Invited Review

CROI 2019: Advances in HIV Prevention and Plans to End The Epidemic

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At the 2019 Conference on Retroviruses and Opportunistic Infections (CROI), a plan for ending the HIV epidemic in the United States was presented. More rapid HIV diagnosis and treatment is a key component needed nationwide. In international settings, substantial scale up of HIV testing and treatment has led to substantial declines in HIV incidence. U=U (undetectable equals untransmittable) is a powerful concept that can reduce stigma and encourage engagement in testing and care, but raises a number of clinical questions. HIV testing remains a gateway to HIV prevention and treatment, and innovative testing strategies, including HIV self-testing, show promise. Opioid overdose deaths are on the rise, highlighting the need for comprehensive prevention efforts. Molecular data are being used to identify rapidly growing clusters of infections for intervention. Rates of sexually transmitted infections have increased substantially in recent years. A new preexposure prophylaxis (PrEP) combination, tenofovir alafenamide/emtricitabine (FTC), was demonstrated to be non inferior to tenofovir disoproxil fumarate/FTC, with improved bone and renal safety. PrEP uptake is increasing globally, but use is lower in several populations, including African Americans, cis- and transgender women, and youth. Same-day PrEP initiations are a promising approach to increasing access, but PrEP discontinuations remain a challenge.

Keywords: epidemiology, prevention, HIV, CROI 2019, U=U, testing, STIs, microbiome, PrEP, adherence, resistance, persistence, end the epidemic, PWID, MSM

Ending the Epidemic

Fauci gave a special presentation at the Opening Session of the 2019 Conference on Retroviruses and Opportunistic Infections (CROI) on the plan for ending the HIV epidemic in the United States. He pointed out that 1.1 million Americans are living with HIV, 14% of whom are unaware of their HIV infection. Approximately 40,000 new infections occur each year, without a substantial decline in recent years. He reviewed the science behind treatment as prevention, demonstrating that people who are durably virally suppressed cannot transmit HIV to their sexual partners. However, only 60% of people living with HIV in the United States are virally suppressed. A daily pill of preexposure prophylaxis (PrEP) is more than 95% effective in preventing HIV acquisition, but only 269,000 people are estimated to be on PrEP, of more than a million who could benefit from this prevention modality. He pointed out that new infections are heavily concentrated in certain demographic populations such as African Americans, men who have sex with men (MSM), and people who inject drugs (PWID). The epidemic is also concentrated in geographic areas; more than 50% of the new infections are concentrated in only 48 counties, along with Washington, DC, and Puerto Rico, and 7 southern states have substantial epidemics in rural areas. The combination of widespread treatment and prevention, if effectively implemented, could theoretically end the HIV epidemic in the United States. Fauci laid out the national plan to end the epidemic, the first time that a number of Health and Human Services Agencies are working together with a focus on increasing treatment and prevention in highly concentrated target populations. The 4 components of the plan are to 1) focus initially on high incidence geographic areas; 2) emphasize early diagnosis, immediate treatment, and engagement in care, with a plan to increase viral suppression from 60% to 90% nationally; 3) expand uptake of PrEP to at least 50% of those who need it; and 4) respond rapidly to emerging clusters of infection. With this plan, the goal is to reduce new HIV infections by 75% in 5 years and by 90% in 10 years.

The combination of widespread treatment and prevention, if effectively implemented, could theoretically end the HIV epidemic in the United States

Several presentations demonstrated the ongoing need for more rapid HIV diagnosis and treatment in the United States. Balaji and colleagues reported on trends in the probability of being diagnosed within the first year after HIV acquisition (Abstract 848). They based their estimates of early diagnosis on modeling, using CD4+ cell counts, and modelled HIV incidence. Based on this

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methodology, they found that early diagnosis increased for persons aged 13 to 24 years but decreased for persons aged 25 to 34 years. The rates were stable in all other groups, suggesting limitations in current testing programs in finding people early in infection.

Crepaz and colleagues reported on the period of time that persons living with HIV might be potentially infectious in the United States, based on data from 27 jurisdictions with complete CD4+ cell count and viral load testing from 2012 to 2016 (Abstract 153). They modeled the duration of infection prior to diagnosis based on CD4+ cell count at presentation, a strategy that may introduce error into estimates. They then evaluated the time from diagnosis to viral suppression based on viral load testing. Overall, median time from infection to diagnosis decreased from 43 months to 39 months over that time, although 25% were estimated to have been infected for 98 months at diagnosis. Time from diagnosis to viral suppression dropped from 8 months to 5 months, with 25% estimated to take 12 months to reach viral suppression. Time from infection to diagnosis was slower in male heterosexuals (median, 63 months) and Latinos (median, 45 months). These data suggest that al though progress is being made in achieving viral suppression more quickly after diagnosis, much works remains to be done, particularly with more rapid diagnosis after infection, where the incremental gains have been substantially smaller.

Several presentations demonstrated the potential impact of increasing HIV testing and treatment on HIV incidence rates in international settings. Hayes and colleagues presented data on the HIV Prevention Trials Network (HPTN) 071 PopART study (Population Effects of Antiretroviral Therapy to Reduce HIV Transmission) (Abstract 92LB). The investigators randomly assigned 21 communities in Zambia and South Africa to one of 3 arms. Arm A received the full PopART package, consisting of universal home-based counseling and testing, voluntary male medical circumcision referral, referral for prevention of mother-to-child transmission for pregnant women, screening for sexually transmitted infections (STIs)and tuberculosis, andprovision of condoms. Persons in Arm A received antiretroviral therapy (ART) regardless of CD4+ cell count. Arm B received the same package, except that treatment was initiated according to country-specific guidelines. These national guidelines changed over the course of the trial, so that ART initiation was immediate for more than 50% of the entire study period. Arm C received the standard of care at current local provision levels. HIV incidence decreased by 30% comparing Arm B with Arm C (adjusted rate ratio, 0.30; 95% confidence interval [CI], 0.55-0.88; $P=.006$). Unexpectedly, no significant decline was seen comparing Arm A with Arm C, and further analyses are underway to try to understand the lack of effect in this study arm. Nonetheless, the trial demonstrates that with substantial scale-up of testing and treatment, HIV incidence can be notably reduced. The data also suggest that additional prevention modalities, such as PrEP, may be needed to have a larger impact at a population level on HIV incidence.

MacKellar and colleagues reported on a study of scale up of HIV testing, linkage, and ART service delivery in Mozambique from 2014 to 2017 (Abstract 98). They attempted to target the 90-90-90 levels of testing, ART uptake, and viral suppression. HIV testing increased from 67% to 88%, ART uptake increased from 60% to 79%, and viral suppression increased from 41% to 66%. Despite not reaching the target levels, the investigators reported a change in estimated incidence of 1.9% per year to 0.9% per year using recency-based testing. If accurate, this demonstrated a 54% reduction in HIV incidence (incidence rate ratio, 0.46; 95% CI, 0.22-0.94). This would suggest that population-level increases in viral suppression can lead to reductions in HIV incidence.

U=U

An entire session was devoted to the concept of U=U (undetectable equals untransmittable), that persons fully virally suppressed on ART cannot transmit HIV to their sexual partners (Symposium S-6). Vernazza reviewed the history of available data in support of U=U (Abstract 116). In 2008, a group of Swiss investigators made the statement that persons on ART with suppressed viral load and without STIs were unable to transmit HIV to their partners, based on seeing no cases of documented transmission in this situation. The motivation for making this statement was both to help people living with HIV to have healthy sexual lives, and to avoid the legal actions being taken against persons living with HIV because of concerns of exposure to their sexual partners. He estimates that at that time, the upper bound of the 95% confidence interval for the risk of HIV transmission would have been approximately 0.2/100 person-years. Vernazza discussed the difficulty of proving a negative result, quoting the philosopher Copi who stated that one can assume reporting of rare events, and thus the absence of detection can serve as positive proof of non-occurrence. Vernazza then reviewed the additional data from HPTN 052, PARTNERS (Partners of People on ART—A New Evaluation of the Risks) -1 and -2, and the Opposites Attract studies that would now indicate that the upper limit of a 95% CI would be 0.07/100 person-years. This provides compelling evidence that transmission does not occur when a person is fully virally suppressed on ART.

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Nwokolo discussed clinical conundrums related to counseling patients about U=U (Abstract 117). She raised the question of whether post-exposure

prophylaxis (PEP) should be recommended for a person with numerous partners, all of whom either state they are on PrEP or have an undetectable viral load. She suggested that without verification of viral suppression, one should presume that viral load may not be suppressed, citing data from last year's CROI that in one study 47% of MSM who reported an undetectable viral load had some virus detected on dried blood spots.[1] The presence of STIs does not appear to affect U=U. In evaluating whether someone should be offered PEP for an occupational needlestick exposure from a patient with an undetectable viral load, she pointed out that guidelines differ between the United States, which recommends offering PEP, versus the United Kingdom and Switzerland, which recommend against PEP. Breastfeeding has been shown to transmit HIV, despite viral suppression in the blood. This may be for several reasons, including: 1) transmission through cell-associated virus, not measured by viral load; 2) the quantity of breastmilk exposure (more than 150 liters over 6-12 months); 3) immune activation in breast milk, where HIV replication occurs 10-times more than in blood; 4) immune vulnerability of the infant gut; or 5) difficulty with ART adherence during the post-partum period. Nwokolo pointed out that little evidence exists about the risk of transmission through needle sharing if detectable, with PEP not recommended in the United Kingdom and Australia, but it is recommended in the United States guidelines. She pointed out that additional challenges may exist in interpreting U=U in developing world settings, where viral load testing may be less frequent or a higher threshold is used than in resource-rich countries. She ended by listing several unanswered questions, including whether there is an actual viral load transmission threshold, what level of adherence is sufficient, how important is cell-associated virus in transmission, how long one has to be undetectable before transmission no longer occurs, and how U=U may be influenced by long-acting agents.

Foote addressed community perspectives on U=U (Abstract 118). She made the case that knowledge of U=U is a human rights issue, and that most people living with U=U are not aware that they cannot transmit HIV sexually if they are fully virally suppressed. More than 820 partners have signed on to the U=U campaign from 97 countries. Foote suggested that the U=U campaign has 4 main effects, including that it: 1) transforms social, sexual, and reproductive lives; 2) dismantles stigma; 3) encourages that persons get tested and remain on treatment and in care; and 4) provides a strong public health argument for the necessity of access to care. However, she recognized that not everyone is able to achieve viral suppression and that "V does not equal V" or that having detectable virus does not equate with a person's value or worth. Foote also provided coaching on language around U=U, urging not to "recommend condoms, just in case" or to say "you're only as good as your last viral load". Rather, she urged recommending that condoms can prevent other STI transmission but are not clinically necessary to prevent HIV transmission in the setting of undetectable viral load, and that persons who are taking their medication and getting tested regularly need not worry about HIV transmission.

