

HIV Epidemiology and Prevention Interventions

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Several presentations at the 2007 Conference on Retroviruses and Opportunistic Infections focused on the underlying factors driving the HIV epidemic in selected regions of the world and on selected populations. The conference also provided updated data on 1 of 2 successful adult male circumcision efficacy trials to prevent HIV acquisition, and a review of 1 of 2 unsuccessful efficacy trials of the microbicide cellulose sulfate. Presentations also focused on strategies to prevent HIV acquisition through pre-exposure prophylaxis, treatment of sexually transmitted diseases, and prevention of mother-to-child transmission through breastfeeding.

The European Epidemic

An overview of factors driving the European AIDS epidemic was presented by Johnson (Abstract 54). The European epidemic is really 3 separate epidemics: 1) western Europe experienced a dramatic decline in newly diagnosed AIDS cases with the introduction of potent antiretroviral therapy in the mid-1990s; 2) central Europe has had a low-level, stable number of AIDS cases since the early 1990s; and 3) eastern Europe experienced dramatic increases in newly diagnosed infections and AIDS cases beginning in the early 2000s. Johnson provided insight into the many social, behavioral, and biologic factors driving these different epidemics.

The eastern European epidemic, now accounting for approximately twice the number of newly diagnosed HIV cases as in western Europe, is primarily driven by injection drug use (IDU) and secondarily through the heterosexual partners of these drug users. This is likely the result of the many political and social changes confronting eastern Europe, including changes in drug trafficking routes and drug prices, leading to an increase in the size of the population using drugs and HIV transmission within drug-sharing and sexual networks.

The western European epidemic was previously largely focused within populations of men who have sex with

men (MSM), where rates continue to be high, driven by increases in unprotected sex. Johnson speculated that the epidemic in IDU in western Europe may have been diminished through use of harm-reduction strategies, such as access to clean injection equipment and drug treatment programs. However, the predominant mode of HIV acquisition in western Europe is now heterosexual sex, with a substantial contribution from immigrant populations displaced by political and social upheaval in sub-Saharan Africa.

Each of the European epidemics is affected by late HIV diagnosis, as 34% of patients are diagnosed when CD4+ counts are less than 200 cells/ μ L, attenuating the effectiveness of antiretroviral therapy for them, and leading to potential increase in transmission to partners when HIV-seropositive individuals with late-stage disease are unaware of their infection status. Johnson called for increased HIV testing and evidence-based prevention interventions to populations at highest risk.

The US Epidemic

Jaffe reviewed the current status of the HIV epidemic in the United States (Abstract 63). By the end of 2005, nearly 1 million people had been diagnosed with AIDS in the United States, and more than 500,000 had died. The death rate of 58 cases per 1 million population in 2005 in the United States was twice that of any country in the European Union. Although the number of new AIDS cases has remained relatively stable throughout the early

2000s, there was an approximate 10% increase in AIDS cases in 2005, which may be an early indicator of an upward trend. MSM account for the majority of US HIV and AIDS cases, and their relative contribution to the total HIV and AIDS caseload in the United States continues to rise. African Americans make up half of all HIV and AIDS cases in the United States, and the HIV and AIDS case rate is 8-times higher in African Americans than whites in the United States.

Jaffe also reviewed prevention interventions that have led to substantial reductions in new HIV infections in the United States (eg, screening of donated blood, prevention of mother-to-child transmission [PMTCT], condoms, provision of clean injection equipment), and contrasted them with the government-supported approach of abstinence-only programs, for which scientific support is quite limited. A Cochrane review of 8 randomized, controlled studies of abstinence-only programs in youth in the United States found no statistically significant reduction in reported risk or biologic outcomes. A more recent unpublished study found a statistically significant reduction of sexual activity in African American youth (aged 10-15 years) randomized to receive an abstinence-only intervention, although 30% of the virgins in this arm of the study initiated sexual activity during the 24 month follow-up period. Jaffe made a plea to focus efforts on prevention interventions known to be successful, abandon those found not to work, and encourage leaders within at-risk communities to prioritize changes in behavior.

