Microbicide Overview

INTERNATIONAL PARTNERSHIP for MICROBICIDES

Why microbicides?

HIV/AIDS ranks among the world's most devastating diseases because it has spread rapidly and mainly afflicts young people in their most productive years. An estimated 33 million people worldwide are living with HIV/AIDS and 25 million already have died from AIDS (UNAIDS/WHO, July 2008). Each day, more than 7,400 more women, men and children become infected with HIV, the virus that causes AIDS. A lack of HIV/AIDS prevention and treatment has also left millions of children orphaned. More than 15 million children are without families and homes due to the epidemic, over 12 million of whom are in sub-Saharan Africa (UNAIDS/WHO, July 2008).

Efforts to address HIV/AIDS have focused mainly on behaviour change and treatment. But history shows that only a comprehensive strategy, including a strong focus on prevention, works to eradicate epidemics.

Women bear an increasing burden of the epidemic as both caregivers for the ill and because of their heightened risk of infection due to biological, economic and social vulnerabilities. Many women lack the power to insist their male partners use condoms or remain faithful. Abstinence is not an option for women who are married, who want children or who are at risk of sexual violence.

History shows that only a comprehensive strategy, including a strong focus on prevention, works to eradicate epidemics.

This is why we urgently need new prevention strategies that women can use themselves and initiate. One such strategy would be microbicides — topical products being developed to protect healthy people from becoming infected with HIV during sex. Some microbicides would be designed only for women as vaginal products, and others would be rectal products that both men and women would use. The International Partnership for Microbicides (IPM) is among several nonprofit organisations focusing on developing vaginal microbicides to protect women from HIV infection during sex with a male partner.

IPM and others are conducting product acceptability studies to help determine what types of microbicide products women really want and would use. Some women might like a vaginal gel used around the time of sex, others a product used once a day or even a vaginal ring that protects for up to 30 days at a time, and still others might prefer a vaginal film. Although no microbicide has yet been approved for use, many products that interrupt HIV infection have been identified, and are currently under extensive study and testing for use as microbicides.

How would microbicides work?

Unlike antiretroviral therapy, which treats HIV infection throughout the body after infection has already occurred, vaginal microbicides are designed to prevent infection from taking hold in the first place. HIV's life cycle presents a number of points at which microbicides could act to prevent infection. It is believed that, to be most effective, microbicides should interfere with the virus before it inserts copies of its genetic material into a host cell's DNA and begins replication. These microbicides could be delivered in a variety of forms — such as a gel, film, tablet or a longer-acting vaginal ring, which might not need to be replaced for 30 days or longer.

continued

IPM Headquarters
8401 Colesville Road, Suite 200
Silver Spring, MD 20910 USA
TEL +1-301-608-2221
FAX +1-301-608-2241

IPM Belgium
Rue du Trône, 98, 3rd floor
1050 Brussels, Belgium
TEL +32(0)2-507-1231
FAX +32(0)2-507-1222

IPM South Africa
PO Box 3460
Paarl 7620, South Africa
TEL +27-21-860-2300
FAX +27-21-860-2308

IPM CTM Facility
3894 Courtney Street, Suite 170
Bethlehem, PA 18017 USA
TEL +1-484-893-1050
FAX +1-484-893-1057

www.ipm-microbicides.org

Early-generation microbicides

The first microbicide candidates to be developed are known as “early generation” products. One early generation product remains in clinical trials. That product, called PRO 2000, is known as a “non-specific entry inhibitor, which would work by electrostatically associating with the HIV virus and blocking it from attaching to target cells in the vagina.

Encouraging results from a preliminary study of PRO 2000 released in February 2009 suggest that the product was 30 percent more effective than any other arm of the study in preventing HIV (for more information, visit *http://www.mtnstopshiv.org*). While data from that study did not reach the statistically significant threshold of 33 percent and are therefore not definitive, they do signal support for the concept that a topical microbicide could prevent HIV infection in women during sex. To bolster those data and provide a more robust estimate of the true impact PRO 2000 may have on HIV transmission, a larger trial of PRO 2000 is ongoing, with results expected by the end of 2009 (for more information, visit *http://www.mdp.mrc.ac.uk*). As important as the current data might be, they also indicate the need for other products that provide a higher level of protection against HIV.

Next-generation microbicides

The “next generation” of microbicides being developed is a newer class of products based on the same classes of antiretroviral (ARV) drugs being used to treat millions of people who are already infected with HIV/AIDS and to prevent mother-to-child transmission of HIV. These next generation products are following the lead of treatments that have been successfully adapted to life-saving prevention methods for other diseases, including malaria, influenza and pneumonia.

Work is underway to identify the most promising ARV drugs or ARV combinations that would be suitable for use as microbicides. ARV-based microbicides would work in a variety of ways by either preventing the HIV virus from attaching to or entering a healthy human cell, or by preventing the virus from making copies of itself once it is inside a cell. Examples of next-generation microbicide candidates include tenofovir gel, dapivirine gel and ring, and UC-781 gel.

The microbicide candidates being studied are both highly active and specific to HIV, and can be formulated for sustained release, either alone or in combination. Some researchers believe that combinations may improve upon the efficacy of single agents, but further clinical evaluation is needed. The table below summarises the main differences between early and next generation microbicide products:

Early-Generation Microbicides	Next-Generation Microbicides
• First microbicides developed, one remains in an efficacy trial	• Newer products in different stages of pre-clinical and clinical trials
• Non-specific to HIV	• Specific to HIV (ARV-based)
• Gel formulations	• Various forms: vaginal gel, ring, film, tablet
• To be applied vaginally within a few hours before sex	• Longer duration of action (sustained protection) — gels may be applied vaginally once a day, rings inserted once a month or less often
• No concern about potential resistance	• ARV resistance is a possible issue that needs further investigation

continued

Formulations and delivery

A drug's formulation helps determine its efficacy, cost and acceptability to the user. The remaining early-generation microbicide candidate, PRO 2000, currently in a large-scale efficacy trial is formulated as a gel that must be applied shortly before vaginal intercourse.

