CROI 2014: New Tools to Track the Epidemic and Prevent HIV Infections

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As discussed at the 2014 Conference on Retroviruses and Opportunistic Infections (CROI), substantial advances have been achieved in using laboratory tools to track the leading edge of HIV transmissions globally. Phylogenetic and phylodynamic studies have identified clusters of new infections occurring along geographic routes and in different groups, including young men who have sex with men. New assays for detecting acute HIV infection are promising; however, additional strategies are needed to increase uptake of HIV testing in a number of populations. Globally, people who inject drugs face numerous barriers to accessing HIV prevention and treatment services and are in need of integrated approaches to deliver services, address stigma and discrimination, and reform drug policies. Young women and individuals in serodiscordant relationships continue to be at high risk for HIV acquisition. Injectable hormonal contraception with progestins may increase the risk of HIV infection. Bacterial vaginosis may also increase HIV acquisition and transmission. Additional evidence suggests antiretroviral therapy lowers HIV transmission in serodiscordant couples, but high levels of diagnosis, linkage, retention, and viral suppression are needed to reduce population-level HIV incidence. Several programs evaluating the implementation of preexposure prophylaxis (PrEP) have shown high uptake in the United States and resource-limited settings. As adherence is a crucial determinant of PrEP efficacy, long-acting PrEP agents are promising approaches being tested.

Keywords: CROI 2014, epidemiology, HIV, injection drug use, phylodynamics, preexposure prophylaxis, PrEP, prevention, seroincidence, TasP, transmission, treatment as prevention

Tracking the Epidemic

This year’s Conference on Retroviruses and Opportunistic Infections (CROI), held from March 3 to 6, 2014, demonstrated the substantial progress that has been made in the implementation of laboratory tools to track the HIV epidemic. Such tools include phylogenetic and phylodynamic mapping of sexual transmission networks and routes, assays to predict HIV seroincidence from cross-sectional population surveys, and identification of acutely infected persons.

Phylogenetic Studies

Several studies have been conducted to track the leading edge of transmission in the United States and identify populations who may benefit most from prevention interventions. Oster and colleagues presented viral sequence data from the US National HIV Surveillance System from 2001 to 2012 (Abstract 211). Of more than 40,000 pol sequences collected from persons aged 13 years or older, 31% were linked to at least 1 other sequence, and 10% were linked to 4 or more other sequences. In multivariable analyses, persons aged 13 years to 29 years, whites, and men who have sex with men (MSM) were more likely to have sequences linked to 4 or more other specimens than were other demographic and risk groups. Similar analyses were conducted in several US cities. Chan and colleagues evaluated sequences from more than 1100 clinic patients in Providence, Rhode Island, who had been diagnosed with HIV infection from 1980 to 2011 (Abstract 212); they found that 31% of viral sequences clustered and that MSM were more likely and injection drug users (IDUs) less likely than heterosexual non-IDUs to belong to a cluster. Using logistic growth modeling, of the 38 members of active clusters with more rapid transmission rates, 90% were MSM and 45% were diagnosed with primary HIV infection.

French and colleagues evaluated 920 newly diagnosed patients in Chicago, Illinois, from 2008 to 2011 and found that viral sequences clustered in 14% (Abstract 210). Similar to the US Centers for Disease Control and Prevention (CDC) study, they found that younger persons and men were more likely to belong to a cluster; unlike the CDC study, French and colleagues found that black MSM were more likely to belong to a cluster than white MSM. The difference between the studies in terms of the association of race with clustering may have been due to the racial makeup of the Chicago cohort (67% black, 23% Hispanic, and 9% white), structural differences in network formation in different...
geographic locations, or sampling biases. Both analyses suggest that young MSM are more likely to be part of sexual network clusters, and interventions to increase testing, treatment, and PrEP are particularly important for these groups.

Wertheim and colleagues analyzed sequences from nearly 4000 HIV infected persons diagnosed in New York, New York, from 2005 to 2012 (Abstract 214). Similar to Chan's analysis of sequences from Providence, Rhode Island, Wertheim's analysis found that MSM were more likely and IDUs less likely to cluster than heterosexual non-IDUs. They also found that acute or early infections were more likely to cluster than prevalent cases, which may reflect the increased transmissibility of infection during the acute or early phases or confounding by sampling strategies (e.g., more frequent sampling and higher proportion of acute diagnoses in more recent years). More than one-quarter of clustered infections was linked to persons who reside outside of but were diagnosed in New York, New York, particularly among MSM. Surprisingly, IDUs were more likely to link with persons from international sites in the Los Alamos Sequence Database. These geographic patterns have numerous implications, including challenges in tracking the impact of local prevention efforts on local HIV incidence among MSM.

Oster and colleagues also evaluated the pairwise connections that exist between their 40,000 sequences from the United States (Abstract 213). Most transmission pairs included at least 1 MSM. Transmission pairs that included blacks were more likely to include same-race pairs (63%) than whites (47%) or Hispanics (27%). These findings highlight the importance of diagnosing and treating MSM to stop transmission within sexual networks. The greater degree of racial homogeneity among black sexual networks may be a factor in the large number of new infections, disproportionate to level of risk, among black men and women.

Little and colleagues took these phylogenetic analyses a step further, assigning each of 478 recently infected patients in San Diego, California, and 170 of their HIV-infected social and sexual contacts a transmission network score (TNS) to quantify the relative interconnectedness of individuals (Abstract 206). In multivariable models, high baseline viral load and high TNS were independently associated with the predicted risk of HIV transmission within 1 year of infection. Additional models suggest that by targeting antiretroviral treatment toward individuals with high TNS, greater reductions could be achieved in lowering HIV transmission rates.

Phylogenetics, or the quantitative study of epidemiology and evolutionary processes that shape viral phylogenetics, can be used to understand the geographic spread of HIV. Faria and colleagues presented an interesting phylogenetic study of HIV transmission from 17 East African regions, including Burundi, Democratic Republic of Congo, Kenya, Rwanda, Republic of Tanzania, and Uganda (Abstract 225). They found that viral transmission was not associated with geographic proximity, nor with train or central highway proximity. However, nearly one-half of the viral migration pathways involved locations situated along or near the northern highway. Such studies may pinpoint geographic hot spots that may help in the development and implementation of innovative prevention strategies. Delaporte and colleagues presented data from more than 3200 blood samples obtained from adults in 26 villages in Cameroon (Abstract 226). In addition to finding clusters linked to a major road for logging transport, they also found several instances of potential new introduction of simian retroviruses other than simian immunodeficiency virus (SIV), raising the concern that conditions for spread of new SIV could exist.

Phylogenetic studies were also conducted to evaluate changes to the HIV epidemic over the past several decades. Bezemer and colleagues presented data on more than 4000 MSM in the Netherlands, and from these isolates identified 91 MSM networks (Abstract 205). Remarkably, 70% of the networks were already circulating before 1996 and 89% of the networks included infections after 2006. Through additional analyses, they estimate that 33% of infections among MSM in the Netherlands were imported and only 6% of these created a local network. They concluded that the subtype B epidemic among MSM in the Netherlands is sustained by numerous, pre-antiretroviral treatment transmission networks and that the widespread introduction of antiretroviral therapy did not bring an end to these networks. Shiino and colleagues found a different epidemic pattern in Japan based on sequences from nearly 4400 newly diagnosed HIV-infected persons from 2005 to 2011 (Abstract 215). They found that subtype B spread through the MSM community mostly in the late 1990s, whereas subtype CRF01 AE spread through heterosexual and IDU routes at the same time. Based on clusters, they report that local heterosexual transmission may have been enhanced by hyperactive male spreaders in that population. They also conclude that CRF01 AE did not spread in the MSM community until the 2000s.

Takebe and colleagues presented data on viral sequences from MSM in China. They reported subclusters that emerged in 1997, 1999, 2005, and 2009, tying this epidemic with MSM epidemics in Japan, Hong Kong, Thailand, Europe, and the United States (Abstract 228). This largely understudied population of MSM in China appears to have been subject to several discrete HIV introductions from geographically diverse areas and presents an important opportunity to prevent further spread within this population.

