

FACT SHEET

About Microbicides

Fast Facts

- Microbicides are products applied inside the vagina or rectum that are intended to protect against HIV through sex. Although microbicides are not yet available for widespread use, researchers are making significant strides in the development and clinical evaluation of both vaginal and rectal microbicide products. Microbicides that incorporate antiretroviral (ARV) drugs are showing particular promise.
- HIV most often is spread through unprotected vaginal intercourse, with women twice as likely as men to become infected. Women represent about 50 percent of all people living with HIV worldwide and account for nearly 60 percent of those with HIV in sub-Saharan Africa. Efforts to promote abstinence, monogamy and the use of male condoms have not been enough to stop the epidemic nor are these approaches practical in many settings. A vaginal microbicide could potentially give women the means to protect themselves against HIV.
- Vaginal microbicides are being designed in many forms, including gels, films and rings, which release an active ingredient gradually over time. Two products are currently in Phase III trials. One is testing a vaginal gel containing the ARV tenofovir used before and after sex, while two trials are evaluating a vaginal ring containing dapivirine that women use for a month at a time.
- Work also is underway to develop rectal microbicides for use by both men and women who practice anal sex. According to some estimates, the risk of becoming infected with HIV through unprotected anal sex is as much as 20 times greater than with unprotected vaginal sex. Like a vaginal microbicide, a rectal microbicide would represent an HIV prevention strategy that doesn't have to be controlled by one's sexual partner. As a gel or lubricant, a rectal microbicide may also enhance sexual pleasure, helping to motivate consistent use.
- In the first Phase II trial of a rectal microbicide, researchers plan to evaluate the rectal safety, drug absorption and acceptability of a reduced glycerin formulation of tenofovir gel. The trial, expected to launch in 2013, will be important for determining whether further testing can be conducted on its effectiveness in preventing HIV through anal sex. Researchers are also looking to develop products specifically for use in the rectum.



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/or in how they're used. One approach may suit some people but not others. Individual needs and preferences can also change, which is why a range of products is needed. 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 for a product to be approved for general use. Thousands of potential compounds may be considered during drug discovery but only the most promising are subjected to rigorous laboratory and animal studies, and fewer still make it to trials with people.

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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 and for short periods, say, one to two weeks. If results of a Phase I study suggest the product is safe, investigation may progress to a Phase II trial to track its safety in more people over longer periods of time. Phase IIb and III trials are much larger studies that are designed to determine a product's effectiveness, as well as to gather more safety information. They can take years to conduct, and their results weigh heavily in a regulatory agency's decision whether to approve the product for widespread use.

Vaginal Microbicides

An Overview

The idea for a microbicide-like product was first proposed about 25 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, but clinical trials found it neither safe nor effective against HIV. Trials of other so-called first generation microbicides also yielded disappointing results. These included products that were meant to strengthen natural defenses in the vagina or create a barrier to protect target cells. Researchers now are evaluating microbicide products that incorporate 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 HIV risk in women who used it before and after vaginal sex in a study called CAPRISA 004 but not effective in another study known as VOICE, which was designed to evaluate its daily use (as well as daily use of either the oral ARV tablet tenofovir or Truvada®). Tenofovir gel continues to be evaluated in an ongoing Phase III trial, FACTS 001, testing the same regimen as CAPRISA 004 – before and after sex. Depending on the outcome of FACTS 001, CONRAD, as co-licensee of the product, may seek regulatory approval of tenofovir gel.

As an alternative to vaginal gels, researchers are evaluating other formulations, including paper-thin quick-dissolve vaginal films that after insertion would melt away and disperse active drug to protect cells in the vagina. Films are in the early phases of clinical testing. Vaginal rings, flexible products that fit comfortably inside the vagina and provide sustained delivery of drugs over a period of time, are being tested in both Phase II and Phase III trials. Vaginal ring products are already used in many countries to deliver hormonal contraception. For HIV prevention, the dapivirine ring is the first vaginal ring – and the first HIV-prevention product intended for monthly use – to enter efficacy testing. As sister studies, ASPIRE, which is being conducted by the Microbicide Trials Network (MTN), and The Ring Study, being led by the International Partnership for Microbicides (IPM), are designed to provide the strength of evidence to support potential licensure of the dapivirine vaginal ring for preventing HIV in women. IPM, which developed the dapivirine ring, is the regulatory sponsor and license holder of the product.

