIV-1 RNA levels below 50 copies/mL at 12 months postpartum. In the intervention arm, 77% of 234 women met the criteria for the primary outcome, for an absolute risk difference between intervention and control of 21% (95% CI, 12-30%; P < .001). The duration of exclusive breastfeeding was also longer in the intervention arm at a median of 3.0 months, compared with 1.4 months in the control arm (P = .001). The cumulative risk of mother-to-child transmission over 12 months was less than 1% and did not show a statistically significant difference between the 2 study arms. Thus, the integration of antiretroviral therapy services into a comprehensive postnatal maternal-child health platform, rather than separate services for mothers and infants, may improve engagement in care and treatment outcomes.

Jani and colleagues (Abstract 26) conducted a cluster randomized trial to assess the impact of point-of-care (POC) diagnostic testing for infants aged 4 weeks to 6 weeks. They
compared POC testing to standard of care testing using dried blood spot samples, which are sent to reference laboratories. Initiation of antiretroviral therapy within 2 months of diagnostic testing was accomplished in 89.7% of 2054 infants in the POC arm and 12.8% of infants in the standard-of-care arm (P < .0001). Retention in care also improved in the POC testing arm (61.6%) compared with the standard-of-care arm (42.9%; adjusted risk ratio [aRR], 1.4; 95% CI, 1.1-1.9). The investigators proposed that adoption of POC protocols for early infant testing can promote earlier antiretroviral initiation and retention in care and may contribute to achieving UNAIDS 90-90-90 targets for pediatric populations.

Adolescents and Young Adults. Adolescents and young adults are increasingly a focus of HIV care continuum interventions, because of high HIV incidence and increased risk of treatment failure in these populations. One themed discussion (Abstracts 835-838) highlighted several innovative strategies to improve UNAIDS 90-90-90 target outcomes in these key populations. Reif and colleagues evaluated a model of community cohort care in which adolescents and young adults newly diagnosed with HIV infection were consecutively enrolled in cohorts of 6 to 8 peers stratified by age (aged 10 years to 14 years, and 15 years to 20 years) (Abstract 835). The cohorts received care through monthly meetings in a community building separate from the clinic, where counseling, clinical management, and antiretroviral therapy distribution are all provided by the same nurse and caregiver each month. Fifty adolescents enrolled in this cohort were compared with a historical control group of 462 adolescents aged 15 years to 19 years who received individual care in an adolescent HIV clinic. The 12-month retention in care was 86% among those in the community cohort care, compared with 66% in the historical control cohort (P < .001). The community cohort care participants also reported decreased stigma, increased social support, and higher acceptance of the care model, but this was not compared directly with data from the historical control group. These data suggest that community cohort care deserves further study as a novel method to reach and engage newly diagnosed youth living with HIV infection.

Brown and colleagues (Abstract 836) examined the impact of having peers living with HIV infection on retention in care and virologic suppression for women aged 15 years to 24 years enrolled in the SEARCH (Sustainable East Africa Research in Community Health) trial. SEARCH is a test-and-treat trial that conducted a baseline census of all residents in 3 rural Kenyan communities between September 2013 and January 2014, including a detailed social network of all participants. The investigators examined retention in care, defined as not more than 90 days late to a scheduled clinic visit, and virologic suppression, defined as plasma HIV-1 RNA levels below 400 copies/mL. They found that women with social contact also living with HIV infection in any domain of their social network were more likely to be retained in care (adjusted HR [aHR], 2.63; 95% CI, 1.10-4.31) than those without social contacts living with HIV infection. Women retained in care were also more likely to achieve virologic suppression if they had a social contact living with HIV infection (adjusted odds ratio [aOR], 3.2; 95% CI, 1.1-9.8). These data suggest that strengthening social networks among young women living with HIV infection may help improve engagement at various stages in the HIV care continuum.

The IeDEA (International Epidemiologic Databases to Evaluate AIDS) collaboration examined loss to follow-up for younger adolescents aged 10 years to 14 years, older adolescents aged 15 years to 19 years, and adults aged 20 years and older at 33 participating health facilities in Kenya, Uganda, and Tanzania (Abstract 837). Loss to follow-up was defined as no clinic visit in 3 months and was statistically significantly higher for older adolescents (45%) than for younger adolescents (27%) and adults (31%). Among older adolescents, pregnant women had the highest risk of loss to follow-up (HR, 1.56; 95% CI, 1.39-1.76) compared with men, but nonpregnant women (HR, 1.36; 95% CI, 1.23-1.49) and women of unknown pregnancy status (HR, 1.28; 95% CI, 1.10-1.48) were also at higher risk than men. Recent enrollment status (2012-2014) was correlated with loss to follow-up risk across all age categories. The authors highlighted the role of pregnancy status in predicting engagement in care, but all youth require specific efforts.

Zanon and colleagues (Abstract 838) provided one of the few bright spots regarding HIV care continuum outcomes in adolescents. Using data from CFAR CNICS (Center for AIDS Research Network of Integrated Clinical Systems), the investigators demonstrated that although those aged 18 years to 24 years had statistically significantly higher rates of current substance use and lacked health insurance compared with adults aged 50 years and older, they did not have decreased risk of retention in care or viral suppression.

Immigrants. Two presentations examined HIV care continuum outcomes for immigrant populations. Marukutira and colleagues (Abstract 1017) examined noncitizen immigrants in Botswana’s Combination Prevention Project (BCPP), and found that 3% of the 48,640 people assessed for HIV serostatus within this cluster randomized trial were noncitizens. Noncitizens were more likely to be unaware of their HIV serostatus than citizens (63% vs 16%; P < .001). Of those aware of their serostatus, noncitizens were less likely than citizens to be receiving antiretroviral therapy (29% vs 71%; P < .001). The investigators suggested that Botswana’s current policy of not providing antiretroviral therapy to noncitizens could limit the country’s ability to achieve the UNAIDS 90-90-90 targets.

Ross and colleagues (Abstract 1016) explored the same question in a different context, using electronic medical record data to examine care continuum outcomes data for undocumented immigrants receiving care in the Bronx, New York. They devised an algorithm to determine undocumented status using missing or invalid social security numbers and insurance status, and validated it with manual medical record review. They found small but statistically significant increases in the rates of retention in care, prescription of antiretroviral therapy, and virologic suppression in undocumented individuals compared with those with valid social security numbers.
These investigators suggested that providing services to undocumented people living with HIV infection would improve the overall HIV care continuum in those areas.

Innovative Interventions to Improve the HIV Care Continuum

Many presentations at the 2017 CROI covered novel, often multidomain interventions to address the HIV care continuum. A plenary session by Daskalakis (Abstract 108) offered an overview of the New York City (NYC) Department of Health and Mental Hygiene’s “End the Epidemic” strategy. The current NYC care continuum data show that 94% of people living with HIV infection in NYC are diagnosed, 86% are retained in care, 82% receive antiretroviral therapy, and 74% are virologically suppressed. The “End the Epidemic” campaign is adopting various strategies to simultaneously improve the HIV care continuum and increase HIV prevention efforts throughout the city. The city’s Sexually Transmitted Diseases clinics are being reconfigured into Sexual Health clinics, with expanded hours, HPV-related services such as colposcopy, and quick-start contraceptives for women. The clinics will also serve as locations where persons can receive immediate antiretroviral therapy or preexposure prophylaxis (PrEP) treatment initiation and navigation to longitudinal care. Other interventions include working closely with community-based organizations and pharmacies to facilitate rapid access to medications, and supporting antiretroviral treatment services with behavioral and housing support services, directly observed therapy, and financial incentives. Finally, Daskalakis proposed a “status-neutral model,” where HIV prevention and care services are linked, and HIV testing leads to treatment engagement or prevention engagement, all of which are integrated. Implementation of the comprehensive “End the Epidemic” campaign began in the fall of 2016, and the data will be much anticipated.

Lester (Abstract 106) gave an overview of mobile technology and the evidence behind its supportive use for adherence to antiretroviral therapy, by first pointing out that cell phones have become so ubiquitous that more people globally have access to them than toothbrushes or flush toilets. Simple text messaging has become the most used data service in the world, representing an affordable and innovative opportunity for adherence intervention. Lester emphasized that using texts for one-way communication, such as adherence reminders, is less effective in randomized controlled trials. Based on the available evidence, optimization of mobile technology adherence support should include 2-way interaction, content written in simple language to avoid issues with disclosing personal health information, and weekly messaging. Lester also emphasized the need for long-term data and the challenges of phone turnover.

Lamb and colleagues (Abstract 110) incorporated support from text messaging into a cluster randomized trial of a combined intervention strategy to improve engagement and linkage to care in 10 clinics in Mozambique. The intervention included same-day CD4+ cell count assessment, point of diagnosis antiretroviral therapy counseling, and fast-track treatment initiation. Participants received text messages regarding health and appointment reminders to encourage linkage and retention, and a subset within the intervention arm received financial incentives in the form of prepaid cell phone cards. This was compared with standard of care using routine CD4+ testing with results in 2 to 4 weeks and separate counseling visits. The primary outcome of linkage to HIV care within 1 month of diagnosis and retention 12 months after diagnosis was more common in the intervention arm (relative risk [RR], 1.6; 95% CI, 1.5-1.8) than in the arm that received standard of care, but did not differ between those in the intervention arm who received financial incentives or not. The increases in linkage were greatest when individuals were linked to care on the day of diagnosis. Also, receiving care at any clinic, rather than just the clinic of diagnosis, substantially improved estimated linkage and retention. The benefits of rapid linkage to care are clear in this study, but 50% of participants still were not linked or retained at any clinic. The notable absence of any impact from the financial incentives deserves further investigation.

The I-Care Trial in South Africa (Abstract 111) compared 2 interventions with a standard-of-care model. The 2 interventions were an automated text message appointment reminder system, including 2-way check-in messages, health promotion messages, and peer navigation, with an emphasis on social modeling. Eighteen clinics were randomly assigned to 1 of the 3 study arms, and the primary outcome was retention in care, defined as at least 4 visits within 12 months for individuals receiving antiretroviral therapy and 2 visits in 12 months for individuals prior to initiating antiretroviral treatment. Participants in the peer navigation arm were more likely to be engaged in care after 12 months (odds ratio [OR], 1.83; 95% CI, 1.01-3.33) than participants in the standard-of-care arm, a difference primarily driven by retention in women. Retention in care was not statistically different between the automated text reminder system and standard of care. The investigators speculate that the personalized attention from the peer navigators is valuable, but emphasize the challenges of bringing such an intensive intervention to scale.

Mallewa and colleagues presented data from the REALITY 2x2x2 factorial open-label randomized trial (Abstract 117), which enrolled adults and children over 5 years of age with CD4+ cell counts below 100µL who were initiating antiretroviral treatment. Participants were enrolled into standard of care (n = 908) or provision of 12 weeks of Ready-to-Use Supplementary Food (RUSF), which provided 1000 kcal/day with multivitamin and mineral supplementation (n = 897). The primary endpoint was mortality at 24 weeks. No difference between the RUSF and the standard-of-care arms was seen, and no statistically significant differences were seen in

Rapid treatment initiation and peer navigators were both effective interventions to improve engagement and retention in care.
CD4+ cell count gain or virologic suppression. Statistically significant gains in body mass index were observed (an additional 0.3 kg/m² in the RUSF arm at 12 weeks; \( P = .004 \)) and mid-upper arm circumference (\( P = .03 \)). This represents the first randomized trial of food supplementation that compared no supplementation with RUSF.

Data from the first 3 years of the HIV Prevention Trials Network 071 “PopART” Trial (Abstracts 1010 and 1011) examined the impact of a universal testing and treatment strategy using community HIV care providers to offer home-based rapid HIV testing and linkage to existing government health services. The intervention was delivered in annual rounds in 4 communities in Zambia between November 2013 and October 2016. Investigators reported UNAIDS 90-90-90 target results from the first 2 annual screening rounds, which reached 45,616 households, representing 95% of the target communities. At the end of the second round, 90% of women and 78% of men were aware of their HIV diagnosis. Of those known to be living with HIV infection, 78% of men and 79% women were receiving antiretroviral therapy. Antiretroviral therapy uptake did not vary by sex, but did increase with age: from 41% among those aged 18 years to 24 years to 82% among those aged 55 years or older. These data highlight that annual community-wide home-based testing and linkage to care, within existing governmental treatment programs, can be an effective strategy to achieve UNAIDS 90-90-90 targets, but that additional outreach for testing in men and care engagement for youth may be needed.

**HIV Treatment Strategies and Outcomes**

**Treatment Strategies in Neonates**

Obimbo provided an overview of the challenges and opportunities in treating infants living with HIV infection (Abstract 103). Gaps in the HIV care continuum for children living with HIV infection in Kenya, where only 45% of such children are diagnosed, were highlighted. Once diagnosed, the majority (91%) receive antiretroviral therapy, but only 63% of those on antiretroviral therapy achieve virologic suppression. Challenges for addressing HIV infection in neonates and infants include few available drugs, poor palatability, nonadherence, lack of fixed-dose combinations, changing pharmacokinetics associated with rapid growth, and the need for cold-chain storage. Current strategies to address these challenges include ongoing studies of lopinavir/ritonavir pellets, which seem to be well tolerated for infants already weaned from breastfeeding; raltegravir oral granules for neonates; and nevirapine. Novel interventions are needed to combat the high attrition and poor rates of virologic response in infants newly diagnosed with HIV infection.

Two studies focused on the impact of early treatment of neonates and infants. Ruhn (Abstract 27) presented data from the LEOPARD (Latency and Early Neonatal Provision of Antiretroviral Drugs) clinical trial, which is a nonrandomized trial of early neonatal diagnosis and rapid initiation of antiretroviral therapy. This analysis examined virologic response up to 48 weeks for 30 infants who were diagnosed with HIV infection at birth and initiated antiretroviral therapy within 48 hours of birth. There was wide variation in virologic response to treatment. Eight treated infants had persistently high plasma HIV-1 RNA levels, 6 had levels below limits of detection but then had rebound, and 13 had levels that declined to below limits of detection or target not detected of the assay. Three infants whose levels were below the limit of detection were HIV seronegative on HIV polymerase chain reaction (PCR) testing, and had rapid declines in plasma HIV-1 RNA after treatment initiation. Of 5 deaths in the cohort, all had plasma HIV-1 RNA levels above 100,000 copies/mL at birth. The investigators highlighted the many clinical and social challenges inherent in engaging and treating neonates, and will continue to follow the cohort to determine if reversion to PCR-negative status is a common phenomenon.

Veldsman and colleagues (Abstract 28) examined HIV-1 RNA and DNA acquired from PCR testing in 11 infants for whom treatment was initiated between 0 and 8 days of life, and found 10 of them had rapidly suppressed viral replication to below the limits of detection for most assays. This poses a diagnostic challenge for the detection of HIV persistence on antiretroviral therapy and to avoid misdiagnosis in uninfected infants.

**Challenges in Antiretroviral Treatment for Adults**

The “Modern ART” symposium, which concluded the conference, provided a data-driven overview of current challenges in antiretroviral treatment.

Arribas reviewed data on the potential for simplification of antiretroviral therapy (Abstract 148). The impact of archived resistance must be considered when switching from antiretroviral regimens that have a high genetic barrier to acquired drug resistance to regimens with a low barrier. However, in settings where individuals whose therapy has not previously failed and risk of archived resistance is low, simplification of regimens is possible. Duration of suppressive therapy may also affect the ability to switch to a simpler regimen. Higher rates of virologic failure and drug resistance were seen with switches from traditional protease inhibitor plus nRTI 3-drug regimens to protease inhibitor plus InSTI or protease inhibitor plus entry inhibitor 2-drug regimens. The only successful simplification trial, the GARDEL (Global AntiRetroviral Design Encompassing Lopinavir/r and Lamivudine vs LPV/r based standard therapy) study, showed equivalent rates of virologic response in those treated with lopinavir/ritonavir plus lamivudine 2-drug regimen and those treated with lopinavir/ritonavir plus 2 nRTIs. Similar challenges are seen in trials involving reductions in drug regimens in individuals who are virologically suppressed, and the only successful trials involve simplification of treatment to lamivudine plus a boosted protease inhibitor. Arribas noted that we do not truly understand the mechanism underlying the success of lamivudine plus a boosted protease inhibitor-based regimen. Newer simplification strategies with 2-drug regimens, including dolutegravir plus lamivudine or rilpivirine, show promising preliminary
results, and newer antiretroviral agents may provide more hope for monotherapy in the future.

Grinsztejn (Abstract 149) summarized requirements for an ideal antiretroviral treatment regimen to address the continuing global HIV epidemic. Improved regimens are needed for treatment of special populations with HIV infection, including those with tuberculosis coinfection, pregnant women, children, adolescents, those with acute infection, and older people. Encouraging improvements in regimen efficacy, safety, tolerability, and convenience raise the question of whether new antiretroviral regimens are needed. However, the rising prevalence of pretreatment drug resistance, described in Gupta’s talk (see below), as well as the need for improved treatments for special populations suggest that we need better treatment strategies and new drugs. The recent inclusion of dolutegravir into national treatment guidelines in Botswana, Brazil, Kenya, Nigeria, and Uganda signal upcoming changes in treatment access in low- and middle-income countries. But issues of global affordability of antiretroviral treatment will remain for countries like China, where generic antiretroviral drugs are less available.

Finally, Grinsztejn demonstrated the impact of nonmedical barriers on antiretroviral treatment uptake by showing unpublished data from Pozniak and Hill that demonstrate a strong correlation between a country’s global peace index score and the percentage of people in that country living with HIV infection on antiretroviral therapy. Even in the setting of newer, simplified, more tolerable, and affordable treatment options, the ideal regimen can only be delivered if structural barriers to treatment are addressed.

HIV Resistance

Increasing Prevalence of Drug Resistance Mutations in Low- and Middle-Income Countries

Gupta (Abstract 146) presented an overview of the impact of HIV-1 drug resistance in low- and middle-income countries, including unpublished data assessing the impact of pretreatment (transmitted) HIV drug resistance. Investigators assumed that current prevalence of pretreatment drug resistance is 10%, and modeling demonstrated that 16% of AIDS-related deaths, 9% of new infections, and 8% of antiretroviral treatment costs could be attributable to drug resistance. He reviewed the rising prevalence in sub-Saharan Africa of tenofovir resistance, now exceeding 50% in those whose tenofovir-based initial therapy failed. Data also show that 15% of individuals whose initial regimens with tenofovir failed also had thymidine analogue-associated mutations (TAMs), which suggest they may have had prior treatment unknown to their clinicians. Gupta advocates the use of the WHO early warning indicators for HIV-1 drug resistance and the need for routine surveillance for drug resistance, considering the increasing prevalence of pretreatment drug resistance in low- and middle-income countries. The following studies support this recommendation.

Pretreatment Drug Resistance

The Caribbean region has the second-highest HIV prevalence in the world but surveillance for drug resistance mutations in this area is limited. In an analysis of pretreatment drug resistance in Aruba (Abstract 504LB), 54% (n = 104) of all newly diagnosed persons had baseline resistance testing between 2010 and 2015 prior to antiretroviral therapy initiation. Rates of pretreatment drug resistance with any mutation among those tested was high at 33%, with prevalence of NNRTI mutations at 32%, all of which were K103N mutations. Prevalence of nRTI and protease inhibitor mutations was low (1.9% each). By 2015, prevalence of K103N was 45%. Phylogenetic analysis identified 4 clusters with K103N-associated resistance, 3 of which had epidemiologic links to neighboring countries. These results led to replacement of the WHO-recommended initial regimen of an NNRTI-based regimen with an INSTI-based regimen and reinforcement of the importance of baseline resistance testing.

From 2012 to 2016, pretreatment drug resistance among antiretroviral therapy–naive persons was evaluated in individuals recruited from 3 regions in Mexico (Tijuana, n = 668; Central Metropolitan Zone [CMZ], n = 1194; and Cancun n = 773) (Abstract 480). Pretreatment drug resistance varied by region with rates of 4.6% in Tijuana, 16.8% in the CMZ, and 15.0% in Cancun. The most widely used antiretroviral regimen in Mexico is efavirenz with tenofovir and emtricitabine. Pretreatment resistance to drugs in this regimen increased over time from 2.9% to 9.6% (P = .0045). K103N was the most frequent drug resistance mutation in CMZ (4.4%) and Cancun (4.2%) but not Tijuana (1.4%). However, pretreatment resistance to efavirenz increased in all 3 regions over time (P < .05). This study highlights the importance of regional surveillance of drug resistance mutations to accurately track the epidemic and tailor policy responses according to regional needs.

