HIV Epidemiology and Breakthroughs in Prevention 30 Years Into the AIDS Epidemic

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Thirty years after the first AIDS cases were reported in the United States, the HIV epidemic continues to be heavily concentrated among men who have sex with men (MSM) in the United States. MSM are heavily impacted throughout most of the world and are the predominant risk group throughout the Americas and Western Europe; heterosexuals are the predominant risk group in sub-Saharan Africa; and injection drug users predominate throughout Eastern Europe and Southeast Asia. In the United States, blacks and Latinos continue to be disproportionately affected, despite overall advances in HIV testing and care. The 2011 Conference on Retroviruses and Opportunistic Infections focused on populations heavily impacted throughout the world: adolescents, women, MSM, and serodiscordant couples. Several presentations focused on the unique relationship between herpes simplex virus type 2 (HSV-2) and HIV-1; although many opportunistic infections increase HIV acquisition risk, HSV-2 is likely the only one whose effective prevention or treatment could substantially influence HIV infection rates, because of the high prevalence and persistence of HSV-2. The 2011 conference also celebrated the substantial advances made in the use of antiretroviral drugs for prevention of HIV acquisition (eg, oral preexposure prophylaxis, topical microbicides) and transmission (eg, antiretroviral therapy). Further progress is also being made in evaluating other prevention strategies and their rollout, including male condoms, male circumcision, and HIV testing and linkage to care.

The US HIV Epidemic

Mermin provided an overview of the US epidemic and strategies for implementing high-impact prevention (Abstract 19). He reminded the audience of the substantial disparities in HIV infection, with new infections more than 40 times more likely to be in men who have sex with men (MSM) than in other men and women and more than 8 times more likely in blacks and 3 times more likely in Latinos than in whites. Tremendous strides have been made in prevention, with community-initiated behavior change leading to an 89% reduction in the transmission rate per 100 HIV-infected persons, thereby averting an estimated 350,000 new HIV infections since the beginning of the epidemic. Through expanded HIV testing, the proportion of people in the United States who have ever been tested for HIV has risen to 45%, and the proportion of persons with AIDS diagnosed within 12 months of their first HIV-seropositive test has dropped to 32%. However, given limited resources, Mermin called for targeted prevention strategies based on knowledge of effectiveness, cost, scalability, and coverage of affected populations.

Millett further explored the US epidemic in MSM, the only risk group in the United States in whom new infections continue to rise (Abstract 69). Modeling suggests that even if MSM and heterosexuals had similar numbers of sexual partners and rates of unprotected intercourse, incidence rates in MSM would be higher because of higher background prevalence rates, increased risk of anal versus vaginal sex, and role versatility in which many MSM serve both insertive and receptive roles, thereby accelerating transmission through partner networks.

MSM are disproportionately affected within all racial and ethnic groups, and young black and Latino MSM are at particularly high risk. In examining drivers of the epidemic in MSM, numerous studies have shown lower levels of reported sexual risk and drug use among black and Latino MSM than among white MSM. These racial and ethnic disparities may arise as a result of differences in background prevalence, patterns of intraracial mixing, prevalence of sexually transmitted infections, access to antiretroviral therapy, and rates of undiagnosed HIV infection, all of which may drive increased rates in black and Latino MSM.

Millett and colleagues also presented data from 1214 black and Latino MSM enrolled in the Brothers y Hermanos study in New York City, Philadelphia, and Los Angeles (Abstract 131LB). Overall, 12% were HIV-seropositive and unaware of their infection, with a higher rate among black than Latino men (18% vs 5%, respectively; $P < .001$). Among both groups, having a low perceived risk of testing HIV-seropositive and endorsing the belief that having sex with men of the same race or ethnicity reduces the risk of HIV acquisition were independently associated with being HIV-seropositive and unaware. Among black MSM, having disclosed sexual identity to a health care practitioner, having health insurance, and having fewer than 3 lifetime HIV tests were also independently associated with HIV-seropositive–unaware status.

Millett pointed to the need to address the misperceived risk of HIV acquisition, including the risk associated with intraracial partnerships. He also highlighted the responsibility of practitioners to offer frequent HIV tests to MSM, as even black MSM who disclose their risk to health care practitioners and who have health insurance appear to be at elevated risk of HIV seropositivity. Millett also called for multilevel approaches to prevention and treatment for MSM, including those using

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individual-, interpersonal-, and structural-level interventions.

Heffelfinger and colleagues reported on recent HIV infections among MSM in 21 high-prevalence US cities enrolled in the 2008 National HIV Behavioral Surveillance System (NHBS) (Abstract 130). Of 6864 evaluable MSM, 4% had new infections, defined as having an HIV-seropositive test result with a reported last HIV-seronegative test result within the past 12 months. Independent risk factors for recent infection (compared with uninfected men) were younger than age 30 years; black, non-Hispanic race; Hispanic ethnicity; other nonwhite race or ethnicity; completing less than a high school education; having no insurance or public insurance; and having had 2 or more HIV tests in the prior 24 months. Risk practices were not statistically significantly associated with recent infection.

This report extends the data reported by Millett and colleagues about the independent association of sociodemographic variables with HIV acquisition risk, in the absence of reported differences in sexual practices or drug use. Heffelfinger suggested 3 possible explanations: (1) increased prevalence and sexual mixing patterns within subgroups; (2) differences in access to care among subgroups; and (3) differential underreporting of risk practices. Regardless of reason, successful, culturally appropriate interventions need to be developed and tested in high-incidence populations.

