INTERNATIONAL PARTNERSHIP for MICROBICIDES

ISSUE BRIEF

IPM Clinical Trials

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2nd Edition

What is the state of the global AIDS epidemic?

AIDS is the world's most deadly infectious disease and claims over three million lives annually. Every day, 14,000 people are newly infected with HIV, the virus that causes AIDS, and over 40 million people are now living with HIV—more than ever before. In many parts of the world, AIDS has become an escalating social and economic disaster as well as a widespread human tragedy. In several African countries, over one-third of the population has HIV, and the epidemic is becoming increasingly severe in parts of Asia, Eastern Europe and other regions.

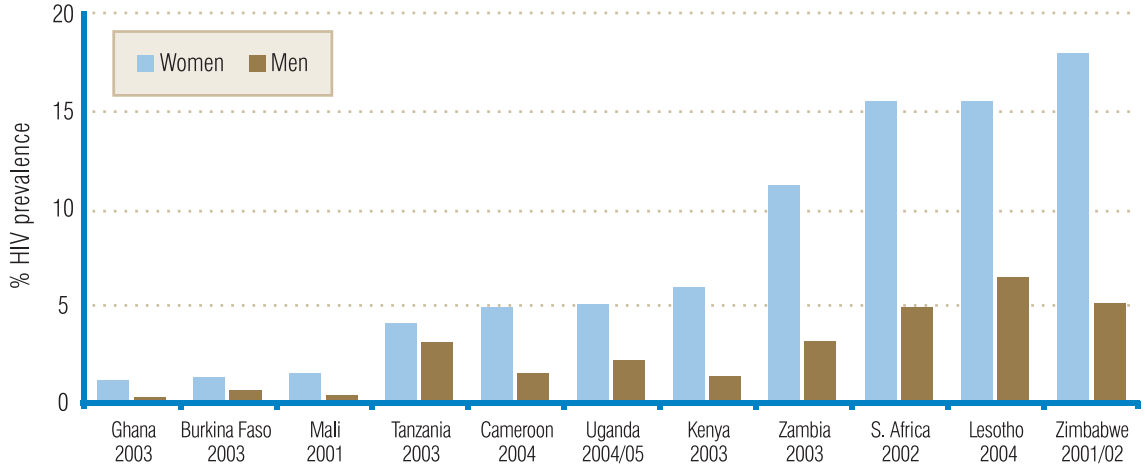
What is the impact on women?

Women and girls bear a severe and increasingly heavy burden in the AIDS epidemic. In sub-Saharan Africa, 57 percent of adults living with HIV are women. In many African countries, women and girls aged 15 to 24 are two-and-a-half times more likely to be HIV-infected than their male counterparts. AIDS also severely affects women in many industrialised countries. In the United States, AIDS is now the leading cause of death for African-American women aged 25 to 34. Today, 17.5 million women in the world are living with HIV.

> A microbicide has the potential to put the power of protection from HIV infection into the hands of women and save millions of lives.

Women are becoming infected with HIV at a faster rate than men due largely to their increased biological susceptibility and pervasive gender inequality. Many women have little or no control over the conditions under which they have sex and often cannot negotiate the use of condoms. A microbicide has the potential to put the power of protection from HIV infection into the hands of women and save millions of lives.

HIV prevalence among 15-24 year-old men and women, selected countries in sub-Saharan Africa, 2001-2005



Source: UNAIDS' AIDS Epidemic Update: December 2005

What is a microbicide?

Microbicides are vaginal products being developed to reduce the transmission of HIV during sexual intercourse. Microbicides could take the form of a gel, cream, film, suppository or sponge, or be contained in a vaginal ring that releases the active ingredient gradually. A microbicide would be a useful complement to other HIV prevention measures, including safer sex education, condom distribution, voluntary testing and counselling, testing and treatment of sexually transmitted infections, anti-stigma campaigns, safe blood supplies and (hopefully, one day) a vaccine.

Microbicide development is a long and expensive process. Though no microbicide has yet been approved for use, there is growing scientific consensus that a microbicide can be developed. Dozens of agents that interrupt HIV infection have been identified and are being studied for use as microbicides.

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How are microbicides tested?

Before being tested in humans, a microbicide first undergoes pre-clinical testing in the laboratory to determine whether it shows promise as an intervention that is both safe and effective. A candidate microbicide then advances through a series of human clinical trials designed to test the product's safety in people as well as its ability (or "efficacy") to prevent infection of HIV and, perhaps, other pathogens. Safety trials can take one to two years. Efficacy trials can last three years or longer, involve thousands of people and cost hundreds of millions of dollars.

