Invited Review

CROI 2016: Hot Spots in HIV Infection and Advances in HIV Prevention

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The 2016 Conference on Retroviruses and Opportunistic Infections (CROI) highlighted hot spots in HIV infection. Men who have sex with men (MSM), transgender populations, people who inject drugs, fisherfolk, migrants, adolescents, and older adults are heavily impacted in a number of regions. Stigma contributes to risk behaviors and HIV acquisition across populations. HIV testing is a crucial first step in the HIV care continuum, and several large community-based surveys are underway in Africa to increase HIV testing, linkage to care, and uptake of antiretroviral treatment. Advances in preexposure prophylaxis (PrEP) featured prominently at CROI 2016. Two large efficacy trials of a vaginal ring containing the investigational drug dapivirine demonstrated efficacy and safety in preventing HIV infections in women in Africa. Data on the safety of long-acting injectable PrEP and several investigational PrEP drugs and formulations were also presented. Knowledge and use of PrEP among MSM in the United States appears to be increasing, and high uptake was seen among black MSM when provided as part of a culturally tailored support program. The use of broadly neutralizing antibodies for HIV prevention is a novel and promising approach to be evaluated in efficacy trials.

Keywords: CROI, 2016, epidemiology, HIV, hot spots, injection drug use, phylogenetics, preexposure prophylaxis, PrEP, prevention, incidence, transmission, men who have sex with men, MSM, transgender populations, fisherfolk, sexually transmitted infections, HIV testing, broadly neutralizing antibodies, vaginal ring, dapivirine, tenofovir alafenamide, TAF, microbicide

Hot Spots of HIV Infection

At the 2016 Conference on Retroviruses and Opportunistic Infections (CROI), investigators reported on current HIV hot spots of populations heavily impacted by high transmission rates, and proposed strategies for intervention.

Men Who Have Sex With Men

Men who have sex with men (MSM) remain one of the populations most heavily impacted by HIV disease worldwide. Hess and colleagues at the Centers for Disease Control and Prevention (CDC) presented estimates of the lifetime risk of HIV acquisition among all populations in the United States from 2009 to 2013 (Abstract 52). They estimate that the lifetime risk of acquiring HIV infection for men overall in the United States is 1 in 64, highest among black (1 in 20) and Hispanic men (1 in 48) and lowest among Asian men (1 in 174). Risk for women was substantially lower (1 in 227 overall), with similar racial and ethnic disparities: black (1 in 48) and Hispanic women (1 in 227) were at substantially higher risk than Asian women (1 in 883). When evaluated by risk group, MSM had a 1 in 6 lifetime risk, with the highest risk among black (1 in 2) and Hispanic MSM (1 in 4) and the lowest risk among white (1 in 11) and Asian MSM (1 in 14). Among people who inject drugs (PWID), the risk of acquiring HIV infection was 1 in 23 for women and 1 in 36 for men. Similarly, heterosexual women were at higher risk than heterosexual men (1 in 241 vs 1 in 473, respectively). Racial and ethnic disparities were also observed among PWID and heterosexual persons.

When analyzed by geographic region, the highest lifetime risks were observed predominantly in the Southern United States. When evaluated by age, MSM were at highest 10-year risk in their 20s and male PWID were at highest risk in their 40s and 50s, perhaps a reflection of late diagnosis rather than late increases in risk. Although estimates from 2009 to 2013 are more hopeful than those from 2004 to 2005, this type of analysis highlights the unacceptable racial and ethnic disparities that continue to exist. These data are a call to action to intervene with highly active prevention, particularly in at-risk black and Latino populations for whom preexposure prophylaxis (PrEP) should be made available.

Finlayson and colleagues reported on data from the 2011 MSM cycle of the National HIV Behavioral Surveillance, a venue-based time location sampling survey conducted in 20 US cities (Abstract 930). This analysis compared black MSM aged 18 years to 24 years with those aged 25 years to 44 years. Investigators reported that HIV prevalence was 21% among younger and 32% among older men in the survey. However, of men who were HIV seronegative or whose HIV serostatus was unknown, younger men were more likely than older men to report engaging in receptive anal sex at their

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last sexual encounter, and to have a sexual partner who was at least 3 years older or black. Among HIV-seropositive, black MSM, younger men were also more likely to have older or black partners and were less likely to be currently taking antiretroviral therapy. These data suggest that the high risk of HIV acquisition among young black MSM may be attributable to sexual networks that may contain sexual partners among whom HIV prevalence is high, some of whom are not taking antiretroviral treatment.

Stigma also figures heavily into populations of MSM globally. Lahuerta and colleagues presented data on HIV prevalence and factors associated with prevalent HIV infection in a cross-sectional survey conducted among 550 MSM in Bamako, Mali (Abstract 921). Overall prevalence of HIV infection was 13.7%, and 90% of those who were HIV seropositive were unaware of their infection status. In a multivariable model of factors associated with prevalent HIV infection, rejection of sexual orientation by family members was associated with an adjusted odds ratio (aOR) of 31.3. If lack of knowledge of HIV serostatus was accurately reported, these results suggest that rejection of sexual orientation by family members contributes substantially to risk behaviors and HIV acquisition.

Stahlman and colleagues presented data on a cohort of 1370 MSM recruited from Abuja and Lagos, Nigeria (Abstract 924). Men seeking sex partners online were more likely to become HIV infected during the study (aOR, 2.2; 95% confidence interval [CI], 1.5-3.2) and also more likely to report 1 or more types of perceived or experienced stigma (eg, having avoided or been afraid to seek health care services, being physically hurt, not feeling protected by police, or being blackmailed, verbally harassed, or scared to walk around in public). Although causality cannot be proven, it is possible that stigma may drive risky partner-seeking and sexual behaviors among MSM.

Holtz presented data on the high rates of acute and early HIV infection among a cohort of 977 MSM with negative results on HIV screening tests in Bangkok, Thailand (Abstract 927). Acute or early HIV infection was detected in 5.3% of these men, who were tested every 4 months. HIV infection was higher among men aged 18 years to 21 years (aOR, 2.6; 95% CI, 1.1-6.1) who tested positive for hepatitis A antibody (aOR, 5.6; 95% CI, 1.5-20.8) or hepatitis B core antibody (aOR, 14.1; 95% CI, 5.6-35.4). Men who reported inconsistent condom use with steady male sexual partners (aOR, 3.8; 95% CI, 1.8-8.3) and who had rectal *Neisseria gonorrhea*, (aOR, 7.5; 95% CI, 1.4-39.1) were also at greater risk of acquiring HIV infection. This suggests that among high-risk populations, more sensitive blood-based HIV tests will be required to detect early or acute HIV infection, during which treatment may limit immune destruction and the size of the HIV reservoir.

Solomon presented data on the high prevalence of HIV among wives of married MSM in India (Abstract 928). In a convenience sample of 149 MSM and their wives from 3 Indian cities, HIV prevalence was 47% (95% CI, 39%-55%) among the men and 27.5% (95% CI, 20%-35%) among their wives. Despite being recruited by their husbands for this study, 31.5% of the wives reported not knowing that their husband was having sex with men, and 34% reported learning of their partner's sexual practices seeing him having sex with a man. Only 15% of the wives reported that their husband had disclosed his sexual contact with men. These results point to the need to identify MSM and their wives in cultures in which marriage to women is common for MSM, to provide treatment for HIV-infected men and PrEP for uninfected men and women.

Transgender Populations

Poteat presented an overview of HIV in transgender communities worldwide (Abstract 79). She clarified for the audience that the term transgender applies to persons whose gender identity differs from the sex assigned at birth, irrespective of any medical, surgical, or other interventions. A 2-step method for assessing gender identity allows for accurate categorization: first asking the current gender identity, and then asking the sex assigned at birth. An estimated 0.3% of the US population (700,000 individuals) is transgender, and 0.1% to 0.5% of the population in Europe is transgender. In India, where *hijra* or "third gender" persons have been recognized for many thousands of years, an estimated 1 million to 6 million persons are living as *hijra*. Several Asian countries officially recognize a third gender on government documents.

As HIV prevalence is quite low among transgender men, with most large estimates being less than 1%, Poteat turned her attention to focus on transgender women, those who identify as women but were assigned male sex at birth. According to Dr. Poteat, several meta-analyses suggest that the overall HIV prevalence among transgender women is 19%

Approximately 700,000 transgender persons live in the United States, with an HIV prevalence among transgender women (identify as women but assigned male sex at birth) of 22%.

globally, compared with estimates of 12% among female sex workers and 13% among MSM globally.[1] In the United States, where the estimated overall HIV prevalence is 22% among transgender women, HIV incidence among black transgender women is double that observed among white transgender women. In sub-Saharan Africa, up to 23% of participants in studies of MSM self-identify as women. HIV prevalence is substantially higher among transgender women; for instance, a study in Lesotho found that 60% of transgender women were HIV infected, compared with 27% of cisgender women and 28% of MSM.[2]

Poteat covered biologic factors that could increase susceptibility to HIV infection among transgender women. Many transgender women use feminizing hormones, including 17-beta estradiol, at doses up to 4-fold greater than doses taken by cisgender women. Estrogens commonly used in birth control products are not recommended for transgender women, as they increase the risk of thromboembolic events. The impact of these hormones on rectal mucosa is unknown.

Poteat stated that only 2% to 15% of transgender women undergo any gender confirmation surgery and that virtually nothing is known about HIV acquisition through the neovagina, which is generally constructed of keratinized epithelium through a penile inversion procedure.

Interactions between feminizing hormones and antiretroviral drugs are also incompletely understood. Some HIV nonnucleoside analogue reverse transcriptase inhibitors (NNRTIs) and protease inhibitors decrease estrogen levels, leading some transgender women to increase estrogen dosing to unsafe levels. The pharmacokinetics of tenofovir disoproxil fumarate (TDF) are affected by exogenous estrogen, although the impact of endogenous estrogens on PrEP efficacy is unknown. Of the 14% of participants in the iPrEx (Chemophrophylaxis for HIV Prevention in Men) trial who were transgender women, those who were receiving hormone therapy had substantial declines in TDF drug levels over time, although it is unclear whether this was a result of poor adherence or altered pharmacokinetics of TDF.[3]

Stigma is a major driver of high rates of HIV infection and poor outcomes among transgender women. Unemployment, poverty, and housing instability arise from stigma and contribute to these health inequities. Among the nearly 5400 transgender persons receiving care through the Ryan White HIV/AIDS Program in the United States, rates of viral suppression were statistically significantly lower than those of nontransgender persons receiving care through the program (74% vs 81%, respectively), and rates of viral suppression were 53% for transgender women aged 20 years to 24 years and 53% for transgender women who were unstably housed.[4]

Among HIV-seropositive transgender women, concerns about antiretroviral therapy and its adverse effects rank fifth in top health concerns, after 1) gender-affirming, nondiscriminatory care; 2) hormone therapy and adverse effects; 3) mental health care; and 4) personal care. An analysis of data from 400 transgender women participating in 9 demonstration projects indicated that those who received hormonal treatment from their primary practitioner had a 3-fold increased likelihood each of viral suppression and of having had a medical visit within the past 6 months. Poteat called for a research agenda for transgender persons to include understanding of drug interactions between hormones and antiretroviral drugs, understanding of comorbidities, integration of gender care with HIV prevention and treatment, and inclusion of transgender community members in all aspects of research.

People Who Inject Drugs

Brooks presented an overview of the explosive HIV outbreak in Indiana discovered in late 2014 (Abstract 132). He noted that new diagnoses of HIV infection among PWID decreased by 63% in the 10 years from 2005 to 2014, so that in 2014, only 6% of new diagnoses in the United States occurred among PWID. However, in late 2014 and early 2015, an outbreak occurred among PWID in Scotts County, Indiana. This county ranked lowest of all Indiana counties in life expectancy, with one-fifth of the population living below the poverty line and 9% being unemployed. As of February 1, 2016, 188 new HIV diagnoses have been linked to this outbreak, almost all of which were among white individuals whose ages ranged from 28 years to 42 years. Most of those who became infected were injecting oxymorphone, the expense of which led those injecting it to use small amounts, 4 to 15 times per day. No syringe access program was available in Indiana at the time. More detailed information on the phylogenetic analysis is discussed in the section on transmission networks.

