CROI 2013: New Tools to Understand Transmission Dynamics and Prevent HIV Infections

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New tools to track HIV incidence and identify transmission networks are providing insights about the leading edge of new HIV infections globally. Phylogenetic analyses point to the continued global nature of HIV transmission patterns and the challenges to reducing HIV infections through targeted antiretroviral programs alone. New methods for measuring acute infection and HIV incidence using cross-sectional surveys are proving useful in tracking the impact of prevention programs at the population level. Globally, men who have sex with men, and young men and women continue to be at highest risk of HIV acquisition; the US South also bears a disparate burden of new HIV infections and poor HIV-related outcomes. The use of injectable hormonal contraception may increase HIV acquisition risk; new, effective contraceptive methods and contraceptive counseling are needed, as simply removing this strategy could lead to a net increase in deaths due to unintended pregnancies. Another preexposure prophylaxis efficacy trial failed to show protection, likely because of poor adherence by women in the trial. Fortunately, new strategies are being developed that could substantially reduce new infections globally, such as methods to increase adherence and the use of long-acting antiretroviral agents.

Keywords: *HIV, epidemiology, prevention, transmission*

New Strategies to Track the HIV Epidemic

This year's Conference on Retroviruses and Opportunistic Infections (CROI) highlighted a number of new tools being used to track transmission patterns, improve HIV diagnosis for individuals, and follow incidence trends within populations, including the impact of interventions at a population level.

Using Phylogenetic Analysis to Probe Transmission Dynamics

Several posters explored the ability of phylogenetic analysis to identify transmission patterns, pointing to the strengths and limitations of particular types of prevention strategies. Wertheim presented data in a themed discussion on the global diversity of HIV, by pooling data from more than 85,000 sequences in public databases (Abstract 488). In the 3.5 billion pairwise comparisons, he and his colleagues were able to demonstrate a number of clusters that highlight the ongoing global nature of HIV transmission. For example, he described 2 global transmission clusters, one of 333 (mainly) heterosexuals and injection drug users (IDUs) in 17 countries, and another of 674 (mainly) men who have sex with men (MSM) and IDUs in 18 countries. Grabowski reported on 189 incident cases from 46 communities in the Rakai district of Uganda (Abstract 489). She noted that 39% of the new transmissions appear to have occurred within stable household partnerships. However, of those occurring outside of such partnerships, 62% occurred from outside of the community, suggesting that test-and-treat strategies within communities may not be sufficient to substantially reduce new infections. Paraskevis and colleagues presented data on a recent outbreak of HIV infections among IDUs in the metropolitan area of Athens, Greece (Abstract 502). They detected a 10-fold increase in new diagnoses among IDUs from 2011 to 2012, compared with 2010. Evaluation of viral sequences from these newly infected persons identified numerous subtypes, suggesting numerous introductions from diverse geographic regions dating from 2008 to 2010, and pointing to the ability of HIV to spread rapidly within IDU populations. Lai and colleagues analyzed 3786 sequences from patients with clade B infection enrolled in the Italian ARCA (Antiretroviral Resistance Cohort Analysis) cohort from 1996 to 2012 from 42 clinical centers (Abstract 494). They identified 157 epidemiological clusters of 3 to 106 patients, accounting for more than a quarter of all sequences. Cluster dating suggests that the number of new infections grew until 1990 and has remained constant since that time, demonstrating that these types of analyses can also be used to identify general trends in HIV infections within a population.

Chan and colleagues presented data on sequencing of approximately three-quarters of the HIV-infected patients in Rhode Island from 2004 to 2011 (Abstract 497). In their analysis of 1277 unique sequences, 45% formed 151 clusters, with a mean of 3.5 persons per cluster (range, 2-23). They estimated that only 16% of infections occurred within 6 months of another infection in that cluster, suggesting that the majority of infections are occurring from chronically infected persons. Parry and colleagues presented data from sequencing of 51 seroconverters

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and more than 500 randomly selected HIV seropositive men and women in 5 fishing communities on the shores of Lake Victoria, Kenya (Abstract 97). Although they also found that a minority of infections were likely due to acute infections (15%-43%), they noted that these infections may not be prevented by test-and-treat strategies, which can miss acute infections. Dennis and colleagues sequenced virus from 177 Latino subjects and 1496 non-Latino subjects enrolled in the University of North Carolina HIV Clinical Cohort from 1997 to 2011 (Abstract 495). In their study, immigrant- and US-born Latino participants were equally likely to be in clusters, but immigrants were more likely to be in clusters with another Latino (78% vs 25%; $P = .006$), pointing to the potential for prevention interventions targeted to this group to spread beyond those directly participating in the intervention. In sum, these presentations point to the power of phylogenetic analyses to provide insight into ongoing transmission dynamics and point to opportunities to have a substantial impact on ongoing HIV transmission within sexual and drug-using networks.

Advances in Monitoring the HIV Epidemic

Laeyendecker and colleagues provided an update on cross-sectional HIV incidence testing (Abstract 164). Advantages of accurate cross-sectional incidence testing include lower cost, ability to estimate incidence on a larger scale (eg, countrywide surveillance of incidence), shorter time required to obtain estimates, and ability to include hard-to-reach individuals. Laeyendecker described a multiassay algorithm (MAA) his group developed that includes CD4+ cell count, 2 serologic assays (BED–capture enzyme immunoassay [CEIA], and avidity assay), and HIV RNA level. This algorithm has a window period of approximately 5 months in a clade B setting. Incidence estimates generated by the MAA were nearly identical to observed HIV incidence in 3 large longitudinal cohorts. CD4+ cell testing, which is costly, can be replaced by a high-resolution melting (HRM) diversity assay that does not compromise the mean window period. Laeyendecker and colleagues also optimized an MAA for use in clade A and clade C epidemics that was used as the primary end-point for Project Accept, described below.

In the same session, Hall presented on the use of viral load measures to guide interventions, evaluate research and treatment program outcomes, assess HIV disparities among populations, and estimate trends in relation to HIV incidence (Abstract 165). Viral load data can be obtained through HIV surveillance systems, care practitioner reports, population surveys, and large cohort studies. Hall pointed out that viral load data can be used to identify individuals who are not in care and intervene to facilitate linkage and reengagement in care. On the aggregate level, community viral load measures can be used to evaluate differences in viral burden by geography, demographics, and risk behaviors, as well as among patients in care at a clinic or facility. These measures can also be used to monitor progress toward achieving the goals of the US National HIV/AIDS Strategy.

Justman and colleagues described the first national population viral load estimate in Swaziland to assess the effectiveness and transmission-lowering potential of antiretroviral therapy programs (Abstract 96). Justman pointed out that community viral load measures do not account for those individuals unaware of their diagnosis and proposed more precise terminology to describe such measures (Figure 1): treatment viral load among HIV seropositive individuals on antiretroviral therapy; diagnosed viral load among individuals who have been diagnosed with HIV infection and may or may not be on antiretroviral therapy; and population viral load among the entire HIV seropositive population, including individuals who are unaware of their HIV serostatus. In a nationally representative household sample of 18,154 men and women in the SHIMS (Swaziland HIV Incidence Measurement Survey) study, 5802 (32%) were HIV seropositive; 63% were aware of their serostatus; and among those, 48% reported antiretroviral therapy use. Population viral load was high overall (94,644 HIV RNA copies/mL), with a higher mean viral load among those unaware of their serostatus than those aware of their serostatus (129,307 and 74,319 copies/mL, respectively) and among those not on antiretroviral therapy than among those on antiretroviral therapy (129,260 and 22,979 copies/mL, respectively). Overall, approximately one-third had a high viral load (more than 50,000 copies/mL). Having a high viral load was associated with being unaware of HIV serostatus (adjusted odds ratio [aOR], 14.6; $P < .0001$), being aware of HIV serostatus but not on antiretroviral therapy (aOR, 13.2; $P < .0001$), and being male (aOR, 1.96; $P < .0001$). Viral load data also provided evidence of an effective antiretroviral therapy program, with 85% of those who reported current antiretroviral therapy use having a viral load less than 1000 copies/mL. However, transmission potential remains high in Swaziland, with 65% of HIV-seropositive adults not virally suppressed.

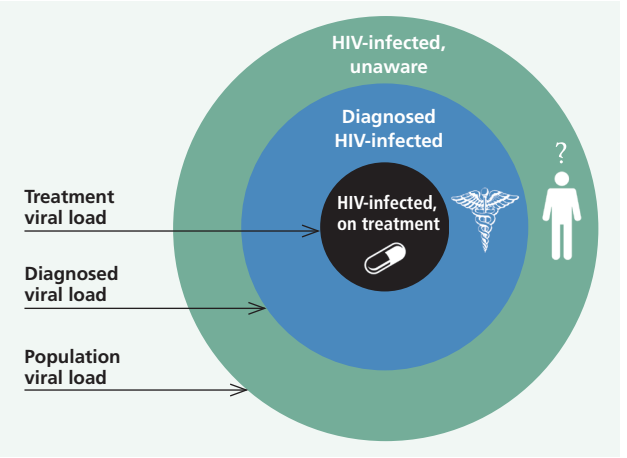

Figure 1. Viral load terminology proposed by Justman and colleagues (Abstract 96). Adapted with the permission of the authors.