Oster and colleagues reported on a network analysis of 23 black men aged 17 years to 25 years newly diagnosed with HIV infection from 2006 to 2008 in Jackson, Mississippi (Abstract 1044). They found that all men were linked by few venues, suggesting that these venues should be targeted for testing and prevention intervention.

Seroadaptation

Several presentations focused on seroadaptation, the practice of altering sexual behavior based on self- and partner HIV serostatus. Truong and colleagues presented data from a study of seroadaptive behavior among 1207 men recruited from December 2007 to October 2008 in San Francisco (Abstract 133). Behavioral practices were evaluated at the individual, dyad, and episode levels, and were categorized into mutually exclusive practices based on highest to lowest HIV transmission risk. Seroadaptation was reported consistently by 39% of men, whereas only 25% reported 100% condom use, 14% no oral or anal sex, and 12% oral sex only. When the unit of evaluation was partnerships, 100% condom use was the most common practice (33%) compared with seroadaptation (26%). When the unit of evaluation was sexual episode, oral sex was the most common practice (65% of acts), and anal sex with a condom was next most common (16%). Overall, more than 90% of all individuals, dyads, and episodes used some form of safer sex or seroadaptation, suggesting that MSM use several strategies to manage their HIV risk.

Golden and colleagues presented data on the differential impact of serosorting by race among MSM in Seattle, Washington (Abstract 1037). In their study of 7620 white and black MSM who received HIV testing at a sexually transmitted diseases clinic in Seattle from 2006 to 2010, 266 participants received a new diagnosis of HIV infection. White and black MSM reported serosorting (unprotected anal sex only with partners of the same serostatus) at 30% and 28% of their clinic visits, respectively. Although serosorting was associated with lower HIV infection risk among white MSM (odds ratio [OR], 0.48; 95% confidence interval [CI], 0.35–0.66), there was no such protection among black MSM (OR, 1.04; 95% CI, 0.47–2.30; *P* value for interaction, .02). The reasons for these differences are not clear, as the mean time since the last HIV test was not different between newly diagnosed white and black men. A possible explanation is a higher rate of undiagnosed or undisclosed HIV infection among partners of black men.

Additional data on the possible contribution of sexual mixing patterns in transmission among MSM were presented from a study conducted in Canada. Brenner and colleagues reported on the spread of HIV among MSM in Montreal, Canada, from December 2005 to September 2009 (Abstract 1046). HIV sequence data were collected from surveillance of primary HIV-1 infections (PHIs) and divided into unique transmissions, small clusters (2–4 PHIs), and large clusters (5–31 PHIs). Large clusters of infection accounted for the fastest growing subepidemic, accounting for 25% of all transmissions in 2005 to 39% in 2009 ($P < .001$). The 34% of infections occurring from MSM born outside of Canada were predominantly unique transmission events. Given the unique sociodemographic and behavioral characteristics of these 3 different types of transmission groups, prevention strategies may need to be targeted differently to reach all 3 subpopulations of MSM contributing to this epidemic.

Populations at High Risk of HIV-1 Acquisition

Youth

Pettifor reminded the audience that approximately half of all new HIV infections globally occur in persons younger than 25 years, with 35% occurring in 15- to 24-year-olds (Abstract 66). There are also marked sex disparities: young women have HIV infection rates 2 to 3 times those of men in sub-Saharan Africa, but HIV-infected men substantially outnumber HIV-infected women in the Americas and Europe, where the epidemic occurs predominantly in MSM. Many potential factors drive this epidemic in younger persons, including biological susceptibility, increased individual behavioral risk, as well as societal forces such as age and power inequities within relationships and poverty driving the need for transactional sex.

Pettifor focused on recent promising results from cash-transfer programs whereby families receive cash incentives either unconditionally or conditional upon some requirements (eg, girls must attend school). The

Schooling Income and HIV Risk (SIHR) Trial conducted in Malawi and reported at the 2010 International AIDS Society meeting in Vienna found that HIV prevalence was 60% lower in communities randomly assigned to the conditional and unconditional cash-transfer groups than in control communities.[1] It appears that changes in individual risk behavior accounted for less than half of the beneficial effect; a possible mechanism was that girls in the intervention groups were less likely to have older male partners and less likely to receive cash from their male partners.

Ott and colleagues also presented data on age mixing in sexual relationships from a population-based surveillance study in rural KwaZulu-Natal, South Africa (Abstract 1030). In this community, casual relationships with "sugar daddies" (ie, men at least 10 years younger than their casual partners) are much less common than marriages in which the woman is substantially younger than the man, leading to an increased risk of HIV acquisition in young women.

Santelli and colleagues found demographic factors, risk practices, and sexually transmitted infections increased the rate of HIV acquisition among youth 15 years to 24 years of age enrolled in the Rakai Community Cohort Study (Abstract 690). Incidence in this group remained at 1% to 2% per year from 1999 to 2008. In multivariate analysis, independent risk factors for women and men were lower levels of education, increased numbers of sexual partners, being separated or divorced, and having sexually transmitted disease symptoms. Alcohol use was an independent risk factor for men, whereas for women, alcohol use by the last partner was an important risk factor.

Women

John-Stewart and colleagues reported on the peripartum risk of HIV acquisition and factors that drive increased HIV acquisition risk among pregnant women (Abstract 67). In combining a number of studies, they observed that HIV incidence in pregnant women in sub-Saharan Africa is high (4.3/100 women-years; 95% CI, 3.9 – 4.6). Data comparing the peripartum risk with risk in nonpregnant women suggest a modest increase in HIV acquisition risk (OR, 1.3; 95% CI, 0.96–1.6). Several factors may lead to this increase in HIV acquisition, including behavior change in male partners, or the biological features (hormonal, immunologic, and local genital tract changes) that occur in pregnancy. This is of concern for the women and their infants, as the risk of HIV transmission through breast milk is substantially elevated during the acute infection period. Moreover, if women are not aware of their HIV-seropositive status, they may also be less likely to receive antiretroviral therapy for prevention of mother-to-child transmission (PMTCT).

