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Microbicides for HIV prevention

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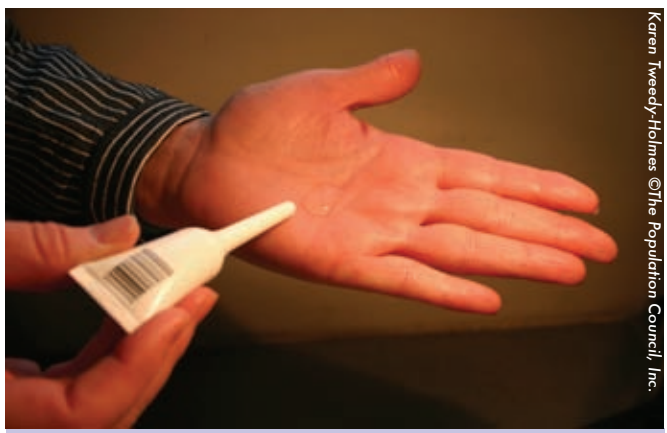
Scientists around the world are working diligently to develop a topical microbicide that can prevent HIV and other sexually transmitted infections (STIs). Advocacy and support for microbicide research is strong, and the availability of an effective product – although likely years away – could help to relieve the HIV epidemic in Africa.

The need for microbicides

The Joint United Nations Programme on HIV/AIDS recently announced that the prevalence of HIV has stabilised or even declined in many parts of sub-Saharan Africa. Current efforts to prevent HIV – including abstinence, mutual monogamy between uninfected partners, condom use, STI treatment, and male circumcision – may have collectively contributed to this encouraging trend.

Nevertheless, sub-Saharan Africa still suffers the most from this epidemic. More than two-thirds of *all* HIV-infected people live in this part of the world. Of these, more than 60% are women. Young women are even more disproportionately affected by the virus. In South Africa, for example, women make up 90% of the HIV-infected population of 15- to 24-year olds.[1]

Women are more likely to be infected with HIV for several reasons. They are biologically more susceptible, they are often economically dependent on their male partners, and many lack the ability to negotiate condom use within their sexual relationships. An HIV-prevention method that a woman could control, such as a vaginal microbicide, would overcome some of these inequities and save many lives.



Most vaginal microbicides are formulated as gels, creams, or foams that can be delivered using an applicator. This disposable plastic applicator was designed to be prefilled with a single dose of gel.

Types of candidates

Almost all microbicide research is being funded by the public sector and is being conducted by nonprofit organisations, academic institutions, and small biotechnology companies. More than 30 different products are currently in some stage of laboratory or clinical development.

Most of the candidates are formulated as topical gels, creams, or foams, but they can also be produced as suppositories or films. They are most often applied to the vagina before each act of sexual intercourse, but some newer candidates (including those loaded in rings or sponges) may be applied on a daily or monthly basis without regard to the timing of intercourse.

The products usually act in one of four ways to prevent HIV and other STI pathogens from infecting cells. Some are surfactants that inactivate a bacterium or virus by damaging its surface proteins. Some work by enhancing the vagina's natural defences against pathogens, for example by maintaining the natural acidity of the vagina in the presence of alkaline semen. Others block viruses so they cannot enter healthy cells. The newest products – often referred to as 'second-generation' microbicides – specifically target HIV, acting later in the viral life cycle by preventing HIV from replicating after it has entered the body.

The majority of candidates act to prevent HIV and at least one other STI. A combination product with more than one mechanism of action may eventually prove to be the most effective way to prevent a larger range of STIs. A microbicide with contraceptive ability could also help meet diverse reproductive health needs.

The research pipeline

After a microbicide candidate is identified, its safety and effectiveness is first assessed in test tubes or animal models. If the product passes this stage of testing, it enters human clinical trials.

In Phase I microbicide trials, scientists assess the local and systemic safety of the product, determine its acceptability among potential users, and identify its appropriate dose and formulation. In Phase II trials, scientists again assess safety and acceptability, but among more participants and for a longer period.

The final stages of microbicide trials (Phase IIb and Phase III trials) are used to evaluate a product's effectiveness in preventing HIV and other STIs, as well as its long-term safety and acceptability. These trials last from 6 months to 2 years, depending on their cost and size, and often enroll thousands of participants.

Of the more than 30 products in development, 12 are in

human clinical trials. Three of these candidates – tenofovir, BufferGel, and PRO 2000 – are in the final stages of clinical testing (see 'Effectiveness trials in Africa'). Three others (ACIDFORM, the invisible condom, and dapivirine) will enter effectiveness trials soon (see Table 1).