Several CROI 2014 posters presented data that back-calculate the introduction of HIV into various human populations. Joy and colleagues presented data from more than 7700 patients from British Columbia, Canada (Abstract 230). They suggest that the HIV epidemic originated in 1897 (interquartile range [IQR], 1883-1923); they identify 1941 (IQR, 1923-1958) as the likely introduction of subtype B. Their analysis also confirms an increase in the MSM epidemic in Canada.
in the 1980s with subsequent decline, in contrast to the IDU epidemic peaking in the mid-1990s. Yebra and colleagues analyzed 162 specimens collected from 2005 to 2010 in 3 Ugandan populations (female sex workers, Lake Victoria fisherfolk, and a rural clinic cohort; Abstract 208). By including more than 400 Ugandan specimens from GenBank, they date the subtype A1 epidemic to 1960, and the subtype D epidemic to 1973. Both subtypes grew exponentially in the 1970s and 1980s and decreased in the 1990s. Unlike some studies that suggest that HIV spread originated in large cities, their data suggest that the southwestern, rural area was the origin of the Ugandan epidemic.

**Incidence Assays**

Another strategy for tracking the leading edge of the epidemic and the impact of prevention and treatment interventions is to measure the rate of new infections within a population. Previously, such measures depended on longitudinal cohort studies, which were expensive and unlikely to represent the larger population. Substantial progress has been made over the last several years in developing assays to estimate population HIV incidence based on cross-sectional specimens.

At this year’s CROI, Kassanjee and colleagues performed a head-to-head comparison of 5 assays from more than 2000 subjects in Africa, Brazil, and the United States with well-defined dates of HIV exposure and clinical data (Abstract 1005). All 5 assays (BED, Limiting Antigen–Avidity Enzyme Immunoassay [LAg-Avidity EIA], Detuned Viroct, Vitros Avidity, and Biorad Avidity) misclassified patients with infections of longer than 6 months duration who were virally suppressed, with the proportion misclassified ranging from 27% to 54%. Longosz and colleagues further evaluated the ability of several assays to perform on specimens from 212 subtype A and 298 subtype D infections among adults in Rakai, Uganda (Abstract 1007). They found that the LAg-Avidity assay performed best, but none of the assays performed optimally with subtype D. In a separate analysis, Longosz and colleagues confirmed that those who are misclassified by the LAg-Avidity EIA are likely to be misclassified for the duration of their infection, based on samples from 667 individuals participating in US cohort studies (Abstract 1008). These studies highlight the importance of multiassay algorithms, which use additional assessments (eg, viral load, CD4+ cell count) for more accurate determination of HIV incidence.

Rottinghaus and colleagues compared the performance of the LAg-Avidity EIA on dried blood spots and plasma and found that it performed equally well on both specimens (Abstract 1006). Multiassay algorithms that perform well on dried blood spots allow researchers to take advantage of these specimens often used in surveillance activities in resource-limited settings.

**Improving HIV Diagnosis, Including Acute Infection**

Identifying newly infected persons is important for individual health (as early treatment may lead to less seeding of viral reservoirs) and public health (as acutely infected persons are highly infectious and may inadvertently expose HIV-uninfected persons prior to diagnosis). Braun and colleagues confirmed that primary HIV infection (PHI; acquired in the previous 6 months) may be difficult to identify based on symptoms alone (Abstract 1001). In their study of 293 patients with PHI enrolled in the Zurich Primary HIV Infection Study, 31% presented without typical symptoms for PHI, a likely overestimate as symptom history was collected retrospectively, after PHI was diagnosed. Powers and colleagues evaluated 342 seroconverters from 9 sites in Africa and found that having a greater number of acute retroviral symptoms was associated with prolonged viremia, but there was substantial variability across subtypes (Abstract 1003).

Several investigators reported on strategies for using antigen-based assays for earlier detection of acute infection in persons with negative results on rapid tests. Eller and colleagues evaluated the proposed CDC algorithm for detection of acute HIV infection (Abstract 619). The fourth-generation Genome Sequencing HIV Combo Antigen/Antibody Enzyme Immunoassay (GS HIV Combo Ag/Ab EIA), followed by the Multispot HIV-1/HIV-2 Rapid Test and nucleic acid testing if required, identified 29 acute infections, using twice-weekly samples from high-risk cohorts in Tanzania, Uganda, Kenya, and Thailand. This algorithm identified acute infections a median of 7 days after the first reactive RNA test, 6 days before peak viral load, and 8 days before third-generation enzyme-linked immunosorbent assay (ELISA) reactivity. The Multispot was not positive until a median of 20 days after the first RNA-positive specimen. Eller and colleagues suggest that their new algorithm enhances detection of acute HIV infection and that optimal detection of acute infection could occur with robust point-of-care viral load testing, to be used for highest-risk cohorts.

Geren and colleagues also evaluated the utility of fourth-generation HIV Ag/Ab testing for screening in an emergency department setting in Phoenix, Arizona (Abstract 618). In screening more than 26,000 patients, they detected 69 previously undiagnosed cases of HIV infection (0.28% positivity), 25% of which were acute infections that were negative or indeterminate on other serologic testing. They suggest that fourth-generation testing is important in identifying persons with acute HIV infection. Hutchinson and colleagues conducted a cost-effectiveness analysis using data from the STOP (Screening Targeted Populations to Interrupt On-Going Chains of Transmission with Enhanced Partner Notification) study, a 12-site prospective study conducted in New York, New York; San Francisco, California; and North Carolina (Abstract 616). Their algorithm called for using a fourth-generation HIV Ag/Ab test on patients with negative results on rapid HIV tests. Of more than 71,000 patients, 963 (1.34%) were HIV seropositive on rapid tests and an additional 127
(0.18%) were HIV seropositive only on the fourth-generation assay. In their cost-effectiveness modeling, screening with the fourth-generation assay was cost-saving (by reducing forward transmission) and remained cost-effective up to a detection rate nearly two-thirds lower than the rate detected in this study.

A cautionary note was added by a poster by Livant and colleagues on the performance of HIV rapid testing in the MTN-003 VOICE (Microbicide Trials Network-003 Vaginal and Oral Interventions to Control the Epidemic) preexposure prophylaxis (PrEP) study (Abstract 617). This study used monthly second-generation rapid tests, followed by confirmatory Western blot and HIV-1 RNA testing as appropriate. In testing more than 5000 women in nearly 78,000 visits at sites in Africa, they found the sensitivity for Determine, Unigold, and OraQuick rapid tests to be 88.78%, 85.86%, and 61.54%, respectively. Because it is important to identify newly infected persons on PrEP as soon as possible to prevent emergence of drug resistance, clinicians must consider testing algorithms that provide sufficient sensitivity to identify acute infection.

Bristow and colleagues presented encouraging data on the sensitivity and specificity of a combined HIV infection and syphilis rapid antibody test (Abstract 627). The group tested several thousand specimens collected from 6 countries at 6 laboratory sites, and found very high sensitivity and specificity, despite diversity in infection rates and antibody profiles. Rollout of this or other combined point-of-care testing for HIV infection or syphilis could improve screening for both infections in resource-limited settings.

**HIV Testing and Strategies to Improve Uptake**

Cooley and colleagues presented data on HIV testing among MSM in 20 high-prevalence metropolitan statistical areas (defined by the US Office of Management and Budget) in the United States, as measured in the National HIV Behavioral Surveillance System (Abstract 968). Surveys conducted in 2008 and 2011 sampled approximately 8000 MSM. Overall testing rates increased by 9% over that time, with statistically significant increases among blacks, persons of other races and bi- or multiracial persons, and persons aged 20 years or older. Among 18- to 19-year-olds, only blacks were statistically significantly more likely to have tested in 2011 than in 2008. The proportion of persons testing 3 or more times in the previous 2 years also substantially increased, from 37% to 44%. However, two-thirds of all men in the survey had not tested in the previous 12 months, indicating that more work needs to be done to increase testing rates among MSM, for whom the CDC recommends at least annual testing; many jurisdictions recommend at least semiannual testing for MSM.

Malna and colleagues compared data from 2 nationally representative population-based surveys in Kenya (the 2007 and the 2012 Kenya AIDS Indicator Surveys; Abstract 149). In the 2007 survey, only 34% of participants had ever received an HIV antibody test; this increased to 72% in the 2012 survey ($P < .001$). Similarly, in 2007, only 16% of HIV-seropositive participants were aware of their HIV serostatus compared with 47% in 2012 ($P < .001$). Although this represents a substantial improvement in overall testing rates, knowledge of HIV serostatus remains relatively low, and additional scale-up is required to identify HIV-seropositive persons.