Photo courtesy of Photoshare, a service of The INFO Project

Efficacy trials must be held in communities with existing high incidence of HIV infection so that researchers can compare infection rates among those who use the candidate microbicide with those who use a placebo. As discussed below, participation in clinical research does not increase someone's risk of HIV infection. In fact, enrolment in trials often decreases one's risk of HIV infection due to the extensive efforts that are made to reduce HIV risk among study enrolees, including safer sex education, treatment of sexually transmitted infections, provision of condoms, etc.

If clinical studies demonstrate a product is safe and effective, national and regional regulatory authorities then consider whether to license the product for use. (See the glossary for more information on clinical trials and basic terminology.)

What is IPM?

The International Partnership for Microbicides (IPM) is a non-profit product development partnership (PDP) founded in 2002. IPM's goal is to reduce HIV transmission by accelerating the development of and accessibility to safe and effective microbicides for women in developing countries.

Through its partnerships with private sector (pharma, biotechnology and clinical research organisations), as well as non-profit and academic organisations, IPM is working to increase the efficiency of microbicide product development and testing.

Under IPM, a variety of microbicide research and development activities are, or will be, taking place.

> IPM is working to increase the efficiency of microbicide product development and testing.

These include:

- screening compounds
- designing optimal formulations
- in-licensing and development of microbicide drugs
- establishing manufacturing capacity for safety trials
- developing clinical trial sites
- conducting safety trials
- conducting a large-scale efficacy trial

IPM identifies the most promising technologies and invests its resources to help develop them into usable products. Building on lessons learned from HIV therapeutic research, IPM is developing and testing a new generation of microbicide candidates that are highly active against HIV. These candidate products are among the first to employ ingredients, such as reverse transcriptase inhibitors, that are intended to interrupt infection by targeting discrete steps in the reproductive lifecycle of HIV.

Photo credit: Karl Grobl

What is the status of IPM's clinical trials?

IPM is sponsoring microbicide safety studies at clinical sites in Belgium, Rwanda, Tanzania and South Africa. These studies are testing the safety and acceptability of dapivirine (TMC120 gel). Dapivirine is designed to prevent or interrupt HIV replication in human cells.

IPM is also in the process of identifying and helping build research capacity at up to 20 additional trial sites in high-incidence areas in preparation for future efficacy studies of dapivirine and other candidate microbicides. IPM's large-scale efficacy trials will be designed to answer one primary question: Is the product safe and effective in preventing HIV transmission in HIV-negative women?

Who will participate in IPM trials?

IPM microbicide trials recruit healthy, HIV-negative women who are at risk of HIV infection. Not all women who volunteer for a microbicide clinical trial are enrolled in the study. There are a variety of reasons why some women are ineligible for participation in microbicide trials, including being pregnant, being HIV-positive, or being unable or unwilling to commit to regular clinic visits or other study requirements.

Protecting the health and well-being of the thousands of women in Africa and Europe who will participate in IPM-sponsored microbicide trials is a top priority for IPM and its research team.

What are "informed consent" and "standard of care"?

Informed consent is the process through which a potential trial volunteer is given information about a clinical study in order to help her decide whether or not to volunteer for that study and by which a volunteer authorises participation. Informed consent is strictly regulated by international codes of conduct and supervised by local ethics committees.

STUDY	STUDY NAME AND LOCATION	n*	STATUS
IPM001	Dapivirine vaginal ring trial, Belgium	12	Completed
IPM003	Dapivirine gel safety trial, Rwanda, South Africa, Tanzania	112	Ongoing
IPM004	Dapivirine gel PK trial, South Africa	18	Completed
IPM005B	Dapivirine gel expanded safety trial, Belgium	36	Completed
IPM007	Seroconverter protocol, Various sites	N/A	Planned
IPM008	Dapivirine vaginal ring trial, Belgium	13	Completed
IPM009	Dapivirine gel efficacy trial, Various sites	TBD	Planned
IPM010	Dapivirine gel male tolerance trial, Belgium	36	Planned

* Estimated number of volunteers in study

IPM is committed to ensuring that all participants in IPM-sponsored trials have provided informed consent based on a clear understanding of the goals of the study and the potential risks and benefits of trial participation. IPM recognises that informed consent is an ongoing process that requires periodic discussions with participants to ensure their continued understanding of the study and their consent to be involved. Study volunteers will be periodically tested for their comprehension of critical concepts discussed in the informed consent process. All participants in any clinical trial are free to leave the trial at any time with no penalty.

