

HIV Epidemiology, Testing Strategies, and Prevention Interventions

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As the HIV epidemic has matured, a substantial proportion of new infections worldwide may be occurring within stable partnerships. Within the United States, blacks are disproportionately affected by HIV disease, and the drivers of this epidemic involve behavioral and structural factors. The 17th Conference on Retroviruses and Opportunistic Infections highlighted new insights into drivers of HIV infection in both of these populations. The conference also focused on new strategies to track the epidemic and to prevent HIV infection, including scale-up of HIV testing and of treatment of HIV-seropositive persons, and the use of oral and topical antiretroviral drugs to prevent HIV acquisition among HIV-uninfected persons.

Populations With High Incidence Rates of HIV Infection

Serodiscordant Couples

In session 3, Bunnell highlighted the high rates of HIV transmission globally that occur in stable partnerships (Abstract 14). For example, it is estimated that 74% of new infections in Uganda occur in married or recently married persons, and 30% to 53% of new infections in Thailand occur in the previously seronegative partners in serodiscordant couples. Similarly, data from the United States and Europe suggest that a high proportion of new infections in men who have sex with men (MSM), perhaps up to two-thirds, occur in steady partnerships.¹ Mwangi and colleagues (Abstract 38) and Kaiser and colleagues (Abstract 40) presented data from Kenya's nationally representative, population-based survey. Of more than 2700 couples interviewed for whom HIV-testing results were available, 5.9% were serodiscordant. Applied at a population level, this result suggests that there are 344,000 serodiscordant couples in Kenya. Among married HIV-infected Kenyans, the vast majority (89%) did not know their own or their partner's HIV serostatus.

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Factors associated with serodiscordance included older age in women, larger number of lifetime partners in women, lack of male circumcision, herpes simplex virus type 2 (HSV-2) positive concordance, and lack of knowledge of HIV serostatus. These studies suggest that prevention strategies should target both testing of and treatment for couples.

Bunnell outlined a number of strategies to identify serodiscordant couples and provided successful examples of these diverse strategies. For example, in Uganda, family members of HIV-seropositive patients were offered HIV testing. Of 2300 family members offered home-based testing, 99% accepted. Importantly, 43% of spouses of HIV-infected adults were found to be HIV-seronegative, and 99% of these partners had not previously been HIV tested, providing an important opportunity to prevent new HIV transmissions.

In Kenya, a program was initiated to identify HIV infection among persons with tuberculosis (TB), and then testing was offered to their partners. Among stable partners of nearly 42,000 patients coinfecting with HIV and TB, 49% were HIV-seronegative, again highlighting important opportunities for HIV prevention. In Uganda, health care practitioners initiated testing among their patients and their partners. Overall, 19% of the couples were found to be serodiscordant, and all were unaware of their serodiscordant status. Rwanda has had an impressive program of testing the male partners of pregnant

women to reduce HIV transmission rates in postpartum women and their partners, in whom HIV incidence is exceptionally high. These efforts have increased rates of testing in male partners from 16% in 2003 to 84% in 2009.

Another strategy to increase the uptake of testing in couples is with door-to-door testing. In Kenya, the home-based testing program has received widespread acceptance, with uptake rates in excess of 85%. Two-thirds of adults in couples were tested together, and 85% of cases were previously undiagnosed; the median CD4+ cell count was 450/ μ L, substantially higher than has been seen in US populations of newly diagnosed cases of HIV infection. A mass testing program in Larambi, Kenya, successfully tested more than 47,000 persons in 7 days (approximately 80% of the total population). Of this population, 82% had never been tested.

Bunnell also pointed out that a substantial minority of infections in serodiscordant couples may occur from outside the partnerships. For example, 2 African studies suggested that 13% to 29% of HIV-uninfected partners in serodiscordant couples who later seroconverted were infected with HIV that was not genetically linked to the HIV from the seropositive partner, suggesting that these infections occurred outside of the primary serodiscordant relationship. Campbell and colleagues presented data on 151 seroconversion events in a longitudinal study of HIV-serodiscordant couples (Abstract 970). Of these, 26.5% were determined to be unlinked. This study demonstrates the importance of sequencing viral isolates from both partners in serodiscordant-couple studies, to understand factors that may drive infection within stable partnerships, and to accurately assess the efficacy of interventions that target the HIV-infected person within these partnerships.