Novitsky and colleagues presented data on the ability of household-based HIV testing campaigns to reach populations at risk of HIV infection in Mochudi, Botswana (Abstract 1043). They surveyed more than 6000 16- to 64-year-olds in northeastern Mochudi; HIV prevalence was 20%. By comparing these data with data from the United Nations, they estimate having reached 88% of women but only approximately half of men and approximately 40% of men aged 25 years to 44 years through this testing campaign. Alternative strategies are needed to increase the uptake of testing among men. Brunie and colleagues presented data from a pilot study in Uganda of integrating HIV testing and counseling services into village health teams, which provide community-based health services, including family planning (Abstract 1042). They were able to conduct 647 HIV-testing visits in the first 3 months of 2015 at 4 clinics; 80% of visits included men and 50% included women. More than one-quarter of those participating had never previously tested, and more than 90% said they would like to test again through the village health teams. This presents one possible approach to increasing HIV testing in men.

Mehta and colleagues pointed to the crucial role that HIV testing plays in the treatment cascade. Theirs was one of several presentations from a large cross-sectional survey of more than 12,000 MSM and 14,000 IDUs across 26 cities in India (Abstract 1065). HIV prevalence was 18% among IDUs and 6% among MSM, with substantial variability by study site. The most substantial drop-off in the treatment cascade was in the proportion of HIV-seropositive persons who were diagnosed: among IDUs, 41% of HIV-seropositive persons were diagnosed (3%–92% by site) and among MSM, 30% were diagnosed (0%–90% by site). The proportion of HIV-seropositive persons diagnosed was higher among participants who were older; had higher educational levels; and received other services, such as IDUs and MSM with previous tuberculosis diagnoses, MSM diagnosed with a sexually transmitted infection (STI), and IDUs receiving opiate substitution therapy. This suggests that integrating HIV testing with other clinical services may reach persons at risk but that substantial additional efforts must be made to increase HIV testing nationally.

**HIV Self-Testing**

Several investigators at CROI 2014 reported on the use of HIV self-testing in the United States and internationally. Nunn and colleagues presented on hypothetical willingness to use the FDA-approved OraQuick in-home HIV test, the first over-the-counter self-test kit, among approximately 1000 residents...
participating in an HIV and hepatitis C virus (HCV) testing program in Philadelphia, Pennsylvania (Abstract 971). Their survey was conducted in areas with high HIV prevalence (estimated 3% of adult population), but with limited HIV testing and treatment services. Stated willingness to use the test kit was high (91%), and more than half were willing to pay, but only 14% were willing to pay current market price.

Martin and colleagues presented data on use of a paper voucher system for free OraQuick in-home HIV tests at 12 Walgreens pharmacies in Los Angeles, California (Abstract 969). They distributed more than 600 vouchers through community-based organizations, student distributors, a clinic, and survey recruitment flyers; 49 vouchers were redeemed for test kits. The most frequently cited barrier was difficulty in travel to available pharmacies, and there were substantial differences in store procedures, some of which caused discomfort for the potential users (eg, needing the store manager to be involved). Three persons reported a positive test and being linked to care; 2 additional persons declined to report test results but also stated they had engaged in follow-up care. The investigators suggest that this mechanism may be used to newly identify HIV-infected persons and link them to care. Myers and colleagues presented data on a survey of 361 pharmacies in New York, New York, in summer of 2013 (Abstract 970). They found that test kits were available in 84% of chain pharmacies but only 9% of independent pharmacies, and kits were kept behind the pharmacy counter in 77% of high-morbidity neighborhoods (based on HIV diagnosis rate) and 55% of low-morbidity neighborhoods (P < .03). Only 80% of pharmacists correctly stated kit availability, and two-thirds of kits were sold above the manufacturer’s suggested retail price of $39.99, identifying potential barriers to use of self-test kits that should be addressed.

Choko and colleagues presented data from a cluster randomized trial of 16,660 adults from 14 high-density neighborhoods (HIV prevalence 18.5%) in Malawi (Abstract 147). Half of the communities received an HIV self-testing intervention that included distribution of self-test kits by 2 trained residents, with linkage to care for those who tested seropositive for HIV. Overall uptake in the intervention neighborhoods was 76%, including 67% of all men and 93% of all 16- to 19-year-olds. In total, 9% reported positive HIV test results, 78% of whom accessed HIV care. No suicides or assaults were reported, but 147 men and 119 women reported coercion to test, mostly by partners. Cambiano and colleagues presented a cost-effectiveness analysis of HIV self-testing in resource-limited settings (Abstract 1045). Using Zimbabwe as an example, they estimated that the introduction of self-testing would be cost-saving, with an estimated savings of $53 million dollars during a 20-year period. This was based on a decrease in the proportion not willing to be HIV tested from 5% to 2.5%, and an increase in first-time and repeat testing of 20%. Because of the substantial uncertainties in many of the inputs into this model, additional data on uptake of HIV self-testing and linkage to care are required to determine whether this may be a feasible and affordable strategy to increase testing in resource-limited settings.

Partner Notification Services

Peters and colleagues compared partners of 579 newly diagnosed persons with established HIV infection with 110 newly diagnosed persons with acute HIV infection in New York, New York; North Carolina; and San Francisco, California (Abstract 1030). Overall, 58% of partners had previously diagnosed infection, 11% were newly diagnosed, and 45% were HIV seronegative, with no difference in partners of persons with acute versus established infections. In addition to linking newly diagnosed persons into care, partner notification services presents the opportunity to ensure that partners with established infection are linked to care and treatment, to reduce further transmission from those partners. In addition, nearly half of the newly diagnosed index cases declined partner notification services, suggesting that new strategies are needed to reach partners of newly diagnosed persons.

Risk Factors for HIV Transmission and Acquisition

Sex

Women bear a disproportionate burden of HIV infection globally, and several epidemiologic studies presented at this year’s conference further elucidated this increased risk. Good news came from Jonas and colleagues who demonstrated a stable HIV prevalence among women aged 15 years to 49 years in Namibia (Abstract 1039). Among women aged 15 years to 24 years, prevalence appears to have decreased by approximately 8%, signaling a likely decrease in HIV incidence in this population of young women. Mills and colleagues found no sex-based differences in HIV incidence in a community-wide, home-based testing campaign in rural, western Kenya reporting an overall incidence of 1.2 per 100 person-years of observation (Abstract 1025). Of more concern were data presented by Huerga and colleagues from a population-based survey in rural Kwazulu-Natal (Abstract 152Lb) showing an overall HIV prevalence of 25%; women had twice the prevalence of men (31% vs 16%, respectively) and a 2.5 times higher incidence than men (1.6 per 100 person-years of observation vs 0.6 per 100 person-years of observation, respectively). Antiretroviral therapy coverage was higher for women than men (79% vs 64%, respectively), which may further fuel sex disparities in HIV acquisition in this population, if leaving men untreated makes them more infectious. Incidence differences between women and men were particularly pronounced in the 20- to 29-year-old age group (4 per 100 person-years of observation vs 1 per 100 person-years of observation, respectively), pointing to the need for prevention interventions for young women.

Nair and colleagues presented risk factors for HIV acquisition in the
MTN-003 VOICE trial (Abstract 1031). Incidence in this study was as high as 10% at some sites, despite provision of condoms and comprehensive prevention counseling. On multivariable analysis, factors independently associated with future HIV acquisition included being younger than 25 years old, being unmarried, having a primary partner who does not provide material support or has other partners, not knowing if a partner has other partners, having a curable STI at screening (ie, chlamydia, gonorrhea, trichomoniasis, or syphilis), being seropositive for herpes simplex virus 2 (HSV-2), and drinking alcohol 2 or more times in the past 3 months.

Previous studies have suggested that age-disparate relationships may account for the higher prevalence of HIV in younger women. Harling and colleagues presented data from a population-based cohort of more than 5000 women in rural KwaZulu-Natal, South Africa, from January 2005 to June 2012 (Abstract 145). Overall HIV incidence was 7.75 per 100 person-years of observation, but having an older partner was not associated with increased incidence among women younger than 30 years of age. Among women aged 30 years and older, HIV incidence fell as partner age rose, suggesting that public health campaigns encouraging women to avoid older male partners could be harmful for older women and may not be helpful for younger women.

Nerlander and colleagues analyzed 2009 US National HIV Behavioral Surveillance (NHBS) data on women who inject drugs to identify risk practices and undiagnosed HIV infection in this population in 20 US cities with high AIDS prevalence (Abstract 1037). They found that approximately one-third of these women exchanged sex and that women who exchanged sex were statistically significantly more likely than women who did not exchange sex to have sex without a condom (88% vs 65%, respectively) and to have a shared injection equipment (56% vs 30%, respectively) in the past 12 months. A small proportion of women who did and did not exchange sex were HIV seropositive and unaware of their status (5% vs 3%, respectively), but only somewhat more than one-half of each group had tested for HIV in the past 12 months. These data point to the need for interventions (including regular HIV testing) that specifically target women who inject drugs, with a special focus on women who also exchange sex. Lucas and colleagues presented data from respondent-driven sampling that recruited nearly 15,000 IDUs at 15 sites in India (Abstract 1036). Overall prevalence was 18%, but women had a fourfold greater odds of HIV infection and were statistically significantly less likely than men to report ever accessing needle exchange or opiate substitution programs. Thus, women who inject drugs may have dual disparities (injection and sexual) for HIV acquisition; women-specific programs are needed to curb the spread of HIV in these populations.

