Review

CROI 2015: Advances in HIV Testing and Prevention Strategies

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HIV testing rates and awareness of HIV serostatus have improved globally, but disparities continue between black and white men who have sex with men (MSM) in the United States, and between women and men globally. The 2015 Conference on Retroviruses and Opportunistic Infections (CROI) was a watershed moment for preexposure prophylaxis (PrEP). Two efficacy trials conducted in MSM were stopped early because of an 86% reduction in the risk of HIV acquisition among men taking tenofovir and emtricitabine. New drugs, long-acting formulations, and different patterns of dosing are undergoing evaluation. Poor adherence has limited PrEP effectiveness in some populations, and new measures of drug levels in dried blood spots and hair appear to be promising new tools. Pharmacokinetic differences of PrEP agents in rectal versus vaginal tissue preclude extrapolating PrEP trial results among MSM to women. Several studies reported no HIV transmissions between HIV-serodiscordant couples when the seropositive partner was successfully treated for 6 months. However, consistent viral suppression does not occur in a substantial minority of patients in many clinics, reducing the potential impact of treatment as prevention.

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Tracking the Epidemic

**Phylogenetic Studies**

At the 2015 Conference on Retroviruses and Opportunistic Infections (CROI), held from February 23 to 26, Fraser provided an overview of how phylogenetic studies can inform HIV prevention efforts (Abstract 127). His first point was that phylogenetics can definitively rule out transmission between pairs of viruses because of the distance of common ancestors, but cannot definitively prove that a specific person transmitted to another. He then described phylogenetic studies of more than 17,000 HIV-seropositive persons in the Netherlands, more than 10,000 of whom are men who have sex with men (MSM). He and his colleagues found that all of the 106 clusters detected continued through to the present day; none of them were eliminated, and 60% of the clusters in MSM originated before 1996.

One cluster accounts for 66% of the injection drug users (IDUs) studied. Although most clusters have similar transmission dynamics, making it unlikely that there is a core group responsible for transmission, the most recent clusters are those that are driving the epidemic, predominantly in younger persons. From these data, investigators estimate that approximately 70% of new HIV infections come from undiagnosed persons and that of this 70% at least 59% come from very early infection. Only 7% come from persons who have achieved viral suppression at least once, and the rest come from persons who have been diagnosed with HIV infection but are not virally suppressed. However, in response to a question after his talk, Fraser pointed out that the role of acute infection could be substantially less in epidemics with less concurrency of partners than in the epidemic among MSM in the Netherlands.

Marzel and colleagues also found that approximately 42% of new HIV infections in the Swiss HIV Cohort Study were due to recent infection (within the past year), and this number dropped to approximately 32% when recent infection was defined as occurring in the past 6 months (Abstract 244). They also found that the total viral load in the chronic phase of infection was negatively associated with the contribution of acute infection (ie, higher viral loads in the chronic phase were associated with a lesser contribution of acute infection to transmission).

Mehta and colleagues reported on the role of bridging individuals in HIV transmission in the San Diego Primary Infection Cohort (Abstract 246). In their analysis, persons with the greatest “uniqueness” scores were most likely to be central to networks, bridging dissimilar individuals. The investigators suggest that disassortative partnerships may disproportionately drive HIV epidemics.

Oster and colleagues presented data on clusters of genetically related viruses from 19 states in the United States (Abstract 241). They examined the growth of clusters from 2007 to 2012, a possible indication of ongoing transmission, and pointed to populations that may benefit from partner...
services and interventions that link newly diagnosed persons with HIV infection to care. They found that growth in the previous year (2006-2007) and the proportion of a cluster that were MSM statistically significantly predicted future cluster growth. Of note, race and ethnicity were not associated with cluster growth. Although most clusters were geographically limited, some clusters spread into other geographic regions, supporting the importance of collaboration between health department jurisdictions.

**HIV Prevalence and Knowledge of HIV Serostatus**

Espinoza and colleagues reported on differences in the rates of new HIV diagnoses in different metropolitan statistical areas (MSAs) in the United States from 2003 to 2012 (Abstract 1040). Overall rates of new HIV diagnoses in the 104 MSAs examined decreased by 3.7% per year. However, increases in rates of new diagnoses were seen in some MSAs among MSM, blacks, and whites. Diagnoses among MSM aged 13 years to 34 years increased or were stable, and rates were stable or decreased among MSM aged 35 years or older. These authors suggest targeted prevention planning within MSAs to address local epidemics and trends.

Wejnert and colleagues presented US Centers for Disease Control and Prevention (CDC) data from nationally representative surveys of MSM in 20 US cities (Abstract 1041). Black MSM were statistically significantly more likely to be HIV infected than white MSM among all age groups, with greatest disparities in the youngest age group; among MSM aged 18 to 24 years, 1 in 5 blacks was HIV seropositive compared with less than 1 in 20 whites and less than 1 in 13 Latinos. The disparities became even greater during 2008 to 2011, particularly for younger men. Knowledge of HIV serostatus was also considerably lower among black MSM than white MSM in all age categories younger than 50 years. Less than half of the black HIV-seropositive MSM younger than 30 years were aware of their serostatus, and less than two-thirds among all age categories were aware. However, black MSM reported statistically significantly lower rates of condomless anal sex than other racial or ethnic groups. These data continue to underscore the high rates of HIV prevalence and low rates of HIV serostatus awareness among young black MSM, and the need to consider factors other than individual risk when addressing this severe epidemic.

In the United States, HIV prevalence is higher among black MSM than among white MSM, and the disparities increased from 2008 to 2011, particularly among younger men.

Hall and colleagues presented data from the US National HIV Surveillance System on the proportion of new HIV diagnoses in 2012 that were considered late (ie, presented with a CD4+ count lower than 200 cells/µL or an opportunistic infection within 3 months of diagnosis) (Abstract 999). In 2012, 24% of all new HIV diagnoses were late, but there was considerable geographic diversity and none of the MSAs achieved a rate lower than 20%. Among men, the proportion of late diagnoses was statistically significantly higher among IDUs and heterosexuals than among MSM. Racial and ethnic disparities existed in many MSAs. Of 105 MSAs, late diagnoses were more common in blacks than whites in 35 MSAs, and late diagnoses were more common in Hispanics than whites in 68 MSAs. These data point to the ongoing challenge of late HIV diagnosis and the need for more widespread HIV testing.

Truong and colleagues presented data on HIV test-seeking behavior among blood donors in Sao Paulo, Brazil (Abstract 1010). Among nearly 12,000 donors, 55% had not heard of alternative public HIV testing sites and 2.7% reported that HIV testing was their primary reason for donating blood. Test seeking was associated with dissatisfaction with a prior alternative testing experience (P = .004) and hepatitis C virus infection (P < .001), suggesting that improvements in the availability and quality of alternative testing sites are needed to deter high-risk persons from donating blood during the window period for HIV detection.

Ellman and colleagues presented data on awareness of HIV diagnosis in the nationally representative Swaziland HIV Incidence Survey, comparing results from 2011 with results from 2007 (Abstract 1013). Of more than 18,000 men and women aged 18 to 49 years, 32% were HIV seropositive. Of these, 38% were unaware of their HIV infection. Fifty-five percent of HIV-infected individuals reported in a 2007 survey that they had never received an HIV test, compared with only 16% of individuals in a 2011 survey. After adjusting for marital status, education, and employment, men were statistically significantly more likely to be undiagnosed than women (adjusted odds ratio [aOR], 2.54; 95% confidence interval [CI], 2.25–2.87), and younger adults were more likely than older adults to be unaware of their HIV infection (aOR, 2.44; 95% CI, 2.04–2.86). These data point to the successful scale-up of HIV testing and the need for testing targeted toward men and younger adults, and for regular HIV screening in areas with high HIV seroprevalence.

Internationally, the proportion of persons who have never had an HIV test has decreased substantially. Men are consistently less likely to be aware of their HIV infection than women, and younger persons are more likely to be unaware in some settings.

Huerga and colleagues presented similar population-based data from KwaZulu-Natal, South Africa (Abstract 1014). Of nearly 6700 persons, 85% agreed to participate. HIV prevalence was 21% among women and 16% among men. In multivariate analysis, factors associated with lack of HIV testing and unawareness of HIV serostatus were younger age (<35 years), male sex, and having more than 1 sex partner in the prior 12 months. These data
show substantial improvement in the proportion of the general population that has received an HIV test, but also support the need for programs targeting men, younger adults, and persons with more than 1 sex partner.

**Improving HIV Diagnosis, Including Acute Infection**

Linley and colleagues presented data from 2008 to 2012 on the proportion of persons newly diagnosed with acute HIV infection from the US National HIV Surveillance System (Abstract 1043). They defined acute infection as having a documented or self-reported negative HIV antibody test result within 60 days of the first HIV antibody–positive specimen. Among more than 48,000 persons with a previous negative diagnostic HIV test result, 3.2% were diagnosed as having acute HIV infection. Acute HIV infection was statistically significantly more common among individuals aged 13 to 29 years, MSM, those with a documented recent negative HIV test result, inpatient and outpatient settings (compared with STI clinics or counseling and testing sites), and being located in the Northeast or West of the United States. Persons with acute HIV infection were also statistically significantly more likely to have a plasma HIV RNA level of greater than 1 million copies/mL.

Hoenigl and colleagues presented data on the risk factors associated with acute and early HIV infection among MSM in San Diego, California (Abstract 1021). In a cohort of nearly 9000 MSM, 200 were diagnosed with acute and early HIV infection. In multivariable analysis, the strongest risk factors for predicting acute and early HIV infection in this cohort included engaging in condomless receptive anal sex with an HIV-seropositive partner or with 5 or more partners, number of male sex partners, a syphilis diagnosis, and methamphetamine use. These behavioral risk factors help identify a population that should undergo frequent screening and should receive highly effective HIV prevention programs, such as preexposure prophylaxis (PrEP).

**Strategies to Improve Uptake of HIV Testing**

A number of investigators have attempted strategies to increase HIV testing in emergency departments (EDs) over the last several years. Two large studies of HIV testing in EDs were presented at CROI this year. Quinn presented data on temporal trends in HIV testing and knowledge of serostatus among patients who visited The Johns Hopkins University ED during the 25-year period from 1986 to 2013 (Abstract 98). The investigators performed identity-unlinked HIV and hepatitis C virus testing and chart abstraction over a 6- to 8-week period on all adult patients who had blood drawn for other reasons in 1987, 1988, 1992, 2001, 2003, 2007, and 2013. The testing was unlinked from patient identification information and was used to monitor trends in a variety of health outcomes. HIV prevalence peaked at 12% in 1993 and declined to 6% in 2015, and knowledge of HIV serostatus increased from 20% in 1987 to 93% in 2013.

Along with this improvement in knowledge of HIV serostatus was an increase in the percentage of individuals linked to care within 90 days of HIV diagnosis from 47% in 2005 to 88% in 2013. Antiretroviral therapy use also increased over this time period (from 27% in 2007 to 80% in 2013) as did viral suppression (from 22% in 2001 to 60% in 2013). Perhaps as a result of increased diagnosis and treatment of HIV-infected persons in the community, HIV incidence declined over this time period from a high of 2.5% per year in 2001 to a low of 0.2% per year in 2013, as measured by a multiasay algorithm used on cross-sectional samples. The investigators concluded that clinical HIV testing of ED patients increased from less than 1000 patients in 2005 to nearly 6800 in 2013, highlighting the value of reaching otherwise underserved populations through ED visits.

