Microbicide Overview

HIV/AIDS ranks among the world's most devastating diseases because it has spread rapidly and mainly affects young people in their most productive years. More than 33 million people worldwide are living with HIV/AIDS, and 30 million already have died from AIDS-related causes (UNAIDS/WHO, November 2010). Each day, about 7,000 more women, men and children become infected with HIV, the virus that causes AIDS. Globally, more than 16 million children ages 0-17 years, the majority of whom live in sub-Saharan Africa, have lost their parents because of HIV (UNAIDS/WHO, November 2010).

Women bear a particularly high burden of the epidemic as primary caregivers for the ill and because of their heightened risk of infection because of biological, economic and social vulnerabilities. Based on the latest comprehensive WHO data, HIV/AIDS is the leading cause of death globally in women 15-44 years of age, particularly in sub-Saharan Africa where the epidemic has hit hardest. Heterosexual sex is the primary mode by which HIV spreads in developing countries.

Although a range of prevention strategies exists, they are not enough to stop the spread of HIV — particularly among women. Many women may be unable to persuade their male partners to 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.

This is why new prevention strategies that women can use themselves are urgently needed. One such strategy would be microbicides — medical products being developed to protect healthy people from becoming infected with HIV during sex. Some microbicides are being designed only for women as vaginal products, and others would be rectal products that both men and women could use.

The International Partnership for Microbicides (IPM) is among several nonprofit organizations focused on developing microbicides to protect women from becoming infected with HIV during sex with a male partner. Microbicides could come in many forms, including gels used around the time of sex, once-daily gels, films, and vaginal rings that could provide protection for a month or longer. Vaginal microbicides would address one of the central gaps in the existing continuum of prevention options by offering a discreet method women would use to protect themselves against HIV.

How would microbicides work?

In contrast with *treatment* regimens for HIV/AIDS, which help manage HIV infection after it has already taken hold in the body, microbicides are designed to *prevent* infection from happening in the first place.

In recent years, a number of organizations have been studying a highly potent class of microbicide products containing antiretroviral drugs (ARVs) formulated as gels to be used around the time of sex, as daily gels and films, and as monthly vaginal rings. These microbicides are based on the same types of ARV drugs being used to treat people living with HIV/AIDS and to prevent mother-to-child transmission of the virus. They act specifically against HIV by attacking at one of a number of points in the HIV life cycle. ARV medicines have extended and saved millions of lives across the globe — adapting those drugs to protect healthy adults from becoming infected with HIV could transform the global response to the epidemic. In fact, ARV-based microbicides are following the lead of other life-saving prevention methods that have been successfully adapted from treatments for diseases such as malaria, influenza and pneumonia.

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New evidence from two recent clinical trials has shown the powerful potential of ARVs to prevent HIV transmission.

Results were announced in July 2010 from the first-ever efficacy trial of a vaginal microbicide containing an ARV. That Phase IIB clinical trial, called CAPRISA 004, established proof-of-concept for tenofovir gel. Overall, tenofovir gel reduced the risk of acquiring HIV infection by 39 percent, and it was shown to be safe as tested when used up to 12 hours before sex and again within 12 hours after sex. Tenofovir is an ARV that prevents HIV from making copies of its genetic material once inside the cell by inhibiting the action of the HIV reverse transcriptase enzyme. Additional research is under way to develop microbicides that attack HIV in various ways, including novel compounds that interfere with the fusion and entry of HIV into the target cell.

Another trial, which established proof-of-concept for ARV-based pre-exposure prophylaxis, or PrEP, released promising results in December 2010. The trial demonstrated that taking the daily oral ARV medication Truvada® —an FDA-approved HIV treatment that contains both tenofovir disoproxil fumarate and emtricitabine—while receiving comprehensive HIV prevention services led to a 44 percent reduced risk of becoming infected with HIV-1 in the clinical trial population. This Phase III trial, called iPrEx, was conducted by the US National Institutes of Health with co-funding from the Bill & Melinda Gates Foundation and study medication donated by Gilead Sciences, Inc. In 2006, Gilead granted both IPM and CONRAD rights to develop tenofovir as a topical microbicide for use by women in developing countries.

Some researchers believe that combinations of ARVs in a single microbicide product may improve upon the efficacy of single drugs, but further clinical evaluation is needed. An ideal combination product might be active against independent targets in the viral replication process and have different mechanisms of action.