Effectiveness

Three products – Carraguard, SAVVY, and cellulose sulfate – have been tested for their effectiveness, and none was shown to prevent HIV.

The Population Council's 3-year Phase III trial of Carraguard was completed in 2007. The Carraguard gel, which works by blocking viral attachment and entry, was found to be safe and acceptable among some 6200 South African women. However, the product did not reduce the women's risk of acquiring HIV. Of the 285 women who became infected with HIV during the trial, 134 were using Carraguard and 151 were using a placebo. This difference was not statistically significant.[2]

The Carraguard trial was the first large-scale effectiveness trial of a microbicide to be completed as planned – an historic accomplishment in the eyes of many microbicide advocates. The other available data on effectiveness are from uncompleted trials of a surfactant called SAVVY and of another inhibitor of viral attachment and entry, called cellulose sulfate.

In 2004, Family Health International (FHI) and its partners began testing the effectiveness of SAVVY among more than 4000 women in Ghana and Nigeria. The Phase III Ghanaian study was closed in 2005 when an independent data monitoring committee determined that the incidence of HIV was so low that the study would not be able to determine whether SAVVY could prevent HIV.[3] FHI also closed its Phase III Nigerian study in 2006, after an independent data monitoring committee concluded that the trial was unlikely to find a protective effect if it continued.[4]

The findings from the SAVVY trial confirmed that surfactants may not be good microbicide candidates. In earlier studies, scientists showed that the surfactant nonoxynol-9 offers no protection against HIV or other STIs. Although spermicides containing nonoxynol-9 remain a moderately effective contraceptive option for women who have a low risk of infection, these products can actually increase the risk of contracting HIV when women at high risk of infection use them frequently.[5]

The outcomes of Phase III trials of cellulose sulfate were similar to those of Carraguard and SAVVY. In early 2007, CONRAD closed its cellulose sulfate trial involving more than 1400 women in South Africa, Benin, Uganda, and India after an interim analysis suggested that the product might increase the risk of acquiring HIV. FHI and its partners closed their trial of cellulose sulfate (involving some 1600 women in Nigeria) at the same time because of concerns for the participants' safety. An analysis of FHI's data later showed that cellulose sulfate did not affect the participants' risk of HIV infection positively or negatively.[6]

Table 1 Promising microbicide candidates

Mechanism of action	Microbicide	Description
Enhances vaginal defences	BufferGel*	A gel that maintains the natural protective acidity of the vagina in the presence of alkaline semen; also creates a physical barrier that prevents pathogens from passing through the walls of the vagina and cervix.
	ACIDFORM*	A bioadhesive gel that maintains the natural protective acidity of the vagina; also forms a protective barrier over the surface of the vagina and cervix.
Inhibits attachment and entry	PRO 2000*	A sulfonated polymer that binds to pathogens, preventing them from entering healthy cells.
	Invisible* condom	A gel containing sodium lauryl sulfate, a common ingredient in soaps and toothpaste, that destroys the membrane proteins of viruses to stop them from binding to healthy cells.
Inhibits replication	Tenofovir	A gel based on the oral form of tenofovir, a nucleotide analogue reverse transcriptase inhibitor that is commonly used to treat HIV.
	Dapivirine	A vaginal gel based on the oral form of dapivirine, a non-nucleoside reverse transcriptase inhibitor that is also being studied for the treatment of HIV.
*Also being evaluated for contraceptive ability.		

A counsellor explains condom use to a woman participating in a recent microbicide trial. If and when an effective microbicide is developed, it will be promoted with condoms as part of a complete HIV-prevention package.

Acceptability and access

Scientists must also consider whether women and men will actually use the microbicides if they become available. Qualitative research on a product's acceptability may help to inform the design and development of new products, estimate how well women will adhere to an eventual microbicide, and decide how microbicides might one day be marketed.[7]

Scientists can evaluate a microbicide's acceptability by simply describing a hypothetical product to potential users, by assessing the use of a surrogate product (such as a non-prescription spermicide), or by allowing women or men to use an actual microbicide candidate as part of a clinical trial.[7]

Most acceptability studies focus on product characteristics such as formulation, colour, texture, and the type of application. For example, a recent study of surrogate products in Zambia found that the 300 or so women in the study generally preferred a dry product rather than a wet one, and they preferred a suppository more than a gel.[8] Other studies have investigated the importance of contraceptive ability among potential users, the influence of sexual partners on product use, and other factors that could differ between individuals or communities.