Several presentations focused on the need for increased HIV testing to detect HIV infections and thus reduce the risk of ongoing transmission. Weis and colleagues presented data on 4221 persons newly diagnosed with HIV infection in South Carolina from January 2001 to December 2005 (Abstract 957). Of this group, 73% had visited

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a South Carolina health care facility at least once prior to testing HIV seropositive, with a median of 4 visits per patient; 42% of this sample developed an AIDS diagnosis within 1 year of their first HIV-seropositive test. Torian and colleagues presented data on very late HIV diagnosis (Abstract 964). Overall, 28% of all newly diagnosed AIDS cases in New York City in 2004 had received their first HIV diagnosis within the previous 31 days. Independent predictors of late presentation were older age, heterosexual or unknown risk, or being foreign-born. Both studies highlight the need to expand HIV testing in health care settings and through outreach to vulnerable populations.

Other studies highlighted the difficulty of implementing broad testing programs in health care settings. Smerd and colleagues conducted a pilot project from January 2006 to August 2006 encouraging HIV testing in inpatient medical wards, ambulatory care, and emergency room settings (Abstract 958). Although there was an overall increase of 54% in the HIV testing rate over this time and 60% of those testing HIV seropositive were newly identified, testing rates remained quite low overall (< 10% in each of the settings). Bernstein conducted a survey of HIV testing practices among 7300 US physicians from 1999 to 2000, using the American Medical Association Master File (Abstract 960). More than 70% of providers responded, but only 28% of physicians reported screening asymptomatic men or non-pregnant women for HIV. At that time, independent predictors of providers offering tests to these patients were female sex, being black or Hispanic, provider practice being located in a large city or public clinic, and provider being a primary care specialist.

Other presentations focused on additional testing strategies to be implemented specifically for high-risk groups. Denning presented data from the 2003 to 2005 Centers for Disease Control and Prevention (CDC) National HIV Behavioral Surveillance survey and analyzed data from MSM offered HIV testing in 5 US cities (Abstract 956). Of the 1593 MSM who reported that their last HIV test was negative, 33%

stated they had not had a follow-up HIV test within the previous year. HIV testing was then conducted and 48% of those testing seropositive had not known their HIV serostatus. Denning concluded that a strategy of targeting only persons without prior HIV testing would have reduced the fraction of unrecognized HIV infection from 48% to 41%, but a strategy of annual testing would have reduced the fraction to 14%. Klausner and colleagues recommended coupling pooled HIV RNA testing with rapid HIV antibody testing in high-risk settings; data from their study of patients attending a sexually transmitted disease (STD) clinic suggested that HIV RNA screening increased HIV case detection by 12% (Abstract 953).

The Global Epidemic in MSM

Several presentations focused on the continued epidemic in MSM in different parts of the world. Van Griensven presented an overview of the topic, starting with a reminder that MSM make up half of the total number of HIV and AIDS cases in all persons (men and women combined) in the United States (Abstract 55). MSM are the only risk group in the United States in whom the proportion of new HIV and AIDS cases is increasing. Ellen also presented data on the US adolescent population, where the most heavily impacted population is young MSM (Abstract 145). In a venue-based sample, HIV prevalence in 15- to 19-year-old men was 7%, comparable with rates in young women in South Africa. In the National HIV Behavioral Surveillance survey conducted in 17 cities, 14% of MSM aged 18 to 24 years were found to be HIV infected.

