Invited Review

CROI 2021: Epidemiologic Trends in the HIV and SARS-CoV-2 Pandemics and HIV Prevention Research

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At the 2021 virtual *Conference on Retroviruses and Opportunistic Infections , several speakers described the disparities in both HIV and SARS-CoV-2 infections and outcomes in racial and ethnic minorities. A household survey suggested that there may have been more than 39 million SARS-CoV-2 infections in the United States by October 30, 2020, with an estimated infection fatality ratio of 0.64%; this compares with an estimated 7.3 million confirmed cases at that time. Several presentations found severe disruptions in HIV testing, prevention, and treatment services during COVID-19-related lockdowns; models suggest that severe interruption of antiretroviral therapy services could lead to a 1.5- to 3-fold increase in mortality. HIV testing remains the gateway to both treatment and prevention, and innovative strategies to improve testing uptake were presented. Preexposure prophylaxis (PrEP) agents may delay detection of HIV infection using standard testing algorithms. Data were presented on promising investigational PrEP agents, including cabotegravir, islatravir, and the dapivirine vaginal ring. Progress is being made in point-of-care assays to measure PrEP adherence with tenofovir-based regimens. HIV incidence remains low in populations of PrEP users, with higher rates among persons who never refilled their prescription. More work remains to be done to increase PrEP uptake among populations most heavily impacted by HIV.*

Keywords: HIV, CROI 2021, SARS-CoV-2, pandemic, PrEP, HIV prevention, COVID, testing, STI

HIV Epidemiology

Hildreth gave an excellent plenary on racial and ethnic disparities in both HIV and COVID-19 (Abstract 15). He traced US governmental lack of involvement in both epidemics in their early phases, leading to worsening situations. He also pointed out that inequities are best understood in terms of their social determinants of health, and named 5 components: 1) education access and quality; 2) health care quality; 3) neighborhood and built environment; 4) social and community context; and 5) economic stability. He gave examples of how inequities in these areas lead to disparities in COVID-19 outcomes, including issues such as poor access to health information, poorly managed chronic diseases, multi-generational households, and mass incarceration. He also pointed out that from 1908 to 2008, the United States never had more than 2.5% of its physicians being black. In fact, currently only 5% of physicians are black and only 5.8% are Latinx, not at all representative of their proportions in the general population. He ended by discussing the importance of health equity (rather than equality), in which each individual and community has their needs met, requiring different interventions for different groups. He called for a coordinated response across disciplines to do the hard work required to address health equity in the United States.

Iqbal and colleagues pointed out that in 2018, 66% of all new HIV diagnoses in the United States were among men who have sex with men (MSM), and most of those were among black and Latino MSM (Abstract 106). The US Centers for Disease Control and Prevention (CDC) funded 7 jurisdictions to conduct THRIVE (Targeted Highly Effective Interventions to Reverse the Epidemic), a collaborative effort between local health departments, community-based organizations (CBOs), health care practitioners, and behavioral and social service providers to improve HIV prevention and care services for black and Latino MSM. Included in the services provided were increased HIV testing, provision of preexposure prophylaxis (PrEP) through CBOs and clinics, practitioner capacity building to provide PrEP, and social and community education campaigns. The 7 THRIVE-funded jurisdictions saw significant reductions in new HIV diagnoses compared with 12 jurisdictions that qualified for THRIVE funding but were not funded: -4.2 vs 0%, respectively, estimated annual percentage change (EAPC) for black populations, and -2.7 vs +1.7, respectively, EAPC for Latinx populations. The authors acknowledged that these were ecological associations only (cannot attribute causality) and that substantially more progress could be made. Nonetheless, these data suggest that supporting collaboration between health departments, CBOs, and clinical and social service providers to drive down infections in these heavily impacted populations may be successful.

Sembajwe and colleagues reported on rates of new HIV diagnoses among American Indians/Alaskan Natives (AI/AN), both nationally, and in persons utilizing services through the Indian

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Health Service (IHS) (Abstract 108). She noted that from 2012 to 2016, there was a 34% increase in new diagnoses among AI/AN overall, and that the rate increased 58% among AI/AN MSM over that time period. In the period of this study (2014-2018), the rates remained stable overall, both nationally and in the IHS, with increases among AI/AN aged 13 to 34 years and aged 35 to 44 years. Among new diagnoses, 63% of them were among MSM, 11% in people who inject drugs (PWID), 12% in MSM/PWID, and 14% in heterosexuals. Overall, death rates declined by 31.4% over that time. The stable rate overall, as well as the increased rates in the 2 age tiers, indicate that we are not making substantial progress in the population of AI/AN, and that more effort is needed to address the disparate rates of diagnoses in these populations.

Golden and colleagues evaluated different methods for determining the proportion of new diagnoses that are designated as "late" – being newly diagnosed with HIV within 12 months of an AIDS diagnosis or a CD4+ count below 200 cells/μL (Abstract 644). He pointed out that in 2018, the rate of late diagnosis was 20.8% nationally. Using data from King County, Washington, from 2010 to 2020, he found that using a standard definition, 25.9% of diagnoses would be designated as late. However, if one were to remove all cases with acute HIV infection or with a negative HIV test within 2 years, that proportion considered "late" would decrease to 20%. If one were further to remove all persons with a self-reported previous HIV diagnosis and persons within 1 year of immigration to the United States, that would further drive down the estimated proportion of late diagnoses to 16.8%. Using the most stringent definition of late diagnosis would have reduced the overall proportion of new diagnoses in King County by 35.1% overall, with even higher proportional reductions among MSM (37.8%) and African-born persons (48.3%).

Based on the natural history of HIV infection and the expected CD4+ count after infection, even if the median time to diagnosis were 9 months, one might expect that a minimum of 8% of new diagnoses would be counted as late. The authors suggest that it is unlikely that we will be able to get late diagnoses to be reduced below 8% to 10%, and that integrated HIV surveillance data into estimates of late diagnoses may improve their accuracy.

Prata Menezes and colleagues presented data on 7380 HIV-negative PWID in India and the association between injection network characteristics and use of HIV prevention services (Abstract 719). They found that the median injection network size was 3 partners, but 17% reported more than 10 injection partners. Overall, only 15% of participants received an HIV test in the previous 6 months, 20% of participants engaged in medication for opioid use disorder in the prior month, and 27% of participants used syringe access services in the prior month; only 3% of participants engaged in all 3 prevention modalities. Injection network size was not associated with receiving HIV testing. However, compared with persons with 0 or 1 injection partner, those with more than 10 partners were less likely to use medication for opioid use disorder (adjusted odds ratio [aOR], 0.55; $P<.01$) but more likely to access syringe services (aOR, 1.54; $P<.01$). Sharing injection equipment with a known HIV-positive partner was associated with having a recent HIV test (aOR, 2.54; $P=.04$). The authors concluded that engagement in prevention services may be associated with perception of need, such as HIV testing among persons injecting with a known positive partner. However, persons with larger injection networks were more likely to use community-based services (ie, syringe access) than facility-based services (ie, HIV testing, medication for opioid use disorder), leading the authors to hypothesize that some of these services should be offered in community settings.

Pines and colleagues presented data on transmission patterns between populations in the Tijuana/San Diego Border Region using phylogenetics (Abstract 652). They found that 50% of transmission events were from people who inject drugs transmitting to MSM, 30% from transgender women who inject drugs to transgender women who do not inject drugs, and 20% from MSM to transgender women. Transactional sex accounted for 32% of transmissions. These results suggest that interventions targeting transactional sex and injection drug use could have a substantial impact on the local epidemic.

Modeling HIV Outcomes

Fojo and colleagues developed a web-based tool to help local policy makers determine the most impactful combination of testing, PrEP, and treatment services within a given jurisdiction (Abstract 668). The user can select a jurisdiction in the United States, and look at the impact of scale up of these interventions in select populations (by age, race/ethnicity, sex, and risk group).[1]

Schnure and colleagues applied the Johns Hopkins model to 4 US cities: Los Angeles, New York, Atlanta, and Baltimore (Abstract 775). Although there were differences in the specifics of what the cities needed, the overall findings were that scaling up PrEP use among MSM led to substantial reductions in new infections, expanding to include older men had a modest marginal benefit. Working toward viral suppression for persons with HIV of all ages also had a substantial impact on the number of new infections. Although they recommended focusing on treatment for all but PrEP only for younger men, combining both approaches still did not reach the Ending the HIV Epidemic (EHE) target of 90% reduction in new HIV infections by 2030. This suggests that broadly applying both PrEP and viral suppression will be required to achieve these targets.

Booton and colleagues evaluated 14 separate transmission dynamic models to evaluate the contribution of key populations to HIV epidemics in Southern and Eastern Africa (Abstract 669). For female sex workers, their clients, and MSM, the models suggested that they transmit more infections than they acquire over a 10-year period, reflecting ongoing secondary transmissions. Young women, on the other hand, appeared to acquire more infections than

they transmit over a 10-year period. The authors concluded that more than one measure is required to adequately describe the impact of key populations in different geographic locations.

Clement and colleagues created a model to predict the risk of HIV acquisition using electronic health records at Duke University (Abstract 773). They evaluated risk within the entire cohort of 368 incident infections among 1.6 million total patients, as well as among the subset of 93 incident infections in women. Globally, the most predictive variables were race, age, and zip code. For the total cohort, the most predictive variables were hepatitis A virus (HAV) infection, receipt of intramuscular ceftriaxone, and receipt of intramuscular or intravenous penicillin, pointing out that acquiring other sexually acquired infections is a marker for HIV risk. For the women-only cohort, the most predictive variables were HAV infection, buprenorphine treatment, and a history of domestic or sexual abuse. They next plan to use this model to tailor PrEP counseling for persons at high risk for HIV acquisition in a clinical setting.

SARS-CoV-2 Epidemiology

Sullivan and colleagues assessed the cumulative incidence of SARS-CoV-2 infection and epidemic metrics in the United States (Abstract 636). They used an address-based probability sampling schema and mailed 39,500 test kits to US households; approximately 15% of eligible households responded. Using data from nasal swabs and dried blood spots, and adjusting for waning antibody levels, they estimated that the cumulative incidence of SARS-CoV-2 on October 30, 2020, was 12.0%, suggesting that the true number of SARS-CoV-2 infections in the US was more than 39 million, with a 95% credible interval of 34 million to 44 million persons; at that time, only 7.3 million confirmed cases were reported in the United States. The estimated infection fatality ratio was 0.64% (95% credible interval, 0.58%-0.75%). Prevalence ratios (PRs) were significantly higher in Latinx (PR, 3.11) and black (PR, 2.15) than white individuals, higher in persons aged 18 to 34 years (PR, 2.7) and 35 to 44 years (PR, 2.96) than those older than 65 years, and higher in persons living in a metropolitan area (PR, 2.52) than persons in nonurban areas. The authors emphasize the role of household surveys in generating unbiased estimates, and the importance of adjusting for waning antibody levels to generate credible epidemic metrics.

The true number of SARS-CoV-2 infections in the United States on October 30, 2020, may be more than 39 million, rather than the reported 7.3 million

Nash and colleagues reported on risk factors for incident seroconversion from May 2020 to January 2021 in the CHASING (Communities, Households, and SARS-CoV-2 Epidemiology) COVID-19 cohort study (Abstract 637). They recruited 6745 adults from all 50 US states, Washington, DC, Puerto Rico, and Guam. Of 3280 persons who were seronegative at the first time point and had an additional specimen at the second time point (from November 2020 to January 2021), 145 seroconverted, indicating a SARS-CoV-2 seroincidence of 9.3/100 person-years. Demographic factors associated with seroconversion included being male (relative risk [RR], 1.3), Hispanic (RR, 2.1), non-Hispanic black (RR, 1.8), living in a rural area (RR, 1.5), and living in the Midwest (RR, 1.6), South (RR, 1.7), or West (RR, 1.3) compared with the Northeast. Essential workers were also at increased risk (RR, 1.7). A number of household and behavioral factors were associated with seroconversion including living in a more crowded household, having a household member with COVID-19, indoor dining, visiting places of worship, indoor grocery shopping, visiting non-household members, working indoors, attending a salon or gym, gathering in groups of 10 or more either indoors or outdoors, and recent air travel. These risk factors for more recent seroconversion emphasize the importance of non-pharmacologic behavioral interventions in controlling the spread of the virus, and the continued increased risk among people of color and essential workers.