Disparities in HIV Disease in the United States

Smith presented a comprehensive overview of disparities in HIV incidence, morbidity, and mortality in blacks in the United States (Abstract 72). Although blacks make up 12% of the US population, they comprise more than half of newly diagnosed cases of HIV infection. Smith explained that this phenomenon is not new, as more than half of the children and women receiving AIDS diagnoses in the mid-1980s were black. However, public health campaigns and public perception, including within the black community, were inadequately focused on this burgeoning epidemic in the early years of the HIV epidemic. These disparities have continued to grow, with higher AIDS case rates and mortality in blacks than in any other racial or ethnic group in the United States.

Smith explored some of the underlying drivers of these health disparities, including behavioral factors (eg, risk practices, overlapping sexual networks, substance use) and environmental factors (eg, poverty, limited health care access, health illiteracy, and incarceration). A number of studies in heterosexuals have demonstrated that normative sexual behaviors can lead to disproportionately high incidence rates of HIV infection if the HIV prevalence in the partner pool is substantially higher than in other communities. For example, a study of HIV-infected persons in Washington, DC, found that nearly half of the HIV-seropositive women had only 1 sexual partner. A similar situation occurs in the acquisition of other sexually transmitted diseases (which may, in turn, increase the risk of HIV acquisition); among young people with lower-risk behavioral characteristics, blacks were 25 times more likely than whites to acquire a sexually transmitted disease. High rates of incarceration (higher in blacks in the United States than in blacks in South Africa during apartheid) also disrupt social relationships and may lead to HIV transmission within and outside of prisons and jails, within more intertwined sexual networks. Adimora and colleagues re-

ported that the 2002 National Survey of Family Growth found higher rates of sexual concurrency (partnerships that overlap in time) among black women, women with nonmonogamous partners, and women with various drug and alcohol patterns (Abstract 968).

Numerous studies have found similar or lower rates of sexual risk taking among black MSM compared with white MSM. For example, Magnus and colleagues reported that among MSM participating in the National HIV Behavioral Surveillance survey in 2008, MSM of color were statistically significantly less likely to report 4 or more sex partners in the past 12 months (42% vs 61%; $P < .05$), unprotected anal intercourse (receptive in 31% vs 56%; $P < .05$; insertive, 30% vs 51%; $P < .05$), and to have ever engaged in “barebacking” (sex without a condom, 58% vs 73%; $P < .05$) (Abstract 972). Despite lower reported risk, HIV prevalence was statistically significantly higher among MSM of color (20% vs 8%; $P < .001$), who were also statistically significantly more likely to be newly diagnosed (8% vs 3%; $P < .001$). As Smith pointed out, this leads to a situation in which there is “no room for error” for HIV-uninfected black MSM if they are likely to choose other black MSM partners. Despite lower levels of risk, their sexual partners may be more likely to be HIV-seropositive, be unaware of their seropositive status, have higher rates of sexually transmitted diseases, and be less likely to be adequately treated, leading to higher transmission rates.

Smith also pointed to the considerable health disparities among HIV-infected blacks in the United States, who may be less likely to access care, less likely to be given antiretroviral drugs early in the course of the disease, and more likely to experience treatment failure if adherence is poor. She urged that public health messages move away from the focus on risk practices to concentrate on populations; encouraged clinical investigators to include more diverse populations in prevention and treatment trials; and challenged clinicians to begin treatment earlier, improve adherence, rapidly link

patients into care, and build culturally competent relationships that address misperceptions and mistrust.

Molecular Epidemiology to Track the Spread of Infection

Investigators have begun to use viral sequencing data to track clusters of sexual and injection-drug-use transmission among populations, leading to new insights about transmission patterns. Weinert and colleagues presented a phylogenetic analysis of HIV transmission among MSM in the United Kingdom (Abstract 449). Of nearly 15,000 subtype-B HIV samples tested, nearly 100 clusters of similar viral strains infecting 10 or more individuals were found, accounting for 1673 individuals. Patterns of transmission suggest that infections have moved out of London into Manchester and Brighton, with further outward migration from these 3 urban epicenters. A similar study in Belgium among 506 patients receiving diagnoses between 2001 and 2009 found that patients belonging to transmission clusters were more likely to be white, younger, and MSM (Abstract 450). These 2 studies point to the influence of sexual networks on the rapid spread of HIV among MSM populations globally.