Pretreatment Drug Resistance and Effects on Viral Outcomes

Derache (Abstracts 43, 491) presented data on the prevalence and impact of pretreatment drug resistance on viral suppression in antiretroviral therapy–naive participants starting initial antiretroviral therapy in the ANRS 12249 TasP (Treatment as Prevention) study in KwaZulu-Natal, South Africa. In this cluster randomized trial of 1537 participants, prevalence of pretreatment drug resistance was 9% for the majority (>20% of the viral population) and 18% for the minority (>2% of the viral population) variants, with no difference in rates of
pretreatment drug resistance between those with recent versus chronic infection. A majority of those with pretreatment drug resistance had NNRTI mutations (73% and 61% of those with pretreatment drug resistance detected as minority and majority variants, respectively), most of which were K103N mutations. There were very low levels of nRTI mutations (mostly TAM and M184V) and even lower levels of protease inhibitor resistance mutations. Among individuals with pretreatment drug resistance, 78% had 1 resistance-associated mutation, 11% had 2, and 11% had 3 or more. Of the 837 individuals who initiated antiretroviral therapy for whom viral load outcome data were available, median time to viral suppression (HIV-1 RNA level < 50 copies/mL) was 3.61 months with a median duration of antiretroviral therapy of 1.36 years. There was a high cumulative probability of suppression by 12 months at 94.5% (95% CI, 92.7-96.0) and no difference in time to viral suppression or probability of viral suppression between those with and without pretreatment drug resistance, regardless of detection as majority or minority variants. In persons with pretreatment drug resistance, low baseline HIV-1 viral load and good adherence were predictors of viral suppression. The authors concluded that achievement and short-term durability of viral suppression despite the presence of pretreatment NNRTI resistance may be due to the ability of tenofovir with emtricitabine to suppress virus. However, the time period on antiretroviral therapy was relatively short at 18 months, and the possibility of viral breakthrough and perpetuation of pretreatment drug resistance warrants further investigation.

Drug Resistance Mutations in Antiretroviral Treatment–Naive and –Experienced Individuals

AFRICOS is a prospective cohort study of 253 adults in Uganda, Kenya, Tanzania, and Nigeria, between 2013 and 2015, who had baseline resistance testing. Participants were evaluated in a cross-sectional analysis of drug resistance mutations (Abstract 481). Seventy-four percent were antiretroviral therapy–naive and 26% were antiretroviral therapy–experienced. Prevalence of pretreatment resistance was 5% in antiretroviral therapy–naive individuals, with the majority due to K103N mutations (4.3%). In antiretroviral therapy–experienced individuals, there were high rates of resistance: 65% with NNRTI resistance, 45% with nRTI resistance, and 6% with protease inhibitor resistance. Rates of resistance with K103N and K65R mutations were 33.8% and 10.8%, respectively. There was regional variation in rates of resistance but the small sample size limits the ability to generalize findings to broader populations.

The first nationally representative study of pretreatment resistance in Cameroon was presented by Tchouwa and colleagues (Abstract 482). Participants were recruited between February 2015 and July 2015 from 24 clinics in randomly selected rural and urban regions. Of the 335 persons who had successful genotype testing, 10% had previous exposure to antiretroviral therapy. The overall rate of drug resistance mutations was 9.7%, with 13.3% in urban regions and 4.1% in rural regions. In antiretroviral therapy–naive individuals, the rate of pretreatment drug resistance was 9.8% with higher rates in urban areas (12.9%) than in rural (5.1%) areas. Ninety-three percent of major drug resistance mutations were NNRTI-associated mutations, which indicates that about 10% of individuals who start initial antiretroviral therapy in Cameroon are receiving 2 instead of 3 effective agents to treat HIV infection, increasing their risk for virologic failure and emergence of additional mutations.

Drug Resistance Mutations in Antiretroviral Therapy–Experienced Individuals

In a study of acquired HIV-1 drug resistance in Cameroon, participants who had been on antiretroviral therapy for 12 to 24 months (ADR1 group; n = 1065) or 48 to 60 months (ADR2 group; n = 391) were recruited between February and August 2015 (Abstract 486). Resistance testing was conducted on specimens from individuals who had an HIV viral load of 1000 copies/mL or higher. A majority of participants were on a regimen of efavirenz or nevirapine with tenofovir and lamivudine (80% of ADR1 and 73% of ADR2 participants) followed by efavirenz or nevirapine with zidovudine and lamivudine (17% of ADR1 and 20% of ADR2 participants) with only 2% of ADR1 and 6% of ADR2 participants on a protease inhibitor–based regimen. Viral suppression was 72% for ADR1 individuals and 67% for ADR2 individuals, and overall prevalence of drug resistance mutations was 10% and 12%, respectively. Prevalence of any resistance mutation in persons with virologic failure (HIV RNA level ≥1000 copies/mL) was 63% and 88%, and prevalence of NNRTI-related mutations was 62% and 88% in ADR1 and ADR2 persons, respectively. The authors noted that substantial efforts will be required to achieve the UNAIDS target of 90% viral suppression in Cameroon by 2020. Improved antiretroviral therapy management and retention in care are needed, along with preventing antiretroviral therapy shortages and increasing access to viral load testing to guide antiretroviral therapy selection.

A nationwide study of Kenyans with suspected secondary antiretroviral therapy failure was conducted to estimate the need for additional options (Abstract 488). Of the 123 participants who had a successful genotype performed, 96.7% were on secondary antiretroviral therapy (ritonavir-boosted lopinavir). Median duration of treatment was 6.4 years and median duration of secondary treatment was 3.1 years. Twenty-five percent of individuals had complete loss of drug activity to available initial (NNRTI-based) and secondary (boosted protease inhibitor-based) regimens. The authors concluded there is a need for routine viral load testing for timely detection of treatment failure and access to affordable additional regimens.

Effectiveness and Cost-Effectiveness of Policy Options Address High Prevalence of Drug Resistance

Phillips and colleagues (Oral Abstract 112) modeled the effectiveness and cost-effectiveness of policy options to address increasing rates of NNRTI-associated resistance in sub-Saharan
A modeling study based on the South African epidemic (Abstract 489) also found that switching to an initial dolutegravir-based regimen from an NNRTI-based one was more effective than the introduction of resistance testing. This study predicted that a switch to dolutegravir-based regimens as initial treatments would reduce the annual incidence of HIV infection by two-thirds and decrease transmitted drug resistance to less than 5% of new infections per year by 2030. The model predicts that introduction of resistance testing would also decrease annual HIV incidence by one-half and would increase K103N mutations, but to a lesser degree than current policy.

**Epidemiology of Drug Resistance Mutations in High-Income Countries**

**HIV InSTI Resistance.** Hernandez and colleagues (Abstract 478) conducted an analysis of InSTI resistance among individuals with baseline (collected ≤ 3 months after HIV diagnosis) and follow-up (collected > 3 months after HIV diagnosis) InSTI resistance testing. The individuals were diagnosed with HIV-1 infection between 2010 and 2014 and reported to the US National HIV Surveillance System (NHSS). In a convenience sample of 9 jurisdictions, 14,468 met inclusion criteria. InSTI-associated resistance was rare with an overall prevalence sample of 9 jurisdictions, 14,468 met inclusion criteria. InSTI-associated resistance was rare with an overall prevalence of 0.4% and a baseline prevalence of 0.04%. The most prevalent InSTI-associated mutations were N155H (38%), E92Q (29%), and G140S (25%). These data show that current InSTI-based regimens are effective, and the authors recommend ongoing monitoring of resistance testing and drug resistance mutations at the population level.

A decline in prevalence of drug resistance mutations was noted among 3681 antiretroviral-experienced participants enrolled in the University of North Carolina Center for AIDS Research Clinical cohort between 2000 and 2015 (Abstract 483). Prevalence and trends of drug resistance mutations from 2000 to 2015 were calculated. Resistance to any drug class and to 2 or more drug classes increased as did NNRTI and NNRTI resistance between 2000 and 2005 but subsequently decreased. Protease inhibitor resistance and resistance to 3 or more drug classes remained stable between 2000 and 2005 but subsequently decreased, and InSTI resistance increased slightly between 2009 and 2015. For those initiating antiretroviral therapy between 2007 and 2015, prevalence of resistance to any drug class, NNRTI, nRTI, protease inhibitor, or InSTI was 21%, 17%, 6%, 2%, and 1%, respectively.

Koulias and colleagues (Abstract 493) conducted a cost-effectiveness analysis for baseline InSTI resistance testing for persons living in high-income settings. Using a decision-tree model of antiretroviral therapy-naive persons who presented for baseline laboratory testing, input parameters included antiretroviral therapy efficacy, quality of life, and costs of laboratory tests and treatment. Costs of the InSTI test ($250/test), dolutegravir-based antiretroviral therapy ($38,150/year), and boosted darunavir-based antiretroviral therapy ($44,400/year) were included. An incremental cost-effectiveness ratio of less than $100,000 per quality-adjusted life year (QALY) was considered cost-effective. In univariate sensitivity analysis, testing for InSTI resistance at baseline was never clinically preferred regardless of InSTI resistance prevalence, even up to 100% prevalence. In multivariate sensitivity analysis with the prevalence of an InSTI pretreatment drug resistance of 0.1%, baseline testing for InSTI resistance also resulted in equivalent or worse clinical outcomes and at a higher cost than no InSTI resistance testing even at high rates of dolutegravir failure with InSTI resistance (<17% suppression). These data do not support baseline InSTI resistance testing.

**Protease Inhibitor Resistance.** An analysis of participants who had completed a phase II or III clinical trial in which they received once-daily boosted darunavir showed that emergence of resistance was rare (Abstract 505). Among a total of 1686 participants, 11% (n = 184) had protocol-defined virologic failure and 182 had genotype testing for resistance at the time of failure. Only 4 of these participants had treatment-emergent protease inhibitor resistance and/or darunavir resistance-associated mutations, and only 1 lost phenotypic susceptibility to darunavir. Among 264 subjects treated with darunavir monotherapy, 34 were evaluated for resistance and only 1 had darunavir resistance mutations during treatment (L33F mutation). This study confirms the high genetic barrier to resistance of once-daily boosted darunavir.

**In the United States, rates of InSTI resistance are low and the test for pretreatment drug resistance is not cost-effective.**
Evolution of Resistance and Novel Resistance Mutations

Dolutegravir Monotherapy. Blanco presented a retrospective analysis of virologic outcomes in persons switched from multidrug antiretroviral therapy to dolutegravir monotherapy (Abstract 42). The 122 individuals analyzed were enrolled in 1 of 3 large international cohorts (MVZ Karlsplatz, Munich, Germany; Clinique Medica Actuel, Montreal, Canada; Hospital Clinic, Barcelona, Spain), had suppressed HIV-1 RNA (<50 copies/mL) at the time of switch, and had no preexisting InSTI resistance mutations. Eleven (9%) experienced virologic failure (2 consecutive HIV-1 viral loads >50 copies/mL), of whom 9 (82%) had InSTI resistance mutations. Median time to virologic failure was 20 weeks (interquartile range [IQR], 11-28 weeks) and median time from virologic failure to emergence of InSTI resistance was 5 weeks (IQR, 3-14 weeks). In the 9 participants who experienced virologic failure on dolutegravir monotherapy, resistance patterns and pathways varied. This study, in addition to a randomized trial of dolutegravir monotherapy (Abstract 451LB), confirms that dolutegravir monotherapy is not to be recommended.

Development of Dolutegravir Resistance in an Adherent Antiretroviral Therapy–Naive Individual. Flucher and colleagues (Abstract 500LB) presented a case report of a 45-year-old man newly diagnosed with HIV infection and Pneumocystis jirovecii pneumonia with a high baseline viral load (1,970,000 copies/mL) and no clinically significant NNRTI or nRTI resistance mutations. Pretreatment InSTI resistance testing was not conducted. He was started on dolutegravir and tenofovir with emtricitabine and despite excellent adherence, developed virologic failure with rapid evolution of InSTI resistance culminating in a Q148K mutation (preceded by G163E, I151V, and I151M mutations). The emergence of resistance mutations was identified through sequential paired and deep sequencing analysis at 3 time points over the course of 8 days. This is the first report of dolutegravir resistance in a treatment-naive individual and indicates this is a rare but clearly important clinical phenomenon.

 Archived Quasispecies with InSTI Resistance. In an interesting study of archived HIV quasispecies in individuals successfully treated with a dolutegravir-based regimen, emerging resistance mutations to dolutegravir were documented in the proviral DNA of persons despite successful viral suppression (Abstract 495). Four treatment groups were evaluated: antiretroviral therapy–naive persons initiating dolutegravir-based regimens with primary HIV infection (group 1), or chronic HIV infection (group 2), and individuals on non–dolutegravir-based antiretroviral therapy who transitioned to a dolutegravir-based regimen in the setting of viral suppression (group 3) or as a result of virologic failure (group 4). Peripheral blood mononuclear cells (PBMCs) were collected at baseline and at weeks 4, 24, and 48, and proviral DNA was analyzed for integrase gene mutations. Despite achievement or maintenance of HIV-1 RNA levels below 50 copies/mL between weeks 4 and 48, InSTI mutations that were not present at baseline emerged in the proviral DNA in 5 of the 20 participants. These mutations included R263K and M50I, which are associated with resistance to dolutegravir and bictegravir. Viral diversity also transiently decreased even in individuals who were virally suppressed for more than a decade on other treatment regimens. The results suggest that archived quasispecies continue to evolve with antiretroviral therapy. The authors have several hypotheses regarding the results: new variants were selected directly in the blood compartment through residual replication in the setting of antiretroviral therapy; the variants were not new but might preexist at very low levels; and variants were selected at very low levels in other reservoirs because of insufficient antiretroviral penetration in those compartments.

 Novel InSTI Resistance Mutations. Hachiya and colleagues (Abstract 496) identified a novel combination InSTI mutation, L74F/V75I, which conferred resistance to first-generation InSTIs and enhanced resistance to second-generation InSTIs, when combined with a major InSTI mutation. The researchers obtained clinical HIV-1 isolates from an individual whose raltegravir-based regimen had failed and who had no InSTI resistance mutations on standard InSTI genotype testing. Sequencing of the integrase region of the clinical isolates identified clinically suspected resistance mutations (L74F, V75I, I60M, and V72I). These mutations were introduced into the integrase region of an HIV-1 DNA clone and drug susceptibility assays were conducted on the recombinant virus. The combination of L74F/V75I increased resistance to raltegravir and elvitegravir; the combination of L74F/V75I with N155H and G140S/148H enhanced resistance to dolutegravir and cabotegravir. The location of the L74 and V75 residues suggest an indirect structural impact of L74F/V75I on the catalytic center of integrase. The authors concluded that these insights help explain the superior resistance profiles of second-generation InSTIs and provide additional data to guide design of future InSTIs.

 Malet and colleagues (Abstract 499) also identified novel InSTI resistance mutations that are located outside of the integrase gene. A virus highly resistant to dolutegravir was selected in vitro by adding high constant concentration of dolutegravir after virus integration. Sequence analysis of this virus showed no mutation in the integrase gene but 5 mutations in the nef region. In drug susceptibility assays, these mutations conferred high resistance to dolutegravir, raltegravir, and elvitegravir. The mechanism through which these mutations cause resistance is unclear.

 Novel Tenofovir Resistance Mutations in Low- and Middle-Income Settings. The use of TDF in low- and middle-income countries is increasing but data on TDF-associated drug
resistance mutations associated with nRTI failure in these settings is limited. Rhee and colleagues (Abstract 485) identified TDF regimen–associated mutations (TRAMs) by comparing the proportion of reverse transcriptase mutations in 2873 persons from low- and middle-income settings failing a WHO-recommended initial TDF-containing regimen to the proportion of reverse transcriptase mutations in a cohort of 50,803 antiretroviral therapy-naive individuals. To identify TRAMs specifically associated with TDF selection pressure, the proportion of TRAMs in persons whose TDF-containing regimen failed was compared with the proportion of these mutations found in 5085 persons with virologic failure on an initial thymidine analogue regimen. A total of 83 TRAMs were identified including 33 nRTI-associated TRAMs, 15 of which were more common in individuals receiving TDF than thymidine analogue-containing regimens. The most common of the TDF-associated mutations were K65R (40%), S68G/N (21%), Y115F (12%), K70E/Q/T (11%), A62V (10%), and L74I (6%). Given the expansion of TDF use in these settings, the frequency of these novel TDF-associated mutations should be monitored and further evaluated to determine which may be clinically significant.

Protease Inhibitor Resistance. It has been hypothesized that mutations in the HIV-1 gag matrix or the cytoplasmic domain of gp41 reduce susceptibility to protease inhibitors but these mutations have not been consistently identified in individuals on boosted protease inhibitors with virologic failure. Manasa and colleagues (Abstract 506) evaluated whether these mutations would emerge in individuals whose boosted protease inhibitor regimens failed. The entire gag and gp41 regions were sequenced in individuals before and after boosted protease inhibitor treatment failure, and gag and gp41 sequence changes were compared with changes in a control group who failed an NNRTI-based regimen. The researchers found many mutations in the gag matrix and gp41, but no discernable difference in the mutations between the protease inhibitor and NNRTI groups.

Drug Resistance Mutations in Investigational Antiretroviral Drugs

Dapivirine, rilpivirine, and MIV-150 (a phenyl ethyl thiazole thiourea analogue) are being evaluated as agents in pre-exposure prophylaxis (PrEP). To characterize the resistance and cross-resistance profiles of these drugs, Giacobbi and colleagues (Abstract 501) studied their in vitro susceptibility to NNRTI resistance mutations spanning 17 codons. Rilpivirine had the best profile with activity against 19 of the 28 variants. Dapivirine and MIV-150 were each active against 15 of the 28 variants. Drug susceptibility with the G190A mutation was unchanged for all 3 agents and rilpivirine showed no resistance with K103N and Y181C mutations and low-level resistance associated with K101E. Dapivirine and MIV-150, however, exhibited decreased susceptibility with K101E, Y181C, and K103N mutations. MIV-150 exhibited high resistance with K103N and intermediate resistance with Y181C. Future studies should evaluate the clinical impact these mutations have on the efficacy of these drugs for PrEP and their use in settings with a high prevalence of NNRTI resistance.

Bictegravir is an investigational INSTI that has excellent efficacy and tolerability in clinical trials. Ragoneet-Cronin compared drug resistance susceptibility and dissociation kinetics of bictegravir with that of other INSTIs in the presence of G140S/Q148H resistance mutations (Abstract 497). In vitro phenotype testing showed bictegravir had better activity against G140S/Q148H mutants than dolutegravir, raltegravir, and elvitegravir. Bictegravir also had a longer dissociation half-life from wild-type complexes than dolutegravir, raltegravir, and elvitegravir and a longer disassociation half-life from G140S/Q148H mutant complexes than dolutegravir only (raltegravir and elvitegravir did not bind efficiently enough to make a comparison). Long dissociation times have been correlated with potent antiretroviral activity and a high barrier to resistance. These findings support the promising in vitro and clinical trial data that bictegravir has demonstrated thus far.