Conversely, Chavez and colleagues reported on the challenges of expanded HIV testing in the HIV Prevention Trials Network (HPTN) 065 study, also called the TLC-Plus (Test, Link to Care, Plus Treat) study (Abstract 1100). They worked with 9 hospitals in the Bronx, New York, and 7 in Washington, DC, encouraging them to increase HIV testing in EDs and inpatient units through a variety of methods, including increased staff and administrative support, simplified informed consent processes, electronic documentation of testing, and a switch from point-of-care testing with dedicated staff to laboratory-based testing. Investigators tracked data from more than 1.2 million ED visits and 360,000 hospitalizations in the Bronx and more than 700,000 ED visits and 150,000 hospitalizations in Washington, DC, from February 2011 to January 2014. Overall, only 6.5% of ED visits and 13% of hospitalizations included HIV testing in the Bronx, with no substantial increase over time. Similar results were seen in Washington, DC, with rates of 13.8% and 22%, respectively. There was also no net increase in the proportion of HIV tests with positive results across the sites. The investigators acknowledged the many logistical and staffing issues faced in these inner city hospital settings.

In another approach to medically based testing, Shaw and colleagues presented data from Canada on pre-diagnosis health care utilization patterns among patients testing positive for HIV (Abstract 1054). Their team found that antibiotics were more than 3 times more likely to be prescribed for HIV-infected persons in the year before their diagnosis than for persons in a control group. Although having a single prescription for antibiotics is not a specific marker of HIV risk—many HIV-uninfected patients were also prescribed antibiotics—dispensing antimicrobials could serve as a reminder to practitioners to offer HIV testing in appropriate situations.

Several investigators have used home HIV self-testing as a strategy to reach persons who are not routinely tested in clinical settings. Medline and colleagues used a geosocial networking app to advertise the availability of free home HIV self-testing kits for MSM provided by mail, a voucher used
at a pharmacy, or via vending machine (Abstract 1098). Online advertising over a 6-week period in April and May of 2014 yielded nearly 12,000 unique visits to their website and 354 requests for HIV tests. Two-thirds of participants requested mailed tests and 30% requested pharmacy vouchers. Of 122 study participants reporting their behaviors and test results, 28% had been tested for HIV more than 1 year previously and 11% had never been tested. Two participants reported newly diagnosed HIV and both reported linkage to confirmatory testing or care. The investigators reported that this is a potential strategy for disseminating HIV testing to a population who do not seek regular HIV testing in a clinical setting.

Sabharwal and colleagues reported on the use of HIV home testing among newly diagnosed HIV-seropositive MSM in New York City (Abstract 1097). Compared with more than 2000 men who had not previously used home HIV tests, those who had used home HIV tests were significantly less likely to be black (23% vs 37%; P = .007) or Hispanic (23% vs 31%; P = .007). Home testers were significantly more likely to have had regular HIV testing (83% vs 62% tested in the past 12 months; P = .002). This suggests that home HIV testing is not reaching the populations most heavily impacted by HIV (those not routinely testing and persons of color). In response, the New York City Health Department plans to offer home HIV testing kits to partners of men newly diagnosed with HIV who decline testing in traditional settings. Although the investigators report that linkage to care within 3 months of HIV diagnosis was similar between home test users and nonusers (65% vs 69%), rates of linkage need improvement in both groups, and this study would not have been able to identify men with positive home HIV test results that do not present for confirmatory testing.

Golden and colleagues presented data from the 28 months before to the 28 months after the launch of an initiative for health departments to provide partner services for all partners of MSM newly diagnosed with bacterial sexually transmitted infections (STIs) in Washington state (Abstract 1099). The proportion of MSM who received partner services increased from 62% preintervention to 76% postintervention (P < .001), as did HIV testing among patients identified through partner services (from 63% to 91%; P < .001). The absolute number of new HIV diagnoses among patients diagnosed with an STI increased from 61 preintervention to 104 postintervention. The investigators conclude that making HIV testing an explicit component of partner services for STI treatment can increase HIV case finding.

**Internationally, hybrid models of community health campaigns and home-based HIV testing appear successful.**

In international settings, community health campaigns (CHCs) and home-based HIV testing have been demonstrated to reach large populations of previously untested or undiagnosed individuals. Chamie and colleagues presented data from the SEARCH (Sustainable East Africa Research of Community Health) trial, which used a hybrid model of both types of testing in 32 communities in eastern and southwestern Uganda and western Kenya (Abstract 1101). Investigators began with a 2-week, mobile CHC that tested individuals for various diseases (eg, diabetes, hypertension, malaria) including HIV. Individuals who did not respond to a CHC were offered HIV testing at home. Eighty-nine percent of all stable adult residents and 80% of all adult residents were reached through this model; 80% were reached through CHC and 20% through home-based testing. HIV prevalence was 9.4%, median CD4+ count was 516 cells/μL, and 43% of adults tested reported no prior HIV testing.

In a multivariate analysis, predictors of testing with home-based tests rather than through CHC included male sex, being unmarried, having HIV infection, having a nonfarming occupation, having a high education level, and spending more time away from the community in the year prior to the start of the study. Despite reaching more men through home-based testing, a sex disparity in testing remained at all ages, with 80% to 90% of stable men compared with 90% to 95% of stable women being tested for HIV in this hybrid model; rates of testing were lower among nonstable populations. This hybrid model reached large populations of untested and undiagnosed persons in these settings but highlights a continued need for strategies to reach men and mobile populations.

**Risk Factors for HIV Transmission and Acquisition**

**MSM**

Baral reported on the state of the HIV epidemic among MSM globally, with a focus on sub-Saharan Africa (Abstract 73). He pointed out that certain characteristics of the epidemic are similar globally: an HIV prevalence of 14% to 18% among MSM throughout most of the world and an increased risk among younger MSM. Surveys from many countries also suggest that 50% to 60% of MSM in sub-Saharan Africa have sex before age 18, pointing to the need to reach adolescent MSM. Baral also reported an HIV incidence rate of 5% to 20% per year throughout much of sub-Saharan Africa, including a consistent incidence rate of 7% to 10% in a single cohort in Kenya over many years. Bacterial STI rates among MSM are quite high (20%-30% each for syphilis and rectal gonorrhea), and these STIs are asymptomatic, therefore requiring regular STI screening. Across sub-Saharan Africa, 50% to 60% of MSM meet their sex partners online. In Lesotho and Swaziland, meeting same-sex partners online was associated with several measures of stigma.
and an increased risk of HIV infection or depression. In Nigeria, after enactment of laws prohibiting same-sex marriage and criminalizing various aspects of MSM behavior, the proportion of MSM seeking health care declined, and other measures of stigma (eg, being blackmailed or verbally harassed) increased. Baral closed his talk with a plea to further evaluate the epidemiology of and risk factors for HIV acquisition among MSM in sub-Saharan Africa; to apply what is being learned about effective biomedical, behavioral, and structural interventions in other contexts to this one; and to frame the implementation science questions central to effectively addressing the MSM epidemic in sub-Saharan Africa.

Scott and colleagues presented data on a personalized, online risk-assessment tool for MSM called SexPro (Abstract 1017). Using data from 561 HIV seroconversions occurring among nearly 9000 MSM enrolled in 2 previous efficacy studies (EXPLORE and VAX004), investigators created an algorithm for predicting risk that they then applied to the 1164 HIV-seronegative black MSM enrolled in the observational HPTN 061 study. All 28 seroconversions in the HPTN 061 study were in the top 4 deciles of risk scores, as measured by SexPro. This suggests that SexPro may be useful in identifying MSM, including black MSM, at elevated risk for HIV infection and, therefore, a group to whom PrEP should be offered.

**Youth**

Santelli and colleagues reported on the marked increase in school attendance among girls and boys aged 15 to 19 years in the Rakai District of Uganda from 1994 to 2013 (Abstract 1036). School enrollment was associated with a lower likelihood of reporting ever having had sex (37% for those enrolled in school vs 88% for those not enrolled). Among sexually active women, those enrolled in school were less likely to have ever been pregnant (6% vs 78%, respectively), and to have HIV infection (2% vs 6%, respectively), and more likely to report consistent condom use (70% vs 17%, respectively). This suggests that strategies that increase school attendance could be useful in reducing HIV risk factors and incidence.

**Injection Drug Use**

Brady and colleagues reported on trends in HIV prevalence and risk among IDUs in Philadelphia, Pennsylvania (Abstract 1028). Philadelphia surveillance reported an 80% decline in new HIV diagnoses among IDUs from 2006 to 2013. Analyzing data from 3 National HIV Behavioral Surveillance (NHBS) cycles (2005, 2009, and 2012), the investigators found no overall trend in sharing of injection drug equipment. Multivariate analysis identified subgroups that were more likely to share injection equipment: IDUs who injected a combination of opiates and stimulants and those with less than a high school education (aOR, 1.43 and 1.56, respectively). Blacks and Latinos were less likely than whites to share injection equipment (aOR, 0.59 and 0.64, respectively). Persons using needle exchange programs were also less likely to report sharing injection equipment than those who obtained their injection equipment from dealers or varied sources (aOR, 0.61 and 0.51, respectively). Despite the tremendous strides made to decrease the number and rate of HIV infections in this population, needle exchange programs should be promoted to those not currently using these services.

**Transactional Sex Among Women**

Sionean and colleagues reported on the prevalence and correlates of transactional sex among heterosexual women in 21 US cities (Abstract 1031). The NHBS system interviewed 5507 women in 2010, of whom 19% reported receipt of money, drugs, or comparable items from a man in exchange for sex during the 12 months before the interview. HIV prevalence in the overall sample was 2.9% and was somewhat higher (4.5%) among women reporting exchange of sex, although this difference was not statistically significant. Characteristics and behaviors in the prior 12 months that were independently associated with exchange of sex in multivariate models (reported as adjusted prevalence ratio [aPR]) were structural (unemployment, aPR, 1.53; homelessness, aPR, 1.53; incarceration, aPR, 1.17), biomedical (STI diagnosis, aPR, 1.56), and individual behavioral (use of crack cocaine, aPR, 1.45). Women who exchanged sex were also more likely to have risky partners on multivariate analysis, including partners older by 10 years or more (aPR, 1.58), HIV-seropositive partners or those with an unknown serostatus (aPR, 1.20), partners who had been incarcerated (aPR, 1.25), and partners who were MSM (aPR, 1.16). This population of women with low socioeconomic status appears to be at greater risk than the general female population and needs access to STI and HIV prevention services.