Phylogenetic analysis among injection drug users (IDU) in Sargodha, Pakistan, identified a single cluster of highly related sequences among 151 IDU, suggesting the recent introduction of a single source of infection in this population (Abstract 451). The authors of each of the studies suggest that phylogenetic analyses may provide useful information about transmission patterns that could help in developing and targeting interventions.

Strategies to Increase HIV Testing

Several investigators presented data on programs to increase HIV testing rates, demonstrating major strides in the rollout of testing strategies while pointing to as-yet-unfilled need. Althoff and colleagues reported on more than 35,000 HIV-infected patients in the United States and Canada participating

in the 11 cohorts in the NA–ACCORD (North American–AIDS Cohort Collaboration on Research and Design) study (Abstract 982). From 1996 to 2007, the median CD4+ cell count at first presentation increased from 234/ μ L to 327/ μ L ($P < .01$), with increases seen in all risk groups. Although the proportion of persons with a CD4+ cell count of at least 350/ μ L at first presentation also increased (34% vs 47%; $P = .01$), more than half of HIV-infected persons in these cohorts did not present until their CD4+ count was below the recommended threshold for treatment.

A number of strategies are being tested to increase HIV testing rates in populations at risk. Castel and colleagues presented encouraging data from a public health initiative to increase HIV testing and linkage to care throughout Washington, DC, one of the most heavily affected cities in the United States (Abstract 34). HIV testing increased 3.7-fold from 2004 to 2008, increasing from fewer than 20,000 tests to more than 72,000 tests over that time. This led to a 17% increase in newly identified HIV-seropositive patients, and the proportion receiving a viral load measurement within 3 months of their first positive HIV test result increased from 62% to 67% over that time. Median CD4+ cell counts increased from 216/ μ L to 343/ μ L. More work needs to be done, however, as 33% of persons were not receiving timely viral load measurements, and of the persons with newly diagnosed AIDS cases, 61% had still first tested HIV seropositive within 12 months of receiving their diagnosis.

Calderon and colleagues presented an approach to increasing HIV testing in hospital emergency departments by using a multimedia tool to deliver prevention messages in addition to providing access to an HIV-test counselor (Abstract 1004). During the 2 years of this demonstration project, nearly 29,000 patients were tested. Patient satisfaction was high, with 89% reporting they had learned a moderate to large amount of new information about HIV. Only 101 HIV infections were newly identified or confirmed, but 86% of these patients were linked to out-

patient care, with a mean of 7 days to the time of their first appointment.

Daskalakis and colleagues presented data on an HIV-testing program delivered to MSM attending commercial sex venues (Abstract 1005). From February 2006 to August 2009, nearly 1000 unique clients were tested, yielding 2.7% newly diagnosed cases of HIV infection, 30% of which were acute or recent infections. Polk and colleagues described a program using mobile vans to provide HIV testing in high-risk neighborhoods in Baltimore (Abstract 1007). They recruited more than 1000 participants at 40 venues and identified 21 non-IDU heterosexuals with HIV infection. Wohl and colleagues presented data on an opt-out HIV testing program in the North Carolina state prison system (Abstract 1006). The proportion agreeing to testing increased from 57% to 91% after the program was implemented. Testing is an essential first step for prevention strategies, so the lessons learned from these pilot programs are important in planning scale-up of testing strategies.

Cherutich discussed the role of HIV testing in treatment and the use of innovative home-based testing in Africa to increase knowledge of HIV serostatus (Abstract 61). Published data suggest that in the United States, the approximately 25% of persons unaware of their HIV infection may contribute from 54% to 70% of new sexually transmitted infections.² In Africa, where 75% of HIV-infected persons are unaware of their infection, more than 90% of HIV transmission likely stems from this lack of knowledge.

Cherutich described 2 innovative programs of home-based testing in which door-to-door testing attempts to achieve broad coverage of all persons, or targeted testing is attempted in which household members of known HIV-infected persons are offered testing. These programs have been highly successful. In Uganda, a study in 2300 families of HIV-infected persons found that 37% of adults and 19% of children under the age of 5 years had undiagnosed HIV infections, and 39% of those without previous testing were eligible for antiretroviral treatment. In

Kenya, door-to-door testing programs have achieved 60% to 77% coverage of individuals offered testing, and 76% to 91% have accepted testing. Among HIV-infected persons, 85% to 90% were unaware of their HIV infections; median CD4+ cell counts were 411/ μ L, representing a major achievement in identifying persons early in HIV infection and increasing opportunities for both prevention and treatment. Both household-member testing and door-to-door testing have been found to be cost-effective, with estimates ranging from \$6 to \$14 per person tested, and \$84 to \$232 per HIV infection detected.

