

FACT SHEET

Microbicides

Fast Facts

- Microbicides are products being developed to prevent or reduce the sexual transmission of HIV or other sexually transmitted infections (STIs) when used in the vagina or rectum.
- If proven effective, microbicides could help prevent HIV in women in developing countries where it most often is spread through unprotected heterosexual intercourse despite efforts to promote abstinence, monogamy and the use of condoms. Microbicides also could help prevent HIV in both men and women who practice anal sex. Unlike condoms, microbicides provide an HIV prevention strategy that is not controlled by one's sexual partner.
- Vaginal microbicides are being designed in many forms, including gels, films and sponges or rings that release an active ingredient gradually over time. Different products are being tested in clinical trials. Products that incorporate antiretroviral drugs are furthest along in testing. A vaginal gel with the ARV tenofovir is being tested in one Phase III trial while a vaginal ring containing dapivirine will be evaluated in another Phase III trial that is expected to be underway by mid-2012.
- Work also is underway to develop rectal microbicides. Most of the research to date has focused on tenofovir gel, which investigators have reformulated for rectal use. A Phase II trial of the rectal formulation of tenofovir gel is being planned.



Overview

The idea for a microbicide-like product was first proposed more than 20 years ago by reproductive health specialists and advocates who recognized the need for female-controlled HIV prevention methods. One of the first products considered was the spermicide nonoxynol-9 because researchers believed it might also be effective against HIV. Unfortunately, research showed it was neither safe nor effective against HIV. Other trials of different so-called first generation microbicides also proved unsuccessful. These included products intended to strengthen natural defenses in the vagina or create a barrier to protect target cells in the vagina.

Researchers now are evaluating HIV prevention products that are based on antiretroviral (ARV) drugs, including ARVs commonly used in HIV treatment. The most studied ARV-based microbicide is tenofovir gel, which was found safe and effective in reducing the risk of HIV in women who used it before and after vaginal sex in a study called CAPRISA 004. Yet, although an interim data review of another study called VOICE found tenofovir gel was safe, it was not effective among the women in the study who were asked to use the gel every day. It won't be possible to understand why tenofovir gel was not effective in VOICE until after the study is completed and results are available in early 2013. In the meantime, tenofovir gel continues to be evaluated in FACTS 001, a Phase III trial testing the same regimen of tenofovir gel used in CAPRISA 004.

Microbicides in the form of vaginal rings are also being developed. Because they can be used monthly, some women may find rings better suit their needs or lifestyles than a product used daily or at the time of sex. Two large-scale trials are being planned to evaluate the safety and effectiveness of a vaginal ring containing the ARV dapivirine. The dapivirine ring and other vaginal rings that are being developed for HIV prevention have a similar look and feel to vaginal ring products that are used for contraceptive delivery or hormone replacement and licensed in both the U.S. and Europe.



What will it take to discover a Safe and Effective Microbicide?

Testing many products is necessary before finding even one microbicide that will be safe and effective against HIV and also easy and acceptable to use. Different products work in different ways, and researchers do not yet know which ones will work best. A handful of candidate microbicides are in various stages of clinical study; additional compounds are in early stages of development.

Drug development is a long and arduous process, often taking up to 20 years before just one product is approved for general use. Thousands of potential compounds may be considered during drug discovery but only the most promising products are subjected to rigorous laboratory and animal studies, and fewer still make it to trials with people. Clinical trials are carried out in several phases under the oversight of regulatory and research authorities and according to strict ethical and scientific guidelines. Phase I trials are designed to evaluate safety in a small number of people who are exposed to study products for short periods, say, one to two weeks. If results of a Phase I study suggest the product is safe, investigation progresses to a Phase II trial, in which researchers continue to track safety over more extended periods of time. Phase IIb and III trials are performed to determine how effective a product may be and are conducted with large numbers of participants, typically at multiple clinical centers. These trials are usually designed to compare a product with an inactive product (a placebo) or another active product. Data from Phase IIb and Phase III trials are often used by regulatory agencies to determine if a particular product should be approved for widespread use.