Formulations, delivery and acceptability

The forms microbicides would take — such as gels, films or vaginal rings — can have a critical impact on their efficacy, cost and acceptability to those who will be using them. An advantage of ARV-based microbicides is that they can be formulated in long-acting delivery methods that can be applied once a day (gels and films) or used for a month or longer (vaginal rings). Because any of these formulations would be used independently of when sexual activity takes place, they would provide protection against HIV infection even during unanticipated sex.

Although no microbicide has yet been approved for use, an ARV-based microbicide has now been shown to reduce the risk of HIV infection in women. Other ARV drugs that target HIV infection have been identified and are currently undergoing extensive study and testing for use as microbicides. In addition to conducting clinical trials to test the safety and effectiveness of microbicides to prevent HIV infection, IPM and other nonprofit organizations are conducting product acceptability studies to help determine which types of microbicide products women really want and would use.

Microbicides will put the power of HIV protection into women's hands, potentially saving millions of lives around the world.

How are microbicides tested for safety and efficacy?

All microbicide candidate products 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 preclinical tests can take one to several years to complete. Once a candidate microbicide satisfactorily passes these tests and additional safety tests in animals, it can be advanced through a series of human clinical trials. This process must be followed for any new product before it can be approved for use.

Clinical trials are carried out sequentially: first to determine the safety of the product (no significant side effects occurred) and then to test its efficacy (the ability of the product to prevent HIV infection). The initial safety trials involve small numbers of women who participate under carefully controlled clinical conditions. Larger safety trials, in which the microbicide is administered to a wider range of women over longer periods, are then conducted to gain broader safety data.

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Only when the *safety* trials have been completed can *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. This allows researchers to better assess the difference in infection rates between those women who use the active microbicide and those who use a placebo (similar to the microbicide, but not containing any active drug). If *significantly fewe*r women become infected in the group that used the microbicide, then researchers know that the microbicide helps to prevent HIV infection.

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

Vaginal microbicides would put the power of HIV protection into women's hands, potentially saving millions of lives around the world. The findings from CAPRISA 004 are encouraging and a true cause for optimism. Additional confirmatory/complimentary trials with tenofovir gel are planned for 2011. A microbicide to reduce the risk of sexual HIV transmission promises to have a significant impact on the epidemic's future.

What ethical standards guide clinical trials?

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

All clinical trials, including microbicide trials, must be conducted according to international and national 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 guidelines for the conduct of clinical trials (for IPM's guidelines, visit www.IPMglobal.org*).* These guidelines are living documents that must continually integrate new scientific information and discoveries, and be responsive to a changing research and policy landscape.

Informed consent is the cornerstone of ethical trial conduct. Clinical research teams must ensure that all participants in microbicide trials have freely given informed consent based on a clear understanding of the trial, including the 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 that requires periodic discussions with participants to ensure their continued understanding of the trial.

In addition, as part of the standard of care guidelines for clinical trials, participants are provided with ongoing HIV and sexually transmitted infection (STI) risk-reduction counseling, condoms, pre- and post-HIV test counseling, family planning counseling and treatment for curable STIs that are identified. Participants are also referred for support, care and treatment in the event that they become infected with HIV or require medical attention for any other condition.

How are local communities supported?

Microbicide product developers are committed to implementing clinical trials that have broad support from the communities hosting the trials. Clinical trials may provide long-lasting benefits such as the construction of new research centers, training of local staff to conduct research, educating clinical trial participants about general and women's health issues, promoting HIV prevention messages within the community and other initiatives that seek to improve the overall health and awareness of communities.

In countries where clinical trials are conducted, IPM and other microbicide developers have implemented broad-based programs 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, ministries of health and others. Ongoing training and support for those involved in the clinical testing process — clinical investigators, research scientists, nurses, counselors, community health workers and project management staff — is also provided.

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How will women's access to microbicides be ensured?

Once developed and approved for use, microbicides must be made widely available and affordable. Historically, it can take decades for the benefits of scientific innovation to reach the developing world. But IPM and the broader microbicide field are committed to expediting widespread availability and access of any effective product, reaching those most in need first. Ensuring access to microbicides is a responsibility that must be shared by trial sponsors, research teams, donors, multilateral and bilateral agencies and national governments.

Conclusion

Lessons learned through years of scientific inquiry have brought the world in 2011 to a milestone in HIV/AIDS research: proof that a topical ARV-based microbicide can reduce the risk of HIV infection. 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.

Microbicides will not only help reduce the burden of death and disease among women — and, indirectly, among men and children — they could also support economic development and help eradicate poverty in the developing world.

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