Prevention of Mother-to-Child Transmission

Through programs such as “Option B+” and “Treat All,” access to antiretroviral therapy has greatly expanded for HIV-infected women prior to pregnancy. In utero exposure from conception to 3-drug antiretroviral therapy, however, has an increased risk of adverse birth outcomes. It is unclear whether these outcomes vary by antiretroviral regimen. Zash and colleagues described 2-year interim results from the Tsepano study in Botswana that compared rates of adverse birth outcomes by exposure from conception to the 5 most common antiretroviral regimens (Abstract 25). Data were extracted from all consecutive births of infants (at least 24 months gestational age) at 8 maternity wards in Botswana. The analysis included 5780 births from 2014 to 2016 that had exposure to antiretroviral therapy from conception. The most common regimens were TDF, emtricitabine, and efavirenz (45%); TDF, emtricitabine, and nevirapine (13%); zidovudine, lamivudine, nevirapine (24%); TDF, emtricitabine, and ritonavir-boosted lopinavir (4%); and zidovudine, lamivudine, and ritonavir-boosted lopinavir (3%). Outcomes included stillbirth, neonatal death (defined as in-hospital mortality <28 days), preterm birth (<37 weeks gestational age), very preterm birth (<32 weeks gestational age), small for gestational age (<10th percentile weight), and very small for gestational age (<5th percentile weight). The combined endpoint of any adverse birth outcome was defined as having stillbirth, neonatal death, preterm birth, or small for gestational age, whereas severe birth outcome was defined as having stillbirth, neonatal death, very preterm birth, or very small for gestational age. After adjusting for maternal age, educational level, and gravidity, exposure to TDF/emtricitabine/efavirenz had a lower adjusted risk ratio of combined total and severe adverse birth outcomes than the 4 other regimens. When added to the model, CD4+ cell count did not attenuate the findings. The authors recommended further investigation into mechanisms...
to explain high rates of adverse birth outcomes associated with specific antiretroviral regimens.

The pharmacokinetics and safety of antiretroviral drugs and monoclonal antibodies for perinatal mother-to-child transmission (MTCT) of HIV infection were covered in a themed poster session. Schalkwijk and colleagues (Abstract 753) simulated fetal exposure of darunavir/ritonavir at term by incorporating bidirectional placental antiretroviral transfer in a previously validated physiologically-based pharmacokinetic (p-PBPK) model of pregnancy. Placental drug transfer parameters were based on an ex vivo, human cotyledon perfusion model. The simulated fetal darunavir plasma concentrations were within the range of observed cord blood concentrations of the drug in vivo. The authors concluded that these findings support the use of this model for evaluating implications of new drug dosing schedules and enhancing maternal and fetal antiretroviral treatment strategies.

Schalkwijk and colleagues presented pharmacokinetic data of rilpivirine used during pregnancy from an open-label multicenter phase IV study of antiretroviral agents in HIV-1-infected pregnant women in Europe (PANNA [Pharmacokinetics of newly developed Antiretroviral agents in HIV-infected pregNant women] Network) (Abstract 754). In this study, 16 women received rilpivirine 25 mg once daily (taken with food) as part of their antiretroviral regimen during pregnancy. The women also underwent intensive, steady-state, 24-hour pharmacokinetic testing in the third trimester and postpartum periods. In addition, whenever possible, cord blood and matching maternal blood specimens obtained at delivery were used to measure placental transfer of rilpivirine. Maternal HIV viral load was undetectable (<50 copies/mL) near the time of delivery in all 16 women. HIV infection was not detected based on DNA PCR in 15 of 16 (96%) infants, with 1 infant’s infection being unknown. There were no reports of birth defects or serious adverse events attributable to rilpivirine. The geometric mean ratios (90% CI) for third trimester and postpartum were as follows: 0.55 (0.46-0.66) for AUC at 24 hours (AUC_{24}), 0.65 (0.55-0.76) for maximum plasma concentration (C_{max}), and 0.47 (0.38-0.58) for predose concentration (C_{pd}). Subtherapeutic C_{min} levels in the third trimester, defined as 0.04 mg/L or less, were found in 2 women, whereas no subtherapeutic levels were detected postpartum. Among 5 individuals with available data, the median (range) ratio of cord blood to maternal plasma rilpivirine concentrations was 0.5 (0.55-0.81). Based on these results, the authors recommended therapeutic drug monitoring in the third trimester to avoid subtherapeutic levels of rilpivirine.

Best and colleagues presented pharmacokinetic data of elvitegravir/cobicistat in pregnancy and postpartum (Abstract 755) from the ongoing IMPAACT (International Maternal Pediatric Adolescent AIDS Clinical Trials Network) P1026s pharmacokinetics and safety study of antiretroviral drugs in HIV-infected pregnant women. The study collected intensive, steady-state, 24-hour pharmacokinetic profiles of elvitegravir and cobicistat dosed at 150 mg and 150 mg once daily, respectively, during the second and third trimesters of pregnancy and 6 weeks to 12 weeks postpartum. In addition, infant washout samples after delivery were examined in infants with birth weight of more than 1000 grams who had no severe malformations or medical conditions. A total of 29 women were enrolled, with pharmacokinetic data available for 16 women in the second trimester, 20 women in the third trimester, and 15 women in the postpartum period. Washout sample data were available for 16 infants. HIV RNA level was undetectable (<50 copies/mL) for 14 of 19 women (74%); 20 of 26 infants (77%) tested HIV seronegative with data for 6 infants indeterminate or pending to date. Two infants experienced congenital malformations (1 with microcephaly, amniotic band syndrome, and intrauterine growth restriction, and 1 with ulnar postaxial polydactyly). The researchers found lower exposure and higher clearance of elvitegravir and cobicistat in the second and third trimesters than in the postpartum period. In infants, the median IQR for half-life of elvitegravir was 7.4 hours (5.9-8.8), similar to that in postpartum women and control groups of nonpregnant adults. Cobicistat was not detected in any of the infant washout samples. The authors cautioned that more pharmacokinetic, safety, and outcome data of elvitegravir and cobicistat in HIV-infected pregnant women are needed before its use during pregnancy can be endorsed.

Balogun and colleagues examined the effect of protease inhibitor–based antiretroviral therapy on estradiol (E2) levels in pregnancy and whether E2 levels are associated with adverse birth outcomes (Abstract 756). In a prospective cohort study of 96 HIV-infected pregnant women in Canada, plasma samples at early (12 weeks-18 weeks), mid (24 weeks-28 weeks), and late (34 weeks-38 weeks) gestation were collected from the following groups: 55 women on protease inhibitor–based antiretroviral therapy; 8 women on protease inhibitor–sparing regimens; and a matched control group of 49 women who were HIV-uninfected.

Maternal and cord plasma specimens were collected. In addition to E2, sex hormone binding globulin (SHBG), and dehydroepiandrosterone sulfate (DHEAS), an E2 precursor) were measured. The researchers found a significant increase in E2 plasma levels from mid to late gestation and at delivery in the women on protease inhibitor–based antiretroviral therapy. This association was not detected in women on protease inhibitor–sparing regimens or in the control group. Similarly, cord E2, DHEAS, and index levels of E2 and SHBG were significantly higher in women on protease inhibitor–based antiretroviral therapy than in the matched uninfected controls. Furthermore, E2 and DHEAS levels in cord plasma were positively correlated (r = 0.06; P < .0001) in women on protease inhibitor–based antiretroviral therapy. An inverse correlation between cord E2 levels and fetal growth restriction (measured by birth weight percentile) was found in women on protease inhibitor–based antiretroviral therapy (r = −0.47); this association was not detected in women with protease inhibitor–sparing regimens and in women in the control group.

Clarke and colleagues presented a dose-finding, pharmacokinetic, and safety study of raltegravir in HIV-1-exposed neonates during the first 6 weeks of life (Abstract 757). Twenty-six HIV-1–exposed neonates were enrolled in cohort 2 in the IMPAACT P1110 study. They were naive to raltegravir.
and received the following dosing regimen: 1.5 mg/kg daily within 48 hours of life through day 7, followed by 3 mg/kg twice daily on days 8 to 28, and 6 mg/kg twice daily thereafter. Pharmacokinetic and 6-week safety data were available for analysis for 25 infants. Following the first dose at 1.5 mg/kg daily, the geometric mean (GM) AUC_{24} for raltegravir was 38.2 mg*h/L, and the trough concentration (C_{trough}) was 948 ng/mL (target trough > 33 ng/mL). During treatment with 3 mg/kg of raltegravir twice daily during days 15 to 18, the GM AUC_{12} at 12 hours (AUC_{12}) was 14.3 mg*h/L and C_{trough} was 176.1 ng/mL. There were no reports of adverse events related to raltegravir and no infants were found to be HIV-infected. The researchers concluded that daily treatment with raltegravir was safe and well tolerated through the first 6 weeks of life, and that the data support the raltegravir dosing schedule outlined in the study in infants.

Bekker and colleagues presented pharmacokinetic and safety data of nevirapine prophylaxis in 40 HIV-exposed infants with low birth weight (<2500 g) in South Africa as part of the IMPAACT P1106 study (Abstract 758). The infants received nevirapine 2 mg/kg once daily from birth to 14 days of age, followed by 4 mg/kg once daily. Mean birth weight was 1675 g (range, 950 g-2460 g). Pharmacokinetic samples were collected at study enrollment and at 4, 6, 10, 16, and 24 weeks of age. Of 27 infants with available nevirapine C_{trough} levels (representing 94 observations), mean C_{trough} of nevirapine across all study visits was 1.87 µg/mL (range, <0.02-10.69 nevirapine g/mL). In 6/94 (6%) observations, nevirapine trough concentrations were below 0.1 µg/mL, which is the target prophylaxis C_{trough}. All samples below target levels were from later visits when the infants had been discharged to home and were receiving nevirapine from a caregiver. At the first visit, higher C_{trough} of nevirapine was associated with lower gestational age (r = −0.47; P = .02), whereas subsequent drug concentrations over the study period decreased with increasing postnatal age across all visits (r = −0.45; P < .001). No adverse events were attributable to nevirapine.

Anugulruengkitt and colleagues examined safety and drug concentrations in 94 high-risk HIV-exposed neonates receiving antiretroviral prophylaxis with zidovudine/lamivudine/nevirapine for 6 weeks after birth in a prospective cohort study in Thailand (Abstract 759). Thirty-one neonates received zidovudine and lamivudine twice daily for 6 weeks, and nevirapine 4 mg/kg once daily for 6 weeks. This group of 31 infants was compared with 63 infants who received zidovudine for 4 weeks. The investigators found no significant difference in rates of adverse events, anemia, neutropenia, and elevations in transaminase levels between the 2 groups. All infants were HIV-uninfected at age 4 months. Of 18 infants with available data, high plasma concentrations of nevirapine were achieved at weeks 1, 2, and 4 (GM concentrations of 3075, 2109, and 1458 ng/mL, respectively); all infants achieved nevirapine concentrations above 100 ng/mL during the first 4 weeks.

Cunningham and colleagues reported the safety and pharmacokinetic results of VRC01, an HIV-neutralizing monoclonal antibody, in 27 HIV-exposed newborns (Abstract 760). In the ongoing, prospective, multicenter, open-label study, 27 HIV-exposed infants at high risk of HIV transmission received a single 20 mg/kg (low dose) or 40 mg/kg (high dose) subcutaneous dose of VRC01 (13 in the low-dose group vs 14 in the high-dose group) within 72 hours of birth. All infants also received antiretroviral prophylaxis to prevent MTCT according to local standard-of-care guidelines. Safety data were presented for 27 infants, whereas pharmacokinetic data were presented for 13 of the 14 infants in the high-dose group and 12 of the 13 infants in the low-dose group. VRC01 was well tolerated with no serious systemic reactions. Local reactions (ie, erythema, induration, bruising, edema) were present in 6 infants (46%) in the low-dose group and 11 infants (75%) in the high-dose group; the local reactions were not considered serious and most resolved within 4 hours of injection. The pharmacokinetic data for the low-dose group showed circulating VRC01 through day 28 that was close to but below the target in 9 of the 12 infants (75%). Mean concentration after 28 days (C_{28d}) in infants receiving the 20 mg/kg dose was 39.33 mcg/mL, whereas mean C_{28d} in infants receiving the 40 mg/kg dose was 75.22 mcg/mL. The mean half-life of VRC01 at the 20 mg/kg dose was 19.73 days. The authors concluded that the half-life of VRC01 allows for administration on a monthly basis for infants who are at risk for HIV transmission through breastfeeding.

**Zika Virus**

The outbreak of Zika virus in 2015 to 2016 prompted a themed discussion that featured presentations on the persistence of Zika RNA in bodily fluids, a promising novel messenger RNA (mRNA) Zika vaccine, an animal model of neurologic consequences of Zika virus, and laboratory testing patterns for the virus in the United States (Abstracts 1054, 1055LB, 1056LB, 1057LB). (A summary of the presentation of Zika RNA in bodily fluids [Abstract 1055LB] appears in the "Basic Science Review" by Dr Stephenson.)

Hogan and colleagues presented data on a novel Zika virus vaccine using an mRNA platform (Abstract 1057LB). The researchers have developed a nucleoside-modified, purified mRNA-lipid nanoparticle (LNP) vaccine that encodes for Zika surface proteins and efficiently elicits neutralizing antibody responses. A single low-dose immunization in mice and rhesus macaques delivered high and sustained neutralizing antibody responses and complete protection from Zika virus weeks to months after vaccination. This is a promising vaccine candidate as it appears to require only a single, low-dose immunization. The mRNA-LNP platform has a favorable safety profile and lends itself to manufacturing scalability and rapid vaccine development for diverse pathogens.
Mavigner and colleagues (Abstract 1056LB) discussed the neurologic changes in the brain and spinal cord in rhesus macaques that were postnatally infected with Zika virus. Questions remain concerning the effects of Zika infection during infancy. Viral loads in the plasma and tissues (including spleen, lymph nodes, brain, and spinal cord) were measured by quantitative polymerase chain reaction (qPCR). The animals also underwent neuroimaging including structural T1-weighted magnetic resonance imaging (MRI), resting-state functional connectivity (rs-fc) MRI, and diffusion tensor imaging (DTI). Zika virus was not detected in the urine, saliva, or cerebrospinal fluid (CSF) of these animals postmortem. In 33% of animals, Zika RNA was detected within the brain (frontal, parietal, and occipital cortices) and the spinal cord (cauda equina). Neuroimaging also showed changes with brain atrophy, decreases in rs-fc, and abnormal white matter connections using DTI. These results suggest that postnatal Zika infection can cross the blood brain barrier into the central nervous system and cause both structural and functional changes.

Volpe and colleagues (Abstract 1054) presented an analysis of 11,129 Zika virus test results obtained in the United States from June 2016 to September 2016. Ninety-four percent of nucleic acid tests were negative, 3% were positive, and 3% were discordant between urine and serum. Not surprisingly, there was significant regional variation in testing, with 48% of tests coming from Florida with a positivity rate of 2%. Montana and Rhode Island sent only 1 test each during that time and had a positivity rate of 100%.

All cited abstracts appear in the CROI 2017 Abstracts eBook, available online at www.CROIconference.org

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Additional Suggested Readings

**UPCOMING ACTIVITIES**

**Summer and Fall 2017**

**Interactive Webinars With IAS–USA Faculty**

*Live, interactive continuing medical education (CME) in the comfort of your home or office, free of charge. Participants can ask questions and receive responses in real time. Visit the IAS–USA website for more on past and upcoming webinars. Upcoming webinars include:*

- **Contemporary Issues in Antiretroviral Therapy**—June 20, 2017
  Presenter: Joel E. Gallant, MD, MPH, Southwest CARE Center

- **Next-Generation Regimens for Hepatitis C Virus Infection: Regimens and Their Role in the Clinic**—June 29, 2017
  Presenter: Susanna Naggie, MD, MHS, Duke University

- **HIV: The Core Principles, Pathogenesis, and Treatment of HIV Infection**—July 27, 2017
  Presenters: Michael S. Saag, MD, University of Alabama; David H. Spach, MD, University of Washington

- **Update from the 9th IAS Conference on HIV Science**—August 3, 2017
  Presenter: Paul E. Sax, MD, Harvard Medical School

- **Finding and Eliminating the HIV Reservoir**—September 7, 2017
  Presenter: Daniel C. Douek, MD, PhD, National Institutes of Health

- **Practical Management Approaches for Transgender Patients at Risk for HIV Infection**—October 24, 2017
  Presenter: Tonia C. Poteat, PhD, PA, The Johns Hopkins University

- **Sexually Transmitted Infections and HIV Disease**—October 26, 2017
  Presenter: Dana W. Dunne, MD

**Cases on the Web**

*A series of web-based, case-driven CME activities, created to offer convenient online access to top-quality professional education. Visit the IAS–USA website for more information. Here’s the latest:*

**New**

**Initial Antiretroviral Therapy in the HIV-Infected Patient**

Authors: Jameela J. Yusuff, MD, MPH, FACP, State University of New York; Katharine Kuntz, MD, State University of New York. Released March 6, 2017.

**Coming Soon**

**Immunizations for HIV-Infected Persons**

Authors: Brian T. Montague, DO, MS, MPH, University of Colorado; Steven C. Johnson, MD, University of Colorado

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Dates above may be subject to change. IAS–USA announcements are paperless, so please watch for e-mail updates or visit www.iasusa.org for course information, agendas, and online registration, or to access archives of educational resources from past activities. These activities have been approved for AMA PRA Category 1 Credit™.

The American Board of Internal Medicine (ABIM) Maintenance of Certification (MOC) program will offer points to participants at live IAS–USA activities in 2017.
The brain is a major target for HIV infection and is a potential viral reservoir even in virologically well-controlled HIV-infected individuals. Data presented at the 2017 Conference on Retroviruses and Opportunistic Infections (CROI) suggested that during early HIV infection, CD4+ T cells in the meninges and choroid plexus serve as an important early site of HIV infection in the central nervous system (CNS), with brain macrophages and microglial cells becoming an important source of viral replication with advancing disease. Longitudinal evaluations of HIV-associated neurocognitive disorder (HAND) demonstrated that cognitive changes occur during early HIV infection and may remain during chronic infection despite virologic control by antiretroviral therapy. Cognitive changes assessed by neuropsychological performance, neuroimaging, cognition, neuropathogenesis, reservoir, stroke, cerebrospinal fluid (CSF) in virologically well-controlled HIV-infected individuals. Data presented at CROI 2017 suggested that during early HIV infection, HIV in the CNS and persistent neurologic dysfunction (as assessed by neuropsychological performance, neuroimaging, and cerebrospinal fluid [CSF]) in virologically well-controlled HIV-infected individuals.

**HIV Neuropathogenesis Using Animal Models**

Animal models of CNS HIV infections potentially afford insight into processes that occur in inaccessible brain tissues during human HIV infection. Mallard and colleagues (Abstract 69) quantitated T lymphocytes and monocytes, and examined viral RNA and phylogenetic relationships between sequences of simian immunodeficiency virus (SIV) in brain parenchyma, CSF, and choroid plexus of 16 SIVmac251-infected and 2 uninfected rhesus macaques (half of these animals were also CD8+ lymphocyte depleted). SIV RNA was detected in CD4+ T lymphocytes and in monocytes/macrophages in the choroid plexus. In animals that developed SIV encephalitis, numbers of monocytes/macrophages were increased in the choroid plexus, and highly compartmentalized SIV was detected in the choroid plexus and brain. The phylogeny of CSF viral sequences included sequences consistent with those from peripheral blood, brain parenchyma, and choroid plexus, indicating mixed systemic and CNS sources of CSF SIV.

Vasan and colleagues (Abstract 70) examined early CNS inflammation and infection in a simian human immunodeficiency virus (SHIV) rhesus macaque model of HIV infection that closely recapitulates human acute and early HIV infection. After 12 weeks of SHIV infection, T cells infiltrated the brain parenchyma, CD4+ T-cell collections surrounded the meninges, and rare SHIV RNA-positive cells were seen in the meninges and brain parenchyma. Demonstration of these processes in a nonaccelerated SHIV infection helps to elucidate the processes that might be occurring in the brains of humans during the natural course of HIV infection, and provides a potential model for understanding CNS reservoirs, neuropathogenesis, and impact of treatment or other interventions at a histological level.

Carryl and colleagues conducted a study of pediatric neurodevelopment in a perinatal SIV infection model (Abstract 373). Investigators infected infant rhesus macaques with SIVmac251 intravenously (IV) on postnatal day 3 (n = 3) or orally at week 9 (n = 15) and compared postmortem (week 6 for IV infection and week 10 for oral infection) pathology with that seen in uninfected control groups at their demise at 22 weeks. Hippocampal neuron loss was found in CA 1 and CA 2 neuronal layers in both groups of SIV-infected macaques compared with the control group, independent of plasma...
viral load. These studies may provide histologic correlates of the cognitive impairment associated with untreated perinatal HIV infection.