Brown and colleagues found that a partner-notification program of patients with newly diagnosed HIV infection more than doubled the proportion of partners who received HIV counseling and testing (from 24% to 51%; $P < .001$), nearly two-thirds of whom were found to be HIV-seropositive (Abstract 960). Substantially more research is needed to optimize the operational components of these testing programs, determine the optimal frequency of home-based testing, and develop the most cost-effective strategies to reduce HIV incidence, morbidity, and mortality.

HIV Treatment as Prevention

Mathematic Models of Expanded HIV Testing and Treatment

There has been great interest in the possibility that increasing HIV testing, linkage to care, and early initiation of antiretroviral therapy could substantially reduce or eventually eliminate new HIV transmissions, the so-called “test-and-treat” or “test, linkage-to-care, plus antiretroviral therapy (TLC plus)” approach. Fauci pointed out that with an estimated 2.7 million new infections each year, for every person receiving treatment, approximately 2.5 new persons become infected, suggesting that we need more effective prevention approaches than we currently have (Abstract 19).

Williams and Dye (Abstract 13) and their colleagues Granich and coinvestigators (Abstract 965) presented several

mathematic models to evaluate the impact of widespread HIV testing and antiretroviral therapy for HIV-infected persons in South Africa. A model that would provide universal, annual HIV testing and antiretroviral treatment for all HIV-infected persons would reduce HIV incidence by 80% compared with a program that begins antiretroviral therapy at CD4+ T-cell counts below 200/ μ L. Although the cost of such programs is high in the first 5 years to 10 years, the overall cost over the life of the program is similar to that of current strategies because of savings from infections averted.

Bendavid and colleagues presented a model of universal testing and treatment showing a 35% reduction in new infections over 10 years with this approach (Abstract 999). The addition of enhanced linkage to and retention in care led to an additional 73% reduction in infections over that time period.

Two models addressed the role of enhanced testing with or without treatment among MSM in the United States. Charlebois and colleagues presented a mathematic model of this universal testing and treatment strategy among MSM in San Francisco, a high-prevalence (23%) population with high rates of awareness about HIV serostatus (Abstract 996). These models suggest that the addition of annual HIV testing and treatment regardless of CD4+ cell count would lead to an 81% reduction in new HIV infections over 10 years compared with current practice.

Golden and colleagues presented a model that explored the relative importance of primary HIV infection, chronic undetected HIV infection, and chronic untreated HIV infection in driving new HIV infections in MSM in King County, Washington (Abstract 1001). Although more than half of new infections in his model were transmitted by persons unaware of their HIV infection, more than half of those (greater than one quarter of the total) were MSM with primary HIV infection, which may not be detected in standard testing strategies. Another substantial source of new infections in this model were those transmitted from persons aware of their HIV infection but not yet

receiving antiretroviral therapy. These investigators are now pilot testing a program to link known HIV-infected persons into care and to address questions and concerns about antiretroviral therapy with these patients.

Other mathematic models focused on the potential impact of more widespread HIV testing and treatment using the new international guidelines for initiating treatment at CD4+ cell counts at or below 350/ μ L. One model presented by van de Vijver and colleagues assumed HIV testing annually for at most 20% of the population in Macha, a rural area in southern Zambia (Abstract 963). Even with this assumption, in this model, the median HIV incidence would decrease in 10 years by 62% (range, 56%–67%), with much of the remaining infections the result of transmission from acutely infected persons. Reducing the annual number of sexual partnerships and implementing strategies to identify newly infected persons could lead to further substantial declines in HIV incidence.

Scott and colleagues modeled the impact of testing every year versus every 3 years and initiating antiretroviral therapy at CD4+ cell counts at or below 350/ μ L or at diagnosis (Abstract 964). Compared with current practice, annual screening and treatment led to a 17% reduction in new infections in 5 years but also to a paradoxical increase of 11% of lifetime cases of secondary HIV transmission. Blower and colleagues also sounded a cautionary note about the potential risk of increases in antiretroviral drug resistance with universal testing in South Africa (Abstract 966). However, Montaner and colleagues showed data from British Columbia, Canada, that refuted these concerns about resistance (Abstract 88LB). In their experience, widespread use of antiretroviral therapy has led to reductions in viral load and substantial reductions in the prevalence of antiretroviral drug resistance within the community.