Ramachadran and colleagues presented data on hepatitis C virus (HCV) transmission in Scotts County during the same time period (Abstract 149). Of 312 persons found to have HCV infection, only 25% were coinfected with HIV. Unlike the HIV epidemic in which a single virus was introduced into the population, several HCV variants were introduced into the PWID population over time, traced back to at least 2010. Phylogenetic analysis using Global Hepatitis Outbreak and Surveillance Technology (GHOST) enabled investigators to identify 23 clusters, of which the largest (130 persons) accounted for nearly half of detected infections. However, minimal overlap was found between HIV contact tracing and HCV networks, suggesting that transmission patterns may differ for HIV and HCV.

Brooks discussed the successful strategies used by local and state health authorities and the CDC to curb the HIV outbreak in Indiana, including syringe access programs, HIV care for those infected, and integrated services delivered within the community such as issuing identification documents, employment assistance, and medical care. He then pointed out that the national increase in deaths caused by drug overdose is now heavily contributed to by opiate prescribing; opiates were the cause of 30% of overdose deaths in 1999 and now account for 60% of overdose deaths. The CDC recently issued guidelines on opioid prescribing for chronic pain.[5] Brooks noted that multiple cities in Asia, Eastern Europe, and the United States, including New York City, New York, experienced increases in HIV prevalence among PWID from near zero to more than 40% within 1 year to 2 years. In contrast to previous outbreaks, the opiate epidemic and its attendant epidemic of hepatitis C appears to be occurring primarily in nonurban settings and predominantly in the southeastern United States. He closed with 3 recommendations to help jurisdictions prepare for similar outbreaks among PWID: 1) improve access to clean syringes and substance use diagnosis and treatment; 2) enhance capacity to detect a change in injection drug use within communities; and 3) prepare an action plan to rapidly address a similar outbreak, should one arise.

Opioid use now accounts for 60% of overdose deaths in the United States, up from 30% in 1999.

Another presentation from Perez and colleagues from the CDC evaluated the rates of opiate prescribing for HIV-seropositive individuals from 2009 to 2013 in the United States as

part of the Medical Monitoring Project (MMP) (Abstract 915). Perez noted that 21% of HIV-seropositive individuals in care through the MMP had been prescribed opiates during that time, with statistically significantly higher rates of prescribing in more vulnerable populations, including those living below the federal poverty limit, those with mental illness, and those with a history of injection and noninjection drug use. Practitioners must protect their patients from opiate overdoses through appropriate use and provision of naloxone to reverse overdoses. Practitioners should also be aware of the potential public health implications of prescribing opiates to individuals in vulnerable populations.

Fisherfolk

Several presentations focused on men and women working in the fishing industry in Kenya and Uganda, a population that is very highly impacted by HIV disease. Kwena presented an overview of the HIV epidemic in these populations (Abstract 171). He pointed out that 800 million persons worldwide depend on the fishing industry for their livelihood, with 80 million of those living in sub-Saharan Africa. He cited several studies of fisherfolk near Lake Victoria in Kenya and Uganda, in whom HIV incidence ranges from 2.4 per 100 person-years to 4.9 per 100 person-years. Kwena enumerated several drivers of high HIV incidence and prevalence in these populations, including high rates of mobility (40%-70%), transactional sex (42%-65%), and heavy alcohol use (52%-62%); HIV incidence is statistically significantly higher among fisherfolk who have these risk factors than among those who do not. He pointed to the dearth of services available to these populations and proposed that broad-based prevention and treatment services be provided in locations and at times that are convenient for the target populations.

High rates of mobility, transactional sex, and heavy alcohol use contribute to high HIV incidence and prevalence among fisherfolk in Kenya and Uganda.

Odongo and colleagues reported on HIV prevalence among 940 fisherfolk near Lake Victoria in Osembo, Kenya, from August 2014 to March 2015 (Abstract 903). HIV prevalence was higher among women than men (27% vs 18%, respectively; relative risk [RR], 1.5; 95% CI, 1.2-2.0). In multivariable analysis, prevalent infection was higher among those who had been previously married (aOR, 6.7; 95% CI, 2.9-15.7) or were currently married (aOR, 2.3; 95% CI, 1.1-4.9). Compared with those aged 30 years to 39 years, prevalent infection was lower among fisherfolk aged 13 years to 19 years (aOR, 0.1; 95% CI, 0.0-0.4) and 20 years to 29 years (aOR, 0.5; 95% CI, 0.3-0.7). Among those aged 20 years to 29 years, women were 3 times more likely than men to be HIV seropositive (24% vs 8%, respectively; $P < .05$).

Kagaayi and colleagues reported on the first and last of 4 rounds of the Rakai Community Cohort Study of more than 4000 residents of a large fishing community on Lake Victoria in Kenya (Abstract 986). They evaluated the impact of scale up of male circumcision and antiretroviral treatment regardless of CD4+ cell count from 2011 (before scale-up) to 2015 (after scale-up). Over that time, the circumcision rate for HIV-seronegative men increased from 30% to 54%, and antiretroviral therapy for HIV-seropositive men and women increased from 19% to 68% in this population. Over that same period, HIV seroincidence declined from 4.0 per 100 person-years to 2.9 per 100 person-years (aOR, 0.71; 95% CI, 0.44-1.15). These data demonstrate that substantial gains can be made in prevention and treatment in this highly affected population and that more remains to be done.

Migrants

Del Amo presented an overview of the magnitude of the HIV epidemic in migrant populations, with a focus on Western Europe and the United States (Abstract 173). In Europe, of the 83% of individuals with new HIV diagnoses from 2007 to 2012 for whom sufficient data on country of origin were available, 39% were migrants. Sub-Saharan Africans accounted for 53% of these migrants, Western, Central, or Eastern

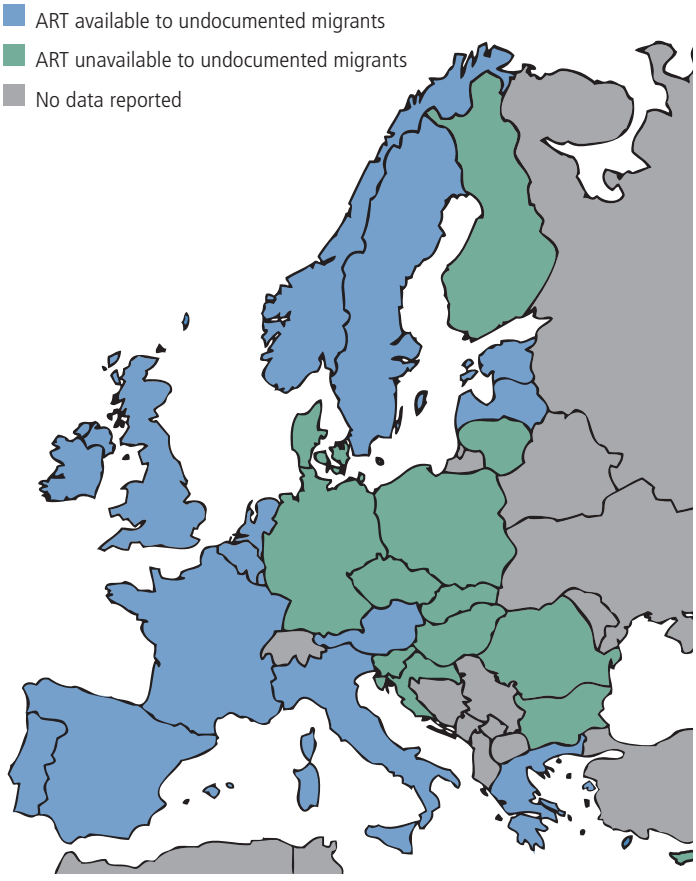

Figure. Provision of antiretroviral therapy (ART) for undocumented migrants in countries in the European Union and the European Economic Area, 2014. Adapted from European Centre for Disease Prevention and Control.[6]

Europeans for 21%, and Latin Americans for 12%. The number of HIV-seropositive migrants to Europe from Eastern and Southern Africa has been declining in recent years, although the number from West Africa remains stable. In the United States from 2007 to 2010, 16% of all new HIV diagnoses occurred in persons born outside of the United States: 41% from Central America, 21% from the Caribbean, and 14% from sub-Saharan Africa. Although most migrants were previously assumed to have been infected with HIV before arriving in Europe, current studies suggest that among newly diagnosed migrants, 75% of MSM and 50% of heterosexual men and women acquired HIV infection in the country of diagnosis. Limited access to testing and treatment likely contributes to later diagnosis (51% of migrants to Europe are diagnosed later) and poorer outcomes. Del Amo pointed out that only one-half of European countries provide antiretroviral drugs for undocumented migrants (Figure),[6] and asked the audience to consider the ethics of a policy of "test but not treat" for some populations.

Within-country migration can also drive local epidemics. Grabowski and colleagues presented data on nearly 23,000 men and women aged 15 years to 49 years who participated in the Rakai Community Cohort Study, which involved 38 communities in the Rakai district of Kenya (Abstract 902). From 2011 to 2015, 29% of participants migrated into or out of these communities, with the proportion varying from 9% to 49%, depending on the community. During this time, 25% of the total HIV-infected population and 57% of those newly diagnosed with HIV infection were migrants, predominantly women. Migrants were much less likely to be taking antiretroviral therapy than nonmigrants. These data provide further evidence of the vulnerability of migrant populations, even within the same country.

Adolescents

Sohn presented at a symposium on adolescents on the epidemiology of HIV infection in this population (Abstract 174). She pointed to a 2014 report by the World Health Organization that found that HIV infection was the leading cause of death among African adolescents and the second leading cause of death for youth worldwide.[7] Among young adults aged 15 years to 24 years, 4.3 million are living with HIV infection, although these estimates are often not divided by perinatally versus behaviorally infected persons. She made the case that perinatally infected youth have unique chronic health problems and long-term HIV management needs, account for a substantial proportion of mortality in this age group, and yet are rarely the focus of initiatives focused on HIV in youth. Only 16% of adolescents are known to be taking antiretroviral therapy according to a 2014 report from the Joint United Nations Programme on HIV/AIDS (UNAIDS),[8] likely based in part on the requirement of low CD4+ cell counts before initiation of antiretroviral therapy. A review of 20 studies of HIV-infected adolescents revealed viral suppression rates varying from 27% to 89%, reflecting substantial interpopulation differences in treatment and retention in care. For instance, a study in Swaziland found that 65% of those aged 10 years to 19 years were virally suppressed.[9] In contrast, the US Adolescent Medicine Trials Network for HIV/AIDS found low rates of viral suppression among HIV-infected adolescents aged 12 years to 26 years: 37% among those who were perinatally infected and 27% among those who were behaviorally infected.[10] Globally, HIV is the second leading cause of death among those aged 10 years to 19 years, the sixth leading cause of disability-adjusted life years, and is the only infectious disease in the top 10 disability causes. Sohn ended with a call to advocate for research and policy to improve outcomes for adolescents, and for more comprehensive and accurate data collection in this vulnerable population.

Worldwide, HIV infection is the second-leading cause of death among adolescents aged 10 years to 19 years.

Older Adults

Remera and colleagues presented data from the first national HIV household survey in Rwanda (Abstract 166). Previous estimates of HIV incidence have been based on models. The investigators suggested that these models substantially underestimate new infections. Models indicate approximately 5000 HIV infections per year, but the number is likely closer to 14,000 based on the national incidence of 0.27 per 100 person-years. In multivariate analysis, HIV incidence increased substantially with increasing age, and those aged 45 years or older were 4 times more likely to become infected than those aged 15 years to 24 years. Compared with single persons, widowers were 2 times more likely to become infected, but married persons were 70% less likely to become infected. The investigators also found unexpected and substantial regional differences, with persons from the Western Province having a 9-fold increased risk compared with those from the Northern Province. Results from this national survey can help shape policy, ensuring that older persons are one of the populations targeted by prevention strategies and that resources are targeted geographically.

