# Epidemiology and Prevention

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*The 2006 Conference on Retroviruses and Opportunistic Infections marked the 13th year of this conference and the 25th anniversary of the first published cases of AIDS in gay men in Los Angeles. As noted in the opening plenary session, HIV has likely been present in the human population since the 1930s, and therefore represents a relatively recent disease for humans. However, by the end of 2005, more than 40 million persons were estimated to be living with HIV infection, and 5 million new infections are occurring annually. Investigators at this year's conference presented a number of abstracts focused on the leading edge of the epidemic, HIV testing strategies, the role of acute versus chronic HIV infection in driving the epidemic, and the substantial progress being made in developing and testing a variety of biomedical prevention strategies.*

## The Global Epidemic

Sub-Saharan Africa continues to account for the majority of new and prevalent HIV infections worldwide. Rehle and colleagues presented data from the 2005 South African national household survey on HIV, behavior, and communication (Abstract 31LB). Among the 15,851 individuals for whom linked anonymous testing was performed, HIV prevalence in persons 2 years or older was 10.8%. As has been demonstrated in a number of other countries in sub-Saharan Africa, the prevalence is higher and peaks earlier in women than in men. For example, HIV prevalence was 4.4% in men 15 to 24 years of age, but was nearly 4 times higher in girls of that age group (16.9%). Because of recent concerns that BED-enzyme immunoassay (an IgG enzyme immunoassay assay to distinguish recent from chronic infection) may substantially overestimate HIV incidence rates, these investigators used a number of methods to estimate HIV seroincidence in the population. Estimates using a lower optical density ratio for BED (0.4 instead of 0.8 cutoff) resulted in similar estimates to those using a birth cohort method, with an overall rate of 1.9 per 100 person-years in adults aged 15 to 40 years. This methodologic issue is of crucial importance in projecting the growth of epidemics and for properly sizing prevention trials in these communities.

High HIV seroprevalence points to the need for HIV counseling and testing services throughout the developing world, particularly as antiretroviral therapy becomes available to larger populations. Weiser and colleagues (Abstract 25) conducted an assessment of attitudes toward HIV testing among a population-based survey of 1268 adults in 5 districts in Botswana. The majority of participants felt that routine testing would decrease barriers to testing (89%), HIV-related stigma (60%), and violence toward women (55%). A substantial minority, however, were concerned that routine testing would lead people to avoid medical care (43%) or were concerned that they could not refuse the test (32%), suggesting that more work needs to be done to reduce stigma and emphasize the voluntary nature of testing.

Although the HIV epidemic continues to be fueled largely by sexual transmission worldwide, there is a burgeoning epidemic of HIV in injection drug users (IDUs) in Eastern Europe and Asia. Two posters focused on this epidemic at different stages in different regions. Beyrer and colleagues presented data from Dushanbe, Tajikistan (Abstract 923). In 2001, HIV prevalence in a cross-sectional sample of IDUs there was 3.85%. By 2004, prevalence had increased to 12.1%. Solomon and colleagues presented data from IDUs in Chennai, India, where HIV prevalence had reached 35.6%, and incidence using the BED assay was 4.5% per year (95% confidence interval [CI], 0.6–8.5; Abstract 922). Prevention interventions must be designed and tested in IDUs as well as those at risk through sexual transmission.

This year's international symposium focused on the intersection of HIV with other infectious diseases, including pneumococcal infection, tuberculosis (TB), and malaria. Klugman pointed out that the leading infectious cause of death worldwide is respiratory infection, with the leading 2 causes in HIV-infected persons being TB and pneumococcal disease (Abstract 10). Pneumococcal disease in HIV-infected adults and children is more likely to be caused by pediatric serotypes and more likely to be resistant to antibiotics. Although conjugate vaccine protects HIV-infected children from invasive disease and has lowered the burden of disease among adults through herd immunity, the total number of pneumoccal infections does not appear diminished in HIV-infected women, probably because women are getting infected through their exposure to children with other pneumococcal serotypes not covered by the conjugate vaccine. The 23-valent vaccine given to adults may protect HIV-infected persons on highly active antiretroviral therapy (HAART), but may not be immunogenic in untreated persons with advanced HIV disease. This highlights the need to detect and immunize HIV-infected patients with pneumococcal vaccine early in disease.