Cowan gave a plenary presentation on the HIV epidemic among female sex workers globally (Abstract 135). The size of the global female sex worker population is unknown, but female sex workers are estimated to be 0.7% to 4.3% of the general population in sub-Saharan Africa, 0.2% to 2.6% of the population in Asia, and 0.2% to 7.4% of the population in Latin America and the Caribbean; rates are higher (≥9.1%) when transactional sex is included in the definition. A meta-analysis of the increased burden of HIV among sex workers found that compared with HIV prevalence in the general population, HIV prevalence among female sex workers is substantially higher: 12-fold higher in Latin America and the Caribbean, 12.4-fold higher in sub-Saharan Africa, and 29-fold higher in Asia. Modes of transmission studies, such as one conducted by the World Bank in Zimbabwe in 2012, suggest that a small proportion of epidemics originate in female sex workers (<5% in this example). However, when taking into account forward transmission of HIV, the population-attributable fraction can grow substantially over time. Structural interventions that reduce violence have been modeled to avert up to 20% of new infections among female sex workers, and decriminalization of sex work has...
been modeled to reduce 33% to 46% of new infections. A meta-analysis of empowerment interventions for female sex workers suggests a reduction of new infections by one-third. Several studies of the care cascade in regard to female sex workers suggest that although progress has been made in some settings, additional interventions are needed to link women to care, provide antiretroviral therapy, and support ongoing retention in care. A cluster randomized trial that provides HIV-seronegative and -seropositive female sex workers with PrEP and antiretroviral therapy, respectively, is currently underway.

Zulu and colleagues reported on HIV incidence among adult patients in an STI clinic in Blantyre, Malawi (Abstract 1047). HIV incidence was 2.3 per 100 person-years, lower than the previous reported rate of 5.6 per 100 person-years. In multivariate analysis that included age, sex, marital status, income, and sexual risk practices, the only factor statistically significantly associated with HIV incidence was transactional sex (relative risk [RR], 2.4; 95% CI, 1.2-4.7).

**STIs**

Laga provided an overview of the impact of the HIV epidemic on global trends in STIs (Abstract 72). She pointed out that there was a substantial increase in the rate of STIs in the 1970s and early 1980s, variably attributed to the availability of oral contraception, changing cultural norms (eg, the sexual revolution, gay rights), urbanization, migration patterns, and increases in survival sex work. The response to the rising rates of STI incidence was primarily focused on improved diagnosis and treatment, with the emergence of antibiotic resistance, and placed little focus on primary prevention. With the early reports of AIDS and the recognition of widespread HIV infection, primary prevention became the focus, resulting in reductions in HIV and other STIs. However, since the rollout of antiretroviral therapy, a resurgence has been seen in the incidence of bacterial STIs such as syphilis, gonorrhea, and chlamydia. Laga pointed out that some HIV prevention interventions, such as male circumcision, may directly reduce STI acquisition (eg, herpes simplex virus 2 [HSV-2], human papillomavirus [HPV], bacterial vaginosis, chancroid). Other prevention strategies (eg, PrEP) will not directly reduce STI rates and must be paired with increased screening, diagnosis, and treatment, as well as searching for other primary prevention strategies.

**Hormonal Contraception**

Herold led a themed session on the enduring controversy of the role of hormonal contraception in HIV acquisition risk (Session TD-S). She began the session by reviewing a meta-analysis that included 18 studies, more than 37,000 women, and 1830 incident infections. In this analysis, compared with women not using any hormonal contraception, women who used depot medroxyprogesterone acetate (DMPA) were at statistically significantly increased risk for HIV infection (adjusted hazard ratio [aHR], 1.50; 95% CI, 1.25-1.83); women using norethisterone enanthate (NET-EN) or combination oral contraceptives were not at statistically significantly increased risk (aHR, 1.24 and 1.03, respectively). Neither age nor HSV-2 serostatus modified the effects of hormonal contraception on HIV acquisition. However, when the authors of the meta-analysis removed studies most likely to have been biased, the association between DMPA and HIV acquisition was attenuated (aHR, 1.22; 95% CI, 0.99-1.50).

Herold also described the various mechanisms by which progesterone could increase susceptibility to HIV infection, including thinning of the vaginal epithelium; disruption of tight junctions between epithelial cells; up-regulation of syndecans; increase in proinflammatory cytokines or decrease in protective cytokines; increased CC chemokine receptor 5 (CCR5+) expression; changes in the microbiome; or increased susceptibility to other STIs which in turn could increase susceptibility to HIV. The authors of the meta-analysis point out that DMPA creates a more hypoestrogenic environment than either NET-EN or estrogen-containing combination oral contraceptives and that DMPA has a higher affinity for binding the glucocorticoid receptor than the progestins used in NET-EN or combination oral contraceptives. Either mechanism could potentially result in increased susceptibility to HIV, even when compared with other progestin-containing regimens.

Herold pointed out that much of the data to date have focused on studies in nonhuman primate models. At this year’s CROI, Kersh and colleagues presented data on 16 pigtail macaques through several menstrual cycles and reported a statistically significant thinning of the stratum corneum of the vaginal epithelium (Abstract 862). In evaluating the 43 pigtail macaques studied in simian-human immunodeficiency virus (SHIV) challenge studies, investigators found a statistically significant correlation between the 4 days of the menstrual cycle that had the thinnest stratum corneum and the risk of SHIV acquisition.

Three posters presented in this themed discussion explored the role of hormonal contraception or phases in the menstrual cycle on expression of CCR5+, the coreceptor for HIV entry. Meditz and colleagues presented data on the effect of age and estrogen replacement following natural or medically induced menopause on CCR5+ expression in CD4+ cells in the peripheral blood (Abstract 859). They reported that after controlling for CCR5Δ32 genotype, older women had significantly increased CCR5+ CD4+ expression (4.2% increase with every 10-year increase in age; P = .003). Contrary to the investigators’ hypothesis, CCR5+ expression did not increase after medically induced menopause, although estrogen replacement in post-menopausal women was associated with reduced CCR5+ expression in CD4+ cells.

Tsibiris and colleagues presented data from 92 women enrolled in the Women’s Interagency HIV Study that had used DMPA, the levonorgestrel-releasing intrauterine device, or
combination oral contraceptives, and from 33 women who did not use hormonal contraception (Abstract 858). The investigators reported that CCR5+ expression in CD4+ and CD8+ T cells from the peripheral blood was higher among women using the levonorgestrel-releasing intrauterine device, with a nonstatistically significant increase in CCR5+ expression among women using DMPA. Haaland and colleagues presented data on changes in CCR5+ expression when moving from the follicular to the luteal phase of the menstrual cycle, when plasma progesterone increases (Abstract 860). They reported an increased proportion of memory T cells expressing CCR5+ and CD53+ during the transition to the luteal phase. When CD4+ T cells were stimulated, investigators found a significant increase in detectable intra-cellular tumor necrosis factor alpha (TNF-α; 31% vs 52%; \( P = .006 \)) but no change in intra-cellular interleukin (IL)-2 or gamma interferon.

Roxby and colleagues presented data on changes to the vaginal micro-biome in 15 HIV-seronegative Kenyan women initiating DMPA, followed up for a median of 8.5 months (Abstract 861). Gardnerella vaginalis, which was present in all the women before initiation of DMPA, declined by 0.21 log_{10} copies per swab per month (\( P = .017 \)). DMPA initiation was also associated with significant declines in IL-6 (\( P = .025 \)), IL-8 (\( P = .041 \)), and the IL-1 receptor antagonist.

Grabowski and colleagues evaluated the association between DMPA use and HSV-2 risk in 682 HIV-seronegative and HSV-2-seronegative female partners of men enrolled in a circumcision trial in Rakai, Uganda (Abstract 28). Although 85% of the women used DMPA at some time during the trial, only 6% used DMPA consistently throughout the trial. Compared with women who were neither pregnant nor using hormonal contraception, consistent users of DMPA had an increased risk of HSV-2 acquisition (aHR, 2.26; 95% CI, 1.09-5.74). When the analysis was restricted to female partners of men with HSV-2 infection, the risk was even higher (aHR, 6.23; 95% CI, 1.49-26.3).

Stigma

Baugher and colleagues presented data on the prevalence and association of stigma with behavioral and clinical outcomes (Abstract 1057). Using data from the 2011 CDC-sponsored Medical Monitoring Project, an annual cross-sectional survey of a nationally representative sample of HIV-infected adults in the United States and Puerto Rico receiving HIV care, they reported that 76% of the 4385 participants endorsed 1 or more HIV-related stigma questions from a 6-item scale. Most commonly endorsed was the statement “It is difficult to tell people about my HIV infection,” with 64% of the sample agreeing with this statement. Stigma scores were associated with depression, binge drinking in the past 30 days, nondisclosure of HIV serostatus to all sex partners, nonadherence to antiretroviral medications, and lack of viral suppression. The investigators emphasized the importance of developing and implementing stigma-reduction strategies to improve the health and quality of life of HIV-infected persons.

Balaji and colleagues presented data on the association between enacted stigma (verbal harassment, discrimination, and physical assault) and HIV-related risk behaviors among 8922 HIV-uninfected MSM recruited into the NHBS system in 2011 (Abstract 1058). Overall, 32% of the men surveyed reported verbal harassment within the past 12 months, 24% reported discrimination, and 8% reported physical assault. These 3 measures were associated with having 4 or more male sex partners, engaging in condomless anal sex, and engaging in exchange sex within the past 12 months. The investigators conclude that interventions that increase the acceptance of sexual minorities and help people to cope with stigma will be important for controlling the HIV epidemic.

Chan and colleagues reported on the association between antiretroviral therapy scale-up and reductions in reported stigma in the general populations of 18 sub-Saharan African countries (Abstract 1059). They reported that 89% of women and 81% of men aged 18 years to 49 years reported HIV-related stigma. However, investigators found that for each 1% increase in antiretroviral therapy coverage, there was a statistically significant decline in the percentage of women and men reporting HIV-related stigma. They note, however, that stigma prevalence was still quite high in all countries, and called for interventions to target HIV-related stigma.

Internationally, increased antiretroviral therapy coverage is associated with declines in reported HIV-related stigma.

Crowley presented an evaluation of HIV-related criminal law in the United States and Africa (Abstract 129). He pointed out that 61 countries, including the United States, have laws making it a crime to expose others to HIV, for HIV-infected persons to engage in certain sexual acts without disclosing their serostatus, and to transmit HIV to another person. Although Africa is the continent with the greatest number of countries with these laws, the United States is the country with the greatest number of prosecutions. Since 2008, there have been more than 200 HIV-related prosecutions in the United States. In all, 33 states have HIV-specific criminal laws, 11 states have laws making it a crime for HIV-infected persons to spit or bite, 29 states have had at least 1 prosecution in the last 2 years, and 10 states have punishments that include being made to register as a sex offender.

Crowley gave several examples, including that of an HIV-infected man in Michigan charged under the state’s antiterrorism statute with possession of a “biological weapon”; that of an HIV-infected man in Iowa who was sentenced to 25 years after a single sexual encounter, even though a condom was used and the man had an undetectable viral load; and that of an HIV-infected man who is currently serving a 35-year prison sentence for spitting at a police officer. Crowley pointed out that many of these laws run counter to scientific estimates of transmission risk and that
data suggest these laws do not deter risky behavior and may, paradoxically, discourage persons from HIV testing and treatment.

In Africa, given the generalized epidemic, laws criminalizing HIV may affect a large proportion of the general population. In addition, homosexuality is illegal in almost all African countries, and MSM have disproportionately higher HIV infection rates than the general population. These anti-gay laws and policies may drive MSM away from needed services and thus contribute to rather than address local HIV epidemics. Crowley ended his presentation with a call to action for practitioners, asking them to seek out and understand local laws, find opportunities to present objective scientific evidence about HIV transmission risk, and to serve as role models for treating heavily impacted populations with respect, while explaining to colleagues why this is so important.