Improving HIV Diagnosis, Including Acute HIV Infection

Several poster presentations evaluated fourth-generation antigen-antibody (Ag/Ab) tests for early detection of HIV infection. Manak and colleagues presented performance characteristics of a combination Ag/Ab enzyme immunoassay (EIA) in the ECHO (Early Capture HIV Cohort) Study conducted in Tanzania, Uganda, Kenya, and Thailand (Abstract 630). This fourth-generation EIA detected acute HIV infection on average 8.8 days earlier than the third-generation EIA and 15.5 days earlier than HIV-1 Western blot. Peters and colleagues presented results from the STOP (Seek and Treat for Optimal HIV/AIDS) study, an ongoing prospective study comparing a combination Ag/Ab test with pooled nucleic acid amplification testing (pNAAT) (Abstract 632). Out of 43 cases of acute HIV infection, the combination Ag/Ab test detected 38 (88%) acute infections, and pNAAT detected 42 (98%) acute infections. The combination Ag/Ab test also detected 100% of established HIV infections. Chang and colleagues also demonstrated high sensitivity and specificity of 3 fourth-generation Ag/Ab combination assays in Taiwan (Abstract 633). In contrast, Duong and colleagues described poor performance of an HIV-1/2 Ag/Ab combination test in detecting early infections in the SHIMS study (Abstract 631), with a 0% sensitivity and positive predictive value for detecting acute infections in this cohort (12/12 individuals who had NAAT positive samples and seroconverted 6 months later were nonreactive on an HIV 1/2 Ag/Ab combination test). These studies point to the progress being made to narrow the window between infection and diagnosis, and to how performance characteristics for different tests vary among populations.

Guanira and colleagues presented data from the iPrEx (Chemoprophylaxis for HIV Prevention in Men) trial to help streamline HIV testing during preexposure prophylaxis (PrEP) use (Abstract 635). In iPrEx, HIV infection was assessed by 2 rapid HIV tests at monthly visits, with Western blot performed if either test was positive. Simulations were performed for 5 different HIV testing algorithms to help streamline HIV testing during PrEP use. An algorithm using 1 rapid HIV test to screen and a second rapid test to confirm infection, followed by Western blot in only those with discordant results performed well, with a high positive and negative predictive value (100% and 99.9%, respectively). Using such algorithms could substantially reduce the delay arising from performing Western blot assays after a single positive rapid test result.

Methods for Delivery of HIV Testing

Myers presented an overview of opportunities and challenges with HIV self-testing (Abstract 162). She reviewed the history of development and evaluation of the rapid HIV self-test kit, leading up to the approval of the rapid HIV self-test by the US Food and Drug Administration for over-the-counter sale in 2012. She highlighted potential uses for HIV self-tests, including encouraging testing among persons unaware of their HIV infection, more frequent testing of persons at highest risk for new infection, and mutual testing of sex partners. She also described a number of concerns raised about HIV self-testing, including the lower sensitivity (91%) of the self-test than its administration in clinical settings (98%), potential for increased risk taking if individuals test their sex partners and subsequently engage in high-risk sexual activities, the high cost of the test in the United States, and concern that HIV-infected individuals will not link to care.

In Session 8, McNaghten and colleagues reported results from Project STATUS (Strengthening HIV Test Access and Treatment Uptake Study), a study to determine which of 3 different models of practitioner-initiated HIV testing and counseling (HTC) work best in outpatient departments (OPDs) in Africa (Abstract 31). In this study, 36 OPDs in South Africa, Tanzania, and Uganda were randomly assigned to 1 of 3 HTC models: Model A, OPD health care practitioners refer eligible patients to on-site voluntary counseling and testing after the clinical consultation; Model B, OPD practitioners offer and provide HTC during the clinical consultation; or Model C, nurse or lay counselors offer and provide HTC before the clinical consultation. All 3 models resulted in high rates of HIV testing. Models A and C had the highest rates of acceptance of HIV testing, and Model C tested the highest proportion of eligible OPD patients (54% in Model C, 42% in Model A, and 34% in Model B). Models did not differ in the proportion of patients who tested HIV seropositive (10%) or HIV seropositive patients who were referred to care and treatment services (94%). McNaghten suggested that high testing rates in Model C could be attributed to having a designated area for testing (patients approached in the waiting area were informed that they would not lose their place in line to see a clinician), delivering a health-oriented talk including HIV information in the waiting area, and having designated staff tasked to provide HTC.

Several posters presented outcome data on implementation of the Centers for Disease Control and Prevention (CDC) guidelines for routine, opt-out HIV testing in clinical settings issued in 2006. Momplaisir and colleagues presented data on HIV testing trends from the Southeastern Pennsylvania (SEPA) Household Survey before and after the guidelines were released (Abstract 1059). Overall, HIV testing increased by 33% (OR, 1.33; 95% confidence interval [CI], 1.24-1.4) after the 2006 CDC recommendations, with testing rates increasing faster among African Americans than among whites, and faster among patients in general seeking care at a community health center compared with private clinics. Giordano and colleagues described outcomes from a routine screening program implemented in an emergency department (ED) setting in Houston, Texas, from 2009 to 2012 (Abstract 1063). This program performed more than 170,000 HIV tests and identified 594 (0.34%) new HIV infections; linkage to

care has improved (44% in 2009 and 62% in 2011; $P = .002$) with focused efforts. Lyons and colleagues conducted a randomized comparison of universal screening (offering HIV testing to all regardless of risk) versus targeted HIV screening (offering HIV testing to individuals with any potential indication of HIV risk or disease from charts, staff referral, or self-disclosure) in the ED (Abstract 1062). Targeted HIV screening, even using broad risk criteria, did not increase the rate of positive results nor reduce the number of HIV tests performed, and the universal testing approach identified more HIV cases. Finally, Spaulding and colleagues demonstrated that routine rapid HIV testing in a high-volume jail identified undiagnosed cases of HIV infection, with costs comparable with a routine HIV screening program in the ED (Abstract 1061).

Two posters presented innovative approaches to increase HIV testing in Africa. First, Van Rooyen and colleagues presented results of a home-based counseling and testing (HBCT) program to identify heterosexual couples for HIV testing and linkage to care and treatment in South Africa and Uganda (Abstract 1065). HBCT achieved almost universal (>95%) uptake of HIV testing among 1384 individuals who identified being in a couple, with almost all (99%) disclosing the results to each other. Second, Black and colleagues presented outcome data from an integrated youth center program in Cape Town, South Africa (Abstract 1066). This multifaceted program increased HIV testing among adolescents compared with testing in a community-based clinic, particularly among 12- to 14-year-old boys and 15- to 17-year-old girls.

In sum, these presentations provided evidence that broad screening programs that include outreach in homes, outpatient departments, and community centers may increase uptake of HIV testing. Although progress has been made in linking HIV-infected persons to care, more needs to be done to ensure this linkage is successful, particularly for home-based self-testing initiatives.

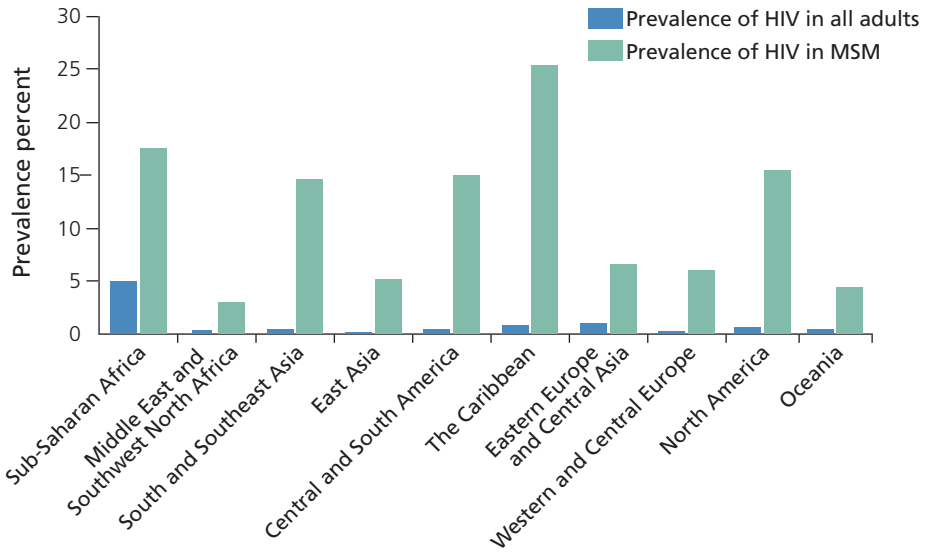

Figure 2. Prevalence of HIV in all adults and men who have sex with men (MSM) worldwide, by region. Adapted from Beyrer C et al. *Lancet*. 2012.