Grulich addressed the population level impact of treatment as prevention, also known as "UTT" or universal testing and treatment throughout generalized epidemics in sub-Saharan Africa, and concentrated MSM epidemics in developed countries (Abstract 119). He pointed to the 5 large UTT trials conducted to date, highlighting the differences in baseline HIV prevalence, knowledge of serostatus, and treatment uptake at baseline across the trials. All of the trials have been impacted by World Health Organization guidelines for immediate testing regardless of CD4+ cell count that occurred after the trials launched, with some trials showing no difference between treatment arms in HIV incidence, and others showing modest (20%-30%) decreases in incidence in the intervention arms. He suggested that these modest effects may indicate that additional combination prevention strategies are needed to further drive down infection rates. He then reviewed new diagnoses in MSM in Australia, England, and the United States, demonstrating in various jurisdictions that increased testing and treatment coincided with substantial declines in new diagnoses. He pointed out that these declines are difficult to attribute solely to testing and treatment scale-up, as PrEP was also rolled out during that time frame. Grulich ended by emphasizing that combination prevention, including PrEP, may be needed to see truly substantial declines in incidence across populations.

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Several posters addressed implementing U=U in clinical settings. Gillani and colleagues evaluated patients being cared for at a clinic in Providence, Rhode Island (Abstract 1056). Among 1242 patients with an HIV RNA level below 200 copies/mL, 5% of patients per year became non-suppressed and another 10% per year did not have viral load data to confirm suppression. Krentz and colleagues evaluated patients with HIV from a clinic in Southern Alberta, Canada (Abstract 1058). They calculated the total days of follow-up for which patients were suppressed (<200 copies/mL), unsuppressed (>200 copies/mL), or transmittable (>1500 copies/mL, a level previously associated with transmission). Overall, 92% of days were spent suppressed, and 8.2% were unsuppressed, including 6.6% of the time as transmittable. However, patients disengaging from care who accounted for 5.5% of all patients accounted for 34% of the days spent unsuppressed and 37% of transmittable days of follow-up. Both abstracts suggest that most patients were able to maintain viral suppression, as long as they were retained in care.

HIV Testing

Testing is the gateway to HIV prevention as well as treatment, and thus an

important component of any efforts to end the epidemic. A number of presentations focused on the use of self-testing to increase uptake of testing and identify undiagnosed persons. Dovel and colleagues presented data on a randomized controlled trial of HIV self-testing among partners of clients on ART in Malawi (Abstract 93). They randomly assigned 135 participants to standard of care (participant given a referral slip to give to partner for testing), and 349 to standard of care plus receipt of HIV self-test kits. Although the HIV testing uptake was significantly higher in those given a self-test kit (73% vs 27%, respectively; adjusted odds ratio [aOR], 10.4), only 22% of self-testers who were positive initiated ART within 6 months. In addition, 65% of self-testers reported needing help in conducting the test, and 8% were unable to interpret the test results. This suggests that additional support is needed in this environment to ensure that persons testing HIV positive on self-testing are linked to care and treatment. Pintye and colleagues presented data on distribution of self-test kits for couple-based testing of the unknown serostatus male partners of HIV uninfected women seek ing routine antenatal care at 10 facilities in Kenya (Abstract 926). They found that 63% of 758 women were willing to take a self-test kit for their male partner, 76% of these offered the self-test kit to their partner, and 93% of men offered the self-test kit used it with their female partner. Of 296 men performing the self-test kit, they identified 4 HIV positive individuals, with an additional 4 who were unable to read their results; the remaining tests were negative. Overall, 4 persons reported experiencing harm from distribution of self-test kits in that their partner was upset; they denied physical or verbal harm from the encounter. However, 8% of women not accepting an HIV self-test kit and 14% of women who took a kit but did not distribute it to their partner cited fear of intimate partner violence as the reason for not distributing the test kits. For women without this concern, this approach appeared to be a safe and effective means of testing a minority of male partners (36% of total).

Medley assessed the interest, HIV positive test yield, and cost of 3 strategies of obtaining HIV testing among male partners of women attending antenatal clinics: 1) facility-based testing through invitation letters; 2) Home-based testing by a trained counselor; and 3) HIV self-testing, with the ability to take up to 3 oral fluid based tests for themselves and their partners (Abstract 928). Men using home test kits were also given incentives of approximately US $2 for receiving posttest counseling and for returning home test kits via text or physically to the facility. Of 1166 women enrolled, 223 male partners were tested at the facility (9% HIV positive rate), 28 men had home-based testing (7% HIV positive rate), and 668 men received an HIV self-test kit (6% HIV positive). Costs per confirmed HIV positive were estimated to be $355 for facility based testing, $1038 for home-based testing, and $2350 for self-testing. Self-testing was most popular, but only 60% received post-test counseling despite incentives, and this modality was the most expensive. Nonetheless, it seems that a variety of testing strategies will be required to maximize uptake of HIV testing by male partners of pregnant women. Cele and colleagues also calculated the cost of facility-based versus HIV self-testing in 30 communities in Zambia (Abstract 1080). Participants randomized to receive HIV self-testing underwent a second randomization to either a self-referral card alone or combined with a patient escort to a local healthcare facility. The yield of newly diagnosed positive tests per person was 1% for HIV self-testing and 3.2% for facility-based testing. Among those testing newly HIV positive in the self-testing group, 34% of those given a self-referral card initiated ART within 3 months compared with 92% of those with an escort. The cost per newly positive diagnosis was $583 for self-testing and $80 for facility-based testing. However, when calculated as the cost per ART initiation, the cost was substantially lower for the self-testing arm offered an escort than the self-testing with referral cost only ($668 vs $1698, respectively) because of the substantially higher linkage rate for the former group. The authors concluded that community-based HIV self-testing may identify youth who would not otherwise have tested for HIV, but that it should be provided with an offer of escort to ART services for those testing newly positive.

HIV self-testing was also evaluated among MSM in several settings. Dunn and colleagues presented baseline data from a randomized controlled trial of HIV self-testing in England that enrolled 10,112 MSM through the internet (Abstract 937). Among men at higher risk of HIV (having 2 or more condomless anal sex partners in the prior 3 months), 12% had never had an HIV test and 47% had tested more than 6 months previously, indicating the strong need for testing in this population. Okoboi and colleagues reported that they distributed 10 HIV self-test kits each through 15 MSM peers in Uganda (Abstract 934). The yield of his testing (10 confirmed positive results) was higher than for usual testing in the local program (4/147, P=.02). Of self-testers, 77% had never tested or had not tested in the prior 12 months. This suggests that distribution of self-test kits through MSM peer networks may be a promising strategy for increasing knowledge of serostatus in this population with high HIV prevalence. HIV self-testing was also assessed for MSM in Brazil, Mexico, and Peru (Abstract 936). Of 18,916 survey respondents, 20% had never tested for HIV; major reasons for never testing include fear of a positive test result (28%), perceived low risk of infection (22%), and the shame of getting tested (21%). Willingness to test was highest in Brazil (44%), followed by Mexico (36%) and Peru (32%). Nearly 90% thought that post-test counseling with a health professional is essential, and more than 80% stated that they think people would have difficulty dealing with a positive test result. Willingness to use a self-test was associated with higher income, education, and willingness to use PrEP in all 3 countries.

Roxby and colleagues conducted a randomized controlled trial of home-based couple education among

391 couples in which the woman was pregnant in Kisumu, Kenya (Abstract 927). Women were randomly assigned to receive home-based couple education with rapid syphilis testing and counseling about prevention strategies, or to receive an invitation letter to give to their male partners to receive HIV testing. Overall, 7% of men tested in the intervention arm and 2% of those tested in the control arm were newly diagnosed with HIV. In addition, men randomly assigned to the intervention arm were significantly more likely in unadjusted analysis to report seeking any STI services (relative risk [RR], 1.6). There was no effect on men seeking voluntary medical male circumcision nor to linkage to HIV care and treatment services. This suggests that a more intensive intervention is needed to improve uptake of prevention modalities for men testing HIV negative and linkage to treatment for men testing HIV positive. Kim and colleagues presented data from a cluster randomized trial of HIV testing for men in Kwazulu-Natal, South Africa (Abstract 54LB). They randomly assigned 45 communities in a factorial design evaluating micro-incentives (approximately US $3), micro-incentives with a mobile App to increase testing, the mobile App alone, or the control condition of annual community-level testing. Testing uptake was low in all 4 arms, but significantly higher in the arms including the micro-incentive (28%, 27%, 17%, and 18% respectively), leading to an RR of 1.54 for the micro-incentives. Men were also given micro-incentives if they linked to care within 6 weeks of a positive diagnosis. Future presentations will evaluate these outcomes, along with an assessment of the seropositivity rates among those who did test.

Drug Use

Bosh and colleagues reported on the increased rate of unintentional opioid overdose deaths in people with HIV infection from 2011 to 2015 (Abstract 147). Although total deaths decreased by 13% among people with HIV during this time, unintentional opioid overdose deaths increased by 43%, accounting for 2% of all deaths in 2015. PWID had the highest rates and increased by the greatest amount (80%) over this time. MSM who injected drugs had the second highest rate. Although rates increased in all age groups, rates were highest among 50 to 59 year olds, followed by 40 to 49 year olds. Rates were somewhat higher in women than men but increased in both groups.

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Rates were highest in the Northeast and lowest in the South, although the rates increased most in the South. The West was the only region in which rates decreased. These data show the intensity and worsening of rates of unintentional opioid overdoses and demonstrate that more comprehensive prevention efforts are needed overall, as well as within groups with the highest rates or fastest growth.

Additional data on overdoses were presented in several posters. Genberg and colleagues reported on fatal and non-fatal overdoses among persons enrolled in the ALIVE cohort in Baltimore, MD (Abstract 883). They reported an overdose death rate of 7.06 per 1000 person-years. People living with HIV were significantly more likely than HIV negative persons to die of overdose deaths (adjusted hazard ratio [aHR], 1.7); older people and women were significantly less likely to die of overdose (aHR, 0.96 and 0.49, respectively). Non-fatal overdoses were very common in this cohort, with an incidence of 24 per 100 person-years. Factors associated with non-fatal overdoses included more recent years (2017 and 2018 compared with 2013, aHR, 3.9 and 4.4, respectively), any opiate use (aHR, 7.0), and any injection drug use (aHR, 6.2). Dorsey and colleagues reported on accidental overdose deaths in Washington, DC, from 2013 to 2017 (Abstract 881). They reported that accidental overdose deaths increased 218% over that time, accounting for 6.8% of all deaths among people living with HIV over that time period. Compared with other causes of death, persons dying of accidental overdoses were significantly more likely to have injected drugs (aOR, 2.9), to have had Stage 1 disease (aOR, 4.6) and to have had a CD4+ count above 200 cells/μL (aOR, 3.6). They pointed out that these are preventable deaths with naloxone and medically assisted therapy, and that providers should pay particular attention to this risk among their patients with a history of injection drug use.

