

Topical Microbicides *Preventing Sexually* *Transmitted Diseases*



U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Institute of Allergy and Infectious Diseases

Topical Microbicides

Preventing Sexually Transmitted Diseases



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What are Topical Microbicides?

Few good strategies exist for preventing the spread of sexually transmitted diseases (STDs). Indeed, women currently have no way to protect themselves from STDs that does not require male cooperation. Topical microbicides could change this. If you have not heard of microbicides, you are not alone. And if you try to buy a microbicide at the pharmacy, you'll be disappointed because none is on the market. Nevertheless, microbicides could one day play a significant role in slowing the spread of STDs, including the virus that causes AIDS.

What is a topical microbicide? It is any cream, gel, or foam that can be applied to the vagina or rectum and that can kill or disable disease-causing organisms such as viruses or bacteria. They may sound simple, but microbicides have proved extremely difficult to design. There are unknowns along the entire pathway from laboratory to pharmacy. For example, while an STD-fighting topical microbicide is theoretically plausible, scientists have not yet gathered data through large clinical studies in humans to prove the concept valid. This lack of "proof of concept" is one reason pharmaceutical companies have remained reluctant to invest in research on microbicides. Another large challenge is designing statistically and ethically sound clinical trials to determine the efficacy of candidate microbicides.

There is a spur, however, driving researchers to surmount these hurdles. It is HIV/AIDS. The National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), plays a major role in federally funded research on STDs, including HIV/AIDS.

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Since the beginning of the AIDS epidemic some 20 years ago, NIAID has been at the forefront of the struggle against this disease. Insights into disease progression and new techniques to better understand HIV's actions are among the results of NIAID's sustained commitment to HIV/AIDS research. Complementing research into vaccines for STDs is research on alternative ways to prevent these diseases. Topical microbicides have the potential to be a key element in STD prevention in the coming decades, and NIAID has shaped a comprehensive plan that will help take these promising substances from concept to reality.

Why Women Need Microbicides

Although AIDS came to world attention as a disease associated with sexual practices of male homosexuals, today most new cases arise through heterosexual intercourse. In 2002, for the first time, women accounted for half of the year's 4.2 million new HIV infections worldwide in adults. In the countries of southern Africa, where women make up almost two-thirds of those infected, HIV/AIDS reduces women's ability to farm, leading to community-wide famine and increased mortality. In some hard-hit regions, HIV/AIDS threatens to wipe out entire generations.

Women are more susceptible than men to infection by HIV and other STD-causing microbes. Several factors account for this difference. Heterosexual intercourse can cause microscopic damage to the lining of a woman's vagina, and these tiny tears may admit infectious organisms. In addition, the female reproductive tract provides more surface area for viruses or bacteria to invade than the male reproductive tract. If a woman already has another STD, such as genital herpes, her risk of acquiring HIV through intercourse increases significantly.

The cost of HIV/AIDS, measured by any yardstick, is staggering. Although less apparent than HIV/AIDS, the silent epidemic of other STDs wreaks enormous financial and emotional damage as well. Excluding HIV/AIDS, STD infections in the United States cost more than \$17 billion annually in lost wages and health

expenses. An estimated 15 million cases of STDs other than HIV/AIDS occur each year in the United States, with teenagers accounting for about a quarter of new infections.

While there are effective treatments available for certain STDs (antibiotics can cure gonorrhea, for example), the majority of people infected with STDs do not know they are infected and so do not seek treatment. Furthermore, the viruses that cause AIDS and herpes, unlike bacterial infections, cannot be eliminated entirely once a person becomes infected. Although a vaccine against HIV is the subject of much promising research, it is likely to be some time before one is ready. For all these reasons, microbicides represent the best near-term hope for protecting not only women, but men and children as well, from STDs.

Even a partially effective microbicide, say experts, could avert more than 2 million HIV infections over a 3-year span. Besides protecting women from initial infection by disease-causing organisms, microbicides could play a critical role in reducing STD transmission from mother to infant during childbirth. Moreover, because female-to-male transmission of HIV is relatively inefficient, men would lessen their risk of infection if their HIV-positive female partners used a microbicide prior to intercourse.

The Ideal Microbicide

Ideally, a microbicide should be

- Colorless and odorless
- Inexpensive to manufacture and purchase
- Safe to use more than once a day and for long periods of time
- Effective against multiple STDs, including HIV/AIDS
- Fast-acting, long-lasting, and non-irritating
- Undetectable to either partner
- Available in contraceptive and non-contraceptive forms
- Available without a prescription

...colorless, odorless, inexpensive, safe, effective against multiple STDs, fast-acting, available without prescription.

