The Epidemiology of New HIV Infections and Interventions to Limit HIV Transmission

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After the disappointing news reported at the 2008 (15th) Conference on Retroviruses and Opportunistic Infections regarding HIV vaccines, microbicides, and herpes virus suppression trials, the 16th conference this year brought welcome advances in the HIV prevention field. In particular, substantial progress is being made in approaches to preexposure prophylaxis in preclinical and clinical trials, and an efficacy trial of a vaginal microbicide appeared to provide women in Africa and the United States with modest protection against HIV acquisition. This review covers presentations on the epidemiology of HIV infection in specific global populations, strategies to improve the uptake of HIV testing, lessons from previous negative prevention trials, and progress in the development of new biomedical interventions.

HIV-Affected Populations

We are now nearly 3 decades into the HIV epidemic, and it is estimated that there were 2.7 million new HIV infections worldwide in 2008.[1] Several presentations at this year's conference highlighted the diverse nature of the epidemic, both in specific risk groups and in specific geographic regions.

Men Who Have Sex with Men

There was renewed recognition of the global nature of the HIV epidemic in men who have sex with men (MSM). Caceres pointed out that, despite limited data, approximately 7% of the populations of men in Latin America and Asia report having had sex with men in the prior year, and much higher rates globally report ever having had sex with men (Abstract 13). Conversely, more than half of MSM globally also reported having sex with women in the prior year, with rates especially high in Africa and Asia, and considerably lower (19%) in Latin America. Two posters at the conference (Abstract 1028 on data from Kenya, Abstract 1029 on data from Senegal) also found more than half of the MSM sampled in these regions reported having sex with both men and women, raising concerns about spread of infection from MSM into female populations. This speaks to the global need to move our thinking beyond risk-group categories and to ask all patients about sexual practices of all types.

Caceres also reviewed data from Baral and colleagues reporting on the high HIV prevalence in MSM compared with heterosexual populations in many regions of the world (odds ratio [OR], 33.3 in Latin America, 18.7 in Asia, and 3.8 in Africa).[2] Van Griensven and colleagues provided longitudinal data on an MSM cohort in Thailand with an HIV incidence rate of 5.7 per 100 person-years over 3 years of follow-up despite ongoing risk-reduction counseling, highlighting the severity of the epidemic in MSM populations (Abstract 1037b).

Caceres addressed some of the structural drivers of the MSM epidemic that limit access to prevention services. His group's survey of antisodomy laws worldwide found that highly prohibitive laws (with punishments of prolonged incarceration or death) still exist in 18 countries in Africa, 14 in East and Southeast Asia, 11 in the Caribbean, and 6 in the Middle East and North Africa. Caceres called for a 3-pronged approach to addressing the MSM epidemic, including collection of more data with better outreach to MSM populations globally, implementation of human rights protections, and an increase in access to prevention services.

There were several cross-sectional studies of MSM in resource-constrained settings. Solomon and colleagues estimated that there are 2.35 million MSM in India but that this population remains largely hidden, in part because of cultural "requirements" that young people marry, and because of Indian law forbidding same-sex relationships (Abstract 171LB). In their respondent-driven sample of 721 MSM, in which initial participants were primarily sex workers, HIV prevalence was 9%, and seropositivity was independently associated with marriage (adjusted OR [AOR], 1.91), herpes simplex virus 2 (HSV-2) seropositivity (AOR, 3.69), and having more than 50 sex partners in the past year (AOR, 3.81). One-third of the men were married, and two-thirds of married men reported having engaged in unprotected vaginal sex with at least 1 female partner in the prior year.

Beyrer and colleagues presented data on the MSM epidemic in Malawi, Namibia, and Botswana (Abstract 172). Overall prevalence was 17% in this sample of 537 men, with men older than 25 years having a 4-fold increased rate of HIV seropositivity (95% CI, 2–8), after adjusting for other demographic and risk variables. More than half of the men had had sex with both men and women in the previous 6 months, and 16% reported concurrent relationships with both men and women. Of note, being in concurrent bisexual relationships was statistically significantly associated with always using condoms with regular sex partners in this sample (AOR, 4.8; 95% CI, 2.8–8.2), which may reduce the risk of transmission to female partners. Stigma and discrimination were high in these populations, with 18% to 20% of men in the 3 coun-

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tries afraid to seek health services, and 18% to 26% reporting that they had been blackmailed because of their sexuality. Being blackmailed was statistically significantly associated with disclosing their same-sex behavior to family members or to a clinic or health care worker, and with not having had an HIV test in the previous 6 months. This report provides concrete evidence of how stigma, failure to protect confidentiality in clinical settings, and laws against homosexuality may directly affect the receipt of health care services.