Standard of care refers to the services, rights and protections provided to clinical trial participants. IPM has developed comprehensive guidelines for the conduct of its clinical trials through a rigorous ethical and peer review process. The guidelines detail its commitment to provide all study participants with ongoing risk reduction counselling, male and female condoms, treatment for those who become infected with HIV during the course of the trial, and treatment and compensation in the unlikely event physical harm results from trial participation. The Guidelines for the Conduct of IPM's Clinical Trials document is available at www.ipm-microbicides.org/guidelines.htm.

What care will be provided to trial participants who become infected with HIV during the course of the trial?

All IPM trial participants receive prevention counselling, testing and treatment for sexually transmitted infections, as well as condoms throughout the study to help them avoid HIV infection. Experience from a variety of recent trials confirms that participation in clinical studies does not put women at increased risk of becoming infected with HIV. In fact, HIV incidence often drops among those enrolled in clinical trials, likely because of the prevention services, condoms and sexually transmitted infection treatment that are provided at study sites. Men will also be recruited for some IPM trials in order to assess the safety and acceptability of microbicide products among male partners.

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As part of the guidelines for the conduct of its clinical trials, IPM has committed to provide all study enrolees who become infected with HIV during the course of the trial with appropriate antiretroviral (ARV) treatment for HIV disease. Treatment initiation will be based on the host government's guidelines for ARV treatment or, if national guidelines are not in place, the HIV treatment guidelines established by the World Health Organization (WHO). IPM will pay for ARV treatment for study enrolees during and after the clinical trial until national HIV programs are able to provide this care.

Individuals who volunteer for IPM trials but "screen out" (i.e. are ineligible to enrol) because they are already positive for HIV infection will be provided with a package of post-test counselling and psychosocial support. These services will initially be provided at the study site and then women will be referred for services in the local community. IPM is establishing

referral agreements with local providers near each study site to ensure women who screen out will be able to receive support services.

How are communities involved in clinical research?

IPM views clinical research as a partnership with host communities. IPM is dedicated to the full participation of communities in all aspects of clinical trial planning, protocol development, recruitment and implementation. Every IPM-sponsored trial site will establish a community advisory board early in the trial planning process. Research teams at IPM sites will also utilise a variety of approaches to learn about community perspectives and engage community members as partners. Community outreach activities may include sponsoring education programs, holding periodic community forums, surveying community members, communicating with local and national media, creating a "community advocate" position on the study staff and collaborating with non-governmental organisations to inform communities about the research and seek their input.

How long before a microbicide is available globally?

With five microbicide candidates now in large-scale efficacy trials and a new generation of microbicides well into safety studies, microbicides could be available in five to seven years. There may be successive "generations" of licensed microbicide products. The first approved microbicide might be only partially effective, for example reducing infection rates by 40 percent. Development and testing of improved microbicides and combinations of microbicides will continue after the first microbicide becomes available. Even a partially effective microbicide could prevent millions of new HIV infections and reduce overall HIV incidence in many parts of the world.

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Microbicides can only make a lasting impact on the AIDS epidemic if they are widely accessible in heavily affected countries. Preparing for rapid global access to microbicides drives several aspects of IPM's work. IPM seeks to identify products for development and testing that inherently cost little to produce. IPM has already established all necessary agreements with commercial partners to ensure its right to make products available in developing countries. IPM is working to identify regulatory strategies to facilitate swift review of new microbicides by regulatory agencies in key developing countries as well as in the United States and Europe. And IPM is collaborating with donors and international organisations to establish adequate financing mechanisms to support global microbicide access.

This document will be revised regularly to reflect the latest information about IPM's clinical trials. For more information, visit us on the web at www.ipm-microbicides.org or contact us by e-mail at info@ipm-microbicides.org.

Glossary of Terms

Adverse event: In microbicide clinical trials, an adverse event is any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom or disease temporally associated with the use of a microbicide, whether or not considered related to the use of the microbicide being tested.

