

## Perspective

# Recent Efforts in Biomedical Prevention of HIV

*Despite major advances in HIV treatment and progress in distribution of antiretroviral therapy in the developing world, staggering rates of new HIV infections persist. Innovative approaches to prevention of transmission are needed. Recent data have confirmed previous observational studies that demonstrated a substantial reduction in acquisition risk with male circumcision and microbicide technology experienced a setback with the early termination of a large-scale vaginal microbicide trial of cellulose sulfate. Limited data from one trial of pre-exposure prophylaxis was not able to validate nor refute efficacy. This article summarizes a presentation on biomedical prevention of HIV infection made by Raphael J. Landovitz, MD, at an International AIDS Society–USA Continuing Medical Education course in Los Angeles in March 2007. The original presentation is available as a Webcast at [www.iasusa.org](http://www.iasusa.org)*

Although substantial progress in distribution of antiretroviral therapy has been made in the resource-limited world, and drug development has yielded new antiretroviral agents and novel classes of compounds, new HIV infections continue to occur globally at the rate of 15,000 per day. New and innovative prevention strategies are needed. It is likely that behavioral interventions will be a necessary, but not singularly sufficient, component of a successful prevention program both domestically and internationally.

Current data support the efficacy of a small number of therapeutics-based strategies for HIV prevention. These include antiretroviral therapy to prevent mother-to-child transmission (MTCT), male circumcision to prevent heterosexual HIV-acquisition, male condoms, sex partner reduction and selection, and use of female conception barriers to prevent MTCT (cervical caps, diaphragms).

Controversial or unproven strategies include herpesvirus type 2 (HSV-2) suppression (Nagot et al, *N Engl J Med*, 2007; Ouedraogo et al, *AIDS*, 2006; Dunne et al, 14th CROI, 2007), malaria prophylaxis and treatment (Filler et al, *J Infect Dis*, 2006), and treatment of curable sexually transmitted infections (STIs). Observational data suggest that suppression of HSV-2 replication reduces genital

compartment shedding of HIV, although conclusions regarding definitive clinical benefit await controlled study results and will likely be available in 2008 and 2009. Thus far, there are conflicting data on the impact of treating curable STIs on prevention of HIV infection, including 1 positive and 4 negative trials (Grosskurth et al, *Lancet*, 1995; Wawer et al, *Lancet*, 1999; Garcia et al, *Sex Transm Infect*, 1998; Harrison et al, *AIDS*, 2000; Kamali et al, *Lancet*, 2003). Experts with an anthropologic overview of the epidemic point out that the differential effects seen on treatment of curable STIs and HSV-2 suppression likely stem from the evolutionary age of the epidemic in locations where studies were performed, with curable STIs maintaining a greater impact on early stages of the epidemic, and HSV-2 having a greater influence in a more well-established epidemic.

Dr Ward Cates, Jr, director of Family Health International (FHI), appropriately emphasizes that availability of oral contraceptive pills, if used to reduce unwanted pregnancy, would dramatically reduce MTCT and have a marked impact on the global HIV epidemic.

Strategies that have been shown not to be useful in HIV prevention include use of nonoxynol-9 or cellulose sulfate as vaginal microbicides and all vaccine strategies to date for which data are available. Despite the federal government requirement that abstinence-only education be part of United States government-funded prevention programs, review of scientifically rigorous data

fails to support the efficacy of this strategy, and notes increased rates of condom non-use during sexual activity (Kirby, 2001; Manlove et al, 2004).

The following article focuses on recent findings or current status of the strategies of male circumcision, pre-exposure prophylaxis (PrEP), and use of anti-HIV microbicides.

## Male Circumcision

On a worldwide basis, approximately 70 % of HIV-seropositive men were infected via heterosexual insertive vaginal intercourse. A much smaller proportion acquired infection through insertive anal intercourse. The risk of acquiring HIV from an act of insertive vaginal intercourse is approximately 0.5 %, whereas the risk of acquiring HIV from an act of receptive vaginal intercourse is approximately twice that, at 1 %. Risk of acquisition from insertive anal intercourse has been estimated at approximately 0.65 % per sex act (CDC, MMWR, 2005).