The authors stated that in the period before initiation of PMTCT programs in Zimbabwe, acute HIV infection accounted for only an estimated 6% of infant infections, whereas after PMTCT programs began, acute infection could account for 44% of new infections in infants. John-Stewart outlined potential behavioral and biomedical prevention strategies to prevent peripartum infections that include recognizing the desire for pregnancy among many women and studying the safety and efficacy of prevention strategies in the peripartum period.

Meditz and colleagues explored immunologic reasons for an increasing rate of infections in women aged 40 years of age or older (Abstract 33). They reported that 24 postmenopausal women had higher CC chemokine receptor 5 (CCR5) expression on CD4+ cells and a higher proportion of activated CD4+ cells in the peripheral blood and the cervix than did 21 premenopausal women. This disparity may provide some explanation for increased susceptibility in these women.

Men Who Have Sex With Men

Beyrer described the current state of knowledge of the global epidemic in MSM and provided modeling for how increased prevention and treatment could substantially alter the overall HIV epidemic (Abstract 68). In a comprehensive review of global prevalence data in MSM, Beyrer split countries into 4 scenarios: (1) countries where the epidemic predominantly affects MSM (much of the Americas, Ghana); (2) epidemics driven by injection drug users (IDUs) (Eastern Europe and Central Asia); (3) countries with a generalized heterosexual epidemic (much of sub-Saharan Africa); and (4) countries with a mixed epidemic in MSM, IDU, and heterosexuals (South and Southeast Asia, Senegal, Egypt). Unfortunately, there are 94 countries for which there are no data for MSM available, including three-fourths of African countries. Of note, HIV prevalence is high in MSM in all 4 scenarios.

In sub-Saharan Africa, prevalence in MSM exceeds that in heterosexual men in all countries and exceeds prevalence in women in all countries except South Africa, Botswana, and Namibia. In modeling the impact of increasing prevention and treatment for MSM (condom and lubricant availability, community-based prevention programs, and antiretroviral therapy availability for HIV-infected MSM), Beyrer showed that such programs would have a substantial impact in countries in all 4 types of scenarios, enhanced by drug treatment for IDUs in scenarios 2 and 4. He ended with a tribute to David Kato, the Ugandan activist recently murdered for his work on human rights for MSM. Beyrer reminded the audience that improving access to prevention and treatment and addressing human rights issues are central to the HIV practitioner community's ability to impact the global HIV epidemic.

New data were presented on MSM in Kenya and Thailand as well. Sanders and colleagues reported that HIV-1 incidence was 6.5 per 100 person-years among 666 men with various sex partners or recent anal sex (within 3 months of screening) at a clinic in coastal Kenya (Abstract 1042). Incidence was highest among men reporting sex with men only (21.7/100 person-years; 95% CI, 15.9–29.5), intermediate in men who reported sex with men and women (4.9/100 person-years;

95% CI, 3.3–7.4), and lowest among men who reported sex only with women (1.1/100 person-years; 95% CI, 0.4–2.8).

Edwards-Jackson and colleagues reported on 200 HIV-seropositive MSM recruited from an anonymous clinic in Bangkok, Thailand (Abstract 1039). At their most recent sexual encounter, 17% of men reported engaging in unprotected anal sex, and only 26% disclosed their HIV-seropositive status. Despite the lack of disclosure, men were more likely to report condom use during anal sex with partners of unknown serostatus (91%) and HIV-seronegative partners (85%) than with HIV-seropositive partners (61%; $P = .001$).

Serodiscordant Couples

Transmission between partners in stable serodiscordant relationships may account for a substantial proportion of new HIV infections globally. Ndase and colleagues point out that interventions for serodiscordant couples also need to take into account the possibility of outside partnerships (Abstract 1040). In their study of 3380 HIV-1 serodiscordant couples observed over a minimum of 24 months, there was a statistically significant decline in the proportion of couples who engaged in sexual activity (from 94% at enrollment to 73% at 24 months; $P < .001$) and an increase in the proportion of HIV-uninfected persons having an outside partner (from 3% to 14%, respectively; $P < .001$). The rate of outside partnerships is likely higher than reported, as 22% of seroconverting participants who reported no outside partners were infected with genetically distinct viruses from their seropositive main partner. This proportion was substantially higher among seroconverting participants who did report outside partnerships (86%; $P < .001$).

Ngolobe reported on 444 serodiscordant couples in Uganda (Abstract 1041). On multivariate analysis, condom use was not associated with antiretroviral drug use (adjusted odds ratio [AOR], 1.26; 95% CI, 0.81–1.96), suggesting no risk compensation associated with treatment. However, condom use at last sex was inversely associated with male-controlled sexual decision making (AOR, 0.49; 95% CI, 0.32–0.77), reminding practitioners of the challenges of condom acceptability among men.

Hughes and colleagues studied a cohort of 3297 serodiscordant couples to probe factors affecting the per-act infectivity of HIV-1 (Abstract 135). They observed a 2.9-fold increase in infectivity per 1 $\log_{10}$ increase in plasma viral load in the infected partner. Differences in male-to-female and female-to-male transmission rate were driven by the plasma viral load in the HIV-infected partner, herpes simplex virus type 2 (HSV-2) serostatus, and the age of the HIV-uninfected partner.