HIV Infections in Diverse Geographic Regions

Other presentations focused on the diverse epidemics within specific geographic locations. For example, Session 16 focused on the global nature of the epidemic as told through the epidemiology and public health response in 4 cities in different regions of the world: Washington, DC (Abstract 57); Capetown, South Africa (Abstract 58); Rio de Janeiro, Brazil (Abstract 59); and Almaty, Kazakhstan (Abstract 60). Hader presented data on the diverse HIV epidemic in Washington, DC, where overall prevalence is 3%, rates are high in nearly all wards in the city, and new infections represent all high-risk-behavior groups (25% MSM, 15% injection drug users [IDU], > 35% heterosexual) (Abstract 57). Rates are particularly high among black men (prevalence, 6.5%) and persons aged 40 years to 49 years (prevalence, 7.2%) and 50 years to 59 years (prevalence, 5.2%). Numerous city agencies have begun implementing a broad array of prevention programs, with early indicators of success in an increased rate of HIV testing, higher CD4+ counts at initial presentation, increased rates of school-based testing for sexually transmitted diseases (STDs), and decreased STD prevalence in several schools.

Gray and McIntyre gave a broad overview of the evolution of the AIDS epidemic in South Africa in this year's N'Galy-Mann Lecture (Abstract 18). Well after HIV was recognized to cause AIDS, the epidemic continued unchecked in South Africa, growing from 160,000 infections in 1987 to 5.7 million in 2007. South Africa is home to 17% of HIV infections worldwide, while making up only 0.7% of the world's population. Gray and McIntyre reiterated Jonathan Mann's statement to the United Nations General Assembly in 1987 that the "social, cultural, economic and political reaction to AIDS [is] as central to the global AIDS challenge as the disease itself." Their informative and moving account of the South African AIDS story can be viewed on the conference Web site at www.retroconference.org.

Coetzee focused on the high rates of sexual concurrency fueling the HIV epidemic in Capetown, South Africa (Abstract 58). HIV prevalence is twice as high among persons living in "informal" (nonpermanent) housing as among persons living in standard housing. He also focused on efforts to roll out antiretroviral therapy and prevention of mother-to-child transmission (PMTCT), which was particularly challenging under the previous South African government that denied that HIV infection caused AIDS. Substantial progress is being made in these areas, and there is now government support for these programs.

El-Bassel discussed the rising epidemic in 2 cities in Khazakstan, the largest country in Central Asia (Abstract 60). Here, the epidemic largely affects IDUs, and the epidemic may be fueled by external forces (eg, drug-trafficking patterns in Asia) and internal policies in the treatment of IDUs (eg, lack of needle-exchange programs, criminalization of drug use, lack of harm-reduction programs). HIV prevalence has increased dramatically since the early 2000s, pointing to the need to act quickly to prevent a much more substantial epidemic in this region of the world.

Uptake and Impact of HIV Testing

HIV prevention and treatment both begin with knowledge of HIV serostatus. A number of presentations focused on the continuing problem of undiagnosed HIV infection in the United States and globally. Campsmith and colleagues at the US Centers for Disease Control and Prevention reported that as of the end of 2006, more than 1 million persons at least 13 years old were infected in the United States, and that 21% of these persons were unaware of their HIV infection (Abstract 1036). More than half of these undiagnosed infections occurred in MSM. The number of undiagnosed infections was highest among blacks (113,100), followed by whites (72,000), and Hispanics (41,900); by age, 35- to 44-year-olds (76,100) had the highest number. The proportion of all HIV-infected persons who remained undiagnosed was highest among MSM (23.5%) and heterosexual men engaging in high-risk behaviors (26.7%), although the absolute number of undiagnosed MSM was more than 4-fold higher than that of undiagnosed heterosexual men (125,900 vs 27,900, respectively). Of note, the proportion of undiagnosed HIV infections was lowest among men and women IDUs, possibly the result of the HIV testing and prevention services offered through drug-treatment programs, medical care, and syringe-exchange programs.

