Volume **26** Issue **1** April/May **2018**

Topics in Antiviral Medicine™

A publication of the IAS–USA

Highlights of the 2018 Conference on Retroviruses and Opportunistic Infections CME

Topics in Antiviral Medicine™

Topics in Antiviral Medicine™

Topics in Antiviral Medicine™ (formerly *Topics in HIV Medicine*) is published by the IAS–USA. This journal is intended to be a resource for practitioners and scientists who are actively involved in medical care and research.

Editorial Policy

The views and opinions expressed in this journal are those of the contributors and do not necessarily reflect the views or recommendations of the IAS–USA. *Topics in Antiviral Medicine* is supported through grants from several commercial companies that are committed to supporting continuing medical education on HIV, hepatitis C virus, and other viral infections. In the interest of an objective, balanced, and scientifically rigorous publication, the IAS–USA seeks funding that is pooled from companies with competing products; these companies have no input or control over the journal content or the selection of contributors.

All authors and contributors provide disclosures of financial interests, and this information is available at the end of each article.

This journal may contain information about the investigational uses of drugs or products that are not approved by the US Food and Drug Administration. Please consult full prescribing information before using any medication or product mentioned in *Topics in Antiviral Medicine.*

Financial Disclosures

Financial disclosures for members of the IAS–USA Board of Directors and the Editorial Board of *Topics in Antiviral Medicine* are available online at www.iasusa.org.

Copyrights and Reprints

The contents of *Topics in Antiviral Medicine* are protected by copyright. We welcome reference to and use of portions of this journal; however, we do require that permission to reproduce or use any part of the journal be obtained from the IAS–USA. In the case of reprinted or adapted materials where the IAS–USA does not own the copyright, permission to reproduce these materials must be obtained directly from the original source. For more information about reprints, please send an e-mail to journal"at"iasusa.org.

Subscription Information

Topics in Antiviral Medicine is published 4 to 6 times a year. To obtain a subscription or notify the IAS–USA of a change in your e-mail address, please create or update your user profile at www.iasusa.org.

Correspondence

Topics in Antiviral Medicine welcomes editorial correspondence. Address correspondence to:

Editor, *Topics in Antiviral Medicine*
E-mail: journal"at"iasusa.org
Mail: IAS–USA
425 California St, Ste 1450
San Francisco, CA 94104-2120

Phone: (415) 544-9400
Fax: (415) 544-9401

Website: http://www.iasusa.org

On the Web

Current and previous issues of *Topics in Antiviral Medicine* (as well as *Topics in HIV Medicine*) are available online at www.iasusa.org/pub.

ISSN 2161-5853 (Online)

Grant Support

IAS–USA funding comes from a variety of sources. The largest single source of revenue is conference and participant registration fees.

This activity is part of the IAS–USA national educational effort that is funded, in part, by charitable contributions from commercial companies. Per IAS–USA policy, any effort that uses commercial grants must receive grants from several companies with competing products. Funds are pooled and distributed to activities at the sole discretion of the IAS–USA. Grantors have no input into any activity, including its content, development, or selection of topics or speakers.

Scan to access the IAS–USA website

IAS–USA
International Antiviral Society–USA

Volume 26 Issue 1 April/May 2018

Topics in Antiviral Medicine™

A publication of the IAS–USA

Highlights of the 2018 Conference on Retroviruses and Opportunistic Infections CME

Announcements

POST TEST **Visit www.iasusa.org/tam/cme-issues or use the QR code in this issue to access the online posttest.**

Topics in Antiviral Medicine™

CME Information

The IAS–USA is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education (CME) for physicians.

The IAS–USA designates this enduring material for a maximum of 10.75 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This CME activity is offered from **May 3, 2018**, to **May 3, 2019**. Participants who successfully complete the activity posttest and submit the evaluation and registration forms are eligible to receive CME credit. Physicians (MDs, DOs, and international equivalents) may receive CME credit for completing this activity. Other health care practitioners will receive a certificate of participation.

- CME credits available: 10.75 *AMA PRA Category 1 Credits*™
- Release date: **May 3, 2018**
- Expiration date: **May 3, 2019**

To claim CME credit, please read each article and successfully complete the posttest and evaluation form, which will help us evaluate this activity and plan future activities. Your responses will not affect your CME credit.

Learning Objectives

On completion of this activity, the learner will be able to describe the important new data presented at the 2018 Conference on Retroviruses and Opportunistic Infections and the potential clinical implications for patients in the areas of:

- Epidemiology of HIV and HIV prevention efforts
- Basic science understanding of HIV
- Complications of HIV disease
- Viral hepatitis
- Antiretroviral therapy for HIV prevention and management

Intended Audience

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

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

Disclosure of Financial Interests

In the interest of maintaining the independence of its CME activities, and in accordance with the policies of the Accreditation Council for Continuing Medical Education (ACCME), the IAS–USA requires all persons with control of content (ie, authors, IAS–USA Board members, and program staff) to disclose any financial relationships that they (or their spouses or partners) have had with commercial companies within the past 12 months. Any real or apparent conflicts of interest of those parties are resolved prior to the continuing medical education activity being delivered. Individuals who refuse to disclose financial interests may not participate in an IAS–USA CME activity.

Financial affiliations with commercial entities: Dr Buchbinder and Dr Liu have participated in research trials that received provision of medicines from Gilead Sciences, Inc. Dr Currier has received grant support awarded to her institution from Theratechnologies. Dr Luetkemeyer has received grant support awarded to her institution from AbbVie, Gilead Sciences, Inc, Merck and Proteus, and had travel paid for by Merck. Dr Wyles has received grant support awarded to his institution from AbbVie, Gilead Sciences, Inc, Merck, and Tacere, and has served as a consultant or advisor to AbbVie, Gilead Sciences, Inc, and Merck. Dr Tieu has received research grant support awarded to her institution from Merck. Dr Wilkin has served as a consultant to and received grant support awarded to his institution from GlaxoSmithKline/ViiV Healthcare, and his spouse owns stock in Johnson & Johnson. Drs Stevenson, Havlir, Taylor, and Jones and Ms Jacobsen have no relevant financial affiliations to disclose.

Independent educational grants for the 2018 *Improving the Management of HIV Disease*® CME program:

PLATINUM SUPPORTERS
ViiV Healthcare
Gilead Sciences, Inc

SILVER SUPPORTERS
Janssen Therapeutics
Merck

Independent educational grants for the 2018 *Management of Hepatitis C Virus in the New Era: Small Molecules Bring Big Changes* CME program:

PLATINUM SUPPORTER
Gilead Sciences, Inc

BRONZE SUPPORTER
AbbVie

Additional Support Provided by Merck

Drug and Product Disclaimer

This activity may contain information about the investigational uses of drugs or products that are not approved by the US Food and Drug Administration. Please consult full prescribing information before using any medication or product mentioned in this activity.

The views and opinions expressed herein are those of faculty and do not necessarily represent the opinions or recommendations of IAS–USA.

Posttest

Use the QR code or visit www.iasusa.org/tam/cme-issues to complete the posttest and evaluation for this activity and claim CME credit.

Invited Review

CROI 2018: Epidemic Trends and Advances in HIV Prevention

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

At the 2018 Conference on Retroviruses and Opportunistic Infections, trends in and risk factors for in HIV infection were highlighted. In the United States, new HIV diagnoses are highest in the South and among African Americans and are increasing in rural areas. Youth remain highly vulnerable to HIV infection globally. The epidemiology of HIV infections among people who inject drugs is changing, with overdose deaths, a major public health concern. Phylogenetics are being used to identify HIV transmission clusters and hotspots, which can inform prevention efforts. Vaginal microbial dysbiosis and proteomic alterations are associated with increased risk of HIV acquisition, as are the pregnancy and postpartum periods. HIV testing is a central first step for the HIV care and treatment continua, and several innovative strategies to expand HIV testing coverage and frequency show promise. Preexposure prophylaxis (PrEP) uptake is rapidly increasing in some cities, with reductions of new infections at the population level, but use is lower among African Americans and Latinos, youth, cis- and transgender women, and people who inject drugs. PrEP continuation remains a challenge. Two open-label extension studies of the dapivirine vaginal ring demonstrated high uptake, adherence, and reduced HIV infections. Several novel systemic and topical prevention agents show promise in non-human primates.

Keywords: CROI, 2018, HIV, prevention, risk factors, testing, PrEP, preexposure prophylaxis, phylogenetics, microbiome

On this 25th Conference on Retroviruses and Opportunistic Infections (CROI), Jaffe reviewed the early days of the AIDS epidemic and thought ahead about how we can apply lessons learned from addressing the epidemic (Abstract 12). He started by highlighting the role of astute clinicians in recognizing the initial cases of AIDS. In 1981, the first cases of young, previously healthy gay men diagnosed with *Pneumocystis* pneumonia were reported in Los Angeles, followed by case reports of Kaposi sarcoma, an uncommon malignancy, occurring in gay men in New York City and San Francisco. The Center for Disease Control and Prevention (CDC) established a case definition of Kaposi sarcoma/Opportunistic Infection to facilitate the diagnosis of a rising number of cases and investigate several causes of the observed epidemic of immunodeficiency in men who have sex with men (MSM), including a putative infectious agent, an environmental toxin such as nitrates, and "immune overload" as a result of exposure to a range of agents that might cumulatively suppress the immune system. Jaffe pointed to the insights learned from relatively simple epidemiologic studies that suggested an infectious etiology and established transmission routes, even before HIV was identified. This was followed by case reports of new groups at risk for AIDS, including transfusion recipients, infants born to mothers with AIDS, female sex partners of men with AIDS, and people who inject drugs.

In 1983, cases of AIDS were also reported in Africans, however the male to female ratio was 1:1, and cases were not associated with risk factors identified in the United States. Fear began to arise that AIDS was transmitted by casual contact or mosquito bites, leading to discrimination in schools and some health care workers concerned about becoming infected while treating people with AIDS; subsequent epidemiologic studies were conducted to disprove these concerns. Jaffe pointed to the importance of health communication messages based on public health evidence to allay fears and reduce stigma.

Another important lesson learned was the role of advocacy and activist groups in expediting the approval of new antiretroviral drugs. US Food and Drug Administration (FDA) regulations rapidly evolved to address the epidemic, including facilitating earlier access to drugs for life-threatening illnesses prior to approval, allowing drug approval based on clinical trials using surrogate endpoints, and implementing "Fast-Track" drug approval procedures. Funding from sources such as PEPFAR (the US President's Emergency Plan for AIDS Relief) and the Global Fund have paved the way for getting more than 20 million people on treatment globally in 2017. Jaffe remarked that the lessons learned from the early AIDS epidemic will be tested by emerging, epidemic-prone infectious diseases. He pointed to the International Health Regulations and Global Health Security Agenda as providing a framework to improve the global response to disease outbreaks. He also highlighted novel approaches such the use of electronic health records and social media to rapidly detect cases of new diseases and the application of genetic sequencing and phylodynamic analyses to track the spread of emerging infections.

Dr Liu is Assistant Clinical Professor of Medicine at University of California San Francisco and Clinical Research Director of Bridge HIV at the San Francisco Department of Public Health. Dr Buchbinder is Clinical Professor of Medicine and Epidemiology at the University of California San Francisco and Director of Bridge HIV at the San Francisco Department of Public Health. Send correspondence to Albert Liu, MD, MPH, Bridge HIV, Population Health Division, San Francisco Department of Public Health, 25 Van Ness Avenue, Ste 100, San Francisco, CA 94102. Received on March 19, 2018; accepted on March 24, 2018.

Epidemiologic Trends and Risk Factors for Infection

Del Rio described the evolving HIV epidemic in the United States, and started by contrasting the distribution of new diagnoses in 1997 with that in 2016 (Abstract 60). The annual number of new diagnoses fell by a third over that time, from approximately 60,000 in 1997 to 40,000 in 2016. However, the proportion of new diagnoses in MSM increased from 35% to 70%, and the proportion of new diagnoses in the South rose from 37% to more than 50% over that time period. In assessing reasons for geographic disparities in new diagnoses, he pointed to potential structural drivers of the epidemic. Maps of the US distribution of lack of health insurance, poverty, failure to achieve a full high school education, and income inequality show the highest rates are in the South, and these map onto areas of greatest HIV incidence. Of the 2.4 million persons who have not benefitted from Medicaid expansion, 89% live in the South. Florida, Texas, Georgia, and North Carolina alone account for 62% of these persons; these 4 states also account for 40% of all new HIV diagnoses. Maps of linkage and retention in care, as well as viral suppression, also show that these aspects are poorer in the South. Watson and colleagues also addressed the geographic disparities in the United States (Abstract 907). Diagnosis rates are highest in the South overall, at 20.2/100,000 population, compared with 13.6 in the Northeast, 12.1 in the West, and 9.2 in the Midwest. Although African Americans have the highest rates of new diagnoses in all regions, they were highest in the South in 2015 at 58.6/100,000 population, which represents an actual decline from 2010. Rates in Latinos have not declined from 2010 to 2015. and remain at 25.5/100,000 population. There has been improvement in the South in diagnoses in the metropolitan statistical areas (MSAs; >500,000 population) and the metropolitan areas (50,000 to 499,999 population) but rates have not declined in the non-metropolitan areas (<50,000 population). This suggests that new strategies are needed to reach vulnerable populations, including persons living in rural areas, and that substantial efforts are needed in the Southern United States to make further gains in reducing new infections nationally.

From 1997 to 2016, the proportion of new HIV diagnoses in the South increased from 37% to more than 50%

Nwangwu-Ike and colleagues presented data on women in the United States, comparing women in MSAs, metropolitan areas, and nonmetropolitan areas (Abstract 917). African American women made up the majority of new diagnoses in the 3 types of communities. Women in nonmetropolitan areas were somewhat more likely to be diagnosed in Stage 3 HIV infection (AIDS-defining illness) and less likely to be virally suppressed than those in MSAs. White women made up twice the proportion of new diagnoses in nonmetropolitan areas than in MSAs (30% vs 15%, respectively). Handanagic and colleagues reported on data from 4 cities in the National HIV Behavioral Surveillance: Chicago, Detroit, Houston, and Seattle (Abstract 920). HIV prevalence was significantly higher in women who exchange sex (4.9%) than other women of low socioeconomic status (1.6%). Women who exchange sex also had a high prevalence of homelessness and poverty across all cities; drug use was also high but varied between cities. Agnew-Brune and colleagues also reported on women who exchange sex from this study, evaluating the potential role of violence in driving HIV acquisition and risk (Abstract 922). They found that violence was prevalent among this population (client partner physical violence 10%; client partner sexual violence 14%; intimate partner physical violence 32%; and intimate partner sexual violence 29%). All 4 types of violence were associated with condomless anal sex, and both types of sexual violence were associated with past-year injection drug use, increasing the risk for HIV acquisition among this vulnerable population. However, 86% of these women had visited a healthcare practitioner in the prior 12 months, suggesting a role for healthcare practitioners in screening women at risk and linking them to social services to reduce their risk of violence and HIV acquisition. Oster and colleagues reported that the number of HIV diagnoses among MSM who also report sex with women has declined from 2011 to 2015, from 30% to 25% (Abstract 911). This decrease parallels the decline in new diagnoses overall in heterosexual women. Taken together, these studies also point to the social and structural drivers of HIV infection in women and confirm that the epidemiology of HIV infection in rural areas in the United States differs substantially from that in urban areas.

Mitsch and colleagues reported on new diagnoses among American Indians and Alaska Natives in the United States from 2010 to 2015 (Abstract 930). Overall, the annual rate of diagnosis in this population increased by 13.3% over that time period, and the number of diagnoses attributable to MSM contact increased by 42.5%. The investigators call for strengthened prevention efforts for this often-ignored population.

Althoff and colleagues reported on the rate and risk of transmissible HIV RNA among adults on antiretroviral treatment (ART) in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) US and Canadian clinical cohorts (Abstract 904). Using the HIV RNA cutoff of 1500 copies/mL or greater that was seen in the original paper linking viral load with risk of transmission,[1] those who had a transmittable level of HIV were more likely to be women, African Americans, and people who inject drugs. The durability of viral suppression was similar among those initiating antiretroviral treatment in 2005 to 2009 and 2010 to 2014.

Vandormael and colleagues evaluated trends in population incidence of HIV infection among men and women following the roll-out of ART between 2004 and 2015 in rural South Africa (Abstract 46). In a longitudinal HIV surveillance cohort administered by the African Health Research Institute of 7,492 men and 9,908 women in KwaZulu-Natal, the HIV incidence rate declined in men from 2.05 to 0.95 events/100 person-years (py) from 2010 to 2015 ($P = .008$), and HIV incidence remained stable in women at 4.9 events/100

py during this period ($P = .45$), with a slight increase in incidence rates in women over the entire period (2004-2015; $P < .001$). The authors hypothesize that these trends are a result of a gender gap in HIV treatment services. From 2010 to 2015, ART coverage among women increased from 29% to 49% and male circumcision rates increased—both of which would benefit men; ART coverage in men did not increase as substantially during this period, conveying less benefit to women. Their findings highlight the crucial need to get more men on suppressive ART and to develop novel HIV prevention strategies for women.

Youth

Closson and colleagues reported on risk behaviors among 589 young black men who have sex with men in Jackson, Mississippi, 30% of whom were living with HIV (Abstract 915). Of this group, 13% were economically dependent on a sex partner. Compared with men not economically dependent, men who were economically dependent were significantly more likely to be living with HIV (41% vs 28%; $P = .03$), have a high school education or less (57% vs 37%; $P = .001$), and be unemployed (62% vs 39%; $P < .01$). In a multivariable model, men who were economically dependent were also significantly more likely to engage in condomless anal receptive sex and have more sexual partners, an example of how structural factors can lead to increased risk. Mustanski and colleagues reported on individual and network drivers of racial disparities among young MSM, aged 16 to 29 years living in the Chicago, IL, metropolitan area (Abstract 906). Black young MSM had a higher prevalence of HIV (32%; $P < .001$) and rectal sexually transmitted infections (STIs) (26.5%, $P = .01$) than white or Latino MSM. Black MSM reported less risky sexual practices and more lifetime HIV tests, but were significantly less likely to achieve viral suppression. In network analyses, black young MSM were more likely than other race/ethnicities to report a greater number of sexual partners identifying as non-male, non-gay, and HIV seropositive ($P < .001$), and had more homogeneous sexual networks and more concurrent sexual partners. These factors suggest that network factors may drive racial disparities in HIV acquisition. The investigators propose that structural interventions may be useful to reduce disparities.

Several presentations focused on risk factors for young women in Southern and East Africa. Cai and colleagues presented data from the Zambia Population-based HIV Impact Assessment, a nationally representative cross-sectional household survey conducted in 2016 (Abstract 918). HIV prevalence among adolescent girls and young women aged 15 to 24 years was estimated to be 5.7%, more than 3 times the prevalence of their male peers (1.8%). Among these girls and young women who were infected with HIV, only 40% reported being aware of their HIV status. Factors associated with HIV infection included older age (20-24 years vs 15-19 years; aOR, 2.2), living in urban areas (aOR, 2.3), and having past or recent syphilis infection (aOR, 2.4 and 2.9, respectively). These data speak to the need for enhanced HIV screening in populations of young women, and interventions to reduce their risk of HIV acquisition.

Chakalisa and colleagues presented data on young women and men (aged 15-24 years) from the Botswana Combination Prevention Project, an ongoing cluster randomized prevention trial (Abstract 926). In this study, young women were more likely than young men to have been diagnosed with HIV prior to the survey (20% vs 4%, respectively) and more likely to be newly diagnosed during the survey (5% vs 2%, respectively). Having intergenerational sex was associated with an increased risk of HIV infection among women (aPR, 1.3), and having early sexual debut was significantly associated with a positive HIV status for young men (aPR, 3.3). Factors associated with transactional sex among women included having occasional food insecurity (aPR, 2.0) and lack of a cellphone (aPR, 2.1), both pointing to economic factors likely driving the HIV epidemic in this population. The investigators urge that interventions targeting economic vulnerability, such as income transfer and preexposure prophylaxis (PrEP) availability, be developed for young women. Mwinyaa and colleagues also reported that age-disparate relationships (5 years or more difference in age) were associated with increased HIV prevalence among women aged 15 to 17 years in Rakai, Uganda (Abstract 933). Secondary education was associated with lower HIV prevalence among women in this age group. The investigators urged efforts for continued education in young women, including education about the dangers of age-disparate relationships.

Age-disparate relationships (≥5 years difference) are associated with increased HIV prevalence among young women in Uganda

Fisherfolk

In Kenya, counties bordering Lake Victoria have the highest national adult HIV seroprevalence rates. Within these areas, fisherfolk (those who catch, sell, or process fish, and their spouses) have been believed to be at exceptionally high risk. Odongo and colleagues investigated the risk of HIV among fisherfolk compared with others living in the same areas who are not involved in fish trade by conducting a cross-sectional bio-behavioral household survey at beaches and adjacent villages in the Asembo area of the Health and Demographic Surveillance System (Abstract 928). Of more than 3000 interviews, 26% were among fisherfolk. HIV prevalence was 18.4% overall, and significantly higher among fisherfolk than non-fisherfolk (25.6% vs 15.8%; $P < .001$). Although most respondents had previously tested for HIV, 21.8% of those found to be HIV seropositive were unaware of their status. The prevalence of risk factors for increased acquisition was higher among fisherfolk than non-fisherfolk, including lack of circumcision (49% vs 38%), having multiple sexual partners among men (35% vs 26%; $P < .006$), and reporting sex

without a condom (77% vs 47%). Only 6% of women reported multiple sexual partners in the prior 12 months, with no difference between fisherfolk and non-fisherfolk populations. Although treatment coverage was high among those with knowledge of their HIV serostatus, coverage was only 61% when taking into account those without knowledge of their HIV infection. The investigators emphasize the need to scale up testing and linkage to care among this very high-risk population.

Kagaayi and colleagues assessed the impact of targeted and rapid scale up of combination prevention strategies on HIV incidence in a hyperendemic fishing village on Lake Victoria in Uganda (Abstract 90). In this open, population-based cohort of 5005 individuals followed up from 2011 to 2017, ART coverage increased from 19% to 81%, and viral load suppression increased from 33% to 78%. ART coverage was lower among younger age groups; this improved for women but not men over time in the cohort. Male circumcision coverage increased from 39% to 63%, with coverage highest in the younger age groups by 2016. During the study period, overall HIV incidence decreased 58% from 3.97 to 1.61/100 py, with similar declines in men and women and across age groups, and HIV prevalence declined from 41% to 36% (P = .002). No substantial differences in sexual behaviors were observed over time. These findings highlight that HIV treatment and prevention strategies can be rapidly scaled up and can reduce population-level HIV incidence in highburden settings.

From 2014 to 2016 in the United States, new HIV diagnoses among people who inject drugs declined in all groups except for whites, persons aged 13 to 34 years, persons in the Midwest/West, and those living outside central metropolitan areas

People Who Inject Drugs

Approximately 1.6 million people living with HIV globally are thought to be persons who inject drugs. Several presentations focused on characteristics of transmissions within this population, as well as the substantial morbidity and mortality seen. Lyss and colleagues presented data on overall trends in new diagnoses among people who inject drugs in the United States (Abstract 970). Although new diagnoses have decreased 34% from 2010 to 2016, the rate of decline appears to have lessened from 2014 onward, and new patterns of infections appear to be emerging from that time period. From 2014 to 2016, new diagnoses declined in all subgroups of people who inject drugs except whites (increase of 19%), persons 13 to 34 years of age (increase of 12%), persons in the Midwest or West (increases of 33% and 5%, respectively), and those living outside of large central metropolitan areas (increase of 6%). These findings have implications for monitoring for and responses to potential outbreaks within these communities. Agnew-Brune presented data, on behalf of the authors, from the 2012 National HIV Behavioral Surveillance in which dried blood spots were collected from people who inject drugs (Abstract 971). Using the Bio-Rad Avidity Incidence Analysis, they were able to compare recently HIV-infected individuals with HIV seronegative and with chronically HIV infected persons. Compared with HIV seronegative people who inject drugs, those recently infected were more likely to inject drugs other than heroin (mostly stimulants), have a greater number of sexual partners, and be MSM. These data point to the need to build safer sexual interventions into prevention efforts with this population, and not solely focus on safer injection practices. They also found that compared with chronically HIV-infected people who inject drugs, those who were recently infected were more likely to be white and high school graduates, suggesting a demographic shift in injection drug users who are recently acquiring HIV. Similarly, Hogan and colleagues reported on a cluster of HIV infections in 15 largely rural West Virginia counties with a historically low HIV seroprevalence (Abstract 976LB). Most were due to MSM contact, although 15% were attributable to injection drugs, and a number of clusters had potentially susceptible contacts (HIV negative or unknown serostatus) who shared injection equipment in the past year or had contacts who did. They recommended timely public health responses to clusters of infection in low prevalence areas to avoid further onward transmission.

Two presentations focused on the HIV epidemic among people who inject drugs in New York City. Torian and colleagues conducted phylogenetic analyses that revealed 2 separate waves of the epidemic in New York (Abstract 973). The first wave started in the mid-1970s was characterized by black and Latino men and women 40 years of age and older, and occurred predominantly in the Bronx and Brooklyn. A second wave began in the late 1990s and focused predominantly in MSM who inject drugs. These persons were younger; had more racial, ethnic, and geographic diversity; and were more likely to use a variety of drugs. The investigators raised concerns that with 16,000 people who inject drugs and 2,800 MSM/people who inject drugs in New York, a third wave could be introduced if a bridge occurs with outside networks of injection and sexual risk. Braunstein and colleagues presented data on people who inject drugs in New York who died of accidental or intentional drug overdoses (Abstract 974). Although overdoses declined from 2007 to 2013, overdose deaths have increased from 2013 to 2016, from 35.5 deaths/100,000 population to 53.8/100,000 population. Approximately 7% of overdose deaths were intentional, and the remainder were accidental. Accidental overdose deaths occurred predominantly in men (69%), African Americans (39%), Latinos (38%), those aged 40 to 59 years (76%), and non-MSM people who inject drugs (48%). Those dying from intentional overdoses were nearly all men (91%), white (71%), older (23% aged 60 or older), and MSM/people who inject

drugs (66%). Overall, 80% had been retained in medical care in the year prior to their death, pointing to the need for linkage to services and overdose prevention measures (such as naloxone) for all substance-using patients.

Kornilova and colleagues presented compelling data from Crimea and Eastern Ukraine (Abstract 961). They found that the prevalence of HIV among people who inject drugs has increased substantially throughout the region, to approximately 33% in several areas. This increase is coincident with a reduction in access to clean needles from 44% to 79% in 2015 to 12% to 54% in 2016. They conclude that the Russian military intervention in Eastern Ukraine and the annexation of Crimea have caused an important public health problem through a ban on opioid substitution therapy and a major reduction in HIV prevention programs.

Ball and colleagues presented data on the relationship of type of opioid injection and the risk of HIV acquisition in London, Canada (Abstract 963). Through carefully constructed epidemiologic and laboratory-based testing, they found that sharing injection drug preparation equipment such as cookers and filters was statistically significantly associated with an increased risk of HIV acquisition: compared with not sharing syringes or needles or preparation equipment, injection drug users had an increased risk of HIV acquisition if they shared preparation equipment only (OR, 22.1) or preparation equipment and needles or syringes (OR, 23.9). There was no increased risk associated with sharing needles or syringes alone. They then went on to test residual levels of controlled-release versus immediate-release hydromorphone, and found the former left 45% residual drug in the syringe, and the latter left only 15%. They suggested that because of the residual drug left in syringes of controlled-release hydromorphone, people who inject drugs are incentivized to frequently wash the preparation equipment to obtain more drug, leading to increased contamination. Moreover, HIV was preserved in syringes with controlled-release but not immediate-release hydromorphone, likely because of excipients in the long-acting preparation. They also found that people who inject drugs who believed it was "unnecessary or harmful" to heat the controlled-release hydromorphone in the preparation equipment were more likely to become HIV infected. Heating the equipment rapidly inactivated HIV. In combination, these behavioral and biologic factors may be leading to an increase in the number of new infections within this community, where controlled-release hydromorphone tablets are the local opioid of choice.

Phylogenetics and Identifying HIV Hotspots

At the annual Clinical Trials Design and Analysis Workshop, Little focused on the methodology and interpretation of phylogenetic studies (Abstract 6), an excellent tutorial for interpreting the many phylogenetic analyses presented at this year's conference. Several investigators assessed the feasibility of using real-time phylogenetics to identify undiagnosed persons and interrupt further onward transmission. Although none actually tested whether interventions based on phylogenetic analysis could interrupt transmission, many were able to identify potential transmission hotspots with the hope that future analyses could evaluate the impact of such interventions.

Mulka and colleagues attempted to identify the potential source of transmission of recently infected persons in Brighton, England and assess the public health utility of such phylogenetic surveillance activities (Abstract 944). They identified a likely source of transmission for 84% of recently infected persons, although many of the sources were not local, requiring access to national data. They also found that 47% of likely sources were undiagnosed at the time of transmission, suggesting that such surveillance activities may allow earlier diagnosis of partners and prevention of further onward transmission.

Ragonnet-Cronin and colleagues evaluated cluster growth using phylodynamic reconstruction in Los Angeles County, and found that cluster growth in the prior year predicted future cluster growth, pointing to networks of transmission that could be prioritized for public health interventions (Abstract 949). Panneer and colleagues used US national data and found that clusters were more likely to grow when at least 1 member was not virally suppressed, although even clusters in which all persons were virally suppressed grew, suggesting individuals outside of the known cluster were likely contributing to onward transmission. They recommended that clusters with low rates of viral suppression be prioritized for cluster investigation and intervention. Wertheim and colleagues also evaluated US national data and found that clustered cases had higher viral loads than non-clustered cases across all stages of infection, although the difference in viral load was relatively small (Abstract 956). Nonetheless, they inferred from these data that US strains associated with higher viral load were more likely to transmit and thus cause clustering. These data would also suggest prioritizing clusters associated with higher viral loads for targeted intervention. McLaughlin and colleagues presented a novel analysis mapping the rate of spread (using phylogenetics) along with community viral load and HIV incidence to identify neighborhoods with high rates of HIV transmission, possibly identifying locations to be targeted for prevention and treatment interventions (Abstract 953). Brenner and colleagues evaluated sequences from MSM in Quebec, Canada (Abstract 946). They found that approximately half of the HIV infections were part of small self-limiting clusters of 1 to 4 persons, but that large cluster sizes (20-145 persons) increased from 13% in 2004 to 2007, to 25% in 2008 to 2011, and 42% in 2012 to 2015. They report that 10 to 12 clusters of 20 or more persons fueled the spread of HIV in each of these periods, suggesting that these large

Among people who inject drugs, sharing injection drug preparation equipment, such as cookers and filters, is associated with an increased risk of HIV acquisition

clusters should be the focus of targeted interventions to reduce onward transmission.

Several presentations focused on new approaches for tracking the epidemic and identifying HIV hotspots in Africa. Cuadros and colleagues assessed the role of geographic HIV hotspots in the spread of the epidemic within the same cohort in rural South Africa (Abstract 43). Among 18,294 individuals located in Kwazulu-Natal, a geographic cluster with high numbers of HIV infections (an HIV 'hotspot') was identified using spatial analysis. This hotspot contained 41% of the total HIV seropositive persons in the region, and individuals located in this cluster had a 46% higher risk of HIV infection. Using phylogenetic analyses of sequences from 1,222 HIV seropositive individuals, 351 transmission links were identified, 79% of which included at least 1 individual located within the HIV hotspot. Microsimulation models showed that the HIV transmission did not follow a random pattern, and the hotspot appeared to play a role in link formation and network configuration. The authors suggest that these geographic hotspots may play a key role in the HIV transmission network, and targeting combination prevention strategies to these regions could not only lower HIV incidence within the hotspot, but also disrupt the dispersion of HIV infection in the entire community.

Using a multidisciplinary approach combining epidemiology, phylogenetics, and social science, Coltart and colleagues identified the emergence of concentrated microepidemics, also using the Africa Health Research Institute cohort data (Abstract 47LB). In a phylogenetic analysis of 2,179 HIV-1 subtype C sequences in Kwazulu-Natal identified between 2000 and 2014, a large, single monophyletic cluster of 75 highly-related sequences was identified. Individuals in this cluster were more likely to be men, have full-time employment, be wealthier, and have higher education. Using geospatial mapping, 2 geographic clusters were identified, each with 40% of cases. Although one of these clusters was located within the known hotspot region described above, the second was located in a rural area with previous low HIV prevalence. Through an ethnographic assessment, it was identified that a new mine was established in this area, resulting in an influx of money and employment (especially young male miners and truck drivers), as well as displacement of households in the area and increased opportunities for transactional sex and access to alcohol. These findings highlight the continued emergence of concentrated microepidemics within an existing endemic region, and the unintended negative health consequences that can arise from rapid economic development. They recommend that HIV prevention services be developed in parallel with economic expansion and be flexible and adaptable to local conditions.

Measuring Population Level Incidence

Several presentations at this year's CROI described novel methods to measure population-level HIV incidence, an important metric to monitor HIV transmission trends, identify at-risk populations, and evaluate HIV prevention strategies. Burnett and colleagues used successive cross-sectional surveys to estimate HIV incidence rates among at-risk populations in the United States (Abstract 44). Using the National HIV Behavioral Surveillance system, which conducts cross-sectional surveys every 3 years among MSM (2008-2014), persons who inject drugs (2009-2015) and heterosexuals at high risk (2010-2016), they simulated a nested retrospective cohort by analyzing data from participants who tested HIV seronegative at the first visit and had at least 1 repeat observation across the surveillance cycles. There were 127 seroconversions or an incidence rate of 2.5/100 py among 1076 MSM; 73 seroconversions or an incidence rate of 0.6/100 py among 2534 injection drug users; and 17 seroconversions or an incidence rate of 0.4/100 py among heterosexuals. These estimates are consistent with previously published HIV incidence rates in these populations. The authors suggest that using successive cross-sectional surveys to simulate a cohort may serve as another strategy to estimate HIV incidence, but recommend that results be triangulated with other incidence estimates.

The Limiting-Antigen Avidity Assay is being utilized internationally for cross-sectional estimation of population HIV incidence, but has not been validated in regions with HIV subtypes A and D. Laeyendecker and colleagues validated the assay's ability to estimate and detect changes in HIV incidence in the Rakai Community Cohort Study in East Africa (Abstract 1001). In this cohort, 45% of sequences were subtype A and 55% were subtype D. The observed HIV incidence declined from 1.05% in 2008-2009 to 0.66% in 2011 to 2013, but per protocol estimates using the Limiting-Antigen Avidity Assay overestimated HIV incidence and showed an increase in incidence. However, after adjusting parameters of the model (mean duration of recent infection and false recent rate), estimated incidence was 0.88% and 0.67% in the first and second periods, more closely matching the observed incidence.