Tordoff and colleagues analyzed the phylogenetics of SARS-CoV-2 introductions into Washington State (WA) (Abstract 138). She reminded us that the first US case was identified in Washington State on January 21, 2020, with the second case on February 28, 2020, which was likely due to a separate introduction. After sampling approximately 6% of confirmed cases in WA (1.8% of all estimated infections), they found at least 287 distinct introductions of SARS-CoV-2 into WA, and 204 exported lineages out of WA through mid-September 2020. Almost 90% of all introductions were with the spike 614G variant, and 42% of the exported variants were of the A clade. Overall, 73% of introductions occurred before May 1, 2020, with the first wave of introductions peaking on March 29, 2020, 6 days before the WA "Stay-Home Stay-Healthy" order. Two waves of exported lineages peaked on January 29, 2020, and March 30, 2020. These patterns suggest that lockdowns can be immediately effective in reducing interstate transmission. They estimated that 61% of introductions into WA were from elsewhere in the United States; with only 28% of introductions in western WA coming from eastern WA, but 65% of introductions in eastern WA coming from western WA. They attributed this to the transportation routes (roadways, airports) providing greater access from out of state to western WA. They estimated that the size of downstream clades from a single introduction ranged from 1 to 2193, with 72% resulting in a single WA sequence, indicating that many introductions do not

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result in substantial local transmission. However, 6% resulted in 6 to 20 sequences and 6% in more than 20 sequences, suggesting long chains of local transmission.

Smith and colleagues presented data on the dynamics of SARS-CoV-2 transmission at the California/Mexico border (Abstract 632). They identified 622 unique introduction events into the region, including 381 clusters of size 3 or greater from 2 or more locations. Their phylogenetic analysis demonstrated bidirectional migration events across the border, and they called for transnational intervention approaches.

Capoferri and colleagues reported on increasing viral diversity of SARS-CoV-2 sequences over time in the United States in 2020 (Abstract 639). They analyzed sequences from 36,299 SARS-CoV-2 genomes accessed before December 15, 2020, when vaccinations began in the United States, and found a 3-fold increase in diversity, with substantial viral divergence over time. They identified at least 47 new amino acid changes, including 3 in the spike protein, that map to known antibody epitopes. They also found mutations in the spike region that were common to the United Kingdom, South African, and Brazilian variants as early as the winter/spring of 2020. The authors underscored the importance of increasing genomic sequencing to track evolution of the virus.

Riou and colleagues presented data exploring the "inverse care law" in Switzerland, a statement that the availability of good medical care varies inversely with the needs of the population served (Abstract 139). They evaluated the association of SARS-CoV-2 testing, test positivity, hospitalizations, intensive care unit (ICU) admissions, and death by socio-economic position (SEP) index, an index by neighborhood that takes into account income, education, profession, and crowding. Among the 1.27 million small neighborhoods in Switzerland, investigators conducted nearly 3 million tests, almost 500,000 of which were positive, with approximately 20,000 hospitalizations, 2000 ICU admissions, and 7600 deaths. They found that increasing SEP index (higher socioeconomic status) was associated with increased SARS-CoV-2 testing but reduced test positivity, hospitalizations, and ICU admissions, with a trend toward reduced mortality, after adjusting all models for age, sex, period, and canton. They concluded that this was an example of the inverse care law, despite universal access to healthcare in Switzerland.

Scully and colleagues reported on sex differences in SARS-CoV-2 outcomes among a cohort of patients presenting for testing and care in the Johns Hopkins Healthcare System (Abstract 140). Test positivity was 8% in women and 9% in men, but differed according to age, with higher positivity rates in men aged 18 to 74 years and higher in women 75 years or older. There were no differences in asymptomatic disease by sex. Among 2626 patients admitted with SARS-CoV-2 infection, Charlson comorbidity scores were similar, although there were differences in the specific comorbidities, with women having more obesity at all ages. Men had higher inflammatory markers, such as ferritin, interleukin (IL)-6, and C-reactive protein. Men aged 18 to 49 years were 2.58-times more likely to have severe disease or die than women. In exploring potential mediators of this difference, adjusting for initial inflammatory laboratory markers dropped the aOR to 1.39, suggesting that the elevated inflammatory markers were a mediator of elevated risk, and should be explored as a possible mechanism of sex differences in outcomes.

Hermann and colleagues evaluated risk factors for hospitalization among 897 patients with polymerase chain reaction (PCR)-positive SARS-CoV-2 infection in Southern Germany (Abstract 633). Overall, 85% of all cases were mild, not requiring hospitalization. Risk factors for hospitalization included age (OR, 1.05/year) and a history of previous lung conditions (OR, 3.09). Female sex was protective (OR, 0.51).

Varshney and colleagues presented data on the association between household overcrowding (defined as having 1 or more persons per room in the household) and the risk of COVID-19 death in the 85 cities in Los Angeles County, the region with the largest number of COVID-19 cases nationally (Abstract 631). They found that the number of overcrowded households had the largest effect on the risk of COVID-19 death (P=.001), followed by the number of cases of COVID-19 (P=.014) and the number of individuals aged 60 years and older (P<.001). This speaks to the structural factors underlying disparities in the distribution of COVID-19 deaths.

Interaction of HIV and SARS-CoV-2

Islam and colleagues evaluated racial/ethnic disparities in COVID-19 diagnoses among people with HIV in the United States (Abstract 141). Using data from the National COVID Cohort Collaborative, a dataset of medical records from 41 sites with more than 3 million patients from January 2020 to January 2021, they found that, among people with HIV, those diagnosed with COVID-19 were more likely to be non-Hispanic black (aOR, 1.59; 95% confidence interval [CI], 1.37-1.86), Hispanic (aOR, 2.17; 95% CI, 1.68-2.83), or non-Hispanic Asian (aOR, 2.18; 95% CI, 1.30-3.63) than white. This study confirms that the racial and ethnic disparities of SARS-CoV-2 infection seen in the general population are also true of the population with HIV.

Research confirms that the racial and ethnic disparities of SARS-CoV-2 infection seen in the general population are also true of the population of people with HIV

Del Amo presented data addressing whether people with HIV are more likely to be tested for SARS-CoV-2, more likely to test positive, and if they test positive, more likely to have more severe outcomes (Abstract 31). The literature is mixed in addressing these questions, but she summarized, that people with HIV are more likely to be

tested for SARS-CoV-2 if their access to health care is the same as persons without HIV, as demonstrated in the VACS (Veterans Aging Cohort Study) database. She also found that in most unadjusted analyses, people with HIV appeared to be more likely to acquire SARS-CoV-2, but in most studies, after adjusting for sociodemographic factors such as age, sex, race/ethnicity, and location, there no longer appeared to be an increased risk. She also found that people with HIV were more likely to have more severe outcomes from SARS-CoV-2 infection in unadjusted analyses, but stated that more data are needed to identify if there is any increased risk after adjusting for comorbidities and other sociodemographic factors. Finally, she asked whether all people with HIV are at equal risk for severe outcomes; this question is not fully answered, with some question about whether or not persons with low CD4+ cell counts might be at higher risk. She cited 3 studies suggesting that persons on tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)-based regimens were at decreased risk of SARS-CoV-2 infection and poor outcomes; there are 2 randomized controlled trials underway to assess the influence of TDF/FTC on prevention and on treatment of SARS-CoV-2.

Park and colleagues evaluated SARS-CoV-2 testing and positivity rates among people with HIV and people without HIV in 6 clinical cohorts in North America (Abstract 626). They found higher testing rates among people with HIV, but similar SARS-CoV-2 positivity among people with and without HIV. Salters and colleagues presented data on SARS-CoV-2 testing positivity among people on antiretroviral therapy (ART) and people on PrEP among drug treatment program patients in British Columbia (Abstract 628). They also found no difference in test positivity between these two populations, that mirrored the overall test positivity in British Columbia.

Lee and colleagues analyzed the impact of HIV infection on COVID-19 outcomes among hospitalized patients in 6 large hospital trusts in England (Abstract 142). They point to the limitations of other analyses, particularly those without matched controls. In this analysis, 6612 patients were admitted to these hospitals during the time of study, with 68 being HIV positive with 181 matched controls. Patients were matched on hospital site, sex, SARS-CoV-2 test date, age, and index of multiple deprivation, a national index that measures socioeconomic deprivation. The primary outcome variable was time from COVID-19 diagnosis to either a 2 point or greater improvement from baseline clinical status, or hospital discharge, whichever came first. On unadjusted analyses, people with HIV had a hospital stay of 10 days, versus 7.5 days for patients without HIV. However, in a multivariable analysis, HIV status was not an independent predictor of SARS-CoV-2 clinical improvement or hospital discharge; clinical frailty score (aOR, 0.79; 95% CI, 0.65-0.95), malignancy (aOR, 0.37; 95% CI, 0.17–0.82), and body mass index less than 25 (aOR, 0.46; 95% CI, 0.21-0.99) were significantly associated with longer time to clinical improvement or hospital discharge.

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Blanco and colleagues also conducted a case control study of death among people with and without HIV who were hospitalized in Spain from February to September 2020 (Abstract 641). They matched 204 controls in a 1:1 fashion to cases based on center, age, sex, and calendar week of admission. People with HIV were significantly more likely to have chronic liver disease (aOR, 8.7) and cardiac disease (aOR, 2.09) and significantly less likely to be obese (aOR, 0.30) than their HIV-negative controls. In a multivariable analysis controlling for chronic liver disease, cardiac disease, and obesity, they found that people with HIV were marginally more likely to die than their HIV-negative controls (aOR, 5.27; 95% CI, 1.00-27.72). In separate multivariable models, factors associated with mortality for people with HIV included age (aOR, 13.72) and chronic obstructive pulmonary disease (aOR, 4.06). Among controls, the only variable significantly associated with mortality was neoplasm (aOR, 8.81). In this analysis, current and nadir CD4+ cell count and CD4+/CD8+ cell ratio, detectable HIV RNA, and specific antiretroviral drugs were not associated with mortality.

Spinelli and colleagues assessed the SARS-CoV-2 seropositivity and binding and neutralizing antibody titers between people with HIV and a matched HIV-negative cohort (matched on age and date of specimen collection) at San Francisco General Hospital (Abstract 627). Using remnant specimens from 955 people with HIV and 1062 without HIV, they found only 3.7% of those with HIV to be seropositive, compared with 7.4% among HIV-negative patients (aOR, 0.48; 95% CI, 0.34-0.71). Latinx patients were significantly more likely than white patients to be SARS-CoV-2 positive (aOR, 7.7; 95% CI, 3.5-17). Severe disease was more common among those with HIV than among HIV-negative patients with SARS-CoV-2 (10% vs 2%; P=.04). IgG titers were 45% lower among people with HIV (95% CI, 22%-61%) than those without HIV, and neutralizing antibody titers were 63% lower (95% CI, 2%-78%). These lower titers raise questions about whether people with HIV have less robust protection against reinfection, and suggest studies need to evaluate the immune response to vaccination among people with HIV.