Chen and colleagues reported on data from administrative claims from 8 US health plans covering 7.8 million insured persons in the United States (Abstract 1044). After excluding persons with known HIV infection, organ-transplant recipients, hospice patients, and those receiving immunosuppressive medications, they found nearly 7500 continuously insured patients with new diagnoses of a potential AIDS-defining event. Overall, 4.3% had received an HIV antibody test, CD4+ count determination, or HIV viral load measure within 150 days before receiving their potential AIDS-defining diagnosis through 60 days after the diagnosis.

It has been estimated that worldwide, only 10% of persons at risk of HIV infection receive HIV testing (Abstract 12). Mohammed and colleagues reported that 63.5% of persons included in a nationally representative survey in Kenya had never received an HIV antibody test (Abstract 137LB). April and colleagues reported that testing rates among the population living near Capetown, South Africa, had increased

substantially from approximately 4% in 2001 to 20% in 2006, although median CD4+ count at the time of diagnosis did not change over that time period (Abstract 1048).

Two presentations documented progress in early HIV testing in some populations. Golden and colleagues reported on the proportion of persons newly diagnosed with HIV through a public health program in Seattle, Washington, from 1995 to 2008 (Abstract 1043). The proportion of newly diagnosed MSM reporting never previously receiving an HIV test declined substantially (from 25% in 1995–1996 to 5% in 2007–2008; $P < .0001$), although no statistically significant improvements were seen in other groups engaging in high-risk behavior (average, 40%). Median CD4+ count at diagnosis improved for both groups (to 487 for MSM, 407 for non-MSM). Bezemer and colleagues also reported reduced time from infection to diagnosis among MSM in the Netherlands (now 2.47 years) (Abstract 1019). Although they estimate that only 20% of HIV-infected men were unaware of their infection at the beginning of 2007, their models indicate that these men account for 89% of new infections, pointing to the importance of locating and frequently testing within this population.

Strategies to Improve HIV Testing Rates

Heffelfinger and colleagues reported on acceptance and completion of opt-out testing among nearly 50,000 emergency department visits in Alameda County (California) Medical Center from August 2007 to March 2008 (Abstract 1038). Only 36.3% of eligible patients accepted testing; younger patients, women, black patients, and patients not acutely ill were more likely to accept screening. Of those who accepted screening, only 62% actually had testing performed; predictors of receiving a test were older age and lack of acute illness. Walensky and colleagues reported results of a randomized controlled trial of counselor- versus emergency department provider–initiated HIV counseling and testing (Abstract 1039). Offer rates were higher in the counselor group (57% vs 27%; $P < .0001$), and provider rates declined statistically significantly over time. Christopoulos and colleagues reported on a program providing 1 dedicated rapid test counselor each to 2 emergency departments during business hours on Mondays through Fridays (Abstract 1040). Of nearly 70,000 emergency department visits, just over 2500 persons underwent rapid HIV testing, which yielded 24 new HIV diagnoses. In these studies, dedicated counselors increased testing rates, although only for a small fraction of the total population of patients seen in emergency departments.

Two presentations described home-based testing programs in Uganda. Lugada and colleagues made the case that family members of HIV-infected persons are among those with the highest HIV prevalence, with more than half of spouses and 5% of the children of HIV-infected persons also found to be HIV-seropositive (Abstract 138). They report on the first direct comparison of home- versus clinic-based testing for family members of HIV-infected persons in Jinja, Uganda. HIV testing rates were higher among home- than clinic-based testers (56% vs 11%, respectively; AOR, 10.4), and the authors estimate that they identified 56% of HIV-infected household members through the home-based group compared with 27% in the clinic-based group.

Gupta also reported on the impact of a door-to-door voluntary counseling and testing program in the Bushenyi district, Uganda, from 2005 to 2007, by comparing responses in a population-based, district-wide survey conducted before and after the intervention (Abstract 139). The proportion of persons who reported ever having been tested increased (from 20% to 63%; $P < .001$), as did the proportion disclosing serostatus to partners (72% to 81%, respectively; $P = .04$). Several measures of stigma also statistically significantly decreased. Self-reported condom use at last intercourse did not change overall (15.5% to 13.8%, respectively), although there was a statistically significant increase in condom use in the small number of HIV-infected men surveyed (1/9 to 21/46, respectively; $P = .02$) and no statistically significant change in women (18.6% to 27.6%, respectively; $P = .4$). These results point to the need to find successful behavior-change strategies that can be incorporated into home-based voluntary counseling and testing programs, including for HIV-uninfected persons.