**HIV Compartmentalization and Reservoirs in the CNS**

Studies of HIV replication and compartmentalization in the CNS in untreated HIV-infected individuals have implications for understanding pathogenesis of HIV-related CNS injury and potential establishment of tissue reservoirs for HIV. Although HIV replication in the CNS, reflected as detectable CSF HIV RNA, is a ubiquitous feature of untreated HIV infection, CSF HIV RNA is typically 1 log lower than that in plasma in chronic infection. In an examination of paired CSF and plasma samples from 155 prospectively enrolled, antiretroviral-naive study participants in Milan, Italy, Bai and colleagues (Abstract 357) detected greater HIV RNA level in CSF than plasma in 24 (15%) participants. In a multivariate analysis, a CSF:plasma HIV RNA ratio greater than 1 was independently associated with a 5-fold higher risk of HIV-associated neurocognitive disorder. This finding supports a pathogenetic relationship between enhanced viral replication in the CNS and CNS injury resulting in clinical neurologic disease, although the causes of heightened CSF HIV RNA in these individuals are unclear. It remains unknown if some individuals have a virus that is more tropic for the brain.

Genetic compartmentalization of CSF HIV also reflects enhanced local CNS replication of HIV with emergence of unique genetic variants within the CNS and a restriction of viral migration between compartments. Deep sequencing, which can detect less frequent (minor) variants within a diverse viral population, was employed in several studies to dissect compartmentalization comparing HIV RNA obtained from the CNS with that from blood. CNS compartmentalization has been previously documented in chronic subtype B and C HIV infection. Adewumi and colleagues (Abstract 369) used traditional single genome amplification with phylogenetic analysis and deep sequencing of paired CSF and blood HIV RNA to demonstrate CNS viral compartmentalization in subtype G and CRF02_AG. These findings suggest that neuropathogenesis may involve local HIV replication with compartmentalized viral evolution occurring in common HIV subtypes in sub-Saharan Africa.

Targeted deep sequencing methods (Sirijatupat and colleagues, Abstract 71) were also used to examine CSF for compartmentalization of subtype CRF01_AE HIV in acute infection in humans. Initial HIV disseminating to the CNS was examined with targeted deep sequencing of protease and reverse transcriptase (RT) genes in HIV derived from paired CSF and plasma samples in 13 participants. In 1 participant at an estimated 19 days postinfection, HIV variants that were present as minor variants (15%-23%) in the blood plasma were present at frequencies more than twice as high in CSF (42%-50%). This is the first indication that enrichment or a sequestration of HIV variants may occur with initial dissemination of transmitted founder viruses to the CNS in acute infection, although its relevance for subsequent development of compartmentalized CNS reservoirs is uncertain.

To assess the clinical relevance of compartmentalization, Price and colleagues (Abstract 364) used deep sequencing of env to investigate the relationship between viral compartmentalization and neurologic injury. They generated sequences from 33 paired CSF and blood plasma samples from individuals with untreated chronic HIV infection, determining the presence and phylogenetic patterns of CNS compartmentalization and relating these to levels of CSF neurofilament light chain (NFL), a cytoskeletal protein marker released in response to damage to myelinated axons. Although HIV-associated dementia (HAD) was associated with elevated NFL level and major (>30%) CSF env compartmentalization, major compartmentalization was also observed in individuals with CD4+ cell counts 200/µL or less and normal NFL levels (25%) and even more frequently in individuals with CD4+ cell counts greater than 200/µL (62.5%). These findings support prior reports that extensive compartmentalized CNS evolution of HIV is associated with severe neurologic injury. They also add to the literature indicating that measurable compartmentalization can predate evidence of clinical neurologic disease and advanced immunosuppression.

Although CSF is the most readily sampled CNS tissue in humans, a few presentations focused on findings from other CNS tissues to investigate HIV neuropathogenesis and compartmentalization. Gelman and colleagues (Abstract 68) examined autopsy tissues from 29 decedents whose samples were collected in the National NeuroAIDS Tissue Bank. One-third of participants had complete viral suppression on antiretroviral therapy, one-third had partial viral suppression on antiretroviral therapy, and one-third had no viral suppression.

The amount of HIV DNA in the brain was very small compared with other tissue compartments in individuals overall, but detection of brain white matter DNA was not reduced in individuals on suppressive antiretroviral therapy and was not different according to HIV RNA level in the periphery. The researchers also found variable concentrations of HIV DNA in white versus grey matter in the brain in distinct decedents.

Gonzalez-Perez and colleagues (Abstract 365) described macrophage-tropic HIV Env in autopsy brain tissue in HIV-infected individuals without neurologic signs or with only minor complications during life. Macrophage-tropic variants were detected in the brain at a much higher frequency than in the spleen or bone marrow, and HIV DNA sequences from the brain demonstrated phylogenetic compartmentalization with respect to immune tissues. These findings complement the findings of Price and colleagues to suggest that even in

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**Compartmentalized HIV infection develops during asymptomatic infection and may be macrophage tropic. Compartmentalization of antibody responses between CSF and blood may reflect distinct levels of HIV antigen in the 2 compartments during therapy.**

The amount of HIV DNA in the brain was very small compared with other tissue compartments in individuals overall, but detection of brain white matter DNA was not reduced in individuals on suppressive antiretroviral therapy and was not different according to HIV RNA level in the periphery. The researchers also found variable concentrations of HIV DNA in white versus grey matter in the brain in different decedents.
neuroasymptomatic HIV infection, CNS infection can be compartmentalized and Env may adapt to facilitate replication in macrophages and microglia. De Oliveira and colleagues (Abstract 367) examined brain tissue from 63 individuals who died after a median of 5.6 years of suppressive antiretroviral therapy, comparing the HIV DNA quantitation (copies/million cells) in 3 brain tissue regions and lymph nodes between women (19% of the cohort) and men. They found that HIV DNA levels in the entire group were inversely associated with speed of information processing tested during life. They also found higher quantities of HIV DNA in the brain, but not lymphoid tissue, in women than men.

This association between sex and proviral DNA in the brain warrants further investigation in concert with the study of sex differences in the HIV reservoir distribution in other tissues. Additionally, methods for assessing brain tissue in living humans are actively being sought for studies of CNS reservoirs. The olfactory mucosa has recently been recognized as a site to directly sample the axons of neurons that pass through the cribiform plate into the brain. Cacagna and colleagues (Abstract 379) used the noninvasive technique of nasal brushing in 19 participants to sample the olfactory mucosa as a source of tissue that might provide insight into HIV reservoir in the brain. They were able to quantify HIV RNA in olfactory mucosa as well as plasma and CSF in 10 HIV-infected participants (in a mixed group of some individuals on and some off antiretroviral therapy), finding levels of HIV RNA in olfactory mucosa that correlated with plasma but not CSF levels. Further studies that examine immunologic, histologic, and viral genetic features of this olfactory mucosa are warranted to evaluate this potentially accessible window into brain tissue.

New biologic measures that detect HIV persistence in disparate tissues are needed to better understand potential HIV reservoirs. Gisslen and colleagues measured antibody responses to 7 different HIV antigens in CSF and blood using luciferase immunoprecipitation systems (LIPS) in different stages of untreated and treated HIV infection (Abstract 391) as a means of examining persistence of HIV antigen in the CNS and in blood. In paired samples across the spectrum of untreated HIV infection, CSF HIV antibody levels were detected at high levels that paralleled those found in blood, and with slightly lower levels following the same pattern in individuals on antiretroviral therapy started during chronic HIV infection. However, treatment initiated during primary infection was associated with a distinct pattern, wherein some individuals had antibody levels in CSF similar to HIV seronegative controls, despite elevated levels in blood. This compartmentalization of antibody levels in the CSF suggests that detection of these responses in the CNS is not based simply on passive transfer of antibodies from the blood, but instead may have importance in reflecting local HIV reservoirs during antiretroviral therapy.

Strategies to assess HIV reservoir persistence often involve interruption of antiretroviral therapy to assess the timing of viral rebound in the plasma and in other tissues. Chan and colleagues (Abstract 363) evaluated the impact of analytic treatment interruption on the CNS in 8 individuals who initially started antiretroviral therapy during Fiebig I (HIV RNA+, p24-, and IgM-) acute HIV infection. No adverse outcomes during treatment interruption or after antiretroviral therapy resumption (triggered by rise in plasma HIV RNA level to >1000 copies/mL) were noted while monitoring CSF for viral rebound and inflammation (n = 4), magnetic resonance spectroscopy (MRS) assessment for changes in metabolites suggesting inflammation or neuronal injury (n = 5), and neuropsychologic testing with the Flanker Task (a tablet-based measure of attention and inhibitory control from the National Institutes of Health [NIH] Toolbox; n = 8). This study demonstrates the feasibility of intensive CNS monitoring during “cure” studies and treatment interruption; further similar studies should be completed to ensure the CNS safety of HIV remission strategies and evaluations.

CSF HIV Escape and Neurologic Disorders During Antiretroviral Therapy

Several presentations focused on variants of CSF HIV escape, a virologically defined state in which HIV is either detectable in the CSF but undetectable in the plasma, or elevated in the CSF compared with levels in blood, despite antiretroviral therapy. Joseph and colleagues (Abstract 73) reported cases of virologic escape in the CSF in a prospective cohort of study participants without neurologic symptoms assessed during systemically suppressive antiretroviral therapy. They observed 2 virologic states of CSF escape: an example of nonpersistent escape, occurring at a single time interval associated with clonal amplification of a viral variant exhibiting X4 coreceptor tropism, and an example of CSF escape persisting over 2 time points associated with a diverse viral population and a heightened ability to infect cells with low-CD4 receptor density, presumably macrophages. In a separate study examining viral characteristics of CSF escape, HIV sampled from the CSF in 9 out of 62 participants in an antiretroviral therapy—suppressed cohort had CSF escape. In 2 participants, CSF escape was characterized by X4 coreceptor tropism, and in a third participant, sequences were associated with defective viruses (Smith and colleagues, Abstract 371). Johnson and colleagues (Abstract 370) observed compartmentalized viral variants and drug resistance mutations in 6 individuals with elevated CSF compared with plasma HIV RNA in the setting of incompletely suppressive antiretroviral therapy. They also used an antibody capture method to investigate cell sources of CSF HIV by targeting host cell proteins incorporated in the HIV envelope detected in CSF, and identified markers for classical monocytes/macrophages, homing monocytes, natural killer cells, and T-helper cells. These experiments suggest that compartmentalized viral populations in the CNS may be sustained by numerous cell types in the setting of partially effective antiretroviral therapy.

Additionally, Pinnetti and colleagues studied the clinical and laboratory factors associated with the risk of CSF escape during antiretroviral therapy in individuals undergoing a lumbar puncture for neurologic symptoms or evaluation of
Abnormally elevated immune activation in treated HIV infection is a universal facet of systemic HIV and likely underlies numerous end-organ complications observed with antiretroviral therapy–treated HIV infection.\(^2\) Inflammation is also frequently detected in the CNS despite virologic suppression. Prior studies have found that abnormal inflammation in the CNS is associated with the presence of cognitive dysfunction in HIV infection despite treatment.\(^3\) One presentation at CROI 2017 supported prior work documenting residual CNS inflammation despite long-term virologic suppression on antiretroviral therapy of 10 years or more (Hammarlund and colleagues, Abstract 340). CSF neopterin, a marker of CNS macrophage activation, was elevated in 55% of 22 virally suppressed participants. However, this study did not detect associations of CSF neopterin levels with either CSF NFL level or neuropsychologic performance on the Cogstate Brief Battery of 4 neuropsychological tests.

Several studies examined novel measures of immune responses in the CNS to investigate neuropathogenesis and to provide new biomarkers of disease. Hermansson and colleagues investigated levels of YKL-40, a chitin-binding glycoprotein, in the CSF of HIV-infected individuals as a putative biomarker of microglial activation during different stages of HIV infection and HAD (Abstract 383). YKL-40 was elevated compared with controls in untreated neuroasymptomatic individuals with a CD4+ cell count of 550/µL or less, and very highly elevated in individuals with HAD, suggesting its utility as a biomarker for HIV-associated neurocognitive disorder (HAND). Furthermore, CSF YKL-40 levels independently strongly correlated with NFL levels in a multivariable analysis across the spectrum of HIV disease, indicating a role for this protein in the pathogenetic dissection of HAND.

Additional studies revealed relationships between systemic immune activation and neurologic and cognitive function. Lipw and colleagues (Abstract 341) evaluated 253 participants in the WHIS (Women’s Interagency HIV Study). Systemic monocyte activation, measured by sCD163 and sCD14 in plasma, was higher in women with impaired neuropsychologic performance. These differences remained statistically significant when the analysis was limited to the 50% of participants with undetectable plasma HIV RNA level. Thus, potential sex-specific monocyte activation and response to antiretroviral therapy warrant further investigation in order to optimize the neurocognitive status of HIV infected-women.

In ACTG (AIDS Clinical Trials Group) 5303, a study of initial antiretroviral therapy, Robertson and colleagues (Abstract 342) also identified a role for monocytes in cognitive functioning during treatment. They identified modest inverse correlations between neuropsychologic performance and frequency of classical (CD14++CD16−) and nonclassical monocytes (CD14+CD16++) after 48 weeks of antiretroviral treatment. Mitchell and colleagues (Abstract 385) described the percentage of blood CD4+ T lymphocytes positive for the programmed cell death protein 1 (PD-1+), indicating an exhausted phenotype associated with smaller regional brain volumes in individuals on at least 3 months of stable antiretroviral therapy. These associations between monocyte activation or T-cell exhaustion and evidence of neurologic impairment or injury during treatment support the concept that ongoing systemic immune perturbation despite antiretroviral therapy may contribute to CNS pathology in HIV infection. Furthermore, a study relating systemic and CNS immune activation and concurrent neuropsychologic performance...
during acute HIV infection with a history of past or active syphilis suggests that coinfections may contribute to immune activation and associated neurologic consequences in HIV infection (Chan and colleagues, Abstract 339).

**HAND Persists in the Antiretroviral Therapy Era**

HAND continues to occur in HIV-infected individuals despite the introduction of antiretroviral therapy. This condition impacts the overall daily activities of HIV-infected individuals. Numerous studies at CROI 2017 focused on longitudinal persistence of HAND. Questions remain as to when cognitive changes occur in HIV-infected individuals. Robertson and colleagues (Abstract 380) studied individuals with acute or recent HIV infection within a subgroup of the Sabes Study in Peru who either immediately started antiretroviral therapy after diagnosis (n = 42), or deferred treatment for 24 weeks (n = 45). Neuropsychologic performance was evaluated at baseline, 12, 24, and 48 weeks. Performance improved over time for both groups. At 48 weeks, mean change in neuropsychologic performance was statistically significantly better for HIV-infected individuals who immediately started antiretroviral therapy than for those who deferred treatment. This potential protection of brain function associated with immediate therapy in individuals recently infected with HIV support current guidelines recommending that clinicians should not wait to initiate antiretroviral therapy. The cognitive trajectories of individuals with chronic HIV infection were also studied by several groups in adults (Abstracts 350, 351, 352LB, and 397) and children (Abstract 826). Rubin and colleagues (Abstract 350) performed repeated neuropsychologic performance testing at baseline, at 2 years, and at 4 years in a large sample of HIV-infected women who were followed in the WIHS. Cognitive trajectories were compared for women not infected with HIV (control group; n = 301), women infected with HIV on antiretroviral therapy who were virologically well controlled (n = 239), and women with HIV infection on antiretroviral therapy but not virologically well controlled (n = 502). HIV-infected women performed worse than the control group in learning, memory, and attention domains. The HIV-infected and uninfected groups had similar overall trajectories (rates of change). Within the group of HIV-infected women, there was substantial heterogeneity. HIV-infected women who were virologically well controlled had better performance in learning and memory, but worse performance in fluency, attention, and speed of processing than HIV-infected individuals without well-controlled suppression. The etiology of these differences is not known, but may reflect differences in viral burden or greater sensitivity to the virus in certain brain areas.

Cole and colleagues (Abstract 352LB) and Sanford and colleagues (Abstract 397) also demonstrated that virologically well-controlled HIV-infected individuals performed worse than a control group of women not infected with HIV in terms of attention, processing speed, and executive function. For both of these studies, the rate of cognitive change was similar between the group with HIV infection and the group without HIV infection. In contrast, Gates and colleagues (Abstract 351) studied 96 men infected with HIV who were virologically well controlled and a control group of 44 men uninfected with HIV longitudinally at a baseline assessment and 18 months later. A greater proportion of the HIV-infected individuals had a subtle subclinical worsening of cognitive impairment (speed and executive function) compared with the control group. Finally, neuropsychologic performance was evaluated at baseline and at 48 weeks in a cohort of children from 4 African countries who were uninfected with HIV, uninfected with HIV but perinatally exposed, and infected with HIV on antiretroviral therapy (Bolvin and colleagues, Abstract 826). HIV-infected children performed worse than children not infected with HIV in numerous cognitive domains. Similar to many of the results in adults, children infected with HIV had no substantial changes detected in cognition between week 0 and week 48, with cognition remaining reduced compared with a control group of children without HIV infection.

Neuropsychologic performance results from several studies indicate that persistent cognitive impairment occurs despite virologic control. These changes in cognition may originate during early infection. Data presented at CROI 2017 suggest that overall neuropsychologic performance trajectory of HIV-infected individuals who are virologically well controlled is similar to individuals without HIV infection. These results suggest that it is not only if but when antiretroviral therapy is administered because persistent impairment may remain even after virologic control is established.

**Screening for HAND Remains Difficult**

Questions still abound as to how to diagnose HAND in the clinical setting. The optimal set of screening tests for HAND is actively being pursued by several groups. Milanini and colleagues (Abstract 355) compared the International HIV Dementia Scale (IHDS) with a standard neuropsychologic performance test battery to evaluate for cognitive impairment within a large group of young individuals with HIV infection (n = 2009) and without HIV infection (n = 405) from a number of African countries. Approximately 25% of the individuals without HIV infection and 40% of the individuals with HIV infection were cognitively impaired in this relatively young cohort. Using various cut points, the authors demonstrated that the IHDS had relatively poor sensitivity and specificity in identifying HAND.

In another series, Trunfio and colleagues (Abstract 360) studied a sample of 279 HIV-infected individuals in Italy using a series of screening tests (3 questions, IHDS, clock...
drawing, and frontal assessment battery) and a longer neuropsychologic performance battery. Each of the screening tests had poor sensitivity and specificity in distinguishing HAND compared with the “gold” standard, which was a neuropsychologic performance battery that covers numerous domains. Results from these relatively large HIV population studies suggest that cognitive screening tests are not reliable for successfully identifying HAND in the clinical setting. Additional biomarkers may instead be needed for assisting in the diagnosis of HAND.

Risk Factors for HAND and Stroke

Risk factors for HAND were also investigated at the conference. Deiss and colleagues (Abstract 358) studied 189 HIV-infected US military personnel. HIV-infected individuals with a previous history of posttraumatic stress disorder (PTSD) were more than 6 times more likely to develop HAND than HIV-infected individuals without a diagnosis of PTSD. Many of the HIV-infected individuals with PTSD also had residual mood disorders that could affect neuropsychologic performance results. Erlanson and colleagues (Abstract 665) studied the relationship between frailty and cognitive impairment in 954 HIV-infected individuals in ACTG 5322, the HAILO (HIV Arterial Dysfunction, Lipids, and Lovaza) study. Frailty was assessed using the Fried criteria, and cognition was evaluated using 3 neuropsychologic tests. Participants were classified into 1 of 4 possible categories: nonfrail and cognitively normal (80%), nonfrail and cognitively impaired (18%), frail but cognitively normal (4%), and frail and cognitively impaired (2%). Frailty was associated with a greater risk of falls regardless of the degree of cognitive impairment. These results suggest that frailty and cognition reflect different spectrums of an HIV-infected individual. Interventions that focus on frail individuals rather than cognitively impaired may have a greater impact on fall risk.