Stigma continues to drive the HIV epidemic and is associated with depression, substance use, nondisclosure of HIV serostatus to all sex partners, non-adherence to antiretroviral medication, and lack of viral suppression.

Smith and colleagues presented data on the incidence and risk factors associated with sexual assault among MSM and young women in coastal Kenya from longitudinal cohort studies since 2005 (Abstract 102). They reported that among 971 men (75% of whom were MSM) and 455 women (81% of whom were sex workers), the incidence of rape was 3.7 per 100 person-years and 4.5 per 100 person-years, respectively. Factors associated with rape among MSM included younger age, engaging in exchange sex, having only male sex partners, and engaging in group sex. For women, risk factors for rape included being HIV seronegative. Among MSM, HIV incidence was 11.7 per 100 person-years in the group who reported being raped, and 7.0 per 100 person-years in those who did not report being raped, a difference that was not statistically significant. These data indicate that rape is common among MSM and female sex workers, and that interventions are needed to reduce sexual, physical, and verbal abuse in vulnerable populations.

Population Mobility

Palk and Blower presented data on the relationship of mobility to risk practices and HIV infection within populations in Lesotho (Abstract 1034). Using data from the 2009 Demographic and Health Survey of Lesotho, they estimated that 30% of women and 32% of men traveled 1 to 4 times in the previous year, and 18% of women and 21% of men traveled 5 or more times. Men and women who traveled more were statistically significantly more likely to have more than 1 sex partner and were more likely to have concurrent sex partners. Men who traveled 5 or more times per year had a 30% higher risk of HIV infection than men who did not travel.

Prevention Strategies

PrEP

PrEP was featured prominently at this year’s CROI. Landovitz’s plenary session provided an update on the state of the science of PrEP and highlighted key implementation considerations (Abstract 20). PrEP involves administering antiretroviral medications to HIV-uninfected, at-risk individuals to lower their risk of HIV acquisition. Currently, the only PrEP regimen approved by the US Food and Drug Administration (FDA) is the fixed-dose combination of daily, oral tenofovir disoproxil fumarate (TDF) and emtricitabine. Several clinical trials have demonstrated the efficacy of TDF alone or in combination with emtricitabine among MSM and transgender women, and among HIV-serodiscordant heterosexual couples and young heterosexual men and women in Africa. However, a lack of efficacy was observed in 2 PrEP trials in African women, owing in large part to low adherence rates in these studies. Nonhuman primate models have demonstrated lower tenofovir concentrations in the cervicovaginal than in the rectal compartment with oral TDF dosing, a finding also confirmed by a single-dose pharmacokinetic study in women. These results suggest that there may be less forgiveness for nonadherence to TDF-based PrEP in protection against vaginal exposures. Landovitz pointed to a pharmacokinetic modeling study that suggested that 6 to 7 doses per week of TDF and emtricitabine is likely required to achieve high levels of vaginal protection against HIV in women.

Although PrEP with daily, oral TDF and emtricitabine was approved by the US FDA in July 2012, adoption of this prevention strategy has been slow. Landovitz highlighted a number of concerns that have been raised regarding PrEP implementation and reviewed available data addressing these issues. One concern is risk compensation, or an increase in risk behaviors as a result of using PrEP, which could lead to a heightened risk of HIV acquisition at the individual and population levels. A modeling study of PrEP in resource-limited settings indicated that although risk compensation had minimal impact on population-level incidence at high levels of PrEP effectiveness, cumulative HIV infections could increase with risk compensation at lower levels of PrEP effectiveness. Although risk compensation has not been observed in placebo-controlled PrEP trials, Landovitz affirmed the importance of monitoring for changes in risk behavior in upcoming PrEP implementation programs in which placebos will no longer be used. He noted an increase in rates of sex with nonprimary partners, observed after unblinding and release of efficacy results in the Partners PrEP study.

Another concern that was raised is the emergence of HIV resistance among individuals who acquire HIV infection while taking PrEP. Modeling studies have yielded conflicting predictions, ranging from doubling of rates of transmitted resistance to a more limited impact on circulating resistance. HIV resistance has been rare in
clinical trials of PrEP, observed in only 5 of 243 (2.0%) individuals who were randomly assigned to an active drug and became HIV-infected after enrollment, and only 0.06% of all those randomly assigned to active study drug. However, resistance with oral PrEP was more common when PrEP was initiated in the setting of undiagnosed primary HIV infection, with resistance seen in 8 of 29 (28%) participants.

HIV resistance appears to be rare with PrEP use and occurs most often in the setting of unrecognized acute HIV infection at the time of PrEP initiation.

A key clinical question is the timing of protection onset after PrEP initiation, and how quickly protection wanes after PrEP is discontinued. Based on data from an intensive pharmacokinetic study of intracellular tenofovir concentrations in peripheral blood mononuclear cells and a pharmacodynamic model derived from the iPrEx (Chemoprophylaxis for HIV Prevention in Men) study, it has been inferred that high levels of protection can be achieved after 5 daily doses of TDF and emtricitabine, and that a greater than 90% risk reduction persists up to 7 days after stopping treatment. Landovitz noted that these estimates are based on daily dosing and pertain only to MSM, as estimates may differ for other populations or routes of exposure.

Landovitz also summarized data on the safety of PrEP with TDF and emtricitabine when used in HIV-uninfected individuals across several clinical trials. First, a start-up syndrome with gastrointestinal symptoms has been observed in up to 18% of participants, although this appears to be self-limited and did not result in substantial PrEP discontinuations. Although TDF has been associated with renal toxicity in HIV-infected individuals, only 0.2% of participants randomly assigned to receive TDF and emtricitabine across PrEP studies experienced creatinine elevations of grade 2 or higher. TDF and emtricitabine has been associated with modest (0.4% to 1.5%) bone mineral density loss in HIV-uninfected individuals but not increased fracture risk, and bone mineral density appears to return toward baseline after drug withdrawal. As low adherence in PrEP trials may result in an underestimation of adverse events, Landovitz highlighted the need for longer-term safety monitoring and follow-up in diverse populations.

PrEP adherence is crucial for effectiveness, and adherence support is an important component of PrEP delivery. Several support strategies are currently being evaluated in PrEP demonstration projects, including counseling approaches, text messaging support, and use of electronic "smart" devices to provide real-time monitoring and intervention in the event of missed doses. Real-time drug-level testing is also being used in a PrEP demonstration project in Los Angeles, California, to triage participants with low drug levels to a staged adherence intervention.

Landovitz highlighted several studies which have indicated that cost-effectiveness is optimized when PrEP is targeted to individuals at highest risk for HIV acquisition. He pointed to an analysis of iPrEx data demonstrating that the impact of PrEP in MSM and transgender women is maximized when PrEP is targeted to those who reported engaging in condomless receptive anal sex, having a recent STI, or using cocaine in the past month. He also provided an example of the importance of PrEP adherence in those at highest risk, by contrasting the iPrEx study, in which drug detection was higher in those reporting higher risk and which demonstrated a 42% overall effectiveness, with the VOICE (Vaginal and Oral Interventions to Control the Epidemic) study, in which drug detection was lower in those at higher risk and in which no overall effectiveness was seen. Early open-label PrEP studies have shown substantial uptake of PrEP, with greater uptake and adherence observed in higher risk populations in the iPrEx OLE (iPrEx Open-Label Extension). Early data from the PrEP Demonstration Project in 3 US cities also show high levels of PrEP uptake and adherence.15,16

Adherence to PrEP is crucial for effectiveness. Novel strategies to measure and support PrEP adherence are being investigated.

There has been debate about the optimal setting for PrEP delivery. Landovitz referred to the "purview paradox" described by Krakower and colleagues: HIV practitioners believe primary care practitioners are best suited to prescribe PrEP because of their access to HIV-uninfected populations, and primary care practitioners do not feel they have the expertise to prescribe PrEP and monitor PrEP patients. Progress is being made to build infrastructure for PrEP delivery, through leadership from community-based organizations, local health jurisdictions, consumers, and practitioners. Online lists of PrEP practitioners and resources are being developed, the national PrEP Warmline has been established, and methods for academic detailing are being implemented to expand practitioner capacity to deliver PrEP. Coverage for PrEP medications and services remains a challenge for some consumers who may face substantial out-of-pocket costs, although a number of programs are being established to address PrEP access issues, including the use of PrEP navigators and state programs to assist with the cost of PrEP medications or services.

Although PrEP with TDF and emtricitabine is a promising, approved prevention strategy, new PrEP drugs and formulations are being evaluated. The entry inhibitor maraviroc is an alternative oral medication being evaluated in the phase II HPTN 069 study. Two long-acting, injectable, investigational PrEP drugs, rilpivirine (formerly TMC278) and cabotegravir (formerly GSK744), are also being evaluated in phase II trials. Implementation of PrEP with TDF and emtricitabine is being evaluated in key at-risk populations, including black MSM and youth, 2 populations at particularly high risk for HIV acquisition.
Landovitz closed the plenary session with a call to combat the stigma faced by individuals seeking to protect themselves from acquiring HIV by using PrEP, recalling the damage of historical efforts to shame individuals seeking syphilis treatment and women seeking contraceptive services. He stressed the importance of supporting research and advocacy for individuals who are proactively seeking PrEP and the importance of “being on the correct side of history.”

**PrEP in Clinical Settings**

Several investigators reported on the impact of PrEP in real-world clinical settings. McCormack and colleagues presented data from the PROUD (Pre-exposure Option for Reducing HIV in the UK) study, which enrolled 545 MSM from 13 sexual health clinics in England (Abstract 22LB). Participants were randomly assigned to receive daily TDF and emtricitabine either immediately or 12 months after enrollment. Based on early demonstration of efficacy, in October 2014 the Independent Data and Safety Monitoring Committee recommended that all MSM in the deferred-treatment arm be offered PrEP. HIV incidence was high in this cohort, with 19 new infections observed in the deferred arm (8.9/100 person-years), despite 174 prescriptions for postexposure prophylaxis (PEP) provided in this group. There were 3 incident infections in the immediate-treatment arm (HIV incidence 1.3/100 person-years), resulting in 86% PrEP efficacy (95% CI, 62%-96%; $P = .0002$) and a number needed to treat of 13 per year to avert 1 HIV infection. STIs were common but did not differ between the groups (57% vs 50% in the immediate- vs deferred-treatment arms, respectively; $P = .08$), and reported risk behaviors remained stable during follow-up (median number of anal sex partners was 10 at baseline and similar at month 12).

Baeten and colleagues presented interim data from the Partners Demonstration Project, an open-label prospective study delivering PrEP and antiretroviral therapy to heterosexual HIV-serodiscordant couples in Kenya and Uganda (Abstract 24). Antiretroviral therapy–naive, high-risk couples ($n = 1013$) were identified using a validated risk-scoring tool. Antiretroviral therapy was offered to all HIV-infected partners according to local treatment guidelines, and PrEP was offered as a bridge to antiretroviral therapy (eg, until the HIV-infected partner had been taking antiretroviral therapy for 6 months). Uptake of PrEP and antiretroviral therapy were high in the cohort (> 95% and approximately 80%, respectively). During 858 person-years of follow-up, PrEP was used during 48% of the follow-up period, antiretroviral therapy was used during 16%, a combination of the 2 was used during 27%, and nothing was used during 9%.