There is interest in identifying persons with primary HIV infection, to interrupt transmission chains and refer newly infected persons into care. A number of posters at this year's conference reported on the sensitivity of fourth-generation assays that measure both p24 antigen and IgM and IgG antibodies in identifying newly infected individuals (Abstracts 988–992, Abstract 997). These assays identified 62% to 98% of persons with primary infection in these studies, substantially better than available third-generation assays, and nearly as sensitive as pooled nucleic acid testing. Most of the specimens that were nonreactive on these combination assays came from patients who had low levels of plasma HIV RNA. The new HIV antigen-antibody combination assay (Abbott ARCHITECT Ag/Ab Combo Assay; Abbott Park, IL) used in most of these reports is not currently sold in the United States and is not a point-of-care test. Although this strategy can detect early infection, it does not differentiate primary from chronic infection, so in situations for which it is important to differentiate primary from chronic infection, other strategies must be used.

Lessons from Negative Trials

The past several years brought disappointing results from efficacy trials of HIV vaccines, HSV-2 suppression, microbicides, and behavioral trials. Symposium 31 focused on lessons from these negative trials, differentiating failed trials (in which study design, selection of study population, or adherence to protocols fail to answer the research question) from trials that are successfully completed but yield negative results. The latter type are part of the scientific process of hypothesis testing and may provide important insights

that guide their respective fields. Buve quoted Popper, who said, "… science is one of the very few human activities—perhaps the only one—in which errors are systematically criticized and fairly often, in time, corrected. This is why we can say that, in science, we often learn from our mistakes, and why we can speak clearly and sensibly about making progress there."

Hunter presented a summary of results from the Step trial (HIV Vaccine Trials Network 502/Merck 023 study) of replication-incompetent adenovirus serotype 5 (Ad5) *gag/pol/nef* vaccine (Abstract 119). Initial results were presented at the 2008 (15th) conference and published last year.[3,4] Hunter made several points about lessons learned. First, he noted that despite robust immune responses among vaccinees, the vaccine failed to prevent HIV infection or control early plasma viral load. He speculated that this indicates that the magnitude, breadth, or quality of the immune response must be improved to provide protection with other T-cell-based vaccines. He noted the success of the test-of-concept trial design in achieving a definitive result relatively quickly (< 3 years). He also stated that the apparent increased acquisition of infection in subgroups of male participants is leading to new insights into the role of preexisting vector-based immunity in vaccine effects, and he called for additional effort in understanding this relationship. He noted that the trial provided insight into development of appropriate nonhuman primate models, stating that simian-human immunodeficiency virus (SHIV) is not an adequate challenge model for T-cell-based vaccines, but that $SIV_{mac239/251}$ challenge studies do indicate that T-cell-based vaccines can control viral replication in the absence of broadly neutralizing antibody, and that T-cell-based vaccines should continue to be pursued.

Hunter also showed data indicating sharp declines in risk behavior in both vaccine and placebo recipients, raising the issue of indirect benefit to participants in clinical trials. He closed with a discussion of unanswered questions in developing HIV vaccines, describing the need to develop and validate immunologic assays that correlate with immune protection, proposing a potential role of systems biology in differentiating protective and nonfunctional immune responses, and speculating about a potential role of nonneutralizing antibody in protection. Hunter also called for close coordination of clinical trials and nonhuman primate studies to ensure maximum relevance in developing an effective HIV vaccine.

Whitley summarized data from 2 trials of long-term acyclovir therapy to prevent HIV acquisition among HSV-2-infected women and men (Abstract 120).[5,6] After summarizing the major findings from the trials, Whitley pointed to several lessons from these trials. Given the substantial epidemiologic data linking HSV-2 infection with an increased risk of HIV acquisition, he speculated about several possible explanations for the lack of efficacy in these 2 well-conducted trials. He suggested that HSV-2 reactivates more frequently than previously appreciated and that more potent drugs may be required. He pointed to the potential need to use drugs that also control the local inflammatory response and reduce CD4 and CD8 activation, which may contribute to the increased susceptibility among HSV-2-infected persons. He also pointed to the importance of developing an effective HSV-2 vaccine to prevent initial acquisition of this STD. In the question-and-answer session, he reminded the audience that data will soon be available from a separate randomized controlled trial of acyclovir suppression among HIV-infected persons, a potential method to prevent HIV transmission to their HIV-uninfected partners.

