Fact Sheet #3

Microbicide Research & Development: *How do they work and How are they tested?*

Global Campaign FOR Microbicides

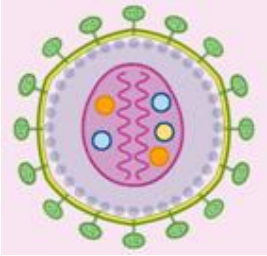
How do microbicides work?

Researchers are exploring diverse and increasingly sophisticated mechanisms of action to block HIV infection. At this point, it is unknown whether the ways in which various microbicides work – their mechanisms of action – will actually prevent HIV infection.

Each mechanism of action is designed to intercept or inhibit HIV infection at different points in the infection lifecycle. Some of these mechanisms of action are specific to HIV, whereas others are broad spectrum and may work against other sexually transmitted infections as well. The chart below describes the five mechanisms of action that have been or are currently being pursued:

Mechanisms of Action for Microbicides

Non-specific to HIV	Specific to HIV
Blocking agents ➤ Prevent the virus or pathogen from entering cells	**Entry inhibitors** ➤ Block specific proteins on the virus ➤ Block specific receptors on target cells
Vaginal defense enhancers ➤ Boost the body's natural defences	**Replication inhibitors** ➤ Inhibit the reverse transcriptase enzyme from initiatng replication (NNRTIs) ➤ Inhibit the replication process once it has started (NRTIs)
Membrane disrupting agents ➤ Inactivate the virus or pathogen	



Visit the Microbicides Essentials course on-line to see a series of animations that depict how different mechanisms of action can interrupt the HIV lifecycle. ***www.hivpreventionresearch.org***

PATH

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Updates available at: www.global-campaign.org/download.htm

There are different consequences for the microbicides depending on whether the mechanisms of action are specific or non-specific to HIV. The chart below summarizes these attributes:

Potential Attributes for Non-specific and Specific Mechanisms of Action

Non-specific to HIV	Specific to HIV
Blocking agents Vaginal defense enhancers Membrane disrupting agents	Entry inhibitors Replication inhibitors
Potentially effective against other STIs	Not effective against other STIs
Potentially contraceptive	Not contraceptive
Large molecules – unlikely to be absorbed	Small molecules – readily absorbed into tissue
Low potential for systemic toxicity	Might be absorbed into the bloodstream
No potential for HIV resistance	HIV resistance requires further study
Must be used at time of intercourse (coitally dependent)	Daily or episodic use possible; may be delivered through vaginal rings or other sustained release methods

How are microbicides tested?

As with any new health technology or drug, candidate microbicides pass through a series of rigorous tests before to determine their safety and efficacy. 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 trials 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.