Hormonal Contraception

Session 10 was a themed discussion focusing on the impact of reproductive hormones on the risk for HIV acquisition and transmission. Cu-Uvin opened the session by reviewing observational data suggesting a potential increased risk of HIV acquisition with the use of injectable contraceptives (depot medroxyprogesterone acetate [DMPA]) but not oral contraceptives. The World Health Organization (WHO) convened an expert panel to review the epide-miologic literature and issued a statement in February 2012 that available evidence was inconclusive and there should continue to be no restrictions on the use of any hormonal contraceptive for at-risk women. Cu-Uvin reviewed possible biologic mechanisms for increased HIV acquisition and transmission with the use of hormonal contraceptives, including changes in vaginal and cervical structure, changes in local and systemic immunity, and heightened STI risk and alterations in vaginal flora.

In this session, Roxby and colleagues presented data on the impact of DMPA on effector molecules of the innate immune response in cervico-vaginal secretions in high- and low-risk HIV-uninfected women (Abstract 846). Among 160 HIV-exposed, seronegative women in serodiscordant relationships and 73 low-risk control women in Kenya, DMPA users had statistically significantly higher mean concentrations of the cationic polypeptides HNP1-3 and LL37. These molecules are potent recruiters of target cells for HIV infection, and it was hypothesized that upregulation of these polypeptides may lead to recruitment of dendritic cells susceptible to HIV infection.

Noguchi and colleagues compared the impact of DMPA with that of nor-ethisterone enanthate (NET-EN), another injectable hormonal contraceptive, on HIV acquisition among women enrolled in the MTN-003 VOICE trial (Abstract 847). Of 3163 injectable hormonal contraceptive users, 65% used DMPA and 43% used NET-EN during follow-up (8% overall used both DMPA and NET-EN). Compared with NET-EN users, DMPA users were older, more likely to be married and to have children, more likely to test seropositive for HSV-2 at baseline, and less likely to report more than 1 sex partner. In adjusted analyses, DMPA users had a higher risk of HIV acquisition than NET-EN users (hazard ratio [HR], 1.42; 95% CI, 1.03-1.97; P = .034). This relationship was modified by HSV-2 status, with an increased risk of HIV acquisition seen only among women who were HSV-2 seropositive at baseline, more likely to test seropositive and NET-EN). Compared with NET-EN users, DMPA users were older, more likely to be married and to have children, more likely to test seropositive for HSV-2 at baseline, and less likely to report more than 1 sex partner. In adjusted analyses, DMPA users had a higher risk of HIV acquisition than NET-EN users (hazard ratio [HR], 1.42; 95% CI, 1.03-1.97; P = .034). This relationship was modified by HSV-2 status, with an increased risk of HIV acquisition seen only among women who were HSV-2 seropositive at baseline (adjusted HR, 2.02; 95% CI, 1.11-3.66; P = .021). Noguchi pointed out that the lack of a nonhormonal contraceptive comparator group in this analysis prevented estimation of the impact of DMPA or NET-EN use versus nonuse on HIV acquisition. These findings support current WHO recommendations that women using injectable contraceptives containing progestins should use other preventive measures against HIV infection.

Radzio and colleagues reported that DMPA did not affect simian-human immunodeficiency virus (SHIV) viremia nor genital shedding in a randomized, controlled pigtail macaque challenge study using 6 animals on DMPA and 6 controls (Abstract 844). These findings suggest that DMPA may not increase
HIV infectivity in HIV-seropositive women. During the discussion period, several attendees made the point that additional data are needed on the risk associated with different hormonal contraception methods, discussing whether randomized controlled trial data are needed to better understand the risk associated with injectable hormonal contraceptives. The WHO will convene a meeting shortly to review emerging data and their recommendations on hormonal contraception. Overall, there was agreement on the importance of expanding contraceptive options for women.

Two posters evaluated whether the coadministration of hormonal contraception and PrEP diminished the efficacy of either intervention in the Partners PrEP study of serodiscordant couples. Heffron and colleagues demonstrated high PrEP efficacy (71%) among women who used DMPA and men whose female partners used DMPA (90% efficacy), with no difference when compared with women and men not exposed to hormonal contraception (Abstract 950). The authors conclude that PrEP use could counterbalance the potential increased risk of HIV acquisition in women using DMPA. Murnane and colleagues compared contraceptive effectiveness in the PrEP arm with that in the placebo arm in the Partners PrEP study (Abstract 957). Women using injectable and implantable contraception had a substantial reduction in pregnancy rates that did not differ by randomization arm. Similar to previous studies, oral contraceptives did not result in substantial reductions in pregnancy incidence, possibly due to low adherence rates. These results suggest that a combination of injectable or implantable hormonal contraception and PrEP could provide effective prevention for pregnancy and HIV acquisition.

Sexually Transmitted Infections

In a symposium on intimate infections (Session S9), Myer reviewed the evidence for the role of bacterial vaginosis (BV) in HIV acquisition and transmission. He highlighted that our basic insights into normal and abnormal vaginal flora are rapidly evolving. Currently, BV is thought of as a polymicrobial condition in which normal vaginal Lactobacillus species are replaced by diverse bacterial communities of anaerobes and facultative anaerobes. BV is clinically characterized by the loss of normal acidic pH and the presence of epithelial cells covered with anaerobes (clue cells). Several factors, including immunologic impairment (eg, advanced HIV disease), changes in hormone levels, cervical and vaginal infections (eg, HSV-2, Trichomonas), and intravaginal practices (eg, douching) may facilitate the development of BV. Although BV is consistently associated with high-risk sexual behaviors, a specific sexually transmitted etiologic agent has not been identified.

BV prevalence is higher in HIV-infected than in HIV-seronegative women, and in a meta-analysis of 3 prospective studies, BV was associated with increased HIV acquisition in women (risk ratio [RR], 1.61; 95% CI, 1.21-2.13). Potential mechanisms behind this increase include loss of healthy mucosal defenses and local inflammation in the vaginal mucosa. BV has also been associated with increased HIV shedding in cervicovaginal specimens of HIV-infected women, and a recent study among serodiscordant couples in Africa demonstrated that BV was associated with increased female-to-male HIV transmission. Treatment of BV can be challenging, as there is a 50% to 50% recurrence rate after standard treatment. Furthermore, treating BV in HIV-infected women has had limited impact on HIV shedding. New BV treatment strategies are emerging, with interventions focused on promoting healthy vaginal flora. Myer recommends future research into the mechanisms through which normal and abnormal vaginal flora affect HIV transmission, and the drivers of the onset and persistence of abnormal vaginal flora.

Racial Disparities

A number of presentations and posters highlighted the racial and ethnic disparities in new HIV infections in the United States. Rosenberg and colleagues presented data from the InVolveMENt study, a longitudinal cohort of black and white MSM in Atlanta (Abstract 38). Of the more than 800 men enrolled, HIV prevalence was 44% in black MSM and 15% in white MSM. HIV prevalence increased with age and was higher in black MSM (34% at 25 years, 45% by 30 years, and 60% if older than 30 years of age) than white MSM at all ages except 18- to 19-year-olds. HIV incidence was 9.6 per 100 person-years of observation among black MSM younger than 25 years; no infections were seen in white MSM in this age group. A change-in-hazard approach was undertaken and it was found that the racial disparity in HIV incidence may be explained by poverty and partner race but not employment, insertive versus receptive sex roles, known serodiscordant partners, drug use, arrest, or homelessness.

Serodiscordant Couples

A central question of the HIV epidemic is what accounts for the substantial differences in HIV prevalence in different countries in sub-Saharan Africa. Bellan and colleagues addressed this question using data from 40,000 couples in 25 countries (Abstract 1041). They developed a couples transmission model to assess whether this variation was due to differences in sexual networks (eg, concurrency) or transmissibility (eg, differences in host or viral characteristics, or sexual practices), concluding that the substantial difference in HIV prevalence (ranging from 1% to 30%) is explained by transmissibility differences and not by differences in sexual networks.