Highly Affected Populations

Men Who Have Sex With Men

This year's CROI demonstrated the considerable work that is being done to understand patterns and factors contributing to the global MSM epidemic. In a plenary session, Beyrer reviewed what is known about the global epidemiology, drivers of risk, and potential for interventions to reduce HIV infections in MSM globally (Session 21). He pointed to the higher HIV prevalence rates among MSM than among other adult populations in all regions of the world (Figure 2), as well as the high and rising rates of new infections in this population globally. He pointed to recent data published by van Griensven and colleagues[1] of a cohort of MSM in Bangkok, Thailand, showing a cumulative HIV incidence of 23% during a 5-year period, with rates as high as 31% among MSM aged 18 years to 21 years. This was seen in Thailand despite widespread antiretroviral treatment, no laws criminalizing homosexuality, and a heterosexual epidemic that has been in marked decline.

Beyrer turned to an exploration of the factors that may be driving the MSM epidemic. The per act risk for receptive anal sex is quite high (1.4%), approximately 18 times higher than with vaginal sex. He also pointed out that because of sexual role versatility (ie, MSM may be both receptive and insertive), there is increased chance for forward spread in this population compared with the heterosexual population. Beyrer also explored the particularly concentrated epidemic among young black MSM in the United States, where networks appear to be both homogeneous and dense. High HIV prevalence rates (eg, approaching 50% in black MSM in Baltimore, Maryland) mean that a relatively low rate of individual risk can spread HIV more rapidly than can higher rates of risky practices in substantially lower-prevalence populations. In fact, a systematic review by Millet demonstrated that after network effects on HIV acquisition rates, the factors most strongly related to increased HIV infection risk for black MSM are biologic and clinical, such as higher rates of sexually transmitted infection (STIs) and undiagnosed HIV infection, fewer HIV-infected men who are virally suppressed, and a greater proportion of HIV-infected partners with low CD4+ cell counts. Many studies have demonstrated fewer individual risk factors for infection among black than with other MSM, including a lower number of sex partners, less methamphetamine use, and a lower proportion of men

reporting having sex while using drugs. Therefore, interventions may more effectively focus on reaching into networks and addressing biologic factors rather than relying on individual risk practices.

Beyrer pointed to both the challenges and the promises of prevention interventions directed toward MSM. Despite great enthusiasm about increasing treatment of HIV-infected persons to reduce HIV transmission, there is biologic plausibility but no direct evidence that antiretroviral treatment reduces the risk of HIV transmission from 1 HIV-infected man to another. The HIV Prevention Trials Network (HPTN) 052 study enrolled only 37 MSM couples, and none had linked transmission during the study. Other factors that could limit the effectiveness of a treatment-as-prevention approach for MSM are the possibility of lower antiretroviral efficacy for transmission during anal sex than during vaginal sex, the potential for a larger proportion of infections to occur from recent (untreated) infection and from younger persons (for whom treatment is less likely), and the possibility of increased risk practices among HIV-infected MSM (as evidenced by increased sexually transmitted infection rates in this population). Beyrer's group has done stochastic modeling that suggests that biomedical and behavioral interventions could have synergistic effects in reducing the HIV epidemic, eg, antiretroviral therapy for HIV seropositive men, a targeted use of PrEP for high-risk HIV seronegative men, and modest reductions in behavioral risk. He ended his presentation with a call to action to address the global MSM epidemic through collection of additional data, dissemination of known effective interventions including provision of condoms and lubricant, and a focus on reducing stigma and increasing access to prevention and treatment services for young, minority, and stigmatized communities.

Session 29 was a themed discussion on HIV prevalence and risk factors among MSM in developing countries. Hakim presented data on 601 MSM recruited using respondent-driven sampling from October 2011 through February 2012 in Abidjan, Cote d'Ivoire (Abstract 1021). Although HIV prevalence in the adult population in this city is 3.5%, HIV prevalence in the recruited sample of MSM was 18%, 86% of whom were unaware that they were HIV seropositive. Only 37% of the cohort had ever received an HIV test. Although approximately one-third of participants reported using condoms consistently with anal sex, only 10% of the total population used both condoms and condom-compatible lubricants, an important adjunct to condom use with anal sex in order to decrease the risk of condom breakage. Independent risk factors for HIV infection included more than 1 male sex partner in the prior 12 months (aOR for 2 partners, 1.8; aOR for 3 or more partners, 3.2), receptive anal sex in the prior 12 months (aOR, 4.9), self-perceived risk of infection (aOR, 4.0), and not having received an HIV test result at last test (aOR, 4.9). Aberle-Grasse presented data from 4 respondent-driven sampling surveys conducted from April through November 2011 in 4 cities in Ghana (Abstract 1022). Although the national HIV prevalence among the general adult population is 1.5%, prevalence in MSM in these 4 sites ranged from 4.7% to 34.3%. Overall, fewer than 10% of men who tested HIV seropositive were aware of their HIV serostatus. In all 4 regions, higher HIV prevalence was associated with increased age, employed status, higher levels of income, a greater number of male sex partners in the previous 12 months, or a lower number of female sex partners during that time period. Corby presented data on male sex workers in Ho Chi Minh City, Vietnam (Abstract 1023). Of the 300 men who were recruited and provided HIV testing, 6.3% were HIV seropositive. HIV positive serostatus was associated with opiate use, an age of 26 years or older, and being a call boy. To evaluate the potential for other syndemics to affect HIV risk, the authors constructed a syndemic scale in which each of the following is assigned 1 point: present symptoms of posttraumatic stress disorder, alcohol use, amphetamine use, suicide risk, low self-esteem, and childhood sexual abuse. The investigators demonstrated a strong dose-response relationship between the number of points scored in the syndemic scale and being HIV seropositive. The studies in Session 29 demonstrate the high prevalence of HIV in developing countries among MSM and low rates of condom use, condom-compatible lubricant use, and HIV testing availability.

Disparities in HIV Infection in the United States

Several presentations focused on MSM in the United States, the group accounting for 63% of all new HIV diagnoses in the nation in 2010. Wejnert and colleagues compared data from the 2008 and 2011 NHBS (National HIV Behavioral Surveillance System) in 20 US cities (Abstract 90). Using venue-based, time-space sampling and limiting this analysis to men aged 18 years or older with at least 1 male sex partner in the previous 12 months and a valid HIV test result, they found the prevalence of HIV infection to be similar (19% in 2008 and 18% in 2011). Prevalence was highest among black participants in both years (eg, 30% in blacks and 14% in whites in 2011). Although awareness of HIV infection among HIV seropositive men improved in all age and race/ethnicity groups between 2008 and 2011 (increasing from 56% to 66% overall), awareness of HIV serostatus was 40% lower among black MSM than among white MSM and remained lower over time. These data demonstrate the substantial improvement in awareness of HIV infection status but highlight the continued racial disparities that may be substantially contributing to the ongoing concentrated epidemic, particularly among black MSM.

Scott explored age and racial disparities in the per contact risk of HIV acquisition among more than 10,000 HIV seronegative MSM participating in 3 cohort studies from 1995 to 2003 (Abstract 91). The risk of HIV acquisition from both unprotected receptive and unprotected insertive anal sex per

episode with a known HIV seropositive partner was highest among men 18 years to 25 years old, and next highest among men 26 years to 30 years old, compared with men older than 30 years, after adjusting for other demographic variables. These estimates also trended toward being higher in black than in white MSM but did not reach statistical significance. Of interest, Latino MSM had statistically significantly higher risk of HIV acquisition for unprotected insertive anal sex with a known seropositive partner than white MSM; one possible explanation for this finding is the lower rate of circumcision among Latino men. By limiting this analysis to contacts with known HIV seropositive partners, these data suggest that higher rates of HIV infection among young MSM and MSM of color may stem from either increased susceptibility in these groups or partner characteristics (eg, higher viral load), rather than individual risk practices, as noted in the Millett meta-analysis cited earlier.

Adimora presented an overview of the epidemiology of HIV in the southern United States and discussed potential ecologic and social factors that may contribute to the disproportionate rates of HIV infections and HIV case fatality in those states (Abstract 55). The South has the highest rates of new diagnoses per 100,000 persons for both men and women, in all types of residential areas (urban, suburban, and rural). New HIV diagnoses among younger men and women (aged 13-29 years) increased substantially more rapidly from 2007 to 2010 in the South than in other US regions. Adimora highlighted the particular disparities in HIV infection rates in African Americans and MSM. Outcomes were also poorer in the South; in 2010, 9 of the 10 states with the highest AIDS case fatality rates were in the South, even after adjusting for race. Time to antiretroviral initiation after acute infection was also substantially longer in the South than in other regions.

