



Is There a Magic Bullet? With No Vaccine in Sight, Emphasis Shifts to Biomedical Prevention Interventions

HIV InSite's Coverage of the XVI International AIDS Conference

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With very little promising information related to new therapeutics or a vaccine, much of the discussion at the XVI International AIDS Conference in Toronto focused on biomedical prevention strategies, particularly preexposure prophylaxis (PrEP) and malecircumcision. Despite encouraging study abstracts demonstrating the potential feasibility, acceptability, safety, and effectiveness of some of these prevention technologies, many issues of ethics and feasibility remain unanswered.

Some speakers, more enthusiastic of the new technologies, alluded to the "failure" of traditional behavioral interventions. Joep Lange, MD, professor of medicine at the Academic Medical Center, University of Amsterdam, cited lack of access, information, and tools in many settings as reasons for stable or increasing HIV incidence in many settings. "We must intensify the search for alternatives to vaccines, including microbicides, PrEP, and circumcision," he said. Others were less enthusiastic and far more guarded about the new technologies.

In a plenary session titled *Prevention: Proven Approaches and New Technologies*, Cristina Pimenta of the Brazilian Interdisciplinary AIDS Association cautioned that the enthusiasm for biomedical interventions could deflect attention from behavioral interventions, such as condom promotion and harm reduction approaches, which have been demonstrated to be effective. These proven interventions fail in many settings because of interference from governments and funding agencies, she said. Pimenta and other speakers stressed that biomedical interventions must complement existing preventive measures. There is a trend toward the "medicalization" of prevention and the expectation of a "quick technical magical solution," she said.

Whose Turf?

But just where these biomedical interventions fit into existing paradigms remains unclear. With the exception of more recent trends toward "prevention with positives" or integrating prevention into clinical care, prevention has remained largely within the realm of behavioral science and outside the sphere of clinical care. Biomedical interventions such as PrEP and circumcision take a clinical approach (obviously requiring the participation of physicians), which is distinctly different from the approach taken with interventions such as voluntary counseling and testing, condom distribution, needle exchange, and individual and group counseling--all of which can be implemented in communities with minimal training.

Successful rollout of interventions such as PrEP, according to experts such as conference cochair Helene Gayle, would have to be part of treatment scale-up, which could "integrate prevention programs into new and evolving systems of HIV care." Others wouldn't necessarily divorce biomedical prevention interventions from clinical care but emphasize that these would have to be added to existing HIV prevention approaches such as condom use and other barrier methods, harm reduction, prevention of mother-to-child transmission (PMTCT), and so forth. Gita Ramjee of the South African

Medical Research Council received applause from the audience when she described prevention methods that could complement the existing "ABC" approach.

In *What if PrEP Works?*, there was discernible anxiety about exactly how biomedical interventions would be incorporated with existing prevention methods. Dawn Smith of the Centers for Disease Control and Prevention acknowledged that historically, "we haven't done a good job of developing prevention advocacy groups [vs treatment advocacy] and we really need to involve both." She went on to muse, "Would we establish HIV prevention clinics?" Many men who have sex with men (MSM), for example, don't have access to or choose not to go to AIDS service organizations.

Preexposure Prophylaxis: Safe but Effective?

Preventing HIV transmission with chemoprophylaxis fits into a conceptual framework that includes the use of drug products for the prevention of infectious diseases such as malaria and influenza. PrEP also has been shown to be effective in animal studies, and PMTCT interventions demonstrate the concept in humans.

In animal models, tenofovir has been demonstrated to prevent HIV transmission, but tenofovir combined with emtricitabine (Truvada) shows more promise based on animal studies. Of 5 ongoing human trials, 3 are studying the use of tenofovir in the following populations: male and female injection drug users in Thailand; MSM in the United States; and high-risk women in Ghana, Cameroon, and Nigeria. Two studies are using tenofovir/emtricitabine and are examining its safety and efficacy in MSM in Botswana and Peru.

Results from one study(1) were presented as a late-breaker abstract. In this study, Leigh Peterson of Family Health International and colleagues enrolled 936 HIV-negative women from Ghana, Cameroon, and Nigeria into a double-blind, randomized trial between June 2004 and March 2005. The treatment arm received 300 mg of tenofovir once daily. Participants were monitored at least monthly for adverse events and HIV infection, and laboratory tests (serum creatinine, phosphorous, alanine aminotransferase, and aspartate aminotransferase) were performed quarterly. The most common adverse events included malaria, candidiasis, headache, abdominal pain, and dizziness, with no significant differences between treatment groups. No significant differences occurred between groups for Grade 3 or higher laboratory abnormalities.

There were 8 HIV infections: 2 in the treatment group and 6 in the placebo group, for a rate ratio of 0.35 (95% confidence interval [CI] = 0.03-1.93). The difference in number of infections between the 2 groups was not statistically significant ($p = .24$).

Circumcision

Interest in male circumcision as an effective prevention intervention began last summer when data presented at the IAS meeting in Brazil and later published in PLoS Medicine(2) revealed that circumcision resulted in a 60% protection rate. Abstracts presented this year in Toronto examined efficacy, social acceptability, and cost effectiveness of male circumcision. Particularly noteworthy were the following 2 studies.

In a study(3) of HIV infection among tea plantation residents in Kenya, 1,719 men were enrolled into 1 of 2 cohorts - circumcised or uncircumcised (as self-reported) - and returned for follow-up HIV testing at 6, 12, and 18 months. In this study, circumcision was found to be a very strong protective predictor of HIV infection. After 1.5 years of follow-up, the overall HIV incidence was statistically significantly lower among circumcised men (0.84/100 person-years; 95% CI: 0.38-1.29) compared with uncircumcised men (2.98/100 person-years; 95% CI: 1.25-4.72), yielding an HIV incidence ratio of 0.28 (95% CI: 0.13-0.63; $p < .001$). The protective effect was observed for all circumcised men regardless of age, level of education, marital status, STD history, or syphilis infection status.

In another study(4) from Kenya, researchers are assuming that the ongoing investigation will demonstrate that circumcision is associated with a 50% reduction in HIV incidence. The interim

analysis presented at the conference focused on adverse events as well as acceptability of the surgery. Notable findings include: Of the 1,334 circumcisions completed, only 27 (or 1.7%) adverse events were "definitely, probably, or possibly" related to circumcision. The adverse events include delayed healing, postoperative wound infections, bleeding, and other events such as swelling, folliculitis, and 1 case of erectile dysfunction.

Nearly everyone was satisfied with the surgery, with 99% of clients saying they were "very satisfied." At their 90-day postoperation visits, 65% reported having resumed sexual intercourse; and 92% of female sex partners (as reported by the men, it turns out) were very satisfied with the outcome.

Whether mass circumcision campaigns will be as successful in wide-scale practice as they were in these controlled studies is anyone's guess and was a topic of much hallway conversation at the conference. Although the data suggesting protective effects of circumcision are quite impressive, it is hard to imagine replicating the successes of these studies in countries and cultures where circumcision is not culturally acceptable. Questions also remain in regard to what the rates of surgery-related adverse events would be outside state-of-the-art Western-based clinical settings in countries where sterile equipment is not the norm.

The practical implications of biomedical interventions--and where they fit into existing and yet-to-come clinical and prevention paradigms--are far from clear. Meaningful conversations seemingly have only begun. It would not be surprising if, at the next International AIDS Conference in 2 years, more data are available but the same questions of feasibility remain unanswered.

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