Rodger and colleagues presented data on an interim analysis from the PARTNER Study conducted in 14 European countries whose aim is to assess transmission rates between serodiscordant couples when the HIV-seropositive partner is on suppressive antiretroviral therapy (Abstract 153LB). They noted that data on condomless sex between serodiscordant couples are limited, with only 330 cumulative
of the study population were MSM discordant relationships, but only 2% seropositive partners in stable sero-
in the risk of transmission from HIV-
Prevention Trials Network) 052 study
literature. In addition, the HPTN (HIV
pair-years of data in the published
antiretroviral therapy. In total, 135 in-
2011, including periods before and
into stable, seronegative heterosexual
evaluation the introduction of HIV
initially HIV-seroconcordant couples
substantially greater (64%) among those
couples in whom the HIV-infected part-
ter was aware of his or her HIV se-
ostatus. These 2 studies point to the
importance of HIV testing and knowl-
dge of serostatus among couples and the
need for prevention interventions
(male circumcision for HIV-seronegative
men, treatment for HIV-seropositive
partners, and other interventions such
as PrEP) to reduce transmission within
serodiscordant partnerships and to
prevent the introduction of HIV into
stable, concordant HIV-seronegative
partnerships.

Emerson and colleagues presented
data from the 2010 through 2011
SHIMS (Swaziland HIV Incidence
Measurement Survey), a population-
based longitudinal cohort analysis (Ab-
tact 1027). Overall, 21% of the near-
ly 10,000 households surveyed were
HIV serodiscordant at baseline. Over
follow-up, HIV incidence was 3.1% for
women and 1.7% for men; 40% of sero-
conversions occurred within serodis-
cordant households. For women, hav-
ing an HIV-infected male household
member was strongly associated with
seroconversion (odds ratio [OR], 3.3).
Men were at increased risk based on
outside sex partners (1 partner: OR,
2.1; 2 or more partners: OR, 4.6) but
were not at increased risk from an
HIV-infected, stable partner. The in-
vestigators suggest that in this context,
identifying women in serodiscordant
relationships allows for efficient tar-
getting of prevention strategies, but for
men, having outside relationships re-
mains the greatest HIV risk.

Risk Practices Among HIV-
Seropositive Persons

Kuhn and colleagues presented data
from 269 interviews of HIV-infected
MSM in Germany to explore risk prac-
tices and serocommunication strate-
gies among men following the viral
load strategy (VLS; Abstract 1040). VLS
is patterned after the so-called
Swiss Statement that HIV transmission
is unlikely to occur within monoga-
mous couples when HIV viral load is
stably suppressed for 6 months and no
other STIs are present. Kuhn reported
that approximately 10% of the men
in this study followed VLS but that in
addition to being more likely than oth-
ers to report condomless anal sex (in-
sertive and receptive), they were also
more likely to engage in anonymous
sex and less likely to disclose their HIV
serostatus to sex partners, particularly
in anonymous settings. These authors
caution against the use of the VLS
outside of monogamous relationships,
where other STIs may occur and thus
increase the risk of HIV transmission.

Mattson and colleagues presented
data from the national Medical Moni-
toring Project, evaluating factors asso-
ciated with nondisclosure of serostatus
among HIV-infected individuals (Ab-
tact 1033). In multivariable analysis,
heterosexual men and women were
more likely than MSM to inform all
partners of their HIV serostatus, as
were white compared with black and
Latino patients. Substance use (binge
drinking, noninjection drug use), home-
lessness, and condomless sex were
also more likely to be associated with
nondisclosure of HIV serostatus.

Lin and colleagues presented data
on risk factors for condomless anal
sex among HIV-infected MSM using
data from the CDC Medical Monitor-
ing Project (Abstract 1038). Overall,
56% of MSM reported condomless anal
sex. In multivariable analysis, independ-
ent risk factors associated with con-
domless sex included use of erectile
dysfunction drugs (adjusted prevalence ratio [aPR], 1.2), white race (aPR, 1.3), 3 to 5 sex partners (aPR, 1.5), 6 or more partners (aPR, 1.6), use of illicit drugs before or during sex (aPR, 1.3), and depression (aPR, 1.2). However, of the 13% of sexually active MSM prescribed erectile dysfunction drugs, only 40% received STI or HIV risk reduction counseling from their practitioner in the previous 12 months. The investigators highlighted the need for practitioners to counsel patients for whom they prescribe erectile dysfunction drugs about strategies to reduce the risk of HIV and STI transmission.

**Injection Drug Use**

The topic of injection drug use was featured more prominently at this year’s conference than in previous years. Kamarulzaman presented a plenary providing an update on the epidemiology of new infections and drivers of the epidemic among IDUs. She presented data from the Joint United Nations Programme on HIV/AIDS (UNAIDS) Global AIDS Report noting that illicit drugs are one of the largest contributors to disability among men and in countries where HIV incidence is increasing, 70% to 80% of HIV infections are occurring among IDUs. Despite numerous studies that support the effectiveness of opiate substitution therapy and needle and syringe exchange programs in reducing HIV acquisition, only 8 of every 100 IDUs are receiving opiate substitution therapy and only 2 needles are exchanged per IDU per month. In countries reporting IDUs, 86 countries have no opiate substitution therapy programs and 76 countries have no needle and syringe exchange programs. Kamarulzaman reviewed progress following the 2010 publication of a *Lancet* review article highlighting punitive drug laws in several countries. Since that time, China, Vietnam, Malaysia, and Ukraine have reduced punitive laws and/or increased access to opiate substitution therapy and/or needle and syringe exchange programs. However, the United States has reinstated its ban on funding for needle and syringe exchange programs, and Russia has reduced the number of IDUs receiving needle and syringe exchange services by 60%.

Among IDUs, women have a much higher prevalence than men, exacerbated by intimate partner violence, sex imbalances in power, sex work, and lack of woman-specific services in many places. Adolescents may also be particularly vulnerable, as estimates are unavailable in many countries, and where data are available, needle sharing appears to be particularly high but access to services is low. Among MSM, use of injection drugs is often episodic but appears to be higher among young and urban men and may be exacerbated by co-use of club drugs, which are increasingly more likely to be injected. IDUs are likely to be incarcerated in many countries, and new data are confirming the danger of increased needle sharing and decreased access to antiretroviral therapy among incarcerated populations, which raise HIV transmission risk.

Studies from several countries have documented the worsening treatment cascade among IDUs. Data from the ALIVE (AIDS Linked to the IntraVenous Experience) cohort of IDUs in Baltimore, Maryland, showed that only 8% of HIV-infected participants were fully virally suppressed, and lack of retention in care and of viral suppression were each associated with lack of consistency in HIV care practitioners, incarceration, and active use of injection drugs. Studies in Central Asia also demonstrate low levels of antiretroviral treatment, due in part to practitioners’ reluctance to prescribe antiretroviral drugs among active IDUs. Providing opiate substitution therapy can increase adherence to antiretroviral treatment, with improvement in viral suppression. Integrating HIV infection, STI, and tuberculosis care has been shown to improve health outcomes in Ukraine. A World Bank study of the cost of scaling up of combination prevention efforts (needle and syringe exchange programs, medically assisted therapy, HIV counseling and testing, and antiretroviral treatment) compared with the status quo in Ukraine, Pakistan, Thailand, and Kenya found that the cost per infection averted was $400 to $1600, highly cost-effective.

The Global Commission on Drug Policy makes the case that the criminalization of drug use fuels the HIV pandemic. Despite enormous funds spent on the criminal justice system and a declared “war on drugs,” the global heroin supply has increased by 380% from 1980 to 2010. A modeling study suggests that eliminating laws against opiate substitution therapy and scaling up needle and syringe exchange programs and opiate substitution therapy to 80% coverage could eliminate 29% of new infections in Nairobi. Portugal decriminalized all illicit drugs in 2001 while continuing to prosecute dealers and traffickers. They scaled up treatment and harm reduction, while guaranteeing a minimum income, and saw a dramatic reduction in the incidence of HIV infection among drug users by more than 75%. A recent editorial in the *Journal of the American Medical Association* pointed out the stigma associated with opiate addiction—rather than recognizing it as a medical disorder—and a failure to attend to other associated mental health and medical issues. In her plenary, Kamarulzaman called for combination, multilevel prevention integrated with treatment, addressing stigma and discrimination (beginning with the medical and scientific community), and reforming drug policies worldwide.