Only 2 incident HIV infections have been observed to date (HIV incidence 0.2/100 person-years) compared with 39.7 HIV infections expected (incidence 5.2/100 person-years) based on a counterfactual simulation model using data from a prior prospective study of HIV-serodiscordant couples, resulting in a 96% reduction in HIV transmission. The 2 transmissions occurred in the setting of low PrEP adherence. Heffron and colleagues presented data on PrEP discontinuations and adherence in the same study (Abstract 969). Among 985 HIV-uninfected partners who started PrEP, 514 (52%) subsequently had an HIV-infected partner who used antiretroviral therapy for at least 6 months, the majority (77%) of whom decided to stop PrEP because of sustained antiretroviral therapy use by their partner. Among a random sample of 133 HIV-uninfected participants using PrEP, plasma tenofovir levels were detected in more than 80% of samples tested during all periods when they were expected to have been using PrEP through month 12, suggesting that PrEP use is sustained among people with ongoing risk.

Glidden and colleagues presented data on PrEP engagement in iPrEx OLE (Abstract 970). Among 1603 HIV-seronegative participants enrolled in iPrEx OLE from prior PrEP trials, 1225 (76%) elected to initiate PrEP. At 1-month follow-up, less than half of the participants overall had a dried blood spot (DBS) level consistent with taking at least 4 pills per week, which varied substantially by site. In a multivariable model, age, education, number of partners, and engaging in condomless anal sex were associated with higher drug levels; cocaine or alcohol use and earning any income in the prior month were negatively associated with PrEP adherence (all $P < .05$). Gastrointestinal symptoms were associated with lower drug levels and explained approximately 7% of the variation in drug levels. Participants who missed their first follow-up visit or had drug levels indicating fewer than 2 pills per week were very unlikely to achieve higher drug levels at future visits. At month 12, only 38% of those who initiated PrEP had drug levels consistent with taking at least 4 doses per week. These results highlight the numerous challenges across the PrEP prevention cascade, which may require addressing factors at the individual and structural level.

The Bangkok Tenofovir Study previously demonstrated that daily oral tenofovir reduced the risk of HIV acquisition by 49% among IDUs. Martin and colleagues presented early data from an open-label extension of this cohort offered 1 year of PrEP with tenofovir (Abstract 971). Out of 1327 IDUs who returned to receive trial results, 59% elected to take tenofovir, with most (84%) receiving doses in clinics. Based on adherence diaries, 78% of participants missed more than 8 doses in the past month, suggesting the need for additional adherence support in this cohort.

972). Based on a review of electronic medical records, PrEP prescriptions increased from 6 in 2011 to 326 in 2014 ($P < .05$ for upward trend), and PrEP users became more ethnically and racially diverse over time. PrEP was being provided by more than 40 practitioners at the health center, and more than 80% of prescriptions were covered by commercial insurance. A substantial proportion of patients were prescribed PrEP after a recent STI or after having used PEP, suggesting high-risk behaviors among PrEP users.

On a less encouraging note, Kelley and colleagues identified numerous barriers to achieving protection from HIV acquisition with PrEP among MSM in the US South (Abstract 975). Investigators proposed a PrEP care continuum similar to the HIV care continuum and projected the proportion of MSM who would reach each stage, based on data from the InvolveMENt study, an HIV incidence cohort of black and white MSM in Atlanta, Georgia. Among 562 participants, 50% were estimated to be aware of and willing to take PrEP, 65% had health insurance (20% were eligible for the Affordable Care Act), 69% of the cohort met eligibility criteria for PrEP, and 51% were estimated to be adherent to PrEP, based on data from the iPrEx study. Integrating these parameters into the PrEP care continuum resulted in only 15% of the overall cohort achieving theoretical protection from HIV acquisition (12% of black MSM and 18% of white MSM). The investigators conclude that disparities at various steps in the PrEP care continuum, particularly in access to health care, could lead to racial disparities in those achieving protection via PrEP; highlight the need for novel strategies for PrEP delivery to at-risk MSM; and point to the need for specific interventions to address barriers at each step of the PrEP care continuum.

Garg and colleagues presented data on PrEP prescribing practices among practitioners surveyed through the Medical Monitoring Project between January 2013 and January 2014 (Abstract 974). Among 1234 HIV practitioners who also cared for HIV-uninfected patients, an estimated 26% reported ever prescribing PrEP. Practitioners who were gay, lesbian, or bisexual were more likely to prescribe PrEP, as were male practitioners and those providing continuity care to more than 50 HIV-infected patients. Approximately 74% of practitioners prescribed PrEP to MSM, 30% prescribed PrEP to women who have sex with men, 23% prescribed PrEP to men who have sex with women, and 23% prescribed PrEP to HIV-serodiscordant couples. The researchers call for targeted efforts to increase PrEP prescribing, particularly among those practitioners who have limited experience prescribing antiretroviral therapy.

**Nondaily PrEP Regimens**

Several researchers presented data on the use of nondaily PrEP regimens for HIV prevention. Molina and colleagues reported results from the IPERGAY study, a randomized, placebo-controlled trial of pericoital PrEP among MSM in France and Canada (Abstract 23LB). Four hundred fourteen participants were enrolled and instructed to take 2 doses of TDF and emtricitabine or a placebo 2 hours to 24 hours before having sex, then 1 additional dose each at 24 hours and 48 hours, respectively, after the first drug intake. In October 2014, based on high levels of efficacy, the Data and Safety Monitoring Board recommended discontinuation of the placebo arm and offering of pericoital PrEP to all participants. There were 14 new HIV infections in the placebo arm (HIV incidence 6.6/100 person-years) and 2 infections in the arm receiving TDF and emtricitabine (incidence 0.94/100 person-years), indicating an 86% PrEP efficacy (95% CI, 40%–99%; $P = .002$) and a number needed to treat of 18. The 2 HIV infections occurred in individuals who had discontinued PrEP several months prior to infection and did not have detectable tenofovir levels in plasma at the time of seroconversion. The median number of pills used per month was 16, an average of 4 pills per week. Given data suggesting that 4 pills per week may yield efficacy levels similar to daily dosing among MSM, additional data are needed to determine how patterns of pill taking are related to sexual risk. Rates of most adverse events were similar across the study arms, with drug-related gastrointestinal events reported more frequently in the TDF and emtricitabine arm (13% vs 6%; $P = .013$). Sexual behaviors remained stable during follow-up though STIs were common, with more than one-third of participants diagnosed with at least 1 STI during the study.

**Pericoital PrEP (before and after sex)** was effective in MSM, with participants using 4 doses per week on average. More data is needed on the effectiveness of PrEP in the setting of less frequent sexual activity and dosing.

Bekker and colleagues presented results from the HPTN 067 study, also called the ADAPT study, of South African women in Cape Town (Abstract 978LB). Of 191 participants enrolled, 179 were randomly assigned to daily, time-driven (twice weekly with a post-intercourse boost) or event-driven (before and after intercourse) dosing. Although fewer pills were required for sexual event coverage in the time- and event-driven arms, coverage of sex acts was higher in the daily arm (75%) than in time-driven (58%) and event-driven (52%) arms ($P < .001$). Adherence to the assigned regimen was also higher in the daily group than in the time- and event-driven groups, and adherence to the postsex dose in the nondaily arms was low. The majority of women had detectable tenofovir levels when sex within the past week was reported, with higher detection rates in the daily arm. Adverse effects were uncommon in the daily arm and were less frequent in the nondaily arms. The researchers concluded that daily dosing may foster better establishment of a pill-taking routine and provide the
A large confirmatory trial of pericoital 1% tenofovir gel in South African women showed no evidence of efficacy.

In a study comparing intermittent and daily PrEP in South African women, coverage of sex acts was highest in the daily-PrEP arm.

Rees and colleagues reported results from the Follow-on African Consortium for Tenofovir Studies (FACTS) 001 study, a phase III trial of pericoital 1% tenofovir gel for HIV prevention in South African women (Abstract 26LB). Overall, 2059 women were enrolled in the study and randomly assigned to receive 1% tenofovir or placebo gel using the BAT-24 (gel use within 12 hours before and after sex, with no more than 2 doses in 24 hours) dosing regimen; this same regimen was used in the Centre for the AIDS Programme of Research in South Africa (CAPRISA) 004 study, which demonstrated a 39% reduction in HIV incidence. Enrolled women were young (mean age, 23 years), mostly unmarried, and the majority lived with parents or siblings. Overall, 123 women became HIV-infected postenrollment, resulting in an overall annual HIV incidence of 4.0 per 100 person-years; 61 HIV infections occurred in the tenofovir arm and 62 occurred in the placebo arm, yielding an incidence rate ratio of 1.0 (95% CI, 0.7-1.4). Based on returned applicator counts, women used the product on average for 50% to 60% of sex acts, a finding consistent with tenofovir drug level detection rates by cervicovaginal lavage. In a case-cohort analysis, having detectable tenofovir levels was associated with a reduction in HIV acquisition rates (HR, 0.52; 95% CI, 0.23-0.97; P = .04). Based on the study’s findings, Rees highlighted the need for new prevention technologies that would be easier for young women to integrate into their lives.

**PrEP Pharmacokinetics and Measurement**

Several presentations focused on the clinical pharmacology of HIV prevention and the use of pharmacokinetic measures to monitor adherence to PrEP. In a scientific overview presented by Boffito (Abstract 80), important pharmacologic properties of various PrEP agents were highlighted, including the ability to rapidly reach and accumulate in genital and rectal tissues, drug persistence in tissues, and protein binding, which may affect ability to penetrate mucosal tissues. For oral tenofovir, Boffito reviewed data showing that the tissue-to-blood plasma ratio was substantially lower in the cervix and vagina in women than in the rectum in men. Similarly, tissue concentrations of oral maraviroc and raltegravir were lower in cervical and vaginal tissue than in rectal tissue.

In the same session (Session O-6), Fox and colleagues presented results of a phase IV study evaluating the pharmacokinetics and ex vivo potency of oral maraviroc against HIV challenge in 56 healthy men and women (Abstract 86LB). This study evaluated pharmacokinetics and pharmacodynamics after a single oral dose of maraviroc 300 mg, with the goal of informing event-driven dosing. Peak maraviroc levels were achieved after 4 hours in vaginal and rectal tissue, with vaginal and rectal tissue levels 3.6 times and 9.7 times, respectively, higher than the levels of maraviroc in plasma. In a tissue explant HIV-1 challenge model, there was a transient reduction in p24 antigen levels at 2 hours in vaginal tissue in women, however, this effect was lost by 4 hours after dosing. In rectal tissue, there were high levels of p24 antigen at all time points, suggesting no evidence of protection.

Although no protective effect was seen after a single dose, Fox noted that these findings do not preclude possible efficacy with repeated dosing of maraviroc, which is currently being evaluated in the HPTN 069 study. Similarly, in a poster presentation, Coll and colleagues evaluated the efficacy of single-dose oral maraviroc in preventing ex vivo HIV infection in a tissue explant model (Abstract 964). Rectal tissue was collected from 10 healthy MSM 4 hours after maraviroc dosing. Despite high maraviroc concentrations in rectal tissue, ex vivo HIV infection occurred in all participant specimens. In contrast, complete inhibition of infection was observed in cultures from 2 participants who received TDF and emtricitabine. In the audience discussion, it was mentioned that maraviroc can dissociate quickly in tissue, which may explain these findings. Boffito stressed the importance of optimizing and standardizing methods for evaluating the pharmacokinetics and pharmacodynamics of samples across studies.