In looking for the underlying causes of these disparities in HIV infection and outcomes in the South, Adimora used an ecosocial framework. She noted that the South has higher STI rates, higher all-cause mortality, higher poverty rates, and higher standards to qualify for Medicaid than other regions. In 2010, more than 90% of all persons on wait lists to acquire antiretroviral therapy through the AIDS Drug Assistance Program (ADAP) resided in the South, and 8 southern states are opting out of obtaining federal support to insure residents through the Patient Protection and Affordable Care Act (PPACA). Sex education is not mandated in 7 southern states; in 4 others, the mandate is for abstinence-only education. Eleven southern states still criminalize sodomy, despite the 2003 Supreme Court ruling that such laws are unconstitutional. These challenges to equitable delivery of health care, inadequate funding for infrastructure, and HIV-associated stigma may all contribute to the disparities in HIV infection and outcomes seen in the US South.

Adolescents

Young people are disproportionately affected by the HIV epidemic. At this year's CROI, a symposium on adolescents and HIV explored ethical issues in conducting prevention research in this population and highlighted challenges and opportunities in preventing HIV infections among gay or bisexual male adolescents and other young MSM and young African women (Session 35).

Philpott provided a framework for considering ethical issues in conducting HIV prevention trials in adolescents (Abstract 115). He first made the case that research in this population is justified based on the principle of distributive justice because adolescents, compared with adults, are particularly susceptible to acquiring HIV and other sexually transmitted infections, and physiologic and sociologic differences in adolescents make it difficult to extrapolate safety and efficacy results in adults to this vulnerable population. Philpott described several legal and ethical challenges in obtaining informed consent in adolescents, including poor harmonization of guidelines and laws across countries on the age of consent for research, who qualifies as a legal guardian, and who can consent if a parent or legal guardian is unavailable, which is a common problem in developing countries. Other considerations include whether the risks posed by the study are justified in adolescents, determinations on whether parental consent can be waived for research related to reproductive health, and local reporting requirements (eg, for statutory rape in some jurisdictions in the United States). As adolescents may not have fully developed cognitive and decision-making capacity, the development of age-appropriate materials and training for study staff are necessary to maximize adolescent decision making in research. Philpott recommends involvement of key stakeholders in all stages of the research process, particularly community members and regulators, to minimize risk and maximize the benefits of research conducted in adolescents.

Harper discussed drivers of the epidemic in gay and bisexual male adolescents and other young MSM (Abstract 116). In the United States, young gay and bisexual men had the greatest increase in diagnosed infections from 2005 to 2008, with the greatest increase among young black MSM. Harper presented a socioecologic model for understanding risk and resiliency in young gay and bisexual men and provided examples of factors operating at the intrapersonal, interpersonal, institutional, community, and public policy levels. An important focus is examining resiliency factors identified in gay male youth, including having positive conceptualizations of being gay or bisexual (eg, flexibility, connectedness with the gay and bisexual community) and maintaining resiliency in the face of oppression (eg, self-acceptance and acceptance by others, self-care behaviors, and rejection of stereotypes). Harper commented that a number of these socioecological factors appear to apply to young MSM in Sub-Saharan Africa. As few prevention interventions have been developed for gay and bisexual male youth, greater attention is needed in this area. To be most effective, HIV prevention programs

should be developmentally and culturally appropriate, address numerous socioecological factors, be designed in collaboration with youth and service providers, and engage cultural icons.

Delany-Moretlwe presented on drivers of HIV infection in young African women and opportunities for intervention (Abstract 117). In South Africa, HIV incidence is 10 times higher in young women than in young men and is the highest of any group in the country. Biologic and developmental changes during adolescence increase the susceptibility of young women to acquiring HIV infection. Important risk factors to consider include early sexual debut, having numerous concurrent partners and sex with older partners, alcohol use, violence, structural factors including poverty (particularly in urban settings), income inequality, and limited access to education. Early interventions focusing on behavior change at the individual level have not shown substantial impacts on behavior change or HIV incidence and suggest the need for combination prevention interventions. Delany-Moretlwe presented several examples of interventions addressing contextual and structural factors, including microfinance interventions, trainings on gender and violence, and conditional cash-transfer programs. Given the expansion of social media and mobile technology use among youth in Sub-Saharan Africa, use of mobile phones to deliver interventions, collect data, and change social norms may be a particularly promising approach.

Two posters explored prevention interventions among adolescents in South Africa. Rosenberg and colleagues (Abstract 1084) evaluated the effect of HTC on HIV acquisition in a longitudinal cohort of South African youth. In a weighted analysis adjusting for risk factors and refusal of testing, HTC was associated with lower HIV incidence (weighted hazard ratio [HR], 0.59; 95% CI, 0.45-0.78). Bekker and colleagues presented data on the safety, adherence, and efficacy of PrEP in MSM aged 18 years to 24 years in the iPrEx study, a group that comprised more than half of the study cohort (Abstract 997). Young MSM had a higher incidence of HIV acquisition in both the active and placebo arms than did older MSM. There was a trend toward lower PrEP efficacy in younger MSM, consistent with lower drug detection in this cohort (3.74 times less likely to have drug levels in plasma; $P < .001$). The investigators recommend additional research to understand the best ways to support PrEP adherence in this age group.

Understanding Risk Factors for HIV Transmission and Acquisition

Hormonal Contraception

Symposium 34 at this year's CROI focused on what is known about the relationship of hormonal contraceptives and the risk of HIV acquisition and transmission. Mauck presented an overview of the mucosal and systemic effects of different types of progestins in women (Abstract 111). She explained that medroxyprogesterone (used as depot medroxyprogesterone acetate [DMPA]) is structurally similar to progesterone, whereas norethindrone (found in the injectable contraceptive norethisterone enanthate [NET-EN]) and levonorgestrel (found in implants, intrauterine devices, and cyclic oral contraceptives) are more similar in structure to testosterone. These structural differences result in different biologic effects. For instance, the progesterone-like progestins bind strongly to glucocorticoid receptors, and the testosterone-like progestins do not. In fact, DMPA binds approximately 3 times more strongly than natural progesterone. Mauck noted that although the direct effects of this enhanced binding are not known, corticosteroids can cause an increase in HIV promoter activity, virus replication, and disease progression in HIV-infected persons. She also noted that DMPA is given in relatively high doses to last for 3 months, and that this degree of suppression of the hypothalamic-pituitary-ovarian axis leads to profound suppression of estradiol production, mimicking levels seen in postmenopausal women. These low estradiol levels, in turn, lead to vaginal epithelial thinning, potential loss of integrity of the mucosal barrier, trafficking of leukocytes into the genital tract, and a change in the microbiome leading to a rise in vaginal pH, all of which could increase susceptibility to HIV infection. Less is known about the other progestins; when estrogen is included, as in combination oral contraceptives, these potentially negative effects of the progestins may be somewhat mitigated.

Garcia-Lerma presented data on the effect of progestins in nonhuman primate (NHP) models and how their effects may influence the results of prevention trials (Abstract 112). From the mid-1990s, when Marx published data on the ability of progesterone implants to increase simian immunodeficiency virus (SIV) acquisition in NHP models, primatologists have been using DMPA to increase the likelihood of SIV infection among control animals in vaginal challenge studies. However, the doses (30 mg) of DMPA used in these challenge models are supraphysiologic, compared with the recommended dosing for women. More recently, pigtail macaques have been used, as their menstrual cycle more closely mimics those of women. Garcia-Lerma demonstrated that DMPA 3 mg (ie, doses 10 times lower than previously used) appears to have effects on the vaginal epithelium in pigtail macaques similar to those in human clinical experience, and he recommended using this as the new HIV prevention model. Dosing has to occur more frequently in this model (ie, every 5 weeks) than in women (ie, every 12 weeks) because NHPs metabolize drugs more rapidly than do women. Garcia-Lerma outlined an ambitious and important research agenda for NHP models, including (*a*) evaluating the potential impact of hormonal contraception on prevention efficacy; (*b*) assessing potential interactions between hormonal contraceptive methods and antiretroviral drug absorption and pharmacokinetics; (*c*) using hormonal contraceptives in the NHP model to identify biomarkers of risk; and (*d*) defining the impact of different doses and methods of hormonal

contraception on cell subpopulations in vaginal tissue. He also pointed out that these models may help in risk ranking of different types of hormonal contraceptives for use in populations.

