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FACT SHEET

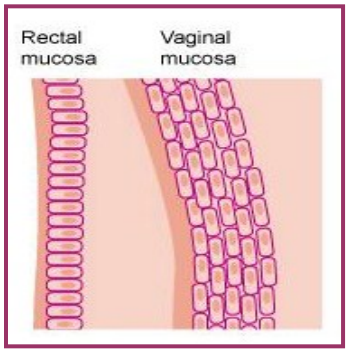
Rectal Microbicides

Fast Facts

- Rectal microbicides are products – that could take the form of gels or lubricants – being developed and tested to reduce a person's risk of HIV or other sexually transmitted infections from anal sex.
- The risk of becoming infected with HIV during unprotected anal sex is 10 to 20 times greater than unprotected vaginal sex. Because the rectal lining is only one-cell thick, the virus can more easily reach immune cells to infect.
- If proven effective, rectal microbicides could protect against HIV in people who are unable or reluctant to use condoms. Unlike condoms, they could provide an alternative way to reduce risk that is not controlled by one's sexual partner and possibly enhance sexual pleasure, helping to motivate consistent use.
- Rectal microbicides are not yet available outside of clinical trials. Researchers need to first be sure they are safe and then conduct additional studies to find out whether they are effective against HIV.

Overview

Microbicides are products designed to prevent or reduce the sexual transmission of HIV or other sexually transmitted infections when applied inside the vagina or rectum. Most vaginal microbicides are being tested as gels or rings, while rectal microbicides are primarily being tested as gels. Microbicides currently being tested contain antiretroviral (ARV) drugs, many of which are commonly used to treat people with HIV. Some of these drugs are also being explored as oral pre-exposure prophylaxis (PrEP) – a prevention approach in which HIV-negative people take an ARV tablet on a daily basis.



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 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. One such product 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. However, researchers from the Microbicide Trials Network (MTN) conducting a study known as VOICE (Vaginal and Oral Interventions to Control the Epidemic), which was designed to evaluate daily use of tenofovir gel (as well as daily use of an oral ARV tablet tenofovir or Truvada), found that tenofovir gel was not effective. An analysis of blood samples from a subset of participants found adherence to product use was low across all groups: drug was detected in 23 percent of blood sample from women in the tenofovir gel group. A third study, FACTS 001, is an ongoing Phase III trial testing the same regimen as CAPRISA 004 – before and after sex.

MTN researchers have been conducting studies of tenofovir gel as a rectal microbicide. Unlike CAPRISA 004, VOICE and FACTS 001, this research is focused on a different population of high-risk individuals who acquire

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HIV through anal sex rather than vaginal sex. Because tenofovir gel may work differently against HIV in rectal tissue, researchers want to learn whether it is safe to use rectally and can reduce the risk of HIV through anal sex. 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 reformulated gel to be safe and acceptable and better tolerated than the vaginal gel when used in the rectum.

Why Do We Need Rectal Microbicides?

Worldwide, 34 million people are currently living with HIV. Since the epidemic began in the early 1980s, more than 60 million people have been infected and nearly 30 million people have died of HIV-related causes. Although the rate of new infections is stabilizing in many countries around the world, HIV continues to disproportionately affect racial minorities and men who have sex with men. In the United States, men who have sex with men account for 60 percent of all new HIV infections and represent more than half of the people currently living with HIV. Globally, men who have sex with men are 19 times more likely to be infected with HIV than the general population. Unprotected anal sex is the primary driver of the HIV epidemic among this population.

According to estimates, 5 to 10 percent of the world's population engages in anal sex. While condoms are an extremely effective method to prevent HIV during anal sex, but many people can't or don't use them for a number of reasons – dynamics in sexual relationships, stigma about the practice of anal sex, or because they aren't readily available in some countries. Because it is not known whether microbicides formulated for the vagina will work the same way in the rectum, it is vitally important to test their safety and acceptability with anal sex. Research must also focus on the development of microbicides designed specifically for rectal use.

What Will it Take to Discover a Safe and Effective Rectal Microbicide?

Drug development can take as many as 20 years before a single agent is approved for use. Thousands of potential compounds may be considered, 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 authorities and according to strict ethical and scientific guidelines. Phase I trials evaluate safety in a small number of people who are exposed to study products for short periods, say, one to two weeks. If results suggest the product is safe, investigation progresses to a Phase II trial, in which researchers continue to track safety over longer periods of time. Phase IIb and III trials are performed to determine the effectiveness a product and conducted with large numbers of participants, often at multiple clinical centers. These trials usually compare a product with an inactive product (a placebo) or another active product. Data from Phase IIb and III trials are often used by regulatory agencies to determine whether a particular product should be approved for widespread use.

Rectal microbicides research is in the early phase of clinical development due in part to scientific challenges related to the biology of the rectum, and cultural reluctance to address anal sex. Three Phase I trials evaluating the rectal safety of microbicides have been completed to date.

Completed, Current, and Planned 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 compared to oral tenofovir. Compared to placebo gel, 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. 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 a reformulated version of tenofovir gel that was found safe and acceptable. Conducted by the MTN.
- **MTN-017** – A Phase II rectal safety and adherence study of reformulated version of 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 Peru, South Africa, Thailand and the U.S., including Puerto Rico.

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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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