Althoff and colleagues reported on suicide rates among adults living with HIV in the United States from 2000 to 2015, using data from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) cohort (Abstract 893). Among men, rates were highest among white PWID (adjusted incidence rate ratio [aIRR], 9.98) followed by white non-PWID (aIRR, 5.92), black PWID (aIRR, 2.21) compared with black non-PWID. Suicide was relatively rare among women. Carrico and colleagues reported on multilevel predictors of suicidality among substance users living with HIV in 11 US cities, based on data from the National Institute on Drug Abuse Clinical Trials Network (Abstract 921). Of 801 participants, 18% reported suicidal thoughts, 7% considered methods for suicide, and 2% had thought of plans for suicide at baseline into the cohort. Suicidality decreased significantly over 12 months of follow-up. Suicidality was associated with a lower rate of viral suppression (aOR, 0.81). Predictors associated with a higher suicidality composite score included Latino ethnicity, CD4+ count below 200 cells/μL, severity of alcohol use, any injection drug use, no college, and poorer social support. The high rates of suicidal thoughts and their association with poorer viral suppression indicate a need to screen for and treat depression in persons living with HIV; substance users may be at particular risk.

Fulcher and colleagues reported on the association between methamphetamine use and viremia among 230 HIV positive patients on ART followed up in a cohort study (Abstract 884). Factors independently associated with viremia included methamphetamine use alone (aOR, 1.9) or meth use with other substances (aOR, 1.8), unstable housing (aOR, 1.3), or reporting having missed at least 1 dose of medication (aOR, 2.1). They calculated that methamphetamine use had an attributable fraction of 46%, suggesting that viremia could theoretically be reduced by that amount if methamphetamine use were to cease. Shoptaw and colleagues reported on 529 HIV positive patients from the same cohort (Abstract 885). They found a dose response relationship between the amount of methamphetamine use and a number of poor outcomes, including unstable housing, intimate partner violence, transactional sex, hepatic abnormalities, neurologic abnormalities, and psychologic abnormalities.

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A symposium focused on the intersection of substance use with HIV covered opioids, chemsex, and alcohol (Symposium S-3). Bluthenthal began by reviewing the history of the opioid epidemic in the United States (Abstract 63). In the 1990s, pain was recognized as the fifth "vital sign" and opioid prescriptions increased substantially. This coincided with the development of long-acting opioids and targeted marketing of these drugs to clinicians. However, it was later documented that 21% to 29% of chronic pain patients receiving prescription opioid meds would misuse these drugs, approximately 8% of these would develop opioid use disorder, and 4% to 6% of those would transition to heroin use. Among those with opioid use disorder, 43% obtained their medication from a prescriber, but an additional 36% obtained it from friends or family for whom these medications had been prescribed. Several actions have been taken to reduce the harmful effects of opioids including changes to drug formulations, drug monitoring programs, and US Centers for Disease Control and Prevention (CDC) guidance on reducing opioid prescribing. However, an unintended consequence has been an increase in use of heroin and increased injection frequency among some users, leading to increased harmful consequences including HIV outbreaks, unintended overdose deaths, and increased rates of hepatitis C, soft tissue infections, and endocarditis. The spread of opioid use disorder has occurred in urban, suburban, and rural settings, making it difficult to predict where outbreaks will occur. Bluthenthal recommended several steps toward addressing the opioid crisis including making medically assisted therapy and syringe access programs more available, increasing PrEP availability for PWID, reducing stigma, and piloting and implementing safer injection sites.

Pakianathan reported on chemsex or the use of substances during sex, generally to enhance pleasure (Abstract 64). He noted that the drugs may be used to increase libido, enhance pleasure, increase self-confidence, reduce inhibitions, promote sexual adventure, or advance intimacy. However, the drugs may also be associated with poorer outcomes, including an increased risk of STIs (aOR, 3.5), increased newly diagnosed HIV (aOR, 5.1) and increased hepatitis C (aOR, 9.2). He pointed to the many potential mechanisms for increased risk, including an association with riskier sexual practices, more prolonged sex, higher community viral load among partners, increased trauma or inflammation at mucosal surfaces, and an increased likelihood of injection drug use. He reported that 70% of patients in his chemsex clinic reported negative consequences, including problems with work, finances, criminal justice, accidental overdoses, and hospitalizations. He concluded that more research is required in understanding the factors that may increase risk for negative outcomes.

Simbayi discussed the relationship between alcohol and poor HIV-related outcomes (Abstract 65). Maps of hazardous alcohol consumption, defined as drinking to become intoxicated, show highest levels in Eastern Europe and parts of sub-Saharan Africa, areas with high HIV prevalence. In several meta-analyses, alcohol consumption was associated with an increased risk of HIV acquisition, with an odds ratio of 1.7. Problem drinkers were more likely to become HIV infected than non-problem drinkers (odds ratio [OR], 2.0 vs 1.6, respectively; $P = .04$). Simbayi pointed out that whereas the negative consequences for men often come from their own drinking, women may be put at increased risk because of their male partner's drinking, which is associated with partner violence. Among people living with HIV, alcohol use is associated with lower CD4+ cell counts, faster HIV disease progression, and poorer adherence to ART. He called for more research on interventions to address the intersection of alcohol and HIV, including the development and evaluation of interventions to reduce harmful effects of alcohol.

In 2017, metropolitan counties accounted for 91% of all HIV diagnoses among people who inject drugs

Lyss and colleagues reported on the new HIV diagnoses among PWID across the United States from 2010 to 2017 (Abstract 886). They point out that the longstanding decline in new diagnoses in PWID has stalled over this period of time, particularly since 2014. In 2017, metropolitan counties accounted for 91% of all HIV diagnoses among PWID. However, comparing 2017 with 2014, the greatest absolute increase in HIV diagnoses in PWID have been in large, fringe metro counties (population >1 million), and the

greatest relative increase has occurred in micropolitan communities (centered on urban areas with population 10,000-49,999). They recommend prompt detection and investigation of clusters occurring in newly diagnosed PWID, and recommend that health departments have HIV outbreak response plans and proactively evaluate such potential outbreaks. Dasgupta and colleagues presented data on injection and sexual behaviors among PWID enrolled in the Medical Monitoring Project (Abstract 887). Among 233 HIV positive participants, 11% reported sharing syringes and 53% reported disposing of syringes improperly. Of the 57% who reported needing drug or alcohol treatment, only 65% had received it. HIV-positive PWID were more likely than HIV-positive non-PWID to report not having sustained viral suppression (48% vs 35%, respectively; $P=.008$), having condomless sex (63% vs 31%, respectively; $P<.001$), having exchanged sex (17% vs 2%, respectively; $P<.001$), and being at risk of HIV sexual transmission (22% vs 7%, respectively; $P<.001$). This reinforces the need for access to clean injection equipment and methods for safely disposing of used equipment, increased access to drug and alcohol treatment programs, better engagement in HIV care, and other strategies to reduce the behavioral risk of HIV transmission.

Samet and colleagues reported on academic detailing for improving physician practices in opioid prescribing (Abstract 889). They conducted a cluster randomized trial of 2 safety-net clinics in which 41 practitioners were randomly assigned to a collaborative care intervention versus standard practice. The intervention consisted of pro viding a nurse care manager with an electronic registry to manage patients, provide education and academic detailing, and provide access to addiction specialists. At 12 months, patients at the intervention clinic were significantly more likely to have 2 or more urine drug tests (70% vs 18% in standard care, respectively; $P<.0001$) and to have an opioid treatment agreement (76% vs 12%, respectively; $P<.0001$). There was a trend toward a lower likelihood of early refills (21% vs 30%, respectively; $P=.11$), with no difference in viral suppression rates (88% vs 84%, respectively; $P=.69$). Practitioners in the intervention arm were somewhat more likely to routinely use a prescription monitoring program (75% vs 45%, respectively; $P=.05$). This suggests that this type of intervention may improve adherence to CDC guidelines for prescribing of chronic opioids.

Female Sex Workers

Mwanamsangu and colleagues presented data on HIV seroconversion among female sex workers (FSWs) in Tanzania (Abstract 832). They measured an HIV incidence rate of 8.6/100 person-years among the 17,977 FSWs who presented for repeat testing. Risk factors independently associated with seroconversion included age 35 years or greater (aHR, 2.4), having a syndromic STI (aHR, 1.8), not using a condom in the last 3 sex acts (aHR, 1.3), and using alcohol at last sex act (aHR, 1.4). The authors state that these data suggest the importance of offering biomedical and behavioral prevention services to this population with exceedingly high rates of HIV seroconversion. Kerrigan and colleagues reported on a 2-community randomized trial of a community empowerment model of combination HIV prevention for FSWs (Abstract 952). Although HIV incidence was high in both the intervention and control arms (5% vs 10.4%, respectively), participants in the intervention community were significantly less likely to become infected at 18 months of follow-up (OR, 0.38; $P=.047$) and demonstrated a greater decrease in inconsistent condom use ($P=.042$). This suggests that community empower ment may be useful for FSWs in reducing the risk of HIV acquisition, although additional interventions are also needed as the infection rate remained high in the intervention condition.

Social and Sexual Networks

Oster presented a plenary talk on the use of molecular data to identify rapidly growing clusters of people living with HIV for intervention (Abstract 68). She described using data from resistance testing to compare sequences, identify closely related viruses, and then identify clusters. Nationally, approximately 40% of people diagnosed with HIV have sequences reported, and sequences are available for more than 340,000 people living with HIV. On average, 4 transmissions occur from every 100 people living with HIV. However, looking at the top 13 clusters identified by cluster analysis, transmission rates were 33/100 persons, and for the first 60 clusters, transmissions occurred in 44/100, demonstrating the ability of such analyses to identify populations who may benefit from interventions. Such interventions include treatment for those diagnosed with HIV and prevention (including PrEP) for the uninfected contacts of the cluster. To date, more than 145 priority clusters have been identified, and data were shared with local health departments for monitoring and intervention. She gave several examples where identifying rapidly growing clusters led to increased efforts for testing, linkage to care, and prevention.