However, the MSM epidemic is not confined to the United States, and van Griensven reviewed this global epidemic (Abstract 55). Throughout many countries in Latin America, MSM are the major risk group affected by HIV and AIDS, and prevalence rates in MSM exceed those in female sex workers by 10 to 15 fold. In Africa, which has been long-assumed to have very low rates of MSM sexual activity, 3 new surveys suggest very high HIV prevalence among popula-

tions of MSM, ranging from 9% to 38%. Because these first studies have been conducted in populations with relatively low HIV prevalence rates in the general adult population, MSM account for up to 36% of the total number of HIV-infected persons in those cities. Similarly, through many areas of Asia and Southeast Asia the prevalence of HIV in MSM is quite high and MSM make up a sizable proportion of the total estimated HIV infections: 28% of HIV cases in Hanoi, 30% in Bangkok, 37% in Yangon, and 69% in Beijing. Van Griensven pointed to the many individual-level (eg, unprotected anal sex, greater number of sex partners, substance use, STDs, lack of circumcision) and societal-level (eg, laws against MSM sex, discrimination, stigma, lack of access to prevention tools) factors contributing to the epidemic. He stated that the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that only 10% of MSM worldwide have access to prevention services.

Prevention of Sexual Transmission

The last few months have brought momentous changes to the field of HIV prevention, with 5 large efficacy trials of biomedical prevention interventions stopped early because of benefit or harm to trial volunteers and their partners. Several of these trials were reported on at this year's conference, including reports on adult male circumcision and vaginal microbicides. Other data presented at the meeting lent support to the potential for antiretrovirals to prevent HIV acquisition when given to HIV-seronegative persons as pre-exposure prophylaxis (PrEP) and the potential for herpes simplex virus-2 (HSV-2) suppression to reduce HIV transmission.

Male Circumcision

Gray and colleagues provided an in-depth review of 1 of the 2 successful adult male circumcision efficacy trials in HIV-seronegative men (Abstracts 155aLB and 155bLB) recently published in *Lancet* (Gray et al, 2007). That study from Rakai, Uganda showed a halving of HIV

acquisition among men aged 15 to 49 years randomized to receive immediate circumcision compared with the wait-list control group (odds ratio [OR], 0.49 on intention-to-treat analysis; 95% confidence interval [CI]; 0.28-0.84). This effect appeared to be strengthened among men with 2 or more partners (incidence rate ratio [IRR], 0.30), extramarital partners (IRR, 0.34), and during later follow-up periods (IRR, 0.25 for the second year of follow up).

Male circumcision was also associated with a statistically significant reduction in the rate of self-reported genital ulcer disease (IRR, 0.53) with no effect on the rate of self-reported urethral symptoms. Moderate or severe adverse events were relatively rare (3.6%) in this controlled clinical trial with highly trained staff; care will need to be given for prevention and management of surgery-associated complications if this intervention moves into community practice. Gray's study also found no evidence that circumcised men increased their risk compared with uncircumcised men (ie, behavioral disinhibition) although the other published paper describing the second successful male circumcision trial found a modest increase in several risk behaviors in the circumcised compared with uncircumcised groups (Bailey et al, *Lancet*, 2007).

Several days after the conclusion of the conference data were released from an early evaluation of the trial of male circumcision among HIV-infected men in Uganda. This trial was stopped early because of a statistically significant increase in the risk of HIV transmission to HIV-uninfected female partners. Exploratory analyses suggest that the increase in HIV transmission was associated with resumption of sexual activity before full healing of the surgical wound, and that the HIV incidence was comparable in the 2 arms when this subgroup was excluded. At best, these data suggest no immediate benefit to HIV-seronegative women from circumcision of their HIV-seropositive male partners and at worst substantial harm may arise. More concrete recommendations are expected after further analyses of this trial.

No recommendations have been made regarding the role of male circum-

cision in prevention of HIV transmission among MSM. Although 1 prospective cohort study of HIV-seronegative men found a doubling in the risk of HIV acquisition among uncircumcised men (Buchbinder et al, *JAIDS*, 2005), the population attributable fraction for this risk factor was only 10%. Begley and colleagues surveyed MSM attending gay pride events in 5 different states and found that 80% of men were already circumcised and 54% of the remainder were willing to undergo circumcision if circumcision were found to protect against HIV acquisition (Abstract 983).