Garcia-Lerma noted that questions about the interaction of hormonal contraceptives and antiretrovirals are increasingly important, as products are being developed to deliver contraception and PrEP simultaneously. His group presented 2 related posters at this year's CROI. Radzio demonstrated that DMPA affects neither the pharmacokinetics nor the efficacy of fixed-dose combination emtricitabine/tenofovir in the pigtail macaque model (Abstract 992). Dobard presented a poster demonstrating that systemic absorption of vaginal emtricitabine/tenofovir gel increases during the luteal phase of the pigtail macaque menstrual cycle and that DMPA creates a luteal-like environment during a 5-week period, effectively increasing drug absorption (Abstract 985). He hypothesized that this increased absorption of vaginal tenofovir may counteract any negative impact of DMPA on increased susceptibility.

Polis reviewed observational data on the relationship between hormonal contraception and HIV acquisition risk (Abstract 113). Data from available studies are mixed, although a systematic review of observational data meeting data quality standards found that DMPA was associated with a 1.5 to 2 times greater risk of HIV acquisition in 3 of 8 studies; the balance showed no statistically significant difference. There was no clear increase in risk for oral contraceptive users in the 7 quality studies assessing oral contraceptive use, and insufficient data on NET-EN in 3. The World Health Organization (WHO) issued the opinion from a meeting of 75 experts in January 2012 that the data were not sufficiently conclusive to change guidance about the type of contraceptive used but that all women at risk for HIV acquisition should be counseled about preventive practices. Since the meeting, 3 additional pieces of data have been published or presented. Heffron conducted sensitivity analyses on her previous meta-analysis and found no evidence that confounding accounted for the substantially increased risk of HIV acquisition among DMPA users. McCoy published a secondary data analysis of the MIRA (Methods for Improving Reproductive Health in Africa) trial that found an increased risk associated with injectable contraceptives when adjusted for study site. After adjusting for other covariates, the point estimate remained essentially unchanged but the CI broadened to include 1. Crook presented a secondary data analysis of an antimicrobial gel for the potential prevention of HIV infection at the meeting of the MDP301 RCT (Microbicides Development Programme Randomised Controlled Trial) that found the gel to have no efficacy in more than 9000 women (Abstract 28). Among the 8663 women included in the analysis, 382 seroconverted, and women using DMPA had a 36% increase in HIV acquisition compared with women not using hormonal contraception. There was no increased risk of HIV acquisition among women using NET-EN or oral contraceptives. The WHO will convene another expert panel in 2014 to review new data and revise recommendations as appropriate. Different opinions were voiced during the question and answer period about the need and appropriateness of a randomized controlled trial (RCT) to better understand the risk associated with different forms of hormonal contraception. Additional systematic reviews were presented that showed no clear association of increase in transmission or disease progression among HIV-infected women.

Smith explored the potential population-level impact of injectable hormonal contraceptives (IHCs) on overall morbidity and mortality (Abstract 114). First, she explored whether differential underreporting of condom use between hormone-users and –nonusers could account for the substantial increased risk of HIV acquisition in observational studies. She demonstrated that even with large differences in reporting of condom use between hormone-users and -nonusers, the result could only be a very modest increase in risk associated with IHCs, which is not compatible with the data found in observational studies (eg, OR, 1.2). For the estimates of the relative hazard generated from meta-analyses (eg, HR, 1.5 or greater), the only way for confounding from condom use reporting to occur would be if nonusers underreported condom use and IHC-users overreported their use, an unlikely scenario. Smith then presented modeling to explore the net population-level impact on morbidity and mortality if IHCs were eliminated and women used other or no contraception, based on background rates of nonhormonal contraception use within that country. Areas with high HIV incidence and high maternal mortality could potentially benefit from eliminating IHCs, if AIDS-related deaths currently outnumber maternal deaths; this applies mostly to South Africa. If the risk associated with IHCs is high enough (approximately a 2-fold increased risk [Abstract 113]), southern and East African countries would benefit. However, without substitution of a highly effective contraceptive for IHCs in much of the rest of the world where HIV incidence is not as high, removal of IHCs could lead to a substantial number of unplanned pregnancies, and a net increase in mortality in women. This is particularly true in Southeast Asia, where maternal mortality rates are high. McGrath presented data from the Africa Centre for Health and Population Studies at the University of KwaZulu-Natal, which has been collecting behavioral and clinical data on a population of 90,000 in the KwaZulu-Natal region of South Africa and performing HIV testing annually since 2003 (Abstract 897). She and her colleagues estimate that only 5.2% of HIV infections would be attributable to IHCs in this population, if the adjusted HR were 1.24, as estimated in some analyses. However, if the risk were as high as 1.98, as estimated in other analyses, they estimate that 18.1% of new infections could be attributed to IHC use.

These data suggest the importance of understanding the degree to which IHCs increase risk, and of increasing contraceptive choices for women. Others at this year's CROI pointed to the need for practitioners to address family

planning with female and male patients, to increase HIV testing among women of reproductive age and their partners, and to help women use contraception more effectively. Matthews presented data on 209 HIV seropositive women and 83 HIV seropositive men with recent births, whose partners were either HIV seronegative or of unknown serostatus (Abstract 895). Among this group, only 11% of women and 5% of men had planned the pregnancy, and only 32% of women and 25% of men had desired the pregnancy. Speaking to the potential role of practitioners in reducing unwanted pregnancies, they reported that only 22% of women and 12% of men had previously spoken with a health care practitioner about fertility.

McCoy presented data from a representative sample of women from 5 provinces in Zimbabwe, recruited from 9 months to 18 months postpartum (Abstract 898). Of the 8659 women in this study, 27% had not intended to get pregnant, and an additional 9% had intended to get pregnant at a future date but not at the time they became pregnant. Slightly more than half of these women were not using contraception at the time of pregnancy, and slightly fewer than half had been using contraception at least some of the time, and could be considered to have had a "contraceptive failure." Among the 12% of the women in this sample who were HIV seropositive, nearly three-quarters were unaware of their HIV infection at the time they became pregnant, and 44% reported that the pregnancy was unintended or mistimed. These data point to the important need for increased family planning discussions that would include HIV testing and selection and adherence to contraceptive method, depending on the individual's and couple's needs.

Sexually Transmitted Infections

Several studies explored the relationship of bacterial STIs and HIV transmission or acquisition risk. Desai and colleagues described the incidence of STIs among men and women attending STI clinics in England from 2008 to 2011 (Abstract 1072). Among this population, the incidence of acute STIs was statistically significantly higher among MSM (13/100 patient-years of observation) than among heterosexual men (1.65/100 patient-years) and among women (1.4/100 patient-years). MSM were also the only population in whom STI incidence rates statistically significantly increased during those years, nearly doubling. In multivariate Cox regression analyses, younger men were statistically significantly more likely than men aged 50 years or older to be diagnosed with an STI, with the increased odds ranging from a 2-fold risk among 35- to 49-year-olds, to a 4-fold risk among 15- to 24-year-olds. Among heterosexuals, the association of younger age with STI diagnosis was even more striking: 15- to 24-year-olds had a 6.6-fold increased likelihood of STI diagnosis compared with men aged 50 years or older, and 25- to 34-year-olds had a 3.7-fold increased risk. Among heterosexuals, the incidence of STIs was statistically significantly higher among white heterosexuals than black heterosexuals or other racial groups. These investigators also assessed HIV incidence among HIV seronegative MSM attending these same clinics over the same period of time and found that gonorrhea or *Chlamydia* spp. infection increased risk for HIV acquisition (adjusted HRs 2.2 and 2.0, respectively) (Abstract 1020). Refugio and colleagues presented data on 99 HIV-infected men in the US military, based in San Diego, California (Abstract 1071). Nearly a quarter of these men had asymptomatic gonorrhea or *Chlamydia* spp. infection in 1 or more locations, pointing to the importance of active STI screening among HIV seropositive persons. Golden and colleagues presented data collected through partner services provided to MSM with bacterial STI diagnoses in King County, Washington, from January 2007 through June 2012 (Abstract 1019). They found that MSM with bacterial STIs and their partners had a high prevalence of undiagnosed HIV infection (9% and 7%, respectively), pointing to the importance of HIV testing for these patients and their partners and perhaps targeting this population for PrEP and other prevention services.