Stephenson and colleagues evaluated a new assay measuring antibody epitope signatures to determine recency of infection (Abstract 1004). Using the HIV-1 Peptide Microarray, they found ART-naive individuals who were recently infected (<12 months ago) had significantly fewer positive HIV Env peptide responses than those infected more than 12 months ago (50 vs 138; $P = .0002$). Findings were similar when comparing recent infections with non-recent infections in ART suppressed patients (50 vs 82; $P = .0554$). The authors conclude that the epitope signature is narrow in recent infection, then becomes broader and more diverse after 12 months of infection. They suggest that further optimization of the microarray assay may allow for incidence estimation in larger cohorts.

Biologic Risk Factors for HIV Infection

Microbiome

Klatt presented an overview of the role of the vaginal microbiome in HIV acquisition in women (Abstract 64). She began by defining the microbiome as microorganisms

in an environment (approximately 10-100 trillion/person), including bacteria, viruses, fungi, protists, and archaea, and their genes, metabolites, and products; and dysbiosis as an imbalanced microbial community resulting from a change in the abundance or function in microbiota. She pointed out that although the high diversity of the microbiome in the gastrointestinal tract is favorable, dominance by the single bacterium, *Lactobacillus*, in the vaginal tract is associated with a low pH and is healthy and protective. In contrast, vaginal microbial dysbiosis is characterized by dominance by polymicrobial anaerobic bacteria (eg, *Gardnerella sp*, *Prevotella sp*, *Mobiluncus sp*, and *Atopobium sp*), which are associated with a high pH, inflammation and barrier damage of the vaginal epithelium, and greater susceptibility to STIs. She explained that the vaginal microbiome can be classified into 4 distinct community type (CT) structures, with CT1/CT2 being lactobacillus dominant and CT3/CT4 being more diverse and anaerobic-dominant. She described bacterial vaginosis as the typical clinical diagnosis of microbiome dysbiosis, which is often refractory to antibiotic treatment, and pointed out that a clinical diagnosis of bacterial vaginosis does not accurately predict vaginal dysbiosis when evaluated by bacterial population sequencing. Klatt showed data indicating that the vaginal microbiome is diverse across ethnicities, with higher lactobacillus populations in white women, and more diverse microbiome communities observed in other ethnicities. She also highlighted that increased vaginal dysbiosis prevalence was observed in regions of high HIV infection rates in women, and across a number of studies, vaginal dysbiosis and bacterial vaginosis were associated with increased risk of HIV acquisition. Furthermore, men who have female sex partners with bacterial vaginosis are at increased risk of HIV acquisition, and there is also a higher risk of mother-to-child transmission in women with bacterial vaginosis.

Vaginal microbial dysbiosis is characterized by diverse, polymicrobial bacteria and is associated with inflammation, barrier damage, and a greater susceptibility to sexually transmitted infections

Klatt discussed the mechanisms by which vaginal dysbiosis increases HIV transmission. First, vaginal microbial dysbiosis is associated with inflammation, characterized by increased cytokines, chemokines, and neutrophils in the vaginal tract. Second, dysbiotic vaginal bacteria can reduce epithelial barrier integrity, with studies demonstrating that *Lactobacillus sp* promoted and *Gardnerella sp* worsened wound healing. Additionally, the vaginal microbiome can also alter the efficacy of topical PrEP. In the CAPRISA (Centre for the AIDS Programme of Research in South Africa) 004 trial of 1% tenofovir vaginal gel, prevention efficacy was 61% in women with Lactobacillus-dominant microbiome, but only 18% in women with non-Lactobacillus dominance. Pharmacokinetic studies have demonstrated increased degradation of tenofovir in the presence of *Gardnerella sp*, suggesting that dysbiotic bacteria directly metabolize tenofovir and therefore lower efficacy.[2] In experiments in which cervicovaginal lavage samples were analyzed from women with and without bacterial vaginosis, degradation of both tenofovir and dapivirine but not tenofovir alafenamide was observed in the presence of dysbiosis. To better understand the impact of dysbiosis on drug metabolism and HIV acquisition risk, she emphasized the importance of collecting mucosal samples in future trials. She ended by pointing to several potential therapeutic interventions for vaginal dysbiosis, including use of probiotics, microbiome material (vaginal fluid) transplant, phage therapy, and gene targeting or editing.

In a themed discussion, Burgener and colleagues reported on cervicovaginal host and bacterial factors that contributed to HIV infection among women in the CAPRISA 004 trial (Abstract 271). Using a metaproteomics approach, they identified a molecular signature that was associated with epithelial disruption and neutrophil activity; this signature was associated with a 4-fold increase in HIV acquisition. These biomarkers associated with sites of HIV susceptibility in rhesus macaques. Additionally, this HIV risk signature was associated with having a highly diverse, non-Lactobacillus-dominant microbiome (CT4). Women with both CT4 and the HIV signature had a 9-fold increased HIV risk, compared with women without the signature and with CT1.

In a nested case control study, Srinivasan and colleagues evaluated the impact of vaginal microbiota on HIV risk among 586 African women (150 cases, 436 controls) in the VOICE (Vaginal and Oral Interventions to Control the Epidemic) Study (Abstract 268). In a multivariable model, 7 bacterial species were significantly associated with increased risk of HIV acquisition: Eggerthella sp Type 1 ($P = .027$), *Gemella asaccharolytica* ($P = .001$), *Leptotrichia* and *Sneathia spp* ($P = .045$), *Megasphaera sp* Type 2 ($P < .001$), *Mycoplasma hominis* ($P < .001$), *Prevotella bivia* ($P = .055$) and *Parvimonas sp* Type 2 ($P = .02$). Additionally, women with the highest concentrations of *Lactobacillus crispatus* had a decreased risk of HIV acquisition ($P = .034$).

Noël-Romas and colleagues reported on microbiome and proteomic alterations with dapivirine use in adolescent girls in the MTN-023/IPM 030 study (Abstract 1057). In an analysis of 35 women (27 in dapivirine arm, 8 in the placebo arm), there were subtle alterations in the vaginal proteome in the dapivirine arm (7.2% human proteins were differently abundant); however, this did not pass statistical significance thresholds. Most women had a *Lactobacillus*-dominant microbiome, which did not differ significantly by study arm. These findings support the mucosal safety of dapivirine for HIV prevention in adolescent girls.

Pregnancy

Heffron and colleagues estimated the per sex act probability of HIV acquisition during periods of pregnancy and

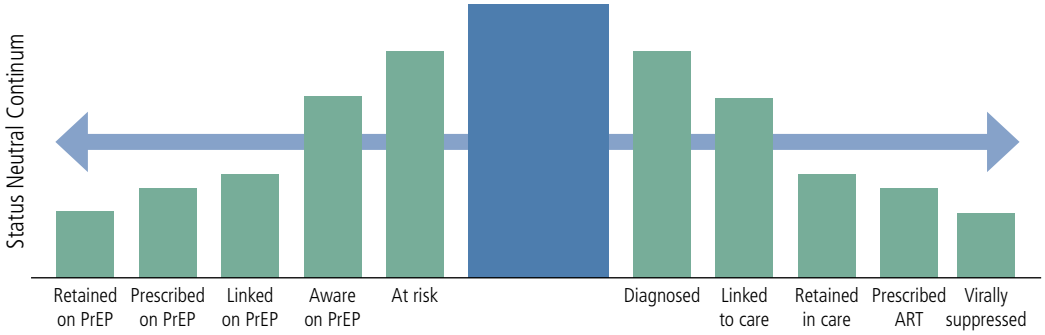


Figure. In the Status Neutral Continuum, the HIV prevention continuum (left) is for individuals who test HIV-negative, and the HIV treatment continuum (right) is for individuals who test HIV-positive. PrEP, preexposure prophylaxis; ART, antiretroviral therapy. Adapted from Abstract 61 and https://www.nastad.org/domestic/hiv-prevention-health-equity.[3]

postpartum in 2 longitudinal prevention studies of HIV serodiscordant couples in Africa (Abstract 45). Among 2,751 HIV seronegative women enrolled in the Partners in Prevention HSV/HIV Transmission Study or Partners PrEP Study, 22% were ever pregnant during follow-up. Although the frequency of sex acts declined during late pregnancy (at 14 weeks gestation to delivery) and the post-partum period (delivery to 6 months postpartum), the HIV infectivity rate per 1,000 sex acts was 1.05 during periods unrelated to pregnancy, 2.19 during early pregnancy (0-13 weeks gestation), 2.97 during late pregnancy, and 4.18 during the postpartum period. After adjustment for condom use, age, PrEP use, and HIV RNA level in the male partner, the probability of HIV transmission per sex act was significantly higher in late pregnancy (aRR, 2.82) and postpartum (aRR, 3.97) than in non-pregnant time. These results suggest that biologic changes associated with pregnancy and postpartum contribute to increased HIV risk and highlight the importance of counseling and promoting women-controlled HIV prevention strategies during these periods.

The probability of HIV transmission per sex act is substantially higher in late pregnancy and postpartum

Tobin and colleagues reported on pregnancy associated alterations in the vaginal proteome that are linked to HIV acquisition (Abstract 267). In a metaproteomic analysis of cervicovaginal lavage samples from 23 pregnant and 25 non-pregnant women in an OB/GYN clinic in Los Angeles, host proteomic changes were seen in pregnancy that were associated with immune system depression, increased blood vessel formation, and decreased mucosal barrier function. Pregnant women with cervical ectopy had the strongest overlap with host proteomic signatures predicting increased HIV risk in CAPRISA 004. Additionally, bacterial metabolic functional pathways were altered in pregnancy, including increased carbohydrate metabolism and neutrophil function. The authors suggest that these observed proteomic and metabolic changes may play a role in increased HIV susceptibility in pregnancy.

Advances in HIV Testing

In a symposium presentation, Scott provided an overview of important issues related to HIV testing and linkage (Abstract 61). He framed HIV testing as being central to the status neutral continuum, as an HIV test result is the first step in engaging the HIV treatment continuum for those who test positive, or the HIV prevention continuum for those who test negative (Figure). He highlighted that a number of structural and social factors (eg, stigma) are significant barriers that impact the ability of individuals to undergo HIV testing and enter these continua of care. He reviewed several new HIV testing approaches, including interventions at the individual, social, and structural levels to increase uptake of HIV testing. Scott also highlighted that linkage to HIV prevention or care services is essential after HIV testing and share common steps including navigating a complex healthcare system, linkage to a knowledgeable, non-stigmatizing clinician, having clinic availability for visits, and coverage for visits, laboratory testing, and medications.

Increasing Testing Coverage

Several presentations assessed strategies to increase HIV testing coverage and identify new diagnoses. Joseph and colleagues evaluated the impact of expanded HIV testing eligibility on the detection of HIV infections in Western Kenya (Abstract 146). In March 2017, 7 Ministry of Health (MOH) facilities in 3 counties (Homa Bay, Siaya, and Kisumu) with high HIV prevalence expanded eligibility for HIV testing from annual HIV testing (having a last negative HIV test ≥12 months ago) to having a last HIV negative test in the last 3 to 12 months or an unverified negative HIV test less than 3 months ago. Among 119,950 individuals screened for eligibility, 79% were eligible, of whom 97% were tested. Twenty-percent met MOH testing criteria, of whom 435 (2.4%) tested HIV-positive, and 80% met the reduced interval testing criteria, of whom 750 (1%) tested positive. Although the MOH criteria testing criteria had a 2.4 fold higher yield in identifying HIV-positive individuals, the expanded testing approach identified 63% of all HIV-positive cases. The greatest incremental gains were observed among women 15 to 24 years of age and men and women 25 to 49 years of age. The authors highlight the continued importance of HIV testing in health facilities to identify young women and men living with HIV, and that reducing the testing interval in high prevalence settings could increase timely diagnosis and treatment.

Joseph and colleagues reported on the uptake of HIV testing through door-to-door home-based HIV testing services in Western Kenya (Abstract 985). Among 177,559 residents

tested, 7% had never tested, 23% were tested over a year ago, and 69% were tested in the past year. Overall, 1937 individuals (1.1%) tested newly positive (1.2% female, 0.9% male), with 57% of infections detected among individuals tested within the last year. Residents whose last test was more than 12 months prior (aOR, 1.54) and who were aged 25 to 34 years versus older than 35 years (aOR, 1.96) were more likely to test positive. Among individuals newly diagnosed with HIV, 76% were linked to ART.

To address lower testing rates and HIV-status awareness among men in sub-Saharan Africa, Casalini and colleagues reported on the role of community-based services in reaching high-risk men in Tanzania (Abstract 983). Through the US Agency for International Development (USAID)-funded Santi Project providing community-based combination prevention, testing, and linkage services, 367,245 men were tested, of whom 49% tested for the first time. More than 13,000 new HIV cases were diagnosed in men. Testing HIV-positive was associated with being older, a first-time tester, and a partner of a female sex worker, and reporting no or inconsistent condom use (all $P < .001$). The authors recommend condom promotion and provision for all men at risk for HIV, and offer of community-based PrEP services to those at higher risk for infection.

Kwarisiima and colleagues evaluated characteristics of people who remained untested for HIV after a 2-year testing intervention achieving near-universal population HIV testing (Abstract 145). The SEARCH (Sustainable East Africa Research on Community Health) test and treat trial employed a novel "hybrid" testing approach using multi-disease community health campaigns followed by home-based testing of campaign non-participants in 16 intervention communities in Kenya and Uganda. Among 77,774 stable residents, 98% had been tested for HIV after the 2-year intervention. Out-migration was the most common reason for not testing. Non-testers were more likely to be men (66% of never tested vs 44% of tested), living in Kenya (50% of never tested vs 35% of tested for not living in Kenya), and have higher education (11% of never tested vs 4% of tested for no higher education). In multivariable models, men between the ages of 25 and 44 years and who were mobile (spent more than 3 months away from the community) were more likely to have never tested, and women who were single, older (≥25 years), and had no known HIV-positive adult in the household were more likely to have never tested. The authors recommend novel strategies to reach migrant populations who represent the greatest proportion of those not tested in this cohort.

Vandormael estimated the percentage of undiagnosed HIV cases within a hyperendemic community in Kwazulu-Natal, South Africa (Abstract 988). From 2006 to 2016, HIV prevalence increased from 22% to 37%, and the percentage of undiagnosed HIV cases declined from 29% to 19%, with an upper bound of 38%. As these levels are much higher than the 10% target set by the UNAIDS, the authors highlight the need for a high level of repeat HIV testing to minimize the time from infection to diagnosis.

Assoumou and colleagues compared rates of test result delivery with rapid versus laboratory-based testing for HIV and hepatitis C virus (HCV) infection within a drug detoxification center in the Boston area (Abstract 991). Two-hundred participants were randomly assigned to receive point-of-care rapid HIV and HCV testing (Orasure) or laboratory-based testing (HIV Combo Ag/Ab EIA, HCV EIA). Overall, 1 (0.5%) had a reactive HIV test, and 96 (48%) had a reactive HCV test. A greater percentage of participants in the rapid testing arm (96%) received their test results than did in the laboratory-based testing arm (51%). In a multivariable model, rapid testing (OR, 22.3) was associated with increased likelihood of test result delivery, and black race (OR, 0.26) was associated with a lower likelihood of result delivery.

Several presentations evaluated barriers to HIV testing in different settings. Nuwagaba-Biribonwoha and colleagues reported on barriers to HIV testing in Swaziland (Abstract 986). Among 2196 HIV-positive participants in Link4Health, a cluster-randomized trial evaluating a combination intervention to enhance linkage and retention in care, more than half (54%) reported no prior HIV test at baseline, and only 11% were aware of their HIV status. Men, youth aged 18 to 25 years and older adults (>50 years), those needing more family support, and those living 45 minutes or farther from the clinic were less likely to be aware of their HIV-positive status. Mabuto and colleagues reported on missed opportunities for HIV testing in primary clinics in South Africa (Abstract 987). Among 2989 exit interviews conducted across 10 clinics, only 289 (10%) clients were offered HIV testing. Women were more likely than men to be offered (11% vs 5%) and accept (87% vs 75%) testing. HIV testing was often offered at the end of a clinic visit, and engaging in HIV testing increased the total visit time by 1 hour and 20 minutes. Barriers to testing in the primary care setting included limited counselor availability, shortage of counseling rooms, queues during peak hours, and clients not wishing to wait for HIV testing. The authors recommend addressing structural barriers to HIV testing, including offering HIV testing earlier in the clinic visit and streamlining the testing and counseling process.

HIV Self-Testing

Several studies evaluated the impact of HIV self-testing in different settings. Lippman and colleagues assessed the acceptability and uptake of HIV self-testing and peer-based distribution among HIV-negative MSM in South Africa (Abstract 149). Participants received their choice of oral fluid or blood fingerstick self-test kits at baseline and 3 months. Among 127 MSM enrolled, 91% used at least 1 HIV self-test kit during the 6-month study. Fingerstick tests were preferred, with 55% MSM choosing only the blood test, 20% choosing the oral test, and 25% choosing both (they were allowed to switch at 3 months). Overall, 68% tested alone, 32% tested with others present, and 24% tested concurrently with another person using a self-test. Participants distributed 728 test kits to friends (52% of kits), family members (30%), and sexual partners (19%). Seven participants seroconverted during the

study (1 during the formative phase), of whom 70% were linked to care, and 40 new diagnoses were reported among recipients of test kits. Among participants who used at least 1 self-test kit, 83% preferred the HIV self-test for their next testing experience, of whom 65% preferred the blood test. Regular testing (at least every 6 months) increased from 38% at baseline to 78% at followup ($P < .01$), and 100% of participants anticipated they would test in the next year if HIV self-testing were available, compared with 86% if only clinic-based testing were available.

In the same region, Pettifor and colleagues evaluated the uptake of HIV self-testing among 284 young South African women (Abstract 992). Among women randomized to a choice of HIV self-testing kits or free HIV counseling and testing (HCT) at a local clinic, 97% reported testing within 3 months, compared with 48% women randomized to standard of care (free clinic-based HCT) (relative risk [RR], 2.00; 95% confidence interval [CI], 1.66-2.40). Almost all (96%) women in the choice arm selected the HIV self-testing kit option. Furthermore, women in the choice arm were more likely to invite peers and partners to test (300 individuals) versus the HCT arm (170 individuals).

HIV infection can be accurately diagnosed at low HIV RNA levels, which should be repeated within 1 week of initiating ART

Pollard and colleagues evaluated an innovative approach of distributing HIV self-test kits via a digital vending machine located in a gay sauna in the UK (Abstract 995). From June to December 2017, 204 self-testing kits were dispensed to MSM, of whom 4% had never tested and 17% had tested more than a year ago. The uptake of self-HIV tests via the vending machine was higher than via community outreach testing at the sauna during the same period (35 vs 4.56 tests per month, respectively). Qualitative interviews and online survey data indicated high acceptability of the vending-machine delivered test kits.

Ortblad and colleagues evaluated the ability of female sex workers to accurately interpret HIV self-test results (Abstract 993). Among 544 female sex workers who completed HIV self-test training by a peer and were asked to interpret color images of HIV self-test results, rates of incorrect interpretation of strong HIV-positive, strong HIV-negative, inconclusive, and weak HIV-positive results were 15%, 18%, 23%, and 61% respectively. Overall sensitivity and specificity were 82% and 85%, lower than in previous studies in which participants interpreted their own self-test results, where results may be biased by prior HIV testing and knowledge of one's HIV risk behaviors. The authors recommend improved training and support to ensure correct interpretation of HIV self-test results, and manufacturer redesign of self-test results to ease interpretation.

As concerns have been raised that HIV self-testing may lead to increases in sexual behaviors, Oldenburg and colleagues evaluated the effect of HIV self-testing on sexual partner numbers in Zambian female sex workers (Abstract 148). In the Zambian Peer Educators for HIV Self-Testing (ZEST) study, 965 women were randomly assigned to direct delivery of HIV self-tests from a peer educator, coupons to be exchanged for an HIV self-test at a facility, or referral to standard HIV testing. At 4 months, participants reported fewer clients per night in the direct peer delivery (mean difference, -0.8 clients) and facility-based coupon (mean difference, -0.7 clients) arms, than with standard of care. Similar declines were seen in non-commercial sex partners (-3.2 partners in direct delivery and -1.8 in coupon arms). Use of condoms with commercial and non-commercial sex partners did not differ across arms.

As self-perceived viral load may influence sexual practices in HIV-positive MSM, Teran and colleagues compared self-reported viral load with HIV RNA assessed via home self-collected dried blood spots (DBS) among high-risk MSM (Abstract 997). Among 337 participants who provided a DBS specimen, 53% had a detectable viral load, despite most reporting ART use and a self-reported undetectable viral load (84%). Furthermore, 48% of participants self-reporting an undetectable viral load had detectable viremia, of which one-quarter had an HIV RNA level above 1000 copies/mL. Men living with HIV for more than a year were more likely to have a disagreeing self-reported viral load and DBS-based viral load (88% vs 77%; $P = .01$), and men who were engaged in care were less likely to have a disagreeing viral load (91% vs 97%; $P = .04$). The authors highlight the need for validation of self-reported viral load status in behavioral surveys.

Diagnosing Acute HIV Infection

The diagnosis and rapid treatment of acute HIV infection has important public health implications, and several presentations evaluated strategies for diagnosing acute HIV infection. Colby and colleagues reported on the diagnosis of acute HIV infection at very low HIV RNA levels (Abstract 998). Among 462 acute HIV infection cases enrolled in an acute infection cohort in Thailand between 2009 and 2017, 54 (12%) were diagnosed with HIV based on low viral load (HIV RNA < 5000 copies/mL) alone (Fiebig stages 1-2). No false-positive HIV RNA tests were identified. ART was started at baseline, and HIV RNA was detectable in all participants through day 7, with 20% having an undetectable RNA at 2 weeks. HIV serology with a third-generation immunoassay demonstrated HIV seroconversion in 87% of participants at 12 weeks. Based on these results, the authors conclude that ART can be started in individuals diagnosed with acute HIV infection based on low viral load, and repeat HIV RNA testing should be done within 7 days, when it should still be detectable; HIV serology can be repeated at 12 weeks, and should be positive in the majority of cases.

Risk- and symptom-based scores have been developed to predict recent HIV infection and may be used to reduce costs by avoiding nucleic acid testing (NAT) and increasing diagnostic yield. Lin and colleagues validated the Amsterdam Risk and Symptom-Based Score (Amsterdam Score) among

a large acute HIV infection cohort among MSM in San Diego (Abstract 999). Among a cohort of 757 MSM (110 with acute HIV infection; 647 HIV NAT-negative), the Amsterdam Score was predictive of acute HIV infection (receiver operating characteristic area-under-the-curve [AUC], 0.88), with a sensitivity of 81% and specificity of 78% when the optimal cut-off score of 1.6 or higher was used. Using this cut-off, 23 of 110 acute HIV infection cases would be missed, however 524 of 647 NAT tests would be avoided. This risk score outperformed previous risk-based scores in identifying acute HIV cases (the San Diego Early Test [SDET] score: AUC 0.70; Menza's risk-based score: AUC 0.67; and Smith's risk-based score: AUC 0.74).

Lin and colleagues also developed and validated the San Diego Symptom Score for identifying acute HIV infection in more generalized populations (Abstract 1000). Among 998 participants in an acute HIV infection cohort in San Diego (113 with acute HIV infection, 885 HIV negative), 11% were cisgender women. Men and women reported the same number of symptoms (P = .60). In a multivariable model, fever (aOR, 10.9, assigned 11 points), myalgia (aOR, 7.8; 8 points), and weight loss of 2.5 kg or more (aOR, 4.1; 4 points) were strongly associated with acute HIV infection. This symptom-based score was predictive of acute HIV infection (AUC, 0.85), with a 72% sensitivity and 96% specificity at an optimal cut-off of 11 or higher. A limitation in this analysis was that there was only 1 cisgender woman with acute HIV infection in this cohort.

Quarterly HIV screening among young men who have sex with men in the United States is cost effective and increases detection of cases, improves the care continuum, and reduces onward transmission

Cost-Effectiveness

Johnson and colleagues evaluated the population-level impact and cost-effectiveness of different HIV testing strategies in South Africa (Abstract 147). Using agent-based mathematical model projected over the 2019 to 2039 period, the researchers found that the most efficient strategies (numbers of new HIV diagnoses per test) included testing the partners of newly diagnosed individuals, patients with opportunistic infections, sex workers on PrEP, and MSM (existing strategies), as well as assisted partner notification, testing female sex workers, MSM, and partners of HIV-positive pregnant women (new strategies). The least efficient testing strategies included school and home-based testing. On the other hand, the most effective strategies to reduce the undiagnosed fraction of the HIV-positive population included home-based testing with HIV self-test distribution, mobile testing, and testing in the workplace and family planning clinics. In examining testing costs alone using incremental cost-effectiveness ratios (ICERs), the most cost-effective strategies included testing MSM, assisted partner notification, and workplace testing, and the least cost-effective strategies included home and school-based testing and mobile testing. When considering costs of the overall HIV program, including ART costs, cost-saving strategies included testing of MSM, sex workers, assisted partner notification, and secondary distribution of self-testing kits to partners of pregnant women. During the audience discussion, concerns were raised about the focus on the yield of different strategies versus maximizing the number of HIV-positive individuals diagnosed and linked to care; a recommendation was made to also evaluate the cost per new HIV case identified.

Neilan and colleagues evaluated the cost-effectiveness of regular HIV screening for young MSM (Abstract 1146). Using a microsimulation model among high-risk, HIV-uninfected 14-year-old MSM, the authors modeled several HIV testing strategies, including every 3 years, annually, biannually, and quarterly, in addition to current US screening practices among young MSM. Any repeat screening program above current testing practices detected a substantial proportion of those HIV-infected by age 23 years (63-97%), with quarterly screening detecting the largest proportion of cases. Additionally, quarterly screening resulted in the greatest improvement in HIV care continuum outcomes at age 23 years, and a 50% reduction in primary transmissions from each person living with HIV by age 30 years. Compared with the next best strategy, quarterly screening was cost-effective (ICER, $31,100/year-of-life saved [YLS]) by US standards (ICER, <$100,000/YLS).

Repeat HIV testing late in pregnancy may identify women who seroconvert during pregnancy, allowing them to initiate ART for their own health and to prevent mother-to-child transmission. Turan and colleagues evaluated the cost-effectiveness of repeat HIV testing during pregnancy in Kenya using a TreeAge model (Abstract 1147). In a hypothetical cohort of 100,000 women, repeat HIV testing during late pregnancy averted 757 perinatal HIV transmissions over 10 years, and was found to be very cost effective ($1098/quality-adjusted life year). This also resulted in fewer deaths among mothers and children during this 10-year period. The total excess cost of repeat HIV testing during pregnancy was $16 per woman, and the cost per infant HIV infection averted was $2,203.

New infections declined in New South Wales, Australia by 32% coincident with scale-up of PrEP to 9000 MSM

Preexposure Prophylaxis: What's New?

PrEP Uptake

Several presentations focused on the rapid expansion of PrEP use among populations of MSM, with a temporally associated reduction in HIV infection rates. Grulich and colleagues

reported on rapid scale-up of PrEP in New South Wales, Australia (Abstract 88). From 2015 to 2017, PrEP was given to more than 9000 MSM. Adherence appeared to be high, with medication possession ratios (the proportion of prescriptions actually dispensed) being greater than 0.80 for 70% of patients. Incidence among PrEP users was only 0.05/100 py, with 1 infection in a person who never started PrEP, and the other in a person who had stopped PrEP for several months before becoming infected. At the same time, new infections in New South Wales overall declined by 32%. However, PrEP uptake was lowest among youth, MSM living outside of neighborhoods with a high proportion of MSM residents, and non-English speaking, overseas-born MSM. These data suggest that PrEP may be having population-level effects, but additional efforts are needed for outreach to more marginalized populations.

Buchbinder reported on PrEP uptake in San Francisco from 2014 to 2017 (Abstract 87). HIV infections declined by 51% in San Francisco from 2012 to 2016, a time during which there was scale-up of PrEP as well as treatment. The authors estimated that the number of MSM in San Francisco on PrEP increased from approximately 4400 in 2014 to 16,000-20,000 in 2017. Overall current PrEP use was reported at the municipal STI clinic by nearly half of PrEP candidates (defined as MSM who were HIV negative and reported an STI, an HIV positive partner, or condomless anal sex). Although PrEP uptake has increased in all racial/ethnic groups and all adult ages, African Americans persist in having lower rates of PrEP use. Primary reasons for non-use among African Americans included not perceiving themselves to be at risk, concerns about PrEP, and access issues, all of which will need to be addressed to realize the potential benefit of PrEP among this population with the highest HIV infection rates nationally.

Beauchemin and colleagues reported on HIV incidence among patients being seen at a Montreal clinic (Abstract 1037). From 2011 to 2016, PrEP consultations increased rapidly, from none to more than 8000 persons over that time. At the same time, HIV incidence in the clinic dropped by 56%. Mayer and colleagues also reported on an increase in PrEP uptake at Fenway Health, a community health center in Boston specializing in care for gender and sexual minorities (Abstract 1014). Of 681 patients screened for rectal STIs in 2012, 2.3% were prescribed PrEP. This increased to 49.2% of 3,333 patients screened for an STI in 2016. PrEP use increased in all age, gender, racial/ethnic, and insurance groups over this time, except for cisgender women. However, PrEP uptake was consistently lower among younger patients, black and Asian/Pacific Islander patients, and those with public health insurance versus private insurance.

Despite the rapid scale-up of PrEP use in a variety of settings, several presentations focused on gaps in PrEP uptake, based on anticipated PrEP need. Smith presented updated estimates of the number of persons needing PrEP in the United States by race/ethnicity and transmission risk group (Abstract 86). She estimated that 1,145,000 persons in the United States have an indication for taking PrEP, including 814,000 MSM, 258,000 heterosexuals, and 73,000 people who inject drugs. Compared with previous estimates, this new method of calculation increases the number of MSM who have a PrEP indication, and decreases the number of heterosexual and PWID who have a PrEP indication. Overall, 43.7% of persons with a PrEP indication are African American, 24.7% Latino, and 26.5% white. The states with the highest proportion of persons with a PrEP indication who are African American are concentrated in the South and Midwest. Overall coverage is quite low, with 14% of white persons with a PrEP indication having received PrEP in 2015 to 2016, and only 1% of African Americans and 3% of Latinos with a PrEP indication had been on PrEP. This is particularly troubling given data presented by Jenness and colleagues (Abstract 1149). In their model of racial disparities in HIV incidence between black and white MSM, they found that current race-specific values of PrEP uptake would be associated with a minimal diminution of HIV incidence among African Americans (7.7-5.9/100 py), but a more substantial reduction among white MSM (1.6-0.8/100 py). Even if African American MSM achieved twice the rate of PrEP coverage as is currently seen in white MSM, HIV incidence would still be higher in African American MSM than in white MSM (1.7 vs 0.7/100 py). These data indicate that it is imperative that substantial scale-up of PrEP occur, particularly for African American and Latino populations.

Kuo and colleagues confirmed the substantial under-utilization of PrEP among injection drug users and heterosexuals at high risk, using data from the National Behavioral Surveillance System (Abstract 1030). Of people who inject drugs with a PrEP indication surveyed in 2015, only 9% had ever heard of PrEP, 1% had ever discussed PrEP with a health care practitioner, and fewer than 1% had ever received a PrEP prescription. None had ever taken PrEP. Of heterosexuals with indications for PrEP surveyed in 2016, only 13% had heard of PrEP, 3% had ever discussed PrEP with a health care practitioner, and fewer than 1% had ever received a PrEP prescription. Clearly, more work needs to be done to increase knowledge and uptake of PrEP in these populations.

Several studies demonstrated poor knowledge and use of PrEP among cis- and transgender women in the United States. Patel and colleagues reported on women in the Women's Interagency HIV study in the southern United States (Abstract 1048). Overall, 32% of the women enrolled were PrEP eligible; of these, 86% were interested in PrEP but only 6% were aware of PrEP and only 1 woman had used PrEP. Scott and colleagues compared patient characteristics of PrEP users with those who were not using PrEP but may have had a PrEP indication (rectal STI screening, syphilis diagnosis, or 3 or more HIV tests in the prior year) (Abstract 1015). In multivariable analysis, women were significantly more likely not to be on PrEP (aOR, 5.64). Poteat and colleagues reported on PrEP willingness among 201 black and Latina transgender women in Baltimore, MD, and Washington DC (Abstract 1045). In their survey, 86.6% of women were aware of PrEP and 77.6% were willing to take PrEP, but only 17.9% had ever taken PrEP. Nearly two-thirds of women not willing to take PrEP cited concerns about interaction with female hormones as the reason for their unwillingness. Taken together, these

studies point to the need for general campaigns to educate cis- and transgender women about PrEP and to address population-specific concerns, such as the potential interaction of PrEP with feminizing hormones for transgender women.

Other studies focused on the under-utilization of PrEP for MSM. Beer and colleagues reported on PrEP use among the HIV-negative partners of US MSM receiving HIV medical care (Abstract 1052). They report that only 6% of the negative partners were on PrEP, including only 27% of those whose HIV-positive partners were not virally suppressed. PrEP use was higher among white MSM and those reporting condomless receptive anal sex. Rao and colleagues reported on PrEP use among Washington State MSM, based on an internet survey of 1080 MSM (Abstract 1019). Of this sample, PrEP would be recommended for a third, based on Washington State PrEP implementation guidelines. Of the subset for whom PrEP was indicated, 31% were actually using PrEP. On multivariable analysis, PrEP use was significantly higher in MSM 25 years of age or older and those with college degrees. They did not find significant racial/ethnic disparities in PrEP uptake, although only 3.9% of their sample were non-Hispanic black individuals. They estimated that 20% of MSM discontinue PrEP within 12 months of initiation.

