Microbicide Overview

Why a microbicide?

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. Each day, 7,000 more women, men and children become infected with the virus that causes AIDS. Globally, the lack of HIV/AIDS prevention and treatment has orphaned more than 15 million children, over 11 million of whom are in sub-Saharan Africa.

Efforts to address the HIV/AIDS epidemic 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, particularly those in developing countries, bear an increasing burden of the epidemic as both caregivers for the ill and because of their heightened risk of infection due to physiological, economic and social vulnerabilities. In many cultures, women do not have the power to insist their male partners use condoms or remain faithful.

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This is why developing prevention strategies that women themselves can initiate and control is essential. One such strategy would be vaginal microbicides — products that would reduce the risk of HIV transmission to women during sexual intercourse. Microbicides can be designed to be used discreetly and independent of sex, and therefore lessen male involvement.

Although no microbicide has yet been approved for use, dozens of agents that interrupt HIV infection have been identified, and are currently under extensive study and testing for use as microbicides.

How do microbicides work?

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, a microbicide must interfere with the virus before it inserts its genetic material into a host cell and begins replication. Unlike antiretroviral therapy, which treats HIV infection throughout the body after infection has already occurred, microbicides are designed to be used within the vagina to prevent infection from taking hold in the first place.

Vaginal 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.

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Early-generation microbicides

The first microbicide candidates to be developed — two now remain in efficacy trials — are generally known as “non-specific” entry inhibitors. They work either by electrostatically associating with the virus and blocking it from attaching to target cells in the vagina (e.g., polyanions like PRO 2000), or by establishing conditions in the vagina that inhibit infection (e.g., vaginal defence enhancers like BufferGel).

Next-generation microbicides

The next generation of microbicides now being developed use antiretroviral (ARV) compounds that specifically target HIV or its target cells. They are highly active and can be formulated for sustained release, either alone or in combination. Combinations may improve upon the efficacy of single agents.

Work is underway to identify the most promising ARV compound or ARV combination that is suitable for use in microbicides. Examples of next-generation microbicide candidates include: tenofovir gel, dapivirine gel and ring, and UC-781 gel.

The differences between earlier microbicide products and the “next generation” are summarised in the table below:

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

Formulations and delivery

A drug’s formulation helps determine its efficacy, cost and acceptability to the user. The early-generation microbicide candidates currently in large-scale efficacy trials are formulated as gels that must be applied shortly before sexual intercourse, known for this reason as being “coitally dependent”.

An important advantage of the ARV-based microbicides candidates is that they can be formulated in long-acting, non-coitally dependent 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.

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How are microbicides tested for safety and efficacy?

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. But microbicide development is a long and expensive process.

All microbicide candidate drugs must first go through a rigorous program 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.

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Clinical trials are carried out sequentially: first to determine safety and then to test efficacy (the ability 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 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 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 should be consistent with International Conference on Harmonization “Good Clinical Practice” and local country guidelines. Informed consent is an ongoing process and product developers may 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; male and female condoms; referrals for women who become pregnant or for those who screen HIV positive at enrolment; pre- and post-HIV test counselling; STI testing and treatment; treatment of any adverse reactions; and care and treatment for those who become HIV-infected 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 leave participating communities better off.

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In countries where clinical trials are conducted, many microbicide developers have implemented broad-based programs of community engagement. Information about microbicides and clinical trials is offered to key stakeholders, including women's groups, ministries of health, medical professionals, the media, traditional leaders and healers, nurse-midwives and others. Ongoing training, networking and support for those involved in the actual 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.

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

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Microbicide donors include the Bill & Melinda Gates Foundation, the European Commission, the Rockefeller Foundation, the United Nations Population Fund, the World Bank and the governments of Belgium, Canada, Denmark, France, Germany, Ireland, the Netherlands, Norway, Sweden, the United Kingdom and the United States.