An advantage of the next generation ARV-based microbicides is that they can be formulated in longer-acting delivery methods that can be applied once a day, or even less frequently, independent of sexual activity. This would provide protection against HIV infection even during unanticipated sex.

How are microbicides tested for safety and efficacy?

Once proven safe and effective, vaginal microbicides could put the power of HIV protection into the hands of women around the world, potentially saving millions of lives. There is good reason for optimism, but it is important to remember that microbicide development is a long and expensive process.

All microbicide candidate drugs must first go through a rigorous programme of laboratory screening and testing to ensure that they have an adequate safety profile before being tested in humans. These intensive pre-clinical tests can take one to several years to complete. Once a candidate microbicide satisfactorily passes these tests, it can be advanced through a series of human clinical trials.

Once proven safe and effective, microbicides could put the power of HIV protection into the hands of women around the world, potentially saving millions of lives.

Clinical trials are carried out sequentially: first to determine the safety of the product and then to test efficacy (the ability of the product to prevent HIV infection). The initial safety trials involve small numbers of women under carefully controlled clinical conditions. Larger safety studies, in which the microbicide is administered to a wider range of women over longer periods, are then conducted to gain broader safety data.

Only when the safety studies have been completed can clinical efficacy trials be performed to test the ability of the microbicide to prevent HIV infection. These trials involve large numbers of women and need to be conducted in locations where new HIV infections are occurring at a high rate, so that researchers can see a difference in infection rates between those women who use the candidate microbicide and those who do not.

Clinical safety trials can take one to two years while efficacy trials can last three years or longer and involve thousands of volunteers. As a consequence, the total development costs for microbicides can run to hundreds of millions of dollars.

What ethical standards guide clinical trials?

All clinical trials, including microbicide trials, must be conducted according to international and local regulatory and ethics guidelines to protect the well-being of trial participants, and to guarantee the ethical and scientific integrity of the results. Microbicide product developers also adhere to their own comprehensive guidelines for ensuring the ethical conduct of clinical trials. These guidelines are living documents that must continually integrate new scientific gains and discoveries, and be responsive to a changing landscape.

Informed consent is the cornerstone of ethical trial conduct. Product sponsors must ensure that all participants in microbicide trials have freely given informed consent based on a clear understanding of the trial, including the potential risks and benefits of trial participation. The informed consent process must be consistent with International Conference on Harmonisation "Good Clinical Practice" and local country guidelines. Informed consent is an ongoing process, and product developers ensure continued understanding of trial participation through periodic post-enrolment discussions with trial participants. In addition, as part of the standard of care guidelines for conducting trials, product developers provide ongoing risk-reduction counselling; condoms; referrals for women who become pregnant or for those who

continued

screen HIV positive at enrolment; pre- and post-HIV test counselling; testing for sexually transmitted diseases (STIs) and treatment for curable STIs that are identified; treatment of any adverse reactions; and support, care and treatment for those who become infected with HIV during the trial.

How are local communities supported?

Microbicide product developers are committed to implementing clinical trials that meet ethical and regulatory standards, sustain broad community support and provide benefit to participating communities.

In countries where clinical trials are conducted, many microbicide developers have implemented broad-based programmes of community engagement. Information about microbicides and clinical trials is offered to key stakeholders, including local women's groups, medical professionals, the media, traditional leaders and healers, nurse-midwives, ministries of health and others. Ongoing training, networking and support for those involved in the clinical testing process — clinical investigators, research scientists, nurse coordinators, counsellors, accountants and project management staff — is also provided.

How will access to microbicides be ensured?

Once developed, microbicides must be widely available and affordable. Historically, it can take decades for the benefits of scientific innovation to reach the developing world. The microbicide field is committed to expediting widespread availability and access of any effective product, reaching those most in need first. Microbicide developers are fundamentally committed to the principle that all participants in trials should have access to the product studied if the product has been proven to be safe and effective, and has been approved for domestic use in the country.

Ensuring access to microbicides is a responsibility that must be shared by study sponsors, the research team, donors, multilateral and bilateral agencies and, ultimately, national governments.

Conclusion

Developing safe and effective microbicides for women in developing countries promises to be one of the great public health accomplishments of our generation. Once developed, microbicides will be a critical element in any comprehensive response to HIV/AIDS — one that takes into account the unequal impact of the epidemic on women — and a much needed tool in achieving the United Nation's Millennium Development Goals.

Developing safe and effective microbicides for women in developing countries promises to be one of the great public health accomplishments of our generation.

Microbicides will not only be integral to improving women's health, they will also help reduce the burden of death and disease for women, and indirectly for men and children, and could significantly help eradicate poverty in the developing world.

March 2009

Microbicide donors include the Bill & Melinda Gates Foundation, the European Commission, the Rockefeller Foundation, the United Nations Population Fund, the Joint United Nations Programme on HIV/AIDS, the World Bank, the World Health Organisation and the governments of Australia, Brasil, Belgium, Canada, China, Denmark, France, Germany, India, Ireland, Italy, the Netherlands, Norway, Spain, South Africa, Sweden, the United Kingdom and the United States.