Mitsch and colleagues presented national data on trends in HIV diagnoses among IDUs in the United States (Abstract 1034). Using data reported to the CDC, they estimate that the number of new HIV diagnoses attributable to injection drugs was down by 10.5% among men and by 12.2% among women from 2008 to 2011. Despite this improvement, IDUs continue to bear a disproportionate burden of HIV infection (6 times higher than overall prevalence), and prevalence does not appear to be increasing, a possible sign of relatively high mortality among this population. Approximately 15% of persons with heterosexual acquired infection were likely to have become infected through sexual contact with IDUs, underscoring the need to
Prevent, diagnose, and treat HIV infection among IDUs to improve the health and well-being of this population and their sex partners.

Prevention Strategies

Preexposure Prophylaxis

Clinical trials have demonstrated the safety and efficacy of daily oral PrEP in several populations, whereas other trials have shown no efficacy. New data on PrEP presented at CROI 2014 focused on understanding efficacy, adherence, and resistance data from completed PrEP trials; describing PrEP implementation efforts and rollout strategies to maximize PrEP’s public health impact; and evaluating long-acting formulations of PrEP to overcome adherence challenges.

Baeten and colleagues presented data from the Partners PrEP study comparing the efficacy of single-agent tenofovir PrEP with dual-agent emtricitabine plus tenofovir PrEP in heterosexual serodiscordant couples (Abstract 43). After the primary study results were released in July 2011 demonstrating a preventive efficacy of 67% for tenofovir and 75% for emtricitabine plus tenofovir, placebo-arm participants were offered randomization to tenofovir or emtricitabine plus tenofovir. Data through December 2012 showed that efficacy for tenofovir was 33% lower than efficacy for emtricitabine plus tenofovir alone, although this was not statistically significantly different (HR, 0.67; 95% CI, 0.39-1.17). Estimated PrEP efficacy was high among participants with detectable plasma drug levels in both treatment arms (85% in the tenofovir and 90% in the emtricitabine plus tenofovir arm), and safety outcomes were similar between treatment arms. These results suggest that once-daily tenofovir and emtricitabine plus tenofovir are safe and provide substantial preventive benefit with comparable efficacy.

Several presentations focused on understanding and validating adherence measures used in PrEP trials. van der Straten and colleagues presented data comparing behavioral and pharmacokinetic measures of adherence in the VOICE trial (Abstract 44). This trial in African women did not demonstrate efficacy of daily oral tenofovir, daily oral emtricitabine plus tenofovir, and 1% vaginal tenofovir gel, due in part to low product use as evidenced by low rates of drug detection in trial participants. In their analysis, van der Straten and colleagues compared behavioral measures of adherence (including face-to-face interviews, clinic pill counts, and audio–computer assisted self-interview) with pharmacokinetic measures of adherence (tenofovir concentrations in plasma and vaginal swabs). Pharmacokinetic nonadherence was defined as having a drug level below a threshold concentration reflecting no dosing in the past week. Although pharmacokinetic nonadherence was high in the oral arms (69%) and the gel arm (64%), rates of nonadherence were lower for the behavioral measures (6% to 49%). Nonadherence detected via behavioral measures did predict pharmacokinetic nonadherence, but this population represented a small proportion of the overall cohort. In logistic regression models to estimate predictive ability, none of the behavioral measures performed well in predicting pharmacokinetic nonadherence and provided only slightly better prediction than a coin toss.

These results highlight the importance of developing accurate real-time, low-cost objective and biologic measures of adherence for use in PrEP trials. Baxi and colleagues presented data evaluating the correlation among pharmacokinetic measures (plasma, intracellular, and hair PrEP drug levels) and traditional measures of adherence (self-report and medication electronic monitoring system [MEMS] counts of medication bottle openings) in 2 intermittent PrEP trials in Africa (Abstract 953). Hair drug levels and MEMS counts were strongly associated, with hair tenofovir and emtricitabine concentrations increasing by 8% to 10% for every 10% increase in MEMS counts; plasma levels and peripheral blood mononuclear cell (PBMC) levels were also associated with MEMS counts. Hair levels and self-reported adherence were only weakly associated, highlighting the limitations of self-reported adherence data for PrEP.

To help inform the use of pharmacokinetic assessments as quantitative, objective measures of PrEP adherence and to guide the evaluation of intermittent PrEP dosing strategies, Hendrix and colleagues presented data on drug concentrations associated with varying dosing patterns in the HPTN 066 study (Abstract 104). In this phase I pharmacokinetic study, HIV-seronegative men and women were randomized to receive directly observed oral emtricitabine plus tenofovir with different dosing frequencies ranging from once a week to daily dosing (100% adherence). Steady-state levels of tenofovir diphosphate were achieved within 1 week of dosing in all blood analytes including PBMCs, which was earlier than predicted based on previous pharmacokinetic studies in HIV-seropositive individuals. Tissue drug concentrations were higher in colon than in vaginal tissue in almost all cases and were generally higher with increasing doses per week. However, dose proportionality was demonstrated only for PBMC tenofovir diphosphate and these findings were inconsistent, with variability by visit week. Steady-state plasma tenofovir concentrations from daily dosing in HPTN 066 were consistent with concentrations reported in trials with high PrEP efficacy and higher than concentrations observed in trials demonstrating moderate or no efficacy. These results suggest that data from smaller pharmacokinetic studies can be used as a benchmark for interpreting drug concentrations and PrEP outcomes in larger efficacy trials.

Similar to the VOICE trial, the Fem-PrEP (Preexposure Prophylaxis Trial for HIV Prevention among African Women) did not demonstrate efficacy of emtricitabine plus tenofovir PrEP among African women, attributable in part to low study product adherence. Corneli and colleagues presented qualitative and quantitative data from a follow-up study with
This study. Estimated emergence of resistance in use in the VOICE trial may have underestimated benefits (eg, medical care) as a reason for study participation, suggesting that these benefits may have encouraged women who were not interested in taking the product to enroll in the study. Although the FEM-PrEP study had an extensive community engagement program, the investigators recommended a review of materials used to improve research literacy and the development of additional strategies to engage partners and communities in future PrEP trials.

The emergence of HIV drug resistance is a concern with the use of antiretrovirals as PrEP. Two posters evaluated the emergence of resistance in PrEP clinical trials. Parikh and colleagues presented data on HIV-1 resistance outcomes among seroconverters in the VOICE trial (Abstract 594). Resistance to PrEP agents was rare when tested using population sequencing, with virus in only 1 of 212 participants receiving active product (1% tenofovir gel, oral tenofovir, or oral emtricitabine plus tenofovir) developing acquired resistance after enrollment (M184V in the emtricitabine plus tenofovir arm). Among participants acutely infected at enrollment, virus in 2 of 9 individuals assigned to the emtricitabine plus tenofovir arm developed M184I/V after 26 days to 29 days of product use. Resistance to tenofovir did not emerge in any participant. Overall, the prevalence of transmitted nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) resistance (2.5%) was higher than acquired resistance to study product (1.4%), although low product use in the VOICE trial may have underestimated emergence of resistance in this study.

As resistance testing using standard consensus sequencing can only detect resistance at frequencies above 20%, Lehman and colleagues utilized 454 ultradep sequencing to detect resistance at frequencies as low as 1% in the Partners PrEP study (Abstract 590LB). Among 121 seroconverters tested, 9 (7.4%) had PrEP-related resistance mutations (K65R, K70E, or M184I/V) detected above 1%, only 2 of which had previously been detected using standard sequencing. Resistance was detected in virus in 3 of 12 (25%) individuals acutely infected at enrollment and randomized to receive active product, and in virus in 4 of 51 (8%) participants in the active arms who became infected after enrollment. Virus in 2 of 58 (3%) placebo arm participants had evidence of M184I/V resistance. Resistance was highest (5 of 25 [20%]) among seroconverters in the emtricitabine plus tenofovir arm (4 M184I/V, 1 M184I/V/K65R). In the tenofovir arm, virus in 2 of 38 (5.3%) participants had resistance detected (1 K65R/K70E, 1 M184I/V). The detection of a PrEP drug in plasma was associated with an increased risk of resistance. Although overall selection of resistance was rare, this finding suggests that acquired resistance was more likely to occur in the presence of PrEP exposure.

Several posters described early PrEP implementation efforts in demonstration projects and open-label studies to evaluate PrEP uptake and delivery in the United States and in resource-limited settings. Cohen and colleagues described high levels of uptake among a diverse population of MSM offered PrEP in STI clinics and a community health center in 3 US cities (Abstract 954). Overall PrEP uptake was 60% among potentially eligible individuals and was associated with study site (higher in Miami, Florida, and Washington, DC, than in San Francisco, California), having prior PrEP awareness, being self-referred to the PrEP project, and reporting higher-risk sexual behaviors at baseline. Tenofovir diphosphate levels in dried blood spots were tested at week 4 and were detected in 98% of samples, with most participants (77%) having a tenofovir diphosphate level consistent with taking at least 4 doses a week. Relatively few transgender women and young MSM of color were assessed for participation and enrolled in the program, highlighting the need for strategies to increase community awareness and engage these populations in PrEP programs.