Golden and colleagues presented data on an HIV outbreak among homeless, heterosexual PWID in a 3-square mile area of North Seattle, Washington (Abstract 891). Based on an astute disease intervention specialist who noted 3 epidemiologically linked cases, a total of 15 cases in the cluster were identified as part of a larger uptick in cases among heterosexual PWID. Although the cluster was identified approximately 9 months after it appeared to have begun, several steps were taken to prevent further spread, including a rapid needs assessment of local PWID needs, increased HIV testing in jails, outreach to local emergency rooms and clinics, expanded mobile syringe exchange, and a community-based mobile clinic providing services, including PrEP, for women who exchange sex. The authors pointed out that molecular epidemiology was not quick enough nor sensitive enough to pick up this cluster, and made recommendations for improvements in these algorithms for the future.

Long and colleagues examined sexual networks using respondent driven

sampling among MSM and transgender women in Lima, Peru (Abstract 841). They found there was little overlap between sexual networks between these populations. Only 7% of partners of transgender women reported a cisgender male partner in the last 3 months. However, 60% reported condomless anal sex in the past 3 months and 54% of partners reported not knowing their HIV status. This suggests that partners of transgender women may need separate outreach of prevention interventions.

John and colleagues reported on using molecular surveillance as a means to expand an outbreak investigation in Massachusetts (Abstract 857). In mid-2016, the Massachusetts Department of Public Health identified an increase in HIV diagnoses among PWID in northeastern Massachusetts. Initially, 36 of 129 cases (23%) were molecularly linked. By December 2018, the addition of molecular data expanded the number of persons linked to the investigation by 44%. Numerous molecular clusters among those being investigated suggests several introductions of HIV into the community of PWID. In addition, a substantial proportion of named partners were HIV positive, indicating the importance of partner services to link persons to care.

Torian and colleagues reported on attempting to use real-time molecular surveillance to inform data-to-care efforts in New York City (Abstract 860). Clusters were inferred based on genetic distance, and cluster members out of care for more than 1 year or with viral loads above 1500 copies/mL were prioritized for assistance with partner services and reengagement in optimal care. They identified 225 clusters containing 2778 members; 91% were among MSM. Of these, 784 were closely linked (first degree partners) and the focus of their investigation efforts. Overall, 147 (5%) were out of care and 108 (4%) were viremic. The team was able to return to care 15% of those out of care, and were able to have a practitioner conference or facilitate optimal care for 77% of those who were viremic but in care. The authors concluded that this helped them prioritize patients for outreach.

McLaughlin and colleagues calculated an HIV lineage-level diversification rate, a measure of between host transmission rates suggesting increased risk of transmission (Abstract 862). They found that among people living with HIV in British Columbia, Canada, the diversification rate (and hence, risk of transmission) was higher for men, younger age, PWID, history of hepatitis C, high viral load, and living in the Northern health authority. Factors associated with lower diversification included being black and ever having had AIDS. The authors suggest that this could help prioritize groups for treatment and prevention services.

In recent years, there have been dramatic increases in bacterial sexually transmitted infections, with a very high burden seen globally

Sexually Transmitted Infections

Marrazzo presented a plenary talk on STIs in the era of effective HIV treatment and prevention (Abstract 12). In recent years, there have been dramatic increases in bacterial STIs, with a very high burden seen globally. In the United States, there were 1.6 million cases of chlamydia in 2017 (5% increase from 2015), nearly 500,000 cases of gonorrhea (19% increase), and almost 30,000 cases of syphilis (18% increase).

Syphilis cases have continued increase in the post-ART era, with 88% of cases occurring in men, of whom 80% were MSM; 46% of these MSM were HIV positive. In women, there was a 156% increase in primary and secondary syphilis compared with 2013, with 918 congenital syphilis cases occurring in 2017. In California, more than half of these cases occurred without prenatal care and often in the setting of methamphetamine and heroin use. Rates of gonorrhea in MSM have increased steeply since 2011, with a considerable number of infections occurring at extragenital (eg, rectal or pharyngeal) sites. There has been an international spread of gonococcal resistance to ceftriaxone, our last reliable drug for gonorrhea. Many of these cases had contacts in South East Asia, where antibiotics are available over-the-counter. Globally, 24% and 81% of countries had evidence of gonococcal resistance to ceftriaxone and azithromycin respectively, and 7 and 30 countries had a more than 5% rate of gonococcal resistance to these drugs. Two topoisomerase inhibitors, zoliflodacin and gepotidacin, are novel antimicrobials under study for gonorrhea treatment. She also pointed to an interesting study in New Zealand showing a 33% decrease in gonorrhea among individuals who received an outer membrane vesicle (OMV) meningococcal vaccine as part of outbreak control. This raises the possibility that the new group B meningococcal vaccine, which also contains the OMV antigen, may also protect against gonorrhea. She also reviewed results of a substudy within the IPERGAY (Action to Prevent Risk Exposure By and For Gay Men) PrEP trial in which participants randomly assigned to doxycycline postexposure prophylaxis administered 24 to 72 hours after sex was associated with a 70% decrease in time to chlamydia and syphilis infection, but had no impact on gonorrhea infection. She noted the advantages of this strategy, including the effectiveness in early studies, relatively safety of the drug, being easy to administer, having few other options for prevention, and considerable interest in MSM. Disadvantages include the limited data on this intervention, unclear duration of treatment, adverse effects, antibiotic resistance, and effects on the microbiome. Marrazzo raised the provocative question on whether STIs need to be controlled to reach Getting to Zero goals for the HIV epidemic. She pointed to data in San Francisco showing declining HIV infections concurrent with decreased condom use and increasing STIs. However, although STIs in MSM are often asymptomatic and seen as inconvenient, STIs in

women are highly stigmatizing and can lead to pelvic inflammatory disease, infertility, and adverse pregnancy outcomes. She also pointed out that although most STIs are asymptomatic, they confer an increased risk of HIV acquisition, with 10% of HIV infections among MSM attributable to gonorrhea or chlamydia infections based on a modeling study. She also highlighted the global shortage of penicillin that can further limit treatment efforts. She concluded with several recommendations, including the need to deploy rapid, accurate diagnostic tests for STIs in high incidence settings, rather than relying on syndromic management; scaling up STI screening in asymptomatic people in HIV care and prevention; expanding partner management strategies; addressing supply chain challenges; and investing in vaccine and therapeutic development.

Several presentations reported increasing STI rates in different populations. Mayer and colleagues assessed trends in bacterial STIs among more than 19,000 men in Boston (Abstract 851). Between 2005 and 2015, gonorrhea and chlamydia diagnoses in creased more than 12- and almost 8-fold, respectively. During this period, there was a 2- to 3-fold increase in screening and a 5- to 8-fold increase in diagnosis rates for gonorrhea, and similar trends were seen for chlamydia, suggesting that the increase in STI rates is not only the result of increased screening. Test positivity rates were highest in HIV-positive and PrEP-using patients, highlighting the need for regular STI screening in these populations.

Li and colleagues evaluated gonorrhea incidence and testing rates among 4727 HIV-positive individuals in the HIV Outpatient Study (Abstract 853). Between 2007 and 2017, both gonorrhea incidence and testing rates increased among MSM and non-MSM. Incident gonorrhea cases were disproportionately represented in younger patients, MSM, and patients with a prior STI. Only half of HIV-positive MSM had gonorrhea testing in the prior 12 months, suggesting missed opportunities for STI diagnosis and treatment. Furthermore, urethral testing only would miss a substantial number of extragenital STIs, highlighting the need for more gonorrhea testing across anatomic sites. Jansen and colleagues presented data on HIV, PrEP, and STI prevalence among MSM in Germany (Abstract 850). Among 2303 MSM recruited in STI clinics, 30% tested positive for an STI. STIs were predominantly rectal, and only 32% reported STI related symptoms; urogenital screening would only have detected 28% of STIs. The prevalence of Mycoplasma genitalium was high at 17%. HIV positive MSM and those using PrEP were independent risk factors for having an STI diagnosis. The high prevalence of extragenital STIs was also reported by Chapin-Bardales and colleagues (Abstract 968). Among 1922 MSM, 15% of PrEP users and 12% of non-PrEP users had a pharyngeal or rectal infection. MSM on PrEP were more likely to have rectal chlamydia (prevalence ratio, 1.6). These findings support STI testing every 3 months for MSM on PrEP and at least annually for sexually active MSM, and testing at all anatomic sites of potential exposure. Delany-Moretlwe and colleagues evaluated the prevalence and incidence of STIs among African women in the HPTN 082 study (Abstract 965). Among 451 participants enrolled, 38% were diagnosed with an STI at baseline. STI incidence during 12 months of follow-up was high, with 1 out of 3 acquiring chlamydia and one out of 10 acquiring gonorrhea. Davey and colleagues evaluated the prevalence and determinants of STIs in 242 pregnant women in South Africa (Abstract 1003). Overall STI prevalence was 33%, with higher prevalence in HIV-positive compared with HIV-negative women (39% vs 28%, respectively; $P = .04$). Among 80 women diagnosed with an STI, only 8% were treated syndromically in antenatal care. Factors associated with having an STI included being unmarried or not cohabitating with the father, being HIV-infected, and having recent STI symptoms. These findings highlight the need for novel approaches to STI diagnosis and management in pregnancy.

These findings support sexually transmitted infection testing every 3 months for men who have sex with men (MSM) on PrEP and at least annually for sexually active MSM, and testing at all anatomic sites of potential exposure

Akselrod and colleagues measured the HIV transmission risk associated with incident STIs among people living with HIV in Washington, DC (Abstract 849). Among 8021 participants followed for a median 3.4 years, 10% had at least 1 STI, of which 40% had 2 or more episodes. Among those with any STI, 17% had a viral load above 200 copies/mL and 13% had a viral load above 1500 copies/mL (sometimes used as a threshold for infectiousness) within 1 month of STI diagnosis. Individuals aged 18 to 24 years, cisgender women, blacks, and people reporting heterosexual HIV acquisition had the highest proportion of viral load above 1500 copies/mL in the setting of an STI. Among those with incident STIs, 52% of participants spent time with viral load above 200 copies/mL and 41% with viral load above 1500 copies/mL. The investigators suggested that health care practitioners should communicate about the risk of transmission in patients who are not virally suppressed, and highlight the importance of rapid testing and treatment of partners.

Bilinska and colleagues presented on the use of an online tool to assist with partner notification of STIs in the United Kingdom (Abstract 1005). This study tested SXT, an online tool that supports easy, anonymous partner notification via text message or email. Overall, 6414 cases initiated partner notification between December 2017 and July 2018. The number of verified tested partners per diagnosis via SXT was higher than national partner notification rates. Electronic partner notification also reduced workload, with

23% to 34% of partner notifications either verified in clinic or self-verified online by partners. In multivariable analyses, being MSM, black, and having a diagnosis of Trichomonas was associated with being less likely to have a partner tested using the tool, highlighting areas for future improvement.

