Microbicides Research & Development

Fact Sheet

How do microbicides work?

Researchers are exploring diverse and increasingly sophisticated ways to block HIV infection. These ways are called "mechanisms of action." At this point, it is unknown which mechanisms of action and therefore which candidate microbicides will be able to reduce the risk of HIV transmission. Some candidate microbicides may even combine more than one mechanism. *This fact sheet provides an overview of the mechanisms of action that are being explored and an overview of how microbicides are tested.*

Early Clinical Research

Candidates in human trials between 2002-2009 were thought to work by one of three main mechanisms:

- Breaking up cell membranes (N-9, Saavy, Invisible Condom)
- Enhancing vaginal defenses (Buffer Gel)
- Blocking the virus from entering the genital mucosa (Carraguard, Cellulose Sulfate, PRO2000)

Current and Future Clinical Research

Most candidates currently in human trials are testing a new strategy: taking antiretroviral drugs now used for treatment and adapting them for topical prevention. In other words, delivering highly potent ARV drugs to the genital mucosa, where sexual transmission first takes place.

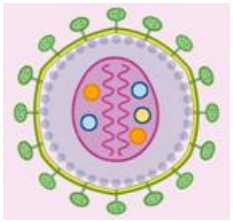
ARV drugs are already being used successfully to prevent mother-to-child transmission and to reduce the risk of acquiring HIV after an accidental needle stick. The drugs being evaluated for prevention are believed to work in a variety of highly specific ways:

- Targeting the virus to prevent it from attaching and entering white blood cells (the cells that HIV must infect in order to reproduce),
- Blocking entry by targeting receptors on the outside of the white blood cell itself.
- Preventing HIV from making more copies of itself (replicating) once it has entered a white blood cell.

Researchers consider ARV-based microbicides to have certain advantages and certain limitations compared to candidates that function in other ways. For example, the fact that ARV-based microbicides are non-contraceptive is both an advantage and a limitation. Some users might want to protect themselves from HIV and still be able to get pregnant. Other users might want a microbicide that protects them from HIV and is contraceptive.

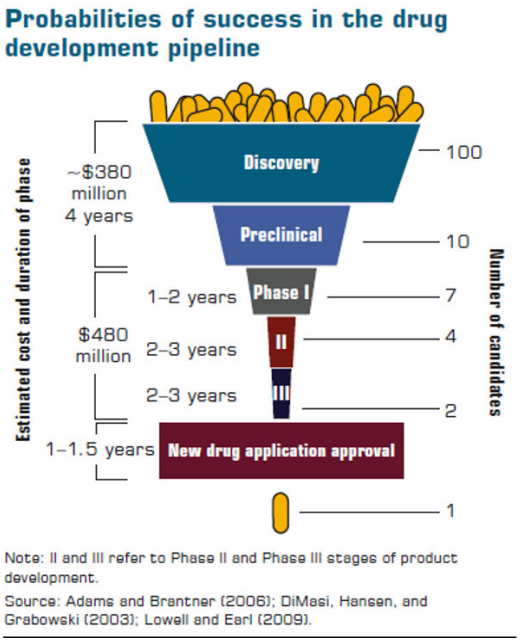
Advantages of ARV-based microbicides	Limitations of ARV-based microbicides
• May be highly effective against HIV • Not contraceptive • Daily or episodic use is possible; may be delivered through vaginal rings or other sustained release methods Opportunity to integrate delivery of product into overall VCT and health care service delivery	• Not effective against other STIs • Not contraceptive. Further study is required to see whether they could be combined with other agents to prevent pregnancy or infection by other STIs. • Further study is required to understand the potential for toxicity and dangers of HIV-negative people taking ARVs • Further study is required to understand whether users would develop resistance to ARVs if they are already or became HIV-positive whilst using the microbicide • Will not be provided over the counter initially, potentially posing challenges to access the product. Women will need to get prescription and regular HIV testing to access the product

Moving forward, it is important that research continue to find new microbicide candidates, especially those that may protect against other STIs in addition to HIV. The field must continue to innovate and broaden the pipeline of products under development.



To find out more about different mechanisms of action—and the HIV life cycle—visit the Microbicides Essentials course on-line at http://www.HIVPreventionResearch.org/

The Cost of Drug Research and Development



The steep increase in drug manufacturers' total research and development (R&D) costs stems largely from the rising costs of clinical testing of new drugs.

The average total R&D cost for new drugs in the late 1990s was $897 million, according to a report by the Tufts Center for the Study of Drug Development. That total was more than double the average total cost of bringing a new drug to market in the 1980s, and more than five times the cost during the 1970s. The costs of clinical testing have grown five times as fast as preclinical testing costs, the center states.

Notably, "postapproval" R&D costs climbed dramatically. This refers to clinical studies performed after FDA approval—known as Phase IV studies—which are often mandated in the case of drugs that are put on a fast track for approval.

Fast-track approval status requires manufacturers to commit to continuing clinical testing after marketing approval.

How are microbicides tested?

As with any new health technology or drug, candidate microbicides pass through a series of rigorous tests to determine their safety and efficacy (see diagram on following page). These tests start in the laboratory, where researchers determine whether a compound fights HIV pathogens, first in test tubes and then in animals. If these tests show that the product is: 1) potentially effective against pathogens, and 2) relatively safe (non-irritating) in animals, then clinical (human) trials can begin. The chart on the following page provides a summary of how microbicides are tested.