Circumcision is associated with reduced risk of HIV acquisition likely because the large surface area of inner foreskin mucosal epithelium is a favorable environment for viral acquisition. The inner mucosal surface of the penile foreskin is not keratinized and is rich in Langerhans' cells, making it particularly hospitable to viral translocation. The keratinized, stratified squamous epithelium covering the penile shaft and outer surface of the foreskin provides a protective barrier against virus acquisition; in circumcised persons, only the distal penile urethra is lined with mucosal epithelium, leaving only a small surface area particularly vulnerable.

Three trials in Africa have shown the effectiveness of circumcision in preventing HIV acquisition (Table 1). Acquisition risk reductions (from intent-to-treat analyses) were 60 % in the Orange Farm trial in semiurban South Africa, 51 % in a rural popula-

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**Table 1.** Results of Male Circumcision Trials in Africa

|                               | <b>Orange Farm</b> | <b>Rakai</b>  | <b>Kisumu</b> |
|-------------------------------|--------------------|---------------|---------------|
| <b>Population</b>             | Semiurban          | Rural         | Urban         |
| <b>Circumcision rate</b>      | 20%                | 16%           | 10%           |
| <b>Baseline HIV incidence</b> | 1.6%               | 1.0%          | 1.6%          |
| <b>Age range</b>              | 18-24 years        | 15-49 years   | 18-24 years   |
| <b>Number of subjects</b>     | 3128               | 4996          | 2784          |
| <b>Stopped</b>                | November 2006      | December 2006 | December 2006 |
| <b>Relative risk (IT)</b>     | 0.40               | 0.49          | 0.47          |
| <b>Relative risk (PP)</b>     | 0.24               | 0.45          | 0.40          |

IT indicates by intent-to-treat analysis; PP, per protocol. Table courtesy of Ward Cates, Jr, Family Health International.

tion in Rakai, Uganda, and 53% in an urban population in Kisumu, Kenya (Auvert et al, *PLoS Med*, 2005; Bailey et al, *Lancet*, 2007; Gray et al, *Lancet*, 2007). As yet, prospective randomized data are not available on how circumcision might affect transmission of virus from infected men. Although an exciting result, an important caveat to these findings is that both cost and infrastructure limitations can be substantial impediments to implementing circumcision programs routinely in the developing world, despite their clear efficacy. Circumcision in these studies was performed by trained personnel using sterile technique in appropriately equipped facilities. The potential for complications, including surgical morbidity and mortality, infection, and need for reoperation, would likely increase under less-controlled conditions. There are many operational, religious, political, and logistic factors that may contribute to reluctance of local or national authorities to institute circumcision programs.

An often overlooked impact of such a highly effective prevention strategy is its impact on the ability to evaluate other prevention strategies. It is likely that circumcision, given the large protective effect in acquisition, will be considered part of a new standard of

care in trials of other preventive strategies. This may obscure the ability to detect additive preventive benefit attributable to new strategies layered on the background of circumcision — and achieving sufficient statistical power to determine efficacy may become prohibitively expensive.

### Pre-exposure Prophylaxis

PrEP is a potentially promising but as yet unproven prevention strategy consisting of continuous (daily) antiretroviral medication taken by HIV-seronegative individuals beginning before potential exposure and continuing throughout periods of risk. The strategy is not intended as an alternative for condom use or other known effective preventive approaches. It has yet to be determined whether such a strategy reduces risk of HIV infection or whether antiretroviral drug use can be considered safe in uninfected individuals.

Modeling of the potential impact of PrEP on HIV transmission in resource-limited settings suggests that under the most optimistic of assumptions, a PrEP strategy could result in a 74% decline in cumulative new HIV infections after 10 years (Abbas et al, 14th CROI, 2007). However, there is considerable concern regarding the potential of

such a strategy to increase sexual risk-taking behaviors. Since PrEP regimens currently consist of 1 or 2 antiretroviral drugs, there is also concern that the use of such regimens for prevention will result in increased emergence of resistance to the drug(s) when infections do occur.

With regard to the potential consequences of PrEP on behavioral disinhibition, it is worth noting that current research on postexposure prophylaxis, and preventive vaccines, both strategies in which disinhibition was considered to be a major danger, does not indicate that high-risk behavior markedly increases in such settings. Circumcision trials had more conflicting results, with 2 studies showing no increase in high-risk sex, but 1 showing a modest increase in risk behavior.