Overall PrEP coverage in the United States is low, with only 14% of white persons, 1% of African Americans and 3% of Latinos with a PrEP indication having been on PrEP

Gaps also exist in the number and geographic distribution of clinicians willing to prescribe PrEP. Siegler and colleagues calculated the ratio of PrEP provision to the number of new HIV infections (so-called PrEP-to-need ratio) in the United States as a method to evaluate the distribution of PrEP uptake compared among populations at greatest need (Abstract 1022LB). They reported that more than 61,000 persons received PrEP prescription in the second quarter of 2017, but that the PrEP-to-need ratio was lower for women, youth, and people in the southern United States. In fact, states in the highest quartile of the percent of the population living in poverty, who are uninsured, and who are African American had lower PrEP-to need ratios, suggesting that specific PrEP scale-up strategies are particularly needed in those states. Weiss and colleagues confirmed the paucity of PrEP clinicians in the southern United States, identifying so-called "PrEP deserts" where MSM would need to drive at least 30 or 60 minutes to access a PrEP clinician (Abstract 1006). More than half of the MSM living in PrEP deserts were in Southern states, and MSM in the Northeast were least likely to live in PrEP deserts. Other characteristics of MSM living in PrEP deserts included living in less urban areas, being less educated, having greater poverty, and having lesser proportions of African American and Latino individuals. Mayer and colleagues reported that distance to clinics were a substantial negative predictor of PrEP uptake and retention in a community in rural Uganda (Abstract 1005); the same is likely to be true in the United States. These studies speak to the need to increase the capacity of practitioners to prescribe PrEP, a fairly simple regimen to administer and monitor given the clear guidelines available.[4,5]

Cost is also a substantial barrier to PrEP uptake and persistence. Pathela and colleagues reported on the PrEP cascade at sexual health clinics in New York City, where 34% of MSM who were referred for PrEP actually received PrEP prescriptions (Abstract 1007). Navigation resulted in improved referrals, and African Americans and Latinos were more likely to accept PrEP navigation (aOR, 1.53 and 1.38, respectively). However, uninsured persons were less likely to be linked to a PrEP clinician (aOR, 0.65). Patel and colleagues also found that being uninsured and having higher out-of-pocket prescription costs were each independently associated with not using PrEP among patients seen at the Washington University in St. Louis Infectious Diseases Clinic (aOR, 3.35 and 2.68, respectively) (Abstract 1008).

Discontinuations and HIV Seroconversion

Several presentations focused on the difficulty of maintaining persons on PrEP and the risk of seroconversion among those who discontinue PrEP. Shover and colleagues reported that among more than 1700 cisgender men and transgender women receiving PrEP at the Los Angeles Lesbian, Gay, Bisexual, and Transgender (LGBT) Center, 37% of patients discontinued PrEP and 16% were lost to followup (Abstract 1009). PrEP persistence was lower in persons 18 to 24 years of age and those who were uninsured or with private insurance (compared with those who had no co-pay through a Los Angeles County PrEP program). The risk of seroconversion was higher among those who discontinued PrEP than among those who remained on PrEP (0.95% vs 0.25%; $P < .04$). Of the 2 patients who seroconverted with active PrEP prescriptions, 1 was likely infected prior to starting PrEP, and the other seroconverted 104 days after his last prescription and reported missing 7 or more consecutive doses. Greenwald and colleagues reported on PrEP discontinuation at a clinic in Montreal, Canada (Abstract 1038). Of more than 1200 patients receiving PrEP, 36% were consistent users, 9% stopped temporarily and re-started, 17% permanently discontinued, and 38% were lost to followup. Three persons seroconverted after stopping PrEP, resulting in an incidence rate of 3.9/100 py during PrEP gaps.

The risk of seroconversion is high among people interrupting their PrEP use

Misra and colleagues analyzed interview data on 3908 newly diagnosed persons in New York City (Abstract 1036). Of these persons, 3% reported PrEP use prior to their HIV diagnosis. PrEP users were significantly more likely to be MSM, transgender women, and white, than non-PrEP users. Among the 81% of PrEP users who had discontinued PrEP prior to

their HIV diagnosis, the median duration on PrEP was only 3 months. Reasons for PrEP discontinuation included payment or insurance issues in 16%, practitioner-discontinued refills or documented poor adherence in 16%, and adverse effects in 12%. Despite these premature discontinuations, self-reported risk was high, with 77% reporting condomless anal sex, 41% reporting sex with an HIV-positive partner, and 32% reporting sex while high or drunk. These data point to the under-utilization of PrEP among the vast majority of seroconverters prior to infection, and the need to support persons to remain on PrEP use during periods of risk.

Thaden and colleagues reported on another case of a breakthrough infection with multi-drug resistant HIV occurring in a person highly adherent to PrEP (Abstract 1041). What is unusual about this case was the ability to measure PrEP adherence for 6 months prior to diagnosis by measuring tenofovir and emtricitabine (FTC) drug levels in hair. Because hair grows at a relatively constant rate, drug levels can be measured in segments of hair to determine PrEP adherence level history. In this individual, self-reported high adherence was confirmed by pharmacy records and hair drug levels. This is one of a handful of cases of well-documented HIV acquisition in a highly adherent patient, reminding clinicians to counsel their patients that PrEP is not 100% effective, particularly when exposed to multi-drug resistant virus.

PrEP Adherence

Some clinicians express concerns about PrEP adherence for substance users. Goodman-Meza and colleagues reported on adherence levels among MSM seen at 2 community-based clinics in Los Angeles (Abstract 1031). They found that participants reporting stimulant use and condomless anal sex had decreased odds of adherence at the first adherence visit, 4 weeks after PrEP initiation. However, over time, stimulant-using MSM who were having condomless anal sex increased PrEP use over time, achieving comparable levels to non-stimulant using men by 36 to 48 weeks. Such increases in adherence were not seen in stimulant-using men reporting less sexual risk. They urge clinicians not to withhold PrEP prescriptions from stimulant users, as those at highest risk appear to do equally well with adherence over time as non-stimulant users.

STIs and PrEP

Given the high rates of STIs among PrEP users, regular STI screening is an essential component for PrEP delivery. Spinelli and colleagues evaluated regular HIV and STI screening among 403 PrEP users seen in safety net clinics in San Francisco (Abstract 1028). Only 77% of PrEP patients received HIV testing within 30 days of initiating PrEP and only 81% had STI testing within 90 days of initiating PrEP. Follow-up HIV and STI testing was also sub-optimal, with only two thirds receiving either type of test during each follow-up interval. Having panel managers who monitor PrEP testing and prescriptions was significantly associated with increased HIV and STI testing, suggesting that having such overall panel management may be an important part of ensuring that patients are getting regular HIV and STI testing.

Alternative PrEP Dosing Strategies

The IPERGAY (Action to Prevent Risk Exposure By and For Gay Men) trial evaluated event-driven PrEP use among MSM in France and Canada and demonstrated an 86% reduction in HIV infections in the active arms versus the placebo arms.[6] To date, only limited data have been available on participants' adherence to the prescribed regimens in this and other studies. Bauer and colleagues reported on PrEP coverage of sexual episodes in a subgroup of participants enrolled in the IPERGAY open-label extension, using pill bottles with electronic measurement of bottle openings (Abstract 1034). Full coverage of sex acts was considered taking at least 1 pill pre- and post-sexual episode, and partial coverage was considered if either pre- or post-sexual dosing was completed. Participants were considered daily PrEP users if they took 5 or more pills per week on average, and intermittent users if PrEP use was less than that. Comparing coverage of sex acts with PrEP pills, daily users had full coverage of 92% of sex acts and at least partial coverage of 95% of sex acts. Intermittent users had full coverage of 68% of sex acts and partial coverage of 82% of sex acts. Complete coverage was highest in both groups for receptive condomless anal sex, the riskiest sexual practice. Although the CDC only recommends daily PrEP, some European guidelines also recommend the IPERGAY intermittent dosing regimen, and some patients, even those in the United States, are attempting to follow the IPERGAY regimen. Data from this study suggest that clinicians might focus adherence counseling on patients using PrEP less frequently, where adherence (and coverage of sex acts) may drop to lower levels.

Some MSM may also have periodic risk, such as during vacations. Egan and colleagues reported on the feasibility of short-term PrEP for such situations (Abstract 1035). They conducted a pilot study of peri-vacation PrEP for MSM in Pittsburgh, Pennsylvania and Boston, Massachusetts, recommending daily PrEP be initiated 7 days before vacation and be continued through 7 days post-vacation. Of 54 enrolled men, 48 completed the post-vacation visit, and only 3 had drug levels below what was considered protective (consistent with 4 or more doses/week). More than three quarters of men reported condomless anal sex during their vacation. One participant seroconverted more than 2 months post-vacation associated with ongoing risk and a lapse in insurance coverage and stopping PrEP use. Nonetheless, clinicians should query their patients about times (such as during vacations) when sexual activity may change, and offer PrEP coverage during those periods of increased risk.

Alternative Systemic PrEP Agents

Tenofovir alafenamide (TAF) is rapidly replacing tenofovir disoproxil fumarate (TDF) in HIV treatment because of its

reduced nephrotoxicity and lesser effects on bone loss. Whether TAF will be an effective PrEP agent is currently unknown, and is being evaluated in the DISCOVER trial in MSM. Non-human primate studies have shown TAF to be effective in combination against rectal simian-human immunodeficiency virus (SHIV) challenge, but similar studies have not been done for vaginal challenge. This is important, because TDF is less active in vaginal tissue, and pharmacokinetic studies suggest that higher levels of adherence are required for protection against vaginal than rectal challenge with TDF/FTC. Massud and colleagues evaluated TAF/FTC in protection against vaginal SHIV challenge in a pigtail macaque model (Abstract 85). TAF/FTC was administered 2 hours before and 24 hours after weekly vaginal challenge, to mimic the non-human primate studies done with TDF/FTC. TAF/FTC protected 5 of 6 animals, with an overall efficacy of 82%. The one animal who was infected inexplicably had tenofovir levels below the level of quantification in the blood, suggesting that the tenofovir component is essential in tenofovir-based PrEP regimens. However, this study does show promise for TAF/FTC for protecting women against vaginally acquired HIV infection.

MK-8591, an investigational NNRTI was highly potent and efficacious in preventing SHIV infection in a non-human primate rectal challenge study

The investigational, long-acting injectable agent cabotegravir, an HIV-1 integrase inhibitor formulated as an injectable nano-suspension with a long half-life, is currently being evaluated as PrEP in MSM, transgender women, and cisgender women at heterosexual risk. Previous non-human primate studies have demonstrated high protective efficacy against rectal, vaginal, and intravenous challenge, but to date no studies have evaluated its efficacy against male urethral challenge. Dobard and colleagues presented data on a novel non-human primate urethral challenge model and evaluated the protective efficacy of long-acting cabotegravir against urethral challenge (Abstract 83). Long-acting cabotegravir was administered monthly for 3 months, and rhesus macaques were challenged weekly throughout this period with SHIV 162p3, a chemokine coreceptor 5 (R5)-tropic virus. Protective efficacy was 93.2%, with 1 of 6 animals becoming infected at week 12, after the blood level dropped below 4-times the protein-adjusted 90% inhibitory concentration (IC_{90}) level, the target level for the trial. The investigators concluded that long-acting cabotegravir is a promising PrEP agent for men whose risk of HIV acquisition is via the insertive sex partner.

Markowitz and colleagues presented data on MK-8591 (EFdA), a novel nucleoside reverse transcriptase translocation inhibitor for PrEP in a non-human primate model (Abstract 89LB). Novel features of this agent include a different mechanism of action from nucleoside reverse transcription inhibitors (nRTIs), rendering it active against many isolates resistant to nRTIs, high potency and a long half-life (120 hours in human), allowing for weekly oral dosing. In their rectal challenge studies, doses of 1.3 mg/kg and 0.43 mg/kg afforded complete protection in 8 animals per stratum, and 2 of 8 animals became infected with a dose of 0.1 mg/kg. No safety issues arose at any dose. The investigators concluded that these protective levels can be achieved with a dose of 10 µg per day or less than 250 µg per week in humans, and that this compound should be pursued as a promising PrEP agent with high potency and less frequent dosing.

Garber and colleagues evaluated the protective efficacy of 2 broadly neutralizing antibodies (bNAb) against vaginal SHIV challenge in rhesus macaques (Abstract 82). They evaluated 3BNC117, a CD4 binding site bNAb alone, or in combination with 10-1074, a V3 glycan bNAb after a single subcutaneous injection of 10 mg/kg followed by weekly vaginal challenges. Both bNAbs reached peak levels at 1 week and had similar half-lives, but 10-1074 had a higher peak level, leading to longer durability. Compared with the control condition in which animals were infected after a median of 2 challenges, those getting 3BNC117 alone were infected after a median of 5 challenges (statistically significantly better than controls), and those getting both bNAbs became infected after a median of 11.5 challenges, (statistically significantly better than either of the other groups). Because 3BNC117 was gone from plasma samples prior to infection in the combined bNAb arm, the investigators speculated that it was 10-1074 that provided all of the protection in the combined arm, and that this increased protection was due to the longer durability of drug in plasma. They also reported that the levels required for vaginal protection within each group were comparable to previously reported levels required for rectal protection. These bNAbs have been found to be safe in phase I human trials, and may move into later stage trials.

Two vaginal ring open-label extension studies modeled a 54% reduction in HIV acquisition compared with historical controls

Topical PrEP Agents

Interim results from 2 open-label extension studies of the dapivirine vaginal ring were presented at this year's conference with remarkably similar results. Baeten reviewed the phase III trial results from both the ASPIRE (A Study to Prevent Infection with a Ring for Extended Use) and Ring studies, which showed approximately 30% efficacy during the placebo-controlled phase of the trial (Abstract 143LB). All HIV-negative women in the ASPIRE trial were invited to enroll in HOPE (HIV Open-label Prevention Extension), the open-label extension of that trial; 57% agreed to participate. Among those participating, uptake of the ring was quite high, ranging from 92% at enrollment to 81% at the month 9 visit. Evaluation of residual levels of dapivirine in the returned rings suggested

that 89% of women were using the rings at least some of the time. Overall HIV incidence was 1.9/100 py in this study. By modeling what might have been the expected HIV incidence in the historical control arm, adjusted for an older population, he estimated that this represented a 54% reduction in HIV incidence. Rosenberg presented data from the DREAM (Dapivirine Ring Extended Access and Monitoring) study, the open-label extension of the Ring study (Abstract 144LB). They found residual levels in returned rings consistent with use in 96% of the women enrolled in DREAM, and an HIV incidence of 1.8/100 py. Using similar methodology to construct an expected incidence based on historical controls, they also estimated a 54% reduction in HIV incidence. Both results suggest that there is a population of women interested in using the ring, and that this ring provides partial protection. Given challenges in some studies for women taking oral PrEP, vaginal rings may be a viable alternative to lower HIV acquisition risk, although the absolute level of effectiveness is lower than has been seen in some oral PrEP trials. Final results may be expected next year, along with an evaluation of maximal efficacy with full adherence, and the dapivirine ring is currently undergoing regulatory review. Future products could include multipurpose prevention, such as inclusion of contraception with HIV protection.

Derby and colleagues assessed novel topical agent, a combination of griffithsin (a small lectin derived from red algae), and carageenan, also derived from algae, for prevention of SHIV, herpes simplex virus (HSV), and human papillomavirus (HPV) in animal models (Abstract 84). These agents have good activity in vivo against all 3 pathogens, are not systemically absorbed, and act through mechanisms unlike ART, suggesting no cross resistance to such agents. Their macaque challenge study protected 8 of 10 animals and all 10 control animals were infected after a single challenge, a 5-fold reduction in the relative risk of infection. This combined microbicide also had good activity against HSV and HPV in mice models, and the authors point to a first in human trial currently underway to test the safety and pharmacokinetics of these agents in women. Discussion at the meeting focused on the impact of less enthusiasm on the part of some sponsors of supporting topical PrEP agent development, but investigators and audience members expressed optimism that products already in development may continue evaluation and regulatory review, and that new options for women, such as multi-purpose technologies, have a role in prevention for women, the population globally with the highest rates of HIV acquisition.

All cited abstracts appear in the CROI 2018 Abstracts eBook, available online at www.CROIconference.org

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

Additional References Cited in Text

1. Puller V, Neher R, Albert J. Estimating time of HIV-1 infection from next-generation sequence diversity. *PLoS Comput Biol.* 2017; 13(10):e1005775.
2. Klatt NR, Cheu R, Birse K, et al. Vaginal bacteria modify HIV tenofovir microbicide efficacy in African women. *Science.* 2017; 356(6341):938-945.
3. National Alliance of State and Territorial AIDS Directors (NASTAD). Hiv Prevention & Health Equity. http://www.nastad.org/domestic/hiv-prevention-health-equity. Accessed on March 30, 2108.
4. Centers for Disease Control and Prevention. Preexposure prophylaxis for the prevention of HIV infection in the United States - 2014: a clinical practice guideline. http://www.cdc.gov/hiv/pdf/guidelines/PrEPguidelines2014.pdf. Accessed on August 16, 2017.
5. Günthard HF, Saag MS, Benson CA, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2016 recommendations of the International Antiviral Society-USA panel. *JAMA.* 2016;316(2):191-210.
6. Molina JM, Capitant C, Spire B, et al. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. *N Engl J Med.* 2015;373(23):2237-2246.

Top Antivir Med. 2018;26(1):1-16.

Invited Review

CROI 2018: Advances in Basic Science Understanding of HIV

Mario Stevenson, PhD

The conference on Retroviruses and Opportunistic Infections represents the most important venue for the dissemination of research advances in HIV and AIDS. The 25th conference, held in Boston, featured presentations that provided insight into the mechanisms of HIV-1 spread in tissues as well as new information on mechanisms of HIV-1 persistence in individuals on effective antiretroviral treatment. The ability of the conference to convey research findings for a general audience is enhanced, to a large part, by preconference workshops. These workshops feature leading researchers who aim to present cutting edge research to a general audience. These sessions rank highly in terms of education and professional value.

Keywords: CROI, 2018, HIV, virology, reservoirs, persistence, cure

Virology

Bjorkman (Abstract 4) discussed studies employing electron tomography to visualize the spread of HIV-1 in tissues. Electron tomography is a variation on 2-dimensional electron microscopy in which 2-dimensional projections of objects of interest, such as viral particles, are visualized on a grid. In electron tomography, various views of objects are recorded using a tilting microscope. This allows 2-dimensional images of an object to be taken at different angles from which a 3-dimensional image of the object can be created. Bjorkman's group used the humanized mouse model to examine HIV-1 infection within bone marrow of these mice.

At least 3 mechanisms for HIV-1 dissemination were found. The first was classic HIV-1 budding from infected CD4+ T cells.

The second involved synaptic transmission by uropods. Although a number of groups have described synaptic virus transmission in which transfer of virus from an infected cell to a target cell occurs through intimate synaptic structures formed between the 2 cells, Bjorkman's study focused on transmission through uropods that are cellular protrusions that form synaptic contacts with other cells. Synaptic transmission of murine leukemia virus (MLV) was first observed by Mothes group.[1] HIV-1 transmission was observed by uropods that contain microvesicles and organelles, which distinguished them from uropods of macrophage origin that are devoid of organelles and vesicles. Uropods appeared to be facilitating transfer of virus particles from infected donor cells to the uninfected target cell. Uropods with budding HIV particles were also found to originate from infected macrophages to facilitate infection of CD4+ T cells.

The third mechanism for HIV-1 transmission that was revealed by electron tomography involved macrophages. Recent studies from the Benichou laboratory described the transfer of virus from CD4+ T cells to macrophages in culture and macrophages infected in this way were found to produce new virus within hours.[2] When macrophages were visualized by electron tomography, mature virus particles were observed budding from the cell surface. However the majority of viral particles appeared in membranes in closed compartments inside the cell. Further analysis revealed that these compartments were not contiguous with the extracellular environment. Although these compartments were enclosed, they had the capacity to fuse with surface invaginations that offered a pathway for virus release from the infected macrophage. This appears to be a novel mode of HIV-1 production that poses many questions, some of which are relevant to the issue of viral reservoirs.

Previous studies have demonstrated the presence of HIV-1 variants within intracellular vesicles of infected macrophages, that those vesicles were contiguous with the extracellular space and further, that those vesicles retained HIV-1 in an infectious form for extended intervals. Therefore, it remains to be determined whether this mode of HIV-1 manufacture in which particles are contained within an enclosed compartment, offers a novel mechanism that allows the virus to persist in an infectious form. Furthermore, this process is likely to bypass the constraints conferred by HIV-1 tropism in which macrophage infection requires a viral envelope with a high affinity for CD4. Viral variants budding into enclosed compartments that were derived from an engulfed CD4+ T cell would exhibit T cell tropism even though they are budding from macrophages.

Mechanisms of Viral Persistence

The majority of presentations in the basic science category focused on mechanisms of viral persistence in the face of effective antiretroviral therapy (ART). At least 3 mechanisms have been implicated in maintaining HIV-1 persistence in infected individuals. Most of the attention has focused on viral latency in which the infected cell harbors an integrated provirus in a transcriptionally silent state. As the provirus is silent, there is little to distinguish the latently infected cell from an

Dr Stevenson is Professor of Medicine and Chief of the Division of Infectious Diseases at the University of Miami Miller School of Medicine in Miami, Florida. Send correspondence to Mario Stevenson, PhD, University of Miami Leonard M. Miller School of Medicine, Life Science Technology Park, 1951 NW 7th Avenue, Rm 2331B, Ste 200, Miami, Florida 33136. Received on April 4, 2018; accepted on April 8, 2018.

uninfected cell. As such, this makes identification and elimination of latently infected cells one of the major challenges facing the HIV-1 cure field. Numerous laboratories have been investigating ways to reactivate the latent reservoir so as to expose the latently infected cell to host immune clearance and additionally, to promote clearance of the infected cell by viral cytopathicity.

A second mechanism proposed to maintain viral persistence involves the homeostatic maintenance of infected cells. If an infected cell undergoes mitosis, the provirus would be duplicated between the daughter cells thereby increasing the number of cells harboring a viral genome. A third and more controversial mechanism involves generation of newly infected cells by de novo viral infection or, as commonly referred to, ongoing viral replication. This terminology creates confusion and angst amongst cure researchers. From a virologic standpoint, ongoing viral replication involves infection of a cell that generates progeny virus that then go on to infect a new cell. Through successive rounds of replication, the virus spreads through the cell population. This is distinguished from single-cycle or limited rounds of infection in which an infected cell generates progeny virions that infect a new cell, but the newly infected cell does not repeat the process. Under conditions of single-cycle infection or limited rounds of infection, there would be less opportunity for viral evolution and development of antiretroviral drug resistance. The term active reservoir is more frequently being used in the HIV cure field to describe infected cells that are discernable by the presence of viral transcripts. Previous studies have indicated that the absolute level of cell-associated viral RNA in HIV-1–infected individuals on suppressive ART predicts the time to viral rebound when treatment is interrupted.[3] This suggests that at the least, cells actively transcribing HIV-1 comprise a biologically active component of the viral reservoir.

Abstract 66 attempted to define the timing of reservoir establishment in acute HIV infection using HIV RNA-positive cells as surrogates of the reservoir. The investigators obtained inguinal lymph node biopsy from acutely infected individuals who initiated ART in Fiebig stages 1 and 2 versus Fiebig stages 3 to 5. Reservoirs were characterized by in situ hybridization to identify viral RNA- and viral DNA-positive cells. Several important observations emerged from this analysis, including that viral DNA-positive cells were established as early as Fiebig stage 1, and the frequency did not change after 48 weeks of ART. Viral RNA-positive cells were also established as early as Fiebig stage 1 and the higher frequency of these cells in Fiebig 1 was associated with fewer HIV-1 specific CD8+ T cells.

The investigators also documented damage to lymph node architecture at the earliest stage of acute HIV-1 infection as indicated by deposition of collagen. Therefore, damage to lymph node architecture could be observed as early as Fiebig stage 1. However, although initiation of ART in Fiebig 1 did not alter the frequency of viral DNA-positive cells, it was able to improve lymph node architecture. These findings are in general agreement with studies from the Ananworanich laboratory, presented at CROI 2017 (Abstract 124), that very early initiation of ART does not substantially delay time to viral rebound when treatment is interrupted. Collectively, these studies suggest that uncontrolled viral replication in the absence of cell-mediated immunity leads to rapid reservoir establishment and this obfuscates attempts to reduce reservoir size and increase possibility of viral eradication through very early initiation of ART. These studies are somewhat at odds with earlier studies[4] indicating that treatment in the acute phase promoted more effective control of the number of cells harboring reactivateable HIV-1 (15809898).

Although early initiation of ART appeared to have limited impact on viral reservoir size in treated adults, the situation appears to be different in children. Abstract 135 examined 2 cohorts of Thai children, one of which was on prophylactic ART and the second cohort initiated ART within 6 months of age. Viral reservoir measurements included total levels of HIV-1 DNA, integrated HIV-1 DNA, and inducible HIV-1 (TILDA). Viral load strongly correlated with levels of total integrated HIV-1 DNA as well as the frequency of cells harboring inducible virus. Importantly, levels of viral DNA and in particular, levels of inducible HIV-1, were markedly reduced in children who started ART before 6 weeks of age versus in children initiating ART after 6 weeks. Therefore, very early ART in the pediatric population dramatically reduces viral reservoir size. Similarly, in Abstract 136, children treated in the first week of life had very low viral reservoir size after 84 weeks of ART and interestingly, the majority of proviruses present in the reservoir by the second year of life were defective, suggesting that early treatment limited the maintenance of the biologic active reservoir.

This theme was continued in Abstract 67 where the investigators characterized early immune responses and reservoir activity in female participants with acute HIV-1 infection. There was a strong correlation between viral burden and the breadth of CD8+ T cell responses in contrast to what was presented in Abstract 66. However, early ART initiation led to a decrease in total HIV-1 DNA levels at 1 month and 12 months. Despite this, in some individuals there was a considerable amount of HIV-1 Gag p24 in lymph germinal centers despite complete suppression of plasma viremia. Although it is unclear whether the viral antigen was being produced in infected cells or whether it simply represented virions trapped on the cell surface, this indicates that analysis of peripheral blood does not provide accurate insight into ARV response in lymphoid tissue.

There has been a lot of attention regarding the role played by homeostatic duplication of integrated proviruses in the maintenance of HIV-1 persistence under ART suppression. Proviruses can be duplicated through the normal process of cell proliferation. However, some clones are overrepresented in the population because they are duplicated more frequently. This occurs if the provirus integrates close to a gene involved in cell cycle control. In this situation, normal transcriptional regulation of the cell cycle control gene is interrupted by the juxtaposed HIV-1 transcriptional unit. This leads to uncontrolled cell proliferation and continuous rounds of proviral duplication. Although provirus insertions close

to genes involved in cell cycle regulation are frequently observed, there is, surprisingly, little evidence that this process can drive T-cell up abnormalities such as leukemia.

Since the demonstration of clonal expansion in HIV-1 infected individuals, it was initially suspected that proviruses expanded through clonal proliferation would predominantly be defective since the process of duplication would be expected to lead to proviral activation and production of viral proteins that could target the cell for immune clearance or cytopathicity. However, work in the last 2 years has demonstrated that functional proviruses can be expanded in this way and serve as a template for infectious virus production that can be detected in the plasma of HIV-1 infected individuals. Studies presented in Abstract 68 provided some insight into the mechanism, through which clonal expansion can occur without activation of the host cell, and further expanded on the theme that the reservoir of expanded clones is dynamic. The investigators followed up on recently published studies demonstrating that a substantial proportion of latent proviruses are generated by clonal expansion. This, by definition, argues that the process of clonal expansion does not lead to viral reactivation to an extent that would result in host immune clearance or viral cytopathicity. Therefore, the investigators set out to determine the process that can drive clonal expansion of latent viruses without triggering activation of the infected cell. The investigators demonstrated that CD4+ T cells containing replication-competent virus can proliferate in response to T-cell receptor activation and cytokine treatment (eg, with interleukin 7 treatment). Although this has been observed previously in the presence of the chemokine CCL19,[5] cytokine-driven proliferation of cells carrying replication-competent virus did not result in virus production. The investigators then explored the dynamics of the clonal population of latent viruses that are maintained in HIV-1 infected individuals. Virus was recovered from 8 individuals on suppressive ART at various intervals over a 2-year period. Proviruses in those cells were then characterized by single cell sequencing. Some clones comprised a large percentage of the viral population at various time points and others only prevailed at individual time points, suggesting that some clones fluctuate in their abundance with time and that this waxing and waning can occur over a period of years. Analysis of the residual viremia in these individuals was also reflected in the residual virus population where viruses matching expanded clones appeared and disappeared with similar dynamics. This indicates that clonal expansion of latent virus can be accompanied by release of virus particles but that duplication of proviruses during cell proliferation can occur in response to cytokines and occur without infectious virus production. As such, this process represents an important mechanism for maintenance of the viral reservoir and poses a formidable challenge to efforts to eradicate HIV-1.

Given the ability of proviruses to be maintained by homeostatic proliferation, there remains a question on the value of proviral DNA as a surrogate with which to gauge reservoir activity and more importantly, to monitor the effect of therapeutic strategies aimed at reducing viral reservoir size. Abstract 69LB presented results on cell-associated HIV-1 DNA measurements at 3 time points over a 3- to 10-year period in more than 1000 infected individuals. Levels of viral DNA decreased steadily over the 10-year period and differences in the levels of cell associated viral DNA between individuals diminished over this time. The slope of viral decay indicated a half-life of between 5 and 11 years for approximately 75% of the individuals. However, despite being on effective therapy, there was no depreciable DNA decay in 25% of the participants. Viral reservoir size, as measured by cell-associated DNA levels, was smaller in individuals who initiated treatment earlier. The investigators also examined the relationship between viral blips and reservoir size. Blips were associated with higher level of cell-associated viral DNA and predicted the decay of the viral reservoirs indicating that blips are a biologically relevant surrogate of the viral reservoir.

The issue of viral reservoir replenishment through ongoing or de novo infection continues to be a hotly debated topic at CROI. Abstract 70 examined proviral genetics in the infected individual prior to and after 2 to 13 years of suppressive ART in paired lymph node and peripheral blood samples. Analysis of integration sites in cells from lymph nodes and peripheral blood suggested that HIV-1 persistence was maintained by the homeostatic proliferation of cells infected prior to ART initiation and not by viral replication in peripheral blood or in lymph nodes. It will be important to determine whether the viral population that rebounds when treatment is interrupted has a genetic composition similar to the population of expanded proviruses. As alluded to earlier, this analysis does not exclude the generation of newly infected cells through single or low cycles of de novo infection. Abstract 71 examined the impact of treatment intensification with the integrase strand transfer inhibitor (InSTI) dolutegravir on episomal viral DNA levels. Previous studies demonstrated that intensification of ART with InSTIs led to a rapid and transient increase in levels of episomal viral DNA in approximately 30% of individuals, and especially for individuals on protease inhibitor (PI)-based regimens.[6,7] Such an outcome can only occur if there were cells in those participants in the process of being infected with the HIV-1. Those earlier studies suggested that a sizeable percentage of infected individuals have some degree of de novo infection even under suppressive ART. Those observations were further underscored by changes in immune inflammation markers such as D-dimer or frequencies of activated CD8+ T cells. Dolutegravir has profound antiviral efficacy to the extent that resistance to dolutegravir is far less common than that observed with individuals on other InSTIs. In contrast to the earlier reports, the investigators saw no significant changes in the frequencies of episomal viral DNA, even though the study was powered to observe as little as 3-fold differences in episomal DNA frequency. Furthermore, there were no changes in T-cell activation status or in plasma markers of inflammation. The reason for the differences between this and earlier studies is unclear. Acute changes in episomal DNA numbers were observed selectively in individuals on PI-based regimens and those individuals were underrepresented in the current study. In addition, earlier studies were

conducted with the InSTI raltegravir, which shows considerable penetration to gut-associated lymphoid tissue (GALT) where most infection events are likely to occur. Therefore it is unclear whether the differences in the studies represent differences in the population or differences in the pharmacokinetic characteristics of raltegravir versus dolutegravir.

Viral Reservoir Elimination Studies

One of the major challenges facing HIV-1 cure researchers is a lack of host cell markers that can be used to identify infected cells in individuals on effective ART. Studies published in the past 2 years[8] identified CD32a as being selectively expressed on CD4+ T cells harboring latent, replication-competent proviruses. This was further expanded in Abstract 155 where CD32+/PD1+ T follicular helper T cells were found to be the major HIV reservoir in individuals on suppressive ART. Follicular helper T cells have previously been shown to have the highest levels of HIV-1 DNA among the CD4 T cell subsets, and additionally, were found to have higher levels of cell-associated viral transcripts in aviremic individuals.[9] However, although high levels of viral DNA and viral transcripts were found in lymph node CD32a+ and in PD1+ CD4+ T cells, cells expressing both markers were found to harbor the highest levels of viral transcription. The authors concluded that CD32 was neither a specific marker for the latent HIV-1 reservoir nor expressed exclusively in HIV-1–infected cells. Three additional abstracts (Abstracts 156, 157, and 158) presented data that further called into question CD32 as a reservoir marker. For example, studies presented in abstract 156 used viral outgrowth assays to determine the size of the latent reservoir in CD32-positive and CD32-negative cells and concluded that the majority of latently infected cells were CD32a negative. Similarly, in abstract 157, viral outgrowth assays showed a lack of association between the amount of replication-competent HIV and the frequency of CD32a+ cells. Furthermore, the point was made that CD32 is expressed on naive T cells and numerous lines of investigation have shown that the latent reservoir resides predominantly in memory CD4 T cells. CD32+ cells were found to be highly activated, which would be biologically inconsistent with maintenance of viral latency. Finally, abstract 158 represented evidence that CD32+ cells were transcriptionally active for HIV-1 rather than latently infected. However, although CD32 expression did not selectively correlate with HIV-1 or simian immunodeficiency virus (SIV) infection in CD4+ T cells in blood or tissues, there was a positive correlation between cell-associated viral DNA and RNA and the frequency of CD32+ cells. Collectively, these studies indicate that CD32a is not a marker of latently infected CD4+ T cells. However, it does appear to be co-expressed with viral RNA in lymph nodes of HIV-1–infected individuals on effective ART. Further studies will be required to determine whether cell-associated RNA reflects a latent reservoir as it exits and whether CD32a can be used to target those cells as they exit. As discussed above, it is possible that the latent reservoir is not static but goes through intermittent intervals of reactivation.