Microbicides

Two large microbicide efficacy trials of cellulose sulfate were also stopped in early 2006 after an early analysis of data from 1 trial suggested an increased risk of HIV acquisition among HIV-seronegative women using this candidate microbicide. The second trial of cellulose sulfate found no evidence of increased transmission in the interim analysis several months earlier, but stopped the trial in the interest of safety for study volunteers.

Doncel presented preclinical data supporting the decision to evaluate cellulose sulfate in clinical trials (Abstract 106LB). Cellulose sulfate is a large sulfated polysaccharide that blocks gp120 and CD4+ coreceptor interactions. In extensive preclinical evaluation, it has been shown to have anti-HIV activity against both X4 and R5 viruses at concentrations that are not cytotoxic. It appears to be active against numerous HIV clades and drug-resistant isolates at concentrations that are orders of magnitude lower than the clinical dose. The product has also been shown to have activity against a number of STDs. Cellulose sulfate did not appear to be cytotoxic to cervico-vaginal cells nor to trigger release of inflammatory cytokines. These findings are markedly different than those seen in preclinical studies of nonoxynol-9. In addition, cellulose sulfate appeared to provide good surface coverage in the vagina and was nonabsorbable, nontoxic to lactobacilli (to maintain a healthy microenvironment), and long-lasting.

Van Damme presented clinical safety data on cellulose sulfate (Abstract 106LB). Eleven safety studies have been undertaken in which product was administered up to 4 times daily, generally for short courses (only 1 lasted to 6 months). In each of these studies, there was no evidence of local or systemic toxicity. A phase II trial of cellulose sulfate as a contraceptive was successfully completed in 200 couples, again with no apparent toxicity. Two large HIV prevention efficacy trials of this product were initiated. Van Damme reported on a multicenter, randomized, placebo-controlled trial that opened in July 2005 with the intention of enrolling 2574 HIV-seronegative women at risk for HIV acquisition. An interim efficacy analysis was planned when half of the 66 anticipated HIV infections in the trial had occurred, with a plan to stop the trial if the 2-sided *P* value was less than 0.10 in the direction of a greater number of infections in the cellulose sulfate arm, as this would indicate either potential harm or futility to find a difference. This interim efficacy analysis occurred on January 26, 2007, with data available on 35 new HIV infections in trial participants. At the time of data analysis, 1333 study participants had enrolled but only 326 had completed the full 12 months of follow up. Van Damme reported that the prespecified boundary for potential harm had been surpassed, but she declined to provide the breakdown of number of infections in each of the 2 arms. She stated that these numbers would change as final data were cleaned and made available.

The trial investigators and study staff moved rapidly to verify product labeling and coding of the randomization, and to confirm these results. They halted the trial on January 29, 2007, notifying study staff who in turn contacted study participants to stop using the product. All final study visits will be completed in April 2007. The investigators anticipate having a final report available by December 2007. A separate efficacy trial of cellulose sulfate had recently undergone an interim analysis that found no basis for early stopping. This trial was also stopped

in late January 2007 as a result of the finding of potential harm to study volunteers in the other efficacy trial.

Although the closure of these trials was a major blow to the field, several other large efficacy trials of different microbicides are currently underway, and results from those trials will be available in the next several years. Other presentations at the conference on microbicides focused on preclinical, *in vitro*, *ex vitro*, and modeling studies (Abstracts 988-1000). There is great interest in using topical antiretrovirals for prevention of HIV acquisition; this subject is covered below in the discussion of PrEP.