Rosenberg and colleagues found older adults in a rural province in South Africa to be at substantial risk for HIV transmission and acquisition (Abstract 905). Among 5059 men and women aged 40 years or older who participated in the Health and Aging in Africa: Longitudinal Studies of INDEPTH Communities study, condom use decreased as age increased. In particular, more than 1 in 5 persons found to be HIV seropositive who reported they were HIV seronegative or that they did not know their serostatus also reported engaging in casual sex, and only 1 in 4 reported any condom use. The investigators concluded that HIV prevention interventions must also target older adults to reduce further transmission and acquisition in similar communities in sub-Saharan Africa.

Risk Factors for HIV-1 Transmission and Acquisition

HIV RNA in Semen

Mujugira and colleagues presented data on the presence of cell-free HIV RNA in semen samples of 231 African men newly initiating antiretroviral therapy (Abstract 164). Within the first 3 months after initiation of therapy, 24% of men continued to have detectable HIV RNA in semen, compared with 10% at 4 months to 6 months and 11% after 6 months. After full viral suppression in the blood was achieved, only 8% of men had detectable HIV RNA in their semen, with 82% of those having fewer than 1000 copies/mL. None of the men had sexually transmitted infections (STIs). In multivariable analysis, blood HIV RNA but not duration of antiretroviral therapy was a statistically significant independent predictor of seminal shedding.

Gowda and colleagues presented data on the risk of HIV transmission over time among 1833 HIV-infected persons enrolled in the University of Pennsylvania Center for AIDS Research Clinical Core Cohort Registry (Abstract 934). The investigators defined persons as being at risk of HIV transmission if their blood HIV RNA level was above 1500 copies/mL and if they reported engaging in sex without condoms. Overall, 9% of this cohort was at risk of HIV transmission over a median of 2 study visits. Risk factors for transmission included drug use, depression, younger age, and less than a high school education, identifying persons who may need additional support and prevention counseling.

Sexually Transmitted Infections

Sweat and colleagues reported on the risk of HIV acquisition after a diagnosis of primary or secondary syphilis in Shelby County, Tennessee (Abstract 929). Among 992 unique patients diagnosed with syphilis from 2005 to 2012, HIV incidence was 6.9 per 100 person-years. MSM had an incidence rate of 20.2 per 100 person-years and were 16 times more likely than heterosexual men and women to acquire HIV infection post-syphilis diagnosis in a multivariable model. This suggests that all individuals with a new syphilis diagnosis should be counseled about PrEP.

Several presentations focused on STI incidence among HIV-seropositive or -seronegative persons. Lachowsky and colleagues presented data on incidence rates for syphilis, *N gonorrhea*, and *Chlamydia trachomatis* infections among a cohort of MSM in Vancouver, Canada (Abstract 1007). Among 575 cohort participants, STI incidence was 17 per 100 person-years for HIV-seronegative MSM and 16 per 100 person-years for HIV-seropositive men. Compared with HIV-seronegative men, HIV-seropositive men were statistically significantly more likely to be diagnosed with syphilis (RR, 3.9; 95% CI, 2.0-7.8), but significantly less likely to be diagnosed with *N gonorrhea* or *C trachomatis* infection (RR, 0.6; 95% CI, 0.4-0.9). Goldberg Raifman and colleagues reported on case detection of *N gonorrhea* and *C trachomatis* in a multisite cohort of HIV-seropositive individuals in 7 US sites (Abstract 1005). The investigators found that in addition to increased screening in all risk groups from 2004 to 2015, case detection also increased in all groups. These studies support the need for regular STI screening for persons living with or at risk for HIV infection.

Two CDC presentations identified inadequate STI screening among HIV-seropositive persons in clinical care. Mattson and colleagues presented trend data on syphilis, *N gonorrhea*, and *C trachomatis* screening for HIV-infected men and women in the MMP, a national surveillance system that produces annual cross-sectional estimates of patients in care (Abstract 1004). The investigators found a significant increase in testing for all 3 STIs from 2009 to 2013 (20% to 36%; $P < .01$, for trend), but overall rates were substantially below the CDC recommendations of at least annual screening for all 3 STIs in HIV-infected persons. Patel and colleagues presented data on STI screening by anatomic site among MSM in the MMP from 2009 to 2012 (Abstract 1006). Of more than 6000 sexually active HIV-seropositive MSM, fewer than 1 in 3 were tested for *N gonorrhea* or *C trachomatis* at any site, and only 5% were tested for *N gonorrhea* or *C trachomatis* at extragenital locations. Positive results for *N gonorrhea* and *C trachomatis* were approximately twice as high in anorectal and pharyngeal sampling as in urine sampling.

Despite CDC recommendations for at least annual screening for STIs among people living with HIV infection, only 36% of HIV-infected individuals in care in the United States were screened for an STI in 2013, and only 5% of MSM were screened at extragenital sites.

Transmission Networks

Campbell and colleagues analyzed phylogenetic data from an outbreak of 181 cases of HIV infection among opioid users and their sex partners in Indiana (Abstract 215). From these analyses, the investigators were able to identify 3 separate clusters of transmission, with a solitary female bridge each between the central cluster and 1 other cluster. The researchers also identified how rapidly the outbreak spread during late 2014 and early 2015 and estimated that 50% of infections had already occurred before the first was diagnosed, 70% before a cluster was identified, and 85% before incident command was established to stop the epidemic. These data demonstrate the speed with which HIV can spread in networks of PWID, particularly among those who inject frequently and those who exchange sex for drugs.

Brenner and colleagues performed phylogenetic analysis of data from more than 4300 MSM newly diagnosed with HIV infection in Quebec, Canada, from 2002 to 2014 (Abstract 218). More recent infections belong to large clusters (10 or more linked transmissions) than in previous years: 29% of infections in 2002 to 2005, 34% in 2006 to 2009, and 46% in 2010 to 2014. Primary or early HIV infection was seen in

57% of large clusters but in only 26% of solitary transmission groups. This may be a result of rapid transmission of acute HIV infection, during which even a small increase in the average number of partners can substantially increase the interconnectedness of populations.

Ratmann and colleagues compared phylogenetic data from MSM diagnosed with HIV infection in the Netherlands from 2004 to 2007 with that from MSM diagnosed from 2008 to 2010 (Abstract 220). They found that men younger than 28 years contributed to a larger proportion of HIV transmissions and that most of these cases of transmission occurred when the young man was still undiagnosed. Although many of these transmissions occur between young men, young men were increasingly transmitting HIV to older men, pointing to the importance of early diagnosis and treatment of young MSM in this setting.

Green and colleagues demonstrated the importance of early partner services for newly HIV-infected persons (Abstract 224). Among 119 sexual partners of 574 persons with acute or early HIV infection, 33% were newly diagnosed with HIV infection and 24% had been previously diagnosed. Partners who were identified within 30 days of the index participant's HIV diagnosis were statistically significantly more likely to be newly diagnosed themselves, emphasizing the importance of early partner services for newly diagnosed persons, particularly those with acute or early HIV infection.

Wejnert and colleagues modeled HIV transmission from men to women in the United States (Abstract 1045). Based on data from 3 CDC surveillance databases, the investigators inferred that 33% of HIV transmissions to women come from MSM or from MSM who also inject drugs. Racial and ethnic disparities exist among these transmission estimates, with two-thirds of MSM-to-women transmissions occurring from black MSM and 20% from Latino MSM. These modeling data are estimates only but reinforce the urgent need to reach persons whose HIV infection has not been diagnosed or who have been inadequately treated for their infection, to address health disparities in both men and women.

HIV Testing

Because HIV testing is the first step in both prevention and treatment cascades, a number of abstracts at CROI 2016 focused on different strategies for increasing knowledge of HIV serostatus. Currently, several large community-based studies are underway to increase testing, linkage to care, and uptake of antiretroviral therapy.

Door-to-door, home-based HIV testing substantially increases awareness of HIV serostatus but also points to populations not adequately reached through these efforts. Shanaube and colleagues presented on the uptake of HIV testing in the HIV Prevention Trials Network (HPTN) 071 trial, also known as PopART (Population Effects of Antiretroviral Therapy to Reduce HIV Transmission), in Zambia (Abstract 981). Of the nearly 50,000 households visited by community HIV care practitioners, overall testing at the end of round 1 for those not known to be HIV-seropositive was 81% for women and 66% for men.

Casavant and colleagues presented data on home-based HIV testing in Mozambique (Abstract 975). Of more than 53,000 residents aged 15 years to 59 years, HIV prevalence overall was 20%, and 38% of these were new diagnoses. However, more women than men (52% vs 41%, respectively) were tested. Testing was also somewhat more common among older (age 25-59 years) than younger (age 15-24 years) residents and in rural than urban areas (50% and 45%, respectively, for each comparison).

A hybrid model of HIV testing, using community health campaigns (CHCs) followed by home-based testing for those not reached through CHCs, appears to achieve high coverage and to be cost-effective. Chamie and colleagues reported on the SEARCH (Sustainable East Africa Research in Community Health) study, a cluster randomized trial of HIV testing and treatment scale-up in 32 communities of 10,000 each in Kenya and Uganda (Abstract 979). From 2014 to 2015 (year 2), investigators repeated their hybrid HIV testing approach in the intervention communities and included additional services such as urgent care and men's health education in Kenya, and male circumcision, family planning, and cervical cancer screening in Uganda. Of the 77,778 community members who had lived in the community for at least 6 months in the previous year, 94% were tested at least once during the 2 rounds of testing, including 82% who received repeat testing. Half of the 11% of participants who were not tested in year 1 were tested in year 2, and 56% of those tested at home in year 1 participated in CHCs in year 2. This demonstrates the widespread appeal and broad coverage possible using this hybrid HIV testing model. An additional analysis reported by Zheng and colleagues found that of 4810 adults for whom there was detailed social network data, those with more dense local social networks were less likely to be tested for HIV infection through the hybrid approach (Abstract 985). This provides basis for strategies to augment the hybrid HIV testing model, to specifically target those who may be at greater risk but who do not take advantage of community-wide testing.

A hybrid model of HIV testing, using community health campaigns followed by home-based testing, achieved high coverage and was cost-effective.

Chang and colleagues estimated the cost of providing HIV testing through the basic hybrid model (Abstract 1062) and found that the cost per adult tested was $13.80 via CHC and $31.70 via home-based testing. Cost per HIV-seropositive adult identified varied based on HIV prevalence, with a range of $87 to $1245. Multidisease testing added little in marginal costs (eg, $1.16 per person for hypertension and diabetes screening, and $0.90 for malaria screening), suggesting that the benefit of multidisease services is quite cost-effective, particularly as it may reach some harder-to-reach

individuals than more traditional clinic or home-based testing models.

Partner notification for individuals newly diagnosed with HIV infection is one approach to identifying undiagnosed HIV-infected individuals, although care must be taken to prevent intimate partner violence that may result from disclosure of HIV serostatus. Cherutich reported on the effectiveness of partner notification services and the importance of early referrals in a cluster randomized study in Kenya (Abstract 50). Among 1305 partners of participants newly diagnosed with HIV infection enrolled in this study, immediate partner notification was more successful than delayed notification (3 months) by a substantial margin (71% vs 15%, respectively); immediate partner services also detected more HIV-seropositive partners (25% vs 5%, respectively) and was more successful at initiating care for HIV-seropositive individuals (16% vs 3%, respectively). Two new cases of intimate partner violence were reported and may have been study related.