One strategy being explored for elimination of the latent reservoir centers on reactivation of the reservoir, thereby rendering the infected cell to viral cytopathic effect or to cell mediated immune clearance. Several agents have been shown to effectively reactivate HIV-1 latency in cells from infected individuals ex vivo without overtly triggering cellular activation. Many latency reactivating agents under investigation are histone deacetylase inhibitors that promote relaxation of chromatin, which facilitates the interaction of cellular transcription factors with the HIV-1 LTR to facilitate proviral transcription. Romidepsin is one of the most potent histone deacetylase inhibitors for the reactivation of HIV-1 ex vivo. Because it is already approved by the US Food and Drug Administration (FDA) for the treatment of T-cell lymphoma, it has been rapidly explored as a latency reactivating agent in infected individuals. However, studies conducted to date with romidepsin and other histone deacetylase inhibitors have been underwhelming; the extent to which they reactivate HIV-1 appeared modest. Abstract 72 examined whether a single romidepsin infusion activated HIV-1 transcription in infected individuals on effective ART. Induction of HIV-1 expression was assessed from changes in plasma viremia using a single copy HIV-1 RNA assay as well as from changes in cell-associated HIV-1 RNA. Following romidepsin administration, the in vivo impact of romidepsin on histone acetylation was assessed from the frequency of CD4 T cells with activated NF-κB as well as histone acetylation levels. Single romidepsin infusions, at concentrations shown to reactivate HIV latency ex vivo, had no impact on plasma viral RNA levels nor cell-associated viral DNA or RNA. Nevertheless, there was a significant increase in T cell activation at the highest dose of romidepsin. These studies contradict earlier published work that numerous romidepsin infusions increased plasma viral RNA levels in HIV-1 infected individuals on effective ART. Study design differences may explain the opposing results, such as single dose versus numerous doses of romidepsin.

On a more positive note, Abstract 73LB presented results that combination of a broadly neutralizing antibody with a TLR7 agonist delayed viral rebound in acutely ART-treated, simian-human immunodeficiency virus (SHIV)-infected macaques. GS-9620 is a TLR7 agonist with the ability to stimulate innate immunity. Studies presented at CROI 2017 (eg, Abstract 338LB) demonstrated that the TLR7 agonist GS-9620 promoted prolonged viral control in infected macaques and furthermore, prevented viral rebound in approximately 50% of infected animals. Abstract 73LB examined the combined effects of the broadly neutralizing antibody PGT121 together with TLR7 administration on viral rebound kinetics and on virologic control. All control animals rebounded within 1.5 months of ART discontinuation and no significant difference was observed with animals receiving the TLR7 agonist alone. There was a 5-fold delay in time to rebound for half the animals receiving antibody and agonist and 50% of the animals showed no viral rebound by day 168. Furthermore, adoptive transfer of lymphocytes from non-rebounders to naive animals failed to transfer infectious virus. The synergistic impact

of combined PGT121 and GS9620 is possibly due to activation of the CD4 T cell reservoir by GS-9620 followed by enhanced clearance of reactivated virus by PGT121. Although these findings are important, one has to keep in mind that these effects were observed in monkeys in which ART was initiated at week 1 and that used an SHIV variant that is highly neutralization sensitive. It remains to be determined whether similar levels of efficacy would occur in chronically infected animals who initiate ART later in their infection course.

All cited abstracts appear in the CROI 2018 Abstracts eBook, available online at www.CROIconference.org

Financial affiliations in the past 12 months: Dr Stevenson has no financial conflicts to report for the past 12 months

Additional References Cited in Text

1. Sewald X, Ladinsky MS, Uchil PD, et al. Retroviruses use CD169-mediated trans-infection of permissive lymphocytes to establish infection. *Science.* 2015;350(6260):563-567.
2. Bracq L, Xie M, Benichou S, Bouchet J. Mechanisms for Cell-to-Cell Transmission of HIV-1. *Front Immunol.* 2018;9:260.
3. Li JZ, Etemad B, Ahmed H, et al. The size of the expressed HIV reservoir predicts timing of viral rebound after treatment interruption. *AIDS.* 2016;30(3):343-353.
4. Strain MC, Little SJ, Daar ES, et al. Effect of treatment, during primary infection, on establishment and clearance of cellular reservoirs of HIV-1. *J Infect Dis.* 2005;191(9):1410-1418.
5. Saleh S, Wightman F, Ramanayake S, et al. Expression and reactivation of HIV in a chemokine induced model of HIV latency in primary resting CD4+ T cells. *Retrovirology.* 2011;8:80.
6. Buzon MJ, Massanella M, Llibre JM, et al. HIV-1 replication and immune dynamics are affected by raltegravir intensification of HAART-suppressed subjects. *Nat Med.* 2010;16(4):460-465.
7. Hatano H, Strain MC, Scherzer R, et al. Increase in 2-long terminal repeat circles and decrease in D-dimer after raltegravir intensification in patients with treated HIV infection: a randomized, placebo-controlled trial. *J Infect Dis.* 2013;208(9):1436-1442.
8. Descours B, Petitjean G, Lopez-Zaragoza JL, et al. Corrigendum: CD32a is a marker of a CD4 T-cell HIV reservoir harbouring replication-competent proviruses. *Nature.* 2017;546(7660):686.
9. Banga R, Procopio FA, Noto A, et al. PD-1(+) and follicular helper T cells are responsible for persistent HIV-1 transcription in treated aviremic individuals. *Nat Med.* 2016;22(7):754-761.

Top Antivir Med. 2018;26(1):17-21.

Invited Review

CROI 2018: Complications of HIV Infection and Antiretroviral Therapy

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

This year marked the 25th Conference on Retroviruses and Opportunistic Infections (CROI), and although there is much progress to celebrate in terms of treatment of HIV infection and expanding ART globally, many challenges remain. Tuberculosis is still the leading cause of death among people with HIV infection globally. This year, the results of investments in research to improve the prevention and treatment of tuberculosis were a highlight of the meeting. Noninfectious causes remain an important source of morbidity. Progress in identifying risk factors for non-AIDS complications and improvements in screening and monitoring for such conditions continue to be reported, but to date, despite the efforts of many investigators around the globe, interventions to effectively reduce HIV-related inflammation beyond effective and safer antiretroviral therapy (ART) remain elusive. This section will review highlights of the meeting on tuberculosis and cryptococcal infection as well as complications of long-term ART.

Keywords: HIV, CROI 2018, complications, tuberculosis, cryptococcosis, cardiovascular, antiretroviral therapy, biomarkers, renal, bone, fat

Tuberculosis

Prevention and Scale-up

The results of a phase III, randomized study in which 1 month of treatment with rifapentine plus isoniazid was noninferior to the standard 9 months of isoniazid for tuberculosis (TB) prevention were a highlight of the 2018 Conference on Retroviruses and Opportunistic Infections (CROI) (Abstract 37LB). Based on a body of evidence suggesting a more potent and sterilizing short-course regimen of isoniazid plus rifapentine would be as effective as the current standard of 6 to 9 months of isoniazid for TB prevention, investigators in the AIDS Clinical Trials Group (ACTG) 5279 study recruited 3000 HIV-infected individuals older than 13 years from 10 countries on 4 continents (Asia, Africa, and North and South America) from 2012 to 2014. Participants in this open-label study were randomly assigned to 1 month of daily rifapentine 450 to 600 mg plus isoniazid 300 mg or to 9 months of daily isoniazid 300 mg. Efavirenz-based or nevirapine-based but not protease inhibitor (PI)-based or integrase strand transfer inhibitor (InSTI)-based ART regimens were allowed. Study participants had a baseline median CDsz+ cell count of 470/µL (interquartile range, 346-635/mL), 54% were women, and 50% were receiving ART at baseline. The primary endpoint (TB infection or death) occurred in 34 participants in the 1-month arm and 35 participants in the 9-month arm. Corresponding incidence rates showed that the 1-month regimen was noninferior to the 9-month regimen. The 1-month regimen was better tolerated than the 9-month regimen, as measured by targeted safety events. Elevated transaminases were much more common with the 9-month isoniazid regimen. Rates of treatment completion were higher in the 1-month than in the 9-month arm. In summary, a 1-month regimen of isoniazid plus rifapentine is as effective, better tolerated, and more likely to be completed than a standard 9-month regimen of isoniazid for TB prevention. These data support the 1-month regimen of isoniazid plus rifapentine as a new global option for TB prevention. With the ongoing global transition to dolutegravir for initial ART, widespread implementation of the 1–month regimen of isoniazid plus rifapentine for TB prevention will depend on drug interaction studies to demonstrate that this course can be safely coadministered with dolutegravir-containing ART.

One month of treatment with isoniazid plus rifapentine was as effective as and better tolerated than the standard 9-month isoniazid regimen for TB prevention

Pregnant women have an increased risk of TB infection, and TB can be transmitted and harmful to an infant during pregnancy. However, TB prevention with isoniazid is most often initiated postpartum, potentially missing the opportunity to prevent TB in the vulnerable antepartum period. Gupta and colleagues in the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network randomly assigned 956 HIV-infected pregnant women from sites in Africa, Asia, and Haiti to receive isoniazid for TB prevention either at 28 weeks antepartum or 12 weeks postpartum in a double-blind study (Abstract 142LB). The primary study endpoint was maternal adverse events. The

Dr Currier is Professor of Medicine and Chief of the Division of Infectious Diseases and Associate Director of the Clinical AIDS Research and Education (CARE) Center at University of California Los Angeles. Dr Havlir is Professor of Medicine at University of California San Francisco and Chief of the HIV, Infectious Diseases, and Global Medicine Division at Zuckerberg San Francisco General Hospital. Send correspondence to Judith S. Currier, MD, UCLA Care Center, 11075 Santa Monica Blvd, Suite 100, Los Angeles, CA 90025. Received on March 20, 2018; accepted on April 6, 2018.

median CD4+ cell count was 493/μL, and all the women were receiving ART. The primary endpoint occurred in 74 women in the antepartum arm and 73 women in the postpartum arm. Rates of TB infection were low: 3 cases each in the 2 study arms. An unexpected finding from this study was that isoniazid received antepartum was associated with higher rates of adverse pregnancy outcomes (fetal demise, low birth rate infant, preterm labor, and infant congenital anomaly) than isoniazid received postpartum (23% and 17%, respectively; $P = .0009$). Thus, isoniazid for TB prevention was comparably safe for women when given during or after pregnancy. However, fetal and infant outcomes were worse when isoniazid was initiated during pregnancy. Guidelines should be updated to recommend administration of isoniazid postpartum rather than antepartum.

Isoniazid preventive therapy is associated with fewer adverse pregnancy outcomes when given postpartum versus antepartum

Despite overwhelming evidence that isoniazid preventive therapy (IPT) reduces TB burden, countries globally have been slow to scale up prevention services. Karanja and colleagues reported impressive scale up of IPT among HIV-infected persons in care in Kenya—a 50-fold increase from 9981 persons in 2014 to 494,436 persons in 2016 (Abstract 1113). Clinics reported a 90% completion rate among persons prescribed IPT. This success of implementation was attributed to the leadership of the central Ministry of Health, integration of IPT into routine HIV care, and President's Emergency Plan For AIDS Relief (PEPFAR) targets and accountability. If reported IPT completion reflects high adherence and if scale-up continues, declining rates of TB infection among the HIV-infected population in Kenya are expected.

Uptake of TB chemoprevention among children younger than 5 years —a group at high risk for tuberculosis infection—is also poor globally. World Health Organization guidelines changed in 2006 from requiring TB skin testing (TST) to identify IPT candidates to symptom screening only, to reduce the barriers to IPT caused by TST logistics. Saladar-Austin and colleagues conducted a clustered, randomized study in 16 clinics, comparing TST to symptom screening only for identification of IPT candidates in nurse-led decentralized HIV clinics in South Africa (Abstract 32). Of index cases of TB infection, 1097 child contacts (550 in the symptom screening arm and 547 in the TST arm) were identified. Overall, there was no difference in IPT initiation between the 2 groups (51.4% in the symptom screening arm vs 54.6% in the TST arm). Rates of IPT completion in childhood contacts were low, at 9% overall in the study. These data emphasize that past and current approaches to TB prevention measures for children at high risk are inadequate and that new approaches are urgently needed.

TB Diagnostic and Case-Finding Strategies

Failure to rapidly diagnose TB among persons with advanced HIV disease, who often have disseminated disease without detectable TB on sputum microscopy, contributes to high mortality rates. Gupta-Wright and colleagues tested the hypothesis that rapid urine TB screening tests (urine lipoarabinomannan [LAM] or Xpert MTB/RIF, which identifies Mycobacterium tuberculosis (MTB) and rifampin (RIF) resistance) added to sputum Xpert MTB/RIF testing, the standard of care (SOC), would reduce mortality by allowing for more rapid identification and treatment of TB infection (Abstract 38LB). The STAMP (Rapid Urine-Based Screening for Tuberculosis to Reduce AIDS-Related Mortality in Hospitalized Patients in Africa) study randomly assigned 2600 HIV-infected, hospitalized persons (72% on ART) in South Africa and Malawi to SOC TB screening or SOC screening plus rapid urine TB screening. Clinicians were informed if any test results were positive for TB, but they were blinded to the randomized arm. Overall mortality rate was 20% at 56 days, and mortality risk difference did not differ between study arms (21.1% vs 18.3%, respectively). However, in 3 prespecified subgroups (persons with a CD4+ cell count <100/μL, hemoglobin level <8 mg/dL, or clinical suspicion of TB infection at baseline), risk differences in mortality were 5.7% to 9.0% lower among those who had urine screening plus SOC screening than those who had SOC screening only. Rate of TB diagnosis was statistically significantly higher in those who had urine screening plus SOC screening than those who had SOC screening only (21.9% vs 14.9%, respectively). In a related study, incorporating rapid urine TB screening tests was cost-effective and was associated with increased life expectancy (Abstract 1117LB). These results call for scale-up and implementation of rapid urine and Xpert MTB/RIF screening tests in hospitalized individuals at high risk for TB infection.

Adding rapid urine diagnostic tests for TB screening to standard sputum evaluations reduced mortality among high-risk hospitalized individuals in South Africa and Malawi

High mortality rates are observed among individuals presenting with CD4+ cell counts below 100/μL, even with more sensitive TB diagnostics. If high mortality rates are attributable to missed TB cases, empiric TB treatment could reduce mortality rates. The STATIS (Systematic Empirical vs Test-Guided Anti-TB Treatment Impact in Severely Immunosuppressed HIV-Infected Adults Initiating ART With CD4 Cell Counts <100/mm^3) study randomly assigned 1047 HIV-infected persons in Cote d'Ivoire, Uganda, Cambodia, and Vietnam to extensive TB screening (Xpert MTB/RIF sputum, urine LAM, and chest x-ray) or to empiric TB treatment (Abstract 29LB). All participants not infected with TB received immediate ART. At 24 weeks, there was no difference between the 2 study

arms in mortality rate, presence of invasive bacterial disease, or the combined endpoint. More TB cases were diagnosed in the arm that underwent extensive TB screening (17.7%) than in the arm that received empiric TB treatment (2.6%). This study confirms and extends the findings of a prior study[2] that failed to demonstrate mortality-related benefits of empiric TB versus IPT among individuals with low CD4+ cell counts.

Another approach to reducing TB-related mortality is to find and treat contacts of persons with TB infection. In Botswana, during the rollout of sputum Xpert MTB/RIF testing to replace sputum microscopy, an enhanced TB case–finding strategy was implemented that included contact tracing and intensified tracking for TB-infected individuals with missed visits in half of the 22 participating clinics (Abstract 31). Among 14,963 individuals, the 12-month mortality rate was lower with enhanced TB case finding with or without Xpert MTB/RIF testing than with preintervention. This study highlights that efforts to reduce rates of TB mortality should include intensified TB case finding and treatment.

TB Treatment and Adherence

Rifamycins are a cornerstone of TB treatment. Recent data suggest that higher doses of rifamycins may decrease time to culture conversion during TB treatment. Velasquez and colleagues conducted a randomized phase II study among 180 smear-positive, drug-susceptible, TB-infected persons to evaluate treatment efficacy (microbiologic response) and drug-related toxic effects of rifampin 10 mg/kg, 15 mg/kg, or 20 mg/kg during an 8-week TB treatment induction phase (Abstract 39LB). Faster declines in microbiologic measures were observed with higher doses of rifampin. Grade 2 adverse events were common and were similar across study arms (38.3%-51.7%). Of note, serious rifampin-associated adverse events were rare: a total of 4 study participants among the 3 arms. These data justify future study of higher doses of rifampin to potentially shorten and improve TB treatment.

Estimates of adherence guide the duration of TB therapy. Dosing of TB treatment is currently measured through directly observed therapy (DOT) that is resource intensive, of unknown accuracy, and variably implemented outside of a clinical trial setting. Browne and colleagues randomly assigned 61 TB-infected persons in the continuation phase of TB treatment to DOT or wirelessly observed therapy (WOT), in which isoniazid and rifampin is coformulated with an edible digital sensor accompanied by an external wearable patch and paired mobile device that can track medication ingestion remotely (Abstract 782). A statistically significantly greater percentage of prescribed doses were confirmed with WOT than DOT. More research is need to determine the effect of WOT on clinical outcomes in TB treatment programs.

Rifamycin and Antiretroviral Drug Interaction Studies

Metabolic pathways of rifamycins interact with InSTIs, nonnucleoside analogue reverse transcriptase inhibitors (NNRTIs), tenofovir alafenamide (TAF), and PIs, requiring drug interaction, genomic, and confirmatory clinical studies to ensure the safety and efficacy of coadministration of HIV and TB treatments. Levels of InSTIs are lowered when coadministered with rifampin. In a 24-week interim evaluation, investigators from the INSPIRING study compared clinical and safety outcomes in TB-infected individuals receiving efavirenz 600 mg daily plus 2 nucleoside analogue RTIs (nRTIs) or dolutegravir 50 mg twice daily plus 2 nRTIs (Abstract 33). Rates of virologic suppression among participants were similar between the 2 study arms, and plasma dolutegravir levels with twice-daily dosing during TB treatment were similar to dolutegravir 50 mg daily without rifampin.

In persons treated for TB infection, double-dose dolutegravir–based ART maintained therapeutic dolutegravir concentrations and had similar levels of viral load suppression compared with efavirenz-based therapy

To determine if twice-daily dosing of the InSTI bictegravir might overcome reduced levels observed when this drug is coadministered once daily with rifampin, investigators conducted a pharmacokinetic study comparing coformulated (/) bictegravir/emtricitabine/TAF twice daily plus rifampin with bictegravir/emtricitabine/TAF once daily in uninfected volunteers (Abstract 34). Bictegravir levels were reduced by 80% when coadministered with rifampin, with levels in some participants falling below minimal targeted concentrations for efficacy. More studies are needed to define optimal dosing for this combination.

Similarly, serum TAF levels are reduced when coadministered with rifampin. The interaction between TAF and rifampin was measured by examining intracellular levels—a key determinant of drug efficacy—of the active TAF metabolite in 17 uninfected volunteers (Abstract 28LB). In the presence of rifampin, intracellular levels of active TAF metabolites were decreased by approximately 40% but were still 82% higher than those achieved with standard dosing of tenofovir disoproxil fumarate (TDF). These results are encouraging and call for continued study and monitoring of clinical outcomes of this combination.

In a study evaluating interactions between efavirenz and rifapentine, Podany and colleagues evaluated the effects of rifapentine on efavirenz levels (Abstract 455). Among 23 individuals receiving daily rifapentine in the ACTG 5279 trial of short-course TB prevention, efavirenz levels remained in therapeutic range.

If countries plan to widely implement efavirenz 400 mg for ART, including among TB-infected persons, it is important to demonstrate that levels of efavirenz remain in therapeutic range when coadministered with rifampin. In a small study of 22 persons not infected with TB who were receiving rifampin and efavirenz 400 mg/TDF/emtricitabine, efavirenz levels

were lowered but remained in therapeutic range (Abstract 457). Larger studies are needed, including among TB-infected persons, if this combination is to be utilized.

Examining the possibility that higher doses of rifampin might become a part of TB regimens, Atwine and colleagues evaluated efavirenz levels with increased rifampin dosing (Abstract 456). Rates of viral suppression were high among TB-infected persons receiving double doses of rifampin with efavirenz 600 mg or 800 mg daily compared with persons receiving efavirenz 600 mg without rifampin (Abstract 456).

Lopinavir/ritonavir and rifabutin remains an important combination for TB treatment. In a randomized trial of the pharmacokinetics and efficacy of rifabutin among 21 individuals in Thailand, rifabutin 150 mg daily and rifabutin 300 mg thrice weekly were safe and effective among those receiving lopinavir 400 mg/ritonavir 100 mg twice daily (Abstract 781).

Cryptococcal Disease

Screening and Treatment for Cryptococcal Antigenemia

Nalintya and colleagues implemented and evaluated a cryptococcal screening and treatment program in 11 clinics in Kampala, Uganda, that tested reflexively for cryptococcal antigen (CrAg) from all samples with CD4+ cell counts below 100/μL (Abstract 785). Preemptive fluconazole treatment and ART were offered for asymptomatic CrAg-positive individuals. Amphotericin B was used for treatment of symptomatic cryptococcal disease. The prevalence of CrAg was 6.5% among 1446 persons. Seven persons died prior to clinical evaluation. Among the 53 persons with asymptomatic cryptococcal disease, the mortality rate was 13% at 6 months. Among the 26 persons with documented cryptococcal meningitis, the mortality rate was 44%. Even with optimized CrAg screening and treatment programs, mortality due to cryptococcosis or other AIDS-related illness remains high among persons in care with CD4+ cell counts below 100/μL and cryptococcal antigenemia.

To provide insight into the excess mortality rates observed among persons taking fluconazole for asymptomatic cryptococcal disease, even when treated with fluconazole and ART, Wake and colleagues performed minimally invasive autopsies on 4 persons with asymptomatic cryptococcal disease and 2 persons with advanced HIV disease and no detectable serum CrAg in a cohort study in South Africa (Abstract 788). At autopsy, all 4 persons with detectable CrAg at cohort entry had evidence of central nervous system (CNS) disease, and the 2 persons with advanced HIV disease did not. Current approaches to treatment of asymptomatic cryptococcal disease likely underestimate the burden and extent of disease, contributing to poor outcomes even among persons treated with fluconazole.

In the REALITY (Reduction of Early Mortality in HIV-Infected African Adults and Children Starting ART) study, which included an enhanced cryptococcal disease prevention regimen that included empiric fluconazole and did not require a positive result for serum CrAg, investigators evaluated baseline CrAg status from stored plasma specimens (Abstract 784). Rates of cryptococcal disease at 24 weeks among those who were CrAg positive at baseline were 20.3% (no fluconazole arm) and 7.8% (fluconazole arm). Rates among those who were CrAg negative were 0.4% (no fluconazole arm) and 0.1% (fluconazole arm). Thus, there was a reduction in new cases of cryptococcal meningitis among persons prescribed fluconazole, regardless of whether CrAg was detected at baseline. The investigators suggest that fluconazole be given to all persons with low CD4+ cell counts—not just those with detectable CrAg—in settings with a high burden of cryptococcal disease, as part of a comprehensive prevention package.

Treatment for Cryptococcal Meningitis

Sertraline, shown to have in vitro and in vivo activity against *Cryptococcus*, was evaluated as adjuvant therapy to amphotericin B–containing treatment for cryptococccal meningitis in a double-blind randomized study of 550 individuals (Abstract 36). The study was prematurely discontinued for futility after enrollment of 460 participants because mortality rates were similar between the 2 arms. Even in this optimized clinical trial setting, overall mortality rates were 52% in the sertraline group and 46% in the placebo group.

Of historical interest, high-dose oral fluconazole 1200 to 2000 mg daily was evaluated in a dose escalation study as induction treatment for cryptococcal meningitis (Abstract 35). Persons who received fluconazole 1600 or 2000 mg had better microbiologic outcomes than those who received fluconazole 1200 mg. Overall mortality rates were more than 30% among persons receiving all doses of fluconazole and 24% among those receiving amphotericin B, supporting current guidelines for low- and middle-income countries (LMIC) that no longer recommend fluconazole alone as induction therapy for cryptococcal disease.

Non-AIDS Complications

Sabin reviewed evidence demonstrating that life expectancy among persons with HIV disease is on the rise (Abstract 102). In some studies, the life expectancy of people with treated HIV infection is near that of the general population, especially among those who initiate ART early, when CD4+ cell counts are high, and among those who do not inject drugs. She pointed out the importance of measuring "health span" and not just life years, to capture the quality of life and the impact of comorbid conditions, an important concept for future studies in this area.

Biomarkers to Predict Non-AIDS Events

The field of HIV medicine continues to examine biomarkers that will identify which individuals with treated HIV infection are at greatest risk for non-AIDS events. Baker and colleagues

from the START (Strategic Timing of Antiretroviral Treatment) trial examined the proportion of ART effect (clinical benefit in reducing events) explained by individual and combinations of the biomarkers interleukin (IL)-6, D-dimer, and CD4+ and CD8+ cell counts at baseline and at month 8 after starting ART (Abstract 74). The CD4+:CD8+ ratio explained most of the treatment effect (20%), IL-6 and D-dimer were additive, and all 3 explained 29% of the treatment effect. These results again demonstrate the potential value of the CD4+:CD8+ ratio as a marker of disease progression and highlight that there is no single biomarker that explains a major portion of the treatment effect.

The drivers and sequelae of CD8+ cell expansion in treated HIV disease remain an active area of investigation. Freeman and colleagues used flow cytometry to compare the populations of CD8+ cells in HIV-infected individuals on ART with those in HIV-negative controls after stimulation with different cytokines (Abstract 222). In the HIV-infected group, IL-15 but not IL-2 induced the generation, proliferation, and survival of a population of senescent CD8+ cells (CX3C chemokine receptor 1 [CX3CR1] + CD57+), the presence of which may be important for the development of cardiovascular complications. These findings were further expanded in work by the same group using aortic endothelial tissue samples from a simian-human immunodeficiency virus (SHIV) nonhuman primate model of atherosclerosis atherosclerosis (Abstract 241). The investigators observed elevated expression of CX3C motif chemokine ligand 1 (CX3CL1) and IL-15 in the vascular endothelium of SHIV/simian immunodeficiency virus (SIV)-infected rhesus macaques and that endothelial cells from these tissues could produce CX3CL1 and IL-15 in vitro, resulting in enhanced CD8+ cell migration to the endothelium.

A higher incidence and greater progression of high-risk (low-attenuation, noncalcified) plaque was demonstrated in HIV-seropositive men than in controls

Whether interventions currently being tested to reduce the risk of cardiovascular disease (CVD) (eg, statins or other immune modulators) reduce IL-15 levels and influence populations of activated, senescent CD8+ cell populations remains to be determined.

In a novel analysis, Kusejko and colleagues examined associations between viral HIV-1 polymerase sequences and the occurrence of comorbidities among participants in the Swiss Cohort Study and found evidence of phylogenetic clustering among participants who experienced some HIV-related complications (Kaposi sarcoma, HIV-related thrombocytopenia, and HIV-related encephalopathy), suggesting a potential role for viral genetic factors in mediating these outcomes (Abstract 169). Of note, non-AIDS complications such as CVD appeared more related to demographic and clinical confounders than viral factors.

Cardiovascular Disease

Cardiovascular complications remain an important cause of potentially preventable morbidity and mortality in individuals with treated HIV infection. Identifying the pathogenesis of CVD and the contributions of traditional and HIV-specific risk factors remains a high-priority area of research. Post and colleagues in the Multicenter AIDS Cohort Study (MACS) reported the results of a longitudinal study using computed tomography (CT) angiography among middle-aged men (mean age, 54 years) with HIV infection compared with controls (Abstract 77). With a median interval of follow-up between CT scans of 4.5 years, investigators measured the presence, quality, and progression of coronary artery plaque in a group of men in their mid-fifties. There was a higher incidence and greater progression of high-risk (low-attenuation, noncalcified) plaque in the HIV-infected men than in controls. Of note, viremia was an important risk factor for plaque progression, underscoring the importance of optimizing ART as an intervention to reduce the risk of atherosclerosis in HIV disease.

Carotid artery intima-media thickness (cIMT) measured by ultrasound has been used as a surrogate measure of atherosclerosis in HIV studies because it is low cost, reproducible, and widely available. When cIMT is used, data are collected on the thickness of arterial segments, the presence of carotid plaque, and measures of arterial stiffness (referred to as Young's modulus of elasticity). Investigators from the Women's Interagency HIV Study (WIHS) and the MACS pooled data on cIMT in a large sample of HIV-seropositive and -seronegative men and women, to examine whether these measures predicted mortality in this group, and found that the presence of plaque and the measure of elasticity, but not common cIMT, were associated with mortality in HIV-seropositive and -seronegative persons (Abstract 78). These findings highlight the importance of studies that evaluate the impact of interventions on these measures.

Most studies of CVD in the context of HIV disease have focused on coronary artery disease (CAD) and to a lesser extent heart failure and arterial stiffness. This year, a group from Denmark reported on the prevalence of peripheral artery disease in a cohort of people older than 40 years who had HIV infection compared with a larger cohort from the general population (Abstract 76). Peripheral artery disease (PAD) was assessed by Doppler test, ankle brachial index was calculated, and symptoms of claudication were collected by self-report. The study found a higher prevalence of PAD in the HIV-infected group (12%) than in the control group, even after adjustment for the higher rate of smoking in the HIV-infected group as well as other factors. The investigators found no evidence that HIV disease severity or duration of ART were associated with the prevalence of PAD. Further studies are needed to determine whether rates of progression and response to treatment of PAD differ in those with HIV infection.

Antiretroviral Therapy and Cardiovascular Disease

CROI 2018 featured studies examining the associations between individual antiretroviral drugs and CVD, 10 years

after the first reports of a link between abacavir and CVD risk. Of reported associations between antiretroviral drugs and CVD, the reversible association between abacavir exposure and myocardial infarction (MI) risk remains of greatest interest. The search for a mechanism between abacavir exposure and MI risk has led several groups to examine the role of platelet function. Measures of platelet reactivity are difficult to perform due to the need for immediate testing of fresh blood samples. Mallon and colleagues utilized the design of a randomized switch study to embed evaluations of platelet and endothelial function in participants who were randomly assigned to switch or continue the abacavir component of their ART regimen (Abstract 677LB).

In the first report, 61 virally suppressed, HIV-infected individuals taking abacavir/lamivudine randomly assigned to switch to TAF/emtricitabine or remain on abacavir/lamivudine had measurements of platelet aggregation at baseline, week 4, and week 12 in response to concentrations of 5 agents known to stimulate platelet reactivity: collagen, thrombin receptor-activating peptide (TRAP), adenosine diphosphate (ADP), epinephrine, and arachidonic acid. Participants who switched from abacavir/lamivudine to TAF/emtricitabine experienced an improvement in platelet reactivity in response to the agonists TRAP and ADP at week 4, and collagen through week 12. A rise in the surface expression of glycoprotein VI (GPVI) was also reported.

The second report from this group focused on the measurement of soluble (s)GPVI in 545 participants from the same switch study. Measurements of sGPVI in platelet-poor plasma taken at weeks 0, 4, 12, 24, and 48 were obtained using electrochemiluminescence. Participants who switched from an abacavir-containing regimen to a TAF/emtricitabine-containing regimen experienced statistically significantly greater increases in sGPVI to week 48, with a 14.7% increase (95% CI; 4.1, 26.3) between groups. The greater increases in sGPVI after a switch from abacavir/lamivudine to TAF/emtricitabine were interpreted as evidence of an improvement in a reversible defect in platelet function.

The clinical studies by Mallon and colleagues align with the findings of Taylor and colleagues who performed in vitro experiments with abacavir, TDF, and TAF in the absence of HIV infection in which they noted that abacavir substantially enhanced expression of platelet activation markers, whereas TAF and TDF had no effect (Abstract 673). Work presented by a Spanish group (Abstract 674) using a mouse model of arterial thrombosis suggested that leukocytes were necessary to observe the thrombotic properties associated with abacavir exposure in their model. Taken together, these studies suggest a mechanism by which abacavir could potentiate the risk of MI. Confirmatory studies of changes in platelet measures among people initiating therapy with abacavir would be valuable to determine risk factors for these changes.

Kovari and investigators from the Swiss Cohort Study examined associations between ART exposure and coronary plaque using coronary artery calcium scoring and CT angiography among 428 participants, predominantly men (Abstract 670). Cumulative atazanavir exposure was associated with calcified plaque, whereas abacavir exposure was associated with noncalcified plaque after adjustment for CAD risk factors. Previous studies have suggested a reduced risk of MI associated with atazanavir exposure, and the possible role of residual confounding in this type of analysis should be acknowledged.

Interventions to Reduce Inflammation in HIV

Low-dose methotrexate has been used to treat chronic inflammation in rheumatoid arthritis, and epidemiologic data suggest a reduction in CVD events when the drug is used in this context. A large clinical endpoint study of weekly low-dose methotrexate is ongoing in the general population and excludes people with HIV disease. Hsue and colleagues performed a randomized trial to evaluate the safety and activity of low-dose methotrexate in individuals with treated HIV infection and risk factors for CAD (Abstract 79). The study enrolled 176 participants, mostly men, with a median age of 54 years and well-suppressed HIV infection.

Measures of inflammation, T-cell activation, and flow-mediated dilation of the brachial artery were assessed and read centrally. During 24 weeks of randomized treatment, safety events (eg, mostly CD4+ cell count decline and infections) were more common among those receiving low-dose methotrexate (12.8% vs 5.6%), but the difference between study arms did not exceed a 15% prespecified margin. No differences in soluble markers of inflammation or flow-mediated dilation were noted by treatment group; however, there was a statistically significant decrease in CD8+ cell activation in the group receiving low-dose methotrexate. In a substudy by Tawakol and colleagues, fluorodeoxyglucose (FDG)– positron emission tomography (PET) scans were performed on a subset of the participants, and there was evidence of reduced arterial inflammation among those receiving low-dose methotrexate (Abstract 684LB). Given the high rate of safety events among those receiving low-dose methotrexate, further studies of this intervention will need to await the findings of the larger ongoing study in the general population.

In addition to the focus on activated CD8+ cells and non-AIDS events, there continues to be intense interest in the role of activated monocytes in the pathogenesis of non-AIDS complications. Mallard and colleagues performed novel studies using ART plus methylglyoxal-bis-guanylhydrazone (MGBG; a polyamine biosynthesis inhibitor that targets myeloid cells) compared with ART alone or no treatment in a SIV-infected macaques model that included measures of CNS infection and atherosclerosis via cIMT (Abstract 421). The animals treated with the combination of MGBG and ART were less likely to have CNS SIV infection and had less cIMT thickening compared with ART alone or no ART. Whether it will be feasible and safe to block myeloid cell activation in humans remains to be demonstrated, but these studies pave the way for future interventions targeting this pathway.