Pre-exposure Prophylaxis

Several presentations at this year's conference focused on the use of antiretroviral agents before HIV exposure, also known as chemoprophylaxis or PrEP. Cranage and colleagues presented data from a study of rectally applied 1% tenofovir gel to prevent simian immunodeficiency virus (SIV)_{mac32H} infection from single high-dose rectal challenge (Abstract 29). In this study, all 4 untreated macaques, 3 of 4 macaques given placebo gel, and 2 of 3 macaques given tenofovir gel 2 hours *after* exposure became infected, with detection of virus beginning 1 week after challenge and persisting through 20 weeks of follow up. In contrast, only 2 of 6 macaques pretreated with rectal tenofovir gel 15 minutes before exposure and 1 of 3 animals pretreated 2 hours before exposure became infected, and virus detection was intermittent or delayed in these animals. It should be noted that pretreated animals had systemic absorption of tenofovir, and those animals with breakthrough infection had lower blood levels of tenofovir than animals who were protected. Because the dose per kilogram was higher in macaques than normally used in humans and the blood levels apparently higher than with vaginal administration in human trials (Mayer et al, *AIDS*, 2006), this experiment may have more closely approximated oral than topical PrEP trials. Cranage also presented data that 4 of 7 uninfected macaques who had received tenofovir gel before or after

rectal challenge had detectable Gag-specific T-cells measured in peripheral blood by gamma-interferon enzyme-linked immunospot (ELISPOT).

There have been no efficacy trials completed to date of oral PrEP, although several safety and efficacy trials are underway (see www.prepwatch.org). Data published last year suggested that a substantial proportion of MSM might know about PrEP as a prevention strategy and that some might already be using it (Kellerman et al, *J AIDS*, 2006). These data were countered by a study of MSM in San Francisco presented at the International AIDS Conference in Toronto in July 2006 (see also Liu et al, *JAMA*, 2006), as well as by a presentation by Voetsch and colleagues from the CDC at this year's CROI (Abstract 982). Voetsch and colleagues surveyed 397 MSM at minority gay pride events in 5 US cities who were HIV seronegative or of unknown serostatus. Of this group, only 19% had heard of either pre- or postexposure prophylaxis, and only 1 person reported ever using PrEP. One of the 60 HIV-seropositive men surveyed reported giving antiretrovirals to his HIV-seronegative sex partner to prevent infection. This study confirms that, at the present time, PrEP use is relatively rare.

Role of Sexually Transmitted Diseases

Wasserheit provided an overview of the role of control of STDs in preventing new HIV infections (Abstract 56). Although numerous observational trials have identified a 2- to 5-fold increase in the risk of HIV transmission and laboratory-based studies have identified mechanisms by which these infections could facilitate transmission, only 1 of 5 randomized controlled trials of STDs completed to date have reported lowered HIV infection rates. Wasserheit reviewed these 5 trials and the likely differences between the populations that may have accounted for these differences. The only trial in which STD treatment lowered HIV incidence rates was in Mwanza, Tanzania (Grosskurth et al, *Lancet*, 2000), where the epidemic was in its early stages. Early stage epidemics are more frequently driven by core populations at very high

risk, where coinfection with bacterial STDs (eg, gonorrhea, chlamydia) may fuel the epidemic. In these situations, treatment of bacterial STDs successfully lowered HIV incidence. The other 4 randomized controlled trials all took place in generalized epidemics in which transmission more frequently occurs in stable partnerships and where bacterial STDs play a lesser role, but viral infections such as genital herpes simplex virus (HSV) may play a larger role. Wasserheit concluded that programs to reduce HIV infection should focus on treatment of symptomatic STDs (often associated with acute HIV infection), and treatment of bacterial STDs in high-risk groups in nascent or concentrated epidemics. She also pointed to the importance of 2 ongoing efficacy trials to evaluate the impact of HSV suppression in reducing HIV acquisition (Abstract 987) and transmission in mature epidemics.

Two studies lent modest support to the hypothesis that HSV suppressive therapy might reduce genital shedding of HIV and therefore lower HIV transmission. Dunne and colleagues presented data demonstrating a modest reduction in HIV shedding (0.44 log₁₀ copies/mL) in cervico-vaginal lavage among Thai HIV-infected women randomized to receive chronic suppressive acyclovir therapy or a placebo in a randomized, placebo-controlled, cross-over design (Abstract 30). In contrast, Delany and colleagues found no statistically significant decrease in the quantity of genital HIV among women randomized to receive acyclovir suppressive therapy in a trial in Johannesburg, South Africa (Abstract 154LB). In their study, acyclovir decreased the proportion of visits in which HIV shedding was detected in cervico-vaginal lavage as well as lowering plasma HIV RNA levels by 0.37 log₁₀ copies/mL.