Kambugu explored the potential impact of the SARS-CoV-2 pandemic on the HIV pandemic globally (Abstract 32). He pointed out that progress was being made in the UNAIDS 90-90-90 goals and the number of new HIV infections globally before the SARS-CoV-2 pandemic, and outlined 3 mechanisms by which COVID-19 may interrupt HIV control measures: 1) COVID-19 mitigation and containment measures (eg, decreased access to health facilities); 2) differential allocation of resources toward COVID-19 responses (eg, diversion of healthcare workers from HIV

to COVID-19 care services); and 3) direct COVID-19 effects (eg, SARS-CoV-2 infection of healthcare workers). He presented models from a consortium of modelers that found that interruption of ART services would have the greatest impact on outcomes, including a 1.5- to 3-fold increase in mortality, should services be severely interrupted. He went on to show global data suggesting substantial declines in HIV testing rates, partner notification services, and PrEP, but lesser impact on ART access. He ended by outlining some mitigation strategies that could be implemented to reduce the risk of decreased services.

Drammeh and colleagues presented data on HIV testing and linkage to care in 11 countries in sub-Saharan Africa (Abstract 143). Practitioner-initiated testing and counseling decreased in 7 countries (64%), and the number of persons testing positive decreased in 10 countries (91%) comparing January to June 2020 with January to June 2019, suggesting that both were impacted by restrictions imposed in health care facilities to limit the spread of SARS-CoV-2. This resulted in an overall decline in the number of persons tested and testing positive of 20% and 23%, respectively. However, in 5 countries, index partner testing and HIV case finding increased by 13% and 17%, respectively, suggesting that this may be a strategy that can be used, even in the midst of a pandemic. Overall, the number of people linked to care decreased in 7 countries, suggesting that more efforts are needed not only to find people with HIV, but to ensure rapid linkage to care.

Menza and colleagues presented data on public health testing of HIV and bacterial sexually transmitted infections (STIs) in Oregon, comparing the period before stay-at-home orders (June-September 2019 and January-February 2020) with during stay-at-home (March-May 2020) and after stay-at-home (June-September 2020), controlling for month (Abstract 144). They found that 4th generation antigen/antibody testing declined by 50% during and by 38% after stay-at-home orders in the state were lifted. Gonorrhea and chlamydia testing decreased by 58% during and 44% after stay-at-home orders. Syphilis testing declined by 58% during and 38% after stay-at-home orders. HIV diagnoses declined by 36% during and increased by 12% after stay-at-home orders, but these differences were not statistically significant. Chlamydia diagnoses were significantly lower during (34%) and after (15%) the stay-at-home period, and gonorrhea diagnoses were only significantly reduced during the stay-at-home period (23%). Primary and secondary syphilis diagnoses increased significantly after stay-at-home orders were lifted (45%), emphasizing the importance of ongoing testing despite the SARS-CoV-2 pandemic. The authors implemented an at-home testing program that delivered HIV and STI testing services through mail-in kits to more than 900 individuals, 38% of whom had never had an HIV test previously.

Primary and secondary syphilis diagnoses increased significantly after stay-at-home orders were lifted, emphasizing the importance of ongoing testing despite the SARS-CoV-2 pandemic

Scott and colleagues compared HIV and viral load testing volume and PrEP visits in San Francisco throughout 2020 (Abstract 730) with volume in 2019, matched by month. They found that HIV testing at 4 laboratories declined to a nadir of 54% of 2019 levels in April 2020, with a partial rebound to 8% to 15% below 2019 levels later in the year. HIV testing volume at a large community-based testing site nadired at 87% lower volume in April 2020 than in April 2019, with a partial rebound to 40% to 45% lower rates later in the year. HIV positivity rate remained stable, raising the possibility of lower HIV case finding. Among those testing positive, linkage to care within 1 month of diagnosis occurred for 93% of patients compared with 97% in 2019. HIV viral load testing from 12 laboratories nadired at 57% below 2019 levels, rebounding to 15% to 20% fewer tests than 2019 later in the year. PrEP visits at a large community site declined by 90% at the nadir in April 2020, with a rebound to 20% to 30% lower than 2019 levels later in the year. These data indicate that the SARS-CoV-2 pandemic had a profound impact on HIV prevention and care services in San Francisco, with partial but not full rebound to pre-SARS-CoV-2 levels. The authors suggest several mitigation strategies, including defining HIV prevention and care services as essential (even during lockdowns), expanding telemedicine services, and safer sex messaging during the pandemic.

Delaney and colleagues reported data from a commercial laboratory in the National Syndrome Surveillance Program run by the CDC (Abstract 739). Like the previous studies, they saw dramatic declines in HIV and viral load testing from March 13 to September 30, 2020, compared with a similar period in 2019: nearly 670,000 fewer HIV screening tests, nearly 5000 fewer HIV diagnoses, and more than 67,000 fewer viral load tests were performed, just from this single laboratory. Although the numbers of tests have rebounded, they were still below 2019 levels by the end of September 2020. The authors suggest that home testing, home sample collection, and telemedicine can help to address this shortfall.

Huang and colleagues drew from a national prescription database (IQVIA [formerly Quintiles and IMS Health, Inc] Real World Data) to evaluate trends in PrEP prescriptions from March 15 to September 30, 2020, compared with an earlier period of time (Abstract 731). Overall, there was a 21% decrease in the number of PrEP prescriptions and a 28% reduction in the number of new PrEP users over that time. Among the 10 states with the highest number of PrEP prescriptions prior to the COVID-19 pandemic, there was marked variability in these changes. For example, the number of new PrEP users declined by 18.2% in Texas but by 47.2% in Illinois. They also reported more decreases

in PrEP prescriptions for 16 to 29 year-olds than for other age groups, and more decreases for cash payers or users of the Medication Assistance Programs than persons with public health insurance. The authors cautioned that it is unclear if the decline was due to decreased access to PrEP or to decreased risk behavior (or both), but urge ongoing follow up to ensure adequate access to PrEP services.

Mitchell and colleagues modeled the impact of changes in sexual practices and HIV prevention and care service delivery from COVID-19 on numbers of new HIV infections and HIV-related deaths among MSM in the United States (Abstract 735). Their inputs to their model (number of sex partners, condom use, HIV testing, viral suppression, PrEP initiations and adherence, HIV testing on PrEP, and ART initiation) came from a published national survey and Boston clinic data. They found that, of different service disruptions, a 10% decrease in viral suppression would have the greatest impact both on the number of new HIV infections and deaths. A 25% decrease in partnerships would offset the negative impact of combined service disruptions on the number of new HIV infections, but would have no impact on the number of deaths. The authors conclude that maintaining access to ART and adherence support are the most important factors to minimize excess mortality, and they called for scale up and evaluation of telemedicine and other delivery models.

Rapid HIV Testing and Self-Testing

Sundararajan and colleagues presented data from a cluster-randomized trial of traditional healers delivering HIV testing in Uganda (Abstract 180). The authors noted that 80% of people in sub-Saharan Africa use traditional healers, and a recent cross-sectional survey found that only 34% of traditional healers had received an HIV test in the prior 12 months. They selected 17 traditional healers and randomly assigned them to the intervention or the control arm of the study. The intervention and control healers were trained to provide HIV education to their patients; intervention-arm healers were also trained to administer a rapid point-of-care oral fluid HIV antibody test, and linkage to care for those testing HIV positive. The primary outcome of the trial was HIV testing within 90 days of seeing the traditional healer; secondary outcomes were the number of new HIV diagnoses, and linkage to care of those individuals. Of the 250 participants seen in each arm of the study, 100% of those seeing the intervention healers received HIV testing, compared with 22.8% of the control arm (risk reduction, 77.2%; 95% CI, 72.8%-81.6%). Ten people in the intervention arm tested HIV positive (4%) compared with none in the control arm (P=.002). Of those found to be HIV positive, 70% were successfully linked to care. The authors concluded that training traditional healers to deliver rapid HIV antibody tests is a highly effective strategy to increase testing among sexually active adults in rural Uganda.

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Dovel and colleagues presented data on a cluster-randomized trial of HIV self-testing to optimize facility testing in Malawi (Abstract 181). Three clinics were each randomly assigned to provide HIV testing through practitioner-initiated testing, passive self-testing (group education, leaving it up to the patient to take the test and seek out medical help if needed), or active self-testing (group education, patients taken to an adjacent space for private self-testing). In total, 3182 participants joined the study. HIV testing rates remained relatively stable for the practitioner-initiated testing clinics (testing rates increased from 9% to 11%, an 18% increase), and for passive self-testing (6% vs 8%, a 33% improvement). Uptake of testing was higher in the clinics assigned to active self-testing (5% to 16%, a 220% increase). However, the authors acknowledged that even in the active arm, testing uptake was low, suggesting more information is needed about why this did not work, and new strategies should be tested to improve on these small numbers.

Jiang and colleagues pointed out that male partner testing remains low, and that self-testing may help increase testing (Abstract 674). They offered 798 pregnant women either clinic or home self-testing for retesting; women choosing HIV clinic testing could refer their partners, and women selecting self-testing could offer their partner either home- or clinic-based testing. By 14 weeks postpartum, 38% of women selecting clinic-based testing and 60% of women selecting home self-testing reported that their partner had been tested, and 87% of the partners had a negative test. Of women who selected home self-testing and whose partners tested, 64% of partners opted for home-based testing and 33% chose clinic-based testing. This suggests that secondary distribution of HIV self-testing to male partners of women receiving perinatal services can successfully increase partner testing coverage.

Peruski and colleagues evaluated whether HIV rapid testing algorithms improve care outcomes compared with standard HIV testing algorithms (Abstract 676). They evaluated national data reported to the US National HIV Surveillance System through December 2019, for all persons aged 13 years or older with HIV diagnosed during 2018 in the United States. Linkage to care was defined as having at least one CD4+ cell count or viral load test recorded. Of 33,500 persons diagnosed with HIV who resided in a jurisdiction with complete laboratory testing reported, 1508 (4.5%) were diagnosed using a rapid testing algorithm. Median time to linkage to care was significantly shorter among persons undergoing the rapid testing algorithm (16 vs 23 days, respectively, in EHE jurisdictions and 19

vs 22 days, respectively, in all other jurisdictions). Median time to viral suppression was also more rapid (2.9 vs 4.0 months, respectively, in EHE jurisdictions and 3.4 vs 3.9 months, respectively, in all other jurisdictions). However, use of rapid testing algorithms has decreased over time, particularly in EHE jurisdictions.

Bien-Gund and colleagues reported on HIV self-testing and risk behaviors among MSM in 23 US cities (Abstract 677). Data were drawn from the CDC National Behavioral Health Surveillance survey in 2017, a venue-based sampling of cisgender MSM. Of 6563 MSM who reported that they were HIV negative or of unknown serostatus and who had an HIV test in the previous 12 months, only 7.7% reported self-testing in the past year. Self-testers were younger, had higher levels of education, and had higher incomes. They were also more likely to report both increased test frequency and more recent testing, without reporting more condomless anal sex, STIs, or new HIV diagnoses than men who did not self-test. The authors posit that HIV self-testing could be very important in the COVID-19 era, when HIV testing rates have declined.

Vaccari and colleagues reported on a highly successful HIV testing program in an emergency department (ED) in London (Abstract 684). They had organizational commitment to opt-out testing, and included prominent signage to inform patients of the opt-out option as well as to routinely test all venipuncture samples, unless a person had opted out in the past 6 months or if this was a repeat HIV test. Patients not receiving testing were sent a text to let them know they could request a home test kit. They report that 97% of 25,366 eligible patients were tested for HIV; of these, 244 had non-negative test results. Of these, 66% were known to be HIV positive and in care, 4% were known positive and reengaged in care, 17% had false positive results, 6% were confirmed as a new HIV diagnosis, 5% were pending follow up, and 2% were lost to follow up. Of the 15 newly diagnosed persons, 13 are now engaged in care and receiving ART, and the other 2 have declined care. Overall, 57% of newly diagnosed persons and 56% of those who had previously defaulted their care had CD4+ counts less than 200 cells/μL.