Dietary interventions to reduce dyslipidemia in the context of HIV disease have reported mixed results. Stradling and colleagues conducted a pilot randomized trial that enrolled adults with stable HIV infection and elevated low-density

lipoprotein (LDL) cholesterol and compared a diet low in saturated fat with a Mediterranean diet that included plant stanols, soy, oats, nuts, and fish (Abstract 703). The study population included 60 adults, 50% of whom were women. After 6 months, those who ate a Mediterranean diet experienced a greater decline in LDL cholesterol and improvement in blood pressure than those who ate a low-fat diet. As is often seen in dietary intervention studies, adherence to the diet varied widely. No differences were noted in body composition, arterial stiffness, or gut function. These results confirm the potential benefits of a Mediterranean diet if people can adhere to it.

Although it is unknown whether guidelines for statin use should differ for people with HIV infection, most experts agree that the guidelines for the general population are reasonable to follow. Adherence to statin guidelines developed for the general population among people with HIV infection remains an area of great interest in various health care settings. Data from the US Military HIV Natural History Study were used to examine adherence to statin guidelines within a health system in which access to care is less constrained (Abstract 705). Using the 2013 American College of Cardiology/American Heart Association guideline[1] the investigators examined the proportion of eligible participants who received statin therapy between 2015 and 2016. Only 55% of eligible participants with HIV infection received a statin, and 58% of those had diabetes. Persons who were older, white, or taking a PI were more likely to receive statins. These results highlight the fact that even within a single payer system, disparities in care persist, as well as the work needed to improve primary health care for people with HIV infection.

Just more than half of statin-eligible patients received statin therapy in a single payer health care system

Renal Disease

Renal disease is a well-described complication of HIV infection and ART, most notably with tenofovir disoproxil fumerate (TDF). Whether the occurrence of kidney disease portends a higher risk for future clinical events is less well understood. Using data from the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study, Ryom and colleagues examined the rates of serious clinical events among participants who experienced confirmed chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2 or a 25% decrease in eGFR in those with a starting eGFR of less than 60 mL/min/1.73 m^2 (Abstract 75). The investigators reported higher rates of death and serious clinical events among people who had CKD compared to those who did not have CKD. These findings, although unsurprising, highlight the need for closer monitoring of individuals once an episode of CKD occurs, and underscore the need for close attention to modifiable risk factors (eg, smoking) for future serious events, as well as the importance of controlling HIV infection.

Renal transplantation is not accessible for some individuals with HIV infection. In a large French study that matched HIV-seropositive persons receiving renal replacement therapy to HIV-seronegative controls (Abstract 728). Two years after initiating renal replacement therapy, 46% of the HIV-infected group had been placed on a waiting list for transplant compared with 64% of controls. Although improvements over time in rates of renal transplantation were observed in the HIV-infected group, access to transplantation for this group remains delayed.

Fat

There is continued interest in the interplay between fat, inflammation, and metabolic health. In addition to the quantity of fat, the quality of fat tissue likely plays an important role. Two studies examined fat quality, using CT scans, and its relationship to metabolic health outcomes (Abstracts 736, 737). On CT scans, small adipocytes appear denser than larger, less healthy adipocytes. Using data from the ACTG 5224s trial, investigators reported gains of visceral and subcutaneous adipose tissue over 96 weeks of ART and a correlation between fat density and measures of inflammation (Abstract 737). Decreases in density of visceral adipose tissue correlated with increases in IL-6 and soluble tumor necrosis factor–α receptor type II, suggesting that the quality of the fat gained was metabolically unhealthy. Using data from completed trials of the growth hormone–releasing factor tesamorelin, Lake and colleagues observed an improvement in fat density (increased density) among those receiving tesamorelin compared with placebo (Abstract 736).

The HIV UPBEAT (Understanding the Pathology of Bone Disease in HIV-Infected Patients) study is a longitudinal assessment of body composition in a group of participants with treated HIV infection compared with an HIV-uninfected control group (Abstract 733). This study addresses the important issue of whether changes in fat and lean body mass observed in those with HIV infection are caused by HIV infection, ART, or the aging process. Each demographically matched group of participants observed increases in arm fat and lean mass over time. These findings provide reassurance that the changes in body composition observed after initiation of ART may not persist over longer-term follow-up, compared with age-matched controls.

Changes in body composition observed after initiation of ART may not persist over longer term follow-up

Bone

Bone loss after the initiation of ART has been well described. What is less clear is whether this persists over longer follow up.

In the results from the bone substudy of the START trial, Carr and colleagues reported the rate of bone loss over 5 years in persons who initiated ART immediately compared with those who deferred until their CD4+ cell count dropped below 350/µL (Abstract 722). Bone mineral density (BMD), measured by dual-energy x-ray absorptiometry (DEXA), dropped more in the group that received immediate ART, over the first year of the study, even after controlling for TDF use. After the first year, rates appeared similar in the 2 groups, suggesting that the rate of bone loss slows after the first year of ART. Such early changes in BMD during ART may have more important consequences for pregnant women initiating therapy, as reported by Nabwire and colleagues (Abstract 721). Interventions to mitigate bone loss include discontinuing TDF, or the use of bisphosphonates (eg, zoledronic acid) to reduce bone resorption. In a follow-up report to a clinical trial that demonstrated that the use of zoledronic acid was more effective than discontinuing TDF, measures of bone turnover showed that bisphosphonate use was associated with a greater reduction in bone turnover than TDF discontinuation (Abstract 723). Pooled data from completed switch studies in which participants changed from a TDF- to a TAF-containing regimen examined changes in BMD and bisphosphonate use over time. The results suggest that both interventions improved BMD but highlight that individuals who both switched to a TAF-containing regimen and added a bisphosphonate had greater improvement in BMD in the spine but not the hip (Abstract 724). The optimal strategy for improving bone density after TDF use is yet to be defined.

Exercise and Functional Status

A randomized controlled trial of an exercise intervention among HIV-infected, sedentary adults aged 50 to 75 years who were virally suppressed found that those randomly assigned to high-intensity exercise showed greater gains in strength than did HIV-seronegative controls. These findings underscore the potential benefits of exercise as a scalable intervention to reduce long-term comorbidities in HIV infection.

All cited abstracts appear in the CROI 2018 Abstracts eBook, available online at www.CROIconference.org

Financial affiliations in the past 12 months: Dr Currier has received research grants awarded to her institution from Theratechnologies. Dr Havlir has no relevant financial affiliations to disclose.

Additional References Cited in Text

1. American College of Cardiology and American Heart Association. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. http://www.onlinejacc.org/content/accj/63/25_Part_B/2889.full.pdf?_ga=2.142815221.1185323657.1522185592-464558588.1522185592. Accessed on March 27, 2018.
2. Hosseinipour MC, Bisson GP, Miyahara S, et al. Empirical tuberculosis therapy versus isoniazid in adult outpatients with advanced HIV initiating antiretroviral therapy (REMEMBER): a multicountry open-label randomised controlled trial. *Lancet*. 2016;387(10024):1198-1209.

Top Antivir Med. 2018;26(1):22-29.

Invited Review

CROI 2018: Highlights of Viral Hepatitis

Anne F. Luetkemeyer, MD; David L. Wyles, MD

At the 2018 Conference on Retroviruses and Opportunistic Infections (CROI), there was a major focus on hepatitis C virus (HCV) elimination and improving each component of the hepatitis C care cascade. Several countries and cohorts have demonstrated the remarkable impact that universal HCV testing and unrestricted access to hepatitis C treatment can have on markedly reducing incident HCV infections and HCV infection prevalence, including in people who inject drugs and HIV/HCV-coinfected populations. However, in many settings, substantial barriers to widespread HCV treatment remain, including undiagnosed HCV infection, particularly in populations outside the standard "baby boomer" birth cohort (ie, born 1945-1965); restricted access to hepatitis C treatment in those with known HCV infection; reinfection with HCV; and migration of HCV-infected populations. Many innovative programs have successfully implemented HCV testing and treatment outside of traditional care settings, expanding access for harder-to-reach populations, which will be crucial to successful elimination efforts. Outbreaks of hepatitis A virus (HAV) infection continue to occur in among men who have sex with men and homeless populations in the United States, Europe, and Southeast Asia, highlighting the need for improved HAV vaccination programs for populations at risk.

Keywords: HIV, CROI, 2018, hepatitis, HAV, HCV, prevention, testing, elimination

The HCV Care Cascade: On the Road to Elimination?

Hepatitis C virus (HCV) drug development has slowed and approvals for all current direct-acting antiviral (DAA) regimens have been in place for some time. The time has come to redouble efforts surrounding HCV diagnosis and treatment, as the prospect of HCV elimination becomes real. To that end, a number of abstracts examined where different communities and populations stand along the hepatitis C care cascade.

Early in the HCV care cascade, it is crucial to obtain HCV RNA confirmation for seropositive persons, as approximately 25% of persons may clear HCV infection spontaneously. Coinfection with HIV may hamper spontaneous clearance of HCV infection, although to what degree remains a matter of debate. Data from the PROBE-C (Prospective Observational Evaluation of the Natural History and Treatment of Acute HCV in HIV-Positive Individuals) study cohort assessed the rate of spontaneous HCV clearance in 464 HIV-seropositive participants with acute HCV infection (in this case, defined as HCV infection within the last 12 months) (Abstract 129). The cohort consisted almost entirely (98%) of HIV-infected men, with sex with men as their HCV transmission risk factor. Their HIV infection was well controlled, and more than 90% of participants had a plasma HIV RNA level below 200 copies/mL on antiretroviral therapy (ART). The HCV genotype distributions were 74% with genotype 1a and 18% with genotype 4, reflective of the genotypes currently circulating in men who have sex with men (MSM) in Europe. The spontaneous HCV clearance rate was 12%, and mean time to undetectable HCV RNA was 13 weeks (interquartile ratio, 12-18). The mean time to HCV treatment initiation was 11 weeks in participants with persistent viremia, raising the possibility that some may have initiated treatment prior to what would have been a spontaneous clearance. The only factor in multivariate analysis that was predictive of spontaneous HCV clearance was a greater than 2 $\log_{10}$ IV/mL decrease in HCV RNA level over the first 4 weeks (odds ratio [OR], >1115 [225-5515]; $P \leq .001$), which occurred in 14% of the entire cohort and 96% of those with spontaneous clearance.

Direct detection of HCV RNA allows for more prompt identification of infection, an important first step to reducing HCV transmission and linking to HCV care. Incident HCV was detectable a median 2 months earlier with an HCV antigen test and with HCV RNA testing (either standard laboratory-based RNA assay or rapid HCV PCR), than with standard HCV antibody (Ab) testing, in MSM undergoing routine screening in the IPERGAY (Action to Prevent Risk Exposure By and For Gay Men) study (Abstract 585). Of note, only 3 of 12 MSM had elevated levels of aspartate aminotransferase at the time of demonstrable HCV viremia, serving as a reminder that early and presumably infectious HCV can be present in the absence of transaminitis.

Low rates of HCV diagnosis, the first step in the HCV care cascade, remain a major barrier to HCV elimination in the United States. In Massachusetts, one-third of individuals diagnosed with HCV infection as part of a universal screening program were unaware of their infection, highlighting that testing remains a substantial stumbling block in the HCV care cascade (Abstract 577). Emergency department (ED)-based HCV testing is a strategy to identify undiagnosed HCV-infected persons or those who remain unlinked to care. An ED HCV testing program in Baltimore, Maryland, identified 446

Dr Luetkemeyer is Associate Professor at the University of California San Francisco. Dr Wyles is Chief of the Infectious Diseases Division at Denver Health Medical Center in Denver, Colorado. Send correspondence to Anne F. Luetkemeyer, MD, 995 Potrero Ave, Box 0874, San Francisco, CA 94110. Received on March 26, 2018; accepted April 9, 2018.

ED patients with active HCV infection, 86% of whom were not in care (Abstract 578). Unfortunately, less than half of the patients were successfully linked to care, and half of those already had advanced fibrosis (Metavir score, F3 or F4). The ED holds promise as a place in which to identify chronic HCV-infected persons in need of care, but there remain substantial missed opportunities to subsequently engage and cure such individuals.

Two abstracts reported on statewide data or programs. Massachusetts has had a robust laboratory testing–based HCV monitoring system in place for years. Leveraging this data-reporting system, Vo and colleagues reported on the HCV care cascade in their state from 2007 to 2015 (Abstract 595). To generate the care cascade, investigators took confirmed HCV Ab–positive tests and then followed their laboratory progression through: 1) HCV RNA confirmation; 2) repeated (>1) HCV RNA or genotype testing in the same year as a marker for engagement in care; 3) specific testing for HCV genotype to indicate intent to treat; and 4) a negative HCV RNA test result at least 12 weeks after genotyping as a surrogate for a sustained virologic response 12 weeks after cessation of treatment (SVR12). Although there are limitations to this approach, it is a reasonable way to assess HCV care cascade parameters on a population level. Notable findings included that most of the population was outside the 1945 to 1965 birth cohort, including 45% who were younger than 40 years, and more than two-thirds resided outside the Boston metropolitan area. These are trends in a changing HCV infection epidemiology that have been seen throughout the United States, largely attributed to growing opioid epidemic.[1] Progression through the HCV care cascade continued to demonstrate several shortcomings: 1) confirmatory HCV RNA testing was only documented for 62%; 2) of those with confirmed detectable HCV RNA, a genotype was recorded for only 39%; and 3) only 2.2% had subsequently undetectable HCV RNA suggesting SVR. Of note, SVR assessment was limited because negative HCV testing results were not reported until 2015. However, it is unlikely that a substantial proportion of this population initiated and completed treatment and follow-up before 2015. The SVR rate may also be falsely inflated, given the likely inclusion of some spontaneous clearances. Hopefully, many of these individuals have been treated in the last 2 years, but much still needs to be done regarding linkage to and retention in HCV care as well as treatment.

The ACTIVE-C (Alabama Coalition for Testing, Interventions and Engagement in Hepatitis C Care) collaborative group presented results on the impact of this program, which included on-site coordinators and education, on HCV testing rates, linkage to care, and treatment since its launch in July 2015 (Abstract 594). Partners in this program include University of Alabama at Birmingham, the Alabama Public Health Department, and community health centers, which combined covered 7 cities and more than 40 clinics across Alabama. The data showed an alarming 11% HCV seroprevalence rate among more than 84,000 HCV Ab screening tests. In community clinics, large increases in the proportions of individuals completing confirmatory testing (ie, HCV RNA) were seen from year 1 (19%) to year 2 (69%) of the program. In aggregate, 29% of individuals initiated HCV treatment, with no difference between community and academic sites. The community clinic population was more likely to be black and have no insurance or Medicaid and less likely to have cirrhosis. Rates of SVR were high (95%-97%) and not statistically different between academic and community sites. Expanding HCV care beyond specialized practitioners and clinics will be essential and is feasible, as demonstrated in the ACTIVE-C collaboration.

In a somewhat similar approach within a large federally qualified health center in San Diego, California, Rojas and colleagues presented updated data on a project to empower primary care practitioners to treat hepatitis C under the guidance of a specialized team consisting of an infectious diseases physician and patient navigators working in conjunction with primary care physicians and nurse practitioners (Abstract 599). Since the project's inception in 2013, the volume of treatment grew steadily, with a shift in treatment from specialists to primary care physicians. To date, 830 patients have been treated in the program, and primary care physicians treated the majority in the last year. Per-protocol SVR12 rate was extremely high (97%), with no difference by treater. A substantial number of individuals had missing data or were lost to follow-up, making the intention-to-treat SVR12 rate only 72%. Of the 13 individuals with documented virologic failure, 11 had cirrhosis. Data from ACTIVE-C and the San Diego project demonstrate a principle initially demonstrated by the ECHO (Extension for Community Healthcare Outcomes) model: the substantial strides that can be made by empowering primary care practitioners in nonacademic settings to treat HCV infection, with excellent results.[2]

Data on the HCV treatment cascade among HIV/HCV-coinfected individuals in HIVRN (HIV Research Network) sites in the United States were presented. Radwan and colleagues compiled HCV testing and diagnosis rates across 12 HIV clinics and examined DAA treatment outcomes for 9 of 12 sites with on-site HCV treatment programs over 2 years (January 2014-December 2015) (Abstract 597). Of more than 28,000 persons with HIV infection, 79% were screened for HCV and 31% were HCV seropositive. HIV-infected persons more likely to be screened for HCV were younger than 40 years, black, or had a history of injection drug use. In contrast, among those who were HCV-Ab positive, older than 40 years of age, Hispanic race and injection drug use were associated with HCV seropositivity. High rates of HCV treatment (85% among persons with detectable HCV RNA) and SVR (96%) were observed in the subset of 9 sites with on-site treatment programs. These data are encouraging, given that they largely occurred before the widespread approval of potent DAA regimens, although the (the off-label DAA combination of sofosbuvir plus simeprevir was possible. The high treatment uptake early in the DAA era may also may reflect the inclusion of academic centers with HCV treatment on-site.

Impact of Unrestricted HCV Treatment on HCV Elimination

The Swiss HIV Cohort Study examined the impact of a comprehensive population-based approach to HCV elimination in HIV-infected MSM (Abstract 81LB). To that end, the Swiss HCVree study systematically tested 3722 MSM, a majority of the larger study cohort, for HCV infection. Of those tested, 177 (4.8%) had active HCV infection and 31 (18%) were judged to be new infections based on prior HCV test results. Of the 177 persons with HCV infection, 61 (91%) were treated with co-formulated (/) elbasvir/grazoprevir (provide by manufacturer) or with other locally provided DAAs if there was a contraindication to elbasvir/grazoprevir; 99.5% attained an SVR12. Testing for HCV was then repeated among the initially tested cohort, and 28 (0.8%) active HCV infections were identified, 16 (57%) of which were incident infections, and the remainder were those who had not been initially treated. Of the 28 HCV-infected individuals, 22 accepted HCV treatment; 100% of these achieved an SVR12. Thus, systematic HCV screening and treatment led to a 49.0% reduction in incident HCV infections and a 92.5% decrease in chronic HCV infections. This study demonstrates the remarkable impact that systematic universal testing and treatment can have on the HCV epidemic, in a setting where there are no barriers to screening or treatment. New infections from outside Switzerland may jeopardize this microelimination strategy (see Molecular Epidemiology of HCV Networks and Resistance-Associated Substitutions section below)

Several country-wide programs have now demonstrated the powerful effect universal HCV testing and treatment programs can have, in a short period, on HCV prevalence and incidence.

Spain implemented a strategy of unrestricted access to HCV DAAs. In a large Spanish HIV/HCV-coinfected "real world" cohort with a high prevalence of injection drug use (87%), 65% initiated DAA therapy, and 94.8% of those with evaluable results attained an SVR12, demonstrating the potential of universal DAA access including populations of persons who inject drugs (PWID) (Abstract 603).

Widespread DAA access in the Netherlands was associated with high SVR12 rates and a marked 51% decline in acute HCV infections in HIV-infected MSM in data presented at CROI 2017.[3] In contrast, in the French Dat'AIDS study cohort, despite high HCV treatment uptake and cure rates, the incidence of acute HCV infection in HIV-infected MSM substantially increased from 2012 to 2016 for both initial infection and for reinfection. Reinfection risk was consistently elevated over risk of first infection (Abstract 591). Of note, acute HCV incidence in HIV-infected PWID also increased but remained lower than in MSM. The reason for the differential rates of acute HCV infection in France versus Switzerland and the Netherlands is unclear but highlights the need for robust HCV reinfection counseling and surveillance to accompanying widespread DAA rollout.

In the Austrian HIV Cohort Study, remarkably high rates of screening (96%; 5364/5613) and HCV RNA confirmatory testing (99%; 1178/1195) were reported from 2014 to 2017 (Abstract 596). However, due to restrictions limiting DAA prescribing to hepatologists in 3 of the 8 HIV clinics examined, comparisons in progress along the treatment cascade were made between sites without (n = 3) and with (n = 5) prescribing restrictions. Unsurprisingly, a higher proportion of participants were treated at clinics in which in-house DAA treatment was allowed (76%) versus required referral to a hepatologist (56%). In multivariate analysis, the only factor predicting DAA treatment was availability in the HIV clinic (OR, 3.36; CI, 2.16-5.24). Higher rates of prescription of interferon-alfa-based treatment by hepatologists is not clearly explained but may have to do with a time bias: more patients were referred to hepatology in the earlier period of the study when DAAs were less available. Although the investigators state that Austria is on route to elimination of HCV disease, these data do not compare well with data from other countries in Europe or even from some HIV clinics in the United States, highlighting the adverse impact practitioner restrictions can have on DAA rollout and progress toward elimination of HCV disease.

In the United States, restricted access to DAAs remains a substantial barrier to HCV treatment. An evaluation of DAA prescriptions from 45 US states found 35% were denied, with the denial rate increasing significantly over the period studied (from 27.7% to 43.8%) (Abstract 600). Denials we more common with commercial insurance (52.4%) versus Medicaid (34.5%) and Medicare (14.7%)

Sexual Transmission of HCV and Risk for HCV Reinfection

HCV reinfection is the Achilles heel of HCV elimination efforts, with reinfection rates in HIV-infected MSM as high as 25% reported in some European settings.[4] In the French Dat'AIDS study cohort, there was an equivalent incidence of acute HCV infection in HIV-infected MSM (1.38/100 person-years) and HIV-uninfected MSM taking preexposure prophylaxis (PrEP), serving as a important reminder that MSM sexual transmission of HCV is not limited to MSM with HIV infection (Abstract 590). Data from Philadelphia, Pennsylvania, showed that younger MSM as well as heterosexual people with HIV infection may be at elevated risk of recent HCV infection via sexual transmission (Abstract 593). Prevalence of HCV infection in men initiating PrEP in New York, New York, was low at 0.26%, which is lower than in the general population (Abstract 592). However, it is clear that PrEP users remain at risk for acquisition of HCV and other sexually transmitted infections. In the GECCO (German Hepatitis C Cohort) study, the HCV reinfection rate in HIV-infected MSM was 14.3 per 100 person-years, substantially higher than the 1.8 per 100 person-years in PWID (Abstract 612). Median time to HCV reinfection was 63 weeks.

Sexual transmission of HCV is more common in those with preexisting HIV infection. One potential hypothesis for this increased risk was presented by Dutch researchers who examined HCV transmission via Langerhans cells, which are known to be present in the anal mucosa (Abstract 588). Immature cells did not transmit HCV to hepatocytes in vitro; however, exposure to HIV was associated with a substantial increase in HCV transmission to liver cells (Abstract 588).

Molecular Epidemiology of HCV Networks and Resistance-Associated Substitutions

Data using HIV phylogenetics have demonstrated the utility of sequence analysis to determine transmission pairs, including transmissions not identified by traditional epidemiologic investigations.[5] Similar data are now emerging for HCV and were presented in 2 abstracts. Data from the UFO (U Find Out) study in San Francisco, California (Abstract 584), a prospective cohort of young HCV-serodiscordant PWID in active injecting relationships, identified 40 partnerships (56 individuals) with documented new HCV infection during follow-up. Using deep sequencing of core nonstructural protein 2 (NS2) and NS5B regions, transmission clusters were identified, and interestingly, more than half of transmissions occurred outside of the primary injecting partnership, including 3 transmission events between persons not identified in an injecting relationship. Minor variant transmissions, which would only be detected by deep sequencing, were identified in at least 3 instances.

A phylogenetic analysis from the ALIVE (AIDS Linked to the Intravenous Experience) study cohort in Baltimore assessed core/E1 sequences in viremic participants from the last study visit (Abstract 581). A less than 4% difference in sequence between participants was considered a linkage in the analysis, which was limited to persons with HCV genotype 1. As expected for this cohort, most participants were black (87%) with HCV genotype 1a infection (83%). Most of the samples analyzed were from 2016 (71%). Although most participants were not in an identified cluster (68% of participants with genotype 1a, and 60% of participants with genotype 1b), 25% belonged to clusters, including 2 large clusters of participants with genotype 1a of 42 and 66 participants, respectively. Factors associated with belonging to a cluster in multivariate analysis included young age, HIV infection, and hazardous alcohol use.

Two abstracts used HCV phylogenetic data to assess large-scale transmission patterns for HCV and develop messages concerning HCV control and elimination efforts and the need for coordination. Within the Swiss HIV Cohort study, whole genome sequencing was carried out on 66 incident genotype 1a HCV infections in MSM from 2012 to 2016 (Abstract 130). The NS5B sequences from these infections were compared with sequences retrieved from public databases to attempt to ascertain the likely origin of the infecting strain. Although most transmissions appeared to originate from other HCV-infected Swiss persons, 14% to 44% (depending on the percentage of Swiss sequences in a cluster required to consider it Swiss overall) appeared to be the result of transmission from sequences originating outside Switzerland, mostly from Germany, the Netherlands, or the United Kingdom. Only 5% to 10% of sequences originating outside Switzerland came from outside Europe. The major limitation of these data is the bias imposed by using sequences uploaded to public databases, which may not accurately represent the circulating viruses in neighboring countries, leading to an underestimation of non-Swiss transmission events.

A similar investigation took sequences from collaborating sites across Europe (not available in public databases; n = 1729)) as well as those reported to public databases (n = 2740) and compared the phylogenies from NS3 and NS5A over time to assess longer-term HCV transmission trends (Abstract 582). Investigators found phylogenetic evidence for extensive HCV sequence movement between European countries, with a major signal for seeding of US sequences into Europe, primarily through jumps into Germany and Italy (although there was evidence of spread from the United States to most European countries). Despite the extensive seeding, no signal for seeding of NS5A resistance-associated substitutions (RASs) was found. As described previously, the NS3 Q80K variant was highly prevalent in North American sequences and its appearance in European sequences could be traced to introduction from North America.

The implications of these abstracts are that the positive impact of localized (even at a country level) test-and-treat strategies to control or eliminate HCV may be severely hampered by international HCV transmissions and that coordinated elimination efforts are needed on a continental or even international level.

The impact of NS5A RASs on HCV treatment outcomes is limited in most settings with currently available, highly potent DAA regimens and often requires other negative predictors to see a meaningful adverse treatment effect (e.g., treatment experience and cirrhosis).[6] In a retrospective analysis of 388 HCV genotype 1–infected DAA treatment–naive individuals, population-based sequencing was used to assess factors associated with NS5A RASs by genotype (1a vs 1b), including the Y93H variant (Abstract 583). The prevalence of NS5A RASs was similar to what has previously been described, with differences in specific mutations and prevalence by genotype 1 subtype (RASs in 6% of individuals with genotype 1a and 10% with genotype 1b). The Y93H variant was only found in sequences of individuals with genotype 1b who were DAA treatment naive. In univariate analysis, severeal factors were found to have associations with the presence of NS5A RASs (P = .05). Factors identified included older age, more advanced fibrosis, lack of HIV infection, and hepatitis B core antigen immunoglobulin G (IgG) positivity. However, correction for multiple comparisons was not made nor was a multivariate analysis undertaken (likely due to the relatively small number with RASs). A simple explanation may be time: with a longer time of infection, more random mutations in the virus are accumulated, which could result in RASs. This could explain the associations with both older age and advanced fibrosis, both surrogates for longer duration of infection. Another possible

explanation is that there is some selective pressure, possibly immune, for RASs, including Y93H. Previous data have associated the Y93H variant in persons with HCV genotype 1b infection with the iIL28B CC genotype,[7] while other data have associated the IL28B CC genotype with more rapid progression of fibrosis.[8] The IL28B genotype was not reported in the study referenced above and could be another unmeasured variable explaining the observed association. Ultimately, the small number of individuals with RASs, numerous comparisons, and lack of multivariate analysis make it impossible to judge if any of the identified associations are meaningful. Although interesting, further study in larger data sets is needed. The one clear conclusion based on the phylogenetic data from this study is that RASs are selected during viral evolution within an individual and not yet transmitted in clusters.

HCV Treatment

Compared with prior CROI conferences, relatively few data were presented on new HCV treatment regimens or approaches. Results have been mixed in terms of the benefit of treating acute HCV infection with shortened durations of therapy with DAAs.[9,10] Boerekamps and colleagues presented interim data from the ongoing DAHHS-2 study (Dutch Acute Hepatitis C in HIV Study), which is evaluating 8 weeks of treatment with elbasvir/grazoprevir in MSM with acute (<6-month estimated duration of infection) HCV genotype 1 or 4 infection (Abstract 128). Exclusions included cirrhosis, a plasma HIV RNA level above 400 copies/mL on ART, or a CD4+ cell count below 500/µL not on ART. Of the 80 participants who initiated treatment, all were MSM, 91% were HIV infected and on ART, and 24% were being treated for HCV reinfection. The majority had genotype 1a infection (64%), and the remainder (36%) had genotype 4 infection. Data on SVR12 were available for 63 of the 80 participants, and the SVR12 rate was 98% (62/63), which included 3 documented reinfections determined by phylogenetic analysis that were counted as SVRs. There was only 1 viral relapse. This study represents the largest to date using a truncated DAA treatment regimen for acute HCV infection with excellent SVR12 results. The high proportion being treated for a reinfection and early occurrence of 3 reinfections after treatment highlight the work that remains to be done on harm reduction and prevention of HCV reinfection among MSM.

Glecaprevir/pibrentasvir was recently approved for HCV treatment and has a broad 8-week length of treatment indication and a high barrier to resistance.[10] In clinical trials, this regimen failed in approximately 2% of individuals, and we do not yet have a proven retreatment strategy. Although sofosbuvir/velpatasvir/voxilaprevir has shown high efficacy in retreatment, no individuals whose treatment with glecaprevir/pibrentasvir failed were included in these studies.[11]

Interim results from an ongoing phase IIIb study of individuals whose treatment with glecaprevir/pibrentasvir failed who were retreated with sofosbuvir plus glecaprevir/pibrentasvir with ribavirin for 12 or 16 weeks were presented (Abstract 127). Participants were assigned to 12 weeks of this combination treatment if they were not infected with genotype 3, did not have cirrhosis, and had not been treated with an HIV NS5A inhibitor or NS3 inhibitor prior to failed treatment with glecaprevir/pibrentasvir. All other participants were assigned to 16 weeks of treatment. Data were presented on 23 participants: 2 treated for 12 weeks and 21 treated for 16 weeks. Genotype 3 was most prevalent (14/23) followed by genotype 1a (6/23), 7 participants had cirrhosis, and all participants had either NS5A RASs (78%) or NS3 plus NS5A RASs (22%) prior to retreatment. Both individuals with genotype 2 who were treated for 12 weeks and 20 of the 21 individuals treated for 16 weeks attained an SVR12 for an overall SVR rate of 96%. The lone viral relapse was a 67-year-old man with genotype 1a infection and cirrhosis whose prior treatments with ledipasvir/sofosbuvir and then glecaprevir/pibrentasvir for 12 weeks failed and who had the Q30K and Y93H NS5A RASs prior to treatment in the current study. The high SVR rate, even with the very limited number, sug gest this is a viable retreatment approach for individuals whose treatment with glecaprevir/pibrentasvir fails. Given the very limited number of treatment failures observed in clinical trials, it is unlikely enough additional patients could be studied to determine if ribavirin is needed or the optimal duration.

Data continue to accumulate showing that populations "less-than-ideal" as candidates for HCV therapy can achieve high SVR rates with DAA therapy, including those who actively use injection drugs or alcohol.

HCV Treatment in People Who Inject Drugs and With Alcohol Use Disorder

Concern for HCV reinfection due to ongoing sexual risk behaviors or injection drug use can be a barrier to practitioners offering HCV treatment. Interestingly, HIV-seronegative individuals with a history of injection drug use demonstrated substantially lower HIV risk-taking behavior scores after the start HCV treatment, particularly those who started both PrEP and buprenorphine (Abstract 589). As HIV risk-taking behaviors can also increase risk for HCV acquisition, these data suggest a decline in risk for HIV infection and potentially HCV infection, at least during the initial months of HCV treatment

In a cohort of HIV/HCV-coinfected PWID, heavy alcohol use was common, with 26% reporting heavy drinking and 33% with an alcohol biomarker indicating heavy alcohol use (Abstract 605). Despite this, HCV therapy resulted in a 91% SVR rate, and no markers of heavy alcohol use were associated with failure to initiate therapy or to achieve HCV cure. These data support current guidelines, which prioritize HCV treatment for those who use alcohol, including those with alcohol use disorder.

HCV in Incarcerated Populations

The incarcerated population is at high risk for HCV infection. Most data have focused on prison populations with HCV seroprevalence rates ranging from 20% to 40%.[13] Jail populations are more challenging, given the transient nature of these populations in the setting of a poorly integrated system with a lack of widespread or consensus approaches to disease screening. In a project centered in the Dallas, Texas County Jail opt-out HIV and HCV screening was offered from April to November 2017, with blood drawn for confirmatory testing and patient navigator support for linkage to care and follow-up after release from jail (Abstract 598). Of 4260 persons screened during the study period, 16.5% were seropositive for HCV. Confirmatory testing was completed in 79%, and 85% of those positive for HCV RNA received HCV education. Most cases of HCV infection (57%) were outside the 1945 to 1965 birth cohort. Of those with chronic infection (HCV RNA positive), injection drug use was the single most common risk factor (39%) and most did not have insurance (86%). Perhaps most interestingly, of 116 HCV RNA–positive persons released to the community, 69 were called, 18 were contacted, and 8 were scheduled for evaluation. Most either could not be reached, did not have a phone, or did not return messages. These data highlight the huge opportunity for HCV screening in this high-risk population and the profound challenges in follow-up and linkage to HCV care.

Complications of HCV Infection and Impact of HCV Cure

Chronic HCV infection is associated with an increased risk of liver disease as well as some extrahepatic complications, including diabetes, renal disease, neurocognitive impairment, and lymphoproliferative disease, which may improve with HCV treatment. Perhaps because of improvement in hepatic and extrahepatic comorbidities, DAA treatment was associated with decreases in inpatient and outpatient health care utilization by 21% and 41%, respectively (Abstract 611).