Baeten and colleagues evaluated the association of genital tract HIV-1 RNA levels with the risk of HIV transmission in the same cohort of serodiscordant couples (Abstract 154). They reported that genital tract HIV-1 RNA level was independently associated with HIV-1 transmission risk after adjusting for plasma HIV-1 RNA levels. A total of 11 transmissions occurred in couples with very low or undetectable genital HIV-1 RNA, but all had detectable plasma HIV-1 RNA.

Herpes Simplex Virus Type 2

HSV-2 causes genital ulcerations and has previously been associated with an increased rate of HIV acquisition among heterosexual men and women as well as MSM. McClellan and colleagues reported that HSV-2 prevalence and incidence were substantially higher among women than men enrolled in a cohort study of 5543 Zimbabweans (Abstract 1028). Prevalent HSV-2 infection more than doubled the odds of acquiring HIV-1 infection in men and women in the study. Hughes and colleagues also found a doubling of HIV-1 acquisition risk among HSV-2-seropositive men and women in 3297 heterosexual HIV-1–serodiscordant couples in Africa (Abstract 135).

Okuku and colleagues evaluated risk factors for HSV-2 acquisition in a cohort study in Kenya (Abstract 29). Among 443 men, HSV-2 incidence was 9.0 per 100 person-years and was associated with incident HIV-1 infection (adjusted incidence rate ratio [aIRR], 3.9; 95% CI, 1.3–12.4). Among 164 women, HSV-2 incidence was 22.1 per 100 person-years ($P < .001$ compared with men) and was associated with incident HIV-1 infection (aIRR, 8.9; 95% CI, 3.6–21.8). Interestingly, genital washing with soap was protective against HSV-2 acquisition in men (aIRR, 0.3; 95% CI, 0.1–0.8), but vaginal washing with soap increased the risk of HSV-2 acquisition in women (aIRR, 1.9; 95% CI, 1.0–3.4).

Tenofovir gel halved the risk of HSV-2 acquisition in the CAPRISA (Center for the AIDS Programme of Research in South Africa) 004 study.[2] Lama and colleagues presented data from the iPrEx (Chemoprophylaxis for HIV Prevention in Men) trial of 2499 MSM, half of whom were assigned to receive oral tenofovir/emtricitabine and half placebo (Abstract 1002). In this study, HSV-2 incidence was similar among those assigned to the active study drug and those assigned to placebo (6.2 vs 5.8 per 100 person-years, respectively). There was no difference in the proportion of genital ulcers in the 2 groups, although there was a reduction in participants with anal ulcers (relative risk [RR], 0.4 vs placebo; 95% CI, 0.22–0.85) and a trend toward a reduction in herpes genital ulcer–defined adverse events of grade 2 or higher (13 in the treatment group vs 24 in the placebo group; $P = .06$).

Tan and colleagues reported no decrease in HSV-1 or HSV-2 shedding from oral, genital, or anal mucosa among 40 HIV-infected patients taking oral tenofovir compared with those not receiving tenofovir (Abstract 979). These data suggest that higher levels of tenofovir at mucosal surfaces may be required to reduce the risk of HSV acquisition and viral shedding among those already HSV-infected.

HIV Testing Strategies

HIV testing among at-risk persons remains suboptimal globally, as does knowledge of HIV serostatus. Oster and colleagues reported on adherence to HIV testing guidelines among 7271 MSM participating in the 2008 NHBS (Abstract 1048). Older men were less

likely than younger men to have been tested in the previous year, and there were no differences in testing rates by race or ethnicity. However, among men reporting an HIV test within the prior year, the proportion testing newly positive was 14% for blacks, 7% for Hispanics, and 3% for whites. Of the 5864 (81%) of the sample reporting 1 or more high-risk characteristics for whom testing is recommended at least every 6 months, only 44% reported receiving an HIV test in the past 6 months. This suggests the need for both better adherence to testing guidelines and guidelines targeted for highest incidence populations. Calderon and colleagues reported on a novel community pharmacy–based HIV testing and counseling program in New York City (Abstract 1052). Nearly three-fourths of eligible patients offered HIV testing accepted.

Delaney and colleagues presented data from a randomized trial of a rapid HIV testing algorithm (RTA), in which a second rapid test was used to confirm an initial positive rapid test result (Abstract 132LB). This approach was compared with standard HIV testing: one rapid test followed by off-site confirmatory laboratory testing. An RTA was implemented at 9 testing sites in Los Angeles and San Francisco to evaluate the impact on referral to health care practitioners and on CD4+ cell counts or viral load within 90 days of the initial positive rapid test, as compared with standard testing at 23 control sites.

The positive predictive value of the RTA was 100% and of the initial rapid test using a standard algorithm was 86%. All persons receiving the RTA received referrals to medical care, whereas only 47% of those with a positive rapid test result who received standard testing (requiring that they return for their confirmatory test results) actually returned for care. Overall, two-thirds of participants referred to care received a CD4+ cell count or viral load test within 90 days of their initial test (regardless of whether they were referred from the intervention or control groups), whereas only half of those not receiving a referral received this clinical testing within 90 days ($P < .001$). Both Los Angeles and San Francisco Public Health Departments plan to use an RTA at all of their test sites by July 2011.

Choko and colleagues reported on the first evaluation of self-testing in Africa using an oral HIV test kit (Abstract 42). Four geographic areas in Blantyre, Malawi, were selected for participation, and 92% of participants opted for self-testing over clinic-based or no HIV testing. Sensitivity and specificity were excellent (97.9% and 100%, respectively), and overall, 99.2% of self-test users read an accurate result on their first try. However, 10% of participants needed help beyond the initial instructions, 10% made some type of error in preparing the test, and more than half stated that they thought that some type of additional counseling was needed with HIV testing. Overall, 99% stated that they would be likely to self-test again, and self-testing was the most common choice for the next test that participants would like to take.