The State of the Field: Clinical Trials of ARV-Based Vaginal Microbicides

Tenofovir Gel

- **CAPRISA 004** – A Phase IIb trial that assessed the safety and effectiveness of tenofovir gel used before and after vaginal sex. The study, which involved 889 women from South Africa, found tenofovir gel reduced the risk of HIV by 39 percent compared to a placebo. However, results, which were reported in July 2010, also indicated that the true level of effectiveness of tenofovir gel – when used before and after sex – could be anywhere between 6 and 60 percent. CAPRISA 004 provided the first proof of concept that a microbicide can help prevent HIV, a finding that was considered a major milestone for the field.
- **VOICE (MTN-003)** – Vaginal and Oral Interventions to Control the Epidemic – is a major HIV prevention trial designed to evaluate the safety and effectiveness of two different ARV-based approaches for preventing sexual transmission of HIV in women: daily use of an ARV tablet (tenofovir or Truvada) or daily use of an ARV-based vaginal gel (tenofovir gel). The study began in September 2009 and enrolled 5,029 women in Uganda, South Africa and Zimbabwe. Testing of tenofovir tablets was halted after an independent review of study data in September 2011 concluded that although the tablets were safe they were no more effective than placebo in preventing HIV. Similarly, a November 2011 routine review indicated that tenofovir gel was safe but not effective among the women in the study. VOICE continues to evaluate Truvada. Final results are due in early 2013.
- **FACTS 001** – A Phase III study testing the same regimen as in CAPRISA 004, in which women use tenofovir gel before and after sex. FACTS 001 was launched October 2011 and seeks to enroll a minimum of 2,200 women at nine sites in South Africa. Being conducted by the Follow-on Africa Consortium for Tenofovir Studies. Results are expected in 2014.
- **CAPRISA 008** – A proposed three-year follow-up study of former participants from CAPRISA 004 that will test the feasibility and effectiveness of providing tenofovir gel in family planning clinics.

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Vaginal Rings

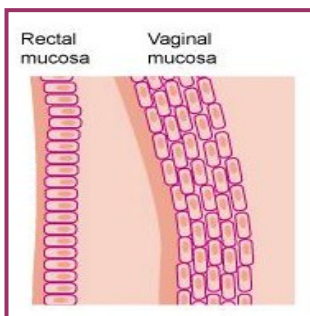
- **ASPIRE (MTN-020)** – A Study to Prevent Infection with a Ring for Extended Use (ASPIRE) - is a Phase III effectiveness trial of a vaginal ring containing dapivirine. It is the first Phase III trial of a vaginal ring for preventing HIV. The study, being led by the MTN, is expected to be launched at several sites in Africa beginning mid-2012. About 3,476 women will be enrolled, who will be randomly assigned to insert either the dapivirine ring or a placebo ring every four weeks for at least one year. The dapivirine ring was developed by the International Partnership for Microbicides (IPM).
- **The Ring Study (IPM 027)** – As part of its strategy to license the dapivirine ring, IPM plans to conduct The Ring Study in parallel with ASPIRE, the study will collect long-term safety and efficacy data among approximately 1,650 women at multiple research centers in Africa. IPM expects to begin enrolling women into The Ring Study in the first quarter of 2012.
- **MTN-013/IPM 026** – A Phase I safety and drug absorption study testing 28-day use of a vaginal ring containing either dapivirine, maraviroc or the two ARVs combined. The study is the first clinical trial of a vaginal ring containing maraviroc, and the first to test a vaginal ring with two active drugs. The MTN study is being conducted at three U.S. sites in collaboration with IPM.

