



Microbicides for HIV Prevention

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We all know about the “feminization” of AIDS. Approximately 8000 women and girls are infected with HIV daily, the vast majority by their husbands or boyfriends. In Africa, women make up 60% of all people living with HIV/AIDS, and girls make up 76% of HIV positive African youth. While fewer than half of all new HIV infections in the United States occur among women, the transmission pattern is similar. Heterosexual contact is the source of at least 78% of all new infections among U.S. women. Biologically, a woman is at least twice as likely as a man to contract HIV from a single act of unprotected vaginal intercourse.

Even with the “female condom,” a woman cannot protect herself during heterosexual sex without the cooperation of her partner. The “ABCs” (abstain, be faithful, use condoms) fail millions of women who lack the social and economic power to negotiate when and how sex occurs and whether protection is used.

Microbicides could change this picture with just a simple cream, foam, or gel that can be inserted vaginally to protect women when condom use isn’t possible. Five candidate microbicides are now in large-scale efficacy trials and dozens more are in the preclinical and clinical trial pipeline. Research to develop rectal microbicides is also finally underway. We now have the scientific means and the public health motivation to put the first totally new HIV prevention technology into the hands of receptive sex partners—male and female—in the very near future.

How Do Microbicides Work?

A microbicide could prevent transmission of HIV and possibly other sexually transmitted diseases (STDs) by:

- Killing or otherwise immobilizing pathogens, such as viruses
- Blocking infection by creating a barrier between the pathogen and the cells of the vagina or rectum
- Preventing infection from taking hold after the pathogen has entered the body

The first generation of microbicides probably will not reduce the risk of HIV transmission by more than 40% to 60%. But for people who cannot or do not use condoms—and particularly for women whose partners refuse to use condoms—microbicides could save lives and have a sub-

stantial impact on the spread of HIV. In fact, mathematical modelling shows that if even a small proportion of women in low-income countries used a 60% effective microbicide for half the sexual encounters in which condoms are not used, 2.5 million HIV infections could be averted over three years.

Over time, microbicides are likely to improve incrementally both in effectiveness and in the range of STDs they prevent. Third-generation products could be up to 85% effective, according to one pharmaco-economic analysis. This improvement is most likely to happen with the advent of combination products; just as it often takes several drugs used in combination to suppress HIV in the body, so also are microbicides likely to be more effective when agents with two or more mechanisms of action (such as blocking viral attachment or inhibiting replication) are employed together.

Advantages and Barriers to Use

Some critics doubt that women will want to use microbicides, fearing that they will be messy, require frequent insertion, and be inappropriate for women who want to become pregnant. These perceptions usually derive from people's experiences with over-the-counter spermicidal products. It is true that the first microbicides are likely to look and feel like spermicidal creams and gels, and they could be difficult for a woman in a long-term relationship to use without her partner's knowledge, because they will noticeably increase vaginal lubrication. However, women who are able to discuss microbicides with their partners may choose to focus on the benefits of these lubricating effects, rather than on the anti-HIV aspect of the product; partners who refuse to wear condoms for HIV protection may be more open to a product that enhances comfort during sex.

Looking to the future, delivery systems are under development that may make microbicides virtually undetectable. A flexible, microbicide-loaded vaginal ring, for example, could be worn for up to a month, providing time-released protection with minimal change in vaginal lubrication. Already in clinical trials, microbicidal rings may meet the needs of women who can't or don't want to discuss the issue of HIV protection with their male partners.

Social scientists have documented an enormous demand for microbicides among women in both developed and developing countries. Interestingly, a large proportion of respondents said that, if they were to use a microbicide in the future, they would probably discuss the issue in advance with their husbands or boyfriends. But rather than interrupting a passionate moment to insert a microbicidal product, a woman might choose to initiate the conversation about microbicides in a neutral setting, simply as a means of sharing information. Getting the partner's passive advance acceptance of a product that the woman applies before sex may be much easier than asking him to actively cooperate with either male or female condom use during the act. This could be a one-time conversation, not one that must be repeated each time the couple has sex.

Many women want to become pregnant, either for personal reasons or to achieve the status and security that, in many societies, they can only attain through motherhood. Because condoms are a contraceptive, women whose partners put them at risk of infection must choose between childbearing and HIV prevention—an unfair and untenable choice. Microbicides, however, are currently being developed in both contraceptive and non-contraceptive forms. A non-contraceptive microbicide would enable women and couples to protect their health and still have children.

