INTERNATIONAL PARTNERSHIP for MICROBICIDES

ISSUE BRIEF

IPM Clinical Trials

FEBRUARY 2008
4th Edition

What is the state of the global AIDS epidemic?

AIDS is the world's most deadly infectious disease – claiming more than 2 million lives annually. Every day, almost 7,000 people are newly infected with HIV, the virus that causes AIDS, and approximately 33 million people are now living with HIV. 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 15 percent of the population has HIV, and the epidemic is becoming increasingly severe in parts of Asia, Eastern Europe and other regions.

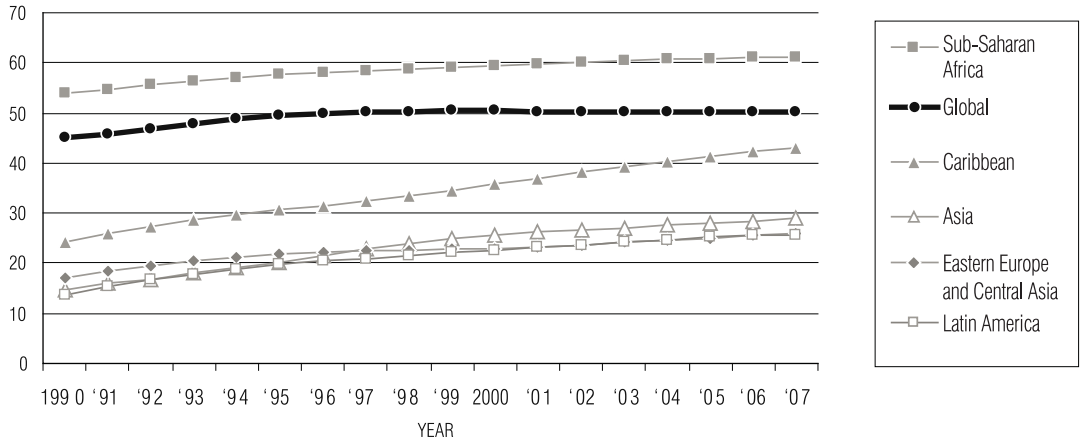
What is the impact on women?

Women and girls bear a severe and increasingly heavy burden in the AIDS epidemic. In sub-Saharan Africa, 61 percent of adults living with HIV are women, and HIV prevalence is three times higher among women ages 15 to 24 than it is among men in that same age group. AIDS also severely affects women in many industrialised countries. In the United States, AIDS is a leading cause of death for African-American women aged 25 to 34. Today, more than 15 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 as well as 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.

Percent of adults (15+) living with HIV who are female, 1990–2007



Source: UNAIDS/WHO, AIDS Epidemic Update, December 2007

What is a microbicide?

Microbicides are vaginal products being developed to prevent and reduce the transmission of HIV during sexual intercourse. Microbicides could take the form of a gel, vaginal tablet, film or 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, male circumcision and hopefully, one day, a vaccine.

Microbicide development is a long and expensive process. Though no microbicide has yet been approved for use, dozens of agents that interrupt HIV infection have been identified and are being studied for use as microbicides.

How are microbicides tested?

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 prior to being tested in humans. This intensive program of 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 in order to gain a broader base of 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. Consequently, the total development costs for microbicides can run to hundreds of millions of dollars.

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 commonly used terminology.)

Photo courtesy of Photoshare, a service of The INFO Project

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 and availability of safe and effective microbicides for women in developing countries.

Through its partnerships with private sector (pharmaceutical, 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 research centres
- conducting safety trials
- conducting product acceptability studies
- implementing large-scale efficacy trials

IPM identifies the most promising technologies and invests its resources to help develop them into 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 and entry 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 research centres in Belgium, Kenya, Rwanda, Tanzania and South Africa. These studies are testing the safety and acceptability of dapivirine (TMC120) gel and vaginal ring. 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 20 additional clinical research centres 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?

In general, IPM microbicide trials recruit healthy, HIV-negative women who are at risk of HIV infection. Men will also be recruited for some IPM trials in order to assess the safety of microbicide products.

Not all women who volunteer for a microbicide clinical trial can be enroled in the study. There are a variety of reasons why some women are ineligible for participation in microbicide trials, including being pregnant or breast-

STUDY	STUDY NAME	LOCATION	n*	STATUS
IPM001	Dapivirine vaginal ring safety	Belgium	12	Completed
IPM003	Dapivirine gel safety	Rwanda, South Africa, Tanzania	112	Completed
IPM004	Dapivirine gel PK	South Africa	18	Completed
IPM005B	Dapivirine gel safety	Belgium	36	Completed
IPM007	Seroconverter protocol	Various	N/A	Planned
IPM008	Dapivirine vaginal ring safety	Belgium	13	Completed
IPM009	Dapivirine efficacy	Various	TBD	Planned
IPM010	Dapivirine gel male tolerance	Belgium	36	Planned
IPM011	Placebo vaginal ring safety and acceptability	Kenya, South Africa, Tanzania	200	Ongoing
IPM012	Dapivirine gel PK	Belgium	36	Ongoing
IPM013	Dapivirine vaginal ring PK	Belgium	60	Planned
IPM014	Dapivirine gel safety	Malawi, South Africa, Tanzania	320	Planned
IPM015	Dapivirine vaginal ring safety	South Africa, Tanzania	280	Planned
IPM017	Dapivirine vaginal ring safety	Belgium	46	Planned
IPM018	Dapivirine vaginal ring PK	Belgium	24	Completed
IPM020	Dapivirine gel safety	United States	140	Planned
IPM021	Dapivirine vaginal ring safety	Europe	140	Planned

* Estimated number of volunteers in trial

Since changes are frequent in trial design, please visit IPM's website (Clinical Activities section) for the most recent listing of IPM clinical trials.

feeding, 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 choose to participate in IPM-sponsored microbicide trials is a top priority for IPM and its research teams.

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. All those who choose to enrol in a trial must legally authorize their participation. Informed consent is strictly regulated by international codes of conduct and supervised by local ethics committees.

IPM is committed to ensuring that all participants in IPM-sponsored trials have provided informed consent based on a clear understanding 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 may 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.

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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.

As part of the guidelines for the conduct of its clinical trials, IPM has committed to provide all study participants who become infected with HIV during the course of the trial with appropriate antiretroviral (ARV) treatment. The start of treatment 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 participants 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 centre and then women will be referred for health services in the local community. IPM is establishing referral agreements with local providers near each study centre 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 clinical research centre will establish a community advisory process early in trial planning. Research teams at IPM study centres 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 liaison position on the study staff and collaborating with nongovernmental organisations to inform communities about the research and seek their input.

How long before a microbicide is available globally?

Of the early generation of microbicide candidates, just two now remain in large-scale efficacy trials. A new generation of microbicides are currently well into safety and acceptability studies. Given current timelines for product development, a microbicide could be available in five to seven years. There may be successive generations of licensed microbicide products. 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.

Microbicides can only make a lasting impact on the AIDS epidemic if they are widely accessible to women at greatest risk of infection. 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 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 microbicides by regulatory agencies in key developing countries as well as in the United States and Europe. In addition, IPM is collaborating with donors and international organisations to establish adequate financing mechanisms to support global microbicide access.

This document is 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 between 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.)

Early- and next-generation microbicides: Early-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. Next-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 enroled 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 formulation 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 number or rate of existing infections 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: Participants 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 participant 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 participant as well as referral of the participant to a sub-study that includes only HIV-positive individuals.

Tolerance studies: Male tolerance studies are designed to examine the safety of microbicides on men.

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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