The same test was evaluated for 987 participants in Singapore (Abstract 1075). Among HIV–seronegative, at-risk participants, sensitivity and specificity of self-testing was 100%. As reported in the previous abstract, participants responded favorably to the testing (eg, 89% liked the privacy of testing, and 96% found the instructions easy to follow), but nearly three-fourths felt the need for confidential pre- and posttest counseling. This suggests that self-testing may increase the uptake of testing in various populations but that accommodations should be made to provide additional counseling, as needed.

HIV Prevention Strategies

Conference presentations on HIV vaccine development are reviewed by Watkins elsewhere in this issue (see pages 36–37).

Condoms

Hughes and colleagues reported data on determinants of per-contact HIV-1 infectivity among serodiscordant couples (Abstract 135). Self-reported condom use reduced risk by 78% (95% CI, 58%–89%). Bachanas and colleagues reported on condom use by 3538 HIV-seropositive patients attending clinics in Kenya, Namibia, and Tanzania (Abstract 136). Overall, 54% of participants had an HIV-seronegative partner or a partner of unknown serostatus. Inconsistent condom use was statistically significantly associated with being female, desiring pregnancy, being a spouse (compared with casual and steady, nonmarital partners), and not taking antiretroviral therapy.

Male Circumcision

Kong and colleagues reported on long-term effects of male circumcision in Rakai, Uganda (Abstract 36). Overall, 80% of control subjects returning for a visit chose male circumcision. Overall efficacy remains high through 4.8 years of follow-up (adjusted effectiveness, 73%; 95% CI, 55%–84%). Risk behavior increased comparably in both circumcised and uncircumcised men, suggesting that risk compensation has not been observed in this setting. Tobian and colleagues reported that male circumcision does not decrease human papillomavirus (HPV) transmission from HIV-seropositive men to their female partners (Abstract 1008). Several other abstracts focused on strategies for scale-up of male circumcision services (Abstracts 1005–1007).

Preexposure Prophylaxis

Efficacy, adherence, safety and resistance. This year, 1 plenary (Session 35) and 2 oral abstract sessions (Sessions 8 and 25) focused on the strategy of using topical or oral antiretroviral drugs to prevent HIV acquisition, that is, preexposure prophylaxis (PrEP). Celum provided a framework for thinking about how and when antiretroviral drugs are used for prevention: drugs initiated before exposure (PrEP), drugs used for postexposure prophylaxis (PEP), and those used as therapy after infection (Abstract 120).

Grant and colleagues presented updated data from the iPrEx trial, a randomized, placebo-controlled trial of

daily tenofovir/emtricitabine in 2499 MSM and transgender women in North and South America, Africa, and Asia (Abstract 92). Extending data from the published interim analysis censored on May 1, 2010,[3] Grant and colleagues presented safety and efficacy data through August 2010, including HIV seroconversions occurring by 8 weeks after the study drug was discontinued. There were 37 additional HIV infections since the interim analysis, but overall efficacy remained largely unchanged (modified intention-to-treat analysis; efficacy, 42%; 95% CI, 18%–60%). These efficacy analyses did not vary by age, race, education, or geographic location.

In exploratory analyses, efficacy was somewhat lower in uncircumcised than in circumcised men (efficacy, 36% vs 83%, respectively; $P = .10$) and lower among men not reporting unprotected receptive anal sex at baseline than among men who did report this risk (efficacy, −25% vs 52%, respectively; $P = .03$). These estimates are not adjusted for other potentially confounding variables but raise the possibility of differential PrEP efficacy by route of exposure. Efficacy data from heterosexual men and women and IDUs should be available in the next few years (see Global Advocacy for HIV Prevention Web site, http://www.avac.org).

Grant and colleagues also presented data demonstrating that efficacy was highest among those reporting taking their study drug more than 90% of the time, intermediate in those reporting 50% to 90% adherence, and lowest in those reporting taking less than half (efficacy estimates, 68%, 34%, and 16%, respectively). Anderson and colleagues reported on drug levels among a subsample of 179 iPrEx trial participants in the active study drug group at the 24-week study visit (Abstract 96LB). Overall, 50% had detectable metabolites of tenofovir and emtricitabine in their peripheral blood mononuclear cells (PMBCs), indicating no study drug had been taken for at least 1 week to 2 weeks before the visit. Participants 25 years or older were more likely to have detectable drug than younger participants (73% vs 44%, respectively; $P < .001$). Drug was most commonly detected in men reporting unprotected receptive anal sex, less common in sexually active men without this risk, and least common in men reporting no sexual activity in the prior 12 weeks (in 76%, 59%, and 35%, respectively; $P = .003$), suggesting that men may have used sexual risk to determine whether or not to take the study drug.

Celum reviewed data from the IAVI (International AIDS Vaccine Initiative) E001 and E002 studies and reminded attendees that adherence by electronic measurement of opening pill bottles was highest with daily dosing; intermediate with fixed-dose, twice-per-week dosing; and lowest for fixed-dose plus postcoital dosing (Abstract 120). There also appears to be substantial heterogeneity between populations, with adherence higher among 34 US iPrEx study participants than among 145 non-US iPrEx study participants ($P < .0001$) (Abstract 96LB). In an adherence substudy from the Partners PrEP efficacy trial in Uganda, median adherence as measured by pill count and unannounced home visits was greater than 99% (Abstract 488).