Overall these models suggest that more aggressive guidelines for HIV testing and treatment could have widespread beneficial impact, with continued attention needed for issues like linkage to and retention in care and

further reductions in behavioral risk. However, empiric data will be essential to develop and validate these modeling projections. Palombi and colleagues presented data on treatment responsiveness and survival from the DREAM (Drug Resource Enhancement against AIDS and Malnutrition) study throughout sub-Saharan Africa as an example of how data from observational cohorts can inform mathematic models (Abstract 998).

Temporal Trends in HIV Incidence in the Effective Antiretroviral Therapy Era

Several studies examined temporal trends in HIV incidence around the time of scale-up of antiretroviral therapy programs. Rehle and colleagues reported on HIV incidence and risk practices in South Africa from 3 national household surveys conducted in 2002, 2005, and 2008 (Abstract 37). South Africa has made enormous progress in rollout of antiretroviral therapy, with only 33,000 receiving treatment in January 2005, increasing to nearly 750,000 in March 2009. From 2002 to 2008, HIV incidence declined, particularly among women aged 15 years to 24 years, in whom incidence had fallen from 5.5 per 100 person-years to 2.2 per 100 person-years. Overall, self-reported risk practices have decreased (condom use at most recent sexual encounter increased from 31% to 65% from 2002–2008), and knowledge of HIV serostatus has increased from 25% to 56%. Wanyama and colleagues confirmed that antiretroviral therapy use was associated with a reduction in risk activities, including increased condom use and a reduction in sex with multiple partners in the 12 months after antiretroviral therapy initiation in patients of an infectious diseases clinic in Kampala, Uganda (Abstract 975).

Montaner and colleagues presented an ecological analysis that demonstrated that concomitant with an increase in rollout of antiretroviral therapy for HIV-infected persons in British Columbia, Canada, was a decline in the plasma viral levels throughout the province (ie, “provincial, or community, viral load”)

and a decrease in new HIV diagnoses (Abstract 88LB). These declines were seen particularly among IDU, who experienced a 50% reduction in new diagnoses. Das-Douglas and colleagues conducted a trend analysis of the mean viral load among HIV-infected persons in San Francisco, California, from 2004 through 2008. Mean viral load decreased overall from approximately 24,000 copies/mL to 15,000 copies/mL and was associated with a drop in the annual number of newly diagnosed HIV infections (from 798 to 434 infections) (Abstract 33). However, an analysis to assess the relationship of mean viral load with a decrease in estimates of HIV incidence was not statistically significant, perhaps because of the uncertainty of incidence estimates from cross-sectional samples. These trends are encouraging and suggest that continued effort to increase HIV testing, linkage to care, and treatment may result in lower HIV infection rates within populations.

A cautionary note was sounded by Jansen and colleagues, who presented data from the Amsterdam Cohort Study (Abstract 35). HIV-related risk practices substantially increased in MSM 30 years of age or younger, accompanied by substantial increases in HIV incidence rates. This result may suggest that increases in sexual risk may be able to overwhelm any reduction in HIV incidence that occurs as a result of any scale-up in antiretroviral therapy.

In addition to these ecological analyses, Donnell and colleagues presented observational data from the Partners in Prevention trial indicating very low rates of HIV transmission among couples initiating antiretroviral therapy (Abstract 136). Of 3381 serodiscordant couples, 349 HIV-seropositive partners initiated antiretroviral therapy during the 12-month to 24-month follow-up period. HIV incidence was 2.24 per 100 person-years among the couples not receiving antiretroviral therapy and 0.37 per 100 person-years of follow-up. After adjusting for time on study and CD4+ T-cell counts, the relative risk of HIV infection was 0.08 (95% confidence interval, [CI], 0.002–0.57), a 92% re-

duction in the risk of HIV transmission. Incidence rates were particularly high among untreated couples with CD4+ cell counts below 200/μL, with no infections in treated couples with these low CD4+ counts, suggesting that even initiating treatment in persons under previous international guidelines could have a substantial impact on reducing HIV transmission rates.