Transmission Behaviors Among HIV-Infected Persons

Landovitz explored unprotected sexual practices among antiretroviral treatment–naive men and –women enrolling in ACTG (AIDS Clinical Trial Group) A5257 (Abstract 1069). Of 704 men and women who had been sexually active in the previous month and with available covariate data, the following variables were independently associated with reporting unprotected sex in the month prior to enrollment: higher number of lifetime sex partners (aOR for 21-50 partners, 1.8; aOR for >50 partners, 2.9), having numerous sex partners in the previous month (aOR, 2.7), and using stimulants in the prior month (aOR, 2.4). Factors associated with a reduced likelihood of unprotected sex in the month prior to enrollment included older age (aOR, 0.4 compared with 18-29-year-olds), Latino ethnicity (aOR, 0.5 compared with non-Hispanic whites), men having sex only with women (aOR, 0.4 compared with MSM), and having had sex only with a nonprimary partner in the past month (aOR, 0.4 compared with having sex only with a primary partner). Despite the limitation of these self-administered surveys, with substantial missing data and lack of information about partner HIV serostatus, this study does identify younger, substance-using MSM having numerous, nonprimary partners as those who may be at greatest risk for forward transmission of HIV. Patel and colleagues evaluated HIV seropositive men prescribed phosphodiesterase type 5 inhibitor drugs (typically used to treat erectile dysfunction) seen at the Albany Medical Center from 2007 to 2010 (Abstract 1073). They noted a modest but statistically significant increased risk of acquiring a sexually transmitted infection among these men compared with other HIV seropositive men, suggesting that these medications may identify men engaging in high-risk sexual practices, who could be targeted for prevention interventions. Freedman

and colleagues presented data from the 2009 national probability sample of HIV-infected adults in medical care in the United States, the Medical Monitoring Project (Abstract 1017). In this first nationally representative study of risk practices of bisexual men, they report that bisexual men reported statistically significantly higher rates of unprotected vaginal or anal sex and a greater number of sex partners than heterosexual men but lower rates of unprotected sex and fewer sex partners than MSM. They suggest that special programs be developed that target bisexual men, as they appear to be different demographically from both heterosexual men and MSM.

Social Determinants of HIV Risk

Two interesting presentations evaluated both individual- and community-level factors associated with HIV transmission or acquisition risk. Haubrich and colleagues presented data from the San Diego Center for AIDS Research Network of Integrated Clinical Systems from 2011 that included geocoding to census block group (Abstract 1076). Their analysis of a number of individual-level demographic (eg, younger age, male sex), risk (eg, substance use), and clinical variables (eg, higher nadir and current CD4+ cell count, no current mental health diagnosis) was associated with high-risk practices. Risk factors were also higher in census block groups with lower income, a greater percentage of men, higher level of education, shorter distance to care, and higher population density. Willis and colleagues presented data on individual- and community-level determinants of HIV infection among blacks in Washington, DC, in 2008 (Abstract 1075). Combining data from the Enhanced HIV Surveillance Reporting System (eHARS) with 2000 Census data and that from municipal Washington, DC, agencies, they found that poverty, lack of home ownership, and a greater number of housing vacancies were associated with higher HIV prevalence among black men and women. These analyses demonstrate the power of using census and geomapping strategies to uncover social and environmental factors associated with HIV risk, pointing to populations with the greatest need for primary and secondary prevention tools.

Prevention Strategies

Medical Male Circumcision

Medical male circumcision (MMC) was the first biomedical intervention definitively shown to reduce the risk of sexually acquired HIV infection, but a scale-up to levels that ensure maximal impact will require approaches to increase both demand and supply. In a themed discussion focused on MMC (Session 14, Abstract 1009), Kong presented data from Rakai, Uganda, the location of two MMC trials from 2004 through 2007 and where MMC has been offered free of charge since 2007. Despite more than 95% of the population understanding the benefits of MMC and knowing where MMC is offered, only 28% of the non-Muslim men aged 15 years to 49 years were circumcised by 2011, with an annual MMC rate of only 4% of eligible men per year. MMC rates were somewhat higher in men with numerous sexual partners but were lower among men who reported never using condoms in the prior year. Kacker suggested that MMC may have an even greater impact at less cost than previously published estimates, as these models generally fail to take into account the impact of MMC on reducing sexually transmitted infections (Abstract 1010). Her model suggests that previous cost estimates may underestimate cost effectiveness by 10% to 50%, and reduction in STIs could account for half of the cost savings from campaigns in the first 5 years of roll out. Hellar found that offering MMC increased screening for STIs in Tanzania (Abstract 1013), further amplifying these benefits.

Several poster presentations focused on strategies to increase demand. Plank presented data on neonatal MMC in Botswana (Abstract 1011). She found that although 93% of the 547 women approached in maternity wards from 2009 through 2010 said they wanted to have their male child circumcised, only 55% brought their child in within 28 days after birth for the procedure. Women who stated they knew that MMC could protect their child from HIV infection, those saying they were one of the decision makers about MMC for their child, and women who said they received no support from their partner were statistically significantly more likely to have their child circumcised. Women who said the father was a decision maker were statistically significantly less likely to have their child circumcised, suggesting that prenatal couples counseling should provide information and opportunity for discussion about wishes for MMC for boys. Mahler and colleagues presented data from the Iringa and Njombe regions of Tanzania from October 2009 through December 2012 (Abstract 1014). They found that outreach campaigns were more likely to bring in younger boys (aged 10-14 years), whereas use of fixed sites with ongoing services was more likely to be taken up by boys 15 years or older.

Other posters focused on strategies to minimize adverse events (AEs) associated with MMC. Chesang presented data from 2008 through 2011 in Kenya, demonstrating substantial decreases in AEs during that time period (20-fold intraoperatively and 4-fold postoperatively), suggesting that experience is an important factor in the safe provision of MMC (Abstract 1008). In that study, AE rates were low in all groups; nurses had particularly low rates, suggesting task shifting can occur safely. Kanyago reported on an RCT of the Shang ring versus forceps-guided adult MMC (Abstract 1007). Shang rings required less operative time and allowed men to return to work more quickly, and men were equally likely to be satisfied with the procedure as with forceps-guided MMC. Infection rates appeared to be substantially higher in the Shang ring group.

Two posters focused on the impact of MMC on the mucosal environment, offering potential explanations for its beneficial effects on HIV acquisition risk. Liu and colleagues presented data on the impact of MMC on the penis

microbiome (Abstract 344). Comparing baseline and 1-year coronal sulcus swabs between men undergoing MMC and those who did not, they noted a substantial decrease in anaerobic bacteria and a decrease in bacterial diversity among the men undergoing MMC. They suggest that these changes may decrease target cell recruitment or proliferation, or both, resulting in a decrease in HIV acquisition rates. Dinh and colleagues reported that in contrast with circumcised men, uncircumcised men have substantial fluctuations in the water content of epithelial cells of the foreskin, correlating with increased entry of HIV virions in an explant model (Abstract 345). These findings may help in the development of topically applied agents.

Impact of HIV Testing on HIV Incidence and Antiretroviral Therapy Uptake

Coates and colleagues presented results from Project Accept (HPTN 043), a community-randomized trial to encourage widespread HIV testing in 48 communities in Africa and Thailand (Abstract 30). Communities were randomized to community-based voluntary counseling and testing (CBVCT), an integrated strategy of community outreach and mobilization, mobile HIV testing, and posttest support services (including stigma reduction and coping-effectiveness training), or to standard clinic-based voluntary counseling and testing (SVCT) normally provided in that community. HIV incidence was evaluated at the community level (including individuals in the community who did not participate in the intervention) and was assessed in a probability sample of more than 54,000 community residents between the ages of 18 years and 32 years using a multiassay testing algorithm described previously. The project performed more than 86,000 HIV tests (69,987 in the CBVCT communities, 7636 in SVCT communities) and increased HIV testing by 45% in men ($P < .0001$) and 15% in women ($P = .01$) in the intervention versus control communities, which were substantial and statistically significant increases. In the postintervention assessment, there was a 14% reduction in HIV incidence ($P = .08$) in the CBVCT communities compared with the SVCT communities, and a 25% reduction in individuals between the ages of 25 years and 32 years. The intervention produced an almost 4-fold increase in detection of undiagnosed HIV cases and also led to a statistically significant reduction in sexual risk, particularly in HIV-infected men. There was no increase in negative effects or social harms observed in the CBVCT communities. These results indicate that a large-scale community-based program to increase HIV testing is feasible and may produce a modest reduction in HIV incidence. Coates pointed out that greater reductions in HIV incidence may be achieved by adding referral and linkage to additional services, including HIV care and early treatment, male circumcision, and PrEP.

MacPherson and colleagues presented results from a cluster-randomized trial evaluating the impact of home-based assessment and initiation of antiretroviral therapy in the context of home-based HIV self-testing in Blantyre, Malawi (Abstract 95LB). In 2012, adult residents in 14 urban neighborhoods were offered HIV self-testing by community counselors, and neighborhoods were randomly assigned to receive facility-based HIV care alone (control arm) or with optional home-based assessment and initiation of HIV care (intervention arm). Overall uptake of HIV self-testing was high (58%), and somewhat higher in the intervention arm (65% vs 53% in control arm; risk ratio [RR], 1.23; 95% CI, 0.96-1.58). The proportion of total adult residents initiating antiretroviral therapy was higher in the intervention arm than in the control arm (2.2% vs 0.7% adult residents; RR, 2.94; 95% CI, 2.10-4.12), as was disclosure of HIV test results to a community counselor (6% vs 3.3%; RR, 1.86; 95% CI, 1.16-2.97). Based on epidemiologic estimates of HIV prevalence in Blantyre, Malawi, the authors estimated that 15% of all HIV-infected adults and 46% of treatment-naive HIV-infected adults with CD4+ cell counts below 350/μL initiated antiretroviral therapy in the intervention arm, compared with 4% and 15% respectively in the control arm. These results suggest the potential for home-based self-testing for increasing HTC but also suggest the need for proactive strategies to link individuals to HIV care.