Castillo-Mancilla and colleagues presented data on the use of emtricitabine triphosphate concentrations in DBS as a marker of recent PrEP dosing (Abstract 83). Although tenofovir diphosphate in red blood cells is a marker of cumulative adherence (half-life, 17 days) and is highly predictive of efficacy, emtricitabine triphosphate reaches maximal concentrations at 4 hours (half-life, 31 hours), and could provide information on more recent dosing patterns. In an analysis of 515 paired plasma and DBS samples in iPrEx OLE, 94% of DBS samples were concordant for detection or nondetection of tenofovir and emtricitabine in plasma, another measure of recent drug exposure, demonstrating that emtricitabine triphosphate concentrations inform recent dosing.

Koenig and colleagues developed and validated a semiquantitative urine assay to measure adherence to PrEP with TDF (Abstract 975). In a series of cohort studies, investigators demonstrated a 100% concordance between presence of TDF in plasma and urine and detectability of tenofovir for more than 7 days in urine after a single dose of TDF and emtricitabine, compared with 2 days to 4 days in plasma. TDF in urine was cleared in a log-linear fashion, with a direct correlation to time since last dose. TDF concentrations of greater than 1000 ng/mL in urine were highly predictive of presence...
of tenofovir in plasma, suggesting that the urine assay could distinguish between recent dosing within 48 hours (> 1000 ng/mL), low adherence (> 100 ng/mL), and no dosing within the past week (<10 ng/mL). Future work will be needed to develop the urine assay into a point-of-care test.

Finally, Gandhi and colleagues explored the use of hair and DBSs as markers of long-term PrEP adherence in iPrEx OLE (Abstract 514). In an analysis of 806 paired hair and DBS samples, there were strong and statistically significant correlations between tenofovir and emtricitabine levels in hair and tenofovir diphosphate and emtricitabine triphosphate levels in DBSs, and high levels of concordance (>80%) in drug detectability in the 2 matrices. As PrEP drug levels in DBSs were predictive of PrEP efficacy in iPrEx OLE, these findings suggest that hair concentrations could also be predictive of protection and that they warrant further evaluation as a tool to monitor adherence in PrEP programs.

Several presentations focused on comparison of different adherence measures used in PrEP clinical trials and evaluated correlates of adherence. Muganzi and colleagues compared several self-reported adherence measures, electronic monitoring, unannounced pill counts, and plasma tenofovir levels among 1145 participants in an ancillary adherence study within the Partners PrEP study (Abstract 976). All measures indicated high adherence: rating question (90%), frequency question (93%), percent question (97%), medication event monitoring system (MEMS; 97%), and unannounced pill counts (98%). For self-reported questions, the rating question “How well have you taken your study tablets?” had the widest distribution, suggesting this item may perform better at distinguishing between adherent and nonadherent individuals. However, no self-reported measure correlated closely with MEMS or unannounced pill counts, or discriminated between detectable and undetectable tenofovir drug levels, although MEMS performed best in distinguishing between detectable and undetectable drug levels. Amico and colleagues compared the performance of self-report with tenofovir drug detection in blood plasma in iPrEx OLE (Abstract 977). Among 1172 participants analyzed, the majority (84%) reported taking at least 1 dose in the past 3 days, 83% of whom had detectable drug levels. Among the 16% who reported not taking any doses in the past 3 days, 82% had undetectable drug levels. Sensitivity of self-report for drug detection was calculated as 96%, however, specificity was only 48%. Participants who were incorrectly assessed as adherent to PrEP by self-report were more likely to be younger, suggesting the need to develop alternative adherence measurement strategies in this population.

van der Straten and colleagues assessed rates and correlates of early tenofovir drug detection in plasma among oral tablet and gel users in the VOICE study (Abstract 979). Among 1146 participants who had plasma drug level testing at month 3, 34% had detectable tenofovir levels in the oral group and 27% had detectable drug in the gel group. Factors associated with drug detection in the oral group included being from Uganda or Zimbabwe, not receiving material support from a partner, no independent income, and alcohol use more than once per week. Factors associated with drug detection in the gel group included being from Zimbabwe, older age, not having a disapproving partner, not reporting any harm, no condom use at last sex, and no alcohol use (all \( P < .05 \)). Having some risk perception was associated with drug detection in both groups. These results suggest that different factors may affect use of oral and topical agents, and highlight the importance of having different biomedical prevention options to address the varying prevention needs of women.

Roberts and colleagues evaluated whether intimate partner violence (IPV) is associated with low PrEP adherence among African women in the Partners PrEP study (Abstract 980). Among 1785 HIV-uninfected women, 16% reported IPV at 437 study visits: verbal, physical, and economic abuse were reported at 85%, 52%, and 37% of visits, respectively. Mean PrEP adherence rate as assessed by clinic pill counts was high (95%). In a multi-variable model, recent IPV (reported to have occurred in the past 3 months) was associated with a 42% higher likelihood of having low adherence (<80%) (aOR, 1.42; 95% CI, 1.09-1.86; \( P = .01 \)). However, previous IPV was not associated with adherence (\( P = .77 \)). The investigators recommend that if PrEP is to be prioritized for women who experience IPV, that the possibility of lower adherence be recognized, and that strategies to promote PrEP adherence be considered.

**Potential Harms With PrEP**

Several researchers evaluated potential harms associated with PrEP use, including renal toxicity, emergence of resistance, and medication sharing. Mugwanya and colleagues reported on the reversibility of kidney function decline among 3924 HIV-uninfected adults discontinuing PrEP in the Partners PrEP study (Abstract 981). Median time on study drug was 33 months. Mean estimated glomerular filtration rate (eGFR) was 2 mL/min/1.73 m² to 5 mL/min/1.73 m² lower at the last on-treatment visit among those taking PrEP than among those taking placebo (\( P = .01 \)), and this difference was reversed by 4 weeks after discontinuation of study drug. The investigators conclude that declines in eGFR resolve within weeks after discontinuation of PrEP.

**Kidney toxicity associated with PrEP with fixed-dose tenofovir disoproxil fumarate and emtricitabine is uncommon.**

Panousis and colleagues reported on minor drug-resistant variants in the VOICE study (Abstract 982). Among 312 seroconverters in VOICE, it was previously reported that only 1 seroconverter had acquired the emtricitabine resistance–associated variant.
M184V, and that none had acquired tenofovir resistance, as detected by standard population sequencing. Using an allele-specific polymerase chain reaction assay, 3 of 276 (1.1%) participants had the K65R mutation, none (0%) had the K70E mutation, 11 of 285 (3.9%) had the M184I mutation, and 2 of 288 (0.7%) had the M184V mutation. Overall, 15 of 289 (5%) seroconverters had low-frequency tenofovir and emtricitabine resistance, which was not associated with treatment arm or detection of tenofovir in blood. The investigators suggest that the low rate of product use in this trial likely explained the infrequent development of resistance mutations among seroconverters. Weis and colleagues evaluated the persistence of PrEP-selected drug resistance after discontinuation of drug in the Partners PrEP study (Abstract 983). It was previously reported that 9 of 121 seroconverters had PrEP-related drug-resistance mutations at detection of seroconversion. Using 454 ultra-deep sequencing, all PrEP-selected mutations were no longer present at 6 months after HIV infection and study drug discontinuation, and remained undetectable at 12 months and 24 months. Penrose and colleagues evaluated cross-resistance between efavirenz or nevirapine and dapivirine, an investigational nonnucleoside analogue reverse transcriptase inhibitor currently being evaluated in intravaginal rings in 2 efficacy trials (Abstract 985). Among 102 plasma samples from individuals whose efavirenz- or nevirapine-containing treatment had failed, 77% showed an at least 10-fold resistance to dapivirine in in vitro testing. However, vaginal dapivirine concentrations seen with monthly ring use exceeded the adjusted 90% inhibitory concentration (IC$_{90}$) of the cross-resistant viruses by more than 23-fold. The researchers suggest that these high concentrations would likely prevent breakthrough infection of these viruses, although breakthrough could occur during a short window period following ring removal.

Naidoo and colleagues presented data on antiretroviral therapy outcomes among tenofovir gel users who acquired HIV infection and initiated therapy (Abstract 984). From 2011 to 2014, 59 participants who acquired HIV infection in a prior tenofovir gel–effectiveness trial were randomly assigned to receive a tenofovir-containing or -sparing regimen. Viral load suppression rates were not significantly different between the arms (86% and 78% in the tenofovir-containing and -sparing groups, respectively, at 12 months; P = .68), and median CD4+ cell count was similar between the groups. Women randomly assigned to receive the tenofovir-sparing regimen had a higher rate of grade 3 or 4 adverse events and had more toxicity-related regimen switches than those who received a tenofovir-containing regimen. Based on these findings, the researchers recommend tenofovir-containing regimens as the preferred treatment option for HIV-infected women with prior exposure to tenofovir gel.

Thomson and colleagues evaluated the extent of medication sharing among African, HIV-serodiscordant couples in the Partners PrEP study (Abstract 988). Drug sharing was reported at 4 of 137,462 (0.003%) HIV-uninfected partner study visits and at 1 of 12,601 (0.0008%) HIV-infected partner study visits, with a maximum of 2 to 4 tablets shared. Among 100 randomly selected HIV-infected partners not taking antiretroviral therapy, tenofovir was detected in plasma in only 1 individual who had an undetectable plasma viral load and tenofovir detected at enrollment and throughout follow-up, suggesting unreported use of tenofovir-containing antiretroviral therapy rather than sharing of PrEP. The researchers conclude that self-reported drug sharing appeared to be rare in this cohort and that concerns about drug sharing should not deter PrEP implementation, although ongoing monitoring outside of clinical trials is recommended.

**PrEP Modeling**

Several researchers modeled the potential population-level impact of PrEP rollout in different populations. Grant and colleagues presented data on current PrEP scale-up efforts in San Francisco, California, and their potential impact on HIV incidence (Abstract 25). Based on survey and surveillance data from 2014, it is estimated that approximately 16,089 HIV-uninfected men and women in San Francisco are behaviorally eligible for PrEP and that approximately one-third (5059 individuals, 31% of those eligible for PrEP) reported using PrEP in the past year. PrEP uptake appears to be strongly correlated with HIV risk behaviors, with 63% of respondents who had 6 or more sex partners reporting any PrEP use. Using a simple forecasting model assuming 62% viral suppression among HIV-seropositive persons in San Francisco, the investigators estimated that a 70% reduction in HIV infections could be achieved if PrEP uptake expands approximately 3-fold in San Francisco and increases proportionally according to risk (up to 95% uptake in the highest risk strata). According to this model, further increases in viral suppression rates would have additive population-level benefits.

Bernard and colleagues modeled the benefits of PrEP scale-up among IDUs in the United States (Abstract 1121). Using a dynamic compartment model of HIV prevalence in the United States, capturing both sexual and injection transmission as well as overlap between these groups, they estimated that providing PrEP to 50% of IDUs could reduce HIV prevalence from 6.2% to 4.2%. The cost-effectiveness of PrEP for IDUs depends greatly on PrEP adherence and efficacy, and whether it is delivered to the subgroups at highest risk. Frequent HIV screening and timely linkage to treatment also enhance the value of PrEP.

