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. About 34 million people worldwide are living with HIV/AIDS, and almost 30 million already have died from AIDS-related causes. Each day, over 7,000 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 their parents because of HIV (UNAIDS/WHO, June 2011).

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 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 HIV during sex with a male partner. Microbicides could come in many forms, including gels used around the time of sex or once-daily and vaginal rings that could provide protection for a month or longer.

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 new generation of microbicide gels and rings containing antiretroviral drugs (ARVs), similar to those 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 — and these drugs are now being adapted to protect healthy adults from becoming infected with HIV.

What have recent microbicide studies and other HIV prevention trials shown so far?

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

Microbicide studies: Results announced in July 2010 from the first-ever efficacy trial of a vaginal microbicide gel containing an ARV called *tenofovir* showed "proof-of-concept" that a microbicide could protect women against HIV. That clinical trial, called CAPRISA 004, showed that tenofovir gel reduced the risk of acquiring HIV infection by 39 percent when used once before sex and once again after sex. In a surprise finding, tenofovir gel also cut in half infections with another sexually transmitted virus, HSV-2, which is the cause of most genital herpes. Two clinical trials called MTN-003, also known as the "VOICE" study (conducted by the NIH-funded Microbicide Trials Network) and FACTS 001 (led by the Follow-On African Consortium for Tenofovir Studies) are under way to confirm these results.

Studies of oral ARV pills: In 2010 and 2011, several large clinical trials also established proof-of-concept that ARVs taken as oral tablets can significantly reduce the risk of HIV infection in various adult populations. This new intervention is called pre-exposure prophylaxis, or PrEP. The iPrEx trial, led by the NIH, showed that taking the daily medication Truvada® — an oral ARV pill that contains both *tenofovir* and *emtricitabine* — led to 44 percent fewer HIV infections among men who have sex with men. Another trial called Partners PrEP conducted in Africa by the University of Washington, found that among heterosexual couples in which one partner is HIV-positive and the other HIV-negative, daily oral Truvada and daily oral tenofovir reduced HIV

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infections by 73 and 62 percent, respectively. The TDF2 trial, conducted by the US Centers for Disease Control and Prevention (CDC) among men and women, reported that daily oral Truvada reduced their HIV risk by 63 percent. Finally, a long-term study by NIH testing 'treatment for prevention' reported that earlier versus delayed initiation of ARV treatment among HIV-positive people led to a 96 percent reduction in new HIV infections among their uninfected partners.

Promise of ARV-based prevention: Taken together, these studies demonstrate the enormous potential for ARV-based technologies to revolutionize HIV prevention. Stopping HIV will require a broad toolkit of products that address individual needs and preferences, including long-acting microbicides that could improve consistent use and adherence, and ultimately enhance effectiveness, while reducing the possibility of resistance.

Microbicide formulations, delivery and acceptability

The forms microbicides would take — such as gels, films or vaginal rings — can have a critical impact on their efficacy and 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, tenofovir gel has been shown to reduce the risk of HIV infection in women, and two additional clinical trials are ongoing to confirm these results. Other ARV drugs that target HIV infection have been identified and are currently undergoing extensive testing for use as microbicides, such as the long-acting, monthly vaginal ring developed by the International Partnership for Microbicides (IPM), which contains the ARV compound *dapivirine*. The ring will advance to long-term safety and efficacy studies in 2012 conducted by the Microbicide Trials Network (MTN) and IPM in Africa.

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, but further study is needed. The first combination microbicide to be tested in a clinical trial will be the *dapivirine-maraviroc vaginal ring* developed by IPM — this new product will be evaluated in a safety study by MTN beginning late 2011. Other combinations are in preclinical development, including combination products with tenofovir as well as dual-purpose products designed to prevent HIV infection and pregnancy or HIV and other sexually transmitted infections.

A microbicide to reduce the risk of sexual HIV transmission promises to have a profound impact on the epidemic.

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.

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.

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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 to guarantee the ethical and scientific integrity of the results. 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 involved?

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 renovation or construction of research centers, training of local staff to conduct research, and working closely with the research center partners to educate clinical trial participants about general and women's health issues, promote 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 its local research partners have implemented broad-based programs of community engagement. Information about microbicides and clinical trials is offered 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 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 to a milestone in HIV/AIDS research: proof that topical ARV-based microbicides and oral ARV pills can reduce the risk of HIV infection. Microbicides, as well as PrEP, 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. Now is the time to build on recent findings and advance the development of long-acting microbicide products women can use to protect themselves.