Amico and colleagues reported on the correlation of self-report, pill count, drug dispensation records, and blood detection of study drug among the same 179 iPrEx study participants included in Anderson's presentation (Abstract 95LB). Men had a median self-reported adherence level of 100% by each of 4 measures, despite no detectable study drug in half of the samples tested. Even among men self-reporting never missing a pill in the prior month, study drug was detectable in only 68%. On the other hand, reports of low levels of adherence (less than half of pills taken) were uncommon (2%), but in this group, study drug was substantially less likely to be detected (22%).

Clearly, better measures of adherence than self-reporting and pill counts are needed. Liu and colleagues reported on drug levels present in hair samples among 15 HIV-uninfected persons taking tenofovir for 2, 4, or 7 days per week under modified directly observed dosing, in a cross-over study design (Abstract 995). Tenofovir levels in scalp hair were strongly correlated with dose, suggesting that this may be a useful strategy for monitoring adherence in clinical trials.

Concerns have been raised about whether tenofovir-based regimens would be associated with an unacceptable rate of adverse events (AEs) in an otherwise healthy population. Grant and colleagues reported that participants randomly assigned to take tenofovir/emtricitabine in the iPrEx trial had no higher rate of serious, grade 3, or grade 4 AEs than did placebo participants (Abstract 92). The only symptoms reported more commonly in participants in the active study group than in the placebo recipients were nausea (2% vs < 1%, respectively; $P = .04$) and weight loss (2% vs 1%, respectively; $P = .04$). Participants given tenofovir/emtricitabine were somewhat more likely to have elevated creatinine levels (2% vs 1%, respectively; $P = .08$), although only 5 participants in the tenofovir/emtricitabine group had elevated creatinine levels lasting for 2 or more visits. All creatinine elevations resolved after drug discontinuation; 4 of the participants restarted the study drug and exhibited no recurrence of creatinine elevation.

Mulligan and colleagues reported on bone mineral density (BMD) among a subset of 503 iPrEx trial participants on 4 continents (Abstract 94LB). At baseline, before initiation of the study drug, BMD was low (ie, z score, < −1.0) in 36% of participants in the spine and in 18% in the hip. There were small but statistically significant decreases in BMD in participants receiving tenofovir/emtricitabine compared with those receiving placebo for the total hip (−0.65 at 24 weeks; −0.95 at 48 weeks) and spine (−0.95 at 24 weeks), although no difference was observed between the groups in bone fractures or international standards for low BMD (z score, < −2.0).

Liu and colleagues also reported on BMD changes in a group of 200 HIV-seronegative men in San Francisco enrolled in a phase II tenofovir PrEP study (Abstract 93). They reported that 10% of men had low BMD at baseline

(*z* score, < −2.0). In addition, low BMD was statistically significantly higher in men reporting amphetamine (OR, 5.9; *P* < .001) or amyl nitrite (OR, 4.6; *P* = .002) use and statistically significantly lower in men reporting use of multivitamins, calcium, or vitamin D (OR, 0.3; *P* < .001). Men receiving tenofovir also had small but statistically significant decreases in BMD in the femoral neck (−0.4%; *P* = .004) and total hip (−0.8%; *P* = .003) but not in the spine (−0.7%; *P* = .13). There was no statistically significant decrease in BMD after 12 months on the study drug, and no differences were observed in fractures between study groups. The clinical importance of both the higher-than-expected proportion of men with low BMD at baseline and the small reductions in BMD in MSM taking tenofovir-based PrEP regimens is not yet known.

Drug resistance is another concern that has been raised about the use of PrEP. Grant and colleagues reported no additional cases of drug resistance in the iPrEx study; the only cases previously reported consisted of 3 participants who were already HIV-infected at enrollment (Abstract 92). Liegler and colleagues searched for minor variant drug resistance among iPrEx trial participants and found 1 K65R minor variant and 1 M184V minor variant in 2 placebo recipients (Abstract 97LB). No minor variants were found among participants given active drug, including the 3 participants with breakthrough infections, in whom low levels of study drug were detected at the first-infection time point. Levels of drug-resistant virus in the 2 participants HIV-infected at baseline who received study drug declined to below the lower limit of detection (< 0.5%) through week 40 of follow-up, suggesting that drug-resistant virus, when it emerges, may revert quickly to wild type.

Garcia-Lerma presented data on the efficacy of oral tenofovir/emtricitabine against an emtricitabine-resistant simian-HIV (SHIV) variant (Cong et al, Abstract 31). In this study, all 5 animals treated with twice-weekly oral tenofovir/emtricitabine (3 days before and 2 hours after challenge) were protected against 14 weekly, low-dose, rectal challenges with $SHIV_{162p3M184V}$. All 5 control animals became infected (*P* = .0008). This suggests that oral PrEP may protect against some resistant viral strains.

Drug penetration into genital tissue. Celum reminded attendees that the effectiveness of PrEP will depend on "getting the right drug to the right place at the right time" (Abstract 120). Several presentations focused on the timing and levels of drug penetration into genital tissues. Dobard and colleagues presented in vitro data suggesting that tenofovir/emtricitabine provides protection only 2 hours after challenge, whereas raltegravir provides protection up to 8 hours to 10 hours after challenge (Abstract 30). In a low-dose, twice-weekly, vaginal-challenge model, 1% raltegravir gel administered 3 hours after challenge protected 5 of 6 macaques through 20 challenges. All 4 control animals became infected. This suggests that integrase inhibitors may be particularly useful as PEP drugs.