Ying and colleagues evaluated the cost-effectiveness of delivering PrEP to high-risk, HIV-serodiscordant couples as a bridge to antiretroviral therapy in the Partners Demonstration Project (Abstract 1106). The annual cost of PrEP delivery was $1,058 per couple in the study and an estimated $453 in public health settings (based on public
sector salaries, lower medication and testing costs, and task shifting. Compared with current spending on couple-based strategies, implementing PrEP as a bridge to viral suppression would cost less than $100 per couple, and the majority of costs are attributed to increasing antiretroviral therapy coverage among HIV-seropositive individuals. The investigators conclude that this PrEP strategy may be cost-effective and could avert 17% of new HIV infections, but broader coverage of PrEP and antiretroviral therapy would be required to further drive down infections.

Mabileau and colleagues modeled the cost-effectiveness of several different strategies to prevent HIV transmission in fertile, heterosexual, HIV-serodiscordant couples in which the woman is HIV-uninfected, the man is HIV-infected and taking antiretroviral therapy with a suppressed viral load, and who want to have a child (Abstract 1122). The model included HIV care costs for both the woman and her child, if born HIV-infected. The likelihood of HIV transmission was highest with unprotected sexual intercourse (treatment-as-prevention approach) and lowest for medically assisted procreation (intrauterine insemination with sperm washing). Targeting unprotected sex on fertile days was associated with the lowest cost. Use of PrEP during the fertile period could further lower HIV transmission risk but had an unfavorable cost-effectiveness ratio compared with unprotected sex alone on fertile days (incremental cost-effectiveness ratio 1,130,000/life-year saved). However, the investigators conclude that PrEP use during the fertile period could become very cost-effective if the cost of PrEP is lowered.

Two investigations evaluated the impact of STIs on HIV risk and PrEP efficacy in macaques. Radzio and colleagues reported results of a vaginal challenge study among 11 female macaques inoculated with Chlamydia trachomatis and Trichomonas vaginalis and exposed weekly to SHIV (Abstract 962). Although all 5 placebo-receiving control animals became infected, 4 of 6 animals treated with TDF and emtricitabine remained uninfected after 16 challenges. Tenofovir diphosphate and emtricitabine triphosphate concentrations in peripheral blood mononuclear cells were similar between the protected and infected macaques. However, animals infected with Chlamydia trachomatis or Trichomonas vaginalis may have higher deoxyadenosine triphosphate and deoxycytidine triphosphate levels in vaginal tissues, thought to be caused by increased cellular activation. The investigators conclude that TDF and emtricitabine maintains efficacy in a macaque model of prolonged coinfection with STIs, although biologic changes caused by persistent STI infections may lower the protection threshold.

Similarly, Makarova and colleagues evaluated the impact of STIs on the efficacy of 1% tenofovir vaginal gel in 10 female macaques (Abstract 963). All SHIV-challenged macaques receiving placebo became infected, all 6 animals treated with tenofovir gel 30 minutes before exposure remained uninfected after 20 challenges, and tenofovir gel applied 3 days before exposure protected 3 of 6 macaques. Evaluation of longitudinal plasma samples showed statistically significantly higher peak tenofovir plasma drug levels in STI-infected animals than in non-STI-infected animals, which may reflect increased tissue permeability and drug loading.

**PEP**

In a themed discussion, several researchers presented new data on the safety and tolerability of different PEP regimens (Session TD-V). Mayer opened the session by reviewing the revised World Health Organization (WHO) guidelines on PEP released in 2014. Key points included 1) not differentiating between occupational and nonoccupational exposures; 2) that 3-drug PEP regimens are preferred over 2-drug regimens, although 2-drug regimens are also effective; 3) that an entire 28-day course of PEP should be prescribed following initial risk assessment, to facilitate course completion; and 4) that adherence counseling and support should be provided to all individuals starting PEP.

**The World Health Organization released new guidelines on PEP in 2014.**

The guidelines recommend TDF plus lamivudine (or emtricitabine) combined with boosted lopinavir or atazanavir as the preferred PEP regimen for adults and adolescents, although raltegravir, boosted darunavir, or efavirenz could be considered as the third drug. For pediatric populations, zidovudine plus lamivudine is recommended with ritonavir-boosted (lr) lopinavir for children aged 10 or younger, with alternative regimens listed for older children.

Leal and colleagues reported results from 2 randomized trials comparing lopinavir/ritonavir, the standard of care, with maraviroc or raltegravir, both taken with TDF and emtricitabine, among patients presenting to the ED after potential sexual exposure to HIV (Abstract 959). PEP discontinuation rates before day 28 were significantly higher in the arm receiving lopinavir/ritonavir (31.5%) than in the arm receiving maraviroc (11.6%) (P = .001), and in the arm receiving lopinavir/ritonavir (56.6%) than in the arm receiving raltegravir (23.7%). The proportion of participants with low PEP adherence was similar in the lopinavir/ritonavir and maraviroc groups (54% vs 46%, respectively; P = .56), but was higher in the lopinavir/ritonavir than in the raltegravir group (49.2% vs 30.8%, respectively; P = .03). Rates of adverse events were also higher in the lopinavir/ritonavir arms in both studies (P < .05). In a multivariable analysis, lopinavir/ritonavir-containing PEP regimens and non-Caucasian race were associated with higher PEP discontinuation rates.

Foster and colleagues presented results of a nonrandomized, open-label study of TDF and emtricitabine coformulated with rilpivirine as a single-tablet PEP regimen (Abstract 958). Among 100 men who initiated PEP in Australia, 92% completed the course,
with 98.5% adherence by self-report and 98.6% adherence by pill count in those who completed the 28-day course. Plasma tenofovir levels were greater than 40 ng/mL (consistent with full adherence) in 88% of participants tested at day 28. Overall, 4% of participants experienced a grade 3 or 4 laboratory or clinical adverse event attributable to the study drug. The investigators conclude that this single-tablet regimen was well tolerated, with patients achieving high levels of adherence and completion.

**New PEP regimens may offer lower toxicity and result in higher PEP course completion rates.**

In a retrospective study between 1996 and 2014, Wiboonchutikul and colleagues described the characteristics of occupational HIV exposures among health care workers and the factors associated with not completing a 4-week PEP course (Abstract 957). Among 225 exposures, 163 resulted from percutaneous injury, 45 from mucosal exposure, 6 from nonintact skin exposure, and 13 from intact skin exposure. Nurses were most frequently exposed (43%), followed by patient or nurse assistants (18%), and medical technicians (15%). PEP was initiated in 155 episodes and was subsequently intentionally discontinued in 26 episodes. Of the remaining 129 health care workers, only 71% completed the 4-week PEP course. In a multivariable analysis, use of a regimen with 2 nucleotide analogue reverse transcriptase inhibitors with efavirenz was the only factor associated with not completing the PEP course (OR, 37.8; 95% CI, 4.2-342.3), and drug was discontinued owing to intolerability in all cases. The researchers recommend that this regimen no longer be used as occupational PEP in resource-limited settings.

Haidari and colleagues presented data from a case series of individuals diagnosed with acute HIV infection after initiation of PEP in the United Kingdom (Abstract 961). In a multicenter, retrospective, case-note review, 19 patients were identified as a PEP failure (1 case) or delayed diagnosis of acute HIV infection (18 cases). All patients accessed PEP within 72 hours and initiated triple therapy with 2 nucleotide reverse transcriptase inhibitors and a boosted protease inhibitor, per local guidelines. Of 18 patients diagnosed with HIV infection while taking PEP, 11 elected to continue antiretroviral therapy once HIV diagnosis was confirmed and 6 chose to discontinue PEP. Two of 17 individuals who had baseline drug resistance testing showed evidence of substantial drug resistance mutations (K103N, T215D) that was likely transmitted resistance unrelated to PEP. The investigators recommend that all point-of-care tests be used in parallel with a fourth-generation test and that HIV polymerase chain reaction (PCR) be considered, to reduce missed acute infections. They also suggest that dual therapy be avoided, to prevent the emergence of resistance. Further, in the setting of an acute HIV infection diagnosis after PEP initiation, they recommend continuing antiretroviral therapy until urgent review by an HIV specialist, as continuing early anti-retroviral therapy initiation may have potential benefits in limiting the viral reservoir.

**HIV testing methods able to detect acute infection (fourth-generation tests, HIV RNA) are recommended in the setting of PEP initiation.**

During the audience discussion, questions were raised about the need for a full 28-day course of PEP. Data from nonhuman primates suggest that a shorter duration may be possible if PEP is initiated very quickly after exposure. Given the lack of data, there was a call for studies to evaluate different durations of PEP regimens. Another question raised was whether PEP delays antibody development in individuals who seroconvert while taking PEP, for which there are few data. It was discussed that having a national registry of PEP cases could help address some of these issues. Finally, it was mentioned that PEP initiation provides an important opportunity to discuss the appropriateness of PrEP, particularly for patients who have recurrent HIV exposures or take repeated PEP courses.

**Medical Circumcision**

In a symposium session on scale-up of interventions (Session S-8), Thomas, who presented on behalf of Reed, reviewed data supporting medical circumcision (MC), including 5 randomized trials showing an approximately 60% efficacy rate of reducing HIV acquisition (Abstract 175). Based on these results, WHO issued guidance on MC for HIV prevention in 2007. Modeling studies conducted in 2011 indicate that reaching 80% circumcision coverage (approximately 20 million circumcisions) could avert 5.4 million HIV infections and have a net cost savings of US $16.5 billion within 15 years, with 1 HIV infection averted for every 9 men circumcised. To achieve successful MC scale-up, key areas of focus have included: fostering community engagement, establishing complex supply chains, conducting clinician trainings, and launching demand-creation campaigns. Thomas presented several lessons learned from MC trials and implementation.

First, loss-to-follow-up rates appear to be higher in MC programs than in randomized controlled trials, and adverse event rates among those lost to follow-up also appear to be higher. In response, there have been increased efforts to minimize loss to follow-up in MC programs, and US President’s Emergency Plan for AIDS Relief (PEPFAR) has instituted mandatory reporting of all deaths and specific MC-related adverse events. MC programs also provide a unique opportunity to engage men who are not already engaged in the health system, by offering HIV testing services and linkage to care for individuals who...
test HIV-seropositive. Reaching those in the highest incidence groups will help avert the greatest number of HIV infections. Further, modeling studies have indicated that circumcising younger men, aged 15 years to 24 years, can achieve substantial population-level impact with fewer MC procedures.

**MC programs can foster engagement of men in the health care system and encourage HIV testing and linkage to care for HIV-infected men.**

In an oral abstract session on demonstrating impact (Session O-13), Kong and colleagues presented data on the impact of MC scale-up on community-level HIV incidence in Rakai, Uganda (Abstract 158). Median MC coverage was 4% prior to randomized trials (from 1999-2003), 9% during the trials (from 2004-2007), and 26% in the posttrial period (from 2008-2011). For every 10% increase in MC coverage, there was a 12% reduction in community-level HIV incidence among non-Muslim men, a robust finding after adjusting for concurrent increases in antiretroviral therapy coverage in women, age, and sexual risk behaviors. However, no association was found between MC coverage and community-level HIV incidence among non-Muslim women. Kong hypothesized that this lack of association among women, which is in contrast to modeling predictions, may have been attributable to the relatively short follow-up period.