Katz and colleagues estimated the impact of replacing clinic-based HIV testing with home-based testing on HIV transmission among MSM in Seattle, Washington (Abstract 1064). Using data from a 2003 risk behavior survey, their mathematical model predicted that home-use tests may increase HIV prevalence among Seattle MSM. This increase is driven mainly by the long window period of the currently approved home-based test compared with fourth-generation and NAAT and was not completely reversed by increasing the frequency of testing. Potential delayed linkage to care also increased HIV prevalence and decreased the proportion of HIV-infected MSM on antiretroviral therapy in the model. One limitation is that this model did not account for MSM who supplement (vs replace) clinic-based testing with home-use tests. Additional research to understand how home-use tests influence HIV testing, sexual behaviors, and linkage to care is recommended.

Antiretroviral Treatment to Prevent HIV Transmission

The use of antiretroviral therapy as a strategy to reduce HIV infection rates was highlighted in several presentations at this year's conference. In 2011, the HPTN 052 study demonstrated a 96% reduction in heterosexual HIV transmission within HIV-discordant couples with early initiation of antiretroviral therapy.[2] In a plenary session on the prospect of ending the AIDS epidemic, Dabis reviewed recent data on the use of antiretroviral therapy as prevention and its potential population-level impact on reducing HIV incidence (Abstract 6). He presented data from a recently published systematic review that found the risk of sexual HIV transmission for heterosexual serodiscordant couples to be minimal

when the HIV seropositive partner was fully suppressed on antiretroviral therapy (0.0-0.14 transmissions/100 person-years; upper limit of the 95% CI, 0.31). He also presented data from a cohort study in rural KwaZulu-Natal, South Africa, where antiretroviral therapy initiation was rapidly scaled up to more than 20,000 patients between 2004 and 2011. This analysis demonstrated a substantial and statistically significant reduction in an individual's risk of HIV acquisition with increasing antiretroviral therapy coverage in the surrounding local community. For example, the risk of HIV acquisition was 38% lower for an individual living in an area with 30% to 40% antiretroviral therapy coverage than for one in an area with less than 10% antiretroviral therapy coverage. Dabis also shared data from the HIV Modelling Consortium forecasting HIV incidence in generalized epidemics over the next 20 years. In 7 different models of the South African epidemic, initiating HIV treatment at a higher threshold (CD4+ cell count < 500/μL) or in all HIV-infected individuals led to substantial reductions in HIV incidence (fewer than 5 new infections per 1000 person-years) compared with antiretroviral therapy coverage at the status quo. Several cluster-randomized trials are planned or under way in Africa and the United States to evaluate the feasibility and acceptability of antiretroviral therapy as prevention, and several of these studies will evaluate its population level impact on HIV incidence.

Several presentations highlighted the importance of addressing gaps in the "HIV care continuum" to maximize clinical benefit in HIV seropositive individuals and reduce transmission to HIV-uninfected populations. In a symposium on preventing HIV/AIDS in the United States, Greenberg presented several national and local estimates of the HIV care cascade, from HIV diagnosis, linkage to care, retention in care, initiation of antiretroviral therapy, and viral suppression (Abstract 58). Based on surveillance data from the CDC, it is estimated that only 28% of HIV-infected persons in the United States were fully suppressed in 2011. Other studies on the continuum of care have demonstrated higher viral suppression rates in some US cities (40%-44% in Los Angeles, San Francisco, and New York) and in different health delivery systems (>50% in the Veterans Administration and >60% in Kaiser Permanente). Greenberg pointed out several challenges to using the HIV cascade as a population-based public health metric, including the use of different types of databases that are not directly comparable, and different measures to calculate cascade steps. The calculation of cascade steps is also likely to underestimate the true proportion at each stage, given that there are individuals who are diagnosed but not reported, are linked or retained in care but move to other jurisdictions, or are virally suppressed but do not have viral load data available. Greenberg described modeled data indicating that optimizing viral suppression will require interventions to address gaps at each step of the cascade.

The US National HIV/AIDS Strategy has incorporated a number of cascade steps into its goals, including increasing testing, linkage to care, retention, and viral suppression. Greenberg described a case study of optimizing the HIV care cascade in Washington, DC, where data from 2005 to 2009 indicate that only 29% of HIV seropositive individuals maintained viral suppression. In response, the district launched a number of efforts to address gaps in the care continuum, including (*a*) expanding publicly funded HIV rapid testing, which has resulted in an increase in median CD4+ cell count at diagnosis, (*b*) developing linkage to care programs, including a "Red Carpet Program" in which residents who are newly diagnosed or returning to care are provided a clinic appointment within 1 to 2 business days, (*c*) implementing a "Recapture Blitz" to find and reengage clients who are lost to care, and (*d*) establishing progressive policies and programs, including achieving near universal health insurance coverage through the PPACA. These efforts appear to be improving metrics in several steps of the HIV care cascade in Washington, DC.

In the same session, del Rio made the case that the use of antiretroviral therapy for treatment and prevention adds substantial value for healthcare dollars spent (Abstract 57). He identified HIV testing as a crucial first step in engaging HIV-infected individuals in care and reducing HIV transmission, referring to data that those who are unaware of their HIV infection account for the majority of new HIV infections each year. He made several recommendations on how to optimize allocation of funds to maximize prevention benefits. These include (*a*) targeting MSM populations, who account for the greatest number of new HIV infections (61%) yet receive only 41% of government funding for prevention, and (*b*) focusing preventive efforts on high-prevalence cities. He described the ECHPP (Enhanced Comprehensive HIV Prevention Planning) project, a demonstration project focused on 12 US cities with the highest number of people living with AIDS. ECHPP incorporates a number of interventions to address gaps at various stages of the treatment cascade, including programs to increase HIV testing, linkage and retention in care, and adherence to treatment, as well as partner services and behavioral interventions. del Rio also highlighted several opportunities to maximize our prevention efforts, including the use of generics for antiretroviral therapy, which could save the United States an estimated $1 billion in healthcare costs; linking data management systems and using consistent indicators to monitor provision of services across the continuum of care; and harnessing the PPACA to capture additional funds for HIV prevention activities.

PrEP

New data from several PrEP studies were presented at this year's CROI. PrEP involves HIV-uninfected persons using antiretroviral medications to lower their risk of becoming HIV-infected. Several clinical trials to date have demonstrated the efficacy of daily oral tenofovir or of emtricitabine/tenofovir in reducing HIV acquisition in MSM

and transgender women across 4 continents,[3] and serodiscordant heterosexual couples and young heterosexual men and women in Africa.[4,5] A trial in South African women also showed a protective effect of 1% tenofovir gel when used vaginally before and after sex.[6] In July 2012, the US Food and Drug Administration approved daily oral emtricitabine/tenofovir as PrEP to prevent sexually acquired HIV infection in adults at high risk for HIV infection.

Marrazzo and colleagues presented data on the VOICE (Vaginal and Oral Interventions to Control the Epidemic) trial, a study of 5029 women at risk for HIV acquisition in South Africa, Zimbabwe, and Uganda (Abstract 26LB). Enrolled women were young, mostly unmarried, and the majority used injectable contraception. Participants were randomized to one of 5 arms: (*a*) daily oral emtricitabine/tenofovir, (*b*) daily oral tenofovir, (*c*) daily oral placebo, (*d*) daily vaginal tenofovir, or (*e*) daily vaginal placebo. The daily oral tenofovir and vaginal tenofovir arms were stopped early because the Data and Safety Monitoring Board determined that these products were safe but not effective. Overall, 312 women became HIV-infected postenrollment, resulting in an overall annual HIV incidence of 5.7 per 100 person-years. None of the study products demonstrated efficacy in reducing HIV acquisition; efficacy was -49% for oral tenofovir (HR, 1.49; 95% CI, 0.97-2.3), -4% for emtricitabine/tenofovir (HR, 1.04; 95% CI, 0.7-1.5), and 15% for tenofovir gel (HR, 0.85; 95% CI, 0.6-1.2). The products appeared safe, with serious AEs and laboratory events well balanced between the active and placebo arms. Although product return and self-reported data suggested high product adherence rates, tenofovir was detected in only 25% to 30% of tested plasma samples collected at quarterly visits, and 50% to 58% of women did not have detectable drug at any visit. Thus, actual adherence to study products was low in this trial, particularly among younger, unmarried women. HIV incidence was also highest in these groups. These negative results are consistent with findings from the FEM-PrEP (Preexposure Prophylaxis Trial for HIV Prevention among African Women) study reported in 2012, which showed a lack of efficacy of daily oral emtricitabine/tenofovir in at-risk women in Africa due in part to low adherence,[7] and support the development of long-acting PrEP delivery systems not dependent on daily product use.