Harries provided an overview of the devastating interaction of HIV and

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TB globally (Abstract 9). In 2004, 24 million people were coinfected with HIV and TB worldwide. HIV-infected persons have 50-times higher rates of progression to clinical TB than HIV-uninfected persons, and the clinical course is more difficult to diagnose and more deadly. This epidemic of coinfection is particularly acute in sub-Saharan Africa, where 60% to 80% of TB-infected individuals are HIV seropositive, and TB accounts for 30% to 40% of deaths in HIV-infected persons. Harries also focused on the negative impact these infections have on the healthcare delivery system. HIV has already led to reduced staffing through illness in healthcare workers and their families. Centralized TB care can lead to nosocomial infections, and HIV-infected healthcare workers are particularly susceptible. A recent survey of 40 hospitals in Malawi found that half of all healthcare worker deaths were due to TB, and an additional 40% due to HIV. Harries called for joint coordination of TB and HIV control programs at all levels, intensified case finding and TB treatment among HIV-infected persons, TB infection control in healthcare and group settings, increased HIV counseling and testing in TB patients, implementation of cotrimoxazole therapy among HIV-infected persons, and continued scale-up of HAART.

Malaria is one of the leading causes of childhood mortality worldwide, with 500 million new cases each year and 1 million deaths. Slutsker (Abstract 8) provided a comprehensive review of the negative impact of HIV on malaria: among HIV-infected adults and children, increased incidence of malaria, poorer response to antimalarial agents; in children born to mothers with placental malaria, low birthweight and infant mortality; and in infants coinfected with malaria and HIV, severe anemia. The evidence for the negative impact of malaria on HIV disease is much more modest, with an average increase of 0.25 $\log_{10}$ plasma HIV RNA copies/mL, a transient drop in CD4+ cell count, and mixed evidence about the role of malaria in mother-to-child transmission of HIV. Slutsker briefly reviewed the therapeutic implications of coinfection with both agents, and the opportunities for prevention and research through interaction between malaria control and HIV prevention and treatment programs.

## The Epidemic in the United States

In the United States, the HIV epidemic continues to be concentrated most heavily in the African American population and in men who have sex with men (MSM). Durant presented some hopeful data from the Centers for Disease Control and Prevention (CDC), suggesting that new HIV diagnoses have declined from 2001 to 2004 among African Americans in the 33 states with named HIV reporting (Abstract 27). However, African Americans comprised 51% of the new HIV diagnoses during those years, despite making up only 13% of the population in those states. The one African American population in whom new diagnoses did not decline was MSM. Previously published CDC data on all racial and ethnic groups have found that MSM continue to account for the largest number of new HIV diagnoses, and are the only risk group with increasing rates of new diagnoses (CDC surveillance report, 2005).

Sifakis and colleagues provided a snapshot of the US MSM epidemic in Baltimore (Abstract 28). In an analysis of 891 men recruited from gay venues in Baltimore as part of the Behavioral Surveillance Research (BESURE) study, overall HIV seroprevalence was 32.2% and HIV seroincidence—calculated using the serologic testing algorithm for recent HIV seroconversion (STARHS or "detuned" assay)—was 9.2% per year (95% CI, 4.3–17.4). Among the 500 African American MSM in this study, prevalence was 45.6%, estimated seroincidence was 15.4% per year (95% CI, 8.7–25.2), and only 36% of the HIV-infected men reported knowing their HIV status. Although it is possible that detuned studies overestimate true population seroincidence rates, these data highlight the very substantial epidemic occurring in MSM, and particularly African American MSM, in the United States and point to the importance of increased access to HIV testing and prevention and care services.

One strategy that is being used by some MSM to reduce the risk of HIV transmission is serosorting, or intentionally selecting sex partners or deciding on condom use based on partner serostatus. Golden addressed the question of the frequency and potential utility of serosorting among MSM as a strategy for decreasing HIV transmission rates (Abstract 163). There is indirect evidence that serosorting is occurring in MSM populations, and that the practice may be increasing. Although serosorting may reduce the risk of HIV transmission, it is an imperfect strategy: several studies estimate that 15% to 30% of new HIV infections in MSM are occurring in men who report having unprotected anal sex exclusively with men believed to be HIV seronegative. Golden concluded that serosorting is likely a useful strategy only for men who are already engaging in high-risk activities, but could paradoxically increase risk in men who are already relatively safe. He recommended that clinicians urge their patients to both know and disclose their serostatus to their partners, and urged further evaluation of the public health utility of serosorting before recommendations are put into place.