Le and colleagues investigated whether the standard clinical laboratory information of CD4+:CD8+ cell ratio was a useful blood biomarker associated with HAND in a longitudinal observational cohort of 109 individuals with early HIV infection over 550 visits of follow-up (Abstract 72). When taking into account clinical factors such as plasma HIV RNA level, treatment status, and age at baseline, CD4+:CD8+ cell ratio emerged as independently associated with neuropsychologic performance in a multivariable analysis. These findings support prior associations observed in chronic infection between lower CD4+:CD8+ cell ratio and poorer cognitive performance, cross-sectionally as well as longitudinally, and suggest that this clinically available test may be useful in assessing the risk of HAND.

Gutierrez and colleagues (Abstract 346) performed a retrospective study that looked at the relationship between immune status and risk of developing stroke in 115 HIV-infected individuals at a single tertiary center. Etiology of strokes were identified and classified as small artery disease; due to an embolus from the heart (cardioembolic); infectious; cryptogenic; or other mechanism. Unlike in other studies, the most common stroke mechanism was cryptogenic (31%) followed by intracranial large artery disease (26%), and infectious etiologies (14%). A decrease in CD4+ cell count was associated with increased risk of infectious etiology for stroke, and individuals who had large gains in CD4+ cell counts after a lower CD4+ cell count nadir were more likely to have intracranial artery strokes. Individuals with immune reconstitution inflammatory syndrome (IRIS) may be at increased risk for stroke. Crane and colleagues (Abstract 347) investigated the types of strokes seen in HIV-infected individuals at 5 institutions. From a total of 23,189 HIV-infected individuals studied, 238 had a stroke. Within this adjudicated sample, ischemic strokes were most common (75%) followed by unknown (13%) and hemorrhagic (12%). Within the ischemic group the etiologies were equally distributed among small vessel (31%), cardioembolic (30%), and atheroembolic (23%). A high proportion of the cardioembolic strokes resulted from illicit drug use. These results suggest strokes occur because of a variety of distinct causes in HIV-infected individuals. Stroke may prove to be an increasing problem in HIV-infected individuals, especially as this population lives longer as a result of antiretroviral therapy.

Neuroimaging of HIV Infection in the Brain

Quantification of changes in cortical and subcortical volumetrics was used to assess the effects of HIV infection in the brain. Van Zoerst and colleagues (Abstract 352LB) studied 134 HIV-infected individuals who were virologically well controlled and 79 HIV–well-matched controls using a variety of neuroimaging methods. Both groups of participants were studied at baseline and at a 2-year follow-up. At baseline, HIV-infected individuals had smaller brain volumes than those without HIV infection. Age-related changes were seen in both groups but no interaction was observed between age and HIV serostatus. For many of the neuroimaging measures the rates of change were comparable for both groups. Similar results were also seen by Sanford and colleagues (Abstract 397). A cohort of 46 HIV-infected individuals who were virologically suppressed and 31 well-matched HIV-seronegative individuals in a control group were studied over a 2-year interval. Statistically significant reductions in volume within the thalamus, caudate, putamen, and globus pallidus were seen in HIV-seropositive individuals compared with HIV-seronegative individuals at baseline. The overall rate of change in volume was similar in the HIV-seropositive and HIV-seronegative groups. These findings support the hypothesis that structural brain changes occur early in HIV-infected individuals during the period of untreated infection. Early initiation of antiretroviral therapy may reduce volume loss associated with HIV infection.

As previously noted, Mitchell and colleagues (Abstract 385) studied the association between blood immune activation and inflammation (in particular, T-cell and monocyte subpopulations) and brain volumetrics in 33 HIV-infected individuals on stable antiretroviral therapy. Using flow cytometry, peripheral blood mononuclear cells (PBMCs) were
evaluated for markers of T-cell activation (CD38+HLA-DR+), senescence (CD57+CD28−), and exhaustion (PD-1, TIM-3, TIGIT). The presence of exhausted CD8+ T cells and CD16+ monocytes was primarily associated with subcortical brain atrophy (putamen and nucleus accumbens) and cerebellar reduction. These results suggest that certain cell types may be responsible for continued volume loss seen in virologically well-controlled HIV-infected individuals. More recently, a fluorodeoxyglucose positron emission tomography (FDG-PET) approach was developed to image CD206+ macrophages. Zanni and colleagues (Abstract 635LB) demonstrated that macrophage-specific immune mechanisms can lead to end-organ damage in HIV-infected individuals who are virologically well controlled. Application of this technique and others that can examine microglial activity in the brain are needed. The continued development of novel imaging methods for inflammatory changes in HIV-infected individuals on stable therapy hold great promise for potentially identifying remaining viral reservoirs.

Other imaging studies used MRS to evaluate metabolite changes in HIV-infected individuals. Hellmuth and colleagues (Abstract 394) performed MRS in 297 acute HIV-infected individuals before the initiation of antiretroviral therapy. Individuals with acute HIV infection who had cognitive impairment had increased glutamine (a marker of excitotoxicity) in frontal grey matter, decreased n-acetyl aspartate (a marker of neuronal function) in frontal white matter, and increased choline (a marker of inflammation) in parietal grey matter, compared with individuals with acute HIV infection and no cognitive impairment. These results suggest that frontal brain regions may be susceptible to HIV infection soon after seroconversion.

Gates and colleagues (Abstract 398) studied 26 men with chronic HIV infection who were virologically well controlled on antiretroviral therapy. Changes in creatinine (brain energy metabolism) and choline (inflammation) were associated with levels of the HIV Tat protein in the CSF. Perez-Valero and colleagues (Abstract 400) evaluated HIV-infected individuals who were randomly assigned to a high CNS penetration but also potentially neurotoxic regimen (abacavir/lamivudine plus efavirenz; n = 11) or a low CNS penetration and less neurotoxic regimen (tenofovir/emtricitabine plus ritonavir-boosted atazanavir; n = 11) at baseline and 48 weeks after therapy began. No statistically significant differences were seen between the 2 regimens with regard to neuropsychologic performance or MRS markers. However, for many of these MRS studies a matched control group of individuals without HIV infection was not included. Additional longitudinal studies using MRS are required comparing HIV-seronegative individuals and HIV-seropositive individuals who are virologically well controlled.

Changes in brain function were assessed in HIV-infected individuals. Kallianpur and colleagues (Abstract 395) studied the relationship between functional connectivity and PBMCs (CD14+ and CD14− cells) in 38 HIV-infected individuals and 46 individuals without HIV infection. HIV-infected individuals had lower resting state functional connectivity (rs-fc) (especially between the insula and prefrontal cortex) than individuals without HIV infection. However, increases in rs-fc were seen between the caudate and superior parietal cortex in individuals with HIV infection compared with those without HIV infection. Among HIV-infected individuals, increases in CD14+ monocytes were associated with decreased rs-fc. Smith and colleagues (Abstract 401) studied the relationship between resting cerebral blood flow (CBF) and performance on the Iowa Gambling Task (IGT), a measure of riskiness. Risky decision-making was supported by affective systems in HIV-infected individuals but by attention systems in individuals without HIV infection. HIV-infected individuals often recruit attention and emotional processing areas to meet increasing cognitive demands.

Finally, Nichols and colleagues (Abstract 403) studied 11 youth with HIV infection and 13 uninfected youth using magnetoencephalography (MEG). HIV-infected individuals had hypoactivation within deeper structures (eg, basal ganglia) and increases in slow-wave (delta/theta) activity were seen in other subcortical areas. Widespread superficial hyperactivation was seen in higher frequency bands, possibly reflecting a compensatory increase in activation within cortical areas. MEG may be a sensitive marker of early changes in the brain seen in young, asymptomatic HIV-infected individuals.

**Treatment Considerations for the CNS**

The question of how best to ameliorate the clinical signs and symptoms of HAND remains of central importance to HIV-infected individuals and HIV practitioners. Ndhllovu and colleagues (Abstract 381) investigated whether antiretroviral intensification with cenicriviroc, an investigational dual CCR2 and CCR5 antagonist, might improve neurocognitive function in individuals on suppressive treatment. In an open-label, single-arm pilot study, 17 participants on stable antiretroviral therapy for 1 year with plasma HIV RNA level of 50 copies/mL or less received once-daily cenicriviroc for 24 weeks. Cenicriviroc treatment was associated with an improvement across several cognitive domains and in global neuropsychologic performance, as well as with improvement in 3 plasma soluble biomarkers of macrophage activation (soluble CD14, soluble CD163, and neopterin). Improvements in some domains of neuropsychologic performance and systemic macrophage activation were correlated. Although the learning effect in a nonrandomized trial with repeated testing cannot be excluded, these findings provide rationale for a randomized clinical trial of cenicriviroc intensification for numerous complications of monocyte activation, including HAND.
Although standard antiretroviral therapy is almost universally associated with improvement in neurologic function, including in limited resource settings and across HIV clades (Sacktor and colleagues, Abstract 359), potential complications of treatment in the CNS require consideration. Viswanathan and colleagues (Abstract 372) reported on a meta-analysis of clinical trial-derived data and suggested that the highly effective integrase strand transfer inhibitor (InSTI) class of antiretrovirals is associated with a risk of neuropsychiatric adverse effects, primarily depression, similar to that of efavirenz and protease inhibitors. The absolute risk of depression in the InSTI group was 7.1%, and the absolute risk of memory loss was 0.5%. It is uncertain whether these symptoms could have been premorbid and not associated specifically with treatment. However, the favorable risk profile of InSTIs should be carefully assessed with further investigation of possible CNS side effects in future studies, potentially including a dedicated prospective study or assessment of neurologic and mental health complications in a randomized controlled trial.


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Additional References Cited in Text

Review

CROI 2017: Complications and Comorbidities of HIV Disease and Its Treatment

Judith S. Currier, MD; Diane V. Havlir, MD

Complications of HIV disease remained a major focus at the 2017 Conference on Retroviruses and Opportunistic Infections (CROI), and included studies focused on non-communicable chronic diseases (e.g., cardiovascular disease, obesity, bone disease, and malignancies) and opportunistic infections (Mycobacterium tuberculosis and cryptococcosis). Progress in identifying predictors of specific complications as well as interventions for the prevention and treatment of these comorbidities are summarized below.

Keywords: CROI, 2017, cardiovascular, tuberculosis, antiretroviral, therapy, biomarkers, risk

Inflammation and Cardiovascular Disease Risk

Previous studies have demonstrated that patients with HIV infection may have evidence of arterial inflammation using novel imaging techniques such as (fluodeoxyglucose positron emission tomography [FDG-PET]). Zanni and colleagues took this one step further in a pilot study that used a molecular imaging strategy that included a radio-labeled tracer binding to CD206+ macrophages (99mTc-tilmanocept) in vivo. They examined the uptake of 99mTc-tilmanocept using single-photon emission computed tomography (SPECT/CT)in 6 HIV-seropositive and 3 HIV-seronegative participants, and related the findings to measures of noncalcified plaque on CT angiography. Increased levels of aortic uptake of the macrophage-labeled tracer were seen in the HIV-infected patients. Correlations between uptake and noncalcified plaque volume and measures of systemic inflammation provided further support that macrophage infiltration underlies excess cardiovascular disease (CVD) risk in HIV-infected subjects (Abstract 635LB).

Hsue and colleagues reported results of a pilot study evaluating the impact of a single dose of canakinumab, the monoclonal antibody targeting interleukin 1ß (IL-1ß), given to HIV-seropositive patients with increased CVD risk. FDG-PET scans obtained 8 weeks after treatment demonstrated a statistically significant reduction in aortic arterial wall inflammation and a reduction in IL-6 and high-sensitivity C-reactive protein (hs-CRP) without evidence of a change in T-cell activation. A larger follow-up study is planned to further evaluate the safety and efficacy of repeated dosing of this novel antiinflammatory agent (Abstract 126).

Biomarkers, Mortality, and Non-AIDS Events

Several studies at the Conference on Retroviruses and Opportunistic Infections (CROI) examined relationships between the biomarkers IL-6, d-dimer, and hs-CRP, and antiretroviral therapy and outcomes this year. In addition, studies evaluating novel biomarkers of inflammation and their associations with clinical outcomes were reported. A few highlights of measures that were reported this year are included in the table.

Does better adherence further reduce inflammation once HIV-RNA levels becomes suppressed? Castillo-Manilla and colleagues used a medication event monitoring system device to study a cohort of individuals in Uganda who started on antiretroviral therapy, in parallel with measures of inflammation. After an initial response to antiretroviral therapy with HIV RNA levels under 400 copies/mL, higher levels of adherence were associated with further reductions in IL-6, D-dimer,

Table. Selected Studies of Biomarkers of Morbidity and Mortality at the 2017 Conference on Retroviruses and Opportunistic Infections

<table>
<thead>
<tr>
<th>Biomarker Studied</th>
<th>Endpoint(s)</th>
<th>Results/Comments</th>
<th>Abstract No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soluble urokinase plasminogen activator receptor (suPAR)</td>
<td>All-cause mortality and non-AIDS events</td>
<td>Higher suPAR associated with all-cause mortality but not non-AIDS events</td>
<td>235</td>
</tr>
<tr>
<td>Serum soluble suppression of tumorigenicity 2 (sST2), a decoy receptor for IL-33</td>
<td>Mortality</td>
<td>Increased risk of death for every 2% increase in sST2 level</td>
<td>630</td>
</tr>
<tr>
<td>F2-isoprostanes (measure of oxidative stress)</td>
<td>Non-AIDS events and mortality</td>
<td>F2-isoprostanes were independent predictors of events after control for hs-CRP, IL-6, and D-dimer levels</td>
<td>647</td>
</tr>
</tbody>
</table>

Abbreviations: IL, interleukin; hs-CRP, high-sensitivity C-reactive protein.
sCD14, and reductions in T-cell activation, suggesting that optimized adherence could potentially contribute to better long-term outcomes (Abstract 675).

Antiretroviral Therapy and Risk of Cardiovascular Disease

Several groups reported data on the associations between specific antiretroviral drugs and risk of CVD. The D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) group reported data on the relationship between newer protease inhibitors and CVD events in 35,711 patients over a median of 7 years of follow-up (Abstract LB 128). The D:A:D database includes more than 1000 events (stroke, myocardial infarction [MI], coronary bypass surgery, endarterectomy, and angioplasty), which is considerably more than other smaller studies. They found that exposure to ritonavir-boosted darunavir was associated with a 59% increase in the risk of CVD compared with not being on darunavir and this did not change after adjusting for lipid levels. In contrast, there was no statistically significant increase in risk of CVD associated with atazanavir use. Overall, 3.2% of participants had a CVD event and the crude incidence of MI after 6 years of exposure was 13.67 for darunavir and 6.68 for atazanavir. Adjusting for factors thought to be on the causal pathway between exposure and outcome, such as CD4 nadir, HIV RNA, and lipid levels, did not explain the excess risk observed with darunavir. The authors acknowledged the limitations of these observational data and called for further study of the potential mechanism underlying this observation.

Previous studies have identified a potential protective effect of atazanavir in reducing the risk of atherosclerosis progression; this is possibly linked to the antioxidant properties of unconjugated bilirubin, which rises in most individuals receiving the drug. Marconi and colleagues examined the relationship between bilirubin levels and MI risk in 96,373 participants followed up in the Veteran Aging Cohort Study and found that higher bilirubin levels were inversely correlated with MI and heart failure risk in all patients and only heart failure risk and marginally MI risk among the HIV-seropositive group (Abstract 127). Notably, the majority of patients with bilirubin elevations in this study were not receiving atazanavir.

Several groups continue to investigate a mechanism to explain the possible association between abacavir use and MI risk. Andujar and colleagues expanded their previous reports on abacavir induction of leukocyte endothelial interactions to study thrombus formation in a mouse model using an endothelium damaging agent to provoke thrombosis in the presence of other agents. They observed a dose-dependent effect of abacavir on thrombus formation, whereas tenofovir had no effect. Using a knockout mouse model, they reported that the abacavir effect was blocked in the absence of ATP-P2X7 (a purinergic system). These results suggest a potential pathway, through interference of ATP-P2X7 by which abacavir could alter thrombus formation. Further studies are needed to confirm these observations (Abstract 609).

Hepatitis C Virus and Cardiovascular Disease Risk

The extrahepatic and metabolic effects of hepatitis C virus (HCV) coinfection continue to be an area of active investigation. Many studies highlighted that patients with HCV infection may be at increased MI risk compared with patients without HCV infection (Abstract 574) and other medical comorbidities (Abstract 528). Treatment with sofosbuvir/ledipasvir and other HCV direct-acting antiviral drugs are associated with increases in low-density lipoprotein even prior to virologic response given that lipids rise before liver disease improves (Abstracts 573, 575, 589) and endothelial function is impaired in patients with untreated HCV infection.

Cardiovascular Disease Risk Reduction and Screening Strategies

The impact of different strategies to reduce MI risk was explored in a Dutch modeling study led by van Zoest and colleagues (Abstract 129). Using data from individual patients followed up in the ATHENA (AIDS Therapy Evaluation in the Netherlands) observational HIV cohort, they constructed a model to estimate CVD events and to examine 4 different prevention intervention approaches that might impact CVD risk: using antiretroviral therapy in patients with no known increased CVD risk; smoking cessation; treatment of hypertension and dyslipidemia; and earlier antiretroviral therapy. Their model estimates the rate of CVD events will increase by 50% by 2030 and demonstrated that although each of these interventions would reduce CVD events, the treatment of hypertension and dyslipidemia would have the greatest impact.

In a related study, Althoff and NA-ACCORD (North American AIDS Cohort Collaboration) colleagues used data with validated type 1 MI events (those due to plaque rupture) to estimate the population attributable risk for factors linked to an increased risk of MI (Abstract 619). This method uses the strength of the association with a factor and the prevalence of that factor in the population and allows the ability to examine the impact of eliminating each factor. In this cohort, elimination of smoking, hypertension, and hypercholesterolemia were each associated with a 40% reduction in MI risk.

Elimination of smoking, hypertension, and hypercholesterolemia were each associated with a 40% reduction in MI risk.
in HIV patients in Malawi that improved on antiretroviral therapy (Abstract 641), and novel programs for screening and treatment of CVD risk factors in Uganda, South Africa, and Swaziland (Abstracts 638, 639, 637) were presented in a themed discussion session this year. Investigators from the SEARCH (Sustainable East Africa Research in Community Health) study proposed a new composite HIV, hypertension, and diabetes metric for HIV care programs that encompasses the multidisease chronic care model. Their study, which screened 40,000 adults enrolled through multi-disease community health fairs, reported on composite endpoint measures for the 193 who had HIV infection and an NCD. Sixty-nine percent achieved control of HIV and NCD after 2 years, lagging behind the 90% control of HIV achieved by the program (Abstract 638). This new composite metric should be used to monitor progress toward HIV-NCD integration globally.

**Statins**

Statins have beneficial effects in primary CVD prevention and are recommended for use in those who meet current guidelines. Investigators from the NA-ACCORD evaluated trends in statin prescriptions from 2003 to 2012 using the Framingham Risk Score and the thresholds for use recommended during that time period. The percentage of patients eligible but not receiving statins fell modestly from 70% in 2003 to 58% in 2012, potentially reflecting underuse of this important intervention for CVD risk reduction (Abstract 619).

Patient beliefs about the value of medications taken to treat comorbid conditions need to be considered in efforts to reduce CVD risk. Kamal and colleagues reported results of a survey performed in the Swiss HIV Cohort study that asked patients about their beliefs and adherence to their medications, separating HIV treatments from medications taken for other conditions. Patients reported higher levels of adherence to antiretrovirals than to medications taken for comorbidities, suggesting that further work is needed to improve adherence to all medications (Abstract 671).

Statins have pleiotrophic effects on inflammation and lipid metabolism but are also active against HIV infection in vitro. Dreschsler and colleagues examined associations between statin use and rates of virologic rebound among US veterans. Continuous statin use was associated with a reduction in rates of virologic rebound after virologic suppression (Abstract 468). In another study, low levels of vitamin D (25(OH)D) blunted the beneficial effects of rosuvastatin on several measures in the SATURN-HIV (Stopping Atherosclerosis and Treating Unhealthy bone with Rosuvastatin in HIV) trial (Abstract 617).

**Exercise**

Connick and colleagues reported results of a study that examined the impact of exercise training on endothelial release of tissue-type plasminogen activator (tPA), an important mediator of fibrinolysis. The capacity of the endothelium to release tPA improved after a home-based exercise intervention (5 days a week of walking for 50 minutes/day), presumably through a reduction in oxidative stress. These findings underscore the potential impact of habitual exercise on endothelial function in HIV disease (Abstract 616).