However, all of these ecological studies and this observational study data provide indirect evidence that have the potential for confounding. Data will be available in the future from a randomized controlled trial of standard versus early initiation of antiretroviral therapy in serodiscordant couples (HIV Prevention Trials Network [HPTN] 052) to inform future directions in treatment as prevention.

Prevention Approaches for HIV-Seronegative Populations

Condoms and Male Circumcision

Two known, effective interventions to reduce the spread of HIV infection, male condoms and male circumcision, are currently underutilized. Warner reviewed the challenges with increasing condom use (Abstract 60). Consistent condom use is relatively low in many surveys of populations in the United States and internationally, including among known serodiscordant couples. Although condom use has been increasing over time, rates still remain below 50% in many populations, including those with multiple partners in high-prevalence countries. Barriers to condom use include access to condoms, device-specific challenges (eg, reduced sensation, difficulty maintaining erection), and partnership-related issues (eg, difficulty negotiating use, concerns that condom use implies mistrust). Warner called for more research into new condom technologies that address some of the current limitations and help individuals overcome these barriers to use.

Dickson and Farley presented an overview of the scale-up of male circumcision in Africa (Abstract 62). Three randomized controlled trials demon-

strated a 60% reduction in HIV acquisition among HIV-uninfected men undergoing male circumcision. In 2007, a set of recommendations was developed to scale-up male circumcision in high-prevalence areas with low rates of male circumcision, and 13 priority countries were identified in eastern and southern Africa. Modeling exercises suggest that if 80% of adult men and newborn boys could be circumcised in 14 African countries by 2015, more than 4 million adult infections could be averted in 15 years. A \$4 billion (US) investment to scale-up male circumcision could lead to more than \$20 billion in savings. A number of countries have begun scale-up of male circumcision, although challenges remain, including development of service-delivery systems that can support scale-up through task shifting and task sharing between health professions.

Microbicides

McCormack presented data (for Chisembele et al, Abstract 87LB) from the MDP (Microbicides Development Programme) 301 Phase III vaginal microbicide trial. The results demonstrated that a gel, naphthalene sulfonate microbicide polymer (PRO 2000; Indevus Pharmaceuticals, Lexington, MA), did not protect women against HIV infection. The summary results of the trial were announced in December 2009, but the presentation at this year's conference was the first presentation of these data at a large scientific meeting. This trial was particularly important because it followed a number of trials of unsuccessful microbicide products based on non-HIV-specific approaches to protection, including nonoxynol-9, C31G (Biosyn, Inc, Philadelphia, PA), Carraguard (Population Council, New York, NY), and cellulose sulfate. However, at the 2009 conference, Karim presented data on the 0.5% naphthalene sulfonate polymer microbicide gel from a trial, HPTN 035, that found a statistically nonsignificant trend toward lower HIV acquisition (30%) among women receiving the gel.³ In subgroup analyses, however, HIV incidence was further reduced in the

subgroup of women who were highly adherent to gel use and not using condoms, the group most likely to benefit from a topical microbicide. This had suggested that the product might be efficacious but required a larger trial with more women to definitively address this question.

Thus, the field eagerly awaited the results of the MDP 301 trial, in which more than 9300 women were enrolled in Uganda, Tanzania, Zambia, and South Africa. Women were randomly assigned to receive 2% naphthalene sulfonate polymer microbicide gel, 0.5% gel, or placebo gel administered prior to sexual intercourse; follow-up was for 52 weeks (or up to 104 weeks in Uganda). The 3 trial groups were balanced in baseline demographic and risk characteristics, and retention was comparable between groups. Overall, 95% of the women had at least 1 follow-up visit, but only 84% of the total duration of follow-up was available in the modified intention-to-treat analysis, which excluded time that women were not using gel because of pregnancy. The 2% trial arm was stopped early for futility in February 2008, at which point the infection incidence was 4.7 per 100 women-years (wy) in the 2% gel group and 3.9 per 100 wy in the placebo group (hazard ratio [HR], 1.21; 95% CI, 0.88–1.68). At the end of the trial, there was also no statistically significant difference in HIV incidence between the 0.5% gel group (4.5/100 wy) and the placebo group (4.3/100 wy; HR, 1.05; 95% CI, 0.82–1.34). This trial definitively ruled out any statistically significant protective effect for either the higher- or lower-dose regimen of naphthalene sulfonate polymer microbicide gel, and it is widely seen as the end of an era of development of non-specific microbicides. In their place, investigators have been developing and testing topical formulations of antiretroviral agents, discussed in greater detail below.