Hosek and colleagues presented data on PrEP uptake and adherence in the iPrEx OLE (Pre-Exposure Prophylaxis Initiative Open Label Extension) among young MSM in the United States who were previously in a randomized pilot study of PrEP feasibility and acceptability (Abstract 951). Approximately two-thirds of eligible young MSM enrolled in iPrEx OLE, and of those, 70% chose to take PrEP. Tenofovir detection in plasma increased from 45% during the randomized phase to 58% in iPrEx OLE. Participants reported numerous social benefits from study participation, and the majority (70%) expressed interest in future use of PrEP if available.

Mayer and colleagues described prevalence and correlates of PrEP use among an online sample of 9179 US MSM using a networking site for seeking a sex partner (Abstract 952). Only 1.2% reported PrEP use. Having a college education, reporting a prior STI, being comfortable talking with their practitioner about sex, and previous use of PEP were associated with prior PrEP use. These results highlight the need for educating health care practitioners on providing culturally competent care and facilitating discussions about sexual health and the potential role of PrEP in reducing HIV risk.

In a symposium on PrEP (Session S3), Mugo presented insights into implementing PrEP in resource-limited settings (Abstract 62). Currently, access to PrEP is limited to demonstration projects in these regions. Demonstration projects can help determine priority populations for PrEP, identify optimal delivery systems, and help evaluate cost-effectiveness and overall public health impact. Mugo pointed to a number of PrEP demonstration projects being planned in resource-limited settings; however, only 1 of these projects is currently under way.
She, along with Heffron and colleagues, presented preliminary findings from the Partners Demonstration Project in HIV-serodiscordant couples in Kenya and Uganda (Abstract 949). In this study, PrEP is used as a bridge to antiretroviral treatment use and is offered to couples in whom the HIV-infected partner declines, delays, or is not eligible for antiretroviral treatment; PrEP discontinuation is recommended after 6 months of antiretroviral treatment when viral suppression is achieved. PrEP uptake was 95% among HIV-seronegative partners at enrollment, and antiretroviral treatment was initiated in 75% of eligible HIV-infected partners. The majority of couples were willing to stop PrEP 6 months after their partner initiated antiretroviral treatment. Although demonstration projects will provide important insights into PrEP implementation, Mugo highlighted the need to expand PrEP access beyond these projects to achieve maximal public health impact.

Also in Session S3, Glidden presented strategies for prioritizing PrEP to have the maximal public health impact (Abstract 64). He described 2 epidemiologic constructs, the number needed to treat (NNT) and population attributable fraction (PAF), to identify populations who may benefit the most from PrEP. The NNT indicates the number of MSM and transgender women who would need to take PrEP for 1 year to prevent 1 HIV infection and is particularly useful for practitioner decisions on whether to initiate PrEP in a patient. At a population level, PAF can be used to identify subpopulations accounting for the largest proportion of new infections and thereby guide programmatic decisions on how to roll out PrEP to maximize population level impact. These 2 variables are plotted against each other in Figure 1: desirable targeting strategies include subpopulations with high PAF and low NNT (lower right quadrant), whereas those less desirable include subpopulations with low PAF but high NNT (upper left quadrant).

As seen in a secondary analysis of data from the iPrEx trial, self-reported receptive anal sex without a condom had the highest PAF and one of the lowest NNT. NNT was also low for MSM and transgender women reporting cocaine use or an STI. In this study population, having a single HIV-seropositive partner accounted for only 2% of new infections; prioritizing serodiscordant MSM couples without including those contributing to the largest number of infections reduces overall population impact. These results suggest that prioritizing PrEP for MSM and transgender women who report condomless receptive anal sex could help achieve maximal impact of PrEP. Unfortunately, among young women in sub-Saharan Africa, risk factors associated with a high PAF (being young and unmarried) were associated with low adherence, and therefore a high NNT. Strategies are needed to improve efficacy of PrEP and other prevention strategies among this very vulnerable population of young women.

Long-Acting Antiretroviral Agents and Microbicides

Given the crucial relationship between PrEP adherence and efficacy, several presentations focused on evaluating long-acting systems for delivering PrEP agents to overcome adherence challenges with daily dosing. Andrew and colleagues presented follow-up data on GSK744LA, a long-acting injectable nanosuspension previously shown to be effective against low-dose intrarectal SHIV challenge in rhesus macaques (Abstract 39). In this study, a single intramuscular (IM) injection of GSK744LA given 1 week prior to first virus exposure protected 12 of 12 macaques for at least 5 weekly challenges and delayed infection by 5 to 10 challenges compared with 12 controls (all of which became infected within 8 weeks). GSK744 plasma concentrations of greater than 3x protein-adjusted IC₉₀ (PAIC₉₀)
resulted in 100% protection and greater than or equal to 1x PAIC50 resulted in 97% protection; these levels can be readily achieved in humans with quarterly 800 mg IM injections. These data support moving GSK744LA forward into phase II PrEP clinical trials that will launch later this year.

Garcia-Lerma and colleagues presented data on the prophylactic efficacy of GSK744LA against vaginal infection in female pigtail macaques (Abstract 40LB). Pigtail macaques have menstrual cycles similar to women and can become infected with doses of SHIV that more closely mimic those that occur in HIV acquisition. None of the 6 animals treated with 3 monthly GSK744LA injections became infected during twice-weekly, low-dose vaginal challenges or 16 weeks after the last viral challenge, whereas all 6 controls became infected. Plasma drug concentrations in macaques were within the range reported in humans receiving GSK744LA 800 mg IM, but vaginal drug concentrations were four- to fivefold lower than plasma, suggesting a contribution of systemic drug to the observed protection. In a related poster, Andrews and colleagues evaluated the efficacy of GSK744LA in protecting macaques against high-dose intravaginal challenge (Abstract 941LB). Macaques were treated with DMPA to simulate the menstrual cycle and thin the cervicovaginal epithelium. Although all 4 control animals became infected after a single high-dose SHIV challenge, 6 of 8 macaques treated with 2 monthly doses of GSK744LA were protected against 3 virus challenges at weeks 1, 5, and 7. Drug concentrations in the 2 treated animals that became infected had fallen below 4x and 1x PAIC50, respectively, at the time of first virus detection. Together, these results support further clinical investigation of GSK744LA as PrEP in women at risk for HIV acquisition.

Vaginal rings are also promising candidates for providing sustained delivery of antiretroviral-based microbicides. Chen and colleagues presented data from a phase I study on the safety, pharmacokinetics, and pharmacodynamics of vaginal rings containing dapivirine and maraviroc, either alone or in combination, compared with placebo (Abstract 41). Dapivirine, a potent NNRTI, is currently in phase 3 trials for HIV prevention in women, and maraviroc, an antagonist to CC chemokine receptor 5 (CCR5), has been approved for HIV treatment but has not been previously evaluated for intravaginal use. In this trial of 48 HIV-seronegative, sexually abstinent women in the United States, all vaginal rings were found to be safe and well tolerated after 1 month of use. Dapivirine levels were detectable in all compartments and were substantially higher in vaginal fluid and cervical tissue than in plasma. In contrast, maraviroc was detected at lower levels in vaginal fluid and was undetectable in plasma and most cervical tissue samples. In an explant model, dapivirine concentrations in fresh cervical tissue correlated with protection against HIV replication, whereas tissue levels of maraviroc were too low to show protection. These results support the delivery of NNRTIs via vaginal rings for HIV prevention.

There has been growing interest in delivering topical microbicides as films, which are inexpensive, scalable, and more discreet, portable, and easier to store than gels. Film formulations also do not require an applicator and minimize drug leakage after use, and their small volume may decrease dilution of innate immune defenses in vaginal fluid compared with gels. Bunge and colleagues presented results from a phase I trial to assess the safety, pharmacokinetics, and pharmacodynamics of gel and film formulations of dapivirine in 60 HIV-seronegative women (Abstract 42LB). Participants were randomized to 7-day use of 1 of 4 study products: dapivirine gel, placebo gel, dapivirine film, or placebo film. The dapivirine gel was found to be safe, with no difference in genitourinary adverse events between arms. Five of 29 women in the film arms were noted to have visible film on the external genitalia at the time of genital biopsy, indicating poor film placement. Comparable dapivirine plasma levels were achieved in the film and gel arms; however, tissue concentrations were higher in the gel users than the film users, possibly due to residual drug adhering to the tissue surface. Importantly, tissue drug concentrations in cervical and vaginal tissues after dapivirine film use were comparable to tissue levels observed after 1 month of intravaginal ring use. Both the dapivirine gel and film were protective against ex vivo HIV-1 challenge in vaginal tissue. This first-in-human trial of dapivirine film provides proof of concept that quick-dissolving films can effectively deliver antiretroviral drugs to genital tissues; the size and shape of the film have been modified to address film placement issues.

