

Microbicide Research & Development: *What's in the Pipeline?*



How does a microbicide work?

This question has several possible answers depending on which microbicide you are talking about. The term “microbicides” really refers to a broad range of products designed to prevent infection by HIV and other sexually transmitted pathogens when applied in the vagina or rectum. However, there are *four basic mechanisms of action* by which various candidate microbicides may work.

HIV and STI pathogens can attack the body in multiple ways, and an effective microbicide will help prevent infection by stopping this attack at one or more stages in the process. The microbicides currently under development act in one or more of the following ways:

1. ***Killing or inactivating pathogens.*** Surfactants disable the virus by breaking up its surface membrane or envelope. They can also disable sperm in the same way so they are also effective contraceptives. The trick is to make sure that surfactants are strong enough to disrupt the invading pathogen, but without damaging the healthy cells that line the vagina's walls.
2. ***Strengthening the body's normal defences.*** This approach builds or improves upon what the body already does to protect itself. For example a healthy vagina is normally acidic, which makes it inhospitable to invading pathogens like HIV. But semen counteracts this acidity, creating an environment where HIV can survive. Some candidate microbicides build on the simple principle of maintaining the vagina's natural acidic even in the presence of semen.
3. ***Inhibiting viral entry.*** Entry inhibitors work by interfering with the virus getting into the body's white blood cells—the target cells of HIV. There are two categories of entry inhibitors: attachment inhibitors that prevent attachment of the virus to the white blood cell and fusion inhibitors that prevent HIV from actually entering the cell.
4. ***Inhibiting viral replication.*** Some candidate microbicides are being developed from the anti-retroviral drugs that HIV positive people use to lower the amount of virus in their bodies. Formulated as gels or creams, these drugs may be able to suppress replication of any HIV that enters the vagina or rectum during sex. If so, they could substantially lower the odds that the microbicide user will become infected.

Eventually, microbicide products will probably combine one or more of these approaches.

Cervical Barriers and Microbicides

Past research has suggested that covering the cervix (with a diaphragm or cervical cap) may offer dual protection: preventing pregnancy while simultaneously protecting against HIV/STIs.¹ The Methods for Improving Reproductive Health in Africa (MIRA) trial, completed in February 2007, was a randomised, controlled trial in South Africa and Zimbabwe that aimed to measure the effectiveness of the diaphragm used with Replens[®] lubricant gel for HIV prevention among women. The trial results, released this summer, have shown that in the context of a comprehensive HIV prevention package (including condoms, counselling and STI screening and treatment) that there is no added protective benefit from the use of a diaphragm and lubricant. Researchers do not recommend use of the diaphragm for HIV protection and urge that condoms remain the best method and only barrier method proven to prevent HIV.

In recent years, new cervical barrier methods have become available, and others are currently under development including the FemCap[™], Lea's Shield, the SILCS diaphragm, and the BufferGel Duet. As interest grows and as research results on efficacy for HIV/STI prevention become available, more methods may emerge to provide women with increased options for dual protection. It is possible that cervical barriers may be used along with microbicides for added protection and researchers are hopeful that some of these

combinations will prove effective. More information and research updates are available at the Cervical Barrier Advancement Society's website - www.cervicalbarriers.org

Microbicides Clinical Trials

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.

There are three phases of clinical trials:

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

Phase Two 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 Three 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 Two trials of microbicides can “roll into” Phase Three trials as long as the data show good results.

There are more than 30 products with various targets and mechanisms of action currently in clinical trials globally. It is crucial that several products with different mechanisms of action be tested simultaneously in order to increase the probability and speed of finding a successful microbicide. The differences between and among various product leads determine how they might be used and by whom. Some product concepts are based exclusively on the ecology of the vagina, for example, while others could potentially offer protection from rectal transmission as well. The following table summarises clinical trials that are on-going, from the Alliance for Microbicide Development (www.microbicide.org).

MICROBICIDES IN ONGOING CLINICAL TRIALS			
JULY 2007			
Phase	Candidate Name and Formulation	Mechanism of Action	Sites by Country
3	Carraguard® gel	Entry/fusion inhibitor	South Africa
	0.5% and 2% PRO 2000/5 gels	Entry/fusion inhibitor	South Africa, Tanzania, Uganda, Zambia
2B	1% Tenofovir gel	Replication inhibitor	South Africa
2/2B	0.5% PRO 2000/5 gel (P) and BufferGel®	Entry/fusion inhibitor and Vaginal defense enhancer	Malawi, South Africa, United States, Zambia
2	1% Tenofovir/PMPA gel	Replication inhibitor	India, United States
1/2	Dapivirine (TMC120) gel	Replication inhibitor	Belgium
	Dapivirine (TMC120) gel	Replication inhibitor	Rwanda, South Africa, Tanzania
	Invisible Condom™ gel	Entry/fusion inhibitor	Cameroon
1	Dapivirine (TMC120) gel	Replication inhibitor	South Africa
	1% Tenofovir/PMPA gel	Replication inhibitor	Dominican Republic, United States
	0.1% UC-781 gel	Replication inhibitor	United States
	0.1% and 0.25% UC-781 gel	Replication inhibitor	United States
	3% VivaGel™ (SPL7013 gel)	Entry/fusion inhibitor	Australia
	3% VivaGel™ (SPL7013 gel)	Entry/fusion inhibitor	Kenya, United States

Waiting in the wings behind these candidate microbicides are over 30 additional 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 entering advanced 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 gonorrhoea. Carbopol 974, the major nonaqueous component of BufferGel, is commonly used as a gelling or tableting agent.

Carraguard is an attachment inhibitor that provides a physical barrier between pathogens and vulnerable cells in the cell wall (epithelium) of the vagina or rectum. It is not expected to be contraceptive, and may protect against HIV, HSV, HPV, and gonorrhoea. The active pharmaceutical ingredient in Carraguard is carrageenan, a substance derived from seaweed. Carrageenan is used as a thickener in foods and as an emulsifier in topical creams and lotions such as those used in the cosmetics industry.

PRO 2000 (naphthalene 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.

¹ Moench TR, Chipato T, Padian NS. Preventing disease by protecting the cervix: the unexplored promise of internal vaginal barrier devices. *AIDS* 2001;15:1595-1602

The Global Campaign for Microbicides is a broad based, international coalition of organisations working to accelerate access to new HIV prevention options. Visit our website: www.global-campaign.org or contact us:

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