Vaginal rings containing both an ARV and a contraceptive are also being developed that would potentially provide women both HIV protection and contraception in a single product. Phase I trials could begin before the end of 2013.

Clinical Trials Snapshot

Tenofovir Gel

- **CAPRISA 004** – A Phase IIb safety and effectiveness trial of tenofovir gel used before and after vaginal sex among 889 women from South Africa that found tenofovir gel reduced HIV risk by 39 percent compared to a placebo, a finding that was considered a major milestone for the field. The results, reported in July 2010, also included a wide confidence interval that in statistical terms means the true level of effectiveness of the gel could be anywhere between 6 and 60 percent. (CAPRISA 004 also unexpectedly found tenofovir gel reduced the risk of HSV-2 by 51 percent, the first time any kind of biomedical prevention method showed an effect against HSV-2.)

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- **VOICE (MTN-003)** – Vaginal and Oral Interventions to Control the Epidemic – a Phase III study that tested the safety and effectiveness of two different HIV prevention approaches among 5,029 women in Uganda, South Africa and Zimbabwe: daily use of an ARV tablet (tenofovir or Truvada) or daily use of a vaginal gel (tenofovir gel). Results, reported in March 2013, found none of the products effective; analysis of blood samples indicated that most participants had not used them daily as recommended. Young, unmarried women were least likely to use their assigned product and the most likely to acquire HIV, indicating the urgent need for safe, effective and practical HIV prevention methods women, like those in VOICE, will actually use. Results of two qualitative behavioral studies, VOICE C and VOICE D, which are expected in the coming months, may help better understand the reasons why so many women did not use the products. VOICE was conducted by the MTN.
- **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 plans to enroll 2,900 women at nine South African sites. Results are expected in 2015.
- **CAPRISA 008** – A three-year, open-label follow-on study of former participants from CAPRISA 004 testing the feasibility and effectiveness of providing tenofovir gel in family planning clinics. Results are anticipated to be available before the end of 2014.

Vaginal Rings

- **ASPIRE (MTN-020)** – A Study to Prevent Infection with a Ring for Extended Use – a Phase III effectiveness study being conducted by the MTN that seeks to determine whether a vaginal ring containing dapivirine is a safe and effective method for protecting against the sexual transmission of HIV when used by women for a month at a time. The study, which was launched in August 2012, will enroll approximately 3,476 women at sites in Malawi, Uganda, South Africa and Zimbabwe. Women will use their assigned product for at least one year, some for as long as two years. Results are anticipated late 2014 or early 2015.
- **The Ring Study (IPM 027)** – As part of its strategy to license the dapivirine ring, IPM is conducting The Ring Study in parallel with ASPIRE. The Ring Study, which is a Phase III trial, began enrolling women in April 2012. Approximately 1,650 women from South Africa and Uganda will participate and be randomly assigned to use either the dapivirine ring or a placebo ring; for every two women using the dapivirine ring, one will be using a placebo ring. Women will use their assigned ring for two years. The study is expected to conclude and release results in 2015.
- **MTN-013/IPM 026** – A Phase I safety and drug absorption study that tested 28-day use of a vaginal ring containing either dapivirine, maraviroc or the two ARVs combined. It was 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 was conducted at three U.S. sites in collaboration with IPM. Results are anticipated in late 2013.
- **MTN-023/IPM 30 and MTN-024/IPM 31** – MTN-023/IPM 30 is a Phase I safety study of the dapivirine vaginal ring in adolescent girls, while MTN-024/IPM 31 is a Phase I safety study of the ring in post-menopausal women. Both studies will be conducted at trial sites in the U.S. and enroll approximately 90 participants each. The two studies are part of a package of studies, with ASPIRE and The Ring Study as the centerpiece, that will be important for determining the ring's possible regulatory approval..