Despite the lack of evidence and ongoing concerns, there have been anecdotal reports in the United States of PrEP use in clubs, bath houses, and circuit parties, including in the form of “party packs” consisting of a methamphetamine stimulant, a phosphodiesterase inhibitor (eg, sildenafil), and antiretroviral medication (eg, efavirenz, tenofovir, or fixed dose combination [fdc] emtricitabine/tenofovir). Articles on this practice have appeared in the *Los Angeles Times* (December 2005), the *New York Times* (January 2005), and *Out* magazine (April 2006 and January 2007). The attention to this phenomenon has not been borne out in epidemiologic surveys in New York and San Francisco, where rates of knowledge about and reported use of PrEP were extremely low (Liu et al, IAC, 2006; Kellerman et al, *JAIDS* 2006).

PrEP trials to date have examined use of tenofovir alone or fdc emtricitabine/tenofovir. Ongoing trials of PrEP include a Centers for Disease Control and Prevention (CDC)-sponsored study in 400 men who have sex with men (MSM) in Atlanta, Boston, and San Francisco; a study of 1200 heterosexual men and women in Botswana; a study of 2000 injection drug users in Thailand, and a National Institutes of Health (NIH)-sponsored study of at least 1400 MSM in Peru and other South American countries.

A number of PrEP trials have been stopped for a variety of reasons, including local government intervention, lack of community-perceived commitment to ongoing care of those who acquire HIV infection during study participation, and apparent lack of optimal communication between trial sponsors and community groups regarding the goals of the studies. Trials of PrEP in heterosexual men in Malawi and a trial of PrEP for commercial sex workers in Cambodia were halted owing to similar concerns.

The only published efficacy data to date are from an FHI-sponsored PrEP trial of tenofovir versus a placebo in HIV-seronegative heterosexual women in Ghana, Cameroon, and Nigeria. This trial, although designed with adequate power to address both safety and efficacy endpoints, was ultimately unable to show sufficient statistical power to evaluate the efficacy of the strategy. This occurred primarily because of drastically reduced sample size after sites in Cameroon and Nigeria were closed. Additionally, there was a lower than expected HIV incidence rate in the placebo arm (Peterson et al, *PLoS Clinical Trials*, 2007).

In this study, 8 seroconversions occurred. Six were in the placebo arm and 2 were in the active tenofovir arm, a difference that did not attain statistical significance.

Although there were no marked safety concerns, including with regard to hepatitis B virus flares with treatment discontinuation, condom use increased. Concern about potential viral resistance in those who seroconvert through PrEP treatment should not be assuaged by the observation that 1 of the 2 seroconversions in the active tenofovir arm did not demonstrate any genotypic evidence of resistance.

### Anti-HIV Microbicides

Properties of an ideal anti-HIV microbicide include: virucidal activity against diverse HIV strains, cell-free and cell-associated virus, activity against other STIs, contraceptive activity, absence of effect on vaginal, cervical, or rectal epithelium and normal flora, and resistance to or enhancement of the low pH in the vaginal environment (itself an antiviral property). In addition, the ideal microbicide would be stable at tropical temperatures, nonteratogenic, and compatible with

latex. And, of course, it would be inexpensive, easy to use, and accessible and acceptable to all.

Microbicides have the advantage of being receptive-partner controlled, an important feature for use in areas of the world in which individuals are not empowered to, or it is not culturally appropriate to, demand use of condoms or other means of HIV prevention. Microbicial formulations that have been developed include vaginally (or rectally) applied gels, foams, and creams consisting of both HIV-specific and nonspecific compounds.

A randomized, double-blind trial of the anti-HIV microbicial effect of cellulose sulfate was recently stopped owing to a trend toward harm in the active treatment group. Cellulose sulfate is a detergent with antifertility activity and in vitro activity against sexually transmitted pathogens, including HIV. The trial, conducted by the Contraceptive Research and Development Program (CONRAD), FHI, and the Institute of Tropical Medicine (ITM), had sites in Durban, South Africa (HIV seroprevalence of approximately 50%), Kampala, Uganda (approximately 32%), Cotonou, Benin (approximately 27%),