Brown and colleagues reported on concentrations of darunavir, ritonavir, and etravirine in seminal plasma and rectal tissue of 12 HIV-seropositive men, to consider these drugs' utility for PrEP in HIV-uninfected persons (Abstract 992). Seminal plasma levels were 80% to 93% lower than blood plasma levels for the 3 drugs, and rectal tissue levels were 3 to 13 times higher, perhaps reflecting fecal elimination of these drugs.

Nel and colleagues presented pharmacokinetic and safety data on the investigational dapivirine vaginal ring in 48 women (Abstract 1001). The ring was well tolerated and was not associated with serious AEs. Drug concentrations remained high through 35 days of use. Celum reported on plans to conduct an efficacy trial of the dapivirine ring (Abstract 120).

Singer and colleagues reported on the ethylene-vinyl acetate (EVA) ring containing 100 mg of the investigational nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) MIV-150 in a macaque high-dose, vaginal-challenge model (Abstract 1003). Only 2 of 14 animals with the MIV-150 ring became infected compared with 3 of 4 control animals (14% vs 75%, respectively; *P* = .04). Silicone vaginal rings tested without study drug were reported to be safe and well tolerated among 169 women in South Africa and Tanzania (Abstract 1004).

Hendrix and colleagues reported on the relative safety, adherence, and acceptability of oral versus vaginal tenofovir (Abstract 35LB). In total, 144 women were enrolled at 4 US and 3 African sites and assigned to receive sequential 6-week periods of vaginal, oral, or both formulations. Although relatively infrequent, women reported substantially more nausea, diarrhea, and headache during periods when they were taking tenofovir orally. Self-reported adherence was high, but drug was detected in only 35% to 65% of samples, with no difference between study groups. Tissue levels observed with vaginal dosing were more than 100 times higher than with oral dosing; addition of oral dosing did not further raise tissue levels. US women preferred the oral formulation, whereas African women were evenly divided between preference for oral and vaginal use.

Rectal delivery of pre- and postexposure prophylaxis. Anton and colleagues reported on the safety and acceptability of this 1% tenofovir gel used rectally among 18 men and women. This hyperosmolar gel was neither well tolerated (ie, many reported lower-gastrointestinal AEs) nor highly acceptable (ie, only 25% of participants liked the gel) (Abstract 34LB). However, a single rectal dose resulted in 100 times the rectal tissue concentration of tenofovir compared with a single oral dose.

Dezzutti and colleagues presented data on a reformulated tenofovir gel prepared for rectal use (Abstract 983). The reformulated gel had lower osmolality, increased spreadability, enhanced transepithelial resistance, and elimination of the epithelial stripping of the colorectal implants that was observed with tenofovir gel. The anti-HIV activity was similar between gels, suggesting that the reformulated gel may be a useful rectal microbicide.

Leyva and colleagues evaluated 3 enemas of varying osmolality in 9 men (Abstract 993). Hyperosmolar enemas (sodium phosphate) caused the most epithelial disruption in the colorectum. Hypoosmolar enemas (distilled water) had the greatest colonic permeability. Isoosmolar enemas had the best colonic distribution and retention and were the most preferred by participants, suggesting that if larger quantities of rectal microbicides are required, isoosmolar enemas may be explored as a vehicle for microbicide delivery.

Models and surveys on preexposure prophlaxis. Abbas and colleagues (Abstract 98LB) and Hallett and colleagues (Abstract 99LB) modeled the relative benefits and risks of using only antiretroviral therapy for HIV-infected persons versus combining antiretroviral therapy with PrEP for HIV-uninfected persons; the models examined effects on the HIV epidemic in South Africa and among serodiscordant couples, respectively. In Abbas and colleagues' model, the use of both antiretroviral therapy and PrEP in a community led to a larger prevention impact on the epidemic than either alone. Antiretroviral therapy is predicted to contribute substantially more HIV resistance at a community level than PrEP, although inadvertent PrEP use among HIV-infected persons would also contribute to cases of resistance.

Hallett and colleagues posed the question of whether it would be more cost-effective in preventing HIV transmission to provide PrEP to the HIV-uninfected partner or antiretroviral therapy earlier to the HIV-seropositive partner. Assuming all HIV-seropositive partners are treated when CD4+ cell count falls below 200/μL, PrEP would be more cost-effective only if the cost of PrEP is less than 40% of the cost of antiretroviral therapy and if PrEP is more than 60% as effective. PrEP would be more cost-effective at lower levels of effectiveness when used by higher-risk couples (eg, in couples for whom the HIV-uninfected partner may be at risk from outside partners). Additionally, if all HIV-seropositive persons are treated when CD4+ cell counts drop below 350/μL, PrEP again becomes more cost-effective at lower thresholds of effectiveness because of the lower possibility of transmission from partners with CD4+ cell counts above 350/μL.

Park presented an evaluation of the cost-effectiveness of PrEP in South African women (Walensky et al, Abstract 37LB). At the efficacy ranges observed in the CAPRISA 004 and iPrEx trials, they report that PrEP would be cost-effective (≤ $4600/year of life saved). If PrEP could be targeted to women at very high risk (ie, incidence > 9%/year), be very effective (ie, > 70%), and cost less than $40 per year, PrEP could be cost-saving for South African women.

Mayer and colleagues examined practitioner preferences for oral versus topical PrEP (Abstract 1000). More than two-thirds of the 121 physicians in Massachusetts completing the survey preferred topical PrEP, because of perceptions of fewer AEs (93%), increased ease of use (66%), and common use of lubricants for sex (54%). Nearly all (97%) stated that the major factor influencing their prescribing PrEP would be formal guidelines from the US Centers for Disease Control and Prevention (CDC).