Linley and colleagues used data from the National HIV Surveillance System to evaluate levels of previous HIV testing among newly HIV diagnosed black persons in the United States from 2013 to 2018 (Abstract 687). They found that of 11,742 black persons newly diagnosed with HIV in 2013, only 66% had had any prior HIV testing; this proportion declined significantly in 2018, with 61% of 10,881 black persons newly diagnosed who had had a previous HIV test. These declines in testing were true among those aged 13 to 44 years, with an average decline of 3% per year over that period of time across all age strata. This decline was seen in MSM, women who injected drugs, and heterosexual men. However, rates were relatively stable in the other groups, indicating that we are not making progress in any subgroups. These data suggest we are missing opportunities to detect infection earlier in black persons, and need substantial attention paid to this deficit.

The 4th pillar of the EHE effort is to respond rapidly to detect and respond to growing HIV clusters and prevent new infections. Curran and colleagues evaluated the baseline timeliness of HIV case and sequence reporting to health departments to determine the feasibility of intervening in these situations (Abstract 688). They considered timely case reporting to occur within 30 days of diagnosis, and timely sequence reporting to be within 45 days of diagnosis. Of 37,428 diagnoses in 2018 in persons 13 years of age or older, 59% had case reports entered within 30 days after diagnosis (median time, 24 days). Timely case reports were less frequent in large metropolitan areas, the Northeast and West, and in EHE jurisdictions. Among 19,289 diagnoses with viral sequences, 71% had specimens collected within 30 days after diagnosis, but only 6% had sequences entered within 45 days after diagnosis, with a median time to reporting of sequences being 74 days (interquartile range [IQR], 31.5-117.5 days). Across facilities, geographic areas, and jurisdictions, fewer than 10% of sequences were entered within 45 days of diagnosis. Targets for the new EHE initiative include 75% of the case reports entered within 30 days after diagnosis, and HIV sequence reporting occurring within 45 days after diagnosis. Much work remains to be done to be able to use sequence data to investigate clusters of transmission.

Sexually Transmitted Infections

Mugo and colleagues reported on rates of herpes simplex virus (HSV)-2 acquisition among HIV-negative women enrolled in the ECHO (Evidence for Contraceptive Options in HIV Outcomes) trial, a randomized controlled trial of 3 contraceptive methods and their association with HIV acquisition (Abstract 152). Several previous studies had found an association between use of intramuscular depot medroxyprogesterone acetate (DMPA-IM) with HSV-2 acquisition, which is of concern as HSV-2 acquisition increases the risk of HIV acquisition by 3-fold in women. However, other studies had not found such an association, and the previous datasets were often small and had potential confounding by sexual activity, as the control condition was often non-contraceptive users. The ECHO study enrolled 3898 women who were HSV-2 seronegative, with definitive HSV-2 serologic results at the baseline and final study visits. Women were randomly assigned to receive DMPA-IM, levonorgestrel implant (LNG), or the copper intrauterine device (IUD). Women were 16 to 35 years of age, recruited from 4 African countries, and followed up for 15 to 18 months. Overall HSV-2 incidence was 12.4/100 person years, without substantial differences between study arms (10.9/100 years in DMPA-IM arm, 12.7 in the LNG implant arm, and 13.7 in the copper IUD arm). HSV-2 seroconversion was associated with HIV seroconversion (incidence rate ratio [IRR], 4.1; 95% CI, 3.2-5.1), *Chlamydia trachomatis* infection (IRR, 1.3; 95% CI, 1.1-1.5), *Neisseria gonorrhea* infection (IRR, 1.6; 95% CI, 1.2-2.2), and having multiple partners (IRR, 1.3; 95% CI,

1.04-1.6). Living with one's partner was associated with reduced risk (IRR, 0.6; 95% CI, 0.5-0.7). The authors suggested that these data support use of long-acting contraceptive methods for young women in sub-Saharan Africa without risk of increased HSV-2 acquisition.

Silhol and colleagues created a mathematical model to determine the impact of HSV-2 infections on new HIV infections globally (Abstract 708). They reported that 37% (95% CI, 33%-43%) of HIV infections from 2009 to 2018 could be attributed to HSV-2 coinfection if HSV-2 only increases HIV acquisition, but 51% of all infections (95% CI, 43-58) if HSV-2 also increases HIV transmission. The contribution of HSV-2 to HIV infection was higher in Africa, and higher in female sex workers, their clients, and older adults, where HSV-2 prevalence is higher; the contribution of HSV-2 to HIV infections was lower in Europe. The authors posit that future HSV-2 control measures, including a HSV-2 vaccine, could have a substantial impact on incident HIV infections, particularly in sub-Saharan Africa.

No participant on doxycycline prophylaxis developed syphilis or chlamydia

Grennan and colleagues reported on results of a pilot randomized controlled trial of doxycycline for preexposure prophylaxis against chlamydia and syphilis in MSM and transgender women in British Columbia (Abstract 709). Fifty HIV-negative participants (49 MSM, 1 transgender woman) were given daily oral PrEP with TDF/FTC, and then randomly assigned to receive daily doxycycline 100 mg starting at baseline (immediate arm) or starting at 24 weeks (deferred arm); follow up was through 48 weeks. No participant on doxycycline prophylaxis developed syphilis or chlamydia, with an odds ratio for development of any STI of 0.18 (95% CI, 0.05-0.68). Ten participants in the deferred arm developed chlamydia in the first 24 weeks, and 1 developed syphilis in this time frame. On the other hand, there were 8 cases of gonorrhea in the first 24 weeks in the deferred arm and 4 cases in the immediate arm; an additional case in the immediate arm occurred after 24 weeks. Tetracycline resistance in *Staphylococcus aureus* was found in 1 of 3 persons in the immediate arm at 24 weeks, and 3 of 6 at 48 weeks; 1 of 3 in the deferred arm after 24 weeks. Self-reported adherence (taking >95% of doses) was 89.5% in the immediate arm and 72.7% in the delayed arm. The authors reported that this was a promising intervention that will be followed up on with a 500-person randomized controlled trial.

Wang and colleagues presented data on a study of 400 adolescent girls and young women (AGYW), aged 16 to 21 years in Kenya (Abstract 721). Of 292 who were sexually active during the follow-up period, 163 developed an STI, on average, 39 months from sexual debut. Seventy had a subsequent STI. In total, 81% of STIs were chlamydia, 11% gonorrhea, 7% *Trichomonas vaginalis* infections, 14% HSV-2, and 13% had multiple STIs. Risk factors for developing an STI included bacterial vaginosis (BV) (RR, 1.49; 95% CI, 1.09-2.03), having a new sex partner (RR, 2.02; 95% CI, 1.26-3.26), and failure to disclose sexual activity (RR, 2.72; 95% CI, 1,93-3.83). These data suggest that AGYW are at high risk of acquisition of STIs shortly after sexual debut, and speak to the need for increased screening (rather than relying on syndromic management) to detect and treat STIs, particularly chlamydia infection.

Roxby and colleagues presented data from the same cohort of 400 AGYW in Kenya, 80.5% of whom reported no prior sexual activity at enrollment, to evaluate risk factors for development of BV. Participants were followed up to 60 months and had a median of 11 BV tests over that time. Prior to sexual activity, only 2.8% of visits resulted in a positive test for BV, and after sexual activity, 13.7% of visits resulted in a positive test for BV. A BV diagnosis was increased after first sexual intercourse (OR, 3.5; 95% CI, 2.3-5.3) and among women reporting more than 1 sex act in the prior 3 months (OR, 1.8; 95% CI, 1.36-2.39). On longitudinal analysis, several sociodemographic and behavioral factors were associated with increased risk (recent sexual activity: OR, 1.4; $P=.03$; urban residence: OR 1.4; $P=.01$; no income: OR, 1.7; $P<.01$). BV was also associated with both chlamydia (OR, 1.78; $P<.001$) and HSV-2 infection (OR, 1.8; $P<.001$). Protective factors included self-reported virginity (OR, 0.4, $P<.01$) and longer time from menarche to first sexual activity (OR, 0.5, $P=.03$). The authors noted that such low rates of BV were uncommon among older women in Kenya, and that products are needed to promote optimal vaginal health.

Liroff and colleagues reported on delayed treatment for syphilis (more than 14 days between diagnosis and treatment) among persons living in Washington, DC, the jurisdiction with the highest rates of syphilis in the United States (Abstract 724). They found 2723 new diagnoses of syphilis from January 2015 to December 2019, 45% of which were in people with HIV, and more than 90% of whom were male. Almost all (99.8%) had adequate treatment for syphilis. Overall, for 5.6% of people with HIV, this HIV test led to a new diagnosis of HIV, and 20.8% of all people with HIV with syphilis diagnoses had an HIV viral load greater than 10,000 copies/mL, suggesting increased transmissibility of HIV. Delayed treatment was associated with viral load below 10,000 copies/mL (aOR, 1.82; 95% CI, 1.03-3.23); black race (aOR, 1.82; 95% CI, 1.01-3.29); race not reported or refused (aOR, 2.11; 95% CI, 1.09-4.10); and early latent syphilis (aOR, 3.2; 95% CI, 1.96-5.24). Compared with receiving care in Federally Qualified Health Centers or community health clinics, patients seen in private practice settings were significantly less likely to be treated late (aOR, 0.08; 95% CI, 0.01-0.69). The authors pointed out that intervening simultaneously for HIV and syphilis in persons coinfected could reduce the transmission of both infections.

Preexposure Prophylaxis

Novel PrEP Agents and Formulations

Landovitz and colleagues presented an updated analysis of laboratory data on

HIV infections in the HPTN (HIV Prevention Trials Network) 083 study, a phase IIb/III randomized trial comparing long-acting injectable cabotegravir (CAB-LA) administered every 8 weeks with daily oral TDF/FTC in cisgender men and transgender women who have sex with men (Abstract 153). This study found that CAB-LA and TDF/FTC were each highly effective for HIV prevention. Overall there were 12 incident infections and 4 participants infected at baseline in the CAB-LA arm, and 39 incident and 3 baseline infections in the TDF/FTC arm. HIV incidence was

CAB-LA can delay detection of HIV infection using standard HIV testing algorithms

0.37 per 100 person years in the CAB-LA arm versus 1.22/100 person years in the TDF/FTC arm, with a hazard ratio of 0.32 (95% CI, 0.16-0.58) demonstrating superiority of CAB-LA over oral TDF/FTC. Retrospective back testing of samples using multiple sensitive assays was performed to determine the time of first infection. Among the 4 baseline-infected participants who received CAB-LA prior to detection of infection, 1 was found to have treatment-emergent integrase strand transfer inhibitor (InSTI) resistance with Q148K and E148K mutations. Another participant with baseline infection detected 10 weeks after enrollment who had received 2 injections of CAB-LA had "escape" viremia during the pharmacologic tail phase (HIV viral load of 76,010 copies/mL about 35 weeks after enrollment) but no emergence of resistance. Five infections occurred after a prolonged hiatus after CAB-LA administration, 3 of which likely occurred during the pharmacologic tail phase; none of these cases had InSTI resistance.

Among 3 participants who acquired HIV during the CAB-LA oral lead-in period, 2 had cabotegravir plasma levels indicative of cabotegravir exposure, and both developed InSTI resistance with the Q148R and accessory mutations. Four participants became infected in the setting of on-time CAB-LA injections and cabotegravir levels consistent with 8 times the protein-adjusted 90% inhibitory concentration ($PAIC_{90}$) at most visits, levels found to be protective in prior nonhuman primate models. Retrospective testing with more sensitive assays detected HIV infection 6 to 17 weeks prior to the detection of HIV infection by site testing. In 2 participants in which genotypic testing could be performed, InSTI resistance with the R263K mutation emerged in one, and with Q148R and G140A mutations in another. Aside from 2 participants who were lost to follow up, all participants were subsequently started on ART and achieved full viral suppression. In the TDF/FTC arm, 37 of 39 of the incident infections occurred in the setting of low adherence based on plasma or dried blood spot testing.