Earlier Clinical Trials of First-Generation Products

- **MDP 301** – A Phase III trial of PRO 2000 that involved 9,395 African women. The study found no evidence that PRO 2000 reduced the risk of HIV. Conducted by the Microbicides Development Programme, and reported in December 2009.
- **HPTN 035** – A Phase IIb trial of PRO 2000 and BufferGel that involved more than 3,000 women in Africa and the United States. Reported in February 2009, the results found PRO 2000 was 30 percent effective compared to a placebo, although this was not statistically significant. BufferGel was found to have no protective effect. Conducted by the MTN.
- **Carraguard** – A Phase III trial of Carraguard, a microbicide developed from carrageenan, a derivative of seaweed, that showed the product was safe and acceptable to women, but did not reduce their risk of acquiring HIV. Conducted by the Population Council.
- **Cellulose Sulfate** – In 2007, two Phase III trials of cellulose sulfate were closed early after a Data Safety and Monitoring Board (DSMB) review of the study conducted by CONRAD suggested an increased risk of HIV infection among women using the gel. As a precaution, the second study, conducted by FHI 360, was also closed, although its DSMB review found no evidence of increased risk.
- **Savvy (C-31G)** – Two Phase III trials of Savvy closed, the first in 2005 and the second in 2006, after interim reviews indicated little convincing evidence that Savvy protected against HIV. Both studies were conducted by FHI 360.

What about rectal microbicides?

Although the majority of microbicide research has focused on products to prevent HIV during vaginal sex, anal sex is common among men who have sex with men, and also practiced by women around the world. According to some estimates, the risk of becoming infected with HIV through anal sex is 20 times greater than vaginal sex because the rectal lining, the mucosa, is thinner and much more fragile than the lining of the vagina.



An important first step to the development of rectal microbicides has been evaluating the rectal safety of microbicides originally formulated as vaginal gels, in particular, tenofovir gel. The first study of vaginal tenofovir gel as a rectal microbicide, RMP-02/MTN-006, found that it was generally safe, but caused gastrointestinal side effects in some participants. Based on these findings, the gel was modified with a reduced amount of glycerin to make it more amenable for

rectal use. The reformulated gel was evaluated in a recent Phase I safety study called MTN-007, whose results are expected in early 2012. MTN-017 is a larger follow-up study to MTN-007 that plans to further explore adherence to and safety of the reformulated gel, as well as Truvada tablets.

Clinical Trials of Potential Rectal Microbicides

- **RMP-01** – A Phase I study of the rectal use of a gel containing UC781 that was found to be safe and well-tolerated in 36 men and women. Conducted by the University of California, Los Angeles (UCLA) in collaboration with the Division of AIDS-sponsored Integrated Preclinical/Clinical Program (IPCP) for HIV Topical Microbicides at National Institute of Allergy and Infectious Diseases.
- **RMP-02/MTN-006** – A Phase I study of tenofovir gel applied rectally and of oral tenofovir. Compared to placebo gel, tenofovir gel significantly inhibited HIV in rectal sampled from the 18 men and women who used it daily for one week. Due to side effects experienced by some participants, researchers subsequently reformulated the gel. Conducted by the MTN and UCLA/IPCP at two U.S. sites.
- **MTN-007** – A Phase I follow-up study to RMP-02/MTN-006 that focused on the safety and acceptability of tenofovir gel reformulated for rectal use, whose results are expected in early 2012. Conducted by the MTN at two U.S. sites.
- **MTN-017** – A Phase II safety and adherence study of a rectal formulation of tenofovir gel used daily and before and after sex, and oral Truvada. As currently planned, the study will include approximately 216 men who have sex with men and transgendered women who will follow each of the three study regimens for eight weeks, with a week-long break between study periods when no product will be used. The study, which is in development, will be conducted by the MTN at sites in South Africa, Peru, Thailand and the U.S.

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More information about microbicides and other HIV prevention approaches is available through AVAC: Global Advocacy for HIV Prevention <http://www.avac.org/>, the Global Campaign for Microbicides <http://www.global-campaign.org/> and International Rectal Microbicide Advocacy <http://www.rectalmicrobicides.org/>.

The Microbicide Trials Network (MTN) is an HIV/AIDS clinical trials network established in 2006 by the National Institute of Allergy and Infectious Diseases with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the U.S. National Institutes of Health. Based at Magee-Womens Research Institute and the University of Pittsburgh, the MTN brings together international investigators and community and industry partners who are devoted to reducing the sexual transmission of HIV through the development and evaluation of products applied topically to mucosal surfaces or administered orally. More information about the MTN is available at www.mtnstopshiv.org.

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