Porphyria cutana tarda is a common skin manifestation of HCV infection. A small Spanish study demonstrated resolution of porphyria cutana tarda in 12 of 13 individuals after HCV cure (Abstract 634). In HIV-infected MSM in the MACS cohort, HCV cure was associated with normalization of most inflammatory biomarkers except for several immune activation markers (interferon-γ, interleukin 10 [IL-10], C-X-C motif chemokine ligand 13 [CXCL13], and soluble IL 6 receptor [sIL6R]) (Abstract 635). The reason for the persistent elevation of these proinflammatory biomarkers compared with HCV-uninfected men is unclear, although one hypothesis is that inflammatory markers may be residual HCV infection in peripheral blood mononuclear cells (PBMCs), which has not been showed to lead to HCV relapse. A pilot study demonstrated a low level of HCV RNA present in PBMCs and plasma in 33% of HCV-monoinfected and 58% of HIV/HCV-coinfected individuals a median of 13 months after attaining an SVR, and investigators postulate that this may contribute to systemic inflammation (Abstract 636)

In a Spanish study of HIV/HCV-coinfected individuals, HCV cure led to an increase in low-density lipoprotein (LDL) cholesterol (and thus an increase in 10-year Framingham cardiovascular risk score) 2 years after treatment initiation (Abstract 631). However, there was no change in carotid intima-media thickness or carotid-femoral pulse wave velocity, each biomarkers of cardiovascular disease. Cardiovascular events were not reported, although this group has previously reported a trend towards an increase in the risk of cardiovascular events after HCV cure.[14] Of note, some published studies have shown a decrease in subclinical and clinical cardiovascular disease after HCV cure.[15,16]

Data continue to demonstrate positive effects of HCV treatment outside the liver and to reduce overall healthcare utilization. Though LDL cholesterol tends to increase after HCV cure, thus far there is no evidence that increased LDL cholesterol in this specific setting is detrimental to cardiovascular health.

Impact of HIV Infection on HCV Treatment

In DAA clinical trials, HIV/HCV-coinfected individuals have generally attained similar cure rates to those of HIV-monoinfected individuals. In the more "real-world" setting of the Center for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort of HIV/HCV-coinfected individuals, SVR12 rate was high at 98.2% (Abstract 610). In contrast, a Spanish analysis found a slightly lower cure rate of 91% in HIV/HCV-coinfected individuals treated with 12 weeks of ledipasvir/sofosbuvir than in their HIV-monoinfected counterparts (97%), a finding that was maintained when restricted to those with HCV RNA levels below 6 million IU/mL. There was no difference in SVR rate between coinfected and monoinfected individuals treated with 8 weeks of ledipasvir/sofosbuvir (94.0% and 96.6%, respectively) (Abstract 607). Factors associated with lower SVR rates in HIV/HCV coinfection include low CD4+ cell count (OR for HCV treatment failure, 5.2, for CD4+ cell counts <200/μL) (Abstract 608), detectable pretreatment HIV RNA (Abstract 610), and active psychiatric illness (OR for treatment failure, 2.7) (Abstract 609).

MicroRNA: Big Applications for Small RNAs

The field of microRNAs (miRNAs) and their impact on chronic viral hepatitis and liver disease is still in its infancy, with the best studied being the unique association between miR-122 and its beneficial effects on HCV replication and prevention of HCV RNA degradation. In a session dedicated to miRNAs, early studies of novel miRNAs were presented, with most studies being associative at this point and further

work needed to define pathophysiologic relationships and mechanisms.

In the only miRNA study to deal specifically with HCV, Kith and colleagues examined global miRNA profiles in PBMCs collected from persons with chronic HCV (n = 32), spontaneously resolved HCV (n = 32), and never HCV–infected controls (n = 32) (Abstract 640); each group had the same number of men and women. In the comparison of miRNAs expression between groups, no miRNAs were significantly differentially expressed between those with chronic infection and resolved infection. In contrast, the same 19 miRNAs were significantly differentially expressed (fold change >2) when comparing never HCV–infected controls with those with resolved or chronic infection. In a pathway analysis, the investigators noted that these 19 miRNAs are associated with pathways involved in fatty acid metabolism as well as myeloid leukemia and estrogen signaling pathways. The investigators suggest that these differences represent a signature left over from prior HCV infection that persists and is similar to those with active infection.

Another abstract focused on different HIV-infected populations with liver disease, including HCV infection, nodular regenerative hyperplasia, or otherwise uncharacterized elevated alanine aminotransferase (ALT), and compared the plasma miRNA signature to uninfected volunteers and HCV-monoinfected controls (Abstract 639). Although some miRNAs appeared to be upregulated (at least 2-fold) in those with HIV or HCV infection compared with uninfected volunteers, 2 groups were examined for further characterization of miRNA upregulation; 1) participants with HIV/HCV coinfection who had minimal fibrosis at initial sampling but showed rapid progression of fibrosis, and 2), HIV-infected participants with normal ALT levels to those with elevated ALT levels or focal nodular hyperplasia. Among the 9 participants with rapid progression of fibrosis, miR-99a-5p and miR-100-5p were substantially upregulated, and levels of expression correlated with ALT and fibrosis levels (kPa, as assessed by elastography). In the HIV-monoinfected group, 2 different miRNAs were substantially upregulated and correlated with ALT and levels of fibrosis: miR-122-3p and miR-193b-5p. Much more work remains to be done before these miRNAs can be considered markers for individuals at risk for progression of fibrosis or otherwise used as biomarkers.

Two abstracts focused on miRNAs in hepatitis B virus (HBV)-infected persons. Meissner and colleagues examined miRNA signatures in persons chronically infected with HBV who were treated with tenofovir disoproxil fumarate (TDF) for 240 weeks (Abstract 637). The investigators separated their analysis based on whether or not participants had regression of liver fibrosis during treatment (n = 14), and looked for changes in miRNA expression that correlated with regression of fibrosis. The investigators also compared changes in miRNA with changes in CXCL10 and sCD163. During therapy, CXCL10 and sCD163 declined but no correlation with regression of fibrosis was found. At baseline, the expression of 2 miRNAs (miR-421 and miR-454-3p) was lower in participants that subsequently experienced regression of fibrosis. A set of 13 miRNAs had differential changes in expression over the course of treatment, with increased expression at week 240 from baseline in those with regression of fibrosis. Although further validation is needed, many of these miRNAs were in pathways dealing with stellate cell activation and fibrogenesis, suggesting biologic plausibility.

Onorato and colleagues specifically examined hsa-miR-125a-5p (Abstract 638), which was previously shown to inhibit expression of HBV surface antigen. Liver biopsy samples from consecutively enrolled participants (n = 64) with chronic HBV infection were analyzed for expression of hsa-miR-125a-5p, fibrosis stage, and expression of HBV DNA. Liver biopsies of an additional 10 participants with hepatocellular carcinoma (HCC) and cirrhosis related to HBV but negative serum surface antigen (occult HBV infection) were also analyzed. Intrahepatic expression of hsa-miR-125a-5p increased substantially with fibrosis stage. Conversely, there was a trend toward lower levels of intrahepatic DNA in participants with cirrhosis, although this was not statistically significant. Only an association between hsa-miR-125a-5p and fibrosis stage was observed; much more study is needed to determine if there is a causal link.

In HIV/HBV-coinfected persons with cirrhosis, a number of serum miRNAs changed after initiation treatment with tenofovir disoproxil fumarate and were correlated with biopsy-proven fibrosis regression, suggesting the potential for development of these miRNAs as biomarkers for fibrosis regression (Abstract 637).

Other Viral Hepatitides: Hepatitis A, B, and E and Human Pegivirus 2

Hepatitis A Virus

Outbreaks of hepatitis A virus (HAV) in at-risk populations with poor vaccination rates continue to occur, including a large outbreak in San Diego, California, primarily among the homeless population. Another major at-risk population for HAV infection are MSM, and 2 abstracts examined transmission of HAV among MSM in France and Thailand, showing that an identical strain is circulating in both populations.

In France, 51 cases of acute HAV infection were described and phylogenetically compared to the 2 strains of HAV genotype IA (IA VRD 521 2016 and IA RIVM HAV16-090) currently associated with cases in MSM across Europe (Abstract 625). From December 2016 to September 2017, 61% of the 51 cases of acute HAV infection were among MSM, and 42% of those MSM were coinfected with HIV. Phylogenetic analysis was completed for approximately 75% of cases, and all viruses belonged to 1 of the 2 circulating strains (the majority were identified as strain IA VRD 521 2016).

A cluster of 5 cases of acute HAV infection occurred in Bangkok, Thailand (Abstract 626), an area in which the last HAV outbreak was described in 2002. Among the 5 cases, 4 were in MSM and strain typing showed 3 of the 4 were identical to the European outbreak strain IA RIVM HAV16-090. The fourth case was very closely related to the same strain,

as was a fifth case in an HIV-uninfected woman in Bangkok (99.7% similarity).

These abstracts highlight the potential for intercontinental transmission of HAV among MSM (an outbreak has also been described in Taiwan) and for redoubled efforts to encourage HAV vaccination in all MSM.

Hepatitis B Virus

Hepatitis B infection is an important driver of comorbidity in the context of HIV disease. Risk factors for HCC and end-stage liver disease in HIV/HBV coinfection include less time with HIV RNA suppression, more baseline fibrosis, and lower CD4+ cell count (Abstract 620). Hepatitis delta virus (HDV) exacerbates liver disease in HIV/HBV coinfection, with HDV antibodies associated with an increased risk of cirrhosis, HCC, and death, despite the use of HBV-active ART (Abstract 622).

Hepatitis E Virus

Hepatitis E virus (HEV) infection may be spread by fecal-oral transmission as well as consumption of undercooked meat or seafood. A high prevalence of seropositivity for HEV has been described in areas of France. Mo and colleagues prospectively assessed rates of HEV seropositivity (IgG and IgM) in HIV-infected persons presenting to a single clinic in Southwestern France over 7 months (Abstract 627). Among 307 HIV-infected persons studied, 72% were men and 21% (n = 64) had evidence of HEV infection. A breakdown between IgG and IgM HEV positivity was not provided, although no persons had detectable HEV RNA by polymerase chain reaction (PCR) testing (performed in those who were positive for IgM). Although HEV seropositivity was statistically significantly associated with higher ALT levels than in the HEV-negative group, the difference was not clinically meaningful (mean ALT, 40 vs 46). No association was found with HEV seropositivity and dietary habits, in contrast to studies in HIV-uninfected – populations in France. The strongest association for HEV seropositivity was withpast or current syphilis infection (positive venereal disease research laboratory [VDRL] test result; OR, 3.79; $P = .002$; positive Treponema pallidum hemagglutination assay [TPHA] result; OR, 2.84; $P = .05$). These data reinforce the concept that HEV transmission in MSM is likely related to sexual practices but is of limited clinical significance.

Human Pegivirus

Human pegivirus (HPgV; formally known as GB virus C) has similar modes of transmission to both HIV and HCV and has been shown to slow HIV progression to a modest extent. Whether these effects are HIV clade specific is unknown and was examined in an abstract that focused on HPgV infection in HIV-infected persons in Chennai, India (Abstract 629). In 154 HIV-infected men tested, 23% were coinfected with HPgV and no differences were found in baseline HIV viral load or current CD4+ cell count in those with or without detectable HPgV RNA. When the subgroup of persons currently taking ART was analyzed, a significantly higher CD4+ cell count was noted in those with HPgV infection ($P = 0.013$; exact number of CD4+ cells not given but was approximately 580/µL vs 375cells/µL). The HPgV-infected group was younger, but baseline CD4+ cell counts were not presented to determine if there was a difference in baseline CD4+ cell count.

In a surveillance study of HCV and HPgV in more than 12,000 samples from Cameroon, a relatively low HCV RNA positivity rate of 2.47% was found. The population was mostly young (71% aged 18-40 years) and female (70%), with HIV-seronegative (n = 7628) and -seropositive (n = 4741) samples. Among samples with HCV infection, 40% also had HIV infection and 15% had evidence of HPgV infection (positive for HPgV antibodies). Interestingly, HCV infection was more revalent in persons older than 40 years (9%), and HPgV seropositivity skewed toward a younger population (15.6% in those <40 years of age vs 11.3% in those >60 years of age) seroprevalence below 40), and 11.3% seroprevalence above 60). Sequences of 5 HPgV viremic samples out of 18 tested showed a greater than 90% genetic relatedness to HPgV circulating on other continents.

It is crucial that practitioners remember that care of the HCV-infected patient with cirrhosis does not end at cure. Variceal screening and HCC surveillance are crucial and must continue after HCV cure.

Steatosis and Cirrhosis

Fatty liver disease is increasing worldwide, including in individuals with HIV infection. Among HIV-infected individuals, the presence of nonalcoholic fatty liver disease (detected by imaging or biopsy) was independently associated with cardiovascular disease and adverse cardiometabolic profiles (Abstract 642). Appropriate screening is important to avoid complications of cirrhosis, which include varices and HCC. HIV-infected individuals with cirrhosis were significantly less likely to undergo appropriate screening with esophagogastroduodenoscopy for esophageal varices than HIV-uninfected counterparts (22.7% vs 87.4%) (Abstract 645).

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

Financial affiliations for the past 12 months: Dr Luetkemeyer has received research grants awarded to her institution from AbbVie, Gilead Sciences, Inc, Merck and Proteus, and had travel paid for by Merck. Dr Wyles has received research grants awarded to his institution from AbbVie, Gilead Sciences, Inc, Merck, and Tacere, and has served as a consultant or advisor to AbbVie, Gilead Sciences, Inc, and Merck.

Additional References Cited in Text

1. Zibbell JE, Asher AK, Patel RC, et al. Increases in Acute Hepatitis C Virus Infection Related to a Growing Opioid Epidemic and Associated Injection Drug Use, United States, 2004 to 2014. *Am J Public Health*. 2018;108(2):175-181.
2. Arora S, Thornton K, Murata G, et al. Outcomes of treatment for hepatitis C virus infection by primary care providers. *N Engl J Med*. 2011;364(23):2199-2207.
3. Boerekamps A, van den Berk G, Lauw F, et al. Substantial decline in acute HCV infections among Dutch HIV+MSM after DAA roll out. 24th Conference on Retrovirus and Opportunistic Infection. 2-16-2017; Seattle, Washington.
4. Ingiliz P, Martin TC, Rodger A, et al. HCV reinfection incidence and spontaneous clearance rates in HIV-positive men who have sex with men in Western Europe. *J Hepatol*. 2017;66(2):282-287.
5. Little SJ, Kosakovsky Pond SL, Anderson CM, et al. Using HIV networks to inform real time prevention interventions. *PLoS One*. 2014; 9(6):e98443.
6. Wyles DL, Luetkemeyer AF. Understanding Hepatitis C Virus Drug Resistance: Clinical Implications for Current and Future Regimens. Top Antivir Med. 2017;25(3):103-109.
7. Itakura J, Kurosaki M, Takada H, et al. Naturally occurring, resistance-associated hepatitis C virus NS5A variants are linked to interleukin-28B genotype and are sensitive to interferon-based therapy. *Hepatol Res*. 2015;45(10):E115-E121.
8. Noureddin M, Wright EC, Alter HJ, et al. Association of IL28B genotype with fibrosis progression and clinical outcomes in patients with chronic hepatitis C: a longitudinal analysis. *Hepatology*. 2013; 58(5):1548-1557.
9. Naggie S, Marks KM, Hughes M, et al. Sofosbuvir Plus Ribavirin Without Interferon for Treatment of Acute Hepatitis C Virus Infection in HIV-1-Infected Individuals: SWIFT-C. *Clin Infect Dis*. 2017; 64(8):1035-1042.
10. Rockstroh JK, Bhagani S, Hyland RH, et al. Ledipasvir-sofosbuvir for 6 weeks to treat acute hepatitis C virus genotype 1 or 4 infection in patients with HIV coinfection: an open-label, single-arm trial. *Lancet Gastroenterol Hepatol*. 2017;2(5):347-353.
11. Zeuzem S, Foster GR, Wang S, et al. Glecaprevir-Pibrentasvir for 8 or 12 Weeks in HCV Genotype 1 or 3 Infection. *N Engl J Med*. 2018; 378(4):354-369.
12. Bourliere M, Gordon SC, Flamm SL, et al. Sofosbuvir, Velpatasvir, and Voxilaprevir for Previously Treated HCV Infection. *N Engl J Med*. 2017;376(22):2134-2146.
13. Spaulding AS, Kim AY, Harzke AJ, et al. Impact of new therapeutics for hepatitis C virus infection in incarcerated populations. *Top Antivir Med*. 2013;21(1):27-35.
14. Berenguer J, Rodriguez-Castellano E, Carrero A, et al. Eradication of hepatitis C virus and non-liver-related non-acquired immune deficiency syndrome-related events in human immunodeficiency virus/hepatitis C virus coinfection. *Hepatology*. 2017;66(2):344-356.
15. Babiker A, Jeudy J, Kligerman S, Khambaty M, Shah A, Bagchi S. Risk of Cardiovascular Disease Due to Chronic Hepatitis C Infection: A Review. *J Clin Transl Hepatol*. 2017;5(4):343-362.
16. van der Meer AJ, Berenguer M. Reversion of disease manifestations after HCV eradication. *J Hepatol*. 2016;65(1 Suppl):S95-S108.

Top Antivir Med. 2018;26(1):35-43.

UPCOMING ACTIVITIES

Spring and Summer 2018

Annual HIV Management Updates

Annual HIV CME courses continue to feature cutting-edge, scientifically rigorous updates presented by leading experts in the field of HIV medicine. Visit the IAS–USA website for details. Upcoming IAS–USA live courses this spring, focusing on the management of HIV infection, will be held in:

San Francisco, California—Friday, May 11, 2018—San Francisco State University—Towers Conference Center
Chairs: Stephen E. Follansbee, MD, Annie Luekemeyer, MD, and Robert T. Schooley, MD

Chicago, Illinois—Friday, May 18, 2018—Loyola University Chicago, Lake Shore Campus
Chairs: John P. Phair, MD, and Paul A. Volberding, MD

Webcasts of prior courses, from spring 2018 and earlier, can be found on the IAS–USA website.

Interactive Webinars

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

Infectious and Other Complications of the New Immunobiologic Agents—May 10, 2018
Presenter: Peter Chin-Hong, MD

Pathogenesis of HIV Infection and Core Principles of Treatment—May 31, 2018
Presenter: Michael S. Saag, MD and David H. Spach, MD

Hepatitis B Virus (HBV) Infection—June 14, 2018
Presenter: Marion G. Peters, MD

Forgotten but Not Gone: Understanding the Hepatitis A Outbreak and Public Health Response in San Diego County—July 19, 2018
Presenter: Darcy A. Wooten, MD

Update From the International AIDS Conference (AIDS 2018)—August 21, 2018
Presenter: Roy M. Gulick, MD, MPH

Treating HCV Infection: It Doesn't Get Much Better Than This—August 30, 2018
Presenter: Susanna Naggie, MD, MHS

Fall 2018

Intensive Small-Group Hepatitis Workshops

Save the date. *These CME workshops continue to feature cutting-edge, scientifically rigorous topics presented by leading experts in the field of hepatitis C virus (HCV) medicine. Visit the IAS–USA website for up-to-date information and webcasts of prior courses. This fall, IAS–USA live courses focusing on the management of HCV infection will be held in:*

Beckley, West VIrginia—Saturday, September 29, 2018
Memphis, Tennessee—Friday, October 12, 2018
Milwaukee, Wisconsin—Tuesday, November 6, 2018
Portland, Maine—Date TBD
New Orleans, Louisiana—Date TBD
Charleston, South Carolina—Date TBD
New York, New York—Date TBD

Year-Round

Cases on the Web

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

Immunizations for HIV-Infected Adults
Authors: Brian T. Montague DO, MPH, MS; Steven C. Johnson MD, University of Colorado
Release date: Thursday, July 13, 2017.

Diagnosis and Management of Major or Persistent Depression in the HIV-Infected Patient
Authors: Jameela J. Francine Cournos MD, Columbia University; Milton L. Wainberg MD, Columbia College of Physicians and Surgeons.
Release date: Monday, February 16, 2015.

Ending the Epidemic in New York City: From Blueprint to Implementation
Author: Demetre C. Daskalakis MD, MPH, New York City Department of Health and Mental Hygiene.
Release date: Wednesday, September 28, 2016.

On-Demand CME Credits for Webinars

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

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

Review

CROI 2018: Advances in Antiretroviral Therapy

Hong-Van Tieu, MD, MS; Barbara S. Taylor, MD, MS; Joyce Jones, MD, MS; Timothy J. Wilkin, MD, MPH

The 2018 Conference on Retroviruses and Opportunistic Infections (CROI) showcased exciting data on new investigational agents including MK-8591 and tri-specific antibody targeting 3 highly conserved epitopes on HIV-1 in a single antibody. Clinical trials of initial antiretroviral therapy (ART) and switch studies involving bictegravir/emtricitabine/tenofovir alafenamide were presented. Intensification of initial ART with integrase strand transfer inhibitors did not increase the risk of immune reconstitution inflammatory syndrome. Pharmacokinetic issues were discussed, including the substantial drug-drug interactions between efavirenz-based ART and hormonal contraception delivered via a vaginal ring. Studies on pre-ART drug resistance and emergence of drug resistance after initial and second-line ART in different settings and populations were highlighted. Novel technologies to identify drug resistance included a free, cloud-based web service for HIV genotyping analysis and a promising technology for point-of-care drug resistance mutations testing. New strategies to improve the HIV care continuum included home-based testing with initiation of same-day ART and stratified care with specialized clinics to serve those disengaged in care, but the data on financial incentives were not encouraging. Several studies provided insights into the impact of early ART on decreasing the size of the HIV reservoir in HIV-infected infants. Pertinent conference findings relating to women's health issues included similar clinical outcomes between breastfeeding and formula feeding HIV-infected women, the problem of viral rebound and ART nonadherence in pregnancy and postpartum.

Keywords: CROI, HIV, AIDS, antiretroviral, therapy, treatment strategies, investigational drugs, reservoir, resistance, infants, women

Investigational Antiretroviral Drugs

MK-8591 is a nucleoside reverse transcriptase translocation inhibitor that mimics deoxyadenosine and is incorporated into the viral DNA by reverse transcriptase. It promotes chain termination by inhibiting translocation. Although MK-8591 has an extremely long half-life, allowing for weekly dosing, Matthews and colleagues presented data on pharmacokinetics of daily dosing of MK-8591 in preparation for coadministration with doravirine as combination antiretroviral therapy (ART) (Abstract 26). They administered 0.25 mg, 0.75 mg, and 5 mg daily to 3 HIV-uninfected cohorts. MK-8591 was well tolerated. Target drug concentrations were achieved rapidly after the first dose in all three groups. After cessation of dosing, drug concentrations remained above target concentrations for more than 30 days in the 0.25 mg daily cohort. Vaginal and rectal biopsies were performed and the concentrations were supportive for use as preexposure prophylaxis (PrEP).

Tri-specific Antibody

Pegu and colleagues presented data on engineered antibodies that target 3 highly conserved epitopes on HIV-1 in a single antibody. (Abstract 113LB) The lead tri-specific antibody inhibited nearly 100% of viral strains tested at low micromolar concentrations. The pharmacokinetic profile of the antibody was similar to that of VRC01, allowing for infrequent dosing.[1] Although antiviral activity has not been established for the tri-specific antibody, it was shown to protect 8 of 8 macaques from simian-human immunodeficiency virus (SHIV) in a challenge model.

Clinical Trials of Initial Antiretroviral Therapy and Switch Studies

Bictegravir/Emtricitabine/Tenofovir Alafenamide

Molina and colleagues presented data from a clinical trial that enrolled 563 participants living with virologic suppression on dolutegravir/abacavir/lamivudine for at least 3 months and randomly assigned them to continue the regimen or switch to bictegravir/emtricitabine/tenofovir alafenamide (TAF) (Abstract 22). Virologic suppression was similar 48 weeks after randomization, with 95% suppression in the dolutegravir/abacavir/lamivudine group and 93.9% in the bictegravir/emtricitabine/TAF group: difference 0.7% (95% confidence interval [CI], -1.0%, 2.8%). Virologic non-suppression was mostly due to missing HIV-1 RNA measurements. Both regimens were well tolerated.

Dr Tieu is an Associate Member at the New York Blood Center and Assistant Professor of Clinical Medicine at Columbia University Medical Center in New York, New York. Dr Taylor is an Associate Professor of Infectious Diseases at UT Health San Antonio in San Antonio, Texas. Dr Jones is a Clinical Associate at Johns Hopkins University School of Medicine in Baltimore, Maryland. Dr Wilkin is an Associate Professor of Medicine at Weill Cornell Medicine in New York, New York. Send correspondence to Hong-Van Tieu, MD, MS, 310 E. 67th Street Suite 3-110, New York, NY 10065, htieu@nybc.org.

Kityo and colleagues presented similar data from a clinical trial enrolling 470 women living with HIV who were receiving an elvitegravir-based single tablet regimen or a ritonavir-boosted (/r) atazanavir-based regimen (Abstract 500). Participants were randomly assigned to stay on their current ART or switch to bictegravir/emtricitabine/TAF. Both groups did extremely well, with 99.2% and 98.7% being virologically suppressed 24 weeks after randomization respectively. Both regimens were well tolerated.

Andreatta and colleagues presented data combining resistance data from bictegravir/emtricitabine/TAF studies (Abstract 506). They reviewed prestudy genotypes and performed sequencing of HIV-1 DNA in baseline samples from those with on-study viremia and a subset of those without viremia. No participants in the bictegravir/emtricitabine/TAF arms developed new mutations. The presence of archived emtricitabine or TAF resistance-associated mutations did not adversely affect virologic outcomes. No participants in the dolutegravir/abacavir/lamivudine group developed resistance. The only treatment-emergent resistance mutations occurred in a participant who received darunavir/r and abacavir/lamivudine who developed an L74V mutation. Similarly, no participants in 2 clinical trials comparing bictegravir with dolutegravir as initial therapy developed resistance (Abstract 536). Baseline resistance did not affect virologic outcomes and responses did not differ by HIV-1 subtype.

Gaur and colleagues presented data on 24 adolescents living with HIV (age 12-18 years) virologic suppression who changed their current ART to bictegravir/emtricitabine/TAF (Abstract 844). All 24 remained virologically suppressed through 24 weeks. Bictegravir exposure was similar to that observed in adults. TAF and emtricitabine exposures were higher in adolescents than in adults, but were similar to that reported for currently approved regimens for adolescents containing these drugs.

Two-Drug ART Regimens

Cahn and colleagues presented data from a clinical trial that randomized 145 treatment-naive adults living with HIV to receive darunavir/r plus lamivudine/tenofovir disoproxil fumarate (TDF) or a generic fixed-dose combination of darunavir/r plus lamivudine (Abstract 489). They found that 94% and 93% were virologically suppressed 48 weeks after randomization, with a difference of -1.0% (95% CI, -7.5%, 5.6%). The TDF-containing regimen tended to have better lipid outcomes, but safety and tolerability were otherwise similar. These results support the continued investigation of 2-drug regimens for initial therapy.

Few data exist on the outcomes of 2-drug ART regimens in clinical practice. Perone and colleagues presented data from the OPERA (Observational Pharmaco-Epidemiology Research and Analysis) cohort, a collaboration of 400 HIV practitioners at 79 health care facilities in the United States (Abstract 510). They compared virologic outcomes for patients switching to 2-drug with 3-drug regimens. Of note, a large majority of the 2-drug regimens included a protease inhibitor (PI); emerging 2-drug regimens (dolutegravir/rilpivirine, dolutegravir/lamivudine, or a PI/lamivudine) were rarely used. Patients switching to 2-drug regimens were older, had more ART experience, and more comorbidities. When considering patients who switched while viremic or while suppressed, the virologic outcomes were generally similar between those switching to 2-drug or 3-drug regimens when adjusted for baseline factors.

Gagliardini and colleagues presented data from the AIDS Research Consortium of Atlanta (ARCA) database on virologic outcomes to 2-drug regimens containing lamivudine in patients with (n=87) and without (n=349) a history of a M184V mutation within the ARCA database (Abstract 498). Those with a history of M184V were older, had a lower nadir CD4+ cell count, and were on ART for a longer time. The virologic failure rate on the 2-drug regimen was not statistically significantly higher for those with a M184V than those without that mutation. There was a significantly higher rate of low-level viremia or "viral blips" in the M184V group. These results should be interpreted with caution as the population of participants with the M184V mutation was relatively small and most participants received a PI/r and lamivudine.

Integrase Strand Transfer Inhibitors and Immune Reconstitution Inflammatory Syndrome

Gibb and colleagues presented data from the REALITY (Reduction of Early Mortality in HIV-Infected Adults and Children Starting Antiretroviral Therapy) trial on the impact of raltegravir intensification of initial ART therapy on the immune reconstitution inflammatory syndrome (IRIS) (Abstract 23). This was a clinical trial that randomized 1805 people living with HIV with a CD4+ cell count below 100/μL in a factorial design to test several strategies to reduce early mortality in this population. One strategy involved randomly assigning participants to an initial standard ART regimen with or without 12 weeks of raltegravir. Raltegravir did not reduce early mortality or World Health Organization (WHO) stage 3/4 events, but did lead to a more rapid decline in plasma HIV-1 RNA level. The analysis compared the risk of IRIS between arms. A blinded endpoint review committee adjudicated all suspected IRIS events. They found that the rate and timing of IRIS events were similar between arms. They concluded that integrase strand transfer inhibitors (InSTIs) do not impact the risk of IRIS despite achieving a faster viral load decline.

Clinical Trials in Antiretroviral-Experienced Populations

Third-Line Antiretroviral Therapy

Few data exist on the outcomes of third-line ART in resource-limited settings. Grinsztejn and colleagues presented data from AIDS Clinical Trials Group (ACTG) Protocol A5288 that enrolled participants in whom first- and second-line ART had failed, with plasma HIV-1 RNA level above 1000 copies/mL after receiving a PI-based regimen for at least 24 weeks

(Abstract 30LB). Participants underwent real-time genotyping to select a new regimen. The study enrolled 545 participants who were divided into one of 4 cohorts based on resistance patterns. Overall, 47% were women, the median CD4+ cell count was 175/μL, the median plasma HIV-1 RNA level was 4.4 $\log_{10}$ copies/mL, and the median duration of ART use was 7.9 years. Nucleoside analogue reverse transcriptase inhibitor (nRTI)-associated resistance was observed in 62%, non-nucleoside analogue reverse transcriptase inhibitor (NNRTI)-associated resistance in 64%, and PI resistance in 36%. A total of 53% of participants enrolled into the trial had little resistance: no resistance to lopinavir/r and 1 or more active nRTI. These participants continued their second-line regimen. Participants in the other cohorts were placed on new ART regimens that generally included darunavir/r and raltegravir. These participants may have also received etravirine and an nRTI depending on their resistance pattern. Overall, a plasma HIV-1 RNA level below 200 copies/mL was achieved in 64% 48 weeks after entering the trial. Virologic suppression was lowest, 44%, in the group with the least resistance that continued their second-line therapy on study entry. Virologic suppression ranged from 74% in the cohort with the most extensive resistance to approximately 90% in the other cohorts. The authors concluded that darunavir/r and raltegravir with or without etravirine was highly effective as third-line therapy in those with resistance to lopinavir, and highlighted the need for real-time genotyping to select third-line ART in these settings. Additional strategies are needed for those in whom lopinavir/r is failing without resistance, a group challenged by adherence.

Subgroup Analyses of the DAWNING Trial

The DAWNING trial randomized people in whom their initial NNRTI plus 2 nRTIs was failing to LPV/r or dolutegravir plus 2 nRTIs. The study was stopped early for superiority of the dolutegravir arm.[2] Aboud and colleagues presented subgroup analyses from this trial examining the impact of choosing second-line nRTI components according to WHO recommendations on virologic outcomes (Abstract 508). Adherence to WHO-recommended, second-line nRTI was associated with better virologic outcomes. These results should be interpreted with caution as genotyping was used to select the second-line nRTI and at least 1 active nRTI was required.

Pharmacokinetic Considerations

Adherence Monitoring

Gandhi and colleagues presented data on the relationship between hair levels of antiretroviral drugs, a measure of longer term drug exposure, to virologic outcomes in ACTG A5257, a randomized clinical trial of 3 initial antiretroviral regimens (Abstract 24). Participants with hair drug levels in the lowest tertile had a much higher risk of virologic failure than the middle and highest tertile (26% vs 6% and 3%, respectively). On multivariable analysis, lower drug levels in hair were strongly associated with virologic failure. Interestingly, black race and lower educational status remained associated with virologic failure after controlling for hair drug levels.

Dried blood spot samples can be assayed for tenofovir diphosphate as a measure of longer term adherence. Castillo-Mancilla and colleagues presented results of a prospective cohort study that related tenofovir diphosphate concentrations in dried blood spots to virologic outcomes to ART (Abstract 25). They found that lower concentrations were associated with viremia. Among those with virologic suppression, lower concentrations were associated with black race, non-use of pharmacologic booster, and higher body mass indices. The authors concluded that tenofovir diphosphate concentrations in dried blood spot samples are a powerful predictor of virologic suppression.

ART Interactions With Vaginal Hormonal Contraception

Scarsi and colleagues presented results from ACTG A5316, a clinical trial that evaluated pharmacokinetic interactions between efavirenz or atazanavir/r-based ART and ethinyl estradiol/etonogestrol components of a vaginal contraceptive ring (Abstract 141). They enrolled cohorts of women living with HIV who were receiving efavirenz-based ART, atazanavir/r-based ART, or no ART. Approximately 25 premenopausal women were enrolled in each cohort. Compared with the control group of no ART, plasma ethinyl estradiol concentrations were reduced 53% to 57% among women receiving efavirenz and 29% to 35% among women receiving atazanavir/r. Plasma etonogestrol concentrations were reduced 76% to 79% among women receiving efavirenz and increased 71% to 79% among women receiving atazanavir/r. All control and atazanavir/r group participants achieved suppression of endogenous progesterone by 14 days of use and no participant had progesterone concentrations suggestive of ovulation. In contrast, efavirenz women were not suppressed until 21 days of use and 2 women had progesterone levels suggestive of ovulation. The authors concluded that the vaginal ring could be used effectively with atazanavir/r, but efavirenz-based ART may decrease the effectiveness of this contraceptive.

Dolutegravir Drug-Drug Interactions

Walimbwa and colleagues presented data on interactions of dolutegravir with 2 artemisinin-based antimalarial regimens, arthemether-lumefantrine and amodiaquine-artesunate (Abstract 459). Each regimen statistically significantly lowered dolutegravir trough concentrations, but this was deemed clinically insignificant given that the trough levels were still well above target concentrations and the short duration of antimalarial therapy. No meaningful interactions on the artemisinin-based regimens were observed and the authors concluded that standard doses can be used with dolutegravir.

Elliott and colleagues investigated the pharmacokinetics of darunavir/cobicistat and dolutegravir when dosed

concomitantly in 20 HIV-uninfected volunteers (Abstract 468). They found a 10% decrease in dolutegravir trough concentrations and a 7% decrease in darunavir trough concentrations. These interactions were felt to be clinically insignificant.

Long-Acting Antiretroviral Therapy

Ostermann and colleagues performed a survey of patients attending HIV clinics to understand patient interest in various strategies being considered for intermittent dosing of ART (Abstract 503). More patients were "very interested" in weekly oral dosing (66%) than were in injections every 2 months (38%) or subcutaneous implants every 6 months (18%).