Table 2. Anti-HIV Microbicides in Advanced Development

|                                    | Sponsor                             | Countries   | Design                | Target Population                                | Sample Size | Mechanism of Action    |
|------------------------------------|-------------------------------------|---|-----------------------|--|-------------|------------------------|
| Carbomer 974 and PRO-2000 0.5% gel | HIV Prevention Trials Network       | Malawi, South Africa, Tanzania, United States, Zambia, Zimbabwe | 4-group Phase IIb/III | Sexually active women                            | 3220        | Acid buffer, detergent |
| Carrageenan                        | Population Council                  | South Africa  | 2-group Phase III     | Sexually active women                            | 6270        | Detergent              |
| PRO-2000 0.5% and 2%               | UK Microbicides Development Program | Cameroon, South Africa, Tanzania, Uganda, Zambia, Swaziland     | 3-group Phase III     | Women likely to be sexually active               | 11,920      | Detergent              |
| C31G                               | Family Health International         | Nigeria   | 2-group Phase III     | High-risk population through own sexual behavior | 2142        | Detergent              |

Adapted from Balzarini, *Lancet*, 2007.

Table 3. Ongoing HIV Vaccine Trials

| Vaccine Candidate  | Antigen (HIV clade)           | Manufacturer                        | Start Date     | Question  |
|--|-------------------------------|-------------------------------------|----------------|---|
| Prime with cowpox vector expressing HIV-1 genes                      | Env (B, E), Gag, Pol (B)      | Sanofi-Pasteur                      | October 2003   | Will gp120 protein vaccine be useful in combination with a live recombinant pox vector prime?   |
| Boost with gp120 protein   | gp120 (B,E)                   | VaxGen                              |                |   |
| Replication-defective adenovirus-5 expressing HIV-1 genes            | Gag, Pol, Nef (B)             | Merck                               | December 2004  | Clinical benefit of adenovirus-based vector in patients infected after vaccination?   |
| Prime with plasmid DNA encoding HIV-1 genes                          | Gag, Pol, Nef(B), Env (A,B,C) | Vical, NIH Vaccine Research Center  | September 2005 | Utility of prime-boost strategy with DNA and adenovirus-based vaccines containing 3-clade envelope proteins as well as structural proteins? |
| Boost with replication-defective adenovirus-5 expressing HIV-1 genes | Gag, Pol (B), Env (A,B,C)     | GenVec, NIH Vaccine Research Center |                |   |

Adapted from Letvin, *National Rev Immunol*, 2006.

and Bangalore (approximately 45%) and Chennai (approximately 16%), India. A total of 2733 HIV-seronegative women were screened for entry into the study; 1400 were excluded, including 1020 who were found to be HIV-seropositive and 94 who were found to be pregnant. A total of 1333 were randomized to use a 6% cellulose sulfate gel or a lubricant placebo. Condom use counseling and free condoms were provided at study visits.

An independent data monitoring committee evaluating the study in a planned interim analysis recommended stopping the study in January 2007. Thirty-five HIV seroconversions were observed, all occurring at sites in Africa. It has not been reported how many of the seroconversion events were in the active treatment group. Final results of the study are expected in late 2007 (Doncel and van Damme, 14th CROI, 2007).

Although an interim analysis of another large-scale FHI-sponsored trial of cellulose sulfate in Nigeria did not yield similar data, this study was also stopped owing to concern regarding the findings of the CONRAD, FHI, and ITM trial. Increased HIV acquisition associated with use of the spermicide nonoxonyl-9 appears to have been due to vaginal

inflammation caused by the product. In the case of cellulose sulfate, colposcopy, evaluation of microflora, and assessment of inflammatory cytokines in preclinical work showed no increased genital irritation after 6 to 14 days of administration, or at 6 months in a subpopulation of participants evaluated at the latter time point.

Ongoing advanced-phase trials of other microbicides are summarized in Table 2 (Balzarini, *Lancet*, 2007). Other HIV-specific agents such as TMC-120 (dapivirine) and tenofovir are in earlier stages of development.

## Vaccines

Progress in HIV vaccine development has been slow, but efforts are ongoing to identify protective and therapeutic vaccine candidates. Ongoing HIV vaccine trials are shown in Table 3 (Letvin, *Nat Rev Immunol*, 2006). Current goals of research are to increase the magnitude and durability of vaccine-elicited immune responses by, for example, using DNA vectors or new viral vectors, and to achieve greater diversity of immune recognition through use of consensus gene sequences. Despite absence of marked progress, the strategies of achieving broadly neutralizing

antibody responses and mucosal immunity are still being investigated.

*Presented by Raphael J. Landovitz, MD, in Los Angeles in March 2007. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Landovitz in June 2007.*

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## Suggested Reading

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