Overall, these findings suggest that CAB-LA can delay detection of infection using standard HIV testing algorithms, and InSTI resistance was seen when viremic "escape" occurs at higher cabotegravir concentrations, but was not seen in the 3 tail-phase infections or 1 tail-phase "escape" case. Taking into consideration these results, the oral lead-in period will be made optional in the upcoming OLE (Open Label Extension) of HPTN 083, which may help avoid early infections associated with possible adherence challenges or delayed time-to-onset of protection. Additionally, the utility of HIV viral load testing at all visits as a primary screen for HIV infection will be assessed in the HPTN 083 OLE. Landovitz highlighted that prompt diagnosis and ART initiation in the setting of CAB-LA are needed to avoid resistance emergence.

Patel and colleagues presented on the pharmacokinetic (PK) threshold and dose selection for monthly oral islatravir for PrEP (Abstract 87). Islatravir is an investigational novel reverse transcriptase translocation inhibitor with high potency, robust activity against drug resistant variants, and a long half-life. Based on efficacious concentrations observed in prior HIV treatment studies, rhesus macaque PrEP and postexposure prophylaxis challenge studies, and data from the literature regarding efficacious concentrations of TDF-disphosphate (DP), an islatravir-triphosphate (ISL-TP) PK threshold of 0.05 pmol/10^6 peripheral blood mononuclear cells (PBMCs) was established for HIV prevention, which is approximately 5-times higher than the in vitro wildtype IC_{50}. In PK model simulations and based on interim data from an ongoing phase IIa islatravir trial, the monthly dose of 60 mg oral islatravir selected for phase III trials resulted in ISL-TP concentrations exceeding this PK threshold within hours, and ISL-TP concentrations were maintained above the PK threshold from the first dose of administration in all participants, even among those with a delayed or missed monthly dose. Interim PK analysis from the phase IIa trial suggested rapid, sustained, and adequate distribution of ISL-TP in target tissues.

Matthews and colleagues presented data on islatravir-eluting implants for yearly HIV PrEP (Abstract 88). This phase I study evaluated the safety, tolerability, and PK of a next-generation radiopaque islatravir implant in healthy HIV-negative men and women. Twelve participants each were randomly assigned to 12 weeks of a 48-mg, 52-mg, or 56-mg implant inserted using the Nexplanon applicator, with an additional 8 weeks of follow up after implant removal. ISL-TP concentrations were above the PK threshold of 0.05 pmol/10^6 PBMCs for the 52- and 56-mg implants. The half-life after removal of the implant was similar to the half-life of orally dosed islatravir (198 hours for the 56-mg implant). Using a population PK model, the 56-mg implant was projected to lead to concentrations above the PK threshold for 52 weeks. The implants were generally well tolerated. All adverse events were mild or moderate in severity, with 61% of participants reporting at least 1 implant adverse event (eg, erythema, tenderness, pruritus, induration). There was no clear relationship between dose and adverse event frequency or severity; no effects on laboratory studies, electrocardiogram results, or vital signs; and no discontinuations due to an adverse event. These findings support the

continued development of the islatravir implant as a potential once-yearly PrEP option.

Li and colleagues described the development of a long-acting coformulated biodegradable implant for HIV prevention and contraception (Abstract 728). Implants tested included one of 2 well-characterized progestins, LNG and etonogestrel (ENG), and 2 antiretroviral drugs (ARVs), TAF and islatravir filled in polycaprolactone extruded tubes. They demonstrated sustained zero-order release of ARVs and hormones up to 1 year with a high level of purity. Although similar ARV-release rates were seen with islatravir as a coformulation and as a single formulation, TAF release was altered by the presence of hormones in the coformulation.

Liu and colleagues presented data on the safety, PK, and acceptability of 2 3-month dapivirine vaginal rings in 49 HIV-uninfected women and those assigned female sex at birth (Abstract 147). Extended duration vaginal rings could reduce user burden and cost, streamline follow-up visits, and encourage adherence. Participants in this phase I trial were randomly assigned in a 1:1:1 fashion to receive the 25-mg dapivirine ring replaced monthly, or the 100-mg or 200-mg vaginal ring worn continuously for 13 weeks. All 3 rings were well tolerated with no statistically significant differences in reported adverse events across arms. Geometric mean dapivirine concentrations for the extended duration rings were 1.3- to 1.9-times higher in plasma and 1.5- to 2.9-times higher in cervicovaginal fluid than for the monthly 25-mg ring, and cervical tissue concentrations were 2.3- to 3.9-times higher in the 200-mg ring arm. Overall, 82% reported being fully adherent to ring use, and most participants reported they liked the ring and would use the ring in the future if effective. These findings support further evaluation of 3-month dapivirine vaginal rings for HIV prevention.

Massud and colleagues reported on the PK and efficacy of weekly oral TAF in protecting macaques from vaginal SHIV infection (Abstract 714). Twelve pigtailed macaques were treated once weekly with oral TAF at either 13.7 mg/kg or 27.4 mg/kg dosing (equivalent to 225 mg and 450 mg, respectively, in humans) and exposed vaginally to $SHIV_{162p3}$ twice a week for 6 weeks. Five out of 6 macaques treated with 27.4 mg/kg or 13.7 mg/kg were protected over the 12 challenges, compared with 9 of 10 untreated controls that became infected, resulting in an efficacy of 92% for both doses. Tenofovir diphosphate (TFV-DP) levels in PBMCs were high and sustained (>1300 fmols/10^6 cells); TFV-DP levels were lower in the animal that had a breakthrough infection in the 27.4 mg/kg arm (405 fmols/10^6 cells) but high in the breakthrough infection in the 13.7 mg/kg arm (3,457 fmols/10^6 cells). Tenofovir exposures in plasma were low and mostly below the limit of detection. These findings suggest that weekly oral TAF may be a feasible option for long-acting vaginal PrEP protection and support further testing in humans.

Makarova and colleagues presented on the PK of TAF/elvitegravir (EVG) rectal inserts in 6 pigtailed macaques and the impact of rectal wash on drug distribution (Abstract 715). Rectal application of a single TAF/EVG insert resulted in high tissue EVG and TFV-DP levels at 4 hours that were within the range associated with vaginal protection and remained detectable after 3 days. There was a linear decline in levels of EVG and TFV-DP from 4 cm to 25 cm from the anal sphincter. Rectal cleansing resulted in fewer samples having levels below the limit of detection and increased colon concentrations of EVG and TFV-DP by 40 to 200 fold.

Bauermeister and colleagues presented on the acceptability and preference for 3 placebo rectal products used with receptive anal sex (Abstract 716). This study enrolled 217 young HIV-negative MSM (79%), transgender women (19%) and transgender men (1%) from 7 sites in the United States, Peru, Malawi, South Africa, and Thailand into a randomized cross-over trial in which participants used a placebo rectal insert, enema, and suppository each for a 4-week period, then completed a conjoint experiment exploring preferences for 7 product features. In conjoint analyses, efficacy was the strongest determinant of stated choice overall (30.4%), followed by product delivery vehicle (18.0%), and adverse effects (17.2%). The preferred bundle of attributes included an enema used approximately 30 minutes before sex, which has 95% efficacy, provides protection for 3 to 5 days, can be dosed once a week, has no adverse effects, and is available over the counter without a prescription. Participants' product preference at the final visit varied by context. For example, the enema was preferred in situations in which the product would make one feel clean after use and make sex more pleasurable, the suppository was most preferred as a good alternative to lubrication, and an insert was most preferred when the product needed to be stored discreetly. These findings highlight the importance of creating behaviorally congruent biomedical options that fit the needs of intended end users.

Measuring Adherence to PrEP

Several presentations reported on advances in pharmacologic assays for measuring adherence to PrEP and ART regimens. Sevenler and colleagues described the validation of a newly developed rapid lateral flow assay for urine tenofovir (Abstract 352). In this assay, the test line intensity becomes brighter with decreasing concentrations of tenofovir and is read by an optical reader or 2 independent people using a visual grading scorecard. In testing 586 urine samples from 28 participants with quantified tenofovir concentrations, the correlation between tenofovir concentration and optical reader intensity measurement was high (Spearman's R, -0.91). The sensitivity and specificity for classifying samples using a 1500-ng/mL cutoff (no dosing in the last 24 hours) were 87% and 92%, respectively, for the visual readout and 85% and 96%, respectively, for the optical reader. When using a cut-off of 150-ng/mL (no dosing in last >4 days), sensitivity and specificity were 84% and 89%, respectively, for visual readout and 87% and 95%, respectively, for the optical reader. As each method provides results in 5

minutes with no sample processing required, the authors suggest that rapid testing for urine tenofovir could be a scalable method to assess recent tenofovir ingestion.

Niu and colleagues presented data on the use of the same urine lateral flow assay to assess tenofovir dose recency in the TARGET (Tenofovir Adherence to Rapidly Guide and Evaluate PrEP and HIV Therapy) study (Abstract 353). In testing 268 urine samples from 28 adults taking daily TDF/FTC in a 6-week directly-observed therapy (DOT) study, average visual scores and optical reader readings were highly correlated with time since last dosing (Spearman's R [r_s] correlation coefficients of 0.80 and 0.83, respectively, [both $P < .01$]). A visual score above 1.5 or optical reading above 1500 correctly identified all samples if the last dose was ingested more than 24 hours ago, and no samples with a visual score above 2.5 or optical reading above 3000 were from participants who dosed in the last 48 hours.

As plasma tenofovir levels are nearly 10-fold lower with TAF than TDF, Johnson and colleagues compared urine tenofovir levels in individuals taking TAF versus TDF (Abstract 355). Using data from TAF in dried blood spot (DBS) samples, a DOT study of 36 participants taking different dosing regimens of TAF, and the TARGET study with DOT TDF, urine tenofovir concentrations were 74% lower with DOT TAF than with TDF ($P < .001$). Given these results, the researchers concluded that a separate, lower tenofovir cut-off level will be needed for any point-of-care assay designed to assess adherence to TAF versus TDF. Using data from TAF in dried blood spot samples, Spinelli and colleagues determined the optimal cut-off for a urine-based point-of-care test for adherence to TAF (Abstract 354). Although 1500 ng/mL was the optimal cut-off for TDF dosing, a urine tenofovir cut-off of 300 ng/mL optimized specificity for daily TAF dosing, with a specificity for nonadherence at 24 hours of 98%, and sensitivity for nonadherence at 120 hours of 98%.

Rosen and colleagues evaluated the use of hair mass spectrometry imaging to identify different patterns of PrEP dosing (Abstract 356). Using infrared matrix-assisted laser desorption electrospray ionization (IR-MALDESI) mass spectrometry imaging (MSI) to assess daily adherence to FTC-based regimens in 8 young MSM over a 2 month period, 4 patterns of longitudinal daily PrEP adherence were identified: consistent high adherence, high adherence with occasional missed doses, improved adherence after study initiation, and intermittent adherence. FTC-TP level was able to detect short-term adherence changes, and a cumulative measure of FTC-TP level in hair over the last 60 days was highly correlated with TFV-DP levels in DBS samples (r_s, 0.79). Rosen and colleagues also used IR-MALDESI MSI to assess daily adherence to maraviroc in the HPTN 069/ACTG (AIDS Clinical Trial Group) 5305 study. Maraviroc, a basic lipophilic compound, is highly bound to melanin in hair strands leading to variation in drug accumulation based on hair color. Accuracy of adherence classification was increased by normalization of maraviroc hair strand concentrations by a melanin biomarker. Among 32 hair samples from 19 individuals analyzed in HPTN 069/ACTG 5035, IR-MALDSI MSI was able to distinguish between individuals who were adherent (8/19) versus nonadherent to daily maraviroc throughout the prior month.