**Medical MC was scaled up to more than 6 million individuals in 2013.**

In a themed discussion on voluntary MC for HIV prevention (Session TD-Y), Njejumeli presented data on the rollout of MC, with more than 6 million circumcisions performed between 2008 and 2013 and rates doubling over the last 2 years. He highlighted key considerations for scaling up of MC, including the age profile of MC clients, human resource constraints, potential for risk compensation, and resumption of sex before wound healing.

Hellar and colleagues described outcomes from MC scale-up strategies in Tanzania (Abstract 1086). MC is being provided through routine, larger health facilities and through campaigns where teams of practitioners move into new communities and do a high volume of MCs in 1- to 3-week bursts. In 2014, mobile services were launched to serve hard-to-reach areas using a roving team of practitioners to provide MC services, often in nonfacility settings. Among 148,880 persons circumcised between October 2013 and August 2014, 76% were younger than 20 years of age. Mobile teams reached more than 5000 individuals who were more likely to be older (≥20 years of age) than those reached by other service-delivery models, and it was noted that mobile outreach provides more privacy for older clients. Follow-up rates were high in the mobile outreach setting, likely because of active client follow-up. The investigators conclude that mobile services could be an efficient strategy to engage with older MC clients.

Rugwizangoga and colleagues presented data on the acceptability of a device for nonsurgical MC (PrePex™) when used in routine, programmatic settings in Rwanda (Abstract 1087). This device offers an alternative to conventional surgery and does not require injectable anesthesia or cutting of tissue. Between 2009 and 2014, 86,284 adolescent boys and adult men were circumcised at program sites, and nearly two-thirds (63%) of circumcisions have used the nonsurgical device since its introduction in February 2014. Overall uptake of MC has increased yearly, with a doubling of the number of clients served from 2012 to 2013. This trend has been attributed to increased efficiencies, including shifting of the task to nurses, use of mobile outreach teams, and the introduction of the nonsurgical device, although the program experienced a stock-out of certain sizes of the device in July 2014, which limited scale-up efforts. The investigators conclude that the device is well accepted by MC clients in Rwanda and recommend that programs ensure adequate availability of the device in all sizes.

Kagaayi and colleagues described characteristics of MC acceptors, risk compensation, and effectiveness in Rakai, Uganda (Abstract 1088). The researchers compared 1192 MC acceptors with 2384 nonacceptors who participated in the Rakai community cohort surveys between 2007 and 2013. MC acceptors were younger, less likely to have been married, had higher education levels, and were more likely to have reported genital ulcers ($P = .006$). After MC, sexual activity increased by 3% per year among MC acceptors, an increase that was more prominent among younger men. Sexual activity with women in occupations with higher risk (eg, bar attendants, alcohol brewers, restaurant workers, traders, fisherfolk, housemaids) increased by 10.2% per year among MC acceptors, with no change among uncircumcised men. However, HIV incidence was lower among MC acceptors (0.61/100 person-years) than among nonacceptors (1.11/100 person-years) (incidence rate ratio 0.50; $P = .05$). These data suggest that men at higher risk self-selected to receive MC, possibly because they were told MC reduces risk for genital ulcer disease. Although there was some evidence of risk compensation in this cohort, this did not attenuate the effectiveness of MC. During the audience discussion, the speakers discussed strategies to increase demand for MC, including use of community mobilizers and peer promoters, radio and media campaigns, and new communication strategies to promote the attractiveness of MC in addition to its potential health benefits.

Although MC decreases risk for genital ulcers and human papilloma virus acquisition in HIV-infected men, a previous study showed that MC increased the rate of HIV transmission to female partners if sex was resumed prior to wound healing. In an oral abstract session on prevention (Session O-1), Manucci and colleagues presented data on penile HIV shedding after MC in HIV-infected men (Abstract 30). In a prospective
study of 236 HIV-seropositive men undergoing MC in Rakai, Uganda, increased HIV shedding was observed 1 week to 2 weeks after MC, but was lower after wound healing at weeks 6 and 12. Among antiretroviral treatment-naïve men, HIV shedding decreased from 8.8% at enrollment to 1.9% at month 3 (prevalence rate ratio, 0.19; 95% CI, 0.06-0.64). Further, suppressive antiretroviral therapy decreased the number of HIV shedding events and penile HIV viral load. These results suggest the potential long-term benefit of reduced penile HIV shedding after MC in HIV-seropositive men. The investigators highlight the importance of preventing HIV transmission during the wound-healing period and propose that initiation of antiretroviral therapy at the time of MC should be considered in order to reduce HIV transmission risk.

**HIV and HSV-2 shedding are increased in the weeks following MC, and sexual abstinence is crucial during this period of wound healing.**

Grabowski and colleagues presented data on HSV-2 shedding among 176 men coinfected with HIV and HSV-2 undergoing MC (Abstract 1084). HSV-2 shedding was detected in 9.7% of men prior to surgery, with a nonstatistically significant increase to 14.8% at week 2 (P = .153) that then decreased to 6.9% by week 6 (P = .33). HSV-2 shedding was noted to be 59% lower among men with healed MC wounds (P = .08). HSV-2 viral load was also somewhat higher at week 1 post-MC. The investigators recommend that MC programs should provide counseling on sexual abstinence during wound healing and use of condoms thereafter.

**Strategies to Reduce HIV Transmission From HIV-Seropositive Individuals**

**HIV-Serodiscordant Couples**

Mujugira and colleagues presented data on the impact of antiretroviral treatment on HIV transmission from an HIV-infected person to a partner of the opposite sex in the placebo arm of the Partners PrEP study (Abstract 989). HIV incidence among 496 HIV-serodiscordant couples in Nairobi, Kenya (Abstract 1035). As has been demonstrated in other studies, a substantial minority of HIV infections of the HIV-seronegative partner originate outside the couple. The investigators reported that only 8 of 12 HIV infections were phylogenetically linked. These data reinforce the need for prevention strategies for HIV-seronegative individuals that extend to relationships outside of known HIV-serodiscordant partnerships.

**Serosorting**

A themed discussion was held on the topic of serosorting, with general consensus that better measures are needed to differentiate between reported risk behaviors and intentional serosorting—choosing sex partners or practices based on the perceived seroconcordance or serodiscordance of one’s partner (Session TD-W). All of the data presented in this themed discussion dealt with reported seroconcordant or serodiscordant behavior among MSM, without knowledge of whether individuals were choosing partners and practices based on serostatus.

Paz-Bailey and colleagues presented data on temporal trends from the NHBS system in the proportion of MSM reporting HIV-seroconcordant or -serodiscordant condomless anal sex from 2005 to 2014 (Abstract 1060). They reported that among HIV-seronegative MSM, -seroconcordant and -serodiscordant condomless anal sex increased among all races and ethnicities (P < .01) and age groups (P < .001). Among HIV-seropositive men, -seroconcordant condomless anal sex increased (P = .001). Khosropour and colleagues presented data from 2 retrospective cohorts of MSM attending an STI clinic in Seattle from 2002 to 2012 (Abstract 1061). They compared 186 HIV-seroconverters and 1000 HIV-seronegative controls, and compared prediagnosis with post-diagnosis visits. The proportion of serosorters remained stable in both cohorts; however, after diagnosis, men who seroconverted switched from engaging in condomless anal sex with HIV-serodiscordant partners in Nairobi, Kenya (Abstract 1035). As has been demonstrated in other studies, a substantial minority of HIV infections of the HIV-seronegative partner originate outside the couple. The investigators reported that only 8 of 12 HIV infections were phylogenetically linked. These data reinforce the need for prevention strategies for HIV-seronegative individuals that extend to relationships outside of known HIV-serodiscordant partnerships.

**HIV transmission may continue to occur up to 6 months after antiretroviral treatment, after which transmission may be rare.**
HIV-seronegative partners to engaging in the same sexual practice with HIV-seropositive partners. This emphasizes the importance of early diagnosis of newly HIV-infected persons to reduce HIV transmission before diagnosis.

Treatment as Prevention

Gardner and colleagues presented data on more than 14,000 HIV-infected patients of clinics in 6 US cities (Abstract 101). They evaluated the proportion of time (April 2009-March 2013) during which these patients had HIV RNA levels of greater than 1500 copies/mL, a threshold associated with HIV transmission in epidemiologic studies. Despite the fact that more than 90% of patients were taking antiretroviral therapy at the time the study was initiated, an HIV RNA level of greater than 1500 copies/mL was observed during 23% of the follow-up time period. Younger patients; black patients; those with longer intervals between viral load testing; those whose care was funded by Medicaid, by the Ryan White HIV/AIDS Program, or by a charity care program; and persons not taking antiretroviral therapy were more likely to have HIV RNA levels above the 1500 copies/mL threshold during the study. MSM were less likely to have viral loads above the threshold. The investigators suggest that particular attention be paid to those patients with more than 6 months between viral load tests, to ensure full viral suppression and reduce the risk of HIV transmission.

Tanser and colleagues presented on the use of population viral load to predict HIV incidence using data from the Africa Centre Demographic Information System in rural KwaZulu-Natal, South Africa (Abstract 991LB). Investigators observed 642 seroconversions across nearly 25,000 person-years of observation. There was no association between the geometric mean viral load within a population and the risk of HIV acquisition among HIV-negative individuals living in that community (P = .49). However, every 1% increase in the proportion of the entire population (irrespective of HIV serostatus) with detectable virus was associated with a 4.9% increase in individual risk of HIV acquisition (P < .001). This suggests that population-wide measures that take into account the spatial variations in population prevalence may provide helpful measures for targeting interventions within communities.

Moore and colleagues presented data on 719 MSM recruited in Vancouver, Canada, using respondent-driven sampling (Abstract 1023). HIV prevalence was 23.4% overall, 98% of individuals were aware of their HIV infection, 93% were taking antiretroviral therapy, and 81.4% were virally suppressed. However, in multivariate analysis, lack of viral suppression was associated with a greater likelihood of engaging in condomless sex with a partner who was HIV seronegative or whose serostatus was unknown (aOR, 3.13; 95% CI, 1.1-8.9). This serves as a reminder that both behavioral and biomedical intervention are needed to reduce HIV transmission from HIV-infected persons.

Other Prevention Strategies

Cash Transfers

Wilson presented data on the impact of social protection programs that address poverty on health, income, and HIV risk (Abstract 75). He pointed out that almost 25% of the world live on less than $1.25 per day, and 50% live on less than $2.50 per day. He presented evidence from 3 randomized controlled trials of how cash transfers affected HIV and STI acquisition in 3 African countries. In a study of nearly 2400 individuals aged 18 years to 32 years in Tanzania in which participants were randomly assigned to receive 1 of 2 levels of conditional cash transfer and those who received a nonconditional cash transfer, there was a 25% decrease in HIV incidence overall, with somewhat better results among younger girls and those in the $100 arm. Wilson concluded by mentioning 2 additional cash transfer studies that will have data available in the next year, which will add considerably to understanding of the generalizability of this approach in decreasing new HIV infections.

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


Additional References