Preexposure Prophylaxis

Antiretroviral drugs hold great promise in the prevention of HIV infections. The use of antiretroviral treatment of HIV-

infected persons to lower HIV transmission rates is summarized above. The remainder of this article focuses on oral and topical use of antiretroviral drugs to prevent HIV acquisition among HIV-seronegative persons.

Mayer summarized the suite of clinical trials now under way that are evaluating tenofovir-based regimens (Abstract 63). Several of these trials are expected to yield data later in 2010, and others should provide data over the next several years. The 3 clinical trials sponsored by the US Centers for Disease Control and Prevention (CDC) (a biomedical and behavioral safety trial of tenofovir in US MSM; an efficacy study of tenofovir/emtricitabine stopped early for operational futility in young heterosexuals in Botswana; and an efficacy study of tenofovir in IDU in Thailand) may all provide data later in 2010 or 2011. CAPRISA 004 (Centre for the AIDS Programme of Research in South Africa 004), an efficacy trial of 1% tenofovir gel used vaginally pre- and postcoitally among women in South Africa, may have results in summer 2010. The iPrEx (Chemoprophylaxis for HIV Prevention in Men) study, an efficacy trial of oral tenofovir/emtricitabine in MSM in North and South America, South Africa, and Thailand may also have efficacy results later this year.

Three other efficacy trials are expected to have results available by 2012 or 2013. The Partners PrEP (Preexposure Prophylaxis) trial is an efficacy study of oral tenofovir versus oral tenofovir/emtricitabine versus placebo in serodiscordant heterosexual couples in Africa. The Fem-PrEP (Study to Assess the Role of Truvada [tenofovir/emtricitabine] in Preventing HIV Acquisition in Women) trial is evaluating oral tenofovir/emtricitabine among women at high risk in Africa. Finally, the VOICE (Vaginal and Oral Interventions to Control the Epidemic) trial will evaluate oral tenofovir versus oral tenofovir/emtricitabine versus topical tenofovir versus placebo among women at high risk in Africa. In combination, these trials will enroll more than 20,000 participants and will address questions about the efficacy of daily oral tenofovir or tenofovir/emtricitabine and daily or coitally dependent,

topical tenofovir-based regimens.

All of the regimens in the first generation of efficacy trials require regular dosing of oral or topical agents. To correctly interpret trial results, investigators will need an understanding of the patterns of pill and gel use by study participants. Liu and colleagues presented data on the correlation of various biomarkers of tenofovir use with pill count and self-reported adherence measures in the US CDC-sponsored PrEP trial (Abstract 86). The biomarkers measured included tenofovir levels measured in plasma, peripheral blood mononuclear cells (PBMCs) and hair. Given the long intracellular half-life of tenofovir diphosphate, plasma levels are thought to reflect tenofovir use in the past few days, whereas PBMC and hair levels reflect tenofovir use in the past month. Hair has the added advantage of being easy and inexpensive to collect, store, and transport to the laboratory.

In this study, all 3 measures demonstrated very high levels of sensitivity and specificity with treatment assignment. For example, 46 of 47 men randomly assigned to receive daily tenofovir had detectable levels of tenofovir in hair, but only 1 of 42 men in the placebo group had detectable levels of tenofovir in hair. This man also had tenofovir detected in his plasma and PBMCs, suggesting that he may have been exposed to the drug outside of the study. Correlation of the biomarkers with pill counts was modest, and correlation with self-reported adherence measures was poor. More work is being done to assess factors affecting the dynamic range of these biomarker measures and to evaluate their correlation with protection in efficacy trials.

Less frequent administration of PrEP would be less expensive and potentially safer than daily PrEP. Garcia-Lerma and colleagues⁴ have been investigating coitally dependent systemic administration of tenofovir/emtricitabine in a low-dose, repeated-rectal-challenge model in rhesus macaques (Abstract 83). They reported that intermittent PrEP, when given up to 7 days before and 2 hours after each challenge, can provide partial or complete protection against sim-

ian-HIV (SHIV) strain 162p3 infection in the rhesus macaque model. However, the postexposure dose is an essential element to achieve protection, an important insight to be taken into account in future clinical trials.