## HIV Testing Issues

Mastro presented the CDC's new recommendations for routine "opt-out" HIV testing in clinical settings, currently under development (Abstract 164). He pointed out that of approximately 1.1 million persons living with HIV in the United States, one fourth are unaware of their infection. He reviewed the substantial benefits that accrue when individuals learn their HIV serostatus: opportunities for treatment with HAART leading to improved survival and quality of life, opportunities for treating pregnant women with antiretrovirals leading to dramatic reductions in the number of newly

infected infants, and substantial self-reported changes in risk behaviors after individuals learn their HIV-positive serostatus. Other recent data suggest that some of the most heavily affected populations, including African Americans and young people, may be significantly less likely to know their HIV serostatus. Nearly half of newly diagnosed AIDS cases had only learned of their HIV-positive serostatus within the 12 months prior to development of AIDS, limiting the benefits they may have received had antiretroviral therapy been started earlier in their course of disease.

The CDC is in the process of developing new testing guidelines that would recommend routine, voluntary HIV screening in healthcare settings for all patients aged 13 to 64 years, eliminating recommendations that only high-prevalence populations or individuals with certain risk behaviors be tested. At-least annual screening of high-risk persons continues to be recommended. Patients would be given an opportunity to ask questions but consent would be covered under the general consent for receipt of medical care, and patients would need to "opt out" of HIV testing rather than "opt in" as is currently practiced in most settings.

Mastro presented data from Texas sexually transmitted diseases clinics in which a substantially larger proportion of patients were tested with an opt-in than an opt-out testing program. This change resulted in a 60% increase in the number of HIV-infected patients identified. Several analyses suggest that routine screening would be cost-effective, even with very low prevalence in a community (0.05%). However, the CDC is recommending that after routine screening is implemented, if prevalence in a particular setting is documented to be below 0.1%, routine screening could be stopped. As part of these guidelines, the CDC also suggests that clinical settings need not provide risk-reduction counseling as part of HIV counseling and testing, but that patients may instead be referred to prevention services in the community. There was a substantial amount of discussion after his presentation from both clinicians and community members, expressing concern about the lack of adequate healthcare infrastructure to handle increased demand once more HIV-infected persons are identified. Concerns were also raised about whether patients are likely to be adequately informed about the testing, and the extent to which true linkages will be made with local HIV prevention services.

Branson and colleagues presented data from a CDC investigation of reports of excessive false-positive test results from oral fluid rapid tests (Abstract 34LBb). A rapid HIV antibody test was approved for use with oral fluid in March 2004. In December 2005, there were several reports in the press suggesting that some clinical sites were experiencing an unusually high rate of false-positive tests, and the CDC investigated these concerns through a number of methods. Combined data from more than 12,000 participants enrolled in 4 prospective studies comparing whole blood and oral fluid testing from 2000 to 2005 showed excellent specificity for both (99.6% for oral fluid versus 99.9% for whole blood). Because a small number of sites recently experienced a slight drop in the specificity of test results, several sites participated in additional analyses to determine the etiology of the relative increase in the rate of false-positive test results. These analyses suggested that neither test lot nor device problems accounted for the difficulty. It seems more likely that the problems encountered were site-specific, but this hypothesis needs to be explored in more detail.

The CDC has developed an interim strategy to help sites deal with this issue that involves a second rapid test on a fingerstick specimen for patients with a positive result on an oral fluid specimen. All positive results require confirmation, but a negative result on a fingerstick specimen could indicate a false-positive result, and would help sites communicate the uncertainty of the screening result and the need for a confirmatory test.

## The Role of Acute HIV Infection

Fraser and colleagues presented a very clear and reasoned overview of the role of primary (acute) HIV infection in driving the epidemic globally (Abstract 162). Early in the course of a local epidemic, when HIV infection rates are low overall, a substantial proportion of new infections occur through transmission from persons with early HIV infection. However, once an epidemic has matured, acute infection is likely to play only a minor role in new infections (eg, projected as 12% of new infections among heterosexuals in Rakai, Uganda), primarily because acute infection lasts a matter of several weeks to months, but chronic asymptomatic infection can last more than a decade. Fraser's colleagues from the Imperial College in London also suggested that transmissions during acute infection alone cannot cause an epidemic (Abstract 913), and that there are not likely to be virologic "super-spreaders" of HIV (Abstract 910). Investigators at the University of North Carolina, on the other hand, have previously published statements to the effect that acute infection does account for a substantial number of new infections (Pilcher et al, ***J Infect Dis***, 2004). At this conference, they presented several studies on the utility of pooled RNA testing to identify acutely infected persons (Abstracts 370, 371, 374.) In these studies, they were able to identify small numbers of acutely infected persons and interrupt small numbers of transmissions between sexual partners or from mother to child. The likely public health utility of this strategy of testing is not yet known, but may depend on the likelihood that acute infection is fueling the HIV epidemic and on the effectiveness of interventions during acute infection at preventing transmission.