Microbiome

Vaginal bacterial community species have been associated with increased risk of HIV acquisition in sub-Saharan African women. Marrazzo and colleagues evaluated the impact of a contraceptive vaginal ring containing estrogen/progesterone on the vaginal microbiome among women in Kenya (Abstract 998). In this study, 122 women treated for bacterial vaginosis (BV) were randomized to continuous versus cyclic use of the contraceptive vaginal ring. Continuous ring use with menstrual suppression was associated with decreased quantities of vaginal bacteria previously associated with increased risk of acquiring HIV, while maintaining *Lactobacillus crispatus,* a species associated with decreased HIV risk. Similar effects were observed in a small subset of 22 HIV-infected women. These findings suggest that contraceptive ring use could be a feasible intervention to promote *Lactobacillus crispatus* abundance as a strategy to reduce HIV risk in women and has implications for the delivery of multipurpose prevention technologies containing both contraceptive and antiretroviral agents.

Two studies evaluated whether BV modifies the effect of hormonal contraception on HIV acquisition. Sabo and colleagues tested this hypothesis in a prospective cohort of 1,985 FSWs in Kenya (Abstract 999). In this cohort, depot medroxyprogesterone acetate (DMPA) and oral contraceptive pills both conferred an increased risk of HIV seroconversion, however BV did not modify this association. Use of a contraceptive implant was not associated with HIV acquisition in the presence or absence of BV in this cohort. Noël-Romas assessed whether the microbiome modifies HIV risk associated with hormonal contraceptives among 685 women in the CAPRISA (Centre for the AIDS Programme of Research in South Africa)-004 trial (Abstract 234). Using a metaproteomics-based approach to quantify the vaginal microbiome in 685 women, they found that DMPA use in women with Lactobacillus dominant vaginal communities was associated with a more than 3-fold increased rate of HIV acquisition relative to women using other hormonal contraceptives. In contrast, this relationship was not seen in women with non-*Lactobacillus* dominant communities. These results highlight the importance of considering the vaginal microbiome when evaluating the safety of hormonal contraceptives.

Aziz and colleagues assessed whether penile bacterial species are associated with increased HIV risk in heterosexual men in Uganda (Abstract 239). In a case control study of 267 uncircumcised men participating in a male circumcision trial, they identified 21 penile bacterial species associated with increased risk of HIV acquisition. These included many of the same anaerobic bacteria shown to be reduced by male circumcision, an intervention that substantially reduces HIV risk in men; many of these species have also been implicated in HIV risk in women (such as *Prevotella bivia*). Each 10-fold increase of these penile bacterial species abundance was associated with a 22% to 57% increase in the odds of HIV seroconversion.

Preexposure Prophylaxis: What's New?

Investigational PrEP Agents

Compared with tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF) achieves more rapid and higher intracellular tenofovir diphosphate (TFV-DP) levels in peripheral blood mononuclear cells (PBMCs), has lower plasma tenofovir levels, and has demonstrated improved renal and bone safety when used for HIV treatment. Hare and colleagues presented the primary results from the phase III DISCOVER study evaluating the efficacy and safety of TAF/emtricitabine (FTC) compared with TDF /FTC for PrEP among cisgender MSM and transgender women at risk for HIV acquisition (Abstract 104LB). Participants were randomly assigned 1:1 to blinded daily TAF/FTC versus TDF/FTC and followed up for up to 96 weeks in this non-inferiority trial. Overall, 5387 adults were enrolled across 94 sites in 11 countries in North America and Europe, with 60% in the United States. The median age of participants was 34 years, 9% were black, and 24% were Latinx/Hispanic; the trial enrolled 74 (1.4%) transgender women. The study observed 22 HIV infections during 8756 person-years of follow-up, with 7 infections in the TAF/FTC arm (incidence rate 0.16/100 person-years) and 15 infections in the TDF/FTC arm (0.34/100 person-years), for an incidence rate ratio of 0.47 (95% CI, 0.19-1.15) favoring TAF/FTC, which was not significantly different and fell below the pre-specified non-inferiority margin of 1.62. Participants who seroconverted were younger and more likely to be diagnosed with a rectal STI or syphilis; no transgender women became infected during the study. Among the 22 new HIV infections, 5 were suspected to be infected at baseline (1 in TAF/FTC arm, 4 in TDF/FTC arm). Furthermore, 5 participants in the TAF/FTC and 10 in the TDF/FTC arms had low levels of TFV-DP in dried blood spots, leaving 1 infection occurring with medium to high TFV-DP dried blood spot levels in each study arm. In a sensitivity analysis that excluded suspected baseline infections, noninferiority was maintained (incidence rate ratio, 0.55; 95% CI, 0.20-1.48). Evidence of FTC resistance was observed in 4 seroconverters in the TDF/FTC arm, all of whom

TAF/FTC was noninferior to TDF/FTC in preventing HIV infection among men who have sex with men and transgender women, with better bone and renal safety outcomes

had suspected infection at baseline. Both study drugs were well tolerated with adverse events balanced between arms, and only 3 leading to drug discontinuation. Overall, 57% participants were diagnosed with an STI and 21% with rectal gonorrhea during the study, with STI incidence rates of 145 and 139 per 100 person-years in the TAF/FTC and TDF/FTC arms respectively. Bone mineral density was measured in a subset of 383 participants at week 48 and showed a 0.5% and 0.18% increase at the spine and hip in the TAF/FTC arm, compared with a 1.12% and 0.99% decline, respectively, in the TDF/FTC arm ($P < .001$). There were small but statistically significant differences in median changes in estimated glomerular filtration rate (eGFR) between the arms (1.8 mL/min increase in TDF/FTC arm vs 2.3 mL/min decline in TDF/FTC arm; $P < .001$), and statistically significant differences in proximal tubular protein to creatinine ratios favoring TAF/FTC. Participants in the TAF/FTC arm had a mean increase in weight of 1.1 kg at 48 weeks compared with no weight gain in the TDF/FTC arm. As this study did not include a placebo comparison arm, the researchers used CDC-reported HIV surveillance data to calculate a counterfactual background HIV infection rate for US MSM not on PrEP of 4.02 per 100 person-years, compared with observed HIV incidence rates of 0.08 per 100 person-years for TAF/FTC and 0.45 per 100 person-years for TDF/FTC at the US DISCOVER sites. However, it was noted that this background rate was not adjusted for race. The investigators concluded that TAF/FTC was noninferior to TDF/FTC in preventing HIV infection among MSM and transgender women, with better bone and renal safety outcomes than TDF/FTC. It is important to note that no cisgender women were included in this study.

A previous study showed that oral TAF/FTC was highly effective in preventing vaginal simian HIV (SHIV) infection in female pigtail macaques.[2] As TAF has potential as a long-acting single agent delivered from an implant, Massud and colleagues evaluated the efficacy of single-agent TAF for protection against vaginal SHIV infection in pigtail macaques (Abstract 102). A clinically equivalent dose of TAF (1.5 mg/kg) was administered orally 24 hours before and 2 hours after weekly vaginal SHIV challenge. Overall, 3 out of 7 animals treated with TAF became infected, with a delay in infection among TAF-treated animals compared with controls, for an efficacy of 73%. Similar TFV-DP levels and TFV-DP/deoxyadenosine triphosphate (dATP) ratios in PMBCs were observed among protected and infected animals receiving TAF. She concluded that a clinically equivalent dose of TAF conferred moderate vaginal protection despite high TFV-DP levels. These findings point to an important contribution of FTC in the protection seen with TAF/FTC and highlight the importance of defining the TFV-DP levels in PBMCs associated with complete vaginal protection from single agent TAF.

Rapidly dissolving inserts are being developed for on-demand topical PrEP and are user-friendly, have a favorable safety profile with low systemic drug exposure, and can be formulated in drug combinations

Rapidly dissolving inserts are being developed for on-demand topical PrEP and are user-friendly, (discreet, easy to carry, and can be self-administered without an applicator), have a favorable safety profile with low systemic drug exposure, and can be formulated in drug combinations. Dobard and colleagues evaluated an on-demand TAF/elvitegravir (EVG) insert in a female pigtail macaque model (Abstract 101). Although both drugs had very low systemic drug exposure in plasma following vaginal dosing, vaginal tissue TFV-DP reached target levels 4 to 24 hours post-dosing, and high EVG tissue levels were observed 2 and 4 hours after dosing. TAF/EVG inserts administered vaginally 4 hours before weekly vaginal challenge protected 5 of 6 animals over 13 weeks, with 1 breakthrough infection occurring after the ninth challenge, for an overall efficacy of 92%. These results support the upcoming clinical evaluation of the TAF/EVG insert administered vaginally or rectally in phase I human trials.

The investigational broadly neutralizing antibodies (bNABs) 10-1074, a V3 glycan bNAb, and 3BNC117, a CD4 binding site bNAb, have protected against rectal and vaginal SHIV challenges in prior macaque studies. Garber and colleagues evaluated the protective efficacy of these bNABs against penile or intravenous SHIV challenges (Abstract 100). Macaques were administered a single subcutaneous injection of 10-1074 alone or in combination with 3BNC117 followed by weekly penile or intravenous (IV) challenges until they were systemically infected. Animals administered 10-1074 became infected after a median of 15.5 penile challenges, compared with the control condition in which they were infected after a median of 2.5 penile challenges. One animal that became infected early had evidence of an anti-drug antibody response. In the IV challenge model, macaques receiving 10-1074 and 3BNC 117 became infected after a median of 5 challenges, compared with a median of 1 challenge in the control animals. There were no differences in peak viremia in animals receiving the bNAbs versus control for either penile or IV SHIV challenges. Both bNABs reached peak levels at 1 week, but 10-1074 reached higher levels and achieved greater persistence in vivo. As levels of 3BNC117 were undetectable at the time of SHIV breakthrough, the authors suggested that protection in these animals was being provided predominantly by 10-1074. They also reported that plasma levels associated with breakthrough infection were similar for all mucosal routes of HIV acquisition (penile, vaginal and rectal), but was higher for IV challenges, which may reflect the higher challenge virus dose. These findings support the continued development of 10-1074 as a long-acting prevention method for men, women, and PWID.