They also presented data on drug levels of tenofovir and emtricitabine in plasma, PBMCs, and rectal secretions in macaques. In these studies, tenofovir diphosphate persists in PBMCs for prolonged periods, with a half-life of 115 hours (5 days), whereas emtricitabine triphosphate has a half-life in PBMCs of approximately 24 hours. Both tenofovir and emtricitabine levels peaked in rectal secretions at 24 hours. However, emtricitabine was detectable in rectal secretions within 2 hours after dosing, whereas tenofovir was undetectable at the 2-hour and 5-hour time points but was detected at 24 hours. These data suggest that the combination of tenofovir/emtricitabine may provide an advantage over single-drug use by providing coverage both early and late in rectal secretions and PBMCs. Moreover, these drugs are synergistic.

Additional data presented by Garcia-Lerma and colleagues raised a cautionary note in predicting efficacy based on pharmacokinetic and pharmacodynamic data. Their group evaluated the tenofovir prodrug GS7340 for protection from SHIV challenge in their rectal-challenge macaque model. This prodrug was believed to be more potent than tenofovir because of results indicating 100-fold-increased levels of tenofovir diphosphate in PBMCs and earlier and higher levels of drug penetration in rectal secretions in macaques. However, the prodrug completely failed to protect macaques against rectal challenge. Additional studies are needed to explore the reasons for the failure of this prodrug to provide protection. Further validation of all nonhuman primate challenge models awaits the results of clinical trials.

Another presentation from this group, by Dobard and colleagues, evaluated 1% tenofovir gel for protection against vaginal SHIV challenge in their rhesus macaque model (Abstract 949). The investigators had previously demonstrated that tenofovir gel provided complete protection when adminis-

tered 30 minutes before each vaginal challenge. In this study, they administered 2 weekly challenges, one 30 minutes after and the other 3 days after a single weekly vaginal administration of 1% tenofovir gel. This regimen provided a 7-fold reduction in SHIV infection ($P = .01$ in proportional hazard model), suggesting that the long half-life of tenofovir may provide prolonged protection. Validation of this model also awaits clinical trial results.

Several investigators evaluated the potential of CC chemokine receptor 5 (CCR5) inhibitors for PrEP. Moore presented results of a study (Veazey et al, Abstract 84LB) in which maraviroc tablets were dissolved to create a topical gel that could be applied in a macaque vaginal challenge model. The investigators demonstrated the dynamic range of drug required to protect against SHIV 162p3 and suggested that the doses required could be substantially lower than required for oral administration. During the question-and-answer session, questions were raised about the decreased potency of maraviroc against cell-associated virus. These animal challenge models use cell-free virus challenges, but the relevance of these challenges to human transmission is unknown.

Brown and colleagues presented data from a clinical trial of oral maraviroc administration in HIV-seronegative men (Abstract 85). Unlike studies in women, in which maraviroc appeared to be concentrated at higher levels in genital secretions, in this study in men, semen concentrations were approximately half those in blood plasma. However, maraviroc was highly concentrated in rectal secretions, reaching an 8-fold increase in the area under the curve after a single dose and a 28-fold increase after repeated dosing. Brown speculated that fecal elimination of the drug may lead to high drug levels in rectal secretions, although the relevance of this to protection against rectal challenge is unknown. These data also suggest that studies of drug concentration in genital secretions should include both men and women, as results between sexes may be discordant.

Concerns have been raised about widespread usage of PrEP before data

are available from clinical efficacy trials. Mansergh and colleagues reported on data from a study in 1011 MSM substance users in Chicago, Los Angeles, New York City, and San Francisco (Abstract 957). In this sample, 2% of HIV-seronegative men reported taking PrEP, and 3% of HIV-seropositive men reported giving their partners antiretroviral drugs for PrEP, confirming that current use appears low in this population.

The current generation of nonvaccine prevention trials focus largely on strategies to increase HIV testing, to increase uptake of antiretroviral drugs for treatment, and for the use of oral or topical antiretroviral drugs for prevention in HIV-seronegative persons. Additional work is needed to understand the social and behavioral drivers of HIV transmission and acquisition, to develop strategies to address HIV transmission in couples, and to prepare to make PrEP feasible to deliver, should it prove effective.

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A list of all cited abstracts appears on pages 93-99.

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