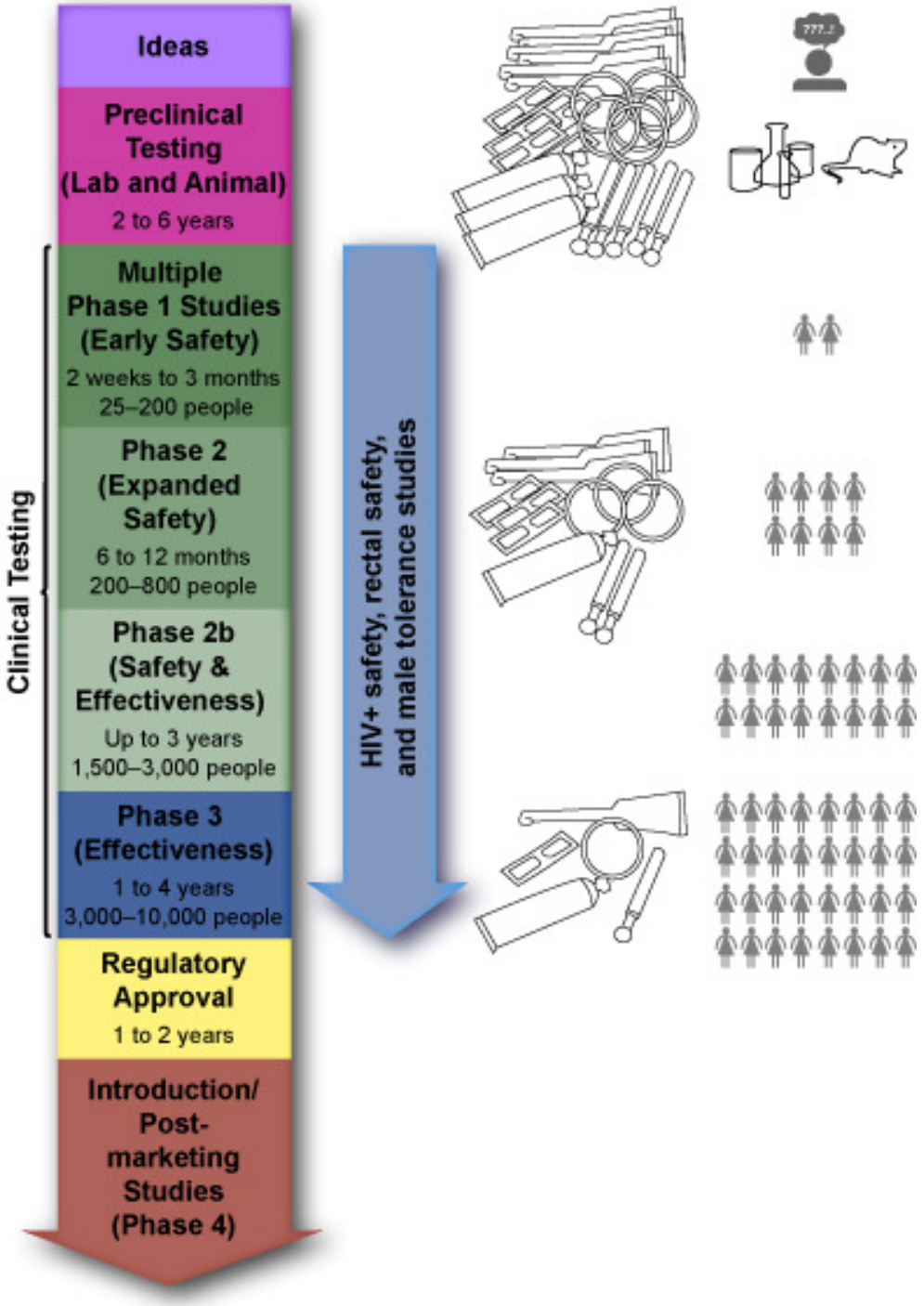
Phase I clinical trials determine the safety of the product when used by a small number of healthy, low-risk women over a few weeks.

Phase II clinical trials also test the safety of the product, this time in a larger number of women, 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 address the difficulty of predicting whether a microbicide will protect against HIV. 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 aren't 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 "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 actually works to prevent HIV and STIs. Some Phase II trials of microbicides can "roll into" Phase III trials as long as the data show good results.

The Microbicide Development Process



There are about one 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 other 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 small biotech companies, non-profit organisations and academic institutions -- all of whom rely on governmental and/or philanthropic grants to pursue their research. Without significantly enhanced public investment, the microbicides research and development pipeline is slowed and inefficient -- thus delaying the day when women and men can protect themselves from HIV and STIs with a safe, effective microbicide.

Three Candidates in Late-Stage Clinical Trials

The following are descriptions of the three candidate microbicides currently in Phase 2B or 3 clinical trials. For more information on these and other candidate products, please visit the Alliance for Microbicide Development's website www.microbicide.org or check out **Factsheet #13: Trials Watch** at www.global-campaign.org/download.htm

BufferGel is an acid buffer that keeps the vagina acidic even in the presence of semen and creates a physical barrier that stops or slows down the passage of pathogens into the vaginal and cervical walls. It is expected to be contraceptive and may protect against HIV, HPV, HSV, chlamydia and gonorrhea. Carbopol 974, the major nonaqueous component of BufferGel, is commonly used as a gelling or tableting agent.

PRO2000 (napthalene sulphonate polymer) is an entry and fusion inhibitor that binds to viruses and bacteria to prevent them from binding to and infecting healthy cells. Its contraceptive efficacy is expected to be dose dependent. It may protect against HIV, gonorrhoea and HSV.

Tenofovir is a highly specific nucleotide reverse transcriptase inhibitor (NRTI). An oral formulation of tenofovir (trade name Viread) is actively marketed by Gilead Sciences for the treatment of HIV. For potential microbicide use, tenofovir has been formulated as a 1% gel. It is likely to be highly potent, so it only takes a small amount of the active ingredient to have an effect. It is non-contraceptive and HIV specific.