PrEP Uptake and the PrEP Continuum

Several studies tested novel strategies to increase uptake of PrEP in black MSM, a population highly vulnerable to HIV infection. Teixeira da Sliva and colleagues evaluated an intervention to link black MSM to PrEP as part of partner notification and network testing services (Abstract 954). In this pilot study, 143 participants were randomly assigned to a 65-minute face-to-face session with an interventionist to develop an individualized linkage roadmap followed by mini-booster sessions by phone or care as usual. Although overall linkage to PrEP care was low, participants in the intervention arm were 2.55-times more likely to be linked to PrEP care than those in the control arm (23% vs 10%), and were more likely to initiate PrEP (19% vs 10%) respectively. Participants linked to PrEP care were more likely to be older and less likely to be gay-identified. Staffing turnover and barriers to contacting participants were implementation challenges in this study.

Several studies tested novel strategies to increase uptake of PrEP in men who have sex with men, a population highly vulnerable to HIV infection

Siegler and colleagues piloted a PrEP telemedicine system for young black MSM aged 18 to 30 years in the rural Georgia and Mississippi areas (Abstract 955). The home-based PrEP care intervention (ePrEP) was designed to overcome geographic- and stigma-related barriers to accessing PrEP and included home specimen self-collection kits for HIV and STI testing and creatinine level monitoring (urine, rectal or pharyngeal swabs, and finger prick blood), a telemedicine visit with a clinician for PrEP prescribing, and PrEP navigation support and linkage to care. Among 50 young black MSM recruited through social media advertisements, 25 completed a telemedicine visit and were prescribed PrEP, and 21 picked up a prescription. Only 9 were linked to care after prescription pick-up, with several refusing linkage to care, suggesting possible dissatisfaction with PrEP referral options available locally. The majority of the participants found all intervention components acceptable, with most (93%) willing to use ePrEP in place of a standard clinic visit, and two-thirds reported they were more likely to remain on PrEP if ePrEP were available.

Marcus and colleagues reported on the use of electronic health record (EHR) data to identify potential PrEP candidates in a large health care system (Abstract 105). They developed an HIV risk prediction model using EHR data in a cohort of Kaiser Permanente Northern California members seen between 2007 and 2014. There were 44 predictors retained in the final model, including demographics, social history, laboratory tests and results, medication use, and diagnoses; this model had a high concordance statistic (C-statistic) (0.86) indicating high discrimination between HIV cases and non-cases. The full model performed well when validated prospectively using 2015 to 2017 data (C-statistic, 0.84), and outperformed simpler models including only MSM status and STI positivity (C-statistic, 0.57-0.66), particularly among black individuals. The full model identified nearly half (46%) of new HIV cases among men, by flagging only 2% of the general population, however the model did not identify any HIV cases among women. The investigators concluded that routinely collected EHR data can be used to identify patients at high risk for HIV acquisition. Additional work is needed to optimize this tool for identifying women at risk for HIV.

Finlayson and colleagues assessed temporal changes in PrEP awareness and use among MSM in the United States (Abstract 972). In an analysis of National HIV Behavioral Surveillance data from 2014 to 2017, PrEP awareness in MSM increased from 60% to 90% overall and across all racial/ethnic groups. However PrEP awareness remained lower among black and Hispanic MSM compared with white MSM in 2017, although this was no longer significant after controlling for income, health insurance, and census region. PrEP use increased overall from 6% to 35% during this period, also with increases across all racial/ethnic groups, however fewer black MSM reported PrEP use when compared with white MSM in 2017 (30% vs 42%, respectively). Several presentations focused on PrEP attitudes and use in the Chicago metropolitan area. Mustanski and colleagues evaluated the association between PrEP stigma and PrEP uptake and adherence in 105 young MSM and transgender women enrolled in the RADAR cohort study (Abstract 988). They found that participants with higher positive attitudes toward PrEP were more likely to report current PrEP use (OR, 5.05), and participants who reported higher PrEP stigma were less likely to report current PrEP use (OR, 0.50). Additionally, participants who reported missing at least 1 dose in the past week had higher stigma scores. These results suggest that interventions to reduce stigma and improve positive attitudes toward PrEP could increase PrEP uptake and adherence. In the same cohort, Phillips and colleagues evaluated the impact of a citywide advertising campaign, PrEP4Love, on PrEP uptake. Overall, 76% of participants had seen an advertisement for PrEP in Chicago (Abstract 974). Those who had seen the PrEP4Love advertisements were 2.8 times as likely to have a conversation with a medical practitioner about PrEP, twice as likely to have initiated a conversation about PrEP, and 1.9-times as likely to have taken PrEP in the past 6 months. Those who had seen the advertisements were also more likely to perceive that their friends and gay or bisexual men nationwide were taking PrEP, which could help reduce perceived stigma. As those who had seen the advertisements were more likely to initiate discussions with clinicians about PrEP, it is recommended that those rolling out PrEP campaigns should host trainings with medical practitioners on PrEP to prepare them for these conversations.

Two presentations focused on PrEP attitudes and uptake in cisgender women in the United States. Hirschhorn

presented on PrEP knowledge, attitudes, and experience among 370 black cisgender women in Chicago (Abstract 978). Overall, 38% met criteria for PrEP, and only 30% had heard of PrEP. Despite low levels of PrEP knowledge, 29% considered starting PrEP in the next 6 months, with Latina women, those with a recent STI or more worried about HIV, and those with increased belief in PrEP's effectiveness more likely to have considered initiating PrEP. In qualitative data, women thought that open communication and trust with their practitioner were key during the PrEP decision-making process. Although women reported seeing PrEP advertisements, they thought they could be better tailored for women and their community. Blumenthal and colleagues presented on HIV risk and characteristics of women seeking PrEP in a demonstration project (Abstract 979). The 136 women enrolled were aggregated into 3 HIV risk groups: being in a serodiscordant relationship (47%), having partners of unknown HIV risk behavior (38%), and engaging in sex work (15%). Sex workers reported higher numbers of partners, and were more likely to report problem drinking and intimate partner violence in the past year. Women in a serodiscordant relationship were less likely to report taking PrEP to protect themselves from HIV (self-focused) compared with sex workers and women with unknown partner risk (33% vs 95% and 85%, respectively; $P<.001$). Although most (80%) women reporting a main partner were aware of their partner's HIV status, black women were less likely to know their partner's HIV status, than white or Latina women (28% vs 58% and 56%, respectively; $P=.03$). Given the differences in HIV risk profiles and motivations, the investigators suggest that interventions to increase uptake of PrEP among women may need to be tailored by HIV risk group.

Interventions to increase uptake of PrEP among women may need to be tailored by HIV risk group

Liu and colleagues evaluated the PrEP continuum in the San Francisco Bay Area using a mobile phone survey (Abstract 973). Among 893 HIV-uninfected MSM and transgender women enrolled between June 2018 and February 2019, PrEP awareness was high (≥95%) in both MSM and transgender women, with 48% of MSM and 41% of transgender women having ever initiated PrEP. Current PrEP use was lower among transgender women than among MSM (20% vs 39%, respectively), as was reported high adherence (17% vs 37%, respectively). The most common reasons for PrEP discontinuation included not feeling at risk for HIV (42%), insurance or access issues (27%), adverse effects or concerns about these effects (20%), and adherence concerns (5%). PrEP initiation was lower in Latinx participants, and younger participants and transgender women had lower PrEP persistence. Participants reported that novel PrEP dosing strategies and formulations, particularly on-demand PrEP, could increase PrEP initiation or reinitiation among those who had previously discontinued PrEP. Of note, on-demand PrEP is not recommended in cisgender women or transgender women on hormone treatment.

Toy and colleagues assessed uptake of PrEP in a publicly funded population-based program in British Columbia, Canada (Abstract 956). During the first year of their program in 2018, there were 3351 PrEP applicants, 98% of whom met eligibility criteria. Almost all were men (98%) and resided in the Greater Vancouver area (84%), with only 2.3% in a rural location. There were 554 enrolling PrEP prescribers in their program, of whom 52% had no previous HIV care or treatment experience. PrEP discontinuations or lapses in PrEP prescription were noted in only 9% of clients, and there have only been 2 cases of HIV seroconversion to date, both occurring in individuals who had discontinued PrEP.

Koppe and colleagues evaluated non-prescription PrEP use in Germany (Abstract 957). Among 2005 PrEP users recruited, 79% completed an anonymous online survey. Overall, 20% of participants used non-prescription sources; these individuals had used PrEP longer than PrEP users with prescription drug use, were more likely to use PrEP intermittently or on-demand, and were at higher risk for not completing medical test prior to initiating PrEP or during PrEP use. The investigators highlighted the need for patients to access PrEP through healthcare systems to support the safe use of PrEP.

Lubwama and colleagues reported on the scale-up of PrEP for key populations in Uganda (Abstract 959). From July 2017 to June 2018, 3846 individuals initiated PrEP through their national program: 67% were sex workers, 9% MSM, 0.4% transgender persons, and 24% other key and priority populations. As uptake was initially low in urban sites, they changed service delivery models to include community-based MSM-friendly drop-in centers, which resulted in a 36% increase in MSM uptake. Retention at 3 and 6 months was low for sex workers and fisherfolk, and somewhat higher for serodiscordant couples. These results indicate that retention strategies should be strengthened, particularly for sex workers and fisherfolk who may be highly mobile.

To inform PrEP delivery to FSWs, Lancaster and colleagues evaluated preferences for PrEP delivery among 150 FSWs in Malawi using a discrete choice experiment (Abstract 958). They found that dispensing location was the most important factor for PrEP delivery, with women preferring family planning clinics or non-governmental organization supported drop-in centers. Provision of additional services was the second important factor, with cervical cancer screening and contraceptive provision being the most preferred services. Clinic wait time was the least important factor, and pregnancy testing and partner risk reduction counseling were less preferred services.

Omari and colleagues evaluated the PrEP cascade among Nigerian MSM (Abstract 977). Among 614 participants recruited through responded driven sampling and approached for PrEP initiation, 93% showed interest in taking

PrEP daily or after a sex act, 73% were successfully contacted, 55% scheduled an appointment, 51% attended a scheduled appointment, and 49% initiated PrEP. Younger MSM under 25 years of age and Muslims were less likely to be successfully contacted and scheduled for a PrEP appointment. Higher social support was associated with being successfully contacted, scheduled for an appointment, and initiating PrEP. The investigators suggest use of online support groups and community pharmacies to increase social network support could improve PrEP uptake among Nigerian MSM. Oluoch and colleagues evaluated PrEP uptake among adolescent girls and young women (AGYW) in a prospective cohort study in Kenya (Abstract 964). Among 400 AGYW aged 16 to 20 years, 42% were assessed as eligible for PrEP, of whom 15% had a laboratory confirmed STI. Of the 168 AGYW eligible for and offered PrEP, only 9 (5%) accepted a PrEP prescription, 4 of whom had a confirmed STI; this was despite over three-quarters of those eligible for PrEP reporting condomless sex at their last sexual encounter. As PrEP uptake remained low in a setting of experienced PrEP counselors and a girl-friendly environment with easy access to PrEP, the investigators highlight the need to gain a better understanding of AGYW perspectives and factors that would support their uptake of PrEP for HIV prevention.