## Biomedical Prevention Strategies

This year's conference featured a number of presentations on the state-of-the-art of biomedical prevention interventions. HIV vaccine research is

summarized in the review by Dr. Johnson in this issue.

Quinn presented the case for male circumcision in a plenary session, reviewing the long-standing history of what is likely the oldest and most common surgical procedure (Abstract 120). A number of ecologic studies have demonstrated an inverse relationship between circumcision rates and HIV prevalence in both Africa and Asia, and data from cross-sectional and longitudinal studies have also demonstrated an association of circumcision and lower HIV prevalence and incidence.

More recent data suggest a protective effect of circumcision on HIV transmission to uninfected female partners (Abstract 128), particularly for HIV-infected men with low viral loads. There is also biologic plausibility that circumcision could reduce HIV acquisition and transmission, as the inner surface of foreskin is a large nonkeratinized surface enriched with HIV target cells, and is prone to microtears that render it susceptible to other sexually transmitted infections. As reported at the International AIDS Society meeting in Brazil in July 2005, one randomized controlled trial of circumcision demonstrated a 60% reduction in HIV infection rates in circumcised men (Auvert et al, IAS, 2005). Two other trials are fully enrolled and due to provide data in the second half of 2007. One trial is evaluating the effect of circumcision on male HIV acquisition, and the other the effect of circumcision on transmission to uninfected female partners. If circumcision is proven to lower HIV infection rates in these trials, it is likely to be a cost-effective strategy that could have a dramatic impact on HIV infection rates in uncircumcised populations.

Much planning will be required to roll out this potentially cost-effective strategy for large populations that could minimize surgical risks, maximize acceptability, and counter the potential increases in risk behavior, which could lead to paradoxical increases in HIV infection rates.

A number of presentations focused on the use of antiretrovirals for prevention of HIV transmission, either initiated after a high-risk exposure (postexposure prophylaxis, or PEP) or through continual therapy (pre-exposure prophylaxis, or PrEP). As reviewed by Cohen (Abstract 54), there are no direct clinical data proving that PEP prevents HIV acquisition, and there have been reported cases of infection despite PEP. Nonetheless, there are abundant animal data suggesting that the approach may be efficacious, and the CDC has recommended PEP for occupational exposures since 1996 and for nonoccupational exposures since 2005. A World Health Organization study indicated that 98% of 41 developing countries surveyed had national PEP guidelines, and 20% of these recommend PEP for nonoccupational high-risk exposures (Abstract 904).

One of the major challenges of implementing PEP is getting treatment administered quickly after the high-risk exposure. Kindrick and colleagues reported that 55% of calls to the National Clinicians' PEP Hotline occurred more than 24 hours after an exposure, and 25% occurred after 72 hours (Abstract 906). Because animal data suggest that efficacy is likely to be highest if PEP is initiated shortly after exposure, it is imperative that clinicians and patients understand that PEP should be initiated as soon as possible after exposure, rather than any time up to 72 hours.

Roland and colleagues presented data on 457 people presenting for PEP for sexual exposures, randomized to 2 versus 5 risk-reduction counseling sessions (Abstract 902). Although both groups had similar reductions in the reported number of sex acts at the 12-month visit compared with baseline, those in a higher risk group (more than 4 unprotected sex acts) had a greater reduction in risk with 5 counseling sessions than with 2 sessions. This highlights the need to provide more intensive counseling services for those at highest risk and emphasizes that the greatest effect of PEP may be in providing clinicians the opportunity to link high-risk patients with more intensive preventive services. Cohen also suggested that drugs for PEP should be selected, in part, based on their concentration in genital secretions, and presented a graphic indicating that nucleoside reverse transcriptase inhibitors (nRTIs) are generally superior to protease inhibitors (PIs) in concentration in genital secretions (Abstracts 54, 129).

Published data suggest that for some high-risk populations, the majority of seroconversions occur in persons with multiple episodes of risk, rather than isolated exposures (Celum et al, ***J Infect Dis***, 2001). For these situations, use of PrEP has several theoretic advantages over PEP providing ongoing protection in which timing of the intervention does not need to be matched to self-identification of exposure. At this conference, Heneine and colleagues presented data from an animal model of PrEP, in which 6 macaques were given daily subcutaneous tenofovir and emtricitabine injections beginning 9 days prior to the first rectal challenge, through 28 days after the last challenge (Abstract 32LB). All 6 macaques were completely protected from weekly rectal simian HIV (SHIV) challenge, comparable in titer to viral levels in semen in acute infection. In contrast, 5 of 6 control animals were infected.

