

Microbicides Research & Development:

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, PRO 2000)

Current and Future Clinical Research

Most candidates currently in human trials are testing a new strategy—adapting existing ARV drugs for topical prevention. In other words, delivering highly potent antiretroviral drugs at 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. They work in a variety of highly specific ways:

- Targeting the virus and preventing 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.

ARV-based microbicides are believed to have certain advantages and certain limitations compared to candidates with different mechanisms of action:

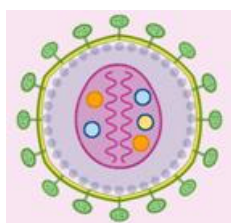


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Advantages of ARV-based microbicides	Limitations of ARV-based microbicides
<ul style="list-style-type: none"> • May be highly effective against HIV. • Not contraceptive. Further study is required to see whether they could be combined with other agents to be or effective against other STIs. • Daily or episodic use is possible; may be delivered through vaginal rings or other sustained release methods. 	<ul style="list-style-type: none"> • Not effective against other STIs. • Not contraceptive. • 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 became HIV-positive whilst using the microbicide.

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 more about the HIV life cycle—visit the Microbicides Essentials course online at <http://www.hivpreventionresearch.org/>

How are microbicide candidates 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 and STI pathogens—first in test tubes and then in animals. If the data from 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 microbicide candidates 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 candidate 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 enrolls enough people to indicate whether the product 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

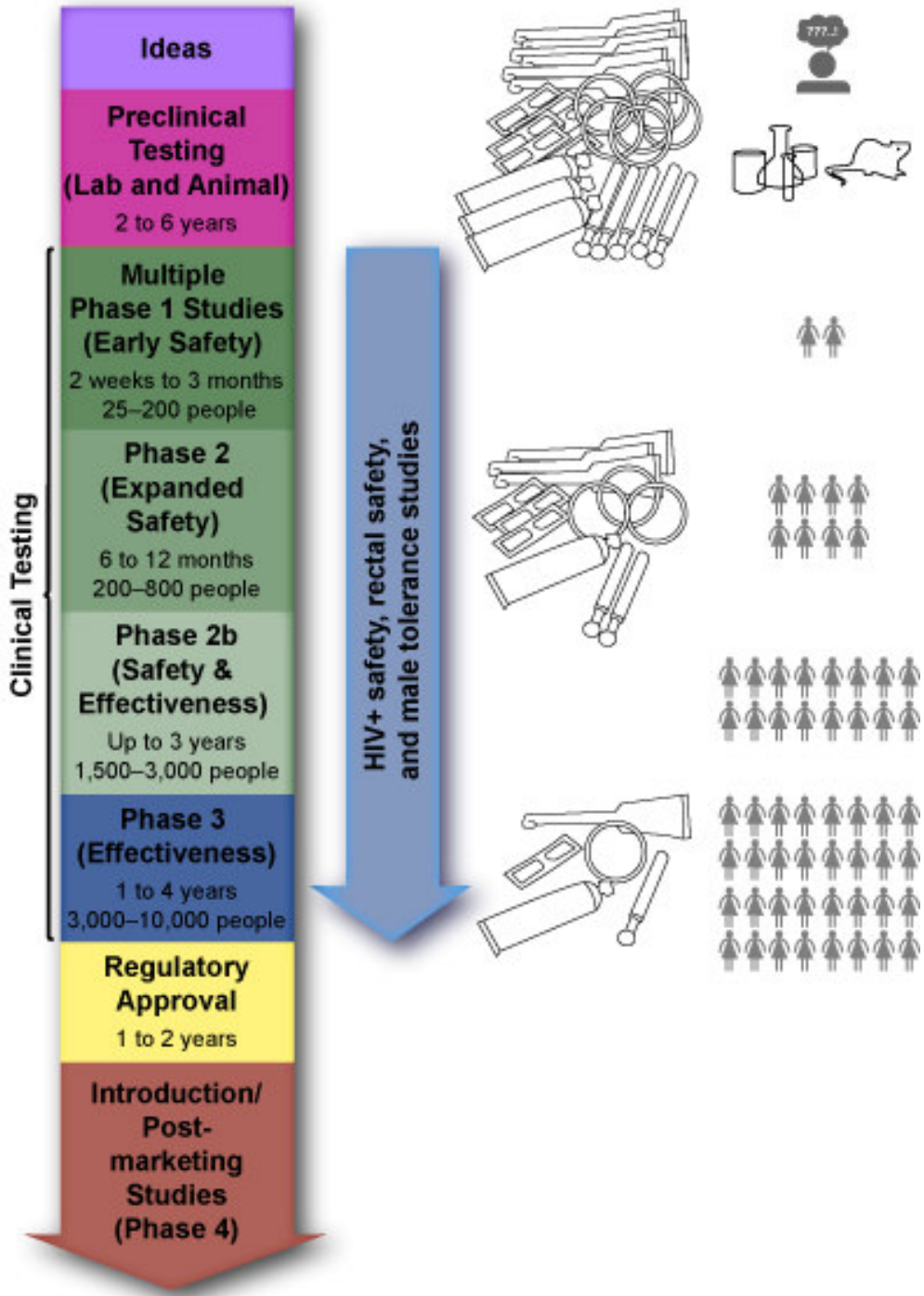
Phase III. In some cases, the same participants who take part in Phase II or Phase IIb trials may choose to continue or “roll over” into a Phase III trial.

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

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

Once a trial shows that a microbicide does work, at least another two to four years will be required for individual countries to go through their own regulatory approval processes and introductory studies to make the microbicide available. Due to these individual country processes, it must be noted that a microbicide will not be available in all countries 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 women and not others during introduction and scale-up.

The Microbicide Development Process



How do you know if a microbicide 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 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 a test gel versus use of a comparator gel. Women are never deliberately exposed to HIV to determine if the product protects them. Instead, researchers follow the two groups over time to see if the rate of new HIV infections resulting from sex with their partners is lower among those who received the candidate microbicide versus those who do not. If it is, this difference is the measure of the experimental product’s effectiveness.

There are about a dozen products with various targets and mechanisms of action currently in clinical trials globally. It is crucial that several products with different mechanisms of action are tested simultaneously 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 in the laboratory, but also the availability of resources to conduct clinical trials. Virtually all microbicide research is currently being conducted by small biotech companies, non-profit organisations, and academic institutions—all of whom rely on governmental and/or philanthropic grants to pursue their research. With additional public investment, the microbicides research and development pipeline can become faster and more efficient, bringing us closer to the day when women and men can protect themselves from HIV and STIs with a safe, effective microbicide.

GCM is a diverse network of advocates and nongovernmental organisations (NGOs) working worldwide to expand HIV prevention options and encourage ethical research that involves civil society.

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