The HIV Care Cascade: Achieving 90-90-90

The HIV care cascade models the sequential steps in effective care in and control of the epidemic: people living with HIV should move from diagnosis, to care engagement, to ART, to virologic suppression. The care cascade model, also called a continuum, was originally proposed at CROI by Carlos Del Rio in 2001,[3] and has been a focus of measuring effective HIV care since the Centers for Disease Control and Prevention (CDC) included it in national strategy in 2011.[4,5] In 2014, the Joint United Nations Programme on HIV/AIDS (UNAIDS) announced its ambitious 90-90-90 treatment goals: that 90% of people living with HIV will know their diagnosis, 90% of those will be on treatment, and that 90% of those will be virologically suppressed by 2020.[6] Encouraging new data on the care cascade across the globe presented at this year's CROI shed light on how close we are to reaching the 90-90-90 goals by 2020.

Perspectives on the US Care Cascade

A symposium entitled "Strategies for Improving the US Care Cascade" featured overviews from 4 researchers on specific aspects of the HIV care continuum. First, Del Rio (Abstract 60) provided an overview of the US HIV epidemic, with specific emphasis on disparities by race and ethnicity and by geography. Del Rio emphasized that social determinants of health, such as lack of health insurance, low educational attainment, poverty, and income inequality contribute to these disparities, which lead to the disproportionate HIV incidence in racial/ethnic minorities and in the US South. African Americans make up 12% of the US population but 44% of new HIV diagnoses. Similarly, the South, although it holds only 38% of the US population, is the venue for 50% of new HIV diagnoses. Even in settings with expanded access to care, such as San Francisco, racial and ethnic disparities exist in the care continuum, particularly when retention in care or virologic suppression are examined over time, rather than in cross-section.[7,8] Del Rio proposed that access to care and political commitment matter and called for all participants to retake our roles as activists.

Next, Scott and Mugavero (Abstracts 61 and 62) provided further insights into the importance of testing and linkage. Scott emphasized that programs involving real-time data sharing and direct outreach for linkage to care were most successful at post-diagnosis linkage to care. Mugavero focused on recent data demonstrating the rarity of sustained virologic suppression and that engagement in care is a dynamic process.[9,10] He proposed the use of missed clinic visits as an easily measurable marker of structural barriers to care and risk for disengagement and mortality.

Dombrowkski (Abstract 63) offered a different perspective on the care continuum, pointing out that public health investigations of "out of care" cases reveal that 50% are not actually out of care,[11] and that virologic suppression rates are often higher than cross-sectional estimates. She reviewed several studies of data to care initiatives where less than 15% of eligible cases were engaged in care through their interventions.[12-15] Dombrowksi proposed that asking patients who are disengaged to relink to the same system of care that failed to engage them in the first place is a failing strategy. Instead, she presented several innovative models of care that increased rates of virologic suppression for high-need patients. Examples include the Maximally Assisted Therapy program in Vancouver, which prioritizes immediate needs, such as housing, food security, and mental health; offers on-site directly observed therapy; and uses outreach teams to find those lost to care. Data from Seattle's Max Clinic, another example of innovative design for those neither engaged in care nor virologically suppressed (Abstract 1125), also suggest that walk-in access to care, immediate access to case management by phone, text, or in person, cross-agency coordinated care, financial incentives, and several other support services, can achieve high levels of virologic suppression compared with standard of care. Dombrowski argued that "tiered" approaches that identify high-need patients for enhanced care models can be a successful approach for achievement of virologic suppression and attainment of the final "90" of the care cascade.

New Data on the Care Cascade in Low- and Middle-Income Countries

Two notable sessions presented data on targeted and rapid scale-up of comprehensive HIV testing and treatment strategies in low- and middle-income countries. Kagaayi and colleagues presented data on the impact of a comprehensive HIV prevention program in an HIV hyperendemic mobile fishing community in Uganda (Abstract 90). The interventions deployed during a targeted and rapid scale-up in this community beginning in 2011 included: free HIV testing, male circumcision, condoms and behavioral prevention counseling, and linkage to HIV care and treatment. Investigators collected data in a series of 5 surveys between 2011 and 2017, interviewing 5,005 participants. Data on the impact of this program on sexual risk behavior, male circumcision coverage, and HIV incidence are reviewed elsewhere in this issue of *Topics in Antiviral Medicine* https://www.iasusa.org/sites/default/files/uploads/26-1-buchbinder-liu.pdf. Between

December 2011 and December 2016, self-reported ART coverage increased from 19% to 81% among people living with HIV, and virologic suppression to below 1000 copies/mL increased from 33% to 78%, although ART coverage was lower in younger age groups and in men over time. Study findings were limited by the high prevalence of out-migration in this community, but the authors conducted appropriate sensitivity analyses and the differences remained statistically significant. These results on the positive impact of this comprehensive HIV prevention, diagnosis and linkage to care strategy in a highly mobile and hyperendemic community are very encouraging.

Another piece of encouraging news came from Thin and colleagues (Abstract 91), who presented country-level data on 90-90-90 targets from the Lesotho Population-based HIV Impact Assessment (LePHIA) study, a national household-based survey including HIV and viral load (HIV-1 quantitative RNA) testing conducted between November 2016 and May 2017. Data on the care cascade showed that: 77.2% of people living with HIV were diagnosed, 90.2% of those were on ART, and 88.3% of those were virologically suppressed. There were clear disparities by age and sex, with better outcomes for women and those of older age.

Several presentations covered what is often the most challenging component of the care cascade, the transition from awareness of HIV diagnosis to linkage to care. Sibanda and colleagues (Abstract 150LB) presented data from a cluster randomized trial within the STAR (HIV Self Testing Africa) initiative exploring the impact of conditional incentives, given to lay HIV self-test distributors, on linkage within 6 weeks of the completion of the testing campaign by their self-testing clients. They found no impact of these financial incentives on linkage to any service: 28.7% in the intervention arm and 31.2% in the control arm. They were surprised to find that most people testing positive for HIV in this study were already on ART, and they did see a small impact of the intervention (adjusted odds ratio [aOR] 1.59; 95% CI, 1.05, 2.39) when they restricted their analysis to those who were newly diagnosed with HIV. They also conducted a nested nonrandomized differences-in-differences study on the impact of HIV self-testing on demand for ART, which did show a statistically significant increase in demand for ART in community health facilities during the self-testing campaign period, though not before and after.

Further highlighting challenges of linkage, Steele and colleagues found that only 36% of those newly diagnosed after community-based testing in KwaZulu-Natal were linked to care within 6 months (Abstract 1089). Ayieko and colleagues used a structured patient-centered phone call from a clinical officer following HIV testing to improve linkage for those newly diagnosed or re-engagement in care for those out of care in 5 Kenyan communities (Abstract 1090). In a randomized controlled trial of 130 participants, they found increased linkage in the intervention arm (41%) compared with the control arm (24%, $P<.05$). It is concerning that less than half of the population was linked to care, even with intervention, across all 3 of these studies.

HIV Treatment Strategies and Outcomes Including Life Expectancy and Mortality

Treatment Strategies: Rapid ART Initiation, Financial Incentives, and Other Services

Several investigators presented data on the impact of innovative treatment strategies on virologic suppression and other treatment outcomes. Highlights included new data on the impact of rapid ART start programs, financial incentives, and integration of substance use treatment.

Rapid ART initiation became standard of care in San Francisco in 2015 as part of the San Francisco Getting to Zero Consortium. The program included linkage to care within 5 or fewer days for all new confirmed HIV diagnoses and initiation of ART at the first care visit. Bacon and colleagues compared San Francisco Department of Public Health HIV case registry data between 2013 and 2016 to examine the impact of this program (Abstract 93). The number of people living with HIV who went from diagnosis to care within 5 days and started ART within 1 day of their first clinic visit increased from 23 (6% of new diagnoses) in 2013 to 80 (30% of new diagnoses in 2016). The time between diagnosis and achieving an HIV-1 plasma RNA level below 200 copies/mL decreased from 134 days in 2013 to 61 days in 2016. Latinos and individuals who were homeless had the greatest improvements in time from diagnosis to initiation of ART and to achieving virologic suppression. Despite these efforts, 16% of those newly diagnosed in 2016 remain without ART. They are analyzing data on long-term retention and durability of virologic suppression but have found retention above 90% at a median of 1.1 years follow-up at San Francisco General Hospital.

Labhardt and colleagues pursued an alternative approach for rapid initiation of ART in the CASCADE trial, which determined the impact of same day home-based HIV testing and initiation of ART in Lesotho.[16] This randomized clinical trial compared standard of care, home-based HIV testing and linkage to care, with the intervention—home-based testing with same-day initiation of ART with a 30-day medication supply. Linkage to care within 3 months was more common in the intervention arm (69%) than in the control (43%, $P<.001$), as was virologic suppression at 12 months: 50% in the intervention arm and 34% in the control ($P<.007$). Retention in care remained statistically significantly higher in the intervention group throughout the 1-year study period. These encouraging results, which achieved higher rates of linkage to care than other interventions presented at CROI, will no doubt lead to similar efforts to collapse the care cascade in other settings.

Several studies explored the impact of financial incentives on virologic suppression in highly divergent contexts. Thirumurthy and colleagues conducted a randomized clinical trial in Uganda, testing the impact of an intervention, unconditional cash transfers as escalating financial incentives to achieve viral suppression to below 400 copies/mL, compared with a control group that received a single unconditional cash transfer at enrollment (Abstract 95). They did not find any impact of the intervention on virologic suppression at 24 or 48 weeks. Investigators believe these findings

may be influenced by high rates of engagement and virologic suppression at baseline in the cohort, although when they limited their findings to those participants who were not virologically suppressed at baseline, there was still no impact of the intervention.

Feaster and colleagues presented long-term outcomes from the Project Hope study, which was a 3-armed randomized clinical trial of hospitalized substance users with HIV infection comparing: 1) 6 months of patient navigation, 2) patient navigation and financial incentives, and 3) treatment as usual. Previous studies showed that the participants randomly assigned to patient navigation and financial incentives had higher rates of viral suppression at 6 but not 12 months after randomization, compared with treatment as usual.[17] Investigators presented follow-up data for 422 participants (53% of the original cohort) who consented to long term follow-up (median observation time, 3.3 years) and found overall low rates of viral suppression (33%). Substance use, determined by urine drug screening, remained high throughout the followup period (60%-71%) and rates of death were high (26% since randomization), but neither differed by study arm. Neither the data presented by Thirumurthy nor Feaster encourage the use of financial incentives as leverage to increase rates of virologic suppression.

In contrast, Springer and colleagues examined the impact of naltrexone use in incarcerated individuals with opioid or alcohol use disorders who were transitioning back into the community (Abstract 96). Investigators conducted 2 separate double-blind placebo-controlled randomized trials, in which those with either opioid use disorders in the NEW HOPE (Needing Extended-Release Wellness Helping Opioid-Dependent People Excel trial) or those with alcohol use disorders in Project INSPIRE were randomly assigned to the intervention of a naltrexone injection within 7 days of release from incarceration followed by 6 monthly injections, or the placebo injections (control group). In NEW HOPE, 37.9% of those receiving naltrexone were virally suppressed (to <50 copies/mL) at baseline and 60.6% at 6 months ($P = .002$). In the placebo arm 55.6% were virologically suppressed at baseline and 40.7% were suppressed at 6 months ($P = .294$). The results of Project INSPIRE were similarly encouraging, with viral suppression increasing from 31% to 56.7% between baseline and 6 months in the intervention arm but decreasing from 42% to 30.3% over 6 months in the placebo arm. The investigators conclude that naltrexone can help maintain or achieve virologic suppression in a context in which maintenance of suppression is rare: those with opioid or alcohol use disorders being released from incarceration.

Perspectives on Living with HIV

In 2018, 50% of adults living with HIV in the United States are over 50 years of age, and people living with HIV are living longer, healthier lives. However, the burden of non-HIV related comorbidities in this aging population is growing, and subpopulations with HIV in the United States and in low- and middle-income countries still experience late presentations to care with advanced HIV disease and early mortality. This year's CROI provided new data on what it means to live with HIV in 2018, and included a symposium entitled "Life Expectancy at 25" that reviewed data on life expectancy, the impact of comorbidities, and the implications of chronic inflammation for people living with HIV (Symposium S-6).

Data from the Veterans Aging Cohort Study (VACS), which includes national Veterans Administration electronic health records, consistently provides insights into the impact of aging with HIV. Justice and colleagues pooled data from the VACS, the CDC HIV surveillance report, and a public HIV clinic based at Yale New Haven Hospital to explore the presentation of HIV by age and whether non-HIV related conditions should trigger diagnostic testing for HIV (Abstract 92). They found that from 2010 to 2015, those 50 years of age or older comprised 48% of new diagnoses in the VACS, 24% at the public HIV clinic, and 18% in the CDC surveillance report. In the VACS and the public HIV clinic cohorts, those over 60 years of age were more than twice as likely as those under 40 years of age to be diagnosed with a concomitant AIDS-defining illness, a CD4+ cell count under 200/μL, or an AIDS diagnosis.

Finally, they used VACS cohort data to demonstrate that age-associated non-AIDS diagnoses of bacterial pneumonia, herpes zoster, anemia, lymphocytopenia, or thrombocytopenia were all more common in older individuals with HIV infection. These 5 diagnoses raised the relative risk of HIV diagnosis in all age groups, although the association was less strong for those over 60 years of age for anemia and lymphocytopenia. The investigators suggest that anyone presenting with bacterial pneumonia, herpes zoster, or thrombocytopenia should be tested for HIV, regardless of the current age-based guidelines that recommend routine HIV testing up to 65 years of age.

There were many notable presentations on mortality in people living with HIV. Gaolathe and colleagues compared mortality rates in those living with HIV with those without HIV who were participating in the Botswana Combination Prevention Project, a pair-matched community-randomized HIV prevention trial in 30 rural and peri-urban communities throughout the country (Abstract 97). This trial has rigorous ascertainment of cause of mortality through household interviews, medical record data, and death certificate review. Among 12,156 participants with a mean duration of vital status follow-up of 2.1 years, morality rates were 257/100,000 person years (py) in those without HIV and 957/100,000 py in those with HIV. Compared with those who were HIV-uninfected, infectious causes of death were more common for those not receiving or in their first year of ART, but nearly half of deaths among those with HIV infection were from non-infectious causes. Cancer led to 24% of deaths in those with HIV and 19% of those without.

Late presentation to care and HIV-related mortality, particularly in key populations, remain a challenge in the global fight to end AIDS. In the past 12 months, the WHO, Médecins Sans Frontières, and ICAP (the International Center for AIDS Care and Treatment Programs) of Columbia University released guidelines relevant to the care of people with

advanced HIV disease,[18-20] and a Themed Discussion led by Nathan Ford provided an excellent overview and discussed new data on this topic (Themed Discussion 11).

Three presenters examined life expectancy within United States- and Canadian- based cohorts. Althoff and colleagues used data from the NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design) to examine life expectancy in key populations living with HIV in the United States and Canada (Abstract 903). For people who inject drugs, life expectancy between 2012 and 2015 was 16 years lower than those not injecting drugs, and for black men who have sex with men (MSM), life expectancy was 14 years lower than for white MSM. Both these disparities persisted when analysis was restricted to those initiating ART with a CD4+ cell count above 350/µL. Black and white women had similar life expectancies, but when analysis was restricted to those initiating ART with a CD4+ cell count above 350/µL, black women had higher life expectancy, likely due to increased risk of deaths from drug or alcohol use in white women.

Sun and colleagues also examined mortality in injection drug users (IDUs) in the ALIVE (AIDS Linked to the Intravenous Experience) cohort in Baltimore (Abstract 891). Overall mortality increased in the 4794 individuals in the cohort (25.8% of whom were living with HIV) from cohort inception in 1988 through the introduction of combination ART in 1997. As expected, for people living with HIV, AIDS- and infectious diseases-related mortality increased until 2000, and then dropped precipitously as the median CD4+ count rose. Mortality from chronic diseases increased throughout the observation period. Mortality from drug overdose or drug-related causes increased from 1988 to 1999 and decreased from 2000 to 2010 as injection drug use prevalence decreased. Of concern, mortality in injection drug users has increased again between 2010 and 2015. The investigators speculate that the recent increase in drug overdose and drug-related deaths is linked to the opioid epidemic.

Palella and colleagues explored a different aspect of mortality risk in people living with HIV by using data from the HOPS (HIV Outpatient Study) to explore the association between long-term HIV viral exposure and mortality (Abstract 901). After examining the associations between overall mortality and several different measures of viral exposure, the most effective model to predict mortality included the most recent HIV RNA value and the percentage of person years with an HIV RNA level above 200 copies/mL. However, each measure of viral load exposure they tested was associated with mortality.

Two presentations in this session explored mortality in the context of hospitalization or advanced HIV disease in low- and middle-income countries. Hoffman and colleagues characterized mortality, readmission, and engagement in care following inpatient hospitalization in 121 individuals in a hospital in South Africa (Abstract 902). They found high rates of mortality (26%) and readmission (53%) 6 months after hospitalization. Factors associated with readmission or death in a multivariate analysis included: skipping clinic visits because it was "hard to get to" and having no recorded post-hospitalization clinic visit, but no specific clinical criteria were associated with death. These data suggest that a systems approach to support outpatient followup after hospital discharge could help reduce the high rates of mortality for hospitalized people with HIV infection.

Teasdale and colleagues used data from ICAP-supported HIV care sites in Ethiopia, Kenya, Mozambique, and Tanzania to determine loss to follow up and death for 3 CD4+ cell count strata within those qualifying as having advanced disease: fewer than 50/µL, 50 to 100/µL, and 101 to 200/µL (Abstract 898). They found that those with fewer than 50 CD4+ cells/µL had a 40% increased risk of loss to follow up or death, and those with CD4+ cell counts of 101 to 200/µL had similar risk to that of those with CD4+ cell count above 200/µL. Considering this heightened risk for poor outcomes, they propose the creation of differentiated service delivery models for those living with HIV who have CD4+ cell counts below 100/µL. Considering that other data from low- and middle-income countries at CROI show that 1 in 5 patients not on ART have a CD4+ cell count below 200/µL (Abstract 887), it is likely that efforts to increase movement through the HIV care cascade will result in more individuals presenting to care with advanced disease, requiring specialized attention and services.

HIV Resistance

Epidemiologic Studies of Drug Resistance

With the international scale-up of ART, epidemiologic surveillance of drug resistance remains crucial to ensure that recommended ART regimens are regionally appropriate and that public health interventions can be initiated if rates of drug resistance mutations (DRMs) are unacceptably high.

Identifying Networks of Transmitted Drug Resistance

In an effort to track transmitted drug resistance (TDR) among patients newly diagnosed with HIV in Mexico City, Matías-Florentino and colleagues (Abstract 523) combined results from baseline HIV-1 resistance tests with genetic network analysis of patients newly diagnosed with HIV infection seen at the Condesa Clinic, the largest HIV clinic in Mexico. Network analysis demonstrated that 39% (747/1916) of sequences had a putative linkage with at least 1 other sequence forming 264 clusters. In 84 sequences, the same DRM was shared (>5% cutoff) with a linked sequence in 33 distinct clusters. The K103N mutation was the most frequently encountered DRM among the linked sequences at 61%. The linked sequences with common DRMs may represent TDR. These findings highlight the need to prevent initiation of TDF transmission chains by improving retention in care and minimizing the turnaround time for clinicians to receive and act on resistance results. They also posited that next generation sequencing (NGS) to detect DRMs at a cutoff of above 5% had a moderate advantage over Sanger-like sequencing (>20% cutoff) as there were a few cases of linked low-frequency DRMs identified.

In a similar analysis of 714 HIV-1 infected ART-naive individuals in the Cologne-Bonn region of Germany (Abstract 524), genetic network, geospatial, and drug resistance mutation analyses were combined to detect and characterize putative transmission clusters of TDR. The researchers identified 77 transmission clusters and the frequency of DRMs was comparable in clustering (17.5%) and non-clustering individuals (17.1%). Of the 133 linked, DRM-containing sequences, 17.3% were between genetically linked partners with shared DRMs. Clustering individuals with or without DRMs were mostly located in the city centers and among men who have sex with men. This methodology could be used to identify hotspots of transmission and TDR to target prevention and treatment interventions.

Regional Variation in Pretreatment Drug Resistance

Several studies highlighted the importance of monitoring pretreatment drug resistance as rates of TDR can be affected by system-wide changes including introduction of new ART to the market, changes in national or regional treatment guidelines, changes in ART accessibility, and introduction of new interventions such as test and treat and PrEP.

A study of the French National Agency for AIDS/HIV Research (ANRS) program for HIV-1 resistance surveillance among 1121 ART-naive patients in 2014 to 2016 (Abstract 529) showed a stable prevalence of overall pretreatment drug resistance (PDR) (10.8%) but a high level of NNRTI-associated PDR (12.9%) and relatively high prevalence of InSTI-associated PDR (5.3%) suggesting that additional public health interventions to prevent TDR are warranted. In Florida, HIV-1 genotype sequences reported to the Florida Department of Health HIV/AIDS Surveillance System were analyzed for patients with newly diagnosed HIV infection (n = 3970; Abstract 526). Overall rates of PDR remained relatively stable from 2015 to 2016 (12.7% and 11.0%, respectively) but NNRTI-associated PDR decreased from 10.2% to 7.8% and InSTI-associated PDR increased from 1.4% to 2.3%. Ongoing surveillance is needed to further delineate trends in this area.

A study of PDR among 5484 ART-naive patients in Spain (Abstract 528) showed that from 2007 to 2017, rates of PDR remained stable around 8%, with a peak in 2013 to 2014 that correlated with inclusion of rilpivirine as an initial agent for ART in the Spanish Grupo de Estudio del SIDA-SEIMC (GESIDA) guidelines. In 2015, recommendations changed to include only InSTI-based regimens in conjunction with nRTIs as initial regimens and subsequently there was a sharp decline in rates of baseline resistance to initial ART (11.8% in 2014 vs 2.2% in 2015-2017). This highlights the positive impact epidemiologic surveillance with appropriate intervention can have on TDR.

Impact of Pretreatment Drug Resistance on Clinical Outcomes

In a study of 564 patients enrolled in a randomized clinical trial of routine virologic monitoring versus targeted monitoring in Vietnam from 2011 to 2017 (Abstract 525), rates of PDR were stable (<10%) and there was no difference in rates of virologic failure (HIV RNA >200 copies/mL) over 36 months in those with and without baseline PDR (aOR, 1.45; 95% CI, 0.41-3.98) nor between those who were randomly assigned to routine virologic monitoring and those who were not (aOR, 0.87; 95% CI, 0.49-1.52).

In a substudy (Abstract 533) of patients the HIV Prevention Trials Network (HPTN) 052 in which serodiscordant couples were enrolled and the HIV-infected index patients were randomly assigned early ART (ART initiation with a CD4+ cell count 250-550 cells/μL) or delayed ART (ART initiation delayed until a CD4+ cell count ≤250 cells/μL), an analysis of PDR among patients with virologic failure in the early (n = 151) and delayed (n = 98) arms was performed. In total, 4.7% of participants had resistance at baseline and 35.5% had new resistance at the time of treatment failure. New resistance at treatment failure was more common among those randomly assigned to the delayed treatment arm (43.4% vs 30.5%; $P = .06$), those on a regimen of efavirenz, lamivudine, and zidovudine (40.5% vs 20.8%; $P = .0074$), and those who had a higher baseline HIV RNA level (per unit $\log_{10}$ copy/mL increment OR, 2.54; 95% CI, 1.63-3.98).

Substantial variation in disease progression among HIV subtypes has been described but variation among non-B HIV-1 subtypes with respect to viral suppression with initial ART has been limited by small sample sizes. Poon and colleagues (Abstract 540) combined HIV-1 sequence and clinical data records from several study cohorts and clinical sites in Uganda to create the largest database of initial treatment failures in Uganda studied to date. In their analysis, they found there were no associations of HIV-1 subtype with treatment failures regardless of subtype. Subtype A and D recombinants, however, were significantly less likely to be among treatment failures and the authors suggest intersubtype recombinations may be an important barrier to the emergence of drug resistance.

Development of Resistance after Initial and Second-Line ART

In resource-limited settings, availability of viral load testing and resistance testing is often limited or nonexistent, which can result in patients with virologic failure remaining on compromised regimens leading to the emergence and accumulation of DRMs.

WHO guidelines do not include resistance testing in the algorithm for patients on a failing initial ART regimen. Rather the recommendation is to continue the regimen, provide adherence counseling, and if the repeat HIV RNA level is above 1000 copies/mL in 3 months, to change to a second-line regimen. In an argument to include resistance testing in the algorithm, McCluskey and colleagues (Abstract 530) conducted a retrospective genotype analysis of Ugandan patients on at least 4 months of an initial ART regimen with an HIV-1 RNA level above 1000 copies/mL. They found intermediate- to high-level resistance in 52% (47/90) of these patients and

in a majority the second-line regimen failed to resuppress regardless of the level of adherence.

Meloni and colleagues (Abstract 538) conducted a retrospective analysis of patients in Nigeria who had virologic failure on an initial regimen containing zidovudine (n=103) versus TDF (n=88) and of the impact of DRMs on second-line options. Patients on zidovudine were almost 10 times more likely to have a compromised second-line option compared those on TDF (aOR, 9.90; 95% CI, 2.58-37.99). Accumulation of DRMs was higher among those who had a delayed switch to a second-line regimen and the delayed switch magnified the effect of zidovudine to limit effectiveness of second-line options. These data reinforce the benefits of a TDF-based regimen over one including zidovudine and support limiting the amount of time between detection of virologic failure and ART switch to limit accumulation of DRMs and increase the likelihood that second-line ART will be effective.

In a study of Ethiopian children enrolled in the EPHIC (Ethiopia Pediatric HIV Cohort; Abstract 539), 12% (94/780) of children on an initial ART regimen experienced virologic failure. Of the participants with virologic failure and successful genotyping, 81% had at least 1 DRM: 69% to nRTI and NNRTI; 10% to NNRTI alone; 1% to nRTI alone; 1% to PI, nRTI, and NNRTI. These mutations had a substantial impact on second-line ART regimens; 100% of those with NNRTI resistance were resistant to the 2 WHO-recommended NNRTIs (efavirenz and nevirapine) and 42% had resistance to all 4 WHO-recommended nRTIs (abacavir, lamivudine, zidovudine, and tenofovir). Resistance testing was performed using dried-blood spot-based genotyping demonstrating its use in settings such as this, where plasma HIV-1 RNA genotyping is not feasible.

In a retrospective analysis of patients enrolled in a cluster-randomized trial of HIV viral load monitoring in Lusaka, Zambia (n=1973; Abstract 537), only 8.4% of patients on an NNRTI-based regimen (efavirenz or nevirapine) had virologic failure over 4446 person years. 23% of those with virologic failure had major NNRTI-associated DRMs at baseline, but in a Kaplan-Meier survival analysis, the presence of these mutations did not affect overall mean time to failure. At virologic failure, 82% had a major nRTI or NNRTI DRM. More DRMs were detected in patients who had a longer time to ART switch after first detection of virologic failure. Among patients on TDF-based regimens that failed, prevalence of TDF-associated resistance increased from 42% at time of failure to 58% for those who had not made a switch until 30 months after failure was first detected. Prevalence of resistance to second-generation NNRTIs in the delayed switch group was 70%. These high rates of failure show the consequences of remaining nonadherent to ART or remaining on a failing regimen. Without viral load and genotype testing, clinicians are hampered from identifying patients who need adherence interventions and/or a change in regimen.

Kityo and colleagues (Abstract 531) investigated the impact of raltegravir intensification on HIV resistance for patients enrolled in the REALITY trial, a randomized controlled trial in Kenya, Uganda, Zimbabwe, and Malawi in which ART-naive patients with a CD4+ cell count below 100 /μL were randomly assigned to 12 weeks of standard ART (2 nRTIs + an NNRTI; Std) or standard ART plus RAL (Std+RAL). At 12 weeks, 6.6% (45/677) of patients randomized to Std+RAL had an HIV-1 RNA level above 1000 copies/mL. Fifteen percent of patients with virologic failure and successful InSTI genotype testing (5/33) had InSTI-associated DRMs, 9% had intermediate- or high-level raltegravir resistance, and none had intermediate- or high-level dolutegravir resistance. At 48 weeks, 11.6% (76/654) in the Std+RAL group and 14% (90/642) in the Std group had an HIV-1 RNA level above 1000 copies/mL. K219E/Q, K101E/P, and P225H mutations were less common in the Std+RAL group and no difference was seen between the groups with other reverse transcriptase mutations, nor with predicted intermediate- or high-level resistance to the most commonly used NNRTIs and nRTIs. The authors concluded that at 48 weeks there was no clinical benefit to raltegravir intensification and it did not substantially protect against clinically relevant nRTI or NNRTI resistance.

In a study of patients with virologic failure on a lopinavir/r-based, second-line ART regimen from 15 clinics in Namibia (Abstract 541), 160 (67%) had genotypes available and 70% had evidence of any DRM, 51% with any nRTI DRM, 63% with any NNRTI DRM, and 13% any DRM. The authors suggest that given the high proportion of patients without PI-associated resistance, many may achieve viral suppression with enhanced adherence strategies and no change in ART. Epidemiologic surveillance of DRMs in patients in whom second-line regimens are failing is important to determine whether or not virologic failure is more of an adherence issue or a resistance issue, to ensure that effective ART is available for patients in whom second-line regimens are failing, and to determine if changes should be made in recommended second-line regimens.

In Abstract 554, Abela and colleagues conducted a case-control study of risk factors for acquired drug resistance (ADR) in patients enrolled in the SHCS (Swiss HIV Cohort Study). There were 115 patients with ADR who were randomly matched with 115 patients without ADR. Patients with difficult psychosocial barriers to adherence such as unemployment (OR, 2.1; 95% CI, 1.9-8.6), limited education (OR, 3.1; 95% CI, 1.1-8.1), and psychiatric comorbidities or adverse effects (OR, 2.1; 95% CI, 1.1-4.3) were at a higher risk for ADR, suggesting that identifying and addressing these barriers may prevent ADR.

Prevalence of DRMs in Different Settings

Zhang and colleagues (Abstract 550) evaluated the prevalence of DRMs among HIV-infected men who have sex with men (MSM) living in sub-Saharan Africa. Baseline laboratory test results of men enrolled in HPTN 075 were analyzed for presence of antiretroviral drugs, HIV-1 RNA level, and HIV-1 resistance. Sixty-five point six percent (120/183) of the men were not on ART, 17.4% (11/63) of men on ART were not virally suppressed, and 54.5% (6/11) of those men had at least 1 DRM, with M184I or M184V being the most common DRMs

identified, followed by K103N. The high percentage of HIV-infected men not on ART, high number men on ART who are not virally suppressed, and high rates of DRMs among those who are not virally suppressed emphasize the importance of improving HIV care for African MSM.

In a similar study of young women enrolled in HPTN 068 (Abstract 551), a prospective cohort study of South African high school women who received annual HIV testing until expected graduation date, enrollment samples and samples from the first clinical visit for women who became infected with HIV-1 after enrollment were studied for the presence of antiretroviral drugs, HIV-1 RNA level, and HIV-1 genotype. Of women with HIV-1 at enrollment, 12.5% (10/80) had antiretroviral drugs detected, and 13.4% (9/67) of the women who had resistance testing had resistance detected. For women who seroconverted during the study, antiretroviral medications were detected at first HIV clinical visit in 9.9% (16/162) and 5.6% (9/162) had major resistance mutations.

Botswana was one of the first countries to implement a test and treat strategy, and in 2016 became the first sub-Saharan African country to use dolutegravir-based ART as the initial regimen. In the context of this countrywide scale-up, prevalence of nRTI- and NNRTI-associated DRMs (Abstract 552) and InSTI-associated DRMs (Abstract 542) was evaluated through a random sample of 2998 HIV-infected individuals enrolled in the Botswana Combination Prevention Project. HIV-1 RNA and proviral DNA templates were used for amplification for genotyping. Overall prevalence of nRTI and NNRTI DRMs was 7.9%, and rates of nRTI-associated and NNRTI-associated DRMs was 2.7% and 6.9%, respectively. 96.7% of patients on ART were virologically suppressed and rates of resistance among those on ART without viral suppression was 17.1% for nRTI-associated DRMs and 27.6% for NNRTI-associated DRMs. Among patients not on ART, overall prevalence of nRTI and NNRTI DRMs was 5.8%, and rates of nRTI- and NNRTI-associated DRMs were 1.6% and 4.8%, respectively. In the evaluation of InSTI-associated resistance (Abstract 542), prevalence of any InSTI-associated DRM was 2.43% and rates of resistance were similar between those who were on ART and those who were ART-naive. The low prevalence of DRMs is reassuring but there was a trend toward moderate but increasing rates of nRTI-associated and NNRTI-associated DRMs over time. These findings highlight the importance of on-going public health surveillance of DRMs to measure treatment success and monitor for concerning trends.

Through the HOPE in Action study, the first successful HIV-positive-to-HIV-positive kidney and liver transplants have occurred in the United States. There is a theoretical risk of superinfection with an ART-resistant or CXCR4-tropic virus from HIV-infected deceased donors (HIVDDs) to HIV-positive transplant recipients. Bismut and colleagues (Abstract 553) evaluated the genotypes and coreceptor tropism in potential HIVDDs and found that rates of ART-resistance and CXCR4-tropism to be comparable to levels in the general population. Twenty-six percent (8/31) of those with samples that were successfully genotyped had at least 1 DRM. The most common DRMs found were associated with NNRTIs (n = 4), followed by nRTIs (n = 3), PIs (n = 2), and InSTIs (n = 1). Successful coreceptor tropism phenotype was performed in 25 participants and a majority had dual/mixed virus (n = 12) followed by exclusive CCR5-tropic virus (n = 10); none had CXCR4-tropic virus identified. These are preliminary results and to fully appreciate if HIVDD drug resistance or tropism status affects the HIV-infected transplant recipient outcomes, surveillance of resistance and HIV tropism should continue in this population.

Low-Frequency HIV-1 Drug Resistance Mutations

The prevalence and clinical impact of minority resistant variants (MRVs), DRMs that occur in less than 20% of the viral population, remain an area of active research.