Plotkin and colleagues reported on a feasibility study of partner notification services in Tanzania (Abstract 978). Three hundred ninety newly diagnosed, HIV-infected men and women were enrolled in the study from June 2015 to September 2015 at 3 hospitals in the region with the highest HIV prevalence in Tanzania; 3 potential index participants were excluded because of the risk of intimate partner violence. Most index participants chose to refer their sexual partners for HIV testing themselves (93%) rather than through their practitioner, and 57% of named partners presented for HIV testing. Of these partners, 62% were found to be HIV-seropositive and 63% of these were successfully enrolled in care. Most successful referrals (61%) occurred within 2 days, although an additional 19% were referred within 2 weeks. These studies suggest that immediate partner services may be most effective and will uncover both seroconcordant and serodiscordant partnerships. Active outreach to sexual partners may be most successful, although these studies did not conduct direct comparisons.

Several studies highlighted missed opportunities for earlier detection of HIV infection. Weissman and colleagues found that of more than 7000 persons diagnosed with HIV infection from 2006 to 2015 in South Carolina, 38% were late testers (ie, developed AIDS within 1 year of HIV diagnosis) (Abstract 965). The proportion of late testers declined from 41% of HIV diagnoses in 2006 to 2010 to 34% of diagnoses in 2011 to 2015 ($P < .0001$). Overall, 73% of late testers had had a health care visit in the 3 years before their HIV diagnosis, although 80% of these visits were in emergency departments. More than 2200 of those with a late diagnosis had been admitted to a hospital in the 3 years before their HIV diagnosis, suggesting that all hospitalized patients should be screened for HIV infection.

Hood and colleagues reported on uptake and perceptions of HIV testing and self-testing among 98 transgender women, 66 transgender men, and 956 MSM recruited during the Seattle Pride Parade in 2014 and 2015 (Abstract 971). Compared with MSM, transgender women and men were more likely to have an unknown HIV serostatus (4% vs 12% and 10%, respectively) and less likely to have undergone at least annual HIV testing in the past 2 years (58% vs 26% and 18%, respectively). Although 19% of MSM had ever used an HIV self-test, only 6% of transgender women and 3% of transgender men had ever used an HIV self-test. Additional strategies are needed to ensure high rates of HIV testing, particularly among transgender women.

Mugo and colleagues evaluated potential testing algorithms for persons with negative results on rapid HIV antibody tests but nonspecific symptoms consistent with acute HIV infection (Abstract 977). Investigators randomly assigned 410 participants to the standard of care (scheduling an appointment for the participant in 2-4 weeks) or an enhanced appointment intervention (utilizing Short Message Service [SMS], telephone, or in-person reminders to encourage participants to return for testing in 2-4 weeks). In multivariable analysis, investigators found that those randomly assigned to the enhanced intervention were twice as likely to return for testing as those given standard referrals for follow-up. Persons older than 25 years were 2.5 times more likely to return, regardless of treatment assignment, than younger adults.

Reaching Heterosexual Men

Ayles spoke about the importance of addressing men's needs when addressing the global HIV epidemic (Abstract 120). Data from the US Agency for International Development (USAID) Demographic and Health Surveys (DHS) program in 2013 documented that in many African countries, men are substantially less likely than women to have been tested for HIV infection. Although this is contributed to by perinatal testing and more frequent visits to clinics by women, many barriers exist for HIV testing of men, including the hours and environment in which testing is provided and the stigma that arises when HIV testing is the sole focus. The SEARCH study offers testing for numerous diseases (eg, diabetes, hypertension, malaria, tuberculosis) and separate spaces for men to be tested, resulting in testing of 90% of men. Home-based testing must be done during weekends and evenings to reach more men. Ayles showed data from the PopART study demonstrating that investigators were able to reach 56% more men aged 25 years to 34 years and 39% more men aged 35 years to 44 years when screening was conducted on Saturdays. Changing from a 9:00 AM to 5:00 PM schedule to an 11:00 AM to 7:00 PM schedule during weekdays increased screening among men aged 25 years to 34 years by 16%, and among men aged 35 years to 44 years by 29%. Ayles emphasized the need to care for men for their own health and not solely for their potential to transmit HIV to women.

Men in sub-Saharan Africa are less likely to know their HIV serostatus than women, but a hybrid model of broad community health campaigns followed by home-based testing resulted in a successful HIV testing rate of 90% in men.

In her oral presentation, Farquhar pointed out that testing of male sexual partners is important regardless of the HIV serostatus of pregnant women (Abstract 49). In addition to the benefit for the male partner, HIV-seronegative women are at substantially increased risk for HIV acquisition during pregnancy and breastfeeding, and HIV-seropositive women are more likely to accept prevention of mother-to-child transmission (PMTCT) measures if their male partners are tested for HIV infection and involved in care. Farquhar and her colleagues presented data from a randomized controlled trial of home-based partner education and HIV testing versus clinic invitation to male partners for uptake of testing, disclosure of HIV serostatus, couples testing, and identification of HIV-discordant couples. Of 601 women enrolled in the trial, 487 male partners had follow-up data available through 6 months postpartum, with approximately equal follow-up in the 2 arms. Overall, 87% of the male partners in the home-based testing arm were tested for HIV infection, compared with 39% in the arm that received clinic invitations. Among those who received home-based testing, women were more likely to be aware of their male partner's HIV serostatus (RR, 2.3; 95% CI, 1.9-2.7), to have been tested as a couple (RR, 3.2; 95% CI, 2.5-4.0), and to be identified as being part of a serodiscordant couple (RR, 3.4; 95% CI, 1.7-6.7). Although women at high risk for intimate partner violence were excluded from enrollment in the trial, 3% of women visiting at 6 weeks reported intimate partner violence; this was not considered by participants or staff to be related to study participation.

Preexposure Prophylaxis

Novel PrEP Formulations and Agents

Discussion of PrEP featured prominently at CROI 2016, which included a number of presentations on sustained delivery formulations of PrEP and novel PrEP agents. Two phase III studies reported efficacy results of a monthly vaginal ring containing the investigational NNRTI dapivirine for HIV prevention among women in Africa. Baeten and colleagues presented data from the ASPIRE (A Study to Prevent Infection With a Ring for Extended Use) study among 2629 women at risk for HIV acquisition in Malawi, South Africa, Uganda, and Zimbabwe (Abstract 109LB). Participants were randomly assigned to receive either a vaginal ring containing dapivirine 25 mg or a placebo ring, with a median of 1.6 years of follow-up. Enrolled women were young, less than half were married, and nearly half reported that they did not use a condom during their last sex act. Adherence was measured by concentrations of dapivirine in plasma and residually in returned rings. Overall, 82% of plasma samples had detectable dapivirine levels, at concentrations above 95 pg/mL, indicating at least 8 hours of continuous use, and 84% of returned rings had levels consistent with some use during the past month. There were 71 new HIV infections among those assigned the dapivirine vaginal ring (HIV incidence, 3.3/100 person-years), and 97 incident HIV infections among those assigned the placebo ring (HIV incidence, 4.5/100 person-years), resulting in a 27% (95% CI, 1%-46%; $P = .046$) RR reduction in HIV incidence. After excluding data from 2 sites with lower adherence in a predefined analysis, efficacy increased to 37% (95% CI, 12%-56%; $P = .007$).

Two phase III trials have demonstrated the efficacy and safety of the monthly dapivirine vaginal ring in preventing HIV infection among women in Africa.

In a post hoc analysis among women older than 21 years, efficacy increased to 56% (95% CI, 31%-71%; $P < .001$). HIV protection was not observed for women aged 18 years to 21 years, and adherence was lower among these women. The dapivirine vaginal ring was found to be safe, with adverse events well balanced between the study arms. Among women who seroconverted, detection of NNRTI resistance–associated mutations did not differ between the dapivirine and placebo arms (11.8% and 10.4%, respectively; $P = .80$).

In the same session, Nel and colleagues reported results from a sister trial, the RING study, conducted among 1959 women in South Africa and Uganda (Abstract 110LB). Participants were randomly assigned (2:1) to receive a dapivirine vaginal ring or a placebo ring over a 2-year period. Adherence was measured by concentrations of dapivirine in plasma and residual drug levels in used rings, similar to the ASPIRE trial. Overall, more than 83% of plasma samples and used rings indicated adherence. HIV incidence was higher than anticipated in the trial, and based on recommendations from an independent data and safety monitoring board, the final analyses were performed before the planned completion of the study. Enrolled women were young, and 89% were unmarried. There were 77 incident HIV infections among women who received the dapivirine ring (HIV incidence, 4.1/100 person-years) and 56 new HIV infections among women who received a placebo ring (HIV incidence, 6.1/100 person-years), resulting in a 31% (95% CI, 0.90%-51.5%; $P = .04$) reduction in the risk of HIV acquisition compared with placebo.

In a subgroup analysis of women older than 21 years, HIV protection increased to 37% (95% CI, 3%-59%), although efficacy was only 15% (-60% to 55%) among women aged 21 years or younger. Notably, HIV incidence was extremely high in this younger age group, with an HIV seroconversion rate of 8.2 per 100 person-years in the placebo arm. Furthermore, efficacy increased with lower residual levels of dapivirine in used rings (indicating increasing adherence), with 65% protection among women whose rings had residual levels of dapivirine of 20 mg or lower. These results strongly support higher levels of protection with increased ring use. Similar to the ASPIRE study, the dapivirine vaginal ring was found to be safe and well tolerated in the RING study, with similar rates of adverse events and drug resistance among those who seroconverted across study arms.

Chen and colleagues presented data on the safety and pharmacokinetics of the dapivirine vaginal ring for post-

menopausal women in the Microbicide Trials Network (MTN)-024/International Partnership for Microbicides (IPM) 031 study (Abstract 872). Women older than 50 years account for 12% of new HIV infections among US women, and postmenopausal women may be at higher risk for HIV infection owing to increased expression of CC chemokine receptor 5 (CCR5), decreased HIV-1 innate activity, low condom use, and low perceived risk. In this phase IIa study, participants were randomly assigned to monthly vaginal rings containing dapivirine 25 mg or placebo for 12 weeks. The mean age of the cohort was 57 years, with a mean age at menopause of 50 years. There were no differences in adverse events across the study arms, and only 2 women in the dapivirine arm chose to discontinue the vaginal ring because of adverse events. Levels of dapivirine in plasma were similar to those seen in women of reproductive age.

van der Straten and colleagues presented data on the acceptability and adherence of the dapivirine vaginal ring in the same cohort (Abstract 873). Overall, 99% reported that the ring was "very easy or easy to use," and 65% of women preferred the ring to condoms; 74% of participants reported that the ring was never out of the vagina, and 91% reported that the ring was never out of the vagina for more than 12 hours. Concerns about the ring (eg, discomfort during normal daily activities or the ring not staying correctly in place) decreased statistically significantly from baseline to month 3.

Adherence to the dapivirine vaginal ring was associated with higher levels of HIV protection.

In a symposium on innovations in PrEP, McGowan highlighted some of the potential promises and challenges of long-acting formulations of PrEP (Abstract 71). Long-acting formulations of medications have been used to improve adherence and address treatment fatigue across a range of fields, including contraception (eg, medroxyprogesterone) and psychiatry (eg, agents used to treat schizophrenia). Qualitative data on MSM indicate a hypothetical willingness to use long-acting PrEP agents and a preference for injections rather than a daily oral pill, and data on women in the VOICE (Vaginal and Oral Interventions to Control the Epidemic) trial indicate a preference for injectable, implantable, or ring-based prevention methods. Ideal attributes of a long-acting injectable drug include infrequent dosing interval (eg, 2-3 months), practical injection volume (eg, approximately 4 mL), and stable formulation without cold chain requirements. Potential challenges with long-acting injectable drugs include the long pharmacologic tail and the possibility of adverse events that would be difficult to manage given prolonged drug exposure. Additionally, HIV infection during periods of declining, subtherapeutic drug levels could result in the emergence of drug resistance, as was observed in 1 participant who received rilpivirine 300 mg, subsequently seroconverted, and in whom NNRTI resistance emerged. These issues have led to operational complexity in trial design for upcoming trials, which will involve a 1-month oral run-in phase to establish tolerability before initiation of injections and a 12-month period of oral PrEP after the last injection, to cover the pharmacologic tail.