**Postexposure Prophylaxis**

Postexposure prophylaxis (PEP), that is, a 28-day course of antiretroviral medication started as soon as possible within 72 hours of high-risk exposure, is recommended after occupational and nonoccupational exposures to HIV. Several posters presented new data on PEP at this year's conference, focusing on evaluating new PEP agents, use of PEP after infected blood transfusion, and strategies to facilitate PEP completion.

Fatkenheuer and colleagues presented data from an open-label, randomized, noninferiority trial comparing ritonavir-boosted (r) darunavir with standard-of-care (SOC) PEP (mainly lopinavir/r) following high-risk HIV exposure in Germany (Abstract 948). For the 312 patients enrolled, the median time to PEP initiation after exposure was 2.5 hours for occupational exposures (22% of cases) and 14 hours for nonoccupational exposures (78% of cases). Early PEP discontinuation occurred in 6.5% of patients in the darunavir/r arm and 11.3% in the SOC arm. Both regimens were well tolerated, with fewer gastrointestinal adverse drug reactions in the darunavir/r group (21 vs 49, respectively; \(P = .0007\)). No seroconversions were observed in either arm of the trial. The investigators concluded that darunavir/r-based PEP was noninferior to SOC PEP with lopinavir/r and can serve as an alternative PEP regimen.
Hajjar and colleagues reported a case of PEP preventing HIV transmission after a transfusion with HIV-infected blood (Abstract 960). A 12-year-old girl with sickle cell crisis inadvertently received 1 unit of packed red blood cells from an HIV-infected donor not on antiretroviral therapy (plasma HIV RNA level was 9740 copies/mL). One day after the transfusion, the recipient had a positive HIV ELISA and Western blot (with bands identical to the donor), but negative HIV DNA by polymerase chain reaction testing. The patient was started on tenofovir, emtricitabine, darunavir/r (subsequently switched to lopinavir/r), and raltegravir 22 hours after transfusion and continued antiretroviral treatment for 13 weeks. Longitudinal HIV RNA and DNA measurements by standard and highly sensitive assays remained negative during and 3 months after stopping antiretroviral treatment, and HIV-1-specific antibodies declined to undetectable levels 6 months after transfusion. Although this may be further evidence that treatment administered shortly after exposure can abort infection, the investigators caution that positive HIV serologies in recipients determined shortly after transfusion with HIV-infected blood may not represent true HIV infection.

Landovitz and colleagues presented results from a randomized controlled trial evaluating contingency management to improve PEP outcomes among stimulant-using MSM (Abstract 961). Participants were randomized to contingency management (with escalating voucher-based incentives) or a noncontingent control group. Contingency management participants were more likely to complete the PEP course than were controls (adjusted OR [aOR], 7.2; 95% CI, 1.1-47.9). There was a trend toward increased self-reported medication adherence in the contingency management group (aOR, 4.3; 95% CI, 0.8-21.9). Contingency management participants were also more likely to have stimulus-free urine samples than were controls (incidence rate ratio [IRR], 1.57; 95% CI, 1.22-2.22), and there was a trend toward fewer episodes of condomless anal sex in the contingency management group (IRR, 0.34; 95% CI, 0.11-1.08). These findings suggest that contingency management may be a useful strategy to support PEP and potentially other biomedical prevention strategies among stimulant-using MSM.

**Treatment as Prevention**

Phillips presented data suggesting that despite high rates of diagnosis and viral suppression among MSM in the United Kingdom, HIV infections have been rising in number since the late 2000s (Abstract 116). He pointed to numerous modeling studies that suggest that increased HIV testing and treatment should lead to overall reductions in HIV incidence. To evaluate potential explanations for increased HIV infections in the United Kingdom, Phillips created a model that was fit to what is known about the natural history of HIV and the effect of antiretroviral treatment on transmission rates. Based on these models, Phillips suggests that this increased HIV incidence is due to increases in condomless sex. He suggests that testing and immediate treatment could substantially reduce transmission rates in future but that adherence and retention on antiretroviral therapy and rates of condomless sex will determine the extent of that reduction. He projects that approximately 90% of HIV-infected persons would need to be virally suppressed to reduce HIV incidence to less than 0.1 per 100 person-years. This would require that approximately 90% of HIV-infected persons be diagnosed within 1 year of infection (albeit the current estimate is less than 50%); linkage, adherence, and retention remain high; antiretroviral treatment be initiated immediately upon diagnosis; and levels of condomless sex increase no further.

**Medical Male Circumcision**

Although voluntary medical male circumcision has been shown to reduce the risk of HIV acquisition among HIV uninfected men, the rate of HIV transmission to female partners was increased when HIV-infected men resumed sexual intercourse prior to wound healing after circumcision. Toblan and colleagues evaluated the time course of HIV shedding postcircumcision among HIV-infected men in Rakai, Uganda (Abstract 966). HIV shedding was detected in 11% of men prior to circumcision but in 60% of men during surgery after foreskin removal. Compared with precircumcision levels, the probability of HIV shedding was increased from week 1 to week 3, declining to baseline levels by week 4. This identifies a period of increased risk postcircumcision for female partners. The importance of condom use during this 4-week period should be emphasized for HIV-infected men and their sex partners.

**Financial affiliations in the past 12 months:** Dr Buchbinder has been a consultant for Clinical Care Options. Dr Li has been a consultant for Clinical Care Options.


**Additional References**


**Cases on the Web**

**NEW! Geriatrics and HIV**
Harjot K. Singh MD, ScM, and Eugenia Siegler, MD
CME Credit Available: **1.50 AMA PRA Category 1 Credits™**
Level: Advanced
The percentage of HIV-infected patients older than 50 years is expected to increase to more than 50% by 2020, based on modeling. Treatment with single-tablet regimens can lead to durable viral suppression. However, viral suppression comes at the price of lifelong treatment and is further complicated by the expected challenges associated with aging itself.

**NEW! Hepatitis C Viral Targets**
Stuart C. Ray, MD, and Justin R. Bailey, MD, PhD
CME Credit Available: **1.50 AMA PRA Category 1 Credits™**
Level: Advanced
A 2008 study by Limketkai and colleagues showed that in patients with HIV/hepatitis C virus (HCV) coinfection, hepatic fibrosis stage was independently associated with risk of progression to end-stage liver disease, hepatocellular carcinoma, and death, and that sustained virologic response after treatment of HCV infection was associated with survival. These findings highlight the importance of staging of liver disease and, whenever possible, treating HCV infection in HIV/HCV-coinfected individuals.

**NEW! Initiating Antiretroviral Therapy in Resource-Limited Settings**
Habib Ramadhani Omari, MD, MPH, MHS, and John A. Bartlett, MD
CME Credit Available: **1.50 AMA PRA Category 1 Credits™**
Level: Advanced
Antiretroviral therapy has been tremendously successful in reducing morbidity and mortality among HIV-infected persons, and an estimated 10,000,000 people globally are now receiving it. Stigma and the need for strict medication adherence are commonly encountered throughout the world. In resource-limited contexts, there is an additional challenge of maintaining a continuous drug supply and having the ability to properly monitor treatment. Early treatment initiation is essential to preserve immunity, prevent the emergence of AIDS-defining illnesses, and decrease HIV transmission.

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**Acute HIV Infection in Men Who Have Sex With Men**
Leah A. Burke, MD, and Kristen Marks, MD, MS

**HIV Cardiovascular Risk**
Michelle N. Zikusoka, MD, and Wendy S. Post, MD, PhD

**SELECTED CURRENT CASES ON THE WEB**

**Selected Endocrine Problems in HIV-Infected Patients**
Todd T. Brown, MD, PhD

**Clinical Significance of Very Low-Level Viremia**
Timothy J. Henrich, MD

**Osteomalacia and Osteoporosis in the HIV-Infected Patient**
Michael Yin, MD, MS, and Emily Stein, MD, MS

**Drug Interactions in Patients on Concurrent Psychiatric and Antiretroviral Regimens**
John J Faragon, PharmD, BCPS

**Sexually Transmitted Infections in the HIV-Infected Patient**
Linda M Gorgos MD, MSc

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