The management of coronary artery disease once diagnosed is an emerging topic of interest to the field. Clement and colleagues examined the rate of CVD procedures in a database of more than a million hospitalizations for acute coronary syndromes in the United States. The 3783 HIV-seropositive patients identified in this sample were less likely to undergo procedures such as cardiac catheterization, percutaneous coronary intervention, or coronary bypass grafting than HIV-seronegative patients after controlling for certain demographic factors. These disparities in care warrant further investigation.

**Lipids: HDL Cholesterol Efflux Capacity**

Several groups reported on the relationship between high-density lipoprotein (HDL) efflux cholesterol capacity or other measures of HDL function, monocyte function, and CVD (Abstracts 611-615). Angelovich and colleagues showed that dysfunctional HDL from HIV-infected patients promoted monocyte-derived foam cell formation in an in vitro model. O’Halloran and colleagues reported that initial antiretroviral therapy improves the antioxidant HDL function observed in untreated HIV, whereas impaired mononuclear cell cholesterol efflux remained increased. In another study, lower CD4+ cell counts and higher HIV RNA levels correlated with impaired cholesterol efflux, which further supported the link between impaired HDL function and immune status. Mannem showed that HDL cholesterol efflux is inversely associated with classical monocyte numbers. This raises the theory that interventions directed at restoring HDL function may have the potential to modulate monocyte function, and possibly CVD.

**Fat**

The rising prevalence of obesity in HIV-infected patients was a widely covered topic (Abstracts 694, 695, 698, 699). Bhagwat and colleagues reported on predictors of severe weight
and body mass index gain with initial antiretroviral therapy using data from the completed ACTG 5257 (comparing raltegravir with atazanavir/ritonavir or darunavir/ritonavir, each combined with tenofovir/emtricitabine). The study focused on weight gain of more than 10% body weight; the mean increase in this group was 14.9 kg. Risk factors for severe weight gain included lower baseline CD4+ cell count, higher HIV RNA level, use of raltegravir, and black race (Abstract 695). A study from Thailand on weight gain after antiretroviral therapy is started reported that rates of obesity increased from 13% at the start of antiretroviral therapy to 21% over an average of 11 years. Those with obesity, not surprisingly, had higher rates of other metabolic abnormalities and evidence of hepatic fibrosis (Abstract 698). A behavioral weight-loss program delivered via the Internet reported 4.4 kg weight loss in the intervention group compared with no change among controls. These findings suggest that interventions to reduce weight can be successful, at least over the short-term (Abstract 694).

**Bone Density**

Reduced bone density appears to occur among many patients after initiation of antiretroviral therapy and progresses over time. The ability to predict fracture risk would help target interventions to improve bone density in this population. The fracture risk assessment tool (FRAX) algorithm predicts a 10-year risk of a major osteoporotic fracture in the general population, and it has been shown to underestimate risk in the HIV cohort data based upon clinical risk factors alone. Yang and colleagues from the WIHS (Women’s Intergenergy HIV Study) cohort found that adding data from dual-energy x-ray absorptiometry (DXA) scans, including a measure of trabecular bone architecture, improved the accuracy of FRAX in HIV-seropositive women. These findings support the current recommendations for DXA screening in HIV-seropositive adults over the age of 50 years and incorporating DXA data in estimating fracture risk using FRAX (Abstract 132).

**Malignancies**

Cancer is a growing cause of morbidity and mortality in the aging, treated population of people living with HIV infection. Several presentations highlighted the changing epidemiology of cancer and provided new data on cervical cancer. Cervical cryotherapy is used in many low- and middle-income countries for screen-and-treat strategies to prevent cervical cancer. Greene and colleagues presented data on a randomized clinical trial that compared loop electrosurgical excisional procedure (LEEP) with cryotherapy to treat high grade cervical squamous intraepithelial lesions (HSIL) in HIV-infected women in Kenya (Abstract 22). The study enrolled 400 women who had cervical HSIL on histology and cervical lesions that made them eligible for cryotherapy according to WHO criteria. After undergoing their treatment, the women were followed up every 6 months with cervical cytology. The women randomized to LEEP were less likely to have recurrent cytologic HSIL through 24 months after randomization (37% vs 26%, *P* = .018) than those who underwent cryotherapy. These data suggest that LEEP may be preferable to cryotherapy for HIV-infected women who screen positive in see-and-treat programs.

Investigators from WIHS presented data on the natural history of cervical intraepithelial neoplasia-2 (CIN2) in HIV-infected women of reproductive age (Abstract 23). Cervical HSIL is the precursor lesion to cervical cancer and is composed of CIN2 and CIN3. CIN2 is more likely than CIN3 to regress and the risks from treating CIN2 may outweigh the potential risk to future pregnancies. The investigators analyzed 102 HIV-infected women diagnosed with CIN2 lesions: 41 HIV-infected women were treated for CIN2; 61 were untreated. The investigators found no statistically significant difference in the risk of progression to CIN3 in women who were treated than those who were untreated. The risk of progression was lower among women using antiretroviral therapy and those with higher CD4+ cell counts. These data suggest that it is reasonable to monitor CIN2 in HIV-infected women seeking pregnancy.

Several studies examined screening strategies for anal HSIL, the precursor lesion to invasive anal cancer. Investigators examined the role of high-risk human papillomavirus (HPV) testing in HIV-infected women (Abstract 591) and men (Abstract 592), and found that HPV testing in conjunction with cytology led to a more accurate diagnosis of anal HSIL than cytology alone. HPV testing in conjunction with cytology led to a more accurate diagnosis of anal HSIL than cytology alone. This risk of abnormal anal cytology was also related to a cumulative number of HPV types detected, which suggests that testing for the various HPV infections may have a role in anal cancer screening (Abstract 594). Serrano-Villar and colleagues reported on an enhanced cytology with p16/Ki67 dual stains. They found that this enhanced cytology did not perform as well as standard cytology and concluded that it should not be studied further (Abstract 595).

The START (Strategic Timing of Antiretroviral Treatment) study, a randomized clinical trial of early versus delayed initiation of antiretroviral therapy, found that early initiation of antiretroviral therapy led to a reduced risk of cancer. An analysis from the Kaiser Permanente health care system found that early initiation of antiretroviral system led to a reduction in cancers similar to the START study findings (Abstract 598). Salters and colleagues reported on the cancer risk among HIV-infected women from British Columbia, Canada (Abstract 599). Cancer diagnosis was less common among women who started antiretroviral therapy at a CD4+
Tuberculosis

Prevention and Earlier Diagnosis

The TEMPRANO (Benefits and Risks of Early Antiretroviral Therapy in HIV-Infected Adults) study conducted in Côte d’Ivoire showed that early antiretroviral therapy and isoniazid preventive therapy (IPT) independently reduced tuberculosis (TB) risk. Badje and colleagues analyzed mortality during an extended follow-up of trial participants in TEMPRANO, according to their IPT randomization (Abstract 78). Overall, there were 86 deaths among the 2056 participants followed up for 9494 patient-years of observation. There were 54 deaths in the IPT arm and 52 in the non-IPT arm; the hazard ratio (HR) was 0.61 (95% confidence interval [CI], 0.39-0.94) after adjusting for immediate versus deferred antiretroviral therapy. Thus, including IPT in the treatment of persons with a high CD4+ cell count prevents TB and is associated with a 39% mortality benefit.

If TB cannot be prevented, then early diagnosis is the key to reducing TB disease burden and spread. Xpert Ultra is the next generation of Xpert MTB/RIF, a rapid diagnostic for identifying Mycobacterium tuberculosis (MTB) and rifampin (RIF) resistance. The Xpert Ultra assay has built-in modifications to improve sensitivity for TB diagnosis. A prospective study compared Xpert and Xpert Ultra against a gold reference standard of 4 TB cultures. The study enrolled 1520 participants from 8 countries who had signs of pulmonary TB. Xpert Ultra was more sensitive than Xpert for TB detection for all cases (5% higher), HIV-associated TB cases (12% higher), and smear-negative TB cases (17% higher) (Abstract 76 LB). However, specificity decreased by 3.2% overall and decreased by 5.4% in persons with a prior history of TB. Whether the false-positive with Xpert Ultra represents detection of nonviable TB or the limitation of the gold standard culture cannot be ascertained from this study. The investigators report that the Xpert Ultra uses the same machine and cartridges at the same cost as the Xpert. The next step will be to determine an implementation of the Xpert Ultra that preserves the sensitivity advantage and optimizes specificity.

Treatment

Defining optimal use of current TB drugs and testing new treatments to shorten and improve regimens is a priority of TB treatment research. Prior clinical and animal studies suggest that isoniazid used throughout a 6-month standard TB therapy contributes to bactericidal activity only during the first few days of treatment. Diacon and colleagues found that among 63 persons with pulmonary TB (94% HIV uninfected) randomly assigned to 1 of 4 different treatment arms (isoniazid, rifampin, pyrazinamide, ethambutol [HRZE] for 14 days; HRZE without isoniazid for days 3 to 14; HRZE replacing isoniazid with moxifloxacin for days 3 to 14; or rifampin, pyrazinamide, and ethambutol for 14 days), early bactericidal activity at 14 days did not differ among the 4 arms (Abstract 79). Failure to identify differences among the study arms may be attributed to overall lower bacterial counts in this study than in prior studies. These results do not support replacement of short-term use of isoniazid for its continuous use in current regimens.

Patients with extensively drug-resistant (XDR) TB and multidrug resistant (MDR) TB are the most difficult to treat and have the highest mortality. Conradie and colleagues presented early findings from the Nix-TB single-arm study treating patients who are culture-positive for XDR or MDR TB patients with bedaquiline (200 mg daily) plus pretomanid (200 mg daily) plus linezolid (1200 mg daily) for 6 months (Abstract 80LB). Among the 61 patients (49% HIV-infected; 79% XDR TB; 21% MDR TB), 4 participants died within the first 8 weeks of therapy from TB complications. All surviving patients had negative cultures by 8 weeks. Because of the high dose of linezolid used, 71% of patients had treatment interruptions for peripheral neuropathy and myelosuppression. Seven cases of grade 3 or 4 hepatic transaminase elevation all resolved with treatment modifications. No surviving patient had to permanently withdraw from the study because of serious adverse events. One microbiologic relapse has been reported to date. Favorable outcomes in historic XDR TB studies occur in only 40% of participants, mortality is more than 20%, and treatments require 6 or more drugs for years. Thus, these small and early results with a 6-month, 3-drug regimen, even with associated toxicities, are encouraging for treating this population and warrant further study.

Dawson and colleagues presented early results of an 8-week phase IIb study for MDR or drug-sensitive TB treated with bedaquiline, pretomanid, moxifloxacin, and pyrazinamide, or standard HRZE (Abstract 724LB). The primary study outcome was bactericidal activity measured by rate of change in time in days to sputum culture positivity. There were 180 participants with drug-sensitive TB and 60 patients compared with historical data.

Isoniazid preventive therapy was associated with a 39% reduction in death in an Ivory Coast study.

An experimental 6-month regimen for XDR/MDR treatment with bedaquiline, pretomanid, and linezolid has shown early favorable outcomes compared with historical data.
with MDR TB enrolled; 22% were HIV-infected. Among the MDR TB patients, the change in time to sputum positivity was 5.3 days for the bedaquiline, pretomanid arm; 5.2 for the bedaquiline, pretomanid, and pyrazinamide arm; and 4.9 for the bedaquiline, pretomanid, moxifloxacin, and pyrazinamide arm, compared with 4.0 days for the HRZE arm. Elevated hepatic transaminases (3-fold elevation) were 10% to 15% in the 3 experimental treatment arms and 5% in the standard HRZE arm. The role of these investigational regimens will depend on larger efficacy and safety evaluations.

A new option for prevention of TB is a short-course, weekly, 3-month combination of rifapentine and isoniazid. This combination can be given safely with efavirenz, but there are no data on safety and interactions with dolutegravir. Brooks and colleagues reported the results of an open-label, fixed-sequence study of dolutegravir 50 mg daily alone, followed by the addition of weekly doses of isoniazid and rifapentine in noninfected volunteers (Abstract 409A). The study was prematurely stopped because 2 of the 5 patients who completed 3 doses of weekly isoniazid and rifapentine developed several adverse events, which included flu-like syndrome and elevation of hepatic transaminase levels that started 8 to 10 hours after the third dose of isoniazid and rifapentine. One patient was hospitalized for hypotension. Dolutegravir levels decreased 15% to 46%, rifapentine and isoniazid metabolite levels were in the expected range, and isoniazid levels were on the high end. The clinical findings were most consistent with rifapentine reaction, but the mechanism is unknown and requires further study.

**Epidemiology**

In KwaZulu Natal, South Africa, an area with a high prevalence of XDR TB, more than two-thirds of cases are attributable to transmission rather than incomplete treatment (Abstract 77). Nelson and colleagues used whole-genome sequencing and spatial analysis to determine if there were unrecognized connections between 671 genetically linked case-pairs and their proximity to health facilities. Only 17% case-pairs lived or were diagnosed at a health facility within 20 km of each other. The investigators speculated that ongoing migration contributes heavily to spread and transmission of XDR TB in this region.

Recurrent TB is common in South Africa accounting for as many as one-third of cases. Hermans and colleagues examined the attributable risk fraction of HIV infection among TB recurrence cases from 2003 to 2015 (Abstract 727). Among 245,495 persons with TB, 16% had 2 or more TB cases. Higher rates of TB recurrence were observed with each subsequent TB episode until episode 5, after which HIV serostatus did not matter. The proportion of retreatment of disease attributable to HIV infection increased from 42% in the second episode to 46% in the sixth episode. Although HIV infection is a risk for recurrence, fewer than half of the total recurrent cases occur in persons with HIV infection. These data would suggest that reinfection or treatment failure with progression to disease after previous TB treatment is a major issue in all persons with TB. Bendavid and colleagues examined TB risk using the TB self-report (HIV serostatus unknown) from the South Africa General Household survey (Abstract 725). They observed that race was independently predictive of socioeconomic status for TB risk. For example, adult TB prevalence among black individuals in the highest socioeconomic households was 4 times that of white individuals in the lowest socioeconomic households. Understanding biologic and behavioral contributions to these observations may help inform TB intervention. Finally, in a population-based study of TB infection among 2093 children and 953 young adults given a purified protein derivative (PPD) skin test in rural Uganda, Marquez and colleagues reported that 23% of young adults 14 to 24 years of age already had evidence of TB infection (Abstract 726). However, only 5% had a known household contact. Undiagnosed household contacts or community- and school-based contacts rapidly establish a lifetime reservoir of TB infection in rural Uganda.

**Tuberculosis Immune Reconstitution Inflammatory Syndrome and Its Association With InSTI Use**

Starting versus delaying antiretroviral therapy in the setting of TB is associated with reduced mortality, but also with increased risk for immune reconstitution inflammatory syndrome (IRIS), particularly in those with TB and low CD4+ cell count. Meintjes conducted a randomized, double-blind, placebo-controlled trial to determine if a brief course of steroids could safely mitigate the IRIS risk in patients starting TB and antiretroviral therapy with CD4+ cell count under 100/µL (Abstract 81 LB). The study enrolled 240 subjects with a median CD4+ cell count of 49 cells/µL. Participants in the intervention arm received prednisone 40 mg/day for 2 weeks, then 20 mg/day for 2 weeks. TB-IRIS was diagnosed in 46.7% in the placebo arm and 32.5% in the prednisone arm ($P = 0.02, RR, 0.70; 95% CI, 0.51-0.96$). Twenty-seven patients were hospitalized in the placebo arm and 17 patients were hospitalized in the intervention arm. Grade 3 adverse events (45.4% and 29.4%, respectively) but not grade 4 adverse events (8.4% and 7.6%, respectively) were more common in the placebo arm. Severe infections occurred in 18 participants in the placebo arm and 11 participants in the prednisone arm. There were fewer interruptions of antiretroviral therapy or TB treatment in the prednisone arm (8.3%) than in the placebo arm (15.8%). This study makes a compelling case to use a brief 4-week course of prednisone for persons with TB and a low CD4+ cell count to reduce TB-IRIS by approximately 50%.

The IRIS risk is associated with rapid HIV RNA level decline after antiretroviral therapy initiation in addition to a low count.
starting CD4+ cell count. Because integrase strand transfer inhibitor (InSTI)-containing regimens are associated with a more rapid decline in HIV RNA level compared with non-InSTI–containing regimens, 2 studies examined whether patients treated with InSTI-containing regimens versus non–InSTI-containing regimens had a higher risk of IRIS. In the Dutch ATHENA observational cohort (Abstract 731), 360 patients starting an initial antiretroviral regimen with a CD4+ cell count below 200/µL had been diagnosed with an opportunistic infection from 2009 to present. Most common opportunistic infections were Pneumocystis jiroveci pneumonia (PJP; n = 172), Candida sp infections (n = 143), mycobacterial infections (n = 51), and Kaposi sarcoma (n = 38). IRIS occurred in 38% of patients treated with InSTI-containing regimens and in 16% treated with non–InSTI-containing regimens. Overall IRIS risk was 2.6-fold higher (HR, 2.6; 95% CI, 1.3-5.1) among patients treated with an InSTI-containing regimen. In a second study conducted in a cohort of hospitalized patients from 15 centers in France (Abstract 752), investigators examined inpatients with CD4+ cell counts below 200/µL starting antiretroviral therapy between 2010 and 2015. The IRIS incidence was 2-fold higher (HR, 1.99; 95% CI, 1.1-3.5) among patients receiving InSTI-containing antiretroviral regimens than those not receiving an InSTI. InSTIs are well established as a component of initial antiretroviral regimens with many beneficial attributes. These data suggest that late-stage patients with opportunistic infections treated with InSTI-containing regimens versus those taking other antiretroviral drug combinations may be at increased risk for IRIS and merit careful monitoring.

Fungal Treatment Studies
Jarvis conducted a phase II randomized study to determine if short-course induction therapy with high-dose liposomal (L) amphotericin (AMB; 5-10 mg/kg) could be a reasonable alternative to standard 3 mg/kg for 2 weeks L-AmB induction (Abstract 82). Eighty patients were randomly assigned to 1 of 4 treatment arms: single-dose L-AmB; 2-dose L-AmB; 3-dose L-AmB; or 2-week standard L-AmB induction. All participants also received high-dose fluconazole 1200 mg daily. Rates of fungal clearance at 14 days for the 3 short-course induction arms were all noninferior to the standard 2-week regimen. Authors report that single-dose induction will be evaluated in a larger phase III clinical endpoint study. Notably, the mortality in this study was 29%, indicating that prevention of this disease is a high priority in addition to optimizing outcomes. The disseminated fungal disease Talaromyces marneffei (formerly Penicillum) is a major cause of mortality among persons with AIDS in South and Southeast Asia. Amphotericin B induction, which is also used to treat cryptococcal disease, is recommended but often not available. Observational and in vitro studies suggest that itraconazole has good activity against T marneffei, but there has not been a direct comparison of itraconazole and AmB. Kinh and colleagues randomly assigned 440 HIV-infected adults with confirmed talaromycosis in Vietnam to a 2-week AmB induction regimen or itraconazole induction regimen (Abstract 83). All patients received continued therapy with itraconazole. The primary study endpoint was mortality. At 24 weeks, mortality was nearly 2-fold higher in the itraconazole group (21.3%) than in the AmB group (11.3%) (HR, 1.88; 95% CI, 1.15-3.09; P = .012). Consistent with these findings, clinical resolution and fungal clearance were faster, and relapse of infection was higher in the itraconazole-treated group than in the AmB-treated group. All-oral itraconazole treatment for talaromycosis is associated with increased mortality than is AmB induction. In the short-term, improving access to AmB in these regions needs to be a priority.