When Will Microbicides Be Available?

More easily developed than an AIDS vaccine, the first microbicides could be publicly available in a handful of countries by 2010. Microbicide research, however, has been severely under-funded and “academically seen as a backwater,” according to Robin Shattock, PhD, a leading microbicides researcher based at St. George's Hospital in London. Talking about microbicides necessarily requires discussing topics that tend to make policy-makers uncomfortable—subjects such as vaginal lubrication, anal sex, gender, and power. As drugs administered systemically by clinicians, vaccines have an aura of respectability that microbicides lack.

Presently, no large pharmaceutical companies have invested substantially in the development and testing of microbicides. All research and testing has been conducted by academics, not-for-profit organizations, and small biotechnology companies—all of which depend on government grants and charitable foundations to support their projects. The speed with which these entities work depends largely on the level of public funding available to support clinical trials. Right now, potentially viable microbicidal products are sitting on laboratory shelves while developers struggle to come up with the funding to test them.

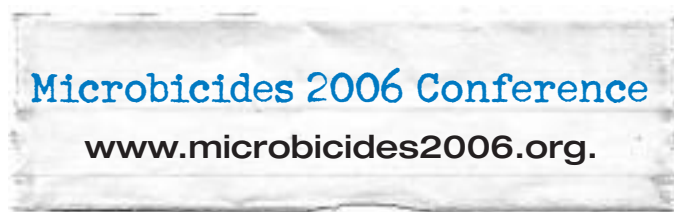
The process of finding a workable microbicide—like the process of developing any new drug—is a long one. Right now, the microbicides field has only about half the funding it requires to move forward as efficiently and rapidly as possible. In 2000, roughly \$65 million was invested globally in microbicide research, development, testing, policy, and advocacy. The vast majority of this money came from governments and the philanthropic sector. By 2004, global investment had more than doubled to \$142 million annually, thanks to sustained activism and growing scientific promise. However, projections by the International Partnership for Microbicides, the Alliance for Microbicide Development, and the Global Campaign for Microbicides (GCM) estimate that the annual global investment to ensure timely development of a safe and effective microbicide must double to \$280 million per year over the next five years—and remain at approximately \$260 million per year until satisfactory products are licensed.

If one of the five candidates currently in advanced clinical trials proves to be effective, distribution of the first microbicide could start (probably in the global South) within the next few years. If none of these candidates turns out to be effective, the time horizon will be longer—although several second-generation products are already in human trials. The microbicide research community is

working hard to accelerate development and ensure that products get to the people who need them as quickly as possible.

Microbicides 2006

Researchers and activists in the microbicides field come together every two years at an international conference to review the field's progress. At the Microbicides 2006 Conference, held April 23–26 in Cape Town, South Africa, a number of exciting developments were reported on the political, scientific, and advocacy fronts.



Immediately apparent was the extent to which microbicides—a peripheral issue for most of the past 15 years—have moved to center stage in HIV/AIDS prevention research and discourse. Conference plenary sessions included presentations by Archbishop Emeritus Desmond Tutu, Justice Edwin Cameron of South Africa's Supreme Court of Appeals, women's and children's rights advocate Graça Machel, Charlayne Hunter-Gault of CNN, three African governmental ministers, one European ambassador, and several eminent scientists. A video message from Nelson Mandela opened the event, and the conference closed with words from Peter Piot, MD, PhD, of the United Nations Joint Programme on HIV/AIDS, as well as an impassioned speech by Zackie Achmat, chair of the Treatment Action Campaign and one of the world's leading AIDS activists.

With more than 1300 international participants in attendance (over half of them from Africa), the field has clearly come a long way since the Microbicides 2000 conference drew less than half that number to Alexandria, Virginia.

New Attention to Community and Advocacy

Several presentations in Track D—a new conference track devoted exclusively to community and advocacy issues—profiled the effective work of microbicide advocacy networks, including GCM, the African Microbicides Advocacy Network (AMAG), the Nigerian HIV Vaccines and Microbicides Network (NHVMAG), and the Canadian Microbicides Advocacy Group Network (MAG-Net). The latter two groups are working with their respective national governments to develop national microbicide

strategies—the first such plans to parallel the national HIV vaccine strategies already in place in several countries.