Poteat and colleagues presented data on PrEP awareness and willingness among transgender women in South Africa (Abstract 981). Among 214 participants enrolled in the T-MAPP (Transgender Women Mobilizing and Preparing for High-Impact Prevention) study, 51% had heard of PrEP. Among those aware of PrEP, 83% knew where to get PrEP, and 40% knew other transgender women taking PrEP. Among HIV-uninfected participants, 15% had ever taken PrEP, and 11% were currently on PrEP; 52% of PrEP-naive participants were willing to take PrEP. Of concern, 21% of PrEP users reported that a healthcare practitioner had told them to stop hormone therapy and 16% had their hormone dose changed by their practitioner because they were taking PrEP. These results highlight the need to increase PrEP awareness in transgender communities. The researchers emphasize the importance of including transgender women in designing strategies to increase PrEP use in these communities.

Among 7250 PrEP users in a commercial research database and 349 PrEP users in a Medicaid database, Medicaid-insured PrEP users had shorter persistence than commercially insured PrEP users

PrEP Persistence, Adherence, and Discontinuations

Huang and colleagues reported on PrEP persistence in 2 cohorts of PrEP users with either commercial or Medicaid insurance from 2011 and 2016 (Abstract 106). Non-persistence was defined as having a gap in prescription fills for more than 30 days. Among 7250 PrEP users in a commercial research database and 349 PrEP users in a Medicaid database, Medicaid-insured PrEP users had shorter persistence than commercially insured PrEP users (median, 7.6 vs 14.5 months, respectively), with 34% versus 56% of PrEP users persisting at 12 months, respectively. In multivariable models, younger age, female sex, and living in a rural area were associated with non-persistence among commercially insured PrEP users; younger age, female sex, and black race were associated with non-persistence among Medicaid-insured PrEP users. The investigators conclude that tailored interventions are needed to improve PrEP persistence in different populations, particularly among those with the highest rates of new HIV diagnoses.

Several presentations evaluated patterns and reasons for PrEP discontinuations in different populations. Serota and colleagues assessed PrEP persistence and discontinuations in an observational cohort of 298 young black MSM in Atlanta (Abstract 963). Among 125 participants who initiated PrEP, 37% remained fully persistent, 63% discontinued PrEP for 2 or more weeks at least once during the study, and 31% had stopped PrEP and never restarted. Frequent stopping and restarting PrEP were common in the cohort; overall person-time on PrEP after initiation was 69%. The median time to first discontinuation was 219 days, and the median time to final discontinuation was 690 days. Younger age, marijuana use, having an STI in the past 12 months, and having fewer than 3 anal sex partners in the past 6 months were associated with PrEP discontinuation. As HIV incidence remained high in this cohort at 6% despite access to PrEP, these results highlight the need for interventions tailored to youth and those who use substances to support PrEP persistence. The investigators suggest future research to evaluate the utility of on-demand PrEP in young MSM who may discontinue PrEP due to lower levels of risk activity. Newcomb and colleagues evaluated predictors of PrEP discontinuation among young MSM and transgender women in Chicago (Abstract 989). Older participants were more likely to discontinue PrEP, and bisexual individuals were less likely to discontinue PrEP. Young MSM and transgender women with increasing condomless anal sex were less likely to discontinue PrEP, as were those with health insurance, and those entering into a relationship were more likely to stop PrEP.

Koppe evaluated reasons for stopping PrEP among PrEP users in Germany (Abstract 990). The most common reasons for stopping PrEP included uses related to taking the medication (45%), a change in partner situation (32%), access issues (28%), and other prevention strategies being sufficient (25%). PrEP discontinuation was associated with younger age, having used PrEP intermittently, being unhappy with their current sex life, and always or often using condoms. However, more than a third of former PrEP users reported inconsistent condom use, highlighting the need for HIV prevention strategies tailored to this population.

Wahome and colleagues evaluated factors associated with refusing or stopping PrEP among MSM in Kenya (Abstract 991). Among 143 MSM who initiated PrEP, 22% stopped PrEP. Lower education and paying for sex were associated with refusing or stopping PrEP. Qualitative data indicated that misconceptions about PrEP and low perception of HIV risk contributed to refusing PrEP, and pill burden, stigma, storage challenges, and adverse effects contributed to stopping PrEP. These results highlight the need for community engagement and education to correct misconceptions, increase awareness, and reduce PrEP-related stigma among Kenyan MSM.

Kagaayi and colleagues presented data on acceptability and retention of clients on PrEP in Uganda (Abstract 997). Among 2980 individuals screened for PrEP, 94% were eligible, and 93% enrolled on PrEP. Overall, 51% were sex workers, 22% fisherfolk, and 13% truck drivers. Retention dropped rapidly, with median retention of 45 days. Among women, loss to follow-up was higher among AGYW and fisherfolk, than among serodiscordant couples. Among men, fisherfolk and truck drivers had lower retention. Similarly, Olsen and colleagues evaluated short-term retention on PrEP in the Democratic Republic of Congo (Abstract 996). Among 356 individuals who initiated PrEP, 77% were FSWs, 20% MSM, and 2% PWID. Overall retention was 64% at month 1 but increased to 82% at month 3 and 86% at month 6 as a result of increased outreach efforts. Irungu and colleagues evaluated PrEP use among African men and women continuing PrEP in public health clinics in the Partners Scale-up Project (Abstract 992). Among 4205 PrEP initiators, 85% had an HIV-positive partner. Overall, 65% continued PrEP use at 3 months. PrEP continuation was associated with age 30 years and older, having an HIV-positive partner, and female sex.Among 71 dried blood samples tested, 96% had detectable TFV-DP, with a median TFV-DP concentration of 515 fmol/punch. These data support the continued programmatic implementation of PrEP in public health settings in Africa, particularly when additional support can be provided for long-term retention.

Several studies focused on PrEP adherence and persistence among young women in Africa. Mugwanya and colleagues evaluated PrEP persistence in African adolescents and young women in maternal child health and family planning clinics in Kenya (Abstract 993). Among 2304 women who initiated PrEP, continuation rates were 21% and 10% at 3 and 6 months, respectively. PrEP continuation rates were higher among women with HIV-positive male partners (52% continuing at 3 months) and in women 35 years and older (37% continuing at 3 months). The most common reasons for discontinuing PrEP included low self-perceived HIV risk, adverse effects, pill burden, and that partner is HIV negative. Celum and colleagues demonstrated high PrEP adherence among AGYW in Cape Town (Abstract 994). Participants were provided adherence counseling including drug level feedback and half were randomly assigned to receive financial incentives for achieving high drug levels in dried blood spots. Among 200 young women (median age, 19 years) who initiated PrEP, half had high adherence based on TFV-DP levels in dried blood spots at 3 months, and 80% had medium or better adherence at 2 and 3 months. High PrEP adherence was associated with having an HIV-positive or unknown status partner, not having sex in the prior 30 days, and disclosing plans to give PrEP to someone else. Celum and colleagues also evaluated PrEP adherence among young African women in the HPTN 082 study (Abstract 995). Among 427 women (median age, 21 years) who started PrEP, 84% had detectable TFV-DP levels at month 3, 25% had levels at or above 700 fmol/punch (associated with 100% PrEP effectiveness in MSM), and 23% had levels between 350 and 699 fmol/punch. At month 3, 70% of women reported they attended at least 1 adherence club offered through the study. Predictors of high adherence at month 3 were attending an adherence club, not reporting symptoms of depression, and number of sexual partners. These disparate results across studies highlight the need for additional research to better understand the support young women need to achieve adherence and persistence on PrEP.

Several posters described the use of urine testing for tenofovir to measure PrEP adherence. Gandhi presented on

Rigorous screening, including nucleic acid amplification testing, can reduce PrEP initiation during undetected HIV infection

the validation of a novel urine tenofovir immunoassay for real time PrEP and ART adherence testing (Abstract 464). When tested on 637 urine samples from patients taking 2, 4, or 7 doses per week using directly observed dosing, the sensitivity and specificity of the urine immunoassay was 99% and 94%, respectively. A cutoff of 1500 ng/mL accurately classified 98% of patients who took a dose within 24 hours as adherent, and was chosen as the cut-off for a point-of-care urine test using a lateral flow immunoassay. This test will be low cost (<$2/assay) with a result available in approximately 5 minutes. She pointed to limitations of the test, including it being a short-term measure and providing a yes or no response. However, a more expensive urine test with a reader will have gradations of adherence. Spinelli and colleagues evaluated the use of this urine assay in the iPrEx Open Label Extension (Abstract 947). Among 125 participants in the urine substudy, the median urine tenofovir level was 15,000 ng/mL in those who remained HIV-negative, 5550 ng/mL among 11 participants who eventually seroconverted, and below 1000 ng/mL in all 9 participants at the time of seroconversion. Low (<1000 ng/mL) versus high (>25,000 ng/mL) urine tenofovir levels were associated with 14-fold higher odds of future seroconversion. The investigators point to the potential utility of point-of-care urine testing to trigger real-time adherence

feedback and interventions in the setting of low adherence.

Drug Resistance and PrEP Failures

Misra and colleagues evaluated the impact of PrEP on drug resistance and acute HIV infection in New York City (Abstract 107). New York State guidelines recommend nucleic acid amplification testing (NAAT) for persons with symptoms of acute HIV infection or a negative antibody test who report condomless sex in the past 4 weeks. Among 3685 recently diagnosed persons assigned for partner services between 2015 and 2017, 2% had reported prediagnosis PrEP use, with a median duration of PrEP use prior to HIV diagnosis of 106 days.