Transmission Through Breastfeeding

This year's conference featured more than 15 abstracts on strategies to reduce the risk of HIV transmission through HIV-infected mothers breastfeeding their newborns. Coovadia provided an excellent overview of the topic in a plenary lecture (Abstract 13). In

wealthy countries, perinatal transmission rates fell from 24.5% in 1993 to 1.5% in 2002, with the widespread uptake of strategies for PMTCT. Although substantial reductions in perinatal transmission have been achieved in resource-limited countries, efficacy of peripartum antiretroviral therapy has been substantially attenuated by breastfeeding, where the risk of transmission appears to be relatively constant at 0.74 transmissions per month of feeding through 24 months. However, the increased risk in HIV acquisition is offset by higher rates of diarrheal disease in non-breastfed infants in resource-limited settings, and this was highlighted in several presentations at the conference.

Creek and colleagues presented the findings from an investigation of a large outbreak of diarrhea among infants in Botswana in 2006 (Abstracts 9 and 770). Botswana implemented a national PMTCT program in 1999 that included antiretroviral therapy, free infant formula for 12 months, and advice to all women to formula feed. Transmission rates in infants born to HIV-infected mothers fell to 7% in 2005. After heavy rains beginning in November 2005, an increase in diarrhea cases was observed in Botswana in the first quarter of 2006, with a 4-fold increase in diarrhea and a 25-fold increase in diarrhea death in children under 5 years of age. On multivariate analysis, the overwhelming risk factor for diarrheal illness was lack of breastfeeding of the infant (adjusted OR, 50). A cohort study of infants with diarrhea in Francistown confirmed the association of diarrhea with lack of breastfeeding, as 90% of infants under 2 years with diarrhea were not breastfeeding. Malnutrition in infants with diarrhea was high (42% developed marasmus and 20% developed kwashiorkor) as was overall mortality (22%) and investigation revealed that many malnourished children had not received sufficient supplies of for-

mula. Other studies at the conference also demonstrated increased rates of diarrheal disease in infants during the rainy season (Abstract 772) and the association of diarrhea with weaning from breastfeeding (Abstracts 772-775).

The dilemma is this: at 18 months of age, HIV infection rates are higher in breastfed than formula-fed infants, but overall mortality is higher in the formula-fed group. Several studies provided data suggesting strategies to further reduce risk in the breastfeeding group. Coovadia presented data from many studies showing a clear benefit for exclusive breastfeeding compared with mixed breastfeeding, with evidence of a dose-response curve favoring breastfeeding (Abstract 13). Sinkala and colleagues presented data from a randomized, controlled trial of early weaning suggesting comparable rates of HIV-free survival at 24 months between the group randomized to wean at 4 months and those assigned to usual weaning practices (median duration of breastfeeding, 16 months). However, 24-month survival was substantially improved in the delayed weaning group for the subset of children born to asymptomatic mothers with CD4+ counts above 350 cells/ μ L. Survival was also significantly improved in infants found to be HIV-infected before 4 months if they received longer periods of breastfeeding. These data suggest promotion of exclusive breastfeeding, breastfeeding beyond 6 months, and prevention of late-stage disease in women of childbearing potential will improve infant morbidity and mortality in resource-limited countries. Attention and resources should be devoted to protecting clean water supplies and to training health care providers to monitor infant growth. Additional studies are underway evaluating the role of infant chemoprophylaxis and immunoprophylaxis in preventing HIV acquisition during breastfeeding.

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A list of all cited abstracts appears on pages 83-91.

Additional Suggested Reading

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