Buve provided an overview of challenges in the topical microbicide field in the past several years and the insights gained from these trials (Abstract 121). Early trials overestimated HIV incidence in trial populations, particularly in populations receiving ongoing risk-reduction counseling. Use of nonoxynol-9 led to increased risk of HIV acquisition, and these results clarified that traditional safety measures of microbicide effects (eg, symptoms, colposcopy) may not correlate with in vitro studies on epithelial integrity and permeability. Buve also pointed out that nonhuman primate models of the efficacy of cellulose sulfate against SHIV challenge also failed to translate into actual protection in human efficacy trials, suggesting additional work is needed in developing animal models that predict clinical results. She noted the challenges in measuring product use (eg, self-report may not correlate well with objective measures of applicator use) and emphasized the importance of using accurate adherence measures in understanding microbicide trial results. She also pointed to the challenges in maximizing adherence and the need to study microbicide effects in pregnant women, to maximize their ultimate utility. Finally, she discussed the lessons being learned from the HIV Prevention Trials Network (HPTN) 035 microbicide trial, described further below.

Koblin described a recent meta-analysis that indicates that behavioral interventions reduce HIV-related risk behavior and sexually transmitted infections,[7] although their impact on HIV incidence has not been studied extensively (Abstract 122). She highlighted several challenges in this field, including the likely substantial behavioral intervention provided even to control participants, which may undermine measurement of effects in the intervention groups. Studies also suggest that maximal benefit from behavioral interventions may occur in the first year, so that trials of shorter duration may report beneficial effects, whereas trials of longer duration will fail to see sustained improvement.

Koblin differentiated between statistically significant reductions in self-reported risk and public health benefit. For example, data from the EXPLORE study (HPTN 015) in MSM in the United States found modest but statistically significant reductions in self-reported risk but no statistically significant reduction in HIV incidence. Initial evaluation of these data suggested that there was no correlation between sites with larger reductions in risk practices and those measuring more substantial declines in HIV incidence in the intervention group. However, additional analysis, in-

cluding use of multiple measures of risk to create a composite score and use of continuous rather than dichotomous variables, did uncover a high degree of correlation between those sites reporting statistically significant reductions in risk practices in the intervention group and statistically significant reductions in HIV incidence in intervention versus control participants. This points to the complexity not only of measuring HIV-related risk, but also of analyzing the data to understand intervention effects. Koblin also noted the wealth of ancillary studies supported by these clinical trials that address a range of important HIV prevention questions.

Progress in Biomedical Interventions

Microbicides

Karim and colleagues reported potentially promising results from an efficacy trial of 2 investigational microbicides (BufferGel, ReProtect, Baltimore, MD; and 0.5% PRO 2000/5 gel, Indevus Pharmaceuticals, Lexington, MA) when used vaginally by women at risk of sexually acquired HIV infection (Abstract 48LB). BufferGel was hypothesized to provide protection through its buffering effects on vaginal pH, and PRO 2000/5 (a polyanionic polymer) through its binding to the variable loop of HIV, thereby blocking attachment. In this 4-group test-of-concept trial, 3087 HIV-uninfected women in Malawi, South Africa, Zambia, Zimbabwe, and the United States were assigned randomly to receive either active product, a placebo gel, or no microbicide. Retention was greater than 90% in all groups in the trial; adherence to gel use was relatively high (81% overall); and adverse events were comparable between all study groups.

No efficacy was seen with the BufferGel product. There was a 30% reduction in infections in the PRO 2000/5 group compared with the placebo and no-gel groups, although neither comparison achieved statistical significance. However, subgroup analyses lent support to the possibility that PRO 2000/5 provided protection against HIV infection. Participants were divided into high-adherence and low-adherence gel users and high-adherence and low-adherence condom users, based on median use of these products. Among high-adherence gel-using women, those receiving PRO 2000/5 were 44% less likely to acquire HIV than were placebo recipients. Among the subgroup of high-adherence gel users and low-adherence condom users (the subgroup most likely to benefit from an efficacious microbicide), HIV incidence was reduced by 78% in PRO 2000/5 recipients compared with placebo recipients.