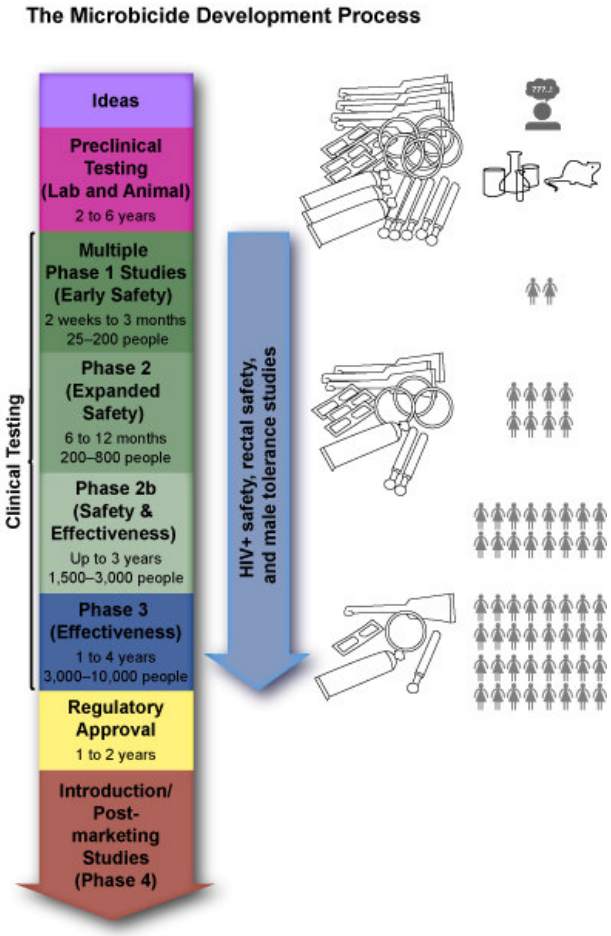
Clinical testing phases:

Phase I clinical trials determine the safety of the product when used by a small number of healthy, low-risk people over a few weeks.

Phase II clinical trials also test the safety of the product, this time in a larger number of people, some of whom may have higher risk factors, over a longer period of time. Some preliminary data about efficacy and acceptability of the product may be collected.

Phase IIb clinical trials, also called proof-of-concept trials, are designed to see whether a microbicide will protect against HIV. In this sense, they are the beginning of efficacy trials. Larger than a Phase II study but often only half the size of a full-scale Phase III trial, a Phase IIb study enrols enough people to offer a suggestion of whether the microbicide can prevent HIV infection.

Phase IIb studies can be used to eliminate products that clearly don't work (and therefore are not worth testing in a full Phase III trial) or to help identify which of several products makes the most sense to move forward into Phase III. Although Phase IIb trials are not a required step in the clinical research process, they are increasingly being used to best use limited resources for HIV-prevention-product development.



Phase III clinical trials enrol thousands of people in several sites, and they measure safety and whether or not the microbicide candidate actually works to prevent HIV.

Phase IV occurs after a drug has been licensed and brought to market, these studies will continue to seek out more information on safety, side effects, and use.

Once a microbicide candidate is proven effective in a clinical trial, what happens next?

Once a trial shows that a microbicide does work, many steps will be needed, and at least another two to four years will be required. Before a microbicide becomes available, regulatory approvals, manufacturing processes, and introductory studies (known as phase IV studies) must be undertaken. Due to the individual country processes, a microbicide will not be available in all locations at the same time, and not all people within a country will get it at the same time. It is likely to be made available to some people and not others during introduction and scale-up.

How do you know if a microbicide candidate is effective?

A very large number of women (several thousand) have to be enrolled and followed over time in a Phase III trial to determine whether the product helps reduce the risk of acquiring HIV. The Phase III trial works by comparing two groups: (a) those receiving the best known HIV-prevention package plus the experimental microbicide gel and (b) those receiving the best known prevention package plus the comparator gel. The comparator gel looks just like the product being studied but does not contain the active ingredient.

Researchers randomly assign women to be in one of two trial groups—known as "arms" of the study. Randomisation ensures that women in each group are similar in every respect except the matter under study—in this case, use of the experimental microbicide gel versus use of a comparator gel. Women are never deliberately exposed to HIV to see if the microbicide protects them. Instead, researchers follow the two groups over time to see if the rate of new sexually transmitted HIV infections is lower among those who received the candidate microbicide versus those who do not. If it is, this difference is the measure of the microbicide's effectiveness in preventing sexual HIV transmission.

There are several products with various mechanisms of action currently in clinical trials globally. It is crucial that numerous products with different mechanisms of action are tested in order to increase the probability and speed of finding a successful microbicide.

Waiting in the wings behind these candidate microbicides are dozens of products that are still in pre-clinical testing. Making the leap from pre-clinical to clinical trials depends not only on the success of the product, but also the availability of resources to conduct clinical trials. Virtually all microbicide research is currently being conducted by non-profit organizations, small biotech companies, and academic institutions—all of which rely on governmental and/or philanthropic grants to pursue their research. Without significantly enhanced public investment, the microbicides research and development pipeline is slow and inefficient—delaying the day when women and men can protect themselves from HIV and STIs with a safe, effective microbicide.

The Global Campaign for Microbicides (GCM) is a civil society organization working to ensure the ethical and accelerated development of, and widespread access to, new and existing HIV-prevention options—especially for women. Visit our website: www.global-campaign.org or email: info@global-campaign.org