New data from the iPrEx study were also presented in this session (Abstract 27). In 2010, the iPrEx trial reported a 44% reduction in HIV acquisition among MSM and transgender women provided emtricitabine/tenofovir compared with placebo, with higher levels of protection among participants who had detectable drug in their blood.[3] At CROI 2013, Grant and colleagues presented data on HIV incidence after stopping PrEP during a gap period between the blind randomized phase of iPrEx that ended in November 2010 and enrollment in the iPrEx OLE (iPrEX Open Label Extension) which occurred between June 2011 and June 2012, depending on the study site. iPrEx OLE enrolled 1529 previously HIV seronegative iPrEx participants, approximately two-thirds of the randomized cohort. Although enrollment in iPrEx OLE did not differ based on prior randomization group, older participants and those who reported higher risk practices or had drug detected in the randomized phase were more likely to enroll in iPrEx OLE. HIV incidence remained high after stopping PrEP, with 78 new HIV infections during the gap phase: 43 among those previously enrolled in the placebo arm (HIV incidence, 4.1/100 patient-years), and 35 among those in the active arm (HIV incidence, 3.3/100 patient-years). These rates were comparable to the HIV incidence rate in the placebo arm of the randomized phase (3.9/100 patient-years). In contrast, HIV incidence in the active arm of the randomized phase was 0.3 per 100 patient-years in those with higher drug levels and 3.1 per 100 patient-years in those with lower drug levels. Thus, there was no evidence of delayed seroconversion or increased HIV risk after stopping oral emtricitabine/tenofovir PrEP. Condomless receptive anal sex, younger age, and herpes simplex virus (HSV) infection were the main risk factors for HIV acquisition during the gap. The effectiveness of open label PrEP and how it affects choice of prevention strategies, adherence, and sexual practices will be evaluated in iPrEx OLE.

As PrEP adherence can be influenced by perception of HIV risk, Curran and colleagues evaluated the relationship between sexual risk practices and adherence through a 2-month, daily short-messaging service survey conducted at the Partners PrEP study site in Thika, Kenya (Abstract 1004). The Partners PrEP study previously demonstrated the efficacy of tenofovir and emtricitabine/tenofovir PrEP in serodiscordant couples in Kenya and Uganda.[4] In multivariable analyses presented in this poster presentation, those who were not having sex were statistically significantly more likely to report missing PrEP doses (aOR, 1.82; 95% CI, 1.31-2.52; $P < .001$). However, although unprotected sex was common, there was no correlation between unprotected sex and PrEP use ($P = .2$). Hosek and colleagues reported on the relationship between sexual behavior and adherence among young MSM enrolled in Project PrEPare (Adolescent Trials Network [ATN] 082), which randomized participants to receive daily emtricitabine/tenofovir, daily placebo, or no pill (Abstract 996). Among participants categorized as high-risk, 26% were nonadherent, 58% intermittently adherent, and 16% consistently adherent based on plasma tenofovir levels, compared with 67% of no-risk participants being nonadherent and none consistently adherent.

Some have hypothesized that PrEP is less efficacious in populations with higher HIV incidence. This hypothesis was evaluated in a subgroup analysis of the Partners PrEP study presented by Murname and colleagues (Abstract 1000). High-risk subgroups included participants who had partners with high plasma HIV viral loads, those in partnerships for less than 2 years, young women, and women with older male partners. PrEP was protective against HIV acquisition in all

subgroups, with efficacy between 52% and 87%. These findings suggest that prioritizing PrEP for individuals at higher risk of HIV-1 will maximize its prevention impact.

In addition to reducing HIV acquisition, tenofovir-based PrEP may also prevent other sexually transmitted viral infections. In the CAPRISA (Centre for the AIDS Programme of Research in South Africa) 004 study, 1% vaginal tenofovir gel reduced HSV-2 acquisition by 51% in South African women.[6] Celum and colleagues reported on a secondary analysis of HSV-2 acquisition among 1522 participants in the Partners PrEP study who were HIV-1 and HSV-2 seronegative at enrollment (Abstract 999). HSV-2 incidence was 6.6 per 100 person-years in the placebo arm and was reduced by 21% (95% CI, -18%-47%; P = .3) in the tenofovir arm, 35% (95% CI, 1-58; P = .05) in the emtricitabine/tenofovir arm, and 28% (95% CI, -2%-49%; P = .06) overall, suggesting that oral tenofovir–based PrEP may modestly reduce the risk of HSV-2 acquisition. Brinkman presented data on behalf of Hueft and colleagues from a retrospective study evaluating the impact of hepatitis B virus (HBV)-active antiretroviral therapy (lamivudine, emtricitabine, tenofovir) on HBV incident infections (Abstract 33). Among 2492 HIV-infected patients attending a large HIV clinic in the Netherlands, 871 were HBV-susceptible at entry, and 35 new HBV infections occurred during follow-up. Although HBV vaccination is recommended for all HBV-susceptible HIV-infected individuals, only 19% had serologic evidence of HBV vaccination during follow-up, possibly reflecting low rates of vaccination or failure to respond to vaccination, which has been reported in 40% to 76% of HIV-infected patients. The risk of acquiring HBV was statistically significantly lower in those who used HBV-active antiretroviral therapy, with tenofovir-based regimens being more protective than regimens containing only lamivudine. These findings suggest that HBV-active antiretroviral therapy may protect individuals against primary HBV infection (and can be considered HBV PrEP); the researchers recommended confirmation of their findings in prospective cohort studies.

Long-Acting Antiretroviral Agents and Delivery Systems

Given the profound relationship between PrEP adherence and efficacy, 2 presentations in Session 8 (Abstracts 24LB, 25LB) focused on evaluating investigational long-acting systems for delivering PrEP agents to help overcome obstacles related to daily product dosing. Andrew and colleagues presented data on GSK744LAP (an investigational long-acting parenteral [LAP]) in a macaque repeated low-dose intrarectal challenge model (Abstract 24LB). The LAP formulation of GSK744, a potent integrase strand-transfer inhibitor, has a half-life of 3 weeks to 7 weeks in humans and supports monthly to quarterly dosing. None of the 8 animals treated with 2 intramuscular injections of GSK744LAP 4 weeks apart (started 1 week prior to first virus exposure) became infected, compared with all 8 placebo-recipient macaques becoming infected. Future studies will determine the minimum protective dose against intrarectal challenge and evaluate this PrEP agent in female macaques. Smith and colleagues reported on a tenofovir disoproxil fumarate intravaginal ring (IVR) containing 120 mg of tenofovir in a repeated low-dose vaginal challenge model in pigtailed macaques (Abstract 25LB). The IVR was replaced every 28 days during a 4-month challenge period (16 weekly virus exposures). All 6 tenofovir IVR-treated animals remained uninfected, and 11 of 12 controls became infected. The tenofovir IVR is expected to enter a phase I clinical testing later this year.

In a themed discussion on new approaches to antiretroviral drug delivery systems, Boffito discussed the potential opportunities and challenges for long-acting agents to optimize antiretroviral delivery for both chronic HIV-infection treatment and PrEP (Abstract 511). A key challenge is that the target drug concentration in plasma or tissue required for protection for PrEP or viral suppression for HIV treatment is currently unknown. She highlighted several important drug characteristics to consider in selecting HIV PrEP agents and implications for long-acting agents. For example, to ensure safety, a lead-in period with an oral formulation that can be quickly discontinued if adverse effects develop may be warranted prior to administration of the long-acting formulation, an initial loading dose may be required to determine optimal dosing, and oral drug intake may also be needed to cover the period of low drug exposure after therapy is stopped (eg, the "pharmacokinetic tail") to minimize the potential for emergence of viral resistance. Other considerations include whether data on drug–drug interactions from studies of the oral formulation apply to long-acting formulations of the drug, given that first pass elimination is bypassed with injectable formulations and given the need for studies to evaluate the acceptability of long-acting formulations globally. She presented data from a recently completed study in the United Kingdom of TMC278LA, an investigational long-acting formulation of the nonnucleoside analogue reverse transcriptase inhibitior rilpivirine. In a pharmacokinetic study of 60 HIV seronegative women, there was evidence of dose proportionality of TMC278LA, with peak concentrations in plasma and cervicovaginal fluid above a proposed target concentration with 600 mg and 1200 mg dosing. In addition, substantial HIV inhibition was observed in an ex vivo model using cervical lavage samples, particularly at the 1200 mg dose. These studies suggest that future strategies to improve adherence to antiretrovirals, both for treatment and prevention, could have a profound impact on reducing new HIV infections and getting us closer to an "AIDS-free generation."

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A list of all cited abstracts appears on pages 90-95 and is available online at www.iasusa.com.

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