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Invited Review
CROI 2017: Highlights of Advances in Viral Hepatitis and Liver Fibrosis

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At the 2017 Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle, Washington, hepatitis C virus (HCV) infection was a major focus in the context of HIV-associated liver disease. Well-tolerated direct-acting antiviral (DAA) regimens have enabled effective treatment of the populations that are hardest to cure, including those with decompensated cirrhosis, and many studies examined the impact of HCV cure on hepatitis and extrahepatic outcomes. Scaling up access to DAA, and their impact that their universal availability can have on reducing prevalence were key topics. There was much discussion of what is needed to eliminate HCV on local and global levels and a focus on ensuring that the populations hardest to reach can access treatment. Prevention of new infections and reinfection will be key to sustaining the benefits of scaled-up HCV treatment, with particular attention to populations at elevated risk for HCV reinfection, including HIV-infected men who have sex with men (MSM) as well as some HIV-uninfected MSM on preexposure prophylaxis. In the hepatitis B virus (HBV) arena, a landmark phase III trial demonstrated that tenofovir disoproxil fumarate given to HBV-infected pregnant women at week 28 of gestation, in combination with postpartum HBV vaccination and hepatitis B immunoglobulin, resulted in zero mother-to-child transmissions of HBV.

Keywords: CROI, 2017, hepatitis, HBV, HCV, treatment, direct-acting antivirals, vaccination

HCV Natural History and Markers of Clinical Fibrosis

HIV coinfection is a well-recognized factor in accelerated progression of liver disease in those with hepatitis C virus (HCV) infection, but this association has not been extensively evaluated in children with mother-to-child transmission (MTCT) of HCV with or without HIV coinfection. In a large, retrospective, multicenter cohort from Spain, liver disease progression was evaluated by transient elastography or liver biopsy in 71 HIV/HCV-coinfected and 71 HCV MTCT-infected children (Abstract 527). The HCV genotype distribution was different between the groups, with HIV/HCV-coinfected children having significantly more nongenotype 1 infections, including 23% genotype 3 HCV (compared with 7% in HCV-monoinfected children), which could impact fibrosis progression.

There was no evidence of progression of liver disease in either group through age 10 years. After 10 years, separation was noted with evidence of significantly more progression of fibrosis in the coinfected group (24% of coinfected individuals with fibrosis stage F3/F4 at age 20 years vs 6% in HCV-monoinfected individuals; \( P = .012 \)). HCV-monoinfected infants were more frequently treated than HIV/HCV-coinfected infants (52/71 vs 22/71, respectively) and were treated at an earlier age despite evidence of slower progression of fibrosis. An explanation for why HCV-monoinfected children were treated more frequently and earlier was not provided.

Prior studies have shown that immune activation is increased in HIV/HCV-coinfected individuals compared with those with HIV or HCV infection alone. An analysis from 2 cohorts, WIHS (Women’s Interagency HIV Study) and VAHH (Study of Visceral Adiposity, HIV, and HCV), sought to further characterize this association by evaluating the contributions of liver fibrosis (by transient elastography and aspartate aminotransferase (AST)-to-platelet ratio index (APRI) and microbial translocation (via I-FABP) to sCD14 levels in HIV/HCV-coinfected (n = 120), HIV-monoinfected (n = 262), HCV-monoinfected (n = 72), and noninfected (n = 170) individuals (Abstract 526). The sCD14 levels were highest in the individuals with HCV/HIV coinfection, followed by those with HIV infection alone, then those with HCV infection alone, and finally the uninfected individuals. Liver stiffness appeared to be the primary mediator of sCD14 levels in those with HCV infection alone. In both of the HIV-infected groups, microbial translocation took on a more prominent role in driving elevated sCD14 levels (although it was not the primary determinant in either group).

The Fibrosis-4 (FIB-4) score is already well validated for predicting liver-related outcomes in HCV-infected and HIV/HCV-coinfected individuals. An updated assessment from the GeSIDA cohort determined that a FIB-4 cutoff of below 1.0 is optimal for predicting an absence of liver-related events (LRE) over the ensuing 5 years (97% negative predictive value [NPV]) (Abstract 533). The hazard ratio (HR) for LRE increased for each unit rise in FIB-4; however, the difference became

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and HIV-uninfected individuals, and was reduced in the presence of cirrhosis as well as unfavorable IL28B TT genotype. The overall impact of ledipasvir on kidney function and correlated with elevated tenofovir area under the curve (AUC), suggesting that elevated tenofovir concentrations may lead to kidney damage during ledipasvir/sofosbuvir–based therapy with TDF. However, the overall impact on tenofovir levels, appears to have little clinical significance in most individuals.

The HCV PI/NS5a combination of glecaprevir/pibrentasvir is expected to become available during the coming year. A noninfected volunteer study found no significant interaction between the fixed-dose combination (FDC) of dolutegravir and abacavir and lamivudine and glecaprevir/pibrentasvir (Abstract 413). Coadministration of FDC elvitegravir and cobicistat and emtricitabine and tenofovir alafenamide (TAF) led to increased elvitegravir and cobicistat concentrations (maximum plasma concentration [C\text{max}], 29%-36%; AUC, 42%-47%; C\text{24}, 71%-72%), as well as increased glecaprevir (AUC increased 3.1-fold, C\text{24}, 4.6-fold) and increased pibrentasvir (AUC\text{24} increased 57%, C\text{24}, 89%). However, the authors suggest that these changes are not expected to be clinically significant based on label recommendation and exposure safety analyses from phase III data. In the EXPEDITION-2 HIV/HCV coinfection study, glecaprevir/pibrentasvir was coadministered with raltegravir, dolutegravir, rilpivirine, abacavir, TDF, and lamivudine/emtricitabine. Efavirenz and etravirine are not expected to be compatible with glecaprevir/pibrentasvir due to drug-drug interactions.

**HCV Treatment in Cirrhosis and Post–Liver Transplant**

One of the important benefits of current DAA therapy is the ability to more safely and effectively treat individuals with cirrhosis, including decompensated disease, than with interferon. DAA-based therapy (with more than half taking ribavirin as well) was generally well tolerated in a Spanish cohort of HIV/HCV-coinfected individuals with compensated cirrhosis, with only 1.2% stopping due to adverse events (Abstract 535). Ninety-three percent attained SVR12, which was lower among treatment-experienced individuals (88.8%) than those who were treatment naive (97.5%) (P = .025). Transient elastography improved by a mean of 5.6 kPa at the time of SVR12.
of SVR12. It should be noted that individuals with cirrhosis are still advised to continue with hepatocellular carcinoma (HCC) screening even if noninvasive measurements suggest regression of cirrhosis. The MADRID-CoRE (Madrid Coinfection Registry) cohort evaluated outcomes of DAA treatment in HIV/HCV-coinfected individuals in clinical practice, across a spectrum of fibrosis stages, including decompensated cirrhosis (Abstract 534). Fifty-two percent received ribavirin with their all-oral DAs. The SVR12 rate was highest among those without cirrhosis (93.5%) than those with compensated cirrhosis (91.2%) and those with decompensated cirrhosis (80.8%), which was significantly lower than those with or without compensated cirrhosis. Among individuals with decompensated cirrhosis, SVR12 rates were 86.7% for Child-Turcotte-Pugh (CTP)-A and 79% for CTP-B, and showed a significant drop-off to 44% in the most advanced disease class, CTP-C, which has been seen in other cohorts of DAA treatment in individuals with decompensated cirrhosis.

HIV-infected individuals are increasingly able to access liver transplantation. In the post–liver transplant recurrence of HCV infection, all-oral DAA therapy led to high SVR rates of 95%, which were similar in HIV-infected and HIV-uninfected individuals and is good news for those developing HCV infection posttransplant (Abstract 540). Unfortunately, HIV-infected individuals are known to experience higher rates of acute rejection after liver transplantation than their HIV-uninfected counterparts; HCV genotype 1 and mismatch in HLA-A, HLA-B, and DR alleles were all associated with increased acute rejection (Abstract 541).

**Impact of HCV on Extrahepatic Disease, Lipid Profiles, and Overall Mortality**

Chronic HCV infection is associated not only with liver disease, but also with all-cause mortality and end-organ disease such as chronic kidney disease (CKD). In a retrospective analysis performed at 2 large health organizations in Denver, the demographics of individuals who are HCV RNA positive versus those who are HCV RNA negative were evaluated, and an association between HCV RNA positivity and common comorbid conditions was assessed in new enrollees from 2008 to 2015 (Abstract 528). Not surprisingly, HCV-seropositive individuals tended to be older men within the birth cohort. They also had significantly higher rates of alcohol abuse and current tobacco use, which may confound other disease associations. Among nonliver comorbid conditions, HCV RNA positivity was associated with depression, coronary artery disease (CAD), CKD, and all-cause mortality. However, odds ratios for these conditions were significant only for depression, CAD, and all-cause mortality. Overall, low rates of HCV screening were seen in both health organizations (5.5% to 7.2%). Among individuals who are HCV RNA positive, only 11% to 17% had been treated for their HCV infection (less than 5% of the predicted population with chronic HCV infection).

Functionally, HCV could impact cardiovascular disease by contributing to endothelial dysfunction. This was evaluated cross-sectionally in a group of 45 HIV-suppressed, HCV-infected persons by measuring the reactive hyperemia index (RHI, a correlate of coronary endothelial function, with low RHI indicating endothelial dysfunction). No clear association between HCV infection or liver fibrosis stage and low RHI (indicating endothelial dysfunction) was found. Even traditional factors such as smoking, dyslipidemia, and hypertension were not significantly associated with poor endothelial function, although trends were observed. This study leaves the question open of whether or not HCV infection itself impacts endothelial function in those with HIV.

Telomere length is a marker of aging, and HIV infection has been associated with accelerated aging. The relative contribution of HCV infection and rapidity of loss of telomere length following seroconversion for either HCV or HIV has not been examined. In a cohort of injection drug users with samples available before and after seroconversion for HIV or HCV, telomere length was assessed on whole blood samples with a quantitative polymerase chain reaction (PCR) method (Abstract 590). In preseroconversion samples, persons who subsequently acquired HCV had significantly shorter telomere lengths than those who subsequently seroconverted for HIV or who were nonseroconverters. Of note, 50% of subsequent HCV seroconverters were already HIV seropositive, suggesting a likely explanation for the shorter preseroconversion telomere lengths. Following seroconversion (median 9 months postconversion) HIV individuals had the lowest relative telomere length, with a significant drop from their preseroconversion length. In contrast, no change in telomere length was seen after HCV seroconversion. Although conducted over a limited time span, these data suggest that HIV infection has more of an acute and dramatic effect on telomere length than HCV infection. Longer term follow-up would be of interest.

Several studies examined the impact of an HCV cure on lipid levels. Sofosbuvir/ledipasvir treatment was associated with an increase in low-density lipoprotein (LDL) and total cholesterol during treatment that was not seen with participants treated with paritaprevir/ritonavir/ombitasvir/ritonavir/ dasabuvir (Abstract 573). However, after treatment completion, LDL and total cholesterol were similar regardless of the DAA treatment assignment, but with a trend toward higher levels than pretreatment. An Italian cohort also demonstrated a significant increase in total cholesterol, LDL, and oxidized LDL during a variety of DAA therapies (Abstract 575). They also noted an improvement in insulin resistance and a significant reduction in the proportion of individuals with prediabetes after an HCV cure.

In a cohort of US veterans, the risk of acute myocardial infarction was higher in HCV-infected individuals than HCV-uninfected individuals with similar lipid profiles, suggesting...
that untreated HCV infection itself increases the risk for cardiovascular events (Abstract 574). Is HCV treatment beneficial or harmful to cardiovascular health? Total cholesterol and LDL are known to be lower in HCV-infected individuals than in uninfected controls, and cirrhosis is also known to reduce lipid levels. Thus, some cholesterol increase with curative therapy may be seen as a “return to health” phenomenon rather than an increase in the risk of cardiovascular disease. These lipid effects may be counterbalanced by improved glucose metabolism and decreased inflammation, which could conversely decrease cardiovascular risk. More data are needed to understand if the DAA-induced rise in lipids has negative clinical impact on cardiovascular disease and if specific patient populations may benefit from lipid-lowering therapy during HCV treatment.

A cohort of HIV/HCV-infected individuals in Scotland reminded us of the high mortality rate in this population, particularly among those who continue to use opiates (Abstract 529). Mortality was 7.78/100 person-years and involved drug overdose in a third of the deaths. Not surprisingly, lower albumin and poor HIV disease control were associated with mortality.

Promising Future HCV Therapeutics

Broadly neutralizing antibodies (bNAbS) hold substantial promise as potential HIV therapeutics. An in vitro screen of HCV bNAb combinations identified a synergistic combination that may prove to be an effective HCV vaccine strategy (Abstract 141).

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is a feared complication of cirrhosis and is more common in those with HIV coinfection. In a cohort of more than 2600 HIV/HCV-coinfected US veterans with cirrhosis, HCC occurred in 3.2% over a median of 5 years, and was associated with older age, but not with race/ethnicity, HIV suppression, or CD4+ cell count (Abstract 539).

There has been ongoing controversy about whether curative DAA therapy may lead to elevated rates of new HCC diagnosis or HCC recurrence. In a Spanish cohort study of 32 centers (GEHEP-002), the rate of new HCC cases in HIV/HCV individuals was statistically significantly increased from 9% to 16% in the era before all-oral DAA treatment to 31.7% in the all-oral DAA era (P < .001) (Abstract 139). The authors attributed this to increased uptake of treatment in individuals with cirrhosis, a nearly 3-fold increase, who are at higher baseline risk for HCC and may be more likely to be screened once evaluated for treatment. HCC recurrence after HCV treatment occurred in a very small number of individuals and was not significantly different in the DAA era compared with the pre-DAA era. Similarly, data from the Italian SCOLTA (Surveillance Cohort Long Term Toxicity of Antiretrovirals/Antivirals) demonstrated that the rate of HCC in individuals with cirrhosis (Metavir stage F4) during the first 16 months after DAA treatment was the same as in untreated historical controls. In those undergoing DAA treatment, cirrhosis was associated with HCC development, when compared with those with Metavir stages F0 to F3 (HR, 4.7; 95% CI, 1.08-20.44), a reminder of the importance of providing HCV treatment before advanced fibrosis develops (Abstract 542LB).

In an analysis from the GEHEP-002 cohort of 317 HCC cases among HIV/HCV-coinfected individuals, 32.5% of those with HCC who were apparent candidates for therapy did not receive treatment or received suboptimal treatment according to the tumor stage at diagnosis. No treatment or suboptimal treatment was more common at more advanced stages of HCC (Abstract 538). However, the proportion of suboptimally treated individuals declined from 43.6% before 2010 to 27.4% from 2010 to 2016, suggesting improved access to appropriate care.

HCV Screening and Diagnostics

Despite recommendations from the Centers for Disease Control and Prevention (CDC) in 2012 and the US Preventative Services Task Force (grade B recommendation) in 2013, an uptake of birth cohort HCV screening for those born between 1945 and 1965 (Baby Boomers) appears to be limited. Indeed, a study from Washington, DC, demonstrated only 12% of more than 80,000 individuals eligible for HCV screening in the birth cohort were tested when a screening prompt was built into electronic health record (EHR) clinical protocols (Abstract 545). Although in more than 50% of the cases, health care practitioners never clicked on the screening prompt, more disheartening is that when the HCV screening prompt was accessed, only 43% of individuals were subsequently screened.

The care cascade generated from those screened was typical, with large drop-offs from documentation of HCV RNA positivity to being seen in an HCV treatment clinic (53%, 80/151), and another sizeable drop-off in completing pretreatment evaluation and having a prescription for HCV therapy written (25%, 37/151). A second study with a different EHR prompt (Abstract 544) yielded more promising results, demonstrating an increase from 6.2% screened during preintervention to 38.6% during postintervention. Differences included a prompt rollout for individuals in a hospital setting as opposed to those in an outpatient clinic, and the appearance of the EHR prompt on screen instead of the need to click the prompt to view screening recommendations.

Cases of acute HCV infection have increased dramatically over the last several years and are likely underestimated. With this rise in acute HCV infection, testing of nonbirth cohort populations will need to occur more frequently. Most HCV cascade data are based on birth cohort populations predominantly. The HCV care cascade for a nonbirth cohort
population was generated from a retrospective chart review within a large health system in the Washington, DC/Maryland area (Abstract 543). Among almost 7000 nonbirth cohort individuals tested for HCV infection, 1.6% were seropositive. HCV RNA positivity was seen in only 60% of those with antibody-positive HCV infection, and advanced fibrosis stage (IF3-4) assessed by FibroSure was present in only 14%. In contrast to the birth cohort-based HCV epidemic in this area of the country, which is predominantly in blacks, the nonbirth cohort were predominantly white men (also presumed younger, but not specifically stated). Younger age and recent infection would also explain the higher spontaneous clearance rate and limited amount of advanced fibrosis.

The remainder of the cascade was typical, with large drop-offs from documentation of RNA positivity to being seen by an HCV specialist (64%, 28/44), and to completing fibrosis staging with HCV treatment ordered (54%, 15/44). Individuals who tested antibody-positive HCV infection in this nonbirth cohort were more likely to be white, to be on Medicaid instead of private insurance, and to report drug use (Abstract 517). In those over the age of 40 using prescription opioids, the risk of antibody-positive HCV infection was elevated 11-fold. Notably, 23% of those with antibody-positive HCV infection reported no HCV infection risk factors, a reminder that testing based on risk factors will miss a proportion of those with HCV infection.

Confirming chronic HCV infection with detection of HCV RNA levels in serum or plasma is a potential stumbling block for widespread roll-out of HCV DAA treatment in resource-limited settings where DAA prices are significantly lower. A self-contained, small-volume PCR methodology with little to no processing requirements could help tackle this issue. Small-volume capillary blood (100 µL) obtained by fingerstick was compared with standard venipuncture for detection of HCV RNA levels on the Cepheid GeneXpert platform (Abstract 549). HCV RNA quantitation was approximately 0.5 log lower using fingerstick; however, no false-negative HCV RNA results were obtained when compared with venous blood. One HCV RNA–positive sample yielded a negative result with both blood sources on the platform. Genotypes 1a, 1b, 2b, 3a, and 4 were tested. Samples remained qualitatively positive for HCV RNA levels for 240 hours at room temperature in capillary tube volumes of 100 µL.

**The HCV care cascade needs continued attention, with a focus on approaches to improving screening and linkage to HCV care and treatment.**

HCV Infection in Men Who Have Sex With Men

Acute HCV infection outbreaks in HIV-seropositive men who have sex with men (MSM) have been well described in several European settings. Evaluation of 80 acute HCV infections occurring in Paris from 2014 to 2016 in a population of largely MSM (81%), 93% of whom had HIV infection, demonstrated that about one-quarter were reinfections and the majority of infections were part of transmission chains (Abstract 52). The SHCS (Swiss HIV Cohort Study) screened 95% of HIV-seropositive MSM in the cohort, identifying approximately 5% with HCV RNA positivity. Of note, 17% of these were incident infections, 6 of these remained HCV antibody-negative, and 2 had normal liver function tests (Abstract 521).

A retrospective cohort of HIV-infected MSM from the University of California San Diego found a steadily rising incidence of HCV diagnoses over time, from 0.36/100 person-years in 2000 to 2003 to approximately 1.1 to 1.14 per 100 person-years in 2004 to 2011, to 1.5/100 person-years in 2012 to 2015. The authors point out that these rates are similar to those reported in London and other European cities with epidemics of acute HCV infection in HIV-seropositive MSM populations, and double the rates observed in the US MACS (US Multicenter AIDS Cohort Study). Intravenous drug and methamphetamine use were each significantly associated with a higher HCV incidence. However, 13.4% denied ever using intravenous drugs or methamphetamines, highlighting that MSM contact alone is an important route of HCV transmission, particularly in the HIV-seropositive population (Abstract 154).

The Amsterdam PreExposure Prophylaxis (AMPREP) project reported 15 MSM who were HCV RNA–positive at the time of enrolling in a PrEP project, including one with likely acute HCV infection (HCV antibody-negative) (Abstract 519). HCV infection was associated with younger age; increased number of encounters involving receptive anal sex while not using condoms; intravenous drug use, amphetamine use, or gamma hydroxybutyrate use during sex; and a recent sexually transmitted infection (STI). The HCV infection strains were closely related to those already circulating in the HIV-infected MSM population. This is an important reminder that HCV can be sexually transmitted among MSM who are HIV-uninfected as well, and that populations on PrEP may have an increased risk for HCV infection. This merits counseling and regular testing for HCV as a potential STI.