HIV Diagnosis and Resistance on PrEP

Colby and colleagues reported on the impact of PrEP use on the diagnosis of acute HIV infection in Thailand (Abstract 179). Among 3117 individuals who started PrEP in the Thai Red Cross Anonymous Clinic, 8 had acute HIV infection at PrEP initiation (approximately 1/400). Five of these acute infection cases were identified by a positive pooled Aptima Qualitative HIV RNA Test, and 3 were identified by positive serology at 1 to 3 months after PrEP initiation, with quantitative HIV RNA detected on retrospective testing of pre-PrEP stored samples. Among 6 of these individuals who enrolled in an acute infection cohort, PrEP use prior to HIV diagnosis ranged from 2 to 91 days; all participants were switched immediately to ART upon diagnosis. Pre-PrEP viral load ranged from 32 copies/mL to 223,361 copies/mL. A 4th generation HIV test was nonreactive in all 6 cases at week 0 (prior to ART initiation), reactive in 1 individual at week 24, and in a second individual at week 48. The 3rd generation test was reactive in 3 of the 6 individuals at week 0 and in 5 of the 6 individuals at week 24. The 2nd generation test was reactive in 1 of the 6 individuals at week 0 and 3 of the 6 cases at week 24. Western blot testing was either indeterminate or negative at all timepoints, and Geenius testing performed at week 48 was nonreactive in all participants. In 1 individual with low viral load (maximum 276 copies/mL) pre-ART, serologies for all tests remained nonreactive through week 48. In this study, the 4th generation antigen/antibody test was the least sensitive at detecting acute infection, and the 3rd generation antibody test was most sensitive. These results suggest that standard serologic testing and algorithms may not confirm HIV infection when PrEP or ART are started early in acute infection, and alternate testing strategies, including nucleic acid amplification testing, may be needed for accurate diagnosis of acute infection.

Chohan and colleagues assessed HIV drug resistance among PrEP seroconverters in Kenya (Abstract 427). More than 2000 service providers were trained and 340 blood collection kits distributed as part of a national study to assess the frequency of drug resistance among PrEP seroconverters. Among more than 26,000 PrEP users in Kenya's national PrEP rollout program, 67 PrEP seroconverters were identified, and 30 blood samples were successfully genotyped. Of these, 10 (33%) had major HIV drug resistance mutations detected: none (0%) had resistance to tenofovir (no K65R or K70E mutations), 5 (17%) had emtricitabine resistance (with M184V), and 9 (30%) had 1 or more major nonnucleoside reverse transcription inhibitor (NNRTI) mutations, including K103N, Y181C, and G190A. These findings highlight the importance of HIV drug resistance monitoring in PrEP seroconverters,

and monitoring the incidence of NNRTI resistance with the upcoming rollout of the dapivirine vaginal ring.

Cox and colleagues reported on drug resistance in the DISCOVER PrEP trial (Abstract 428). Resistance testing was performed using standard Next Generation Sequencing (detecting ≥2% of the viral population) and ultrasensitive resistance testing using unique molecular identifiers for application of viral variants (detecting ≥1% of the viral population). Of 5335 participants randomly assigned to either TDF/FTC or TAF/FTC in the study, 27 acquired HIV through week 144 (11 in the TAF/FTC arm, 16 in the TDF/FTC arm). Five had suspected baseline infection and 19 had low levels of TFV-DP in dried blood spot samples suggesting suboptimal adherence. Four seroconverters in the TDF/FTC arm had the M184V/I mutation detected on standard and on ultrasensitive testing, which was thought to be transmitted resistance at baseline, and 1 seroconverter in the TAF/FTC arm had the M184V mutation detected only by unique molecular identifier testing. An additional 8 participants had resistance to other drug classes and were thought to be transmitted drug resistance mutations. All participants with virus that resistant to study drugs were successfully treated with ART and virologically suppressed.

PrEP and Gender-Affirming Hormones

Yager and colleagues evaluated whether the PK of estradiol and testosterone were altered with daily PrEP use in transgender adolescents (Abstract 366). In a DOT study of 24 transgender men (50% receiving testosterone intramuscularly and 50% subcutaneously) and 25 transgender women (52% receiving oral estrogen and 48% intramuscular estrogen) aged 15 to 24 years, there were no statistically significant differences in concentration area under the curve (AUC) or maximum concentration (C_{max}) levels in estradiol or free or total testosterone before or after DOT dosing with TDF/FTC. Furthermore, estradiol and testosterone levels in the study pop-ulation were at or above the target range recommended by current Endocrine Society guidelines (100-200 pg/mL for estradiol and ~300-1000 ng/dL for testosterone).[2] These findings provide reassurance for transgender men and women that taking PrEP does not impact concentrations of gender-affirming hormones. From the same study, Yager and colleagues presented data on intracellular TFV-DP and FTC-TP levels in PBMCs in transgender adolescents taking gender-affirming hormones and TDF/FTC PrEP (Abstract 367). After 2 to 3 weeks of DOT TDF/FTC dosing, transgender men had significantly higher PBMC concentrations of TFV-DP (56.0 vs. 75.1 fmol/10^6 PBMCs, respectively; geometric mean ratio [GMR], 1.34; P=.049) and FTC-TP (4.29 and 6.19 pmol/10^6 PBMCs, respectively; GMR, 1.44; P=.003) than transgender women. Differences in TFV-DP concentrations were partially driven by higher baseline renal function in transgender women. Despite these differences, the geometric mean PBMC concentrations were within the ranges of median concentrations observed in prior studies (36.3-71.2 fmol/10^6 cells for TFV-DP and 2.2-5.34 pmol/10^6 cells for FTC-TP). In a post-hoc analysis, PBMC concentrations were lower among transgender women using intramuscular than those using oral estradiol for both TFV-DP (GMR, 0.58; 95% CI, 0.38-0.88; P=.01) and FTC-TP (GMR, 0.58; 95% CI, 0.43-0.79; P=.001), a finding that warrants further study.

PrEP Use in Pregnancy

Davey and colleagues reported on the impact of common adverse effects on PrEP persistence in pregnant South African women (Abstract 149). Of 846 women enrolled into an observational cohort study, 90% reported recent condomless sex, and 31% were unsure of their partner's HIV serostatus. Baseline STI prevalence was high (34%), with 65% of infections being asymptomatic that would have been missed under syndromic management. Following counseling, 90% of women initiated PrEP at their first antenatal visit. Having a same-day STI diagnosis was a facilitator of adherence, and being married and reporting high internalized PrEP stigma were barriers to PrEP initiation. PrEP persistence (returning for repeat PrEP prescription) was 59% for post-partum and 74% for pregnant women at month 1, and 41% and 53%, respectively, at month 6. PrEP persistence was lower in postpartum women who did not return to the same facility for antenatal care (aOR, 0.31). Self-reported adherence was 74% to 82% at month 1 and 77% to 79% at month 3, and 61% of those who reported taking PrEP in the last 30 days had detectable levels of TFV-DP in dried blood spot sampling. Overall, 31% of women reported adverse effects at the 1 month follow-up point, including dizziness (25%), nausea/vomiting (22%), and headache (8%). Women in the first or second trimester of pregnancy had 2.6-times the odds of reporting adverse effects than postpartum women. Reporting adverse effects at the month 1 visit was associated with 0.5 the odds of PrEP persistence and adherence at month 3; being at 20 or more weeks of gestation and having a lower educational level were also associated with poorer PrEP persistence and adherence. As the reporting of PrEP adverse effects can overlap with pregnancy symptoms, these findings highlight the opportunity for improved clinical management of nausea/vomiting during pregnancy and counseling to normalize early, transient adverse effects that may improve maternal PrEP use.

PrEP adverse effects during pregnancy were associated with lower PrEP adherence and persistence

Kinuthia and colleagues presented results of a cluster randomized trial evaluating risk-based versus universal PrEP delivery during pregnancy in Kenya (Abstract 707). In the PrIMA (PrEP Implementation for Mothers in Antenatal Care) study, 20 maternal/child health clinics were randomly assigned to either universal offer of PrEP (universal) or targeted PrEP offer guided by an HIV risk assessment score and partner HIV self-test (targeted). Among

4447 pregnant women enrolled (2250 to the universal arm, and 2157 to the targeted arm), PrEP acceptance was 19.6% in the universal arm and 17.6% in the targeted arm. Appropriate PrEP use (PrEP use in women at high risk and no PrEP use in women at low risk) was similar in the universal (68.4%) and targeted (59.1%) arms (aRR, 1.1; 95% CI, 0.8-1.5). Median duration of PrEP use was 8.6 months in the universal arm and 8.9 months in the targeted arm. HIV incidence was similar in the universal (0.4/100 person years) and targeted (0.3/100 person years) arms (aRR, 0.7; 95% CI, 0.2-2.1). The researchers highlighted several benefits of universal PrEP offer, including less stigma and being female controlled and readily scalable.

Pintye and colleagues reported on tenofovir hair levels among pregnant and postpartum PrEP users in the PrIMA study (Abstract 710). Among 164 hair samples (32% collected during pregnancy and 68% postpartum) from 109 women, median hair tenofovir concentration was 0.005 ng/mg (IQR, 0.002-0.030) across pregnancy visits and 0.005 ng/mg (IQR, 0.002-0.028) across postpartum visits. Overall, 29% of samples had tenofovir levels of 0.023 ng/mg or higher indicating 4 or more PrEP doses per week, with no differences during pregnancy versus postpartum (28% vs. 31%, respectively; P= .68). Having a partner with HIV was associated with higher tenofovir hair levels during pregnancy (0.024 ng/mg) and postpartum (0.036 ng/mg). These findings suggest that hair tenofovir levels provide a cumulative measure of PrEP exposure and may not need adjustment for PK differences in the perinatal period.

Adolescents, Youth, and PrEP

Symposium 10 entitled "Adolescents, Youth, and PrEP" addressed different aspects of the challenges and potential solutions to applying PrEP in young populations. Kinuthia presented on PrEP use during pregnancy and breastfeeding (Abstract 66). He pointed to the increased risk of HIV acquisition during the peripartum period, citing that approximately 30% of infant infections are thought to be due to acute infection in the mother during pregnancy or the breastfeeding period. He reviewed data on infant safety during PrEP use during pregnancy and postpartum. PK data suggest that high levels of adherence are important for pregnant women, due to increased renal clearance of tenofovir as well as hemodilution. Kinuthia also discussed strategies to integrate PrEP services into maternal/child health clinics to improve PrEP uptake and persistence of PrEP. Mellins presented on adolescent brain development, and the many factors that may influence adolescent health (Abstract 68). She pointed out that in 2019, 25% of new infections globally occurred in adolescents, aged 10 to 24 years. PrEP was only approved for adolescents (under 18 years of age) in the US in 2018, and although uptake is increasing in some settings, adherence has been poor in numerous studies globally. Mellins likened the adolescent brain to a car with a well-developed accelerator but only partially developed brakes, a function of the limbic system development outpacing that of the prefrontal cortex. However, she made the case that the increased brain plasticity can be harnessed to come up with creative solutions that address the bio-pyscho-socio-neurocognitive factors that serve as barriers to healthy practices, and put forth some concrete steps that should take place at the practitioner and clinic levels to address adolescent needs.

Hosek reviewed a number of different interventions that have been developed to support PrEP adherence and persistence for young women in sub-Saharan Africa, and young MSM (Abstract 67). Very light touch interventions and drug level feedback did not appear adequate to support PrEP use over time. Disclosure of PrEP use to friends, family, and partners and use of adherence clubs were strongly associated with PrEP adherence. Rousseau spoke about how we might market PrEP to youth (Abstract 69). Just like fast food, youth want PrEP that is quick, easy to access, inexpensive, with lots of choices, incorporates socializing, and takes into account busy lifestyles. Her talk included a number of insights into what young people may want to make PrEP more appealing, with examples of ways to reach out to youth.