These are promising data from a challenge model that may more closely mimic human sexual exposure. Some have compared these results with data presented last year from the same group in which macaques given lower doses of oral tenofovir were all infected, albeit several weeks later than the control animals. What is not clear is whether the difference between last year's and this year's experiments was the addition of a second drug, or whether the problem in the earlier experiment was in giving the animals too low a dose of tenofovir, and administering it orally, when ingestion cannot be assured. Heneine also presented preliminary data from an ongoing study of emtricitabine alone in the macaque model, and in this trial, 1 macaque was infected after the fifth exposure and a second after

the tenth. The relevance of all of these data requires validation from human trials, which are currently underway.

Cohen summarized the state of clinical PrEP trials (Abstract 54) in which several trials have been closed or not allowed to open (Cambodia, Cameroon, Nigeria, Malawi), 1 trial site has been completed (Ghana), and several other studies are underway (Thailand, Botswana, San Francisco, Atlanta) or planned (Peru). Some of the factors leading to study-site closure were concerns expressed by community groups or governments about protection of study participants (access to medical care including antiretrovirals for participants becoming infected in trials and coverage for trial-related injuries) and concerns about emergence of drug resistance in the community. These studies have reinforced the importance of community involvement in the planning and implementation of trials, and of creating sufficient clinical and regulatory infrastructure in locations in which clinical trials are performed. Current trials are working closely with community groups and should provide important information on the safety of daily oral tenofovir in HIV-uninfected subjects, the impact of PrEP on risk behaviors, and preliminary estimates of PrEP efficacy.

Hillier presented an overview of physical and chemical barriers to protect women from HIV acquisition (Abstract 55). She noted that in many countries, HIV seroprevalence is much higher for young women than for men of the same age, pointing to the need for methods of prevention controlled by women. The most promising physical barrier approach, apart from male and female condoms, is the use of diaphragms. A large efficacy trial of diaphragms (the Methods for Improving Reproductive health in Africa, or MIRA, study) is currently underway in South Africa and Zimbabwe, with results expected in 2007. A number of approaches are being taken to developing topical microbicides, and efficacy trials are currently evaluating 5 different products (cellulose sulfate, Pro 2000, C31G, carbopol 974P, and a lambda carrageenan microbicide). Moore reviewed the spectrum of new products in early stages of development, including antiretroviral agents, monoclonal antibodies, small interfering RNA, chemokines, and live commensal bacteria (Abstract 121). There are limited nonhuman primate data supporting the efficacy of some of the investigational products and approaches, and of combination approaches, but few are yet in clinical trials. Hillier and Moore both pointed to major challenges that remain including the development of better animal models and their relevance for human experience; measuring the relative safety, effectiveness, and effect on resistance of antiretrovirals administered topically; the need to develop products that can be applied daily or less frequently (eg, weekly, monthly); and the cost and acceptability of products. A number of investigators are also developing better ex vivo explant models (Abstract 893) and validating biomarkers of vaginal mucosal integrity (Abstract 896) to allow for more rapid evaluation of products prior to entry into clinical trials.

Nagot presented data on the impact of herpes simplex virus (HSV)-suppressive therapy on HIV-1 genital tract and serum levels in HIV-infected women with high CD4+ cell counts, not requiring HAART (Abstract 33LB). Suppressive therapy with 1000 mg of valacyclovir daily led to a 0.39-$\log_{10}$ reduction of plasma HIV-1 RNA (compared with a 0.12-$\log_{10}$ increase in placebo recipients) and a 0.26-$\log_{10}$ reduction of plasma HIV-1 RNA in genital secretions (compared with a 0.09-$\log_{10}$ increase in placebo recipients). Valacyclovir also had a beneficial effect on HSV-2 shedding in these women. This is the first randomized controlled trial demonstrating a reduction in HIV levels in patients with HSV treated with HSV-suppressive therapy. Two large efficacy studies are currently underway to further test this approach in reducing the number of new HIV infections. One study is nearing enrollment completion of more than 3000 participants in the United States, Peru, and sub-Saharan Africa to evaluate the efficacy of twice-daily acyclovir in preventing HIV acquisition in HSV-2-infected men and women at risk for HIV infection. The second study is evaluating the impact of daily oral acyclovir in the prevention of HIV transmission from HIV-infected persons with HSV-2 to their HIV-uninfected partners. Data are expected from these trials by 2007 or 2008.

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**A list of all cited abstracts appears on pages 63 to 70.**

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