Track D presentations also explored the role of civil society stakeholders in defining and shaping the microbicides research agenda. Speakers noted that it is insufficient for research institutions to simply inform communities of what they are doing in clinical trials or seek their advice through community advisory boards (CABs). Rather, authentic partnerships must be cultivated between civil society (including affected community members) and researchers to ensure a trial's success.

Admittedly, such partnerships are labor-intensive and require ongoing communication, collaboration, and transparency. Conference panelists cited the clinical trial program developed by the BOTUSA Project (a joint effort of the Botswana government and the U.S. Centers for Disease Control and Prevention) as possibly the best-realized example of this kind of partnership. BOTUSA is initiating microbicide trials after extensive efforts to integrate the project into existing community and civil society networks.

Rectal Microbicides

Track D also brought greater attention to a full range of community needs that the microbicides field must address. Demand is escalating, for example, for expanded efforts to develop rectal microbicides. The international Rectal Microbicides Working Group, barely a year old, unveiled a landmark report called "Rectal Microbicides: Investments and Advocacy" at the conference's Rectal Microbicides Symposium. The report documents that only \$34 million was spent on rectal microbicide research between 2000 and 2006, and calls for an investment of \$350 million over the next decade to develop products to prevent HIV transmission through anal sex. The report also emphasizes the synergies between rectal and vaginal microbicide research, noting that, ideally, rectal and vaginal studies should proceed in parallel. The symposium presentations reviewed the status of basic and pre-clinical research in this area, but noted that no candidate rectal microbicide products have advanced to human trials.

Microbicides for HIV Positive Women

Another area that historically has received little attention was highlighted in a roundtable discussion on "HIV Positive Women and Microbicides," convened by the GCM and the International Community of Women Living with HIV/AIDS. Among the issues raised was the importance of conducting safety trials among women who already have HIV, since microbicides will likely be used by women who don't know their HIV status, as well as by those using the product to avoid transmitting the virus to their partners.

Without these safety trials, how will HIV positive women anticipate potential side effects, possible drug interactions, the impact that a microbicide might have on their vaginal ecology, and the risk of developing drug-resistant virus due to using an antiretroviral drug-based microbicide?

Also of concern are the benefits and risks a microbicide could have for HIV positive women who wish to conceive. When and how will research be conducted to see what safety issues a noncontraceptive microbicide might raise for both the pregnant woman and her future child?

Research is underway to answer some of these questions (in particular, pharmacokinetic studies to assess the risk of resistance mutations), but the tools to evaluate microbicide safety are still evolving, and more refined measurements are needed. All participants agreed that these issues should be revisited at Microbicides 2008 to assess the progress made in the intervening two years.

Safety Trials

The scientific sessions in conference Tracks A and B noted that evaluation of safety is a “moving target,” even though all candidate products undergo rigorous safety studies. Frequent genital examinations, colposcopy (examination of the cervix and vagina with a lighted microscope), blood testing, and participant reporting of symptoms are the primary tools used to collect safety data. These measures, while extremely useful, can be difficult to interpret, so researchers are now investigating the potential utility of other biomarkers of product safety, such as inflammatory cytokine levels.

Researchers in these sessions also reported on the wide array of compounds currently in the microbicides pipeline. Researchers anticipate that the first-generation candidates (those now in Phase III trials) will provide relatively broad potency against a range of STDs, but only limited anti-HIV activity. These candidates are also coitally dependant products that must be inserted prior to sex.

The second-generation candidates, most of which are based on existing antiretroviral drugs, may have increased specificity and potency against HIV. One such agent, tenofovir (Viread), is being tested as a microbicide in a gel formulation, and appears safe and well tolerated in early studies (see “News Briefs” on page 12). These may also be coitally independent products that could be applied once daily or administered through a sustained-release device, such as a vaginal ring that remains in place for a month or longer. However, these products may lack efficacy against other STDs. Another issue under study is the possibility of drug resistance in women who are (or who become) HIV positive.

Presenters at Microbicides 2006 reported rapid progress in designing strategies for creating these

second- and third-generation products, including advances in the development of CCR5 blockers and combinations of entry inhibitors (CCR5, gp120, and gp41 blockers) that have demonstrated vaginal anti-HIV activity in animal studies. Combination products are strongly supported by the research community, because they may boost efficacy against HIV while simultaneously protecting against other STDs—particularly herpes simplex virus (HSV), a co-factor in HIV transmission—and reducing the risk of resistance.