**Toward Eradication: Cohort Studies**

Since November 2015, unrestricted DAA therapy has been available to all HIV/HCV-coinfected individuals in the Netherlands, leading to widespread treatment of HCV infection. In the ATHENA (AIDS Therapy Evaluation in the Netherlands) cohort, which collects data from 95% of HIV-infected individuals in that country, 65% of HIV/HCV-coinfected individuals had been cured or were on treatment. Those who completed treatment had an impressive 98% SVR rate (Abstract 136). These data demonstrate the remarkable impact that unrestricted access to DAA can have on HCV treatment uptake and cure over a short time. During the same time, acute HCV infection in HIV-seropositive MSM decreased by 52%, with a drop in both first-time infections and reinfections, a real-world demonstration of HCV treatment as prevention (Abstract 137).

In the French Dat’AIDS cohort (16 centers with almost 33,000 individuals) HCV treatment rates among the 15% who...
were coinfection were analyzed from 2012 to 2015 (Abstract 550). HCV treatment rates increased dramatically over time in all groups (men, women, treatment naive, treatment experienced, Metavir stages F0 to F2 and stages F3 to F4) and with all genotypes. The nadir in rates of HCV treatment initiation was seen in 2013 during the transition from interferon (IFN)-based therapies to DAA-based therapies. By 2015, essentially all therapy was DAA-based. With this rollout, by the end of 2015, 50% of the HIV/HCV-infected individuals in this cohort had been cured, 30% were untreated, and 8% had failed prior therapy and were (presumably) awaiting retreatment. Unfortunately, over the same period HCV incidence increased from 3.5/1000 person-years to 6.9/1000 person-years in line with other Western European countries. Predictably, the majority were HCV genotype 1a and 4, matching the known epidemiology of acute HCV infection in HIV-seropositive MSM in this area. Reinfection rates were even higher than incident infection rates (although without a consistent trend over the time analyzed) at 25.6/1000 person-years. It is hoped that with a continued focus on high levels of treatment in this population (along with counseling on prevention) a decrease in incident infection and reinfections will be realized as shown in the Netherlands.

To understand the impact of scaled-up DAA treatment on HCV prevalence in France, modeling by the Dat’AIDS cohort projected that with continued treatment coverage of 30% per year, which was the treatment rate in 2015, HCV prevalence in HIV-infected individuals would drop to 1.31% by 2021 and to 0.55% by 2026. However, due to a higher predicted acute infection and reinfection rate, high-risk MSM would need higher treatment uptake to 70% to decrease prevalence to the same degree. Importantly, with increased treatment of those with known HCV infection, undiagnosed individuals will make up a larger proportion of HCV-infected individuals who have untreated disease. This highlights the need to pair increased treatment with increasing detection and engagement in care to effectively achieve HCV eradication (Abstract 135).

Similar to the French experience, a dramatic increase in uptake of HCV treatment was seen in the Duke Medical System from 2013 to 2015 (particularly 2015) (Abstract 552). Although the majority of individuals were treated in 2015 for both HCV and HIV/HCV coinfection, only 12% of individuals infected with HCV and 17% of individuals infected with HIV/HCV-coinfected individuals with cirrhosis), although liver disease parameters were similar among groups of individuals with HIV/HCV coinfection and individuals with HCV infection and cirrhosis. Of interest, 17% of individuals with HIV/HCV coinfection modified their antiretroviral therapy to accommodate DAA treatment.

The uptake of HCV treatment from 2013 through 2015 in several specific vulnerable populations in Canada was assessed in the CCC (Canadian Co-Infection Cohort) (Abstract 553). As in other cohorts, the uptake of treatment bottomed out in 2015 (7/100 person-years), with a slight rise in 2014, and a dramatic increase by 2015 (25/100 person-years). Vulnerable populations evaluated were active persons who inject drugs (PWID), women, and indigenous/aboriginal persons. Although lower uptake was seen in all 3 groups, in the adjusted model, indigenous (adjusted odds ratio [aOR], 0.51; 95% CI, 0.31-0.85) and active PWID (aOR, 0.58; 95% CI, 0.35-0.98) maintained significantly lower odds ratios for uptake of DAA treatment. The uptake of treatment in MSM was significantly higher (aOR 1.75; 95% CI, 1.20-2.55). Disease characteristics such as suppressed HIV viral load and advanced fibrosis were also predictive of treatment starts.

**HCV Treatment in Traditionally “Harder-to-Treat” and Vulnerable Populations**

Although not a consistent finding, some studies have found black race to be associated with lower response rates to DAA treatment. In a prospective cohort from 2014 to 2016, 255 consecutive HIV/HCV-coinfected individuals, in a predominantly black clinic population, were evaluated for their response to DAA treatment (Abstract 560). Demographics in the cohort were 73% men, 88% black, 69% PWID, and 57% persons with a psychiatric diagnosis. HIV RNA suppression was attained in 85%. The vast majority in the cohort (91%) were treated with a fixed-dose combination of sofosbuvir and ledipasvir. The SVR12 rate for the entire cohort was 96%, including 96% in black individuals (95% CI, 93%-98%) and 97% in nonblack individuals (95% CI, 83%-99%). Among the 9 non-SVRs, potentially significant factors included noadherence (3), proton pump inhibitor (PPI) use (2), and inadequate (nonguideline-recommended) therapy (2). An HIV RNA level above 20 copies/mL and a recent change in antiretroviral therapy were associated with non-SVR in univariate analysis.

Another vulnerable population traditionally viewed as difficult to treat are the homeless or marginally housed. Responses to DAA therapy were assessed in this population through the Boston Health Care for the Homeless Program (Abstract 557), which used a multidisciplinary team and weekly adherence phone calls for those on therapy. Among those who completed therapy, 97% (62/64) achieved an SVR12. The 2 treatment failures were individuals with cirrhosis: 1 genotype 1 individual treated with 12 weeks of sofosbuvir/ledipasvir (no ribavirin) and 1 genotype 2 individual treated with 12 weeks of sofosbuvir plus ribavirin prior to a change in guideline recommendations.

Data from HCV treatment programs in various countries suggest that widespread, unrestricted access to DAA therapy for HCV-infected persons, incidence rates of HCV may decrease in shorter time frames than predicted.

HCV had been treated by the end of 2015. Interestingly, in the DAA era there was a trend toward better SVR12 rates in the coinfected group (91% HCV infected vs 96.5% HIV/HCV coinfect, P = .05). Data suggested this may have been driven by differences in SVR12 rates in individuals with cirrhosis (88.2% HCV-infected individuals with cirrhosis vs 96.3% HIV/
Comorbid behavioral health conditions (mental health or substance abuse disorders) are prevalent in those with HCV infection and certainly impacted eligibility for interferon-based therapies. In the DAA era, less data are available on the impact that comorbid psychiatric conditions may have on SVR (or on uptake of treatment). In a study at a Federally Qualified Health Center (FQHC) with treatment provided by primary care practitioners, 326 individuals completed therapy from 2015 to 2016 (Abstract 554). Response rates were assessed by the presence of psychiatric conditions or substance abuse disorders. In an intent-to-treat analysis, among 70% of the treatment population who had behavioral health conditions, the SVR12 rate was 94% compared with 93% of individuals without diagnosed behavioral health issues. One limitation is that no mention of uptake rate in this group was given compared with those without behavioral health conditions.

Marginalized populations may not be able to effectively navigate the health care system to access HCV therapy. One approach is to bring HCV therapy to them (Abstract 555). At a syringe exchange program, 45 individuals were evaluated and 26 were treated on site. Among those not treated, the largest group was excluded (7) due to denial of insurance or late approval. All individuals had injected within the last month, and 58% were also on opiate substitution therapy (OST). Twenty-three completed treatment (22/23 with SVR per protocol; 22/26 overall, or 85%). There were 2 discontinuations due to dropouts (1 because of loss of insurance coverage) and 2 early relapses with a genotype switch from 1a to 3. Both early relapses had injecting risks, but each had only a single injecting partner who was not infected with genotype 3. Although reinfection seems most likely, the possibility of mixed infection at baseline should be considered.

Field delivery of HCV therapy with minimal monitoring was evaluated in Chennai, India (Abstract 559). Fifty current or former PWID were randomly assigned 1:1 with sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks, or sofosbuvir plus ribavirin for 24 weeks. Injections were delivered in-clinic weekly, and directly observed therapy (DOT) of pills, which were delivered with food, was used daily. Monitoring consisted only of a monthly complete blood count. The majority of participants were genotype 3a (~80%), and 20% had cirrhosis (greater than 12.3 kPa). Most individuals (88%) completed treatment in both arms. Participants in the sofosbuvir plus peginterferon alfa and ribavirin arm had an SVR rate of 88%, and those in the sofosbuvir plus ribavirin arm had an SVR rate of 60%.

Despite intensive efforts, only 76% of sofosbuvir plus peginterferon alfa and ribavirin and 80% of sofosbuvir plus ribavirin doses were completed; achieving high rates of adherence was difficult (greater than 95% adherence in 68% of the sofosbuvir plus peginterferon alfa and ribavirin arm, and 64% of the sofosbuvir plus ribavirin arm). Interferon-based therapy appeared to be less sensitive to noncompliance or missed doses with no drop-off shown in SVR rates with decreasing levels of adherence. Ongoing substance use appeared to be a significant issue with treatment adherence and efficacy.

Limited clinical trial data with DAAs have suggested similarly high rates of SVR in individuals on OST. Data from 2 Spanish cohorts (HEPAVIR-DAA and GEHEP-MONO) further support this assertion (Abstract 555). The cohorts consisted of prior injectors (male, younger, and predominantly genotype 1a and genotype 3) both on OST and not on OST compared with persons who did not inject. Individuals on OST had significantly higher liver stiffness than those not on OST and noninjectors (21.1 kPa vs 14.1 kPa and 12.2 kPa, respectively). The percentage of individuals with cirrhosis was also higher in both PWID groups than in noninjectors (57% and 52% vs 45%, respectively). Significant differences in rates of sustained virologic response 4 weeks after cessation of therapy (SVR4) were seen across these groups following DAA therapy (interferon-free): never injected (n = 803), 93%; PWID not on OST (n = 740), 91%; and PWID on OST (n = 190), 88% (P < .001). However, SVR4 rates according to an observed treatment or per protocol analysis were no different among the 3 groups (differences were ascribed to higher drop-out rates in the PWID groups).

Continued follow-up from GECCO (German Hepatitis C Cohort) compared outcomes utilizing DAA therapy in 1156 HCV and 349 HCV/HIV-coinfected individuals (Abstract 551). In the cohort, HIV-seropositive individuals were more likely to be men, have genotype 4, and have higher baseline HCV RNA levels (27% vs 17%, > 6 million IU/mL). Surprisingly, cirrhosis was more prevalent in HCV-monoinfected individuals (31% vs 22%). Overall, the SVR rate (95%) was identical in HCV versus HCV/HIV-coinfected individuals (95% vs 94%). In univariate analysis, HIV-seropositive individuals with a CD4+ cell count below 350/µL or who had cirrhosis were less likely to achieve SVR. On multivariate analysis, only cirrhosis remained a significant predictor of non-SVR. This is in line with other studies that have not shown a consistent negative impact of a low CD4+ cell count on SVR12. Lower CD4+ cell counts may be a marker for portal hypertension; but when controlled for cirrhosis, the effect was lost.

Another presentation from GECCO looked at HCV reinfection rates among those who had follow-up through at least SVR4 (n = 1483) (Abstract 567). Reinfections were documented in 1.7% of participants (n = 24). All reinfections were in men (despite being only 63% of the cohort) and occurred at a mean of 41 weeks after treatment. Risk populations were PWID (21%), MSM (58%), and MSM plus PWID (21%). Eighty-three percent were HIV coinfected. Consistent with prior studies, the reinfection rate in MSM (11%) was higher than that in PWID (1%).

These data suggest that DAAs have fulfilled their promise of high efficacy and tolerability among many diverse and traditionally difficult to treat populations with HIV.
work is needed on screening and rolling out DAAs in a more systematic fashion to reach populations at highest risk and those that are most marginalized, particularly if HCV treatment as prevention is to live up to its promise.

Expansion of HCV Treatment by Nonspecialists

Nonspecialist practitioners will be required to effectively treat the large number of chronically HCV-infected persons in the United States and globally. Using the Project ECHO (Extension for Community Healthcare Outcomes) model, HCV specialists at a large FQHC clinic serving a low-income population were able to dramatically increase the proportion of individuals treated for their HCV infection by primary care practitioners (PCPs) in a short period of time (Abstract 548). In a span of 1 year, PCPs went from treating 1.25% of all individuals treated for HCV infection in a given 6-month period to 60%, while the overall volume of HCV treatment increased by almost 80%. SVR12 rates were 94% in a per protocol analysis, but substantially lower by ITT (73%) because of significant loss to follow-up with missing data at the SVR12 time point.

Origins and Impact of HCV Resistance and Retreatment

Resistance-associated substitutions (RASs) at position 93 (Y93) in nonstructural protein 5A (NS5A) inhibitors are of significant clinical impact. A comprehensive in vitro assessment of Y93 position variants in genotype 1a and 1b was undertaken (Abstract 563). As expected, the impact on NS5A inhibitor susceptibility was largest in genotype 1a, with most amino acid variants conferring a greater than 100-fold shift in 50% effective concentration (EC_{50}) to all currently available NS5A inhibitors. In addition, most variants (with the exception of Y93D) were relatively fit for replication (>10%, particularly in the presence of drugs). In genotype 1b, the impact of Y93 variants was variable, with minimal impact on elbasvir and VEL EC_{50} (less than a 10-fold shift). These data fit well with clinical observations that also suggest a limited impact of baseline NS5A RASs in genotype 1b. The impact of Y93 variants in genotype 3 was not assessed.

A retrospective NS5A sequencing analysis of 112 individuals treated with DAAs in Spain found a trend toward more frequent multiple (2 or more) baseline NS5A RASs in individuals who experienced treatment failure (18% vs 5%, P = .085) (Abstract 562).

Optimal approaches to retreatment and a better understanding of the role of resistance testing in retreatment of DAA failures is needed. A large survey of 274 DAA failure patient samples submitted for sequencing to a reference laboratory in Spain was reported, with 88% treated with NS5A inhibitor-containing regimens (Abstract 566). As expected, given that the majority had failed NS5A-based regimens, NS5A RASs were seen most frequently, either alone or in combination with NS3 RASs. Retreatment regimens were variable and the numbers too small for any one genotype and retreatment regimen to draw conclusions on optimal retreatment regimens or the impact of RASs on responses. Mixed genotype infections were found in only 2% of 255 samples evaluated by deep sequencing. Reinfections also appeared rare in this cohort.

An abstract combining results from 2 studies (GS-US-357-1746 and ACTG A5348) shed some light on retreatment approaches for individuals whose condition failed to improve with sofosbuvir therapy without an NS5A inhibitor (Abstract 568LB). In study 1746, 12 weeks of sofosbuvir/ledipasvir with or without ribavirin were given to those without cirrhosis and 12 weeks of sofosbuvir/ledipasvir with ribavirin versus 24 weeks without ribavirin were given to those with cirrhosis. In study A5348, 12 weeks of sofosbuvir/ledipasvir plus ribavirin versus 24 weeks without ribavirin were given to participants randomized by their cirrhosis status. Despite the different regimens, several clues to optimal retreatment emerged. Twelve weeks of sofosbuvir/ledipasvir without ribavirin should not be used in the retreatment of DAA failures (3 relapses, 81% [13/16] SVR). In individuals with cirrhosis, an extension of therapy to 24 weeks appears preferable to 12 weeks with ribavirin (no relapses vs 5 relapses, respectively). No treatment failures were seen in A5348 but numbers were small (7 total). Baseline NS5A and NS5B RASs did not have a clear impact. Although the results were too small for firm conclusions, overall they support the approach of both studies to extend duration to 24 weeks and adding ribavirin until well-validated next-generation regimens for retreatment of DAA failures are available, later in 2017.

HCV Immunology

Immune correlates of successful DAA therapy are difficult to identify given the high success rates of current DAA therapies. Studying less potent therapies when immune function remains with an impact on treatment outcomes may provide valuable insights. The whole blood transcriptome was analyzed and compared in individuals treated with sofosbuvir and ribavirin for 24 weeks who achieved SVR (n = 24) and relapsed (n = 16) (Abstract 586). Individuals experiencing relapse had higher baseline expression of genes associated with inhibition of the inflammatory response. At the end of therapy, those who relapsed had a higher expression of a T-cell–inhibiting gene, PD1 D1, and a lower expression of genes involved in interferon signaling.

Mucosal-associate invariant T (MAIT) cells play an important and innate immune function, particularly to bacterial pathogens, and have been shown to be depleted early in HIV infection. Peripheral and intrahepatic MAIT cell frequencies were evaluated in controls as well as in HCV-infected and HCV/HIV-coinfected individuals with minimal and advanced fibrosis (Abstract 587). In peripheral blood, MAIT cells were depleted significantly in all groups with chronic viral infection (HCV and HIV) compared with controls. MAIT cells appeared to be relatively more depleted in those with coinfection and advanced fibrosis. MAIT cell function, as assessed by interferon gamma or granzyme B production, was significantly impaired in those with advanced fibrosis than in those with...
minimal fibrosis. Intrahepatic MAIT cell frequencies were relatively preserved. Whether the decreased MAIT cell frequencies in peripheral blood account for part of the susceptibility to bacterial infections in these populations remains to be determined.

**Other Hepatitides**

**Hepatitis B Virus**

Hepatitis B virus (HBV) coinfection is an important driver of morbidity in HIV individuals around the world. In HIV/HBV-coinfected individuals initiating TDF-based antiretroviral therapy at urban sites in Zambia and in rural settings in Mozambique, the 1-year mortality rate was high at 16% and 8%, respectively (Abstract 581). Individuals had advanced HIV disease as indicated by 40%, with WHO HIV stage 3 or 4, and median CD4+ cell counts of 208/µL to 232/µL. It would have been of interest to have comparator mortality data for HIV-monoinfected counterparts.

In a phase III double-blinded trial, HBV-monoinfected pregnant Thai women who were positive for hepatitis B surface antigen (HBsAg) and who were positive for the e antigen (eAg), median HBV DNA level 8.0 log₁₀ IU/mL (interquartile range [IQR], 7.1, 8.5) were randomized to receive TDF 300 mg versus placebo from 28 weeks of gestation through 2 months postpartum. All infants received HBV vaccine and HBIG, and were breastfed (Abstract 584LB). No transmission occurred in the mothers who were randomized to TDF, whereas 2% of infants treated with HBV vaccine and HBIG developed HBV infection, which is the lowest transmission rate that has been reported in a study of HBV-untreated mothers whose infants received vaccination and HBIG at birth. The difference was not statistically significant, as the study was not powered to detect a difference with the low transmission rate in the control arm. TDF was safe and well tolerated and represents an important tool to prevent mother-to-child transmission of HBV infection, which this study demonstrates can be brought to zero with a combination approach. Placed in context, prior data have shown that 8% to 12% of infants are HBV-infected at birth when born to HBV-infected mothers with high level viremia or who were positive for eAg, despite administration of HBV vaccination and/or HBIG.³

**Hepatitis Delta**

Acute hepatitis delta (HDV) infection was frequent in the 1990s in Spain, particularly in HIV-infected individuals. In a Spanish cohort of PWID, the prevalence of individuals who were positive for HBsAg dropped markedly from 35% in 1993 to 1996 to 6.4% in 2011 to 2014, with a similar decline in HDV from 30% to 4.2% during the same time periods, reflecting, at least in part, the impact of widespread HBV vaccination and implementation of successful needle exchange programs (Abstract 578). Hepatitis delta prevalence was quite high, at 40%, in individuals who were positive for HBsAg from Cameroon, placing them at a higher risk for more severe hepatitis (Abstract 577).

**In HBV-infected mothers with a high HBV DNA level, TDF started at 28 weeks of gestation, in addition to postnatal HBV vaccine and HBIG, led to no mother-to-child transmission of HBV infection.**

**Additional References Cited in Text**


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