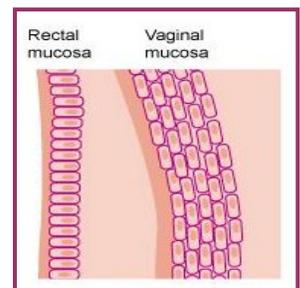
Rectal Microbicides

An Overview

Although the majority of microbicide research has focused on products to prevent HIV through vaginal sex, anal sex is common among men who have sex with men and practiced by women around the world. According to some estimates, the risk of infection 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

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gel. An early study found that the vaginal formulation of tenofovir gel caused gastrointestinal side effects when used in the rectum, so researchers tested a reformulated version of the gel with less glycerin in a follow-up study called MTN-007. That study found the reduced glycerin gel safe, acceptable and better tolerated than the vaginal gel when used in the rectum.

MTN researchers are now poised to launch MTN-017, the first Phase II trial of a rectal microbicide, to test whether the reduced glycerin formulation of tenofovir gel safe and acceptable among men who have sex with men (MSM) and transgender women in Peru, South Africa, Thailand and the United States, including Puerto Rico. In another trial called MTN-014, to be conducted among women in South Africa and the United States, researchers will examine drug absorption patterns in both rectal and vaginal tissue when the gel is applied either vaginally or rectally.

Research teams are also focusing on products developed specifically for use in the rectum. Two ongoing studies, part of the Combination HIV Antiretroviral Rectal Microbicide (CHARM) Program, are testing a microbicide gel based on the ARVs tenofovir and maraviroc to find out whether the combination product is safe and acceptable as a rectal microbicide. Another study, Project Gel, is assessing its rectal microbicide safety and acceptability in young men who have sex with men.

Clinical Trials Snapshot

- **RMP-01** – A Phase I study of the rectal use of a gel containing UC781 found the gel 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 compared to oral tenofovir that found the gel significantly inhibited HIV in rectal tissue taken from 18 men and women in the U.S. who used it daily for one week. To address side effects in a few participants, researchers subsequently reformulated the gel with less glycerin. Conducted by the MTN and UCLA/IPCP.
- **MTN-007** – A Phase I follow-up study to RMP-02/MTN-006 testing the rectal use of the reformulated reduced glycerin version of tenofovir gel found it safe and acceptable. Conducted by the MTN.
- **MTN-017** – A Phase II rectal safety and adherence study of reduced glycerin tenofovir gel used daily and before and after sex, and oral Truvada. The study will include approximately 186 men who have sex with men and transgender women who will follow each of the three study regimens for eight weeks, with a weeklong break between study periods when no product will be used. The study will be conducted by the MTN at sites in South Africa, Peru, Thailand and the U.S., including Puerto Rico. Conducted by the MTN.
- **CHARM-01 & CHARM-02** – Phase I studies comparing the safety, acceptability and distribution of three formulations of tenofovir gel – a vaginal formulation, a reduced glycerin formulation and a rectal-specific combination formulation including tenofovir and maraviroc. Conducted by the CHARM Program.
- **Project Gel** – Multi-stage trial focused rectal microbicide acceptability, safety and adherence in young men who have sex with men at sites in the U.S., including Puerto Rico.

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More information about microbicides and other HIV prevention approaches is available from AVAC:Global Advocacy for HIV Prevention <http://www.avac.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 whose work is focused on the development and rigorous evaluation of promising microbicides – products applied inside the vagina or rectum that are intended to prevent the sexual transmission of HIV – from the earliest phases of clinical study to large-scale trials that support potential licensure of these products for widespread use. More information about the MTN is available at www.mtnstopshiv.org.

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