A study of PDR detected using NGS was performed (Abstract 527) using baseline stored plasma specimens from 3365 patients who enrolled in the START (Strategic timing of Antiretroviral Treatment) study, an international trial of immediate versus deferred ART in ART-naive individuals with CD4+ cell counts above 500/μL. The investigators found that a detection threshold of 2% or higher identified more PDR than a higher than 20% threshold, with prevalence for PDR as follows: any 19.7% versus 8.3%; nRTI-associated 6.1% versus 2.7%; NNRTI-associated 7.0% versus 4.3%; PI-associated 9.0% versus 2.1%; and InSTI-associated 0.9% versus less than 0.1%. The clinical impact of these MRVs is unknown and warrants further investigation.

In a study (Abstract 545) of the impact of MRVs on virologic response to InSTI-based regimens, Sanger sequencing and ultra-deep sequencing (UDS) were performed on samples from 134 patients in whom an InSTI-based regimen (with raltegravir, elvitegravir, or dolutegravir) was failing. At least 1 InSTI-related DRM was identified in 40% of subjects. In addition to DRMs identified through Sanger sequencing, UDS detected additional InSTI-related DRMs in 9% (>5% cutoff) and 18% (>1% cutoff) of sequences leading to a change in the InSTI-resistance interpretation among 7% and 13% using greater than 5% and 1% cutoffs, respectively. Prevalence of MRVs at baseline was similar among patients with virologic failure (14.7%) and those with virologic success (12.9%). The MRVs present at baseline were not associated with virologic failure and did not emerge with virologic failure.

Boltz and colleagues (Abstract 536) hypothesized that MRVs with dual-class resistance are associated with virologic failure but that MRVs with single-class resistance are not. Using a novel, ultrasensitive, NGS assay that can detect rare variants with linked DRMs, the researchers sequenced baseline samples from women in the nevirapine/emtricitabine/TDF arm of the ACTG A5208/OCTANE trials. The study supported their hypothesis as the percent of patients with linked DRMs on the same genome was statistically significantly higher in the virologic failure group than the virologic success group whereas linked single-class DRMs were not associated with failure in either trial.

Using a case-control study nested in the multi-country PASER (Pan-African Studies to Evaluate Resistance) cohort,

Inzaule and colleagues (Abstract 534) evaluated different detection thresholds of PDR to predict risk of virologic failure. They concluded that a 5% cutoff appears adequate as the sensitivity to detect cases was higher than that 20% (standard) and 10% cutoff with minimal compromise to specificity, but the marginal gain to the 20% cutoff is small.

Characterization of Drug Resistance Mutations

InSTI Drug Resistance Mutations

T97A is a polymorphism found infrequently in (InSTI)-naive individuals that also emerges in patients in whom InSTI-based regimens are failing. T97A by itself has minimal effects on InSTI susceptibility but in combination with major InSTI DRMs, it synergistically reduces susceptibility to elvitegravir and raltegravir. The contribution of T97A to dolutegravir resistance in the setting of other InSTI DRMs is poorly characterized. Kuriakose and colleagues (Abstract 543) described 2 highly treatment-experienced individuals with pre-existing multidrug resistant (MDR) HIV-1 including with the Q148H and G140S integrase DRMs who developed virologic failure while on dolutegravir as part of a salvage regimen. Both patients had isolated emergence of T97A that led to a greater than 10-fold increase in dolutegravir 50% inhibitory concentration (IC50) suggesting a synergistic effect of T97A on the susceptibility of dolutegravir in the setting of Q148H and G140S.

The E157Q polymorphism is present in about 3% to 5% of ART-naive patients but in 2 case reports has been associated with virologic failure in the setting of raltegravir-based regimens and non-suppression to a dolutegravir-based regimen in a patient with a baseline E157Q mutation. Charpentier and colleagues (Abstract 547) evaluated more than 8500 integrase sequences from InSTI-naive patients in routine clinical care and found an overall prevalence of E157Q of 2.7%, with a higher prevalence among the CRF02_AG subtype (5.6%) than the subtype B (1.7%). In vitro analysis of E157Q site-directed mutants demonstrated minimal fold change to raltegravir, elvitegravir, and dolutegravir with the greatest impact found on elvitegravir especially in CRF02_AG subtypes (2.4-fold decrease in susceptibility). Based on these data, the authors suggest avoiding elvitegravir in patients with the baseline E157Q polymorphism, with particular caution in patients with subtype CRF02_AG.

Pham et al (Abstract 548) described the emergence of the S230R integrase substitution in 2 patients who experienced virologic failure while on dolutegravir monotherapy and further characterized the effects of this mutation on activity, infectivity, replication capacity, and InSTI susceptibility. The investigators noted that compared with wild-type virus, this mutation resulted in a 63% reduction in strand transfer efficiency, a 1.29-fold decrease in infectivity, no change in replication capacity, and a variable effect on InSTI susceptibility with a decreased fold change of 3.85, 3.72, 1.52, and 1.21 on dolutegravir, cabotegravir, raltegravir, and elvitegravir, respectively.

Brenner and colleagues (Abstract 549) evaluated the relative emergence of DRMs in response to increasing concentrations of dolutegravir, elvitegravir, bictegravir, and cabotegravir in vitro among HIV subtype B (n = 7) and non-B subtypes (n = 5) isolates amplified from peripheral blood mononuclear cells (PBMCs) of individuals with primary HIV infection. The time to resistance and number of strains that developed resistance was faster and higher in isolates exposed to elvitegravir, followed by cabotegravir, and then by bictegravir and dolutegravir. Furthermore, elvitegravir and cabotegravir selected for strains with complicated patterns of high-level resistance, which led to viral escape whereas the dolutegravir- and bictegravir-exposed mutants were singleton mutations that conferred low level resistance and reduced replicative fitness. These findings support evidence of a high genetic barrier to resistance for bictegravir and dolutegravir, compared with cabotegravir or elvitegravir.

Abstract 544 described selection of mutations by dolutegravir in vitro located in the 3'-PPT (polypurine tract), a region located outside of the integrase gene, that confer very high level resistance to all InSTIs. They report that these mutants replicated efficiently with or without dolutegravir and hypothesized that replication occurs without integration through unintegrated viral DNA via 1-LTR circles. These results warrant further investigation as HIV-1 DR mutants that skip the integration step in replication have not previously been described. Furthermore, during the oral abstract presentation, there was substantial controversy regarding the measurement of 1-LTR circles in this study, calling to question whether or not these mutants truly replicate without integration.

Through a series of ex vivo and in vivo experiments, (Abstract 546) bictegravir resistance pathways were further characterized and provide evidence that bictegravir has a high genetic barrier to resistance. After extended culture of wild-type HIV-1 with bictegravir, 2 patterns of integrase region resistance that conferred no to low-level reduced susceptibility to bictegravir were identified: R263K with or without M50I (<3-fold reduced susceptibility), and S153F or S153Y (2-fold susceptibility to bictegravir). Extended culture of InSTI-resistant HIV-1 with bictegravir led to no to slow development of additional integrase substitutions and all selected viral pools remained sensitive to bictegravir and dolutegravir aside from 1 variant that had high-level resistance to all InSTIs but had very low replication capacity and may not be viable in vivo.

Protease Inhibitor Resistance Mutations Outside of the Protease Gene

In clinical trials, virologic failure in patients on initial, ritonavir-boosted PI-based regimens is rarely associated with selection of resistance mutations in the protease region (PR). Two studies (Abstracts 558 and 559) sought to identify mutations outside of the PR that might contribute to virologic failure with boosted PIs. Perrier and colleagues (Abstract 558) evaluated the baseline sequences in the protease, Gag, and gp41 regions of ART-naive patients initiated on a PI-based regimen. Of 154 individuals enrolled, 36 experienced virologic failure.

Through ultra-deep sequencing, 4 PR-associated (T4A, S37T, I72M, E21D), 3 Gag (G62d, n315h, y441s), and 1 gp41 (I270T) region mutations correlated with virologic failure. One gp41 mutation (I4L) was associated with virologic success. These findings require further investigation to determine whether or not these mutations have a direct impact on PI activity.

In Abstract 559, Blanch-Lombarte and colleagues investigated HIV-1 Gag mutational patterns related to virologic failure in patients on darunavir or lopinavir monotherapy without PI-associated resistance mutations. They evaluated Gag-PR amplified sequences from 9 plasma samples and found a novel set of Gag mutations (K95R, E203D, V215M, R286K) related to PI-associated resistance and that Gag acted as a direct contributor to PI resistance in the absence of PI-associated resistance mutations. The authors suggest that these findings could be used to optimize genotype analysis of resistance and that additional studies in non-B clade viruses are warranted.

Relative In Vitro Efficacy of ART in the Setting of Resistance Mutations

Margot and colleagues (Abstract 560) compared the in vitro efficacy of TDF and TAF on site-directed and patient-derived mutants containing varying numbers of thymidine analogue mutations (TAMs) with or without M184V. The authors found that TAF susceptibility decreased with increasing number of TAMs, M184V increased antiviral activity of TAF similarly to tenofovir, TAF inhibited viral breakthrough (>28 days without breakthrough) of most TAM-containing HIV-1 (11/14) compared with 0/14 with TFV suggesting that TAF has a higher genetic barrier to resistance than TDF.

White and colleagues (Abstract 532) presented an integrated analysis of resistance from 2 phase III studies of bictegravir, emtricitabine, and TAF in treatment naive individuals. In this pooled analysis, PDR did not affect efficacy and no drug resistance emerged through week 48 in any of the study arms (bictegravir/emtricitabine/tenofovir alafenamide, dolutegravir/abacavir/lamivudine, emtricitabine/TAF plus dolutegravir). One patient with pretreatment G140S and Q148A mutations and virus that was phenotypically sensitive to bictegravir and partially sensitive to dolutegravir achieved an HIV-1 RNA level below 50 copies/mL on bictegravir/emtricitabine/TAF at week 4, which was sustained through week 72. These results support other studies that show InSTI-based regimens maintain a high barrier to resistance.

New Technologies to Identify HIV Drug Resistance

Herms and colleagues (Abstract 555) noted that cost-effective, scalable tools for epidemiologic surveillance of HIV drug resistance in low- and middle-income countries are needed to address the increasing prevalence of resistance in these areas. They described the performance of PASeq.org, a free, cloud-based web service for HIV genotyping analysis of NGS data that could address this need as it is inexpensive, simple to use, web-accessible, secured, and can be scaled up to thousands of samples with a short turn-around time (<1 hour). The investigators compared the genotyping analysis of 12 HIV plasma samples using routine Sanger-based technology and manual analysis using ViroSeq System software v2.8 to PASeq.org analysis of NGS. They concluded that PASeq.org analysis of NGS data provided Sanger-like information with improved resolution and increased sensitivity and provides a cost-effective alternative to multi-sample, high-throughput genotyping.

Abstract 556 described a deep-sequencing platform (long-read Single Molecule Real Time [SMRT], Pacific Biosciences) that can identify DRMs in HIV-1 from full-length pol amplicons. Through full-length sequencing, the authors found evidence of minority DRMs during acute or early infection, the role of which in treatment failure requires further investigation.

Clutter and colleagues (Abstract 557) described a methodology in development for point-of-care genotypic resistance testing. Using a solid-phase nucleic acid melt-curve analysis platform, nucleic acid target sequences are identified through analysis of hybridization kinetics of nucleic acid targets to surface-bound oligonucleotide probes. They validated this technique with in vitro experimentation and demonstrated good sensitivity and specificity in a large set of diverse global HIV-1 samples. This promising technology for point-of-care DRM testing will require further modifications before this will be useable in real-world settings.

Issues Related to HIV Maternal and Infant Health

ART in Pregnancy

Zash and colleagues investigated the relationship between gestational hypertension, ART use, and adverse pregnancy outcomes (Abstract 803). Nevirapine use was strongly associated with gestational hypertension and this relationship was not modified based on nRTI use. They found that hypertensive women receiving nevirapine accounted for 30% of stillbirths, even though only 13% of women received nevirapine.

Sibiude and colleagues reviewed a cohort of 2837 women receiving raltegravir or 1 of 3 PI/r regimens (atazanavir, darunavir, lopinavir) when becoming pregnant (Abstract 805). No obvious differences in pregnancy outcomes, neonatal outcomes, or virologic control based on regimen received were found, although the number of women on raltegravir-based regimens was limited. The proportion with plasma HIV-1 RNA level above 50 copies/mL at delivery was 4.7% for women receiving raltegravir and ranged from 9.8% to 14.5% for women receiving the one of the 3 different PI regimens.

Early ART Effects on the HIV Reservoir in HIV-Infected Infants

Two oral abstracts described the impact of early ART on the size of the HIV reservoir in infants infected with HIV as a result of mother-to-child transmission. Using data from 2 Thai cohorts (HIVNAT 194, a cross-sectional cohort with n = 46, and HIVNAT 209, a longitudinal cohort with n = 42), Massanella and colleagues (Abstract 135) evaluated markers of

HIV persistence in infants and children who received antiretroviral prophylaxis followed by ART continuously without interruption since birth and compared them with those of children who had antiretroviral prophylaxis with an interruption interval prior to ART initiation. The researchers measured total and integrated HIV DNA in CD4+ T cells using real-time polymerase chain reaction (PCR), and used the Tat/rev Induced Limiting Deleting Assay (TILDA) to measure the size of inducible reservoir by determining the frequency of latently infected CD4+ T cells that generate multiply spliced RNA. Total and integrated HIV DNA levels decreased substantially during the first year of ART but remained detectable after that timepoint in almost all the children. In half of the children, the TILDA measures of inducible reservoir decreased rapidly after commencement of ART, and were undetectable in half of the children after 1 year of treatment. Children who had received ART without interruption since birth, with direct conversion from ARV prophylaxis to ART, had lower levels of total and integrated HIV DNA (ie, lower HIV reservoir) compared with those who had a delay. They also noted a positive correlation between age at ART initiation and levels of total and integrated HIV DNA and frequency of CD4+ T cells with inducible reservoir:infants who started ART before 6 weeks of age had lower levels of HIV persistence markers.

Shapiro and colleagues (Abstract 136) assessed markers of HIV reservoir size and development of early immune responses in HIV-infected children in Botswana's Early Infant Treatment Study (EIT) who were immediately commenced on ART within 7 days of age (median, 2 days; range 1-5 days), and compared them with children who started ART at a later age ranging from 30 to 365 days (control group). Quantitative HIV DNA testing was performed on PBMCs at various visits, along with qualitative DNA PCR testing on PBMCs and HIV-1 and -2 antibody dual enzyme linked immunosorbent assay (ELISA) at 84 weeks. Compared with controls, children who were treated within 7 days after birth had low HIV viral reservoir at enrollment and after 84 weeks of ART. Qualitative DNA PCR reversion from detectable to undetectable and negative HIV ELISA were seen in those children with consistent viral suppression, with 6 of the children (67%) having reversion and 5 of the children (56%) having negative EIA. The authors suggested that qualitative HIV DNA PCR and EIA HIV antibody tests could be employed as markers of HIV reservoir size in HIV-infected children who receive early ART.

Clinical Outcomes in Breastfeeding HIV-Infected Women

Hoffman and colleagues (Abstract 138) performed a cross-study analysis to compare the clinical outcomes of HIV-infected women who were predominantly breastfeeding in the multi-center, multi-country, randomized PROMISE (Promoting Maternal and Infant Survival Everywhere) 1077BF/FF trial with those reported in formula feeding women in the PROMISE 1077HS study. In the PROMISE 1077BF/FF study, 1612 HIV-infected women with baseline CD4+ cell counts above 350/μL and who initiated 3-drug ART during pregnancy were randomly assigned to continue ART or discontinue ART during the postpartum period (though discontinuation of ART during the postpartum period based on CD4+ cell count level is no longer recommended by the WHO and other guidelines). The preferred ART regimen in the study was lopinavir/ritonavir and TDF/emtricitabine. The primary efficacy endpoint was a composite of time to an AIDS event (defined as WHO Stage 4 clinical event) or death. Secondary endpoints included time to a composite endpoint of an HIV/AIDS-related event (defined as WHO stage 4 clinical event, pulmonary tuberculosis, or other serious bacterial infections) or a WHO stage 2 or 3 event, time to stage 2 or 3 event, and grade 2 to 4 safety endpoint. The median age at entry into the PROMISE 1077BF/FF trial was 26 years, and the median CD4+ cell count was 698/μL. A vast majority (95%) of the women were breastfeeding. The median follow-up period was 1.6 years. The authors did not find any statistically significant difference in the primary efficacy endpoint of clinical disease progression between the ART continuation and discontinuation arms (hazard ratio [HR], 0.55; 95% CI, 0.14, 2.08), as well as rates of safety events (HR, 0.95; 95% CI, 0.76, 1.17). Rates of WHO stage 2 and 3 events were significantly lower in those who continued ART than in those who discontinued ART (HR, 0.60; 95% CI, 0.39, 0.90). In cross-study comparison, the rates of the primary efficacy endpoint, WHO stage 2 and 3 events, and safety endpoints in the women in the PROMISE 1077BF/FF trial were similar to those previously reported in each of arms of the formula feeding women in the PROMISE 1077HS study. Based on these findings, the authors concluded that prolonged breastfeeding in the postpartum period had no adverse effects on clinical and safety outcomes in HIV-infected women with CD4+ cell counts of above 350/μL and had comparable clinical outcomes to those among formula feeding women.

Clinical efficacy and laboratory safety outcomes were further compared in 557 HIV-infected women in the PROMISE trial who had maintained CD4+ level at or above 350 cells/μL and who were randomly assigned to continue (n = 289) or discontinue ART (n = 268) post cessation of breastfeeding during the postpartum period (Abstract 139). As noted previously, the preferred ART regimen was lopinavir/r and TDF/emtricitabine. Women assigned to the discontinuation arm received the standard of care in the local country, with resumption of ART as needed during follow up. The primary composite efficacy endpoint was similar to that described in Abstract 138, namely a composite endpoint of time to progression to an AIDS-defining illness (defined as WHO stage 4 clinical event) or death. Secondary endpoints were grade 3 or higher laboratory and clinical findings and some grade 2 renal and hepatic laboratory findings. The baseline characteristics of the women were similar across both arms, with a median age of 28 years, 93% being WHO clinical stage 1, and 95% of the women having a CD4+ cell count of above 500 cells/μL. The median follow-up period was 84 weeks. Overall, the rate of primary efficacy endpoint across both arms was very low, with an incidence rate of 0.23%/100 py, with no statistically significant difference between the 2 arms (HR, 1.04; 95% CI, 0.06, 16.59) and with 1 maternal death reported in

each arm (causes of death were ruptured ectopic pregnancy and chronic renal insufficiency). Higher rates of grade 2 or higher adverse events were observed in the ART continuation arm although this finding was not statistically significant ($P = .08$). When restricting the analysis to include only grade 3 or 4 clinical adverse events, there were higher adverse event rates observed in the ART continuation arm than in the discontinuation arm (incidence rate, 4.9; 95% CI 3.8, 6.3 vs incidence rate, 1.7; 95% CI 1.1, 2.6; $P = .01$), with the most common clinical event being weight loss.

HIV Rebound Viremia and ART Nonadherence in Pregnant and Breastfeeding Women

ART adherence and resistance during HIV viremic episodes (defined as >1000 HIV RNA copies/mL) after initial viral suppression (<50 HIV RNA copies/mL) in pregnant and breastfeeding HIV-infected South African women were analyzed in Abstract 140. In this nested case-control study comparing women with viremic episodes after initial suppression (cases, n = 107) with those with continuously maintained suppression (controls, n = 124), the women were started on ART consisting of efavirenz/TDF/emtricitabine and underwent intensive viral load testing, starting from the initial antenatal visit through 12 months postpartum. Presence of antiretrovirals in plasma samples was assessed in cases and controls, as was drug resistance mutations. Overall, 30% of the women had a viremic episode after virologic suppression by 12 months postpartum. Presence of any antiretroviral drug was detected in 18% of cases at time of viremic episode and in 94% of controls at matched time points ($P < .001$). The authors calculated a 36.8-fold increased odds of ART nonadherence in women who had viremic episodes compared to controls (OR, 36., 95% CI, 15.5, 90.5) and an attributable fraction of 97% for viremic episodes due to ART nonadherence. Before the initiation of ART, detected drug resistance mutations were all NNRTI-related, with 11% in cases and 5% in controls ($P = .15$) with most being major NNRTI mutations. At the viremic episode timepoint, 45% of cases had any drug resistance mutation detected, with a majority being NNRTI mutations. Merely 18% of cases with drug resistance mutations detected at the time of a viremic episode had drug resistance mutations pre-ART, suggesting emergence of drug resistance mutations during 12 months postpartum while on ART. The authors highlighted the importance of addressing barriers to ART adherence in pregnant and postpartum HIV-infected women.

All cited abstracts appear in the CROI 2018 Abstracts eBook available online at www.CROIconference.org.

Financial affiliations in the past 12 months: Dr Tieu received grant support, paid to her institution, from Merck. Dr Taylor has no relevant financial affiliations to disclose. Dr Jones has no relevant financial affiliations to disclose. Dr Wilkin has served as a consultant to Glaxo-SmithKline/ViiV Healthcare and has received grant support, paid to his institution, from Glaxo-SmithKline/ViiV Healthcare. His spouse owns stock in Johnson & Johnson.

Additional References Cited in Text

1. Xu L, Pegu A, Rao E, et al. Trispecific broadly neutralizing HIV antibodies mediate potent SHIV protection in macaques. *Science*. 2017;358(6359):85-90.
2. Aboud M, Kaplan R, Lombaard J, et al. Superior efficacy of dolutegravir (DTG) plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) compared with lopinavir/ritonavir (LPV/RTV) plus 2 NRTIs in second-line treatment: interim data from the DAWNING study. 9th International AIDS Society Conference on HIV Science. 7-26-2018; Paris, France.
3. del Rio C, Green S, Abrams C, Lennox J. From diagnosis to undetectable: the reality of HIV/AIDS care in the inner city. 8th Conference on Retroviruses and Opportunistic Infections (CROI). February 4-8, 2001;287; Chicago, IL.
4. Centers for Disease Control and Prevention (CDC). Vital signs: HIV prevention through care and treatment--United States. *MMWR Morb Mortal Wkly Rep*. 2011;60(47):1618-1623.
5. Gardner EM, McLees MP, Steiner JF, del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. *Clin Infect Dis*. 2011;52(6):793-800.
6. Joint United Nations Programme on HIV/AIDS. 90-90-90: An ambitious treatment target to help end the AIDS epidemic. http://www.unaids.org/sites/default/files/media_asset/90-90-90_en.pdf. Accessed on March 21, 2018.
7. San Francisco Department of Health. HIV Epidemiology Annual Report 2016. https://www.sfdph.org/dph/files/reports/RptsHIVAIDS/Annual-Report-2016-20170831.pdf. Accessed on March 28, 2018.
8. Colasanti J, Kelly J, Pennisi E, et al. Continuous retention and viral suppression provide further insights into the HIV care continuum compared to the cross-sectional HIV care cascade. *Clin Infect Dis*. 2016;62(5):648-654.
9. Marks G, Patel U, Stirratt MJ, et al. Single Viral Load Measurements Overestimate Stable Viral Suppression Among HIV Patients in Care: Clinical and Public Health Implications. *JAIDS*. 2016;73(2):205-212.
10. Powers KA, Samoff E, Weaver MA, et al. Longitudinal HIV Care Trajectories in North Carolina. *J Acquir Immune Defic Syndr*. 2017;74 Suppl 2:S88-S95.
11. Dombrowski JC, Bove J, Roscoe JC, et al. "Out of Care" HIV Case Investigations: A Collaborative Analysis Across 6 States in the Northwest US. *J Acquir Immune Defic Syndr*. 2017;74 Suppl 2:S81-S87.
12. Buchacz K, Chen MJ, Parisi MK, et al. Using HIV surveillance registry data to re-link persons to care: the RSVP Project in San Francisco. *PLoS One*. 2015;10(3):e0118923.
13. Sena AC, Donovan J, Swygard H, et al. The North Carolina HIV Bridge Counselor Program: Outcomes From a Statewide Level Intervention to Link and Reengage HIV-Infected Persons in Care in the South. *J Acquir Immune Defic Syndr*. 2017;76(1):e7-e14.
14. Tesoriero JM, Johnson BL, Hart-Malloy R, et al. Improving Retention in HIV Care Through New York's Expanded Partner Services Data-to-Care Pilot. *J Public Health Manag Pract*. 2017;23(3):255-263.
15. Dombrowski JC, Hughes JP, Buskin SE, et al. A Cluster Randomized Evaluation of a Health Department Data to Care Intervention Designed to Increase Engagement in HIV Care and Antiretroviral Use. *Sex Transm Dis*. 2017;[Epub ahead of print]
16. Labhardt ND, Ringera I, Lejone TI, et al. Effect of Offering Same-Day ART vs Usual Health Facility Referral During Home-Based HIV Testing on Linkage to Care and Viral Suppression Among Adults With HIV in Lesotho: The CASCADE Randomized Clinical Trial. *JAMA*. 2018;319(11):1103-1112.
17. Metsch LR, Feaster DJ, Gooden L, et al. Effect of Patient Navigation With or Without Financial Incentives on Viral Suppression Among Hospitalized Patients With HIV Infection and Substance Use: A Randomized Clinical Trial. *JAMA*. 2016;316(2):156-170.
18. World Health Organization (WHO). Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy. http://www.who.int/hiv/pub/guidelines/advanced-HIV-disease/en/. Accessed on March 28, 2018.
19. Medecins Sans Frontier and - Southern African Medical Unit (SAMU). MSF HIV/TB Guide: Hospital Level. https://samumsf.org/sites/default/files/2018-02/MSF%20HIVTB%20Guide_Hospital%20Level_February%202018.pdf. Accessed on March 28, 2018.
20. ICAP: HIV Coverage, Quality and Impact Network CQUIN Learning Network. Differentiated Care for Adults at High Risk of HIV Disease Progression: A Call to Action. http://icap.columbia.edu/resources/detail/differentiated-care-for-adults-at-high-risk-of-hiv-disease-progression-a-ca. Accessed on March 28, 2018.

Guidelines for Authors and Contributors

The IAS–USA publishes *Topics in Antiviral Medicine*™ as a resource for physicians and other health care practitioners who are actively involved in the care of patients with HIV or other viral infections. This open-access journal is now available as an online resource only. It is indexed in Index Medicus/MEDLINE and PubMed.

The following guidelines describe the types of articles and contributions published in the journal, outline its policies, and provide instructions for authors. For further information, contact *Topics in Antiviral Medicine*™ at journal"at"iasusa.org.

Categories of Articles

Perspectives. *Perspective* articles are summaries of selected talks given at IAS–USA continuing medical education courses. An IAS–USA medical writer prepares a summary manuscript from a transcript of the talk. The manuscript is reviewed and edited by the presenter and the journal's appointed peer reviewer(s).

Reviews. *Topics in Antiviral Medicine*™ welcomes original review articles on current issues related to infection with HIV or other viruses. *Topics in Antiviral Medicine*™ does not publish original research. Manuscripts should be 3000 to 6000 words (excluding references, tables, and figures) and should include numbered references and a brief introductory abstract of approximately 100 to 200 words. Original, adapted, or reprinted figures and tables may be included and should be cited in the text and accompanied by a brief title. Adapted and reprinted work requires proof of permission obtained from the original publishers and authors. Authors interested in submitting unsolicited manuscripts are encouraged to submit an outline or abstract of the proposed manuscript first; please contact the editor for further information.

Editorials. *Topics in Antiviral Medicine*™ invites submission of editorials. Editorials should be approximately 500 to 1500 words (excluding references) and should include numbered references.

Special Contributions. A special contribution article often represents the unique contribution (such as a consensus statement) of an author or group of authors.

Cases From the Field. *Topics in Antiviral Medicine*™ invites submission of case reports accompanied by a scholarly literature review of the topic. Each case report should be 1500 to 3000 words (excluding references, tables, and figures), include numbered references, and seek to teach an important lesson for HIV or viral hepatitis care practitioners.

Stories. Stories for the *Telling Stories* column share the experiences of those involved in the care of people infected with HIV or other viruses. Stories may be approximately 800 to 3500 words; submissions are welcome for consideration.

Commentaries. Discussion on a current issue in the management of viral diseases is welcome as a Commentary. Commentaries should be 500 to 1500 words and include numbered references as appropriate. Commentaries may be invited by the editors; unsolicited submissions are also welcome for consideration.

Letters to the Editor. Letters to the editor are welcome and should be sent to the address listed below. Please limit letters to 300 words.

Special Issues. *Topics in Antiviral Medicine*™ often publishes issues with a special focus, such as summaries of IAS–USA continuing medical education courses and reports from scientific meetings.

Reprints. Reprints of articles by expert panels convened by the IAS–USA are included periodically in *Topics in Antiviral Medicine*™.

Submission of Manuscripts

Manuscripts should be submitted via mail or e-mail to the address below. Each author should complete an Authorship Form, which is available online at www.iasusa.org/pub or may be obtained by contacting the editor at the address below. Outlines or abstracts of proposed manuscripts are welcome and may be sent via mail or e-mail.

Editor, *Topics in Antiviral Medicine*™
IAS–USA
425 California St, Ste 1450
San Francisco, CA 94104-2120

E-mail: journal"at"iasusa.org

Receipt of submitted manuscripts will be acknowledged by editorial staff, and submissions will be reviewed by peer reviewers. Acceptance for publication is based on the quality and relevance of the work.

Copyright

Copyright to all manuscripts and graphics published in *Topics in Antiviral Medicine*™ is owned by the IAS–USA unless noted otherwise. All authors and contributors of manuscripts accepted for publication, with the exception of US federal government employees, must sign a copyright transfer form as a condition of publication.

Authorship Requirements

Topics in Antiviral Medicine™ uses the definition of authorship formulated by the International Committee of Medical Journal Editors and published in its *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*.[1] This definition states that authorship "should be based on the following 4 criteria: (1) Substantial contributions to the concept or design of the work; or the acquisition, analysis, or interpretation of data for the work; (2) drafting the work or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work ensuring that questions related to the accuracy of integrity of any part of the work are apprpriately investigated and resolved… acquision of funding; general supervision of a research group or general adminstrative support; and writing assistance" do not constitute authorship. *Topics in Antiviral Medicine*™ will not consider ghostwritten articles for publication.

Financial Disclosure

It is the policy of the IAS–USA to ensure balance, independence, objectivity, and scientific rigor in all of its educational programs. To that end, all authors and contributors of articles published in *Topics in Antiviral Medicine*™ are required to disclose to readers any significant financial interest or other relationship with any organization having financial interest in the content of the manuscript. Financial interests include employment, consultancy, honorarium, grant/research support, major stock ownership, or membership in a speakers bureau and directly paid lectures, or other contributions. The complete financial disclosure statements for all authors and contributors are published with the articles.

1. International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. Updated December 2015. Available at http://www.icmje.org. Accessed April 4, 2018.

The 2018 Clinical Conference at the National Ryan White Conference on HIV Care & Treatment

If you are an HIV physician, nurse practitioner, or physician assistant in a Ryan White HIV/AIDS program (RWHAP)-funded clinic or program, Register Now to attend the 2018 Clinical Conference at the National Ryan White Conference on HIV Care & Treatment. Additional information about the conference can be found here.

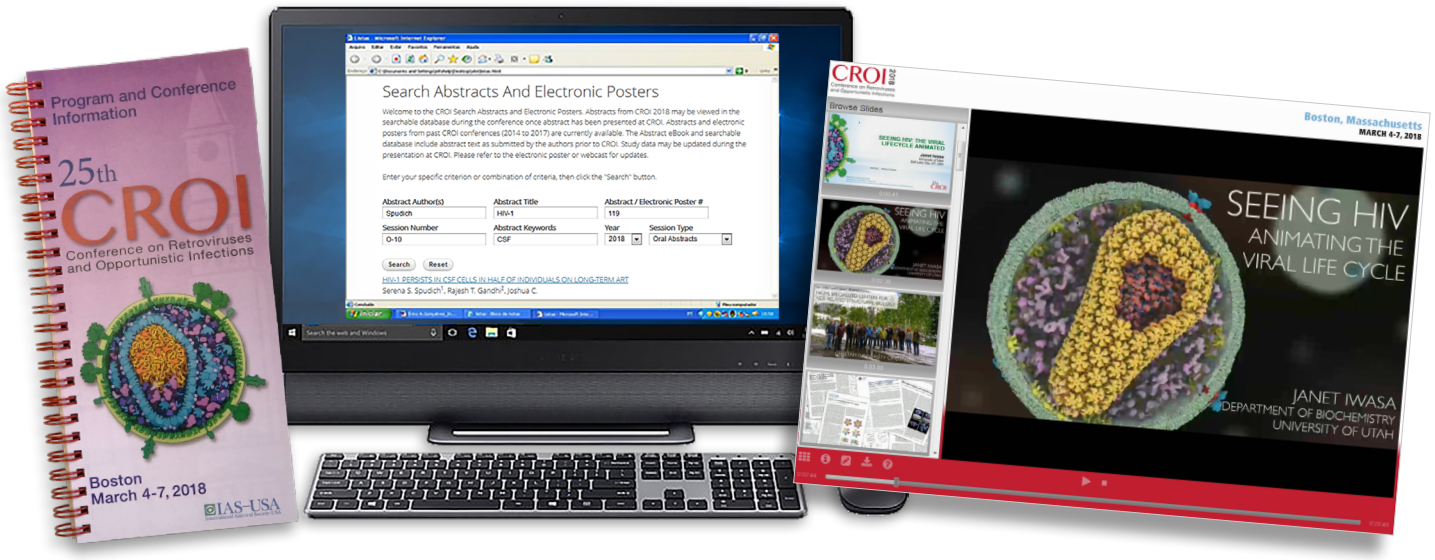
Coming Soon

NEW IAS–USA website

- Improved user experience
- Mobile-friendly
- Same great content:
  - Webcasts and podcasts of previous live courses, including spring 2018 courses and the 2017 Ryan White Clinical Conference
  - Cases on the Web activities
  - Up-to-date guidelines for clinical HIV treatment and drug resistance mutations
  - More information about upcoming courses and activities

CROI 2018 Resources

Webcasts and electronic posters from CROI 2018 and information about CROI 2019, to be held in Seattle, Washington, from March 4 to March 7, can be found at www.CROIconference.org The Electronic Materials page includes the following resources and more.



The CROI Program and Information guide includes information about sessions, speakers, and other details about CROI 2018.

In addition to the Special Issue of *Topics in Antiviral Medicine*™, abstracts from CROI 2018 can be viewed in the Abstract eBook and searchable data base.

Plenaries, symposia, oral abstract sessions, and themed discussions are available as webcasts. Visit www.CROIwebcasts.org to access webcasts from CROI 2014 to CROI 2018.