Karim was careful to point out that these exploratory analyses are not definitive and that potential for protection must be corroborated through additional clinical trials. A Microbicides Development Programme (MDP) trial of PRO 2000 (MDP 301) is currently under way that was designed to evaluate high-dose (2%) and low-dose (0.5%) PRO 2000 in women at high risk in South Africa, Tanzania, Uganda, and Zambia. Based on an interim analysis in February 2008, the high-dose group was stopped because of futility. However, the trial's independent Data and Safety Monitoring Board has recommended continuing follow-up of the low-dose group (identical to the product used in the HPTN 035 trial), and this follow-up is due to be complete in August 2009, with results released publicly by the end of 2009.

A themed poster discussion session focused on novel microbicide gels and rings (Session 41). Progress has been made in sustained delivery of antiretroviral drugs from vaginal rings, an approach that would not require coitally dependent administration (Abstracts 1065, 1069, 1070). Investigators are also beginning to explore methods for studying the safety (Abstract 1066) and potential efficacy (Abstract 1067) of topical microbicides for rectal use, which will be important both for heterosexual and MSM populations.

Preexposure Prophylaxis

Hillier provided an overview of the field of preexposure prophylaxis (PrEP), the use of antiretroviral medications in HIV-uninfected persons before and during periods of risk to prevent HIV acquisition (Abstract 73). She reviewed the 8 trials currently under way or soon to be launched that will include more than 20,000 participants worldwide. These trials each address somewhat different research questions, including PrEP efficacy in different populations (women engaging in high-risk behaviors, MSM, IDUs, serodiscordant couples), different regimens (tenofovir or combined tenofovir/emtricitabine), different routes of administration (oral or vaginal), and different dosing regimens (continuous or coitally dependent). The first results from the efficacy trials are expected in 2010, and results will be compared within and across trials. Additional work is being done to plan alternative strategies (eg, intermittent dosing, methods for sustained systemic or topical delivery). Further work is needed to enhance adherence in these trials and to consider how to scale up access to any particular strategy, should it prove efficacious.

Two nonhuman primate studies provided support for topical and intermittent dosing regimens. Dobard and colleagues reported on the success of a topical gel containing tenofovir or tenofovir/emtricitabine in protection against low-dose SHIV intravaginal challenge (Abstract 46). Gel was applied 30 minutes before challenge, twice weekly. Ten of 11 control animals were infected after a median of 4 challenges, but none of 6 animals receiving tenofovir gel and none of 6 animals receiving tenofovir/emtricabine gel became infected after 20 challenges. Systemic levels of the study drug were quite low, with absorption less than 0.03% of either drug.

Garcia-Lerma and colleagues reported on protection against rectal challenge with intermittent pre- and postexposure tenofovir/emtricitabine dosing (Abstract 47). In these experiments, animals were each given 2 oral doses of tenofovir/emtricitabine by gastric feeding tube at levels comparable to human dosing. Weekly rectal challenges used 10 50% tissue culture infectious doses of an R5-tropic SHIV strain to more closely mirror human exposures. Two groups of animals re-

ceived study drug 1 or 3 days before exposure followed by an additional dose 2 hours postexposure. These were the most successfully protected, with 5 of 6 animals protected in each of these 2 groups. Moderate protection was seen when the initial dose was earlier (7 days before) followed by the second dose 2 hours later (4/6 animals protected), or when dosing was given around the time of exposure (first dose 2 hours before or 2 hours after exposure) followed by a dose at 1 day postexposure (3/6 animals protected in each of these 2 groups). The authors stated the postexposure dose was needed to improve the protection seen in earlier experiments that used only a single preexposure dose. Protection did not seem to be associated with plasma drug levels or area under the curve, and no drug resistance was apparent in infected animals. The relevance of these animal models for predicting human efficacy is not yet known.

Treatment as Prevention

There has been substantial focus on the potential role that treating HIV-infected persons may play in reducing HIV transmission globally, including a recent publication suggesting that widespread roll-out of testing and treatment globally could substantially reduce new infections and provide cost savings within several decades.[8] Fraser focused on several questions related to the effect of HIV treatment on transmission (Abstract 14). The model used in the paper by Granich and colleagues[8] presumes a 99% reduction in transmission, although this effectiveness level has yet to be measured directly. In Fraser's models, lower levels of effectiveness would substantially diminish the effect of this approach, and levels of 80% would actually lead to a paradoxical increase in HIV transmission rates as HIV prevalence rises.