Two drugs under investigation in long-acting injectable formulations are the NNRTI rilpivirine and the investigational integrase strand transfer inhibitor (InSTI) cabotegravir. Two phase I dose-escalation trials of rilpivirine were recently completed. Drug levels in rectal tissue were higher than those in vaginal tissue, and in explant challenge studies, HIV suppression was observed for rectal tissue but not for cervical or vaginal tissue. These findings were further explored in in vitro and explant studies conducted by Dezzutti and colleagues (Abstract 874). Rilpivirine penetrated colonic tissue more so than ectocervical tissue by more than 10-fold in vitro. Although concentrations achieved in rectal tissue were 5-fold higher than those needed to suppress viral infection in tissue explant studies, levels in cervical and vaginal tissue were 2.5-fold lower than suppressive levels. Based on these findings and additional issues of potential resistance and cold chain requirements, McGowan stated that it was unlikely that rilpivirine would advance into phase III trials for HIV prevention, although the drug is still being developed for HIV treatment.

Several researchers presented promising data on a long-acting, injectable formulation of cabotegravir at CROI 2016. Andrews and colleagues presented data on the effectiveness of PrEP with long-acting cabotegravir in an intravenous challenge model in rhesus macaques (Abstract 105). Two doses of long-acting cabotegravir 50 mg/kg given before and after intravenous challenge resulted in 7 of 8 animals being protected from simian immunodeficiency virus (SIV) infection through week 24, and 8 of 8 macaques were protected after a single dose given prior to injection. Further, 6 of 8 macaques given one dose of long-acting cabotegravir 25 mg/kg followed by one dose of long-acting cabotegravir 50 mg/kg were protected through week 24. Overall, long-acting cabotegravir provided 88% protection (21/24 macaques) against intravenous challenge, with lower concentrations of cabotegravir in plasma at the time of challenge among SIV-infected macaques than among those that remained uninfected. Investigators concluded that these results support the evaluation of long-acting cabotegravir as PrEP in PWID.

In the same session, Markowitz and colleagues presented data on the safety and pharmacokinetics of long-acting cabotegravir among 127 uninfected men at low risk for HIV acquisition in the ÉCLAIR study (Study to Evaluate the Safety, Tolerability, and Acceptability of Long-Acting Injections of the HIV Integrase Inhibitor GSK1265744 in HIV Uninfected Men) (Abstract 106). Participants were randomly assigned to receive cabotegravir or a placebo (5:1) in a 4-week oral phase, and following a safety assessment, eligible participants received 3 intramuscular injections of long-acting cabotegravir 800 mg or saline placebo at 12-week intervals. Eleven participants discontinued during the oral phase, 7 because of adverse events (mostly laboratory abnormalities). Long-acting cabotegravir was generally well tolerated; 7 participants discontinued during the injection phase, 4 because of injection site

reactions. Overall, 92% of participants who received long-acting cabotegravir experienced injection site pain, compared with 27% of those who received a placebo: approximately 50% were mild, 40% were moderate, and 10% were severe in grade, with injection site reactions lasting an average of approximately 5.4 days (compared with 2 days in the placebo arm). Pharmacokinetic data showed that peak levels of drug were higher and trough levels were lower than expected, such that 70% of participants had trough levels less than 4 times the protein-adjusted 90% inhibitory concentration, a level affording 100% protection in a macaque rectal challenge model. These findings likely reflect faster absorption from the depot injection site. Based on these results, an alternative dosing strategy of 600 mg every 8 weeks is being investigated in current studies of long-acting cabotegravir. Participant satisfaction with long-acting cabotegravir injections was high, with most participants favoring continuing injections of long-acting cabotegravir rather than taking oral cabotegravir.

Cabotegravir, a long-acting injectable PrEP agent, was well tolerated among HIV-uninfected men, and future efficacy trials are being planned.

Gulick and colleagues presented results from the HPTN 069/AIDS Clinical Trials Group (ACTG) 5305 study conducted among 406 MSM in the United States (Abstract 103). This phase II study evaluated the safety and tolerability of PrEP regimens containing maraviroc, a CCR5 antagonist that concentrates in the genital tract and is not commonly used for HIV treatment. HIV-uninfected MSM were randomly assigned to receive 1 of 4 treatments: maraviroc alone, maraviroc and emtricitabine, maraviroc and TDF, or TDF and emtricitabine, for 48 weeks. The rates of adverse events and study drug discontinuation did not differ among study arms. Study drugs were detectable in plasma in approximately 80% of participants at weeks 24 and 48. In a pharmacologic substudy among 72 participants, there were no significant drug interactions observed between maraviroc and TDF or emtricitabine. Overall, 5 participants seroconverted during the trial, all with R5 virus and no evidence of drug resistance; 1 seroconversion occurred in the maraviroc and TDF arm and the others occurred in the arm that received maraviroc alone. Two participants had undetectable drug levels at every study visit, and the other 3 had low or variable drug concentrations around the time of seroconversion. The investigators concluded that the maraviroc-based regimens were comparably safe and well tolerated to TDF and emtricitabine when used as HIV PrEP.

McGowan and colleagues presented data from a tissue substudy among 60 men enrolled in the HPTN 069/ACTG 5305 study (Abstract 104). Although in prior studies maraviroc was associated with increased gut-associated lymphoid tissue (GALT) T-cell activation and CCR5 expression in HIV-infected individuals, this study demonstrated no statistically significant changes in CD4+ T-cell activation or in CCR5 phenotype in any study arm. In colorectal explant HIV challenge studies, viral suppression was observed in samples from the 3 arms that received combination therapy through week 48, but viral suppression was not observed at week 24 or 48 in the arm that received maraviroc alone. McGowan noted that pharmacokinetic data on adherence are pending and also that previous studies have shown loss of maraviroc from explant tissue in culture, which could explain these findings.

Cranston and colleagues presented data from the MTN-017 study, the first phase II study evaluating the safety and acceptability of a rectal microbicide (Abstract 108LB). In this crossover design study, 195 MSM and transgender women were randomly assigned to different sequences of 3 study regimens, each taken for an 8-week period: reduced-glycerin 1% tenofovir gel daily, reduced-glycerin 1% tenofovir gel used before and after receptive anal intercourse, and daily oral TDF and emtricitabine. Rates of grade 2 or higher adverse events did not differ across study arms. Overall acceptability of the 3 regimens was high, with highest acceptability for the oral regimen: 90% acceptability in the arm assigned to oral TDF and emtricitabine, 80% acceptability in the arm assigned to gel used before and after receptive anal intercourse, and 70% acceptability in the arm assigned to daily gel use. There was a trend toward lower ease of use ($P = .08$) and lower intention to use product in the future ($P < .001$) for the daily gel compared with the oral regimen. Ease of use and future intention to use did not differ between the group that used gel before and after receptive anal intercourse and the group that used the oral regimen. Overall adherence to study product was high in all arms (>80%), as measured by drug detection in plasma, SMS diary, and product returns, but was lower in the daily gel arm than in the oral arm (OR, 0.35; 95% CI, 0.19-0.63; $P < .001$). The investigators concluded that rectal 1% tenofovir gel was safe when used daily or before and after receptive anal intercourse in this population and that use of gel in the latter instance was more acceptable. These results support further evaluation of reduced-glycerin 1% tenofovir gel for HIV prevention in men and women.

Given the low acceptability of applicators used to administer gel in rectal microbicide studies, Shieh and colleagues evaluated the rectal distribution of gels when applied as sexual lubricants compared with an applicator (Abstract 169bLB). Five HIV-seronegative MSM were administered 3.5 mL or 10 mL of ^{99}mTc-DTPA-radiolabeled hydroxyethyl cellulose (HEC) gel intrarectally using an applicator. After a washout period, the same participants were asked to self-administer radiolabeled wet gel lubricant to the anus manually, followed by simulated receptive anal intercourse with a phallic device. Single-photon emission computed tomography was performed 4 hours after each administration to measure gel distribution in the colon. The manual application method resulted in more variable distribution, compared with a more uniform distribution with an applicator. Further, only 3% of the initial dose was retained in the colon with manual application, compared with 88% and 95% of gel retained when an applicator was used for 3.5 mL and 10 mL, respectively. Additionally, manual application delivered 32-fold less volume of gel. These results suggest that manual application of a rectal microbicide gel may not

provide adequate drug concentrations or mucosal coverage for HIV protection, and application of gel as a lubricant may require distinct formulations to achieve higher antiretroviral loading.

Fast-dissolving vaginal films may provide more efficient vaginal drug delivery than gels, because they dissolve directly into vaginal fluid and are low cost. Bunge and colleagues presented data on the safety, pharmacokinetics, and pharmacodynamics of film and gel formulations of tenofovir (Abstract 871). In this study, 78 women were randomly assigned to receive 1 of 5 treatments: tenofovir 10 mg film, tenofovir 40 mg film, placebo film, 1% tenofovir gel, or HEC placebo gel. There were no differences in urogenital complaints across groups, and film users were less likely to report discomfort after insertion ($P = .02$) and product leakage ($P < .001$) than gel users. Median levels of tenofovir in plasma and genital tissue were comparable in the arms that received tenofovir 40 mg film and 1% tenofovir gel. In an ex vivo challenge model using cervical tissue, higher concentrations of tenofovir diphosphate correlated with lower HIV replication.

Fast-dissolving films may provide more efficient vaginal drug delivery than gels, because they dissolve directly into vaginal fluid and are low cost.

Tenofovir alafenamide (TAF) is an oral prodrug of tenofovir that achieves 90% lower plasma tenofovir exposure and is associated with fewer renal and bone toxic effects; however, its efficacy as a PrEP agent for HIV prevention is unknown. Garcia-Lerma presented data on the pharmacokinetics and efficacy of TAF and emtricitabine in preventing simian-human immunodeficiency virus (SHIV) infection in a repeat low-dose challenge model in macaques (Abstract 107). In a single-dose pharmacokinetic study, TAF 1.5 mg/kg achieved levels of tenofovir diphosphate in peripheral blood mononuclear cells (PBMCs) similar to those observed in human exposure; however, levels of tenofovir in plasma and of tenofovir diphosphate in rectal tissue were lower than those seen with TDF. In a repeated challenge model, 6 animals received TAF 1.5 mg/kg and emtricitabine 20 mg/kg orally 24 hours before and 2 hours after each virus challenge, and 6 received a saline placebo. All 6 macaques that received TAF and emtricitabine remained uninfected after 19 virus challenges, and all 6 that received a placebo became infected. Intracellular levels of tenofovir diphosphate and emtricitabine triphosphate achieved in PBMCs were high and accumulated approximately 2.5 fold and 1.5 fold, respectively, after 7 weeks to 14 weeks of dosing. These results support the development of PrEP with TAF and emtricitabine as an alternative to TDF and emtricitabine to prevent against rectal HIV infection.

Garrett and colleagues presented pharmacokinetic data on the genital and rectal tissue of women after a single dose of TAF (Abstract 102LB). Eight HIV-uninfected women were given a single dose of TAF 25 mg and had pharmacokinetic measurements taken over 14 days. In the first 48 hours, tenofovir exposure in plasma was 19-fold lower with TAF than with TDF, and tenofovir diphosphate exposure in PBMCs was 9-fold higher with TAF than with TDF, a finding consistent with prior studies. In mucosal tissues, tenofovir exposure was 2- to 10-fold lower with TAF than TDF, and tenofovir diphosphate exposure was 13-fold lower in rectal tissue and 1.3-fold lower in the female genital tract. Further, tenofovir diphosphate levels were below the limit of detection in 63% of rectal and 75% of genital tract samples from women who received TAF, compared with 0% and 25%, respectively, of samples from women who received TDF. These findings highlight the need for additional investigations on the pharmacology of TAF in mucosal tissues. Whether emtricitabine may be contributing to the protection observed with TAF and emtricitabine in the macaque challenge study (Abstract 107) merits further investigation.