PrEP Uptake, Adherence, and Implementation

Molina and colleagues presented updated data on daily and on-demand PrEP use in the ANRS (French National Agency for Research on AIDS and Viral Hepatitis) Prevenir Study (Abstract 148). In this open-label prospective cohort study of 3067 participants (98% MSM) in the Paris area, participants could opt for either daily or on-demand PrEP at baseline and could switch their PrEP regimen during the follow-up period. At baseline, 49% of participants chose on-demand PrEP, and 10% to 15% switched regimens during follow up. On-demand PrEP users had fewer condomless sex acts and fewer sex partners at baseline. Overall, 96% of daily PrEP users reported using PrEP at their last sexual intercourse, compared with 82% of on-demand PrEP users, with condom use reported in 17% to 20% of episodes. As expected, TFV-DP levels were higher among participants using daily PrEP than among those using on-demand PrEP (1264 and 691 fmol/L, respectively; P<.0001), and the proportion with undetectable FTC-TP, an indicator of recent PrEP use, was higher in the on-demand than the daily PrEP users (55% and 10%, respectively; P<.001). The self-reported median number of pills taken in the past week was 7 among daily PrEP users and 2 in on-demand users (P<.0001). Overall HIV incidence in the study was 0.11/100 person years with a mean follow-up time of 22.1 months. Three HIV infections occurred among daily PrEP users, and 3 among on-demand PrEP

HIV incidence was low (0.11/100 person years) among PrEP users on daily or on-demand PrEP regimens

users, resulting in a similar HIV incidence of 0.12/100 person years in both groups (IRR, 0.99; 95% CI, 0.13-7.38). All HIV infections occurred in the setting of stopping PrEP in the weeks to months before infection. Only one of these 6 participants had drug resistance (with an M184V mutation) at baseline, occurring in an on-demand PrEP user. Based on the HIV incidence of 6.6/100 person years observed in the placebo arm of the IPERGAY (Antiretroviral Pre-Exposure Prophylaxis for HIV Infection in Men Who Have Sex With Men) study, it is estimated that 361 HIV infections were averted by PrEP use in this cohort. The number of sexual encounters and condomless sex acts increased after PrEP initiation, particularly among PrEP-naive participants, although the overall number of sexual partners decreased in both PrEP-naive and -experienced participants. The incidence of STIs was high (66.5-75.5/100 person years) in this cohort, although STI rates declined during COVID-19 lockdown (32.4/100 person years). Hepatitis C incidence was high (0.69/100 person years) with 39 new diagnoses during the study. The rate of PrEP-related adverse events was low overall but higher in the on-demand group (7.52 and 5.82/100 person years, respectively), mostly due to an increase of gastrointestinal events, but only 3 participants (2 on daily and 1 on demand PrEP) discontinued PrEP due to gastrointestinal adverse events. Incidence of low creatinine clearance rate (<50 mL/min) was low (0.5/100 person years) and did not differ by PrEP arm, with no permanent discontinuations due to declining renal function. Overall, these findings further support the use of on-demand PrEP as an effective prevention strategy among MSM.

Tassi and colleagues presented data on the first 3 years of PrEP implementation in France (Abstract 698). Using data from the French national health database between 2016 and 2018, they identified 9893 PrEP users (99% men), with 95% of PrEP prescriptions from a hospital prescriber. The median number of PrEP dispensations per patient was 9 (IQR, 4-14), and 8% never refilled their PrEP prescription. HIV testing was completed in 64% of PrEP users at 1 month in 81% at quarterly testing, which remained stable over time. PrEP users were more likely to complete HIV testing if their last prescription was written by a hospital prescriber (OR, 2.04; $P<.001$) but were less likely to test if they never refilled their PrEP prescription (OR, 0.06-0.15; $P<.001$). There were 29 HIV diagnoses identified during the follow-up period, resulting in an HIV diagnosis rate of 0.19 cases per 100 person years (99% CI, 0.12-0.30). Among 18 infections that occurred more than 3 months after PrEP initiation, the median duration between last PrEP dispensation and HIV diagnosis was 180 days (IQR, 124-490). In this subgroup, PrEP users who never refilled their prescription were more likely to become HIV infected (RR, 4.7; 99% CI, 1.2-18.2).

Hoover and colleagues reported on trends in TDF/FTC and TAF/FTC prescriptions for PrEP in the United States

After approval of TAF/FTC for PrEP in the United States, 36% of new PrEP users were prescribed TAF/FTC, and 29% of TDF/FTC users switched to TAF/FTC

(Abstract 696). Based on data from the IQVIA prescription database, 36.3% of new PrEP users were prescribed TAF/FTC after its approval for PrEP on October 3, 2019, and 28.5% of 228,299 TDF/FTC users switched to TAF/FTC. PrEP users who switched from TDF/FTC to TAF/FTC were more likely to be older (aRR, 1.13 per 10-year increase), male (aRR, 3.15), Hispanic/Latino (aRR, 1.11), or living in the Midwest (aRR, 1.17), South (aRR, 1.56), or West (aRR, 1.08) compared with the Northeast, and were less likely to be cash payers (aRR, 0.71) or beneficiaries of other third party payers (aRR, 0.57) than those who had public insurance. These findings highlight the importance of monitoring the use of new patented and generic PrEP drugs as they become available to better understand implications for US healthcare expenditures.

Henny and colleagues reported on trends in PrEP users and prescribers in 48 EHE phase I urban jurisdictions by federal funding status (Abstract 703). From 2014 to 2019, based on data from the IQVIA national prescription database and the Healthcare Resources and Services Administration (HRSA) Uniform Data Systems, the number of PrEP users increased more rapidly in Federally Qualified Health Centers (FQHCs) (81-3625 respectively; estimated annual percent change [EAPC], 101.5) than in non-FQHCs (1575-23, 854; EAPC, 56.2). Similarly, the number of PrEP prescribers increased more quickly in FQHCs (22-229; EAPC, 49.1) than in non-FQHCs (564-3406; EAPC, 37.8).

Pathela and colleagues reported on the use of remnant sera testing to assess PrEP uptake in New York City sexual health clinics (Abstract 699). Among 744 patients with a newly diagnosed STI, 33% had serum samples with detectable tenofovir/FTC levels using liquid chromatography/mass spectrometry (LC-MS). Prevalence of PrEP use was highest in MSM with syphilis (44%) and lowest in women with gonococcus or syphilis (2%). PrEP use was also lower among black (20%) and Hispanic (28%) clients than among white clients (45%). Agreement between LC-MS and self-reported PrEP use was high (91%). In a multivariable model, PrEP use was associated with age 24 to 44 years (compared with age 15-24 years), having 6 or more sex partners in the past 3 months, having any partners with HIV in the past 6 months, and inconsistent or no condom use.

Dean and colleagues reported on the use of pharmacy reversals as a novel population-based metric of gaps in the PrEP care continuum (Abstract 700). They defined a PrEP reversal as an adjudicated and approved PrEP prescription that is not picked up by the patient and the claim is withdrawn from the pharmacy. Using a national claims database including up to 85% of all PrEP prescriptions in the United States, they identified 59,219 patients who were prescribed TDF/FTC as PrEP.

Among the 11,388 (19.2%) patients who did not pick up their prescription and had a reversal, 2344 (20.6%) had a delayed PrEP initiation (filled their prescription within 90 days), 962 (8.4%) had a very delayed initiation (filled a prescription within 90-365 days), and 8082 (71%) abandoned their prescription (did not fill a prescription within 365 days). Subsequent HIV diagnosis was more common among patients who abandoned their PrEP prescription (5.7%) than those who had picked up their initial prescription (2.2%) or had a delayed PrEP initiation (2.4%). The researchers suggest that intervening at pharmacy point-of-sale may be an opportunity to support PrEP engagement, and the first 90 days are crucial for retention.

Having a social network contact who started PrEP was associated with PrEP uptake in Kenya and Uganda

Koss and colleagues reported on the role of social networks in predicting PrEP uptake in the SEARCH (Sustainable East Africa Research in Community Health) study in rural Kenya and Uganda (Abstract 151). Among 8898 persons at elevated HIV risk with at least 1 network contact within PrEP intervention communities, 29% initiated PrEP. Individuals with a serodifferent partner or in a polygamous marriage were more likely to initiate PrEP, whereas those under age 25 years; in a fishing, bar, or transportation occupation; or who were mobile were less likely to initiate PrEP. For both men and women, having a network contact who started PrEP was associated with starting PrEP (aRR, 1.57; 95% CI, 1.44-1.70). In contrast, having a network contact with HIV was not associated with PrEP uptake, after adjusting for serodifferent partner and other predictors. These findings suggest that interventions that leverage existing peer networks and strengthen social connections to other PrEP users may help foster PrEP uptake.

Wagner and colleagues reported on predictors of PrEP uptake in a sexual health clinic offering immediate PrEP initiation (Abstract 705). Individuals eligible and interested in PrEP were immediately referred to a pharmacist for a 30-day supply of TDF/FTC and a case manager for PrEP care navigation. Among 2149 individuals tested, 1348 were eligible for PrEP. Of these, 517 (38%) were interested in PrEP and referred to the pharmacist, 333 (24%) started PrEP, 278 (21%) were linked to PrEP, and 78 (6%) were retained in PrEP care at 3 months. The mean number of days from HIV testing to PrEP dispensation was 4.1, and the mean number of days from dispensation to PrEP start was 1.1. Black individuals were less likely to start PrEP (aOR, 0.50) and be linked to PrEP care (aOR, 0.32), and those with private insurance were more likely to be linked to PrEP care (aOR, 1.85) and be retained in PrEP care (aOR, 3.94). Those with a greater number of sex partners in the past 3 months were more interested in PrEP (aOR, 1.06/partner increase) and were more likely to be retained in PrEP care (aOR, 1.13), and those with gonorrhea at screening were more interested in PrEP (aOR, 2.44), be more likely to initiate PrEP (aOR, 5.00) and be linked to PrEP care (aOR, 2.31).

Townes and colleagues reported on linkage to a PrEP prescriber and PrEP prescription among black women in the THRIVE Demonstration Project (Abstract 701). Among 7137 black cisgender women who were HIV negative enrolled across 7 THRIVE sites in the United States, 38% were eligible for PrEP and 35% were referred to a PrEP prescriber. However, only 3% were successfully linked with a PrEP prescriber and only 2% were prescribed PrEP. Approximately two-thirds of women were screened for STIs, with a 3.2% positivity rate for syphilis, 4.6% positivity rate for gonorrhea, and 4.8% positivity rate for chlamydia. These findings highlight the need for programmatic activities focused on meeting the HIV prevention needs of black women.

Watson and colleagues reported on rates of PrEP counseling among black youth after diagnosis with an STI in 2 primary care/government-subsidized clinics in Philadelphia (Abstract 723). Among 416 PrEP-eligible youth (63% assigned female sex at birth, 13% sexual/gender minority), 35 received PrEP counseling within 6 months of STI diagnosis, of which more than 80% were sexual/gender minority patients assigned male sex at birth. Receipt of PrEP counseling was associated with being assigned male sex at birth (aOR, 40.2; 95% CI, 3.32-487) and having a rectal STI (aOR, 61.7; 95% CI, 6.63-574), but was not associated with receipt of primary care services (aOR, 0.3; 95% CI, 0.05-1.84). Only 14 patients started PrEP, 12 of whom were sexual/gender minority patients assigned male sex at birth who received primary care services. Among 54 sexual/gender minority patients assigned male sex at birth, 5 (11%) seroconverted during this period. These findings support the need for PrEP inclusive sexual health services for black youth, including cisgender heterosexual women.

Rao and colleagues presented data on PrEP use and referral to PrEP care among black partners of people with HIV in the HIV partner services program in the United States (Abstract 702). Among 710 HIV-negative black partners of people with HIV identified through partner services across 20 health departments, only 52 (7.3%) reported taking PrEP at the time of contact. PrEP use did not vary by age, sex, or geographic region. Among 608 HIV-negative black partners not on PrEP, 251 (41.3%) were offered referrals to a PrEP prescriber. Black partners living in the South were less likely (14%; adjusted prevalence ratio [aPR], 0.25) and those in the Midwest more likely (70.4%; aPR, 1.23) than those in the Northeast (55.4%) to have been referred to PrEP prescribers. The researchers call for partner services programs

Cisgender women reporting physical or sexual violence had lower adherence to PrEP

to identify and remove barriers to improve PrEP services among black women at risk for HIV.