Treatment as Prevention

One themed discussion session (Session 42) and several additional posters addressed how summary measures of viral load within communities (community viral load, CVL) are related to HIV infection rates and provision of care in different US cities. Das and colleagues reported that progress has been made in San Francisco in mean CD4+ cell count at diagnosis, rates of antiretroviral therapy initiation, and time to virologic suppression (Abstract 1022). In particular, time from diagnosis of HIV infection to virologic suppression decreased substantially from 32 months in 2004 to 8 months in 2008 ($P < .001$). Decreases in CVL also correlated with decreases in newly diagnosed and reported HIV cases ($P < .001$).

Similarly, HIV incidence decline correlated temporally with a reduction in CVL among a cohort of IDUs in Baltimore (Abstract 484). Castel and colleagues reported on CVL as a population-based biomarker of HIV transmission in Washington, DC, from 2004 to 2008 (Abstract 1023). Although only half of the more than 15,000 HIV cases diagnosed during that time had a viral load measurement available, mean CVL decreased substantially over that time. CVL was highest in geographic areas with the highest levels of poverty and unemployment and the lowest proportion of high school graduates. The mean of the most recent viral load was highest among women, blacks, and those infected heterosexually, through IDU or "other" modes of transmission.

Laraque and colleagues also showed disparities in CVL in New York City, with higher viral loads observed in men, young and middle-aged adults, MSM, persons with AIDS or low CD4+ cell counts, persons with more recently diagnosed cases, and persons in specific neighborhoods (Abstract 1024). Terzian and colleagues also reported on CVL in New York City to monitor the effectiveness of care (Abstract 1025). Most HIV-seropositive persons had repeated viral load testing, suggesting they were receiving ongoing clinical care. Although nearly half had fully suppressed viral load over the prior year, a small proportion had sustained high viral load, and these persons were more likely to be younger, black, or female.

Several models suggest that although treatment is likely to have a beneficial effect on HIV transmission rates, prevention interventions must also be used to change the course of the current HIV epidemic. Prabhu and colleagues used data from South Africa, Kenya, Malawi, and Mozambique to project the proportion of new infections attributable to different stages of HIV infections (Abstract 482). Less than 10% of new infections are attributable to untreated HIV infection, whereas two-thirds to three-fourths of new infections are associated with chronic, undiagnosed infection, and one-fifth to one-fourth are attributable to acute infection. This would suggest that substantial effort should be focused on increasing HIV

testing uptake, particularly for those with established infection.

Van Sighem and colleagues used a mathematic model to evaluate the impact of various interventions on the annual number of new infections in MSM in the Netherlands (Abstract 483). Although immediate treatment for all HIV-infected persons would lead to a rapid decrease in HIV infection rates, this decline would not be sustained. Decreasing risk practices and reducing the time from infection to diagnosis (leading to a decrease in risk behaviors) are needed to fundamentally alter the trajectory of new HIV infections.

Bongaarts presented models from a 2010 Institute of Medicine report (Bongaarts and Pelletier, Abstract 173).[4] In projecting the future of the African epidemic, increasing rates of treatment would slow the rates of new infections and AIDS deaths but increase costs over time. Only by adding prevention to treatment would new infections and AIDS deaths decline and costs decline over time. This led to the conclusions from this report that "treatment costs…are unsustainable" and "greater emphasis must be placed on prevention of new infections."

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A list of all cited abstracts appears on pages 99–106.

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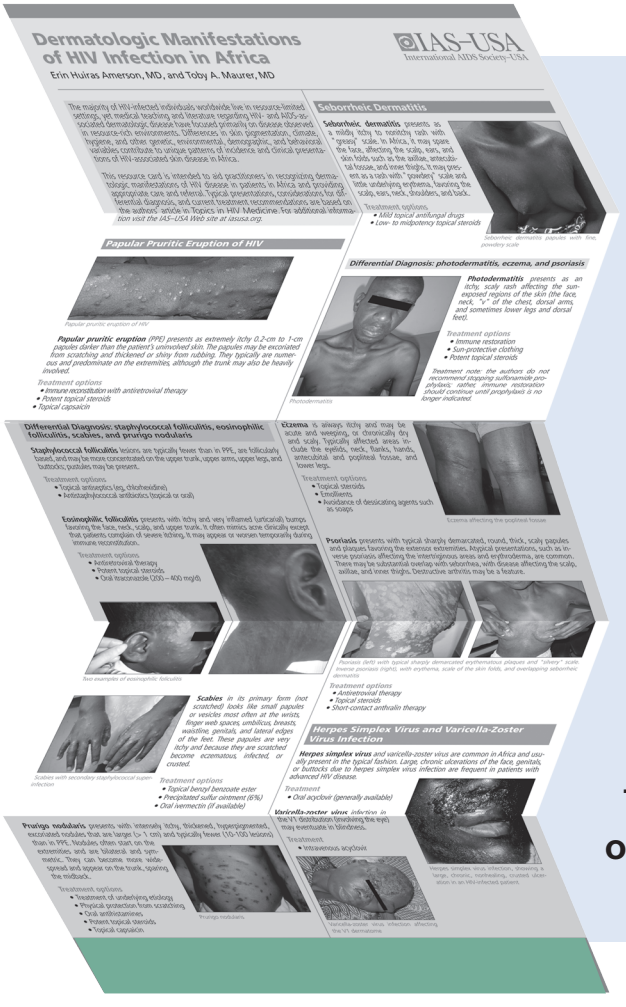

Dermatologic Manifestations of HIV Infection in Africa Resource Card

Based on the *Topics in HIV Medicine* article from February/March 2010, this folding card is available on request by visiting www.iasusa.org. Included are brief descriptions of selected dermatologic manifestations, along with their differential diagnoses and treatment options.