Data were also presented that should lay to rest the idea that lime or lemon juice (historically used for contraception and hygiene purposes by women without access to other options) might be an effective microbicide. The CONRAD Program reported the results of a Phase I study in which women applied water or one of three concentrations of lime juice (25%, 50%, or 100%) to the vagina for six consecutive days. The results showed a dose-dependent effect: the stronger the solution of lime juice, the greater the negative side effects observed. Among the women using 100% juice, more than 65% experienced genital irritation, 50% experienced deep epithelial abrasions, and more than 70% reported pain. Rather than protecting against infection, vaginal application of lime juice may actually increase a woman’s likelihood of contracting or transmitting HIV by creating irritated, broken tissue through which the virus can pass.

Lower concentrations of lime juice (10%–20%) do not appear to cause side effects, but neither do they inactivate HIV. According to two laboratory studies, exposure to a 50% concentration of lime juice for 30 minutes is required to completely inactivate the virus in semen. *The Economist* magazine, reporting on these findings, concluded that, “as a microbicide, lime juice is safe when it is ineffective and effective when it is unsafe.”

Controversial Issues

Track C raised some controversial issues in the microbicides field, including such topics as male involvement in trials, informed partner consent, and the level of care that researchers should be required to provide to study participants who become infected with HIV during the course of a trial.

Worldwide, more than 15,000 HIV negative women are currently enrolled in vaginal microbicide trials. Researchers directing these trials face many challenges, including high pregnancy rates among participants (which requires that those participants immediately discontinue using experimental agents), the unreliability of self-reported adherence to protocol, and unexpectedly low HIV incidence in trial areas (good news for the population, but also a complicating factor in assessing the experimental product’s efficacy).

While male involvement has always been encouraged, mandating partner consent or involvement in trials that recruit women impedes a woman's right to make autonomous choices about participation. The importance of involving male partners was addressed repeatedly, however, because educating men about clinical trials and test products can help ensure adherence to the trial protocol, as well as the safety and well-being of women whose partners may react negatively if they later find out about their participation in a trial. The availability of male partner and couples counseling is now seen as vital to adherence and acceptability.

In light of the recent cancellation of some clinical trials evaluating oral tenofovir as a potential prophylactic against HIV infection—although others are still ongoing—the issue of post-trial care for participants who become infected during an HIV prevention trial was also a hot topic. Solomon Benatar, PhD, a noted South African ethicist, observed that the field has made real “moral progress” in this area. Conference chair Gita Ramjee, PhD, described the South African Medical Research Council Reproductive Health and Research Unit's tremendous efforts to create and sustain networks that can provide such care in resource-poor settings.

The Road Ahead

The need for additional investment in microbicide research and development was apparent to all participants at Microbicides 2006. While funding has tripled over the past five years, current levels are still only about half of what is needed to keep the microbicide trials pipeline moving rapidly. Advocacy is also necessary to ensure that regulatory and licensure pathways are prepared for efficient product evaluation and approval, and to promote rapid mass distribution of successful products. The World Bank, United Nations Population Fund, International Planned Parenthood Federation, United States Agency for International Development, and the United Kingdom's Department for International Development are developing mechanisms to ensure timely procurement and access.

One of the most exciting future directions under discussion is a proposal to develop a mucosal vaccine specifically targeted to activate immune cells in the vaginal epithelium. A vaccine formulated for delivery as a needle-free, topical product could be combined with a microbicide and thus would be “re-boosted” every time the microbicide is applied. This method might even induce immunity specifically in the vagina—the most probable site of infection for women—and eventually confer whole-body immunity. An international team of researchers, led by Shattock,

has embarked on the development of such a product. The research consortium is funded for the next five years and hopes to have a candidate ready to enter clinical trials within that time.

Throughout Microbicides 2006, the sense of urgency with which all participants—scientists, policy-makers, and community advocates—approach this work was clear. Achmat closed the conference with a call for others to respond to this urgency, as well.

“HIV/AIDS represents the most critical challenge for humanity and our response to it must be based on a vision of social justice, freedom, and equality,” he said. “Governments and the private sector have a legal and moral duty to meet the resource demands of the epidemic. This includes the demand that the pharmaceutical industry must invest in microbicides research and development.”

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