Johnson reported results of early preclinical development studies of a long-acting, biodegradable, subcutaneous implant of TAF for HIV PrEP (Abstract 879). The research team developed a thin-film polymer device with a polycaprolactone membrane that controls drug release from a reservoir. In vitro prototype devices demonstrated linear release over 3 months, and release rates were tunable to estimated target ranges by changing device surface area and membrane thickness. TAF remained chemically stable in the device reservoir for at least 89 days, and ambient shipping and sterilization did not impact device performance. In vivo studies of this device are being planned.

Likely Breakthrough Infection on PrEP

Knox and colleagues presented a case report of HIV infection with multiclass HIV resistance in an individual taking PrEP (Abstract 169aLB). This individual, a 43-year-old man who has sex with men, seroconverted to HIV-1 after 24 months of successful PrEP, despite data suggesting long-term adherence to PrEP with TDF and emtricitabine. Pharmacy dispensing records showed consistent prescription refills, and levels of tenofovir diphosphate in dried blood spots tested 24 days after HIV infection was detected indicated consistent PrEP dosing in the preceding 1 month to 2 months. Further, tenofovir was detected in plasma on the day HIV infection was first detected, before the patient was aware of his HIV serostatus. Standard population and deep sequencing were performed on day 7 after HIV infection and demonstrated mutations conferring resistance to nucleoside analogue reverse transcriptase inhibitors (41L, 67G, 69D, 70R, 184V, 215E), NNRTIs (181C), and InSTIs (51Y, 92Q), suggesting transmitted rather than acquired drug resistance. Phenotypic drug resistance testing showed decreased susceptibility to all InSTIs

A likely breakthrough infection on PrEP occurred in an individual who reported high levels of adherence to PrEP and became infected with multiclass-resistant HIV while taking PrEP.

and mild reduced response to tenofovir (1.3×). Phylogenetic analyses revealed a very narrow range of sequence diversity, suggesting infection from a single source. Ritonavir-boosted darunavir and raltegravir were added to the individual's regimen on day 9 after detected HIV infection, and he achieved viral suppression by day 21. Subsequently, his antiretroviral regimen was optimized to dolutegravir, cobicistat-boosted darunavir, and rilpivirine, and his viral load has remained undetectable to date.

Bone and Renal Safety of PrEP

Oral PrEP containing TDF and emtricitabine has been associated with small decreases in bone mineral density (BMD). Grant and colleagues evaluated the recovery of BMD after PrEP was discontinued among MSM and transgender women enrolled in the iPrEx trial (Abstract 48LB). Among 498 participants enrolled in a dual-energy X-ray absorptiometry (DXA) substudy, decreases in BMD were observed during the first 24 weeks of PrEP use in those who had tenofovir diphosphate levels in PBMCs associated with a 90% reduction in HIV risk (16 femtomole/million cells). After PrEP was discontinued, average BMD recovered completely within 6 months in the spine and by the start of the iPrEx OLE (iPrEx Open Label Extension) study in the hip (a median of 1.5 years after PrEP was discontinued). There was a full recovery in BMD among younger (<25 years) and older individuals, and after adjustment for differences in study retention.

Several investigators reported on the renal safety of tenofovir-based PrEP in a themed discussion (Session TD-12). Gandhi and colleagues evaluated the relationship between cumulative levels of tenofovir and emtricitabine and declines in renal function in the iPrEx OLE study (Abstract 866). Among 1225 participants receiving PrEP, estimated glomerular filtration rate (eGFR) decreased modestly (2.5%) over 18 months. There was a monotonic relationship between percent decrease in eGFR and increasing quartile of tenofovir level in hair ($P = .008$), and the odds of eGFR falling below 70 mL/min (observed at 6% of person-visits) increased with increasing quartile of tenofovir concentration (OR, 4.4; 95% CI, 1.1-17.4) for fourth tenofovir hair quartile ($P = .045$, for trend); this event was more common in those with a baseline eGFR below 90 mL/min or those older than 40 years.

Liu and colleagues reported on changes in renal function in the US PrEP Demonstration Project (Abstract 867). Among 557 MSM and transgender women who received PrEP in STI clinics or a community health center, mean eGFR declined by 2.8% from baseline to week 12 ($P < .005$) and remained stable through week 48 ($P = .91$). Only 3 participants had TDF and emtricitabine stopped for elevated creatinine (>1.5× baseline per protocol); however, these elevations were not confirmed on repeat testing, and PrEP was restarted in all cases without further interruptions. Having levels of tenofovir diphosphate in dried blood spots consistent with taking 4 or more doses per week (≥700 femtomoles/punch) was associated with a statistically significant mean decline in eGFR of 4% at week 12 ($P = .01$). Similar to results seen in iPrEx OLE, a baseline eGFR below 90 mL/min and age older than 45 years were associated with eGFR falling below 70 mL/min. Together, these results support the safety of TDF and emtricitabine as PrEP and suggest that individuals with low baseline eGFRs and older individuals may warrant additional monitoring.

Mugwanya and colleagues assessed the frequency of proximal tubular dysfunction among HIV-uninfected African men and women in the Partners PrEP study (Abstract 868). In a subset of 1549 participants who received randomized treatment with TDF and emtricitabine or a placebo for at least 24 months and had urine and serum samples obtained, proximal tubulopathy (defined as having ≥2 of the following markers: tubular proteinuria, normoglycemic glycosuria, increased urinary phosphate, or increased uric acid excretion) was rare, occurring in 1.7% of participants who received TDF and emtricitabine and 1.3% of those who received a placebo ($P = .68$). Isolated tubular proteinuria and increased urinary excretion of uric acid occurred more frequently in those who received TDF and emtricitabine ($P < .01$, for each). In a case-control analysis, no association was observed between proximal tubulopathy and clinically relevant decline in eGFR (defined as a ≥25% decline in eGFR from baseline) ($P > .99$). The investigators concluded that monitoring urine markers of proximal tubular dysfunction is not an efficient approach to identify cases of tubulopathy, and suggested that creatinine clearance monitoring is sufficient for safety monitoring of kidney function in uninfected persons taking tenofovir-based PrEP.

PrEP and Sexually Transmitted Infections

In a symposium presentation, McCormack reported on trends in STIs in Europe, where PrEP has not yet been implemented (Abstract 69). Rates of *N gonorrhea* infection among MSM have increased sharply between 2008 and 2013, and rates of syphilis infection showed a similar trend during this period, all before the introduction of PrEP. Populations disproportionately affected by STIs in the United Kingdom include young women and men, black and mixed-race individuals, and MSM. McCormack highlighted 3 pillars of STI control: test, treat, and trace. Treatments for bacterial STIs have improved, although resistance to commonly used antibiotics is increasing. Important principles of treatment include having a short time from diagnosis to treatment (same day is ideal) and advising that sex be forestalled until treatment is completed or a test of cure is performed. For tracing infections, partner notification can be self-initiated or practitioner initiated. This strategy is usually preferred for regular sexual partners but can be difficult with anonymous sexual partners; however, internet and peer-facilitated notification may overcome some of these challenges.

Three pillars of STI control are testing, treatment, and tracing.

PrEP studies in Europe have been able to engage MSM at elevated risk for STI and HIV acquisition. In the PROUD PrEP

study among MSM who received PrEP in STI clinics in the United Kingdom,[11] 26% were diagnosed with rectal *N gonorrhea* infection and 21% were diagnosed with rectal *C trachomatis* infection in the year prior to enrollment (baseline STI rates were similarly high in the IPERGAY study[12]). In PROUD, the median number of anal sex partners at baseline was 10, and at 12 months of follow-up, participants that received immediate PrEP reported engaging in receptive anal sex without a condom with a greater number of partners than those that received deferred PrEP (P = .04). STI rates did not differ between the immediate and deferred arms during this initial period. However, there was a substantial increase in STIs in both arms in the second year of PrEP delivery, which may reflect temporal trends of increasing STIs. Despite high rates of STIs in PROUD and high HIV incidence in the deferred arm (9.0/100 person-years), PrEP was highly effective, resulting in an 86% reduction in HIV infections, with a low number needed to treat of 13. Since PROUD was completed, there have been more than 600 new HIV infections across the STI clinics, and more than half have been diagnosed in clinics in which PrEP could have been offered, highlighting important missed opportunities and the need for PrEP in this population.

Although the CDC recommends STI screening for MSM at least every 6 months, the optimal frequency of STI screening among MSM who are taking PrEP is unclear. Golub and colleagues presented data on STI diagnoses that would have been missed if participants had not received routine screening every 3 months in SPARK, a community-based PrEP demonstration project in New York City (Abstract 869). Among 280 participants who began PrEP, 21% were diagnosed with an STI in the 6 months before starting PrEP, and 43% were diagnosed with an STI after starting PrEP. Seventy-seven percent of STIs diagnosed at 3 months and 68% of STIs diagnosed at 9 months were diagnosed as a result of routine screening rather than symptomatic presentation. Rectal STIs, which are less likely to be symptomatic, were observed in 71% to100% of individuals with STIs at each visit. Among those with STIs, the proportion of individuals with repeat STI diagnoses increased steadily over time (33% at month 3, 77% at month 12).

Similarly, Cohen and colleagues reported data on potentially missed STI diagnoses among 557 MSM and transgender women enrolled in the US PrEP Demonstration Project (Abstract 870). A substantial proportion of gonorrhea (34%), chlamydia (40%), and syphilis (20%) infections would have been missed if screening had been conducted every 6 months instead of every 3 months as conducted in the study. Further, 83% of *N gonorrhea* and 76% of *C trachomatis* infections would have been missed without extragenital screening. Among visits in which at least 1 asymptomatic STI was diagnosed, 89% of individuals reported anal sex without a condom at the subsequent visit, with a median of 3 anal sex partners during this interval, suggesting substantial STI transmission potential among participants with asymptomatic STIs who are taking PrEP. Results from these 2 studies provide support for quarterly STI screening, including extragenital screening, among MSM taking PrEP.

Testing in Trials of PrEP

Several researchers reported data on the performance of different HIV testing algorithms in clinical trials of PrEP. Parikh presented data on the detection of acute HIV infection using fourth-generation combination antigen/antibody rapid tests in the VOICE trial, a large study of the safety and effectiveness of tenofovir-based products for HIV prevention among 5029 African women (Abstract 521). Among 229 presero-

Fourth-generation antigen/antibody HIV tests were more sensitive in detecting acute HIV infection in the setting of PrEP trials.

conversion samples tested for HIV-1 RNA, 68 had detectable HIV-1 RNA, of which 57 had a negative result by a third-generation rapid test. Among these 57 infections, a fourth-generation antigen/antibody enzyme-linked immunosorbent assay detected 33% more early infections than a third-generation HIV 1/2-O antibody-only enzyme immunoassay (EIA) (27 vs 8 infections detected, respectively). A Conformité Européene (CE)-marked fourth-generation rapid test detected 28% of infections missed by third-generation rapid testing, and the CE-marked test detected 21% more early infections than a US Food and Drug Administration (FDA)-approved HIV-1/2 combination antigen/antibody test (P = .0005). In contrast, HIV-1/2 antibody differentiation immunoassays and Western blot testing were insensitive (< 10%) in confirming acute HIV infections detected by fourth-generation testing. The investigators concluded that fourth-generation rapid testing with HIV RNA testing will be important for earlier detection of acute HIV infection in trials of PrEP.

