Invited Review

CROI 2018: Epidemic Trends and Advances in HIV Prevention

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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.

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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

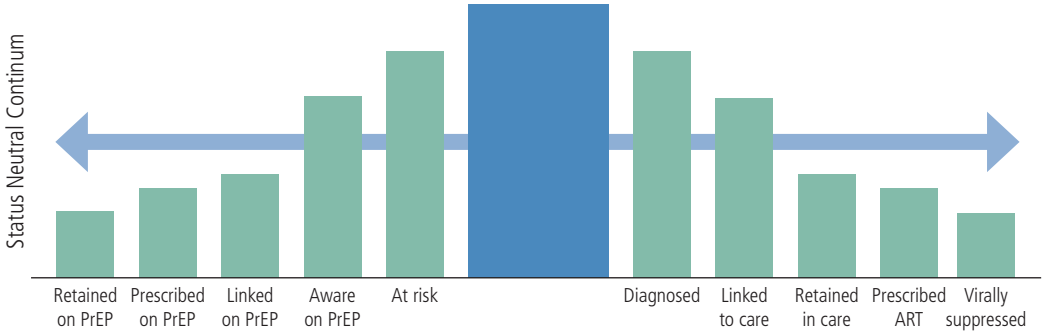

Figure. In the Status Neutral Continuum, the HIV prevention continuum (left) is for individuals who test HIV-negative, and the HIV treatment continuum (right) is for individuals who test HIV-positive. PrEP, preexposure prophylaxis; ART, antiretroviral therapy. Adapted from Abstract 61 and https://www.nastad.org/domestic/hiv-prevention-health-equity.[3]

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.

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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

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