Control group: The control group is a subset of the clinical trial population. Generally, individuals in the control group are given a placebo instead of the microbicide or other intervention being studied. At the end of a microbicide trial, researchers compare the rate of HIV infection among people in the "intervention group" (those who used the candidate microbicide) and the control group. If there is a statistically significant difference in the number of infections in the intervention and control groups, with fewer infections in the group using the microbicide, this indicates the microbicide likely provided some level of protection against infection.

Efficacy: Efficacy refers to the capacity of a product to achieve a desired effect. In the case of microbicide clinical trials, efficacy refers to the ability of the product to protect someone from infection with HIV and, perhaps, other pathogens. (See below for more information on the phases of clinical research.)

First- and second-generation microbicides: First-generation microbicides were developed in the 1990s and include products that form physical barriers to HIV or change the chemistry of the vagina with the goal of making HIV less likely to infect someone. Second-generation microbicides are products that are specifically active against HIV, including microbicides that use antiretroviral drugs. IPM is focusing its product development efforts on this next generation of microbicide candidates.

Incidence: Incidence refers to the number or rate of new infections in a given period. For example, an annual HIV incidence rate of two percent means that two percent of the population was newly infected with HIV in a given year.

Mechanism of action: Mechanism of action refers to the way in which a microbicide or other product protects against infection. Several different mechanisms of action are being studied in different microbicide candidates. A microbicide might work by killing or otherwise immobilising HIV; it may form a barrier between the virus and the vaginal tissue; it could boost the natural defences of the vagina against HIV; or it could prevent the virus from replicating once it enters cells.

Pharmacokinetics (PK): Pharmacokinetics refers to the study of the action of drugs in the human body, in particular the time required for absorption of the drug, its duration of action, its distribution in the body and how it is excreted. PK studies help researchers determine appropriate usage and dosage of drugs.

Phases of clinical research: There are three standard "phases" of human clinical trials that preventives undergo: safety, expanded safety and efficacy.

- ***Safety studies:*** These studies enrol a small group of people to evaluate a product's safety, determine a safe dosage range, identify side effects and measure the acceptability of the product to trial volunteers. Safety studies are also known as "Phase I" studies.

- ***Expanded safety studies:*** The product being evaluated is tested in a larger group of people

for a longer duration to further evaluate its safety, appropriate dosage range and acceptability. These studies are also referred to as "Phase I/II" or "Phase II" trials.

- ***Efficacy studies:*** These studies evaluate a product's efficacy. In the case of microbicides, efficacy studies test a product's ability to protect people from infection with HIV and, perhaps, other pathogens. Large numbers of people are usually enrolled in efficacy trials of HIV prevention interventions. Thousands of women will participate in some microbicide efficacy trials. These trials are also referred to as "Phase III" trials.

Placebo: A placebo is an inactive gel or pill that has no preventive or therapeutic value and which has been established to be safe for use. In most clinical studies, participants in the control group receive a placebo instead of the product being evaluated. This allows researchers to compare the effects of the intervention under study against the placebo.

Prevalence: Prevalence refers to the total number or rate of infection currently in a population. For example, an HIV prevalence rate of 15 percent means that 15 percent of the population is living with HIV infection at the present time.

Primary endpoint: The primary endpoint is the overall outcome that the clinical trial protocol is designed to evaluate.

Protocol: All clinical trials are based on a protocol or study plan. The protocol details how a study will be organised and implemented so that it answers specific research questions and safeguards the health of trial volunteers. The protocol describes what types of people may participate in the trial, the schedule of tests, procedures, medications and dosages, and the length of the study.

Randomised double-blind control trials: Enrolees in efficacy studies are usually randomly assigned to either an intervention group (which receives the candidate microbicide) or a control group (which receives a non-active, no-drug placebo). These trials are called "double-blind" because neither the trial participant nor the on-site research staff know whether the trial volunteer has received the candidate microbicide or the placebo.

Seroconverter protocol: The seroconverter protocol is the research team's plan of action in the event a trial enrolee becomes infected with HIV during a trial. The seroconverter protocol is part of the official study protocol and may call for regular HIV-related care and treatment for the enrolee as well as referral of the enrolee to a sub-study that includes only HIV-positive individuals.

Tolerance studies: Male tolerance studies are designed to examine the effects of microbicides on male sexual partners. These studies seek to identify both the possible physiological impact of the microbicide on men, as well as men's attitudes towards use of the product by their female sexual partners.

IPM MISSION:

The mission of IPM is to prevent HIV transmission by accelerating the development and availability of safe and effective microbicides for use by women in developing countries.

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