Freeman and colleagues presented data on the use of PrEP among MSM who experienced sexual violence in 23 US cities (Abstract 712). Among 7121 HIV-negative MSM participating in the 2017 National HIV Behavioral Surveillance, 5% reported sexual violence in the past 12 months. MSM who reported sexual violence were more likely than those not reporting sexual violence to have a clinical indication for PrEP (83% and 77%, respectively; P=.08) and use PrEP in the past year (35% and 26%, respectively; P=.01). Although percentages of PrEP use among black and Latino MSM were similar among those reporting versus not reporting sexual violence, white MSM who experienced sexual violence were more likely to use PrEP (44% and 32%, respectively; P=.028). MSM reporting sexual violence were more likely to use PrEP regardless of age, insurance status, or experience of same-sex discrimination in healthcare settings. These findings suggest that screening for sexual violence in clinical settings may provide an opportunity to identify PrEP needs and assess safety of MSM.

Anderson and colleagues reported on the impact of violence on PrEP adherence among cisgender women in the United States (Abstract 711). Among 136 women (38% black and 19% Latina) enrolled in the AEGiS (Adherence Enhancement Guided by Individualized Texting and Drug Levels) open-label PrEP study, 22% reported violence in the past year, including 16% reporting physical violence and 15% reporting sexual violence; 30% reported lifetime sexual violence. At week 4, 43% of participants were highly adherent, defined as having tenofovir diphosphate levels in DBS consistent with 4 or more doses/week. The odds of high adherence were lower among women reporting past year physical violence (aOR, 0.24; P=.03), past year sexual abuse (aOR, 0.25, P=.04), past year physical or sexual violence (aOR, 0.20; P<.01), and lifetime sexual abuse (aOR, 0.27; P<.01). These findings suggest that PrEP programs should emphasize trauma screening and care as a strategy to improve PrEP adherence.

Blumenthal and colleagues reported on PrEP adherence and retention among 136 cisgender women in the AEGiS open-label PrEP demonstration study (Abstract 713). At week 48, 61% of women were retained, and 31% had TFV-DP concentrations in DBS sampling consistent with 4 or more doses/week. In univariate analysis, black women (OR, 0.31), those attending sites in Los Angeles versus San Diego (OR, 0.37), and those having partners of unknown HIV risk (OR, 0.29) were less likely to have consistent TFV-DP levels with 4 or more doses/week across visits. In multivariable models, only black race and having partners of unknown HIV risk remained significantly associated with suboptimal adherence. For retention, severe drug abuse on the Drug Abuse Screening Test-10 was associated with lower likelihood of retention (OR, 0.23), and interest in becoming pregnant in the next 6 months was associated with greater likelihood of retention (OR, 3.07). In multivariable models, only pregnancy interest remained significantly associated with study retention.

Sullivan and colleagues presented results of a randomized trial of a Mobile App to improve HIV prevention and care outcomes among MSM (Abstract 706). The M-Cubed App was built on social cognitive theory and incorporated prevention messages on condoms, PrEP, STI, and HIV care; core services including establishing an HIV testing plan and service locators for PrEP, HIV testing and HIV care; and ordering of condoms and HIV/STI test kits. Among 1220 MSM enrolled in Atlanta, Detroit, and New York City, 427 were assessed as higher-risk HIV-negative, 410 lower-risk HIV-negative, and 383 with HIV. Higher-risk HIV-negative MSM randomized to receive the App had increased HIV testing at the immediate post-intervention assessment (PR, 2.02) and increased PrEP use 3 months post intervention (aOR, 2.41), however no significant effects were seen for lower-risk HIV-negative MSM and those with HIV.

Symposium 8 entitled "What Does PrEP Deliver", Palanee-Phillips discussed key considerations and lessons learned in implementing PrEP in young women (Abstract 53). Of the more than 300,000 people globally who have initiated PrEP, she highlighted that only a minority are women. PrEP demonstration projects have shown that women can initially adhere to PrEP. Early drop off is seen in approximately half of women, although restarting PrEP is also common. She recommended measuring prevention effective adherence, or adherence to PrEP during periods of risk. Flexibility in refill timing is important, as young women may not use PrEP daily and may only come for refills when they are out of pills. She emphasized the importance of awareness and demand creation; recognizing high rates of STIs, depression, and a history of intimate partner violence; and including messaging on the importance of adherence while at high risk for HIV exposure. As stigma is a barrier to sustained use, framing PrEP in a positive, empowering way that avoids linking it to relationship risk, may encourage PrEP uptake.

Millett spoke about challenges and opportunities in implementing PrEP in key populations (Abstract 54). He reminded us that currently, key populations make up more than half of all new infections globally, including 80% of new infections outside of sub-Saharan Africa, and 25% in sub-Saharan Africa. In a series of studies evaluating the PrEP cascade, he showed that knowledge of PrEP was low in many key populations, including MSM in low and middle income countries, and female sex workers and transgender persons globally. Despite high proportions of these key populations expressing willingness to take PrEP, uptake is low, and persistence, even after just a few months, is almost nonexistent. Some of the barriers to PrEP uptake and persistence include criminalization of sex work or homosexuality, stigma, cost, and access to care. He also presented data that, in countries in which sex work or homosexuality is criminalized, HIV prevalence is markedly higher, suggesting that this

restricts use of effective prevention strategies.

Kamya discussed innovative models and lessons learned in delivering PrEP in East Africa (Abstract 55). In 2019, there were 177,000 new HIV infections in the East Africa. As of December 2020, there were an estimated 83,000 PrEP users in Kenya, 68,000 in Uganda, 23,000 in Tanzania, and 5500 in Rwanda. He provided examples of several different PrEP delivery models, including facility-based models providing PrEP to serodifferent couples in HIV clinics, integrating PrEP service delivery into maternal/child health and family planning clinics where women are already receiving reproductive health services, and diversifying service delivery settings into community settings through community clinics and safe spaces, drop-in centers, mobile testing units, and in fishing communities. Although PrEP continuation rates were modest across a number of programs,

Diversifying PrEP delivery sites and simplifying service delivery can facilitate scale-up of PrEP

Kamya emphasized that we should not expect that the PrEP cascade look like the ART cascade because of varying patterns of risk, and continuation may be higher among persons with ongoing risk. Several programs have shown evidence of lower HIV incidence in PrEP programs than in historical controls or models, including the SEARCH study, in which PrEP initiators had a 74% lower HIV incidence than matched controls. For the next phase of PrEP scale-up, he highlighted the need to further diversify and simplify service delivery, including reducing laboratory monitoring and providing longer refills, streamlining facility-based care, expanding to additional community sites such as pharmacies and home delivery services, and training and supporting prescribers, including via virtual networks.

Pillay discussed important considerations in incorporating injectable PrEP and newer formulations in lower- and middle-income countries (LMICs) (Abstract 56). He pointed out that LMICs are not homogenous, but vary by a number of factors including demography, economy, leadership and decision making, regulatory environment, and role of development and implementing partners. Uptake of PrEP has been low in a number of LMICs, with only 1325 PrEP initiations in India as of December 2020. He discussed several strategies to enhance delivery and uptake of long-acting PrEP agents in LMICs, including use of social media to introduce new products, leveraging online delivery platforms, and use of community-based services such as pharmacies and community health workers. He reviewed a framework for planning for the introduction of new technologies, including regulatory and policy considerations, implementation and financial planning, preparing for service delivery, and developing communication and social mobilization to create demand. He discussed the need for strategies to manage ambiguous HIV test results in the setting of long-acting PrEP, including mechanisms to facilitate discussion between clinicians and virologists. Key informant interviews with PrEP users highlighted the importance of choice in PrEP options. He recommended that long-acting PrEP be offered in a mainstream approach and should not be stigmatized as was done with oral PrEP, which was focused in marginalized communities.

Modeling the Impact of PrEP and Cost

Neilan and colleagues presented on the cost effectiveness of long-acting PrEP among MSM and transgender women in the United States (Abstract 150). Using a microsimulation model to simulate a PrEP-using population with characteristics similar to US HPTN 083 trial participants, they examined the cost and impact of 4 PrEP strategies: no PrEP, generic TDF/FTC, branded TAF/FTC, and CAB-LA. Model parameters included an annual cost of $8300 for generic TDF/FTC, $16,600 for branded TAF/FTC, and $25,800 for CAB-LA (based on the price for injectable cabotegravir/rilpivirine for ART) plus program costs of $400 for TDF/FTC and TAF/FTC and $700 for CAB-LA to admininster injections. Over a 10-year period, the model estimated that the no PrEP strategy would result in 178,000 HIV transmissions at a cost of US $33 billion, generic TDF/FTC and branded TAF/FTC 122,000 transmissions ($45 and $60 billion, respectively), and CAB-LA 107,000 transmissions ($76 billion). CAB-LA yielded the highest total quality-adjusted life expectancy (QALY). Despite assuming a more favorable safety profile with TAF/FTC, the incremental QALY of branded TAF/

To be cost effective, CAB-LA should be priced competitively with generic TDF/FTC

FTC over TDF/FTC was only 2000 per QALY. The incremental cost effectiveness ratio (ICER) for CAB-LA compared with generic TDF/FTC was $1,069,000 per QALY, much higher than commonly accepted cost-effectiveness thresholds ($100,000/QALY). The ICER for branded TAF/FTC indicated that this regimen had a higher cost and delivered fewer benefits than generic TDF/FTC and CAB-LA combined. CAB-LA was found to be cost effective if the price was reduced to $11,600 (maximum price premium over generic TDF/FTC, $3300) and cost-savings if CAB-LA cost was reduced to $10,200 (price difference, $1,900 with generic FTC/TDF). The researchers conclude that CAB-LA would not be cost-effective if CAB-LA for HIV prevention is priced the same as combination cabotegravir/rilpivirine used for treatment, and instead should be priced competitively with generic TDF/FTC.

Jacobson and colleagues modeled the effects of additional HIV prevention and treatment spending on the likelihood of achieving EHE goals in the United States (Abstract 704). Using an estimate of current public and private HIV prevention spending of $2.8 billion, they projected the impact of an additional $0.5 billion/year spending in 2020 and 2021, an additional $1.5

billion per year in 2022 and 2024, and an additional $2.5 billion per year in 2025 and 2029. They also considered 3 scenarios of spending optimization (allocating spending to the most effective intervention until no one else can be reached, then shifting spending to the next most effective intervention): no optimization, optimization started in 2025, and optimization started in 2022. Over a 10-year period, new HIV infections decreased by 186,737 to 239,881 infections with additional spending. Annual new HIV infections in 2029 dropped to 7814 with no optimization, 3194 with optimization starting in 2025, and 2368 with optimization starting in 2022. These findings suggest that increased funding with early spending optimization is required to reach target EHE goals (<3000 cases by 2029), although this may be difficult due to barriers in reallocating funds among public and private funds.

Luz and colleagues modeled the impact of PrEP uptake on HIV transmission among MSM in urban centers in Brazil (Abstract 771). Using the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) model, they estimated that increasing PrEP uptake to 60% over a 2-year period could decrease HIV incidence by 32% to 36% in 5 years and 39% to 45% in 10 years in Rio de Janeiro, Salvador, and Manaus. In sensitivity analyses, mean age of the cohort, PrEP dropout rates, and PrEP adherence significantly impacted the number of HIV infections averted.

Bórquez and colleagues modeled the impact and cost-effectiveness of PrEP among MSM and transgender women in Peru (Abstract 772). Using a dynamic HIV transmission model and data on PrEP uptake, retention, and adherence from the ImPrEP demonstration project, they estimated that 26% of new HIV infections could be averted by scaling up PrEP coverage to 20% of the MSM and transgender women populations between 2022 and 2030. The impact would be highest among transgender women and male sex workers. The cost of one year of PrEP was estimated at $680, and cost per disability-adjusted life year (DALY) averted was $3953, which would be considered cost-effective under most thresholds.

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