He also pointed out that HIV testing strategies may need to differ for different types of epidemics. For example, in generalized epidemics fueled by serial monogamy, almost all transmissions occur from persons with chronic HIV infection, so standard testing strategies would reach the appropriate populations. However, in subgroups of persons with numerous concurrent sexual partners, approximately one-third of new infections may come from persons with acute HIV infection, suggesting new strategies would be needed to reach and test these persons frequently using the appropriate diagnostic tests. Fraser called for more direct data to assess the impact of treatment on HIV transmission (such as data on serodiscordant couples, described below, and data from the HPTN 052 randomized controlled trial of the effect of treatment on transmission to uninfected partners). Fraser also encouraged more investigators to conduct mathematical models of the public health impact of various approaches to testing and treatment.

Two groups reported on HIV transmission rates in observational studies of serodiscordant heterosexual couples. Reynolds and colleagues (Abstract 52a) reported on data from 205 serodiscordant couples in Rakai, Uganda, observed from 2004 to 2007, 20 of whom initiated antiretroviral therapy. There were 34 transmissions in 396.4 couple-years of follow-up among couples not receiving antiretroviral therapy (incidence, 8.6/100 couple-years) versus no transmissions in the 24.6 couple-years of follow-up among treated couples. These are promising data, albeit on a relatively small group of serodiscordant couples.

Sullivan and colleagues reported on a larger group of serodiscordant couples from Lusaka, Zambia, and Kigali, Rwanda (Abstract 52bLB). In their study of 2993 serodiscordant couples, HIV incidence was 3.4 per 100 person-years among untreated couples and 0.7 per 100 person-years among treated couples, indicating a 79% reduction in transmission risk (95% CI, 41%–92%). Although they collected only limited behavioral risk data, there appeared to be a reduction in risk association with antiretroviral therapy, suggesting no behavioral disinhibition among treated couples. However, Smith and colleagues reported data on 1833 persons surveyed in a population-based, cross-sectional study in Kisumu, Kenya (Abstract 1017). Among this largely untreated sample, the belief that antiretroviral therapy cures HIV was associated with higher-risk sexual activity, particularly among younger participants, pointing to the need for broad education within communities, and not just directed at those receiving antiretroviral therapy.

Although these presentations point to the likely beneficial impact of treatment on risk of transmission to uninfected partners, 2 presentations focused on the potential for ongoing viral shedding in semen despite antiretroviral therapy. Sheth and colleagues used the branch DNA assay to measure virus levels in blood and semen (Abstract 50). Of 25 treatment-naive persons initiating antiretroviral therapy, suppression of virus in blood preceded suppression in semen. Overall, there was virus detectable in semen but not in blood at least once in 48% of study participants, with HIV RNA levels of 6600 copies/mL to 16,000 copies/mL in 3 of these 12 participants. All isolated virus was wild type. The investigators tested the individual with the highest semen viral load for infectivity in vitro and found this virus was infectious. They also found isolated semen shedding in 4 (31%) of 13 patients with long-term antiretroviral therapy suppression of plasma viremia (minimum, 4 years; median, 82 months). Marcelin and colleagues reported on 145 HIV-infected men seen in an assisted reproductive technology program (Abstract 51). In 264 paired semen and blood specimens tested using an in vitro nucleic acid amplification HIV-1 assay, 5% had low levels of seminal HIV RNA despite undetectable blood levels, most of whom were RNA positive at several time points.

A themed poster discussion session on genital tract HIV shedding in women confirmed the possibility of genital tract shedding in women receiving antiretroviral therapy, as well as factors associated with increased shedding (Session 11). Cu-Uvin and colleagues pointed out that in women switching antiretroviral therapy because of failed regimens, rebound may occur, but one-third of women with HIV RNA rebound had virus that was first detectable in the genital tract, rather than plasma (Abstract 973). Coleman and colleagues reported that cytomegalovirus and HSV-2 reactivation lead to increased HIV shedding among Kenyan women (Abstract 970). Graham and colleagues reported that genital tract shedding decreased by more than 2 $\log_{10}$ copies/swab

on average when 98 Kenyan women initiated antiretroviral therapy, although shedding continued to be detected in cervical samples from 33% of women and in vaginal fluid from 51% of women (Abstract 971). Poorer adherence and use of hormonal contraception with depot medroxyprogesterone acetate were associated with higher levels of genital tract shedding. Although there is no consensus on the quantitative or qualitative measures of genital tract HIV RNA levels that are likely to lead to HIV transmission events, these studies suggest that viral suppression in blood does not guarantee viral suppression in genital secretions.

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