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 affects young people in their most productive years. About 35 million people worldwide are living with HIV/AIDS, and almost 36 million already have died from AIDS-related causes. Each day, over 6,000 more women, men and children become infected with HIV, the virus that causes AIDS. Globally, nearly 17 million children, the majority of whom live in sub-Saharan Africa, have lost one or both parents due to HIV (UNAIDS, 2013).

Women bear a particularly high burden of the epidemic as primary caregivers for the ill and because of their heightened risk of infection due to 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, especially among women. Many women are 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 HIV prevention strategies that women can use themselves are urgently needed — and one such strategy would be microbicides.

What are microbicides?

Microbicides are medical products being developed to protect healthy people from becoming infected with HIV during sex. Some microbicides are being designed for women as vaginal products, and others would be rectal products that both men and women could use. Microbicides for women could come in many forms, including vaginal gels used around the time of sex or once-daily and rings that could provide protection for a month or longer. A safe and effective microbicide could have a profound impact on the epidemic. Microbicides 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 — and these drugs are now being adapted to protect healthy adults from becoming infected with HIV.

The International Partnership for Microbicides (IPM) is among several nonprofit organizations focused on developing microbicides to protect women from HIV during sex with a male partner.

Microbicide trials recently completed and underway

Taken together, new evidence from multiple clinical trials has shown the powerful potential of ARV-based HIV prevention. See below for information on clinical trials of ARV-based microbicides for women that have been recently completely or are underway.

Microbicide trials on tenofovir gel

CAPRISA 004: In July 2010, the CAPRISA 004 study showed that a vaginal microbicide gel containing the ARV drug *tenofovir* reduced study participants' risk of acquiring HIV infection by 39 percent when used once before sex and again afterward. In a surprise finding, tenofovir gel also reduced by half the number of infections of another sexually transmitted infection, HSV-2, which is the cause of most genital herpes.

VOICE (MTN-003): VOICE trial, led by the US National Institutes of Health (NIH)-funded Microbicide Trials Network (MTN) and designed to evaluate both oral and topical forms of the ARV drug tenofovir when used daily. The study results found that 1% tenofovir did not reduce the risk in women.

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FACTS 001 (Follow-On African Consortium for Tenofovir Studies): Enrollment in the FACTS 001 trial began in October 2011. This is a large-scale trial of tenofovir gel in South Africa women which is testing the same dosing strategy as CAPRISA 004. FACTS 001 results are expected in late 2014.

SUMMARY: While the CAPRISA 004 showed that a vaginal microbicide gel containing the ARV drug *tenofovir* reduced study participants' risk of acquiring HIV infection, data from the VOICE trail found that 1% tenofovir did not reduce the risk in women due to low adherence to the daily dosing regimen used in that trial, which highlights the challenge of developing and delivering a product women can and want to use. The field is looking to the results of FACTS 001, which uses the same before-and-after sex dosing regimen as CAPRISA 004 trial, to confirm whether 1% tenofovir gel can be used as an HIV prevention tool.

Microbicide trials on the dapivirine ring

IPM 027 (The Ring Study) and MTN 020 (ASPIRE):
IPM 027 (The Ring Study), now underway by IPM is designed to determine whether a monthly vaginal ring that delivers the ARV drug dapivirine helps prevent HIV infection in women and is safe for long-term use. The first efficacy study of a vaginal ring for HIV prevention, The Ring Study is expected to enroll 1,950 women ages 18-45 across six sites in South Africa and one in Uganda. Results are expected by 2016.

MTN 020 (ASPIRE) is evaluating the efficacy and safety study of the dapivirine ring and is being led by the MTN. It is expected to enroll across 15 sites in Malawi, South Africa, Uganda and Zimbabwe. Results are expected in 2015.

Together, the two studies will involve thousands of women volunteers across Africa and last about three years (2012-2015). Should both studies show the ring to be safe and effective, IPM will seek regulatory approval for product licensure and collaborate with key partners to help ensure the ring is made available at low cost as soon as possible to women in developing countries.

SUMMARY: For the first time, a vaginal ring is being tested in two large-scale microbicide safety and effectiveness trials for HIV prevention. Because the ring is designed to deliver an ARV continuously over one month, it has the potential to address the challenge of adherence and help ensure effectiveness.

Why is product choice important?

Stopping HIV requires a toolkit of products that address individual needs and preferences. Some women may prefer taking a pill every day; some may prefer a gel used before and after sex; while others may prefer a product like a vaginal ring that they replace monthly. It's about giving women options, because a product that best suits a woman's needs and preferences is much more likely to be used consistently and correctly. And only when a product is used can it be effective. An advantage of ARV-based microbicides is that they can be formulated at an affordable cost in multiple delivery methods — from short-acting gels and films to long-acting rings — and deliver the drug locally where it is needed with low systemic absorption.

Combination products and MPTs: Some researchers believe that microbicides combining two or more ARVs in a single product may target HIV at different points in the life cycle and increase the level of protection, as is the case with ARVs used in treatment. The first combination microbicide to be tested in a clinical trial is IPM's *dapivirine-maraviroc vaginal ring*, which was conducted in partnership with MTN; results expected in 2014. Also in preclinical development are multipurpose prevention technologies (MPTs) designed to prevent HIV infection and pregnancy — such as IPM's 60-day dapivirine-contraceptive ring — as well as products designed to prevent HIV and other sexually transmitted infections.

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. 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.

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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). Initial safety trials involve small numbers of women who participate under carefully controlled clinical conditions. Larger safety trials involving a wider range of women over longer periods are then conducted to gain broader safety data.

Efficacy trials are then 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.

What ethical standards guide clinical trials?

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 guarantee the ethical and scientific integrity of the results.

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 and ongoing 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 involved?

In countries where clinical trials are conducted, IPM and its local research partners have implemented broad-based programs of community engagement. Information about microbicides and clinical trials is provided in local languages not only to trial participants but also to key stakeholders, including local officials, women's groups, medical professionals, the media, traditional leaders, 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.

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

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. IPM and the broader microbicide field are committed to expediting widespread availability and access of an 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

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 global health development goals. Science has shown the powerful potential of ARVs to prevent HIV infection and save millions of lives — now delivering on that promise requires financial resources and political will needed to conduct this important work. Developing safe and effective microbicides for women in developing countries promises to be one of the great public health accomplishments of our generation.