Delaugerre and colleagues presented data on the usefulness of rapid tests for HIV diagnosis in the Agence Nationale de Recherche sur le Sida (ANRS) IPERGAY trial of PrEP (Abstract 522). Overall, 31 participants were diagnosed with HIV infection during the study. Nine were diagnosed at a preinclusion visit, 5 were diagnosed between preinclusion and initiation of PrEP, and 17 were diagnosed after initiating PrEP. Among 28 patients with stored sera samples, results of a fourth-generation combination antigen/antibody test were positive in 26 (93%) cases but missed 2 patients during acute HIV infection who had low HIV RNA levels (110 copies/mL and 450 copies/mL, respectively), compared with results of a rapid antibody test that were positive in only 15 (54%) cases. Western blot antibody titer and timing of diagnosis were used to determine stage of infection. The sensitivity of the rapid test was 100% for chronic infection, 78% for recent infection, and only 15% for acute infection (P < .002). These results support the use of fourth-generation assays to detect acute HIV infection early and to minimize the risk of selecting for drug resistance among individuals taking PrEP.

Bacon and colleagues reported on the performance of rapid EIA, fourth-generation antigen/antibody assay, and HIV-1 RNA testing in the US PrEP Demonstration Project (Abstract 524). Among 635 MSM and transgender women screened for the

study, 18 infections were detected at screening or initiation of PrEP, and 2 were detected during study follow-up. Although most HIV infections were detected using rapid EIA (14/15) and lab-based fourth-generation testing (13/13) at screening, acute infection was detected in 3 participants at initiation of PrEP using HIV-1 RNA testing only (120 copies/mL, 3343 copies/mL, and 51 copies/mL, respectively), and all 3 individuals had negative results on HIV rapid EIA and fourth-generation testing. Two participants became HIV infected during study follow-up; both had positive results on rapid EIA and fourth-generation testing. Both of these participants had low or undetectable drug levels at seroconversion and no evidence of drug resistance. Rates of false-positive results were low during follow-up for the rapid EIA (6/2680 tests) and fourth-generation antigen/antibody test (2/2673 tests). The investigators suggested that HIV-1 RNA testing should be performed before initiation of PrEP if available, particularly in individuals with recent HIV exposure, to detect acute infections early. In this cohort with high adherence to PrEP, rapid EIA and laboratory-based fourth-generation tests were adequate to detect HIV infection during follow-up.

Uptake, Coverage, and Delivery of PrEP

Black MSM are disproportionately impacted by HIV disease, comprising less than 0.4% of the US population but accounting for more than 20% of all new HIV infections in 2013. Wheeler and colleagues presented data on the uptake of PrEP and its use among black MSM in the HPTN 073 study (Abstract 883LB). This study enrolled 226 black MSM in Washington, DC, Los Angeles, California, and Chapel Hill, North Carolina, and all participants were offered 12 months of daily oral PrEP with TDF and emtricitabine along with client-centered care coordination, a theory-based approach to support adherence to PrEP by combining service-referral, linkage, and follow-up strategies to address unmet psychosocial needs. Overall, 40% of enrolled participants were younger than 25 years, 27% were unemployed, 31% were uninsured, and 31% had a history of incarceration. PrEP was accepted by 178 (79%) participants, and 68% remained on PrEP at 26 weeks. Self-reported adherence of greater than 50% was observed in 85% of participants at week 4 and 78% at week 26. Retention was high in the cohort, with 92% completing 12-month follow-up. Participants who initiated PrEP utilized a median of 6 client-centered care coordination sessions, compared with a median of 4 sessions among men who did not initiate PrEP. Five individuals who initiated PrEP seroconverted during 172 person-years of follow-up (HIV incidence 2.9/100 person-years; 95% CI, 0.9-6.8); 2 of these individuals discontinued PrEP before seroconversion. In comparison, 3 men who never initiated PrEP seroconverted during 39 person-years of follow-up (HIV incidence 7.7/100 persons-years; 95% CI, 1.6-22.5). These data suggest that theory-based, culturally tailored programs can potentially increase uptake and use of PrEP among black MSM.

Levy and colleagues evaluated correlates of uptake of HIV prevention interventions among black MSM in Washington, DC (Abstract 893). Two nonclinic-based samples were recruited, including a face-to-face sample of 75 black MSM with barriers to health care obtained through peer referral, and an internet-based sample of 93 black MSM regardless of health care status. The proportion of black MSM who received HIV prevention interventions was higher in community-based clinic settings (90%) than in primary (53%) or acute (44%) care settings ($P = .005$). In the internet sample, independent correlates of uptake of PrEP included being younger than 30 years (aOR, 5.51; 95% CI, 1.25-24.32), not having private insurance (aOR, 0.12; 95% CI, 0.02-0.69), trusting one's social network for advice about health issues (aOR, 5.65; 95% CI, 1.14-27.98), and having been offered an HIV test at last visit with a health care practitioner (aOR, 6.92; 95% CI, 1.25-38.16). Black MSM reported several structural barriers to accessing HIV prevention services in primary care settings, including stigma, difficulty disclosing sexual behavior without fear of judgment, and low cultural competence of practitioners. The investigators highlighted the importance of addressing these structural barriers to increase uptake of PrEP and other prevention interventions..

PrEP uptake was high among black MSM in the United States when provided as part of a culturally tailored support program.

Several poster presentations at CROI 2016 highlighted increasing knowledge and use of PrEP among MSM in the United States. Delaney and colleagues reported trends in awareness and use of PrEP from 3 nationwide internet surveys of US MSM between May 2012 and March 2015 (Abstract 889). Among a total sample of 10,097 MSM surveyed, awareness of PrEP increased from 45% in 2012 to 69% in late 2014 and early 2015; use of PrEP also increased substantially during this period and was higher among those at higher risk, including individuals with a recent bacterial STI (adjusted prevalence ratio (aPR), 2.45; 95% CI, 1.95-3.09) and those who reported having more than 10 sexual partners in the past 12 months (aPR, 3.47; 95% CI, 2.67-4.49). The prevalence of PrEP use was more than 10% in 4 US cities by early 2015 (New York City; San Francisco, California; Seattle, Washington; and Washington, DC).

Despite increasing knowledge about PrEP and interest in PrEP, there remains a large gap between those willing to use and those who have actually used PrEP. Scanlin and colleagues presented data on trends and correlates of recent use of PrEP among MSM in New York City participating in the Sexual Health Survey, a cross-sectional behavioral surveillance survey conducted from 2013 to 2015 (Abstract 888). Among 1572 respondents, use of PrEP in the past 6 months increased from 2.1% in 2013 to 14.8% in 2015. In bivariate models, use of PrEP was associated with being insured. In multivariable models, use of PrEP was associated with calendar year and several indicators of risk, including no con dom use at last sex, having an HIV-seropositive last sex partner, and engaging in sex without condoms with 3 or more

partners, or use of postexposure prophylaxis (PEP) in the past 6 months.

Mayer and colleagues reported on rates of PrEP use among MSM in Boston who received care at Fenway Health, the largest primary care center for MSM in Massachusetts (Abstract 890). Use of PrEP increased from 5 individuals in 2011 to 537 individuals in 2014 ($P < .001$), and 80% of individuals were still taking PrEP in 2015. During this period, 5 MSM who were taking PrEP became HIV infected (< 0.5%), compared with 93 (2.2%) MSM who did not initiate PrEP. STIs were common among PrEP users, and 36% of MSM who initiated PrEP in 2014 had a recent bacterial STI.

Novel approaches to increasing the capacity of practitioners to deliver PrEP are being evaluated. Edelstein and col leagues presented results of a public health detailing campaign to increase prescribing of PrEP among primary care and infectious disease practitioners in New York City (Abstract 892). Representatives from the New York City Health Department visited practices and provided short, individual-level presentations using the PrEP and PEP Action Kit at an initial and then a follow-up visit. Among 881 practitioners, 18% prescribed PrEP at initial visit (early adoption), and 13% prescribed PrEP after initial follow-up visit (incident PrEP prescribing). Early adoption and incident PrEP prescribing were more likely among infectious diseases practitioners, suggesting a high level of willingness to prescribe PrEP among these practitioners. Early adoption was also associated with working in a community health clinic and having a history of prescribing PEP, suggesting that prescribing PEP may be a gateway to prescribing PrEP; this finding supports the promotion of PrEP and PEP simultaneously in detailing efforts. Incident PrEP prescribing was associated with having an initial visit of 10 minutes or longer, suggesting a potential impact of public health detailing and supporting further evaluation of this innovative approach.

Patel and colleagues described missed opportunities to prescribe PrEP in primary care settings and the potential role of infectious diseases and HIV specialists in expanding PrEP implementation (Abstract 891). The researchers conducted a cross-sectional survey of 102 individuals seeking PrEP from the HIV clinic at Washington University in St Louis, in Missouri. The median age of this cohort was 29 years, 88% were MSM, 31% were black, and 70% reported engaging in anal sex without a condom in the past 3 months. Overall, 65% had a primary care practitioner (PCP), and 48% asked their PCP for PrEP, which was not prescribed. Thirty-nine percent of individuals seeking PrEP from their PCP reported feeling uncomfortable discussing sexual practices with their PCP. Sixty-one percent of those who reported feeling comfortable discussing sexual practices with their PCP asked for PrEP but were not prescribed it. As part of provision of PrEP, the physicians in the HIV clinic referred 83% of those seeking PrEP to a culturally sensitive PCP for primary care and continued provision of PrEP. The investigators concluded that PrEP can be a gateway to health care (as 35% had no PCP in this cohort) and that infectious diseases and HIV specialists can be a gateway to PrEP and can help link individuals to primary care facilities and practitioners. Further, the investigators proposed a PrEP-to-PCP implementation continuum in which infectious diseases and HIV specialists play leadership roles in developing and supporting a network of primary care clinics and practitioners to whom patients taking PrEP can be transitioned for ongoing PrEP and primary care.

As adherence is crucial for PrEP effectiveness, several researchers presented data on rates and correlates of adherence to PrEP and coverage of sex events by PrEP at CROI 2016. Marcus and colleagues reported results from a cohort study of 972 individuals who initiated PrEP in the Northern California Kaiser Permanente health care system (Abstract 894). The mean age at initiation of PrEP was 37 years, 98% were men, and 70% were white. Median adherence was 97% as measured by pharmacy refills, with only 3% with less than 60% adherence. Younger age, black or Hispanic race, and smoking were associated with low adherence ($P < .01$, for all). Overall, 219 (23%) individuals discontinued PrEP. In multivariate analyses, women (RR, 2.1; 95% CI, 1.4-3.2), recreational drug or alcohol use (RR, 1.6; 95% CI, 1.1-2.2), and a copay of more than $50 per month (RR, 1.4; 95% CI, 1.0-1.9) were independently associated with discontinuation of PrEP. There were no seroconversions among 850 person-years of individuals taking PrEP; however, 2 individuals seroconverted after discontinuing PrEP. These findings highlight the importance of developing strategies to support continued use of PrEP during periods of risk.

Holtz and colleagues reported on predictors of coverage of sex events among Thai MSM and transgender women taking PrEP in the ADAPT (Alternative Dosing to Augment PrEP Pill Taking) trial (Abstract 884). Participants in this study were randomly assigned to 1 of 3 self-administered dosing regimens for 24 weeks: daily, time driven (twice weekly with a postsex dose), or event driven (before and after sex). For all 3 arms, coverage was defined as having taken 1 or more pills in the 4 days before sex and 1 or more pills in the 24 hours after sex. Among 178 participants enrolled, the proportion of sex acts covered by PrEP was similar in the daily (85%) and time-driven (84%) arms, with fewer tablets required in the time-driven arm. In a multivariable model, age of 25 years to 35 years (compared with age of < 25 years), completion of college, and moderate or high reported alcohol use at baseline (as measured by Alcohol Use Disorders Identification Test [AUDIT] score) were associated with higher coverage of sex acts by PrEP, and baseline use of stimulant drugs and higher frequency of sex in the past 3 months were associated with lower coverage ($P \leq .05$, for all).