PrEP failures can occur at any point along the PrEP continuum of care, including the user, system, health care practitioner, assay, and drug level

Among individuals with genotypes available (75% of PrEP users and 62% of never users), M184I/V/IV/MV was more prevalent among prior PrEP users versus never-users (29% vs 2%, respectively). No K65R mutations were observed among prior PrEP users. Prediagnosis PrEP users were more likely to be diagnosed with acute HIV infection than never users (33% vs 9%, respectively), possibly due to them receiving regular healthcare. Although a quarter of PrEP users had a negative NAAT prediagnosis, only 5% had a negative NAAT in the 0 to 2 day window before PrEP start, a possible indication of PrEP screening. The investigators suggest that rigorous screening, including NAAT, can reduce PrEP initiation during undetected HIV infection, and highlight the importance of routine genotype testing at HIV diagnosis for persons with a recent history of PrEP use. In a symposium presentation, Molina provided an overview of different types of PrEP failures (Abstract 160). He highlighted that PrEP failures can occur at any point along the PrEP continuum of care, including the user, system, health care practitioner, assay, and drug level. He showed that most PrEP users in 2019 are located in North America, with 275,000 PrEP users in the United States, and called for increased awareness and access to PrEP globally. Challenges with HIV diagnostic testing include ruling out acute HIV infection during PrEP initiation, diagnosing HIV infection during PrEP follow-up, and managing false-positive HIV tests. He reviewed the sequential appearance of viral markers and antibodies during acute HIV infection, with the eclipse period being about 11 days, p24 antigen appearing 6 days later, and the first antibody test appearing in an additional 5 days. In the IPERGAY trial, there were 13 HIV infections in which the Western Blot assay was initially negative; only the fourth-generation antigen/antibody Architect test was able to identify most (11) of these infections, with the remaining 2 with HIV RNA levels under 500 copies/mL. Similarly, there was an 18% non-reactivity rate for the fourth-generation assay in an acute infection study in Thailand. As most individuals are asymptomatic during acute HIV infection, he highlighted International Antiviral Society–USA (IAS-USA) guidelines recommending fourth HIV antigen/antibody testing to determine PrEP eligibility, and to send an HIV RNA assay if acute HIV infection is suspected, even without symptoms.[3] He reviewed data from the Partners PrEP study that showed a delay in detection of HIV infection in the PrEP arm, associated with lower plasma HIV RNA level, but no differences in the Architect signal to cut-off at any stage. In the case of ambiguous HIV test results during PrEP, he reviewed guidelines that recommend repeating serologic tests, RNA tests, and possibly DNA tests, and using tests from another manufacturer, to confirm the presence or absence of infection. Another consideration is whether to continue or stop PrEP: if PrEP adherence has been high and the likelihood of infection low, an option is to continue PrEP to maintain protection, although this may increase the risk of resistance if the individual is infected. Another option is to stop PrEP and reassess HIV status, which may facilitate diagnosis but may put the individual at risk for acquiring HIV during the period off PrEP; a. A third option is to initiate ART, which may be the recommended option if the individual was not adherent to PrEP, raising the likelihood of infection. However, it is important to confirm HIV diagnosis in this scenario.

He pointed to a toll-free PrEPline (1-855-448-7737) in the United States for expert guidance on managing ambiguous HIV test results. Another concern raised is the acquisition of virus resistant to TDF/FTC in the setting of high PrEP adherence; however, to date there have been only a few cases reported in the literature. He reviewed data from animal studies showing 100% protective efficacy of TDF/FTC in macaques challenged rectally with SHIV containing the M184V mutation, which may be due to hyper-susceptibility to TDF in the setting of the M184 mutation. In contrast, reduced TDF/FTC efficacy was observed with the presence of the K65R mutation. Rates of transmitted HIV-1 resistance to TDF/FTC have remained low (<1%) across a number of studies, although in the discussion it was mentioned that rates of K65R mutation may be higher when using more sensitive assays. A case of PrEP failure with TDF/FTC-sensitive virus has been reported in Amsterdam; potential explanations of this breakthrough infection include high virus inoculum, concomitant STI infection with inflammation, possible exposure during a brief period of nonadherence, or variable pharmacokinetics of TDF/FTC in the blood or rectal mucosa. Molina reviewed data from PrEP clinical trials showing that emergence of drug resistance occurred most commonly at enrollment when PrEP was started in the setting of acute HIV infection, with 41% having resistant virus, in almost all cases with the M184V mutation. In contrast, rates of resistance were below 3% among individuals who seroconverted after enrollment. He highlighted the importance of ruling

out acute HIV infection before starting PrEP, and testing for HIV RNA level in baseline samples, if available, in cases of infection being detected at the first follow-up visit. In terms of treatment of HIV infection occurring when on PrEP, he recommended starting ART immediately with a regimen with high barrier to resistance, including a TDF/FTC or TAF/FTC backbone plus boosted darunavir or dolutegravir/bictegravir. Regimens can then be simplified after HIV genotype is available. It is important to reinforce adherence to ART in these scenarios.

Safety of PrEP

In a themed discussion, 2 presentations focused on renal safety and monitoring among TDF/FTC PrEP users (Themed DIscussion TD-14). Liegeon and colleagues assessed the renal safety of on-demand TDF/FTC PrEP in the National Agency for AIDS Research (ANRS)-IPERGAY randomized trial and open-label extension (Abstract 960). A median of 15 and 18 pills per month were used during the blinded and open-label phases of the study respectively. Among 389 participants enrolled in the blinded phase, the mean slope of eGFR decline per year was not statistically significantly different between the TDF/FTC and placebo groups (-1.53 mL/min vs -0.88 mL/min, respectively; $P = .27$). Furthermore, the slope of eGFR reduction was not greater in participants with baseline eGFR below 90/mL/min, age above 40 years, or with hypertension. A dose-response relationship was seen between higher TDF/FTC exposure as measured by number of pills taken and tenofovir plasma concentrations and lower eGFR at the following visit. The investigators suggest that the overall reduction and intermittent exposure to TDF/FTC may explain the good renal safety observed with on-demand PrEP. Pintye and colleagues evaluated the implementation of point-of-care creatinine testing within a large-scale PrEP program in Kenya (Abstract 961). From June 2017 to December 2018, 4149 HIV-uninfected women seeking routine antenatal, postnatal, and family planning services were screened for PrEP per national guidelines, which recommend, but do not require, creatinine testing prior to PrEP initiation. In this PrEP implementation program, the feasibility of assessing creatinine level using validated, handheld point-of-care machines was demonstrated. Overall, low creatinine clearance rate was rare, with only 8 (0.2%) having a creatinine clearance rate below 50 mL/min, and 122 (3%) having a creatinine clearance rate below 60 mL/min. These findings support the recommendation of not mandating creatinine testing at TDF/FTC PrEP initiation.

Spinelli and colleagues assessed declines in bone mineral density associated with long-term TDF/FTC exposure in the iPrEx Open-Label Extension study (Abstract 946). Among 254 MSM and transgender women in a dual-energy X-ray absorptiometry (DXA) substudy, there was dose-dependent decline in spine bone mineral density by increasing average weekly adherence as measured by TFV-DP levels in dried blood spots, with a 1.2% and 0.5% mean decline in spine and hip bone mineral density, respectively, in highly adherent PrEP users. Additional decline did not occur after 24 weeks of DXA assessment. The investigators suggest that dose-limiting strategies such as intermittent PrEP, should be evaluated for their impact on toxic effects.

Mikati and colleagues assessed the safety of same-day PrEP starts within sexual health clinics in New York City (Abstract 962). Following a negative rapid HIV test, PrEP candidates were provided a 30-day supply of TDF/FTC prior to return of other laboratory results if no medical contraindications are present, including acute HIV symptoms, history of kidney disease, or hepatitis B infection. Among 1437 PrEP initiation candidates evaluated, 97% started PrEP the same day, of whom 99% had no medical contraindications to PrEP. The prevalence of having any PrEP contraindication was higher among delayed versus immediate PrEP patients (14% vs 0.7%, respectively; $P < .001$). Among 1387 immediate PrEP patients, 10 had medical contraindications, including 2 with positive HIV NAAT, 2 with GFR below 60 mL/min, and 6 with reactive hepatitis B surface antigen (HbSAg), considered a relative contraindication. Among the 50 (3.5%) individuals who delayed PrEP, 7 had a medical contraindication, including 1 with a positive HIV NAAT, 4 with GFR below 60 mL/min, and 2 with reactive HbSAg. Patients older than 40 years were 6-times more likely to have a medical contraindication than younger patients, although these were uncommon in both age groups (3% vs 0.5%, respectively; $P = .01$). Among the 43 delayed PrEP patients who did not have medical contraindications, only 35% initiated PrEP within 60 days. Delayed PrEP patients were more likely to be women, older than 40 years, and have medical contraindication to PrEP initiation; none of the 58 women evaluated for PrEP had actual medical contraindications to PrEP initiation. The investigators concluded that immediate PrEP initiation is a safe and promising model to increase PrEP initiations among patients within walk-in settings such as sexual health clinics.

Immediate PrEP initiation is a safe and promising model to increase PrEP initiations among patients within walk-in settings such as sexual health clinics

Cost-effectiveness

Wang and colleagues evaluated the cost-effectiveness of PrEP among black and white adolescent MSM aged 16 to 18 years in the United States (Abstract 1083). The incremental cost effectiveness ratio was $33,064 per quality-adjusted life year (QALY) gained for black MSM, and $427,788 for white MSM. Using a below $100,000/ QALY gained as a benchmark for cost-effectiveness, these results suggest that PrEP is cost effective in black but not white adolescent MSM in high prevalence US settings.

Roberts and colleagues evaluated the incremental costs of PrEP delivery in antenatal, post-natal, and family planning

clinics in Kenya (Abstract 1082). Overall, the cost per client-month of PrEP dispensed was $26.52, which is similar to costs reported for delivery to other key populations. Total annual costs could be reduced by postponing creatinine testing and prioritizing PrEP to those at high risk for HIV acquisition. Van Vliet and colleagues evaluated the cost-effectiveness of targeting long-acting injectable PrEP to injectable contraceptive users in South Africa (Abstract 1077). The impact of long-acting PrEP on number of infections averted depends on its effectiveness. Long-acting PrEP will only be cost-effective at a price of $40 or less, assuming ART coverage of 85% in 2030; PrEP will not be cost-effective at an ART coverage of 95%. If low prices are not possible, they recommend targeting long-acting PrEP for women at highest risk of HIV infection.

All cited abstracts appear in the CROI 2019 Abstracts eBook, available online at www.CROIconference.org

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Additional References Cited in Text

1. Teran RA, Downing MJ, Chiasson MA, et al. Comparing self-reported viral load with home-collected HIV-RNA among high-risk MSM [CROI Abstract 997]. In Special Issue: Abstracts From the 2018 Conference and Opportunistic Infections. *Top Antivir Med*. 2018;26(suppl 1):454s.
2. Massud I, Cong M, Ruone S, et al. Oral FTC/TAF combination prevents vaginal SHIV infection in pigtail macaques [CROI Abstract]. In Special Issue: Abstracts From the 2018 Conference on Retroviruses and Opportunistic Infections. *Top Antivir Med*. 2018;26(1s (suppl 1):35s-36s.
3. Saag MS, Benson CA, Gandhi RT, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2018 recommendations of the International Antiviral Society-USA panel. *JAMA*. 2018;320(4):379-396.

Top Antivir Med. 2019;27(2):**$$$**-**$$$**.

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