In a review of 61 acceptability studies conducted worldwide between 1995 and 2002, only four studies evaluated the role that healthcare providers will play in promoting microbicides.[7] Yet, if and when a vaginal microbicide becomes available, health professionals will strongly influence whether women can access the product and how they will use it alongside other methods for preventing HIV and, in some cases, pregnancy.

Even if scientists develop an effective microbicide, condom use and behavioural changes will continue to play an important role in HIV prevention. That is because no microbicide will ever fully protect a woman against HIV and other STIs. Providers will need to inform their clients of the microbicide's limitations. Even on its own, however, a partially effective microbicide would offer some protection to women who are not able to negotiate safer sex with their partners.

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Web resources

http://www.global-campaign.org/

The *Global Campaign for Microbicides* is a network of more than 285 nongovernmental organisations that is building support for microbicides through international advocacy, policy analysis, and social science research. See the campaign's Website for specific information about advocacy efforts in Africa.

http://www.microbicide.org/

The *Alliance for Microbicide Development* includes representatives of more than 200 biopharmaceutical companies, research organisations, and advocacy groups dedicated to accelerating the development of an effective microbicide. The alliance's Website offers a comprehensive database of up-to-date information on microbicide research and development.

http://www.ipm-microbicides.org

The *International Partnership for Microbicides* is a global collaboration between public-sector and private-sector organisations that promotes the rapid development and availability of microbicides. Visit the partnership's Website to learn more about its own clinical trials and how it supports access to future microbicides.

Effectiveness trials in Africa

Results of the first large-scale clinical trials to test the effectiveness of microbicides were disappointing, but three newer trials are providing an opportunity to collect more data.

One trial is testing the safety and effectiveness of tenofovir gel at two sites in South Africa. This unique trial is the first to test the effectiveness of an antiretroviral-based microbicide, and it is the first time an institution based in the developing world has led a microbicide trial.

The oral form of tenofovir is one of at least 20 antiretroviral drugs that are being used to treat HIV infections throughout the world. Tenofovir is only now being tested for its ability to *prevent* HIV infections. The Centre for the AIDS Programme of Research in South Africa (CAPRISA) and its partners are testing the safety and effectiveness of a tenofovir-based gel among 980 sexually active women who are not infected with HIV. Half of the women are receiving a 1% tenofovir gel, and the other half a placebo gel, to use in a coitally dependent manner. The results of this Phase IIb trial are expected in 2010.[1]

The second trial is unique because it is the first time that the effectiveness of two different microbicides – BufferGel and PRO 2000 – is being tested at the same time. The Microbicide Trials Network is testing the safety and effectiveness of the two gels at seven sites in Malawi, Zambia, Zimbabwe, South Africa, and the United States.

Approximately 3100 sexually active women were randomly assigned to one of four trial arms – BufferGel alone, 0.5% PRO 2000 gel alone, a placebo gel, or no gel (condoms only) – in which they use the product before each act of vaginal intercourse. In a Phase IIb portion of the trial, the scientists are assessing the effectiveness of the microbicides for preventing HIV and several STIs, including syphilis, ghonorrhea, and chlamydia infections. Results are expected in 2009.[2]

In the third trial, the Microbicides Development Programme (a partnership between African and European scientists) is testing the safety and effectiveness of the PRO 2000 gel at six sites in Zambia, Uganda, Tanzania, and South Africa. This Phase III study was originally randomising women to receive 2% PRO 2000, 0.5% PRO 2000, or a placebo. However, the 2% PRO 2000 arm of the study was closed in February 2008 after an independent data monitoring committee reported that the 2% gel was unlikely to protect against HIV. The 0.5% PRO 2000 arm of the trial continues, and the results are expected in 2009.[3]

These three trials, like the effectiveness trials that came before them, are primarily concerned about the safety of the participants. They are designed according to rigorous international standards for ethics, and are closely monitored by internal and external safety boards. All women in the trials receive free condoms, frequent counselling on how to reduce the risk of HIV and other STIs, and ongoing diagnosis and treatment of STIs.

A technician examines blood samples in a laboratory in Durban, South Africa. This is the same laboratory where samples from CAPRISA's trial of tenofovir gel are being evaluated.

References

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2. Microbicide Trials Network. *HPTN 035*. Available: http://www.mtnstopshiv.org/node/62. April 20, 2008.
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More information

http://www.caprisa.org/
Centre for the AIDS Programme of Research in South Africa

http://www.mtnstopshiv.org/
Microbicide Trials Network

http://www.mdp.mrc.ac.uk/
Microbicides Development Programme