In the ADAPT trial, the proportion of sex events covered by PrEP was similar with daily versus time-driven dosing in Thai MSM and transgender women.

In the same study, Mannheimer and colleagues examined factors associated with coverage of sex events among 179 MSM and transgender women taking PrEP in the Harlem

neighborhood of New York City (Abstract 885). The median age was 30 years and 60% were black in this cohort. Coverage was highest among those receiving daily PrEP (66%), compared with time-driven (47%) and event-driven (52%) PrEP. Across both sites, incomplete coverage among those not taking PrEP daily was most often attributable to missing the postsex dose. In multivariate analyses, being in the daily dosing arm, older age, employment, and higher motivation to take PrEP (based on the information-motivation-behavioral Skills model) were associated with higher coverage by PrEP in the Harlem cohort, and black race and heroin use were associated with lower coverage ($P \leq .05$, for all). The investigators recommend further research to assess determinants of racial differences in coverage of sex events by PrEP.

Molina and colleagues presented data from the open-label phase of the IPERGAY trial of on-demand PrEP among MSM (Abstract 886). The randomized phase of this study evaluated a regimen of 2 pills of TDF and emtricitabine 2 hours to 24 hours before sex and 1 pill each 24 hours and 48 hours after sex, and demonstrated an 86% reduction in HIV infections in the group that received TDF and emtricitabine compared with placebo. Participants who were being followed or screened in IPERGAY were offered open-label TDF and emtricitabine and continued follow-up every 2 months. Among 362 participants enrolled, only 1 individual seroconverted during the open-label phase, resulting in an HIV incidence of 0.40 per 100 person-years (95% CI, 0.01-2.25 person-years), compared with 0.91 per 100 person-years and 6.6 per 100 person-years in those who received TDF and emtricitabine and placebo, respectively, in the double-blind phase. This participant did not elect to use PrEP in the open-label phase, had undetectable drug in plasma, and no drug resistance was detected. Overall, 33% acquired at least 1 STI during open-label follow-up. Median number of sex partners and episodes did not differ between the open-label and blinded phases of the study. Participants used a median of 18 pills per month—based on pill returns—although this may overestimate pill use, as participants were somewhat reluctant to return pills because TDF and emtricitabine was not available outside of the study. Few serious adverse events were reported (4% of participants), and only 1 participant discontinued PrEP because of elevated creatinine. Drug-related gastrointestinal events were reported in 10% of participants.

Sagaon-Teyssier and colleagues identified behavioral trajectories for use of PrEP and condoms over time in the blinded phase of the IPERGAY trial (Abstract 887). Among 332 participants who reported engaging in anal sex at least once during follow-up, 4 patterns of PrEP use were identified using a tailored methodologic framework: systematic use (high levels of PrEP use at last sex throughout follow-up) (40% of cohort); high-level progressive use (moderately high levels of PrEP use during follow-up) (31% of cohort); declining use (high levels initially, then declining over time) (13% of cohort); and low-level use (PrEP use low throughout follow-up) (16% of cohort). For condom use, 2 trajectories were identified: high-level use (70% of cohort) and low-level use (30% of cohort). Among those who reported low-level condom use, 23% reported declining or low-level use of PrEP, constituting the most at-risk group. This highest-risk group was more likely to be older (OR, 1.05; $P < .001$), have a lower level of education (OR, 1.91; $P = .02$), and to report sexual dissatisfaction (OR, 2.09; $P < .001$). The investigators concluded that although most MSM in IPERGAY used PrEP, condoms, or both during their most recent sexual episode, a substantial proportion did not use either and may benefit from additional prevention support.

Modeling the Impact of PrEP

Glaubias and colleagues modeled the potential impact of scaling up the dapivirine vaginal ring as PrEP in KwaZulu-Natal, South Africa (Abstract 1057). Prioritizing PrEP to 80% of sex workers was cost saving, and scaling up PrEP had greater preventive impact when focused toward women aged 20 years to 29 years (8% of infections averted, $3,309 per infection prevented) compared with women aged 15 years to 24 years (5.5% of infections averted, $5,209 per infection prevented).

Scaling up of PrEP with the vaginal ring decreased the prevalence of drug resistance, even when adherence was low.

The cost per infection averted decreased by more than half with increased adherence to PrEP (from 50% to 95%). Scaling up of PrEP decreased the prevalence of drug resistance, even when there was low adherence; however, these reductions in resistance diminished by 2% to 12% when resistance was tracked in both the blood and genital compartments. The investigators concluded that the dapivirine vaginal ring could have a substantial impact on HIV prevention at reasonable cost when prioritized by age, and could decrease drug resistance even at lower adherence levels.

Smith and colleagues presented modeling data on the cost-effectiveness of the dapivirine vaginal ring in South Africa (Abstract 1058). In a deterministic model in which the dapivirine ring was prioritized to female sex workers, young women, and those with more than 1 sexual partner and efficacy ranged from 25% to 75%, the dapivirine ring could prevent up to 13,000 new HIV infections per year on average and could be cost-effective if prioritized to those at greatest risk. Uniform coverage of the ring across risk groups had a larger impact due to high numbers of low-risk women being covered; however, this approach was more expensive than a more targeted strategy. The researchers concluded that the dapivirine ring could be cost-effective even in circumstances of low efficacy, and highlighted that the success of the ring is also affected by real-world user interest and adherence, which will be evaluated in upcoming open-label studies.

Yaylali and colleagues presented modeling data on the impact of improving HIV care and treatment and initiating PrEP in the United States (Abstract 1051). The researchers modeled

the impact of increasing HIV diagnoses, care, and treatment to the US National HIV/AIDS Strategy 2020 goals: 90% of infected individuals diagnosed, 85% of newly diagnosed individuals linked to care, and 80% of diagnosed individuals virally suppressed, and the marginal benefit of delivering PrEP to individuals at risk for HIV acquisition. In the base case, PrEP reduced new HIV infections by 18% over 5 years. Increasing diagnoses, care, and treatment to National HIV/AIDS Strategy 2020 goals had the largest impact on reducing new HIV infections (63%) in the United States. Although the marginal benefit of PrEP decreased as rates of viral load suppression increased, PrEP continued to achieve further reductions in HIV incidence, particularly among MSM.

Nichols and colleagues modeled the impact and cost-effectiveness of daily and on-demand PrEP among MSM in the Netherlands (Abstract 1052). Using a deterministic mathematical model of the HIV epidemic in the Netherlands, PrEP is targeted to 4500 MSM (approximately 2%-3% of all MSM in the Netherlands) with at least 1 new sexual partner per year. Over 12 years of PrEP scale-up and implementation, PrEP is predicted to avert between 1000 and 2500 (7%-13%) new HIV infections. The cost-effectiveness of PrEP increases with higher effectiveness of PrEP, decreased medication costs, and if the HIV epidemic remains stable (compared with the HIV epidemic declining as a result of HIV treatment scale-up). Under most scenarios, the use of PrEP is only cost-effective (< €20,000/quality-adjusted life-year gained) when used on demand. The authors recommended a price reduction of greater than 30% to ensure that on-demand PrEP remains cost-effective in the Netherlands, regardless of future declines in the epidemic.

Antibodies for HIV Prevention

In a plenary presentation, Mascola provided an overview of the use of passive immunization with antibodies for HIV prevention and treatment (Abstract 15). Antibodies have been used for prevention or early treatment of numerous viral infections, including the hepatitis A and B, varicella-zoster, rabies, and respiratory syncytial viruses. Since 2009, several potent neutralizing monoclonal antibodies (mAbs) against HIV-1 have been identified. These mAbs differ in potency and breadth of coverage of different HIV strains, and newer antibodies are up to 500-fold more potent than first-generation mAbs. Several preclinical studies of nonhuman primates have demonstrated the ability of neutralizing mAbs to protect against mucosal SHIV challenge when administered before or soon after viral exposure. mAbs to 4 major HIV binding sites are under development and several of these will be tested in clinical trials over the next few years. VRC01 is an mAb that attaches to a functionally conserved region of the CD4+ cell binding site, blocking viral entry, and neutralizes 80% to 90% of diverse viruses, regardless of clade. Preclinical studies have identified serum levels of VRC01 predicted to provide protection, and pharmacokinetic data from a phase I study suggests that protective levels of antibodies can be achieved with infusions every 2 months.

Key unanswered scientific questions include whether antibodies can prevent HIV infection in humans, what level of mAb is needed for protection, where and how mAbs work, and whether Fc receptor–mediated effector functions (antibody-dependent cell-mediated cytotoxicity) are needed for protection. Mascola described the phase IIb AMP (Antibody Mediated Prevention) study, conducted jointly by the HIV Vaccine Trials Network (HVTN) and the HPTN, which was designed to address a number of these questions. This trial will enroll 2700 MSM and transgender women in the Americas and 1500 women in Africa and is anticipated to launch in the second quarter of 2016. If VRC01 is found to be safe and effective in this proof-of-concept trial, it could pave the way for developing a subcutaneous injectable antibody product that could be given once every 3 months to 4 months for larger-scale use. Laboratory studies are underway to develop antibodies with greater potency and breadth, and strategies to combine antibodies could achieve higher levels of coverage. In addition, approaches to extend the half-life of antibodies are under investigation. In particular, mutations in the constant region of the antibody have resulted in prolonged circulating half-life, and a new version of VRC01 with this mutation is currently under study in a phase I trial.

The use of broadly neutralizing antibodies for HIV prevention is a promising approach to HIV prevention and will be evaluated in upcoming efficacy trials.

Mayer and colleagues presented data on the safety and pharmacokinetics of multiple doses and schedules of VRC01 in the HVTN 104 study (Abstract 90). In this trial, 88 low-risk men and women were randomly assigned to receive 1) a 40 mg/kg intravenous loading dose followed by 20 mg/kg intravenously every 4 weeks or 10 mg/kg, 30 mg/kg, or 40 mg/kg of VRC01 intravenously every 8 weeks; or 2) a 40 mg/kg intravenous loading dose followed by a 5 mg/kg subcutaneous dose of VRC01 or a placebo every 2 weeks. Infusions and injections were generally well tolerated in this study; mild pain or tenderness was observed in 28% of infusions and 14% of injections, and very few had erythema or induration. Overall, 57% of participants had at least 1 systemic symptom during the trial, most of which were mild; malaise and fatigue, headaches, and myalgia were the most common. For 76% of injections, no systemic symptoms were reported. Only 6% of adverse events were assessed as product related and all were mild and transient, and product was discontinued for 3 participants out of caution. After a 40 mg/kg intravenous loading dose, the mean VRC01 nadir level was 14 mcg/mL after 6 months of biweekly subcutaneous injections and 45 mcg/mL for 20 mg/kg VRC01 given intravenously monthly. For the regimens of 10 mg/kg, 30 mg/kg, and 40 mg/kg, peak concentrations were between 113 mcg/mL and 486 mcg/mL and nadirs were between 4 mcg/mL and 16 mcg/mL, with evidence of drug accumulation

after each dose. Trough concentrations for the 10 mg/kg and 30 mg/kg regimens were associated with high levels of coverage of clade B and C viruses in other studies of in vitro neutralizing activity. These safety and pharmacokinetic results support the use of these regimens in the upcoming phase IIb AMP study evaluating the efficacy of VRC01 for HIV prevention.

Conclusion

In summary, studies of HIV transmission and prevention were prominently featured at CROI 2016, providing insights into populations heavily impacted by HIV infection across the globe, and identifying gaps and potential strategies to address disparities in the epidemic. PrEP could have a substantial impact on HIV incidence, and data suggest increasing knowledge and uptake of PrEP in certain populations. Advances in novel PrEP drugs and formulations are promising but also raise potential implementation challenges. Additionally, harnessing antibodies for prevention is a novel, emerging approach currently under investigation.

All cited abstracts appear in the CROI 2016 Abstracts eBook, available online at www.CROIconference.org.

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

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