In theory, creating an effective topical microbicide should be easy. Simply identify chemicals that kill disease-causing organisms, blend the chemicals with an inert gel or foam, and place it in the vagina. Experience, however, has shown that the simple approach may not work. The failure of the widely used contraceptive nonoxynol-9 (N-9) to prevent HIV transmission is a case in point. In both test-tube and animal experiments, N-9

appeared to prevent infection by HIV and other STD-causing microbes. Tests in women, however, revealed that instead of preventing infections, frequent use of the detergent-like N-9 caused damage to cervical cells and actually increased the risk of HIV infection. It became clear that formulating a safe, effective topical microbicide was anything but simple.

N-9's failure as a microbicide nevertheless unveiled important new clues about the details in the multi-step process of HIV infection. What investigators learn in the clinic is taken back to the lab and informs the next round of experimentation. For example, researchers are now testing potential microbicidal compounds that are gentler on cells. This process, in which each round of hypothesis and experiment brings improvement, is a hallmark of most medical research. It is especially important in a field such as microbicide development where so many basic questions remain unanswered.

The Research Pipeline

Like a new drug or vaccine, topical microbicide development will follow a pathway—the research pipeline—from basic research to commercial production. The key points along the pipeline are basic research, product formulation and preclinical testing, and clinical testing. Basic biomedical research sets the foundations for later-stage research. In basic research on topical microbicides, scientists are

- Determining exactly how HIV and other STD-causing organisms gain entry into cells and spread from cell to cell
- Characterizing the bacterial ecosystem that exists normally in the cervix and vagina and learning more about natural defenses against infection
- Finding better ways to quickly test large numbers of candidate microbicides for safety and efficacy against multiple STDs
- Creating gels or foams with optimal chemical and physical properties for carrying the microbicide

Once a promising candidate is identified, preclinical testing may begin. Typically, the pharmaceutical industry performs preclinical development of new drugs. But microbicides have attracted little commercial interest.

Therefore, government funding and partnerships between academic institutions, Federal labs, and small businesses are needed to take promising topical microbicides from the most basic

discovery stage to clinical testing. NIAID priorities in preclinical topical microbicide research include

- Improving techniques for rapidly screening large numbers of compounds for microbicidal activity
- Developing better small animal models for assessing safety of candidate microbicides
- Identifying compounds that act against more than one STD-causing microbe
- Developing non-human primate models of disease that more accurately mimic STDs in humans

If preclinical tests demonstrate the safety and efficacy of a trial product, human clinical testing can begin. Such testing is usually done in three phases. Small Phase I tests measure product safety, and larger Phase II trials provide additional safety data. Phase III trials involve thousands of people and confirm the safety and efficacy of a test product, monitor side-effects, and compare the new product to existing treatments, if any.

Designing meaningful clinical trials of topical microbicides is more difficult than the equivalent process for new drugs. The value of a new therapy, such as a test drug, can be measured directly by seeing if it cures sick people. Microbicides, by contrast, are a preventive technique. Researchers must measure the continued absence of disease and confirm that the trial intervention, such as a microbicide, is the responsible factor.

At each point along the pipeline, the number of viable candidates decreases while the cost to test the remaining products increases. By some estimates, it would cost almost \$57 million to move a candidate microbicide through preclinical development, clinical trials, and into commercial production. Most of the cost is associated with the final phase of human testing. While the estimated cost of developing a microbicide is dwarfed by the \$800 million it costs to develop a marketable drug, pharmaceutical companies have remained

microbicides be available by then. For now, however, programs such as NIAID's, which fund coordinated and comprehensive research, development, and testing strategies, will be critical to microbicide advancement. The remainder of this brochure highlights some ways NIAID-supported investigators and others are addressing the challenges of microbicide development.

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hesitant to invest in microbicides. An economic study by the non-profit organization Global Microbicide Initiative predicts a global market of at least \$1.8 billion by 2017 should one or more

Looking for a Few Good Candidates

One challenge at the basic research end of the pipeline is attracting a critical mass of scientists to a new field. Finding efficient ways to identify possible microbicides is another necessity. Until recently, microbicide discovery was a by-product of the search for anti-HIV drugs. Early in the search for microbicides, for example, attention focused on detergents because of their ability to disrupt HIV's coat. Most such easily testable candidates, however, failed as microbicides. Now that scientists know more about HIV's life cycle, they are beginning to identify multiple points at which the virus could be stopped. A more detailed picture of the initial moments of infection permits researchers to begin to design, rather than merely stumble upon, possible microbicides. In 2003, some 60 microbicide candidates were under study. These candidates can be grouped by their mechanism of action, including

- Enhancers of vaginal acidity or natural vaginal bacteria
- Detergents that break down the outer coats of bacteria or viruses
- Inhibitors that prevent various STD-causing microbes, including HIV, from entering cells
- Substances that hinder the spread of HIV from cell to cell

Sour Power

The human vagina is moderately acidic. This acidity makes it difficult for microbes to survive and thus provides some natural protection against infection. Indeed, the acidity of the vagina is

enough to kill human sperm. To survive, sperm travel in seminal fluid, which is acid-neutralizing and temporarily makes the vagina a less hostile place. The effect lasts about seven hours, long enough for sperm to fertilize any eggs and, unfortunately, long enough for disease-causing microbes to gain a foothold.

With all the bad publicity bacteria get, it is easy to forget that many bacteria are essential to good health.

One candidate microbicide, BufferGel, enhances the protective effect of the vagina's acidity. Developed by NIAID-supported researchers at The Johns Hopkins University and at the biotech company ReProtect in Baltimore, BufferGel is a mildly acidic lubricant. Significantly, BufferGel is based on a compound already widely used in such things as lipstick, hand lotion, and vaginal lubricants and, as such, has a proven safety record. In preclinical testing, BufferGel was found to inhibit both HIV and the genital herpes virus as well as the bacterium chlamydia, one of the most common STD organisms.

The Secret Garden

With all the bad publicity bacteria get, it is easy to forget that many bacteria are essential to good health. The vagina is teeming with bacteria, also referred to as microflora, and their absence can spell trouble. Lactobacilli, which produce lactic

acid, are some of the most common microflora and are critical to maintaining the vagina's acidity. Unfortunately, there are a variety of factors, including having sex frequently, which can result in a woman having depleted colonies of lactobacilli. This can lead to colonization by disease-causing bacteria. In formulating microbicides, scientists have to consider the impact of a microbicide on naturally occurring microflora. This is a challenge for several reasons, not the least of which is the ever-changing nature of the vaginal environment. Much is still unknown about how microflora change month to month and throughout a woman's life.

With support from NIAID, scientists at the Magee-Womens Research Institute in Pittsburgh are developing a vaginal suppository that will boost the amount of lactobacilli and, the researchers hope, crowd out bacteria that cause bacterial vaginosis and prevent chlamydial infection.

Other research teams are using genetic engineering to make "super" microflora that have increased power to fight invasion. For example, NIAID intramural researchers are engineering lactobacilli to act as a kind of viral flypaper. The engineered bacteria have, on their outer walls, the human cell surface molecule that HIV uses as a gateway into its target cells. Theoretically, entering HIV would attach to the lactobacilli instead of to its normal targets. Antibodies engineered into the bacteria would then inactivate the trapped HIV. Another group of researchers is

engineering the bacterium *Streptococcus gordonii* to produce a microbicidal protein that captures HIV.

Sorry, No Entry

Mucous membranes, such as those lining the nose, throat, and gastrointestinal and urogenital tracts, form a critical first barrier against invasion by microbes. Sexual transmission of HIV clearly involves a breach of natural mucous defenses, although the details are not fully understood. In particular, researchers want to know more about the interaction of HIV and the cells and molecules of the mucosal immune system and how those interactions change if other STDs are present.

PRO 2000/5 and Carraguard, two candidate microbicides set to enter advanced safety and efficacy testing, work by preventing disease-causing organisms, including HIV, from entering their target cells in the vagina or the cervix. Both are clear gels that do not require refrigeration and that retain effectiveness following lengthy storage. The active ingredient in Carraguard, derived from seaweed, is widely used as a thickening agent for foods. In laboratory tests, it blocked HIV and the virus that causes genital herpes. Carraguard is not a contraceptive and would be attractive to women who wish to protect themselves from STDs but still conceive. PRO 2000/5 has also shown effectiveness against multiple STD organisms. In contrast to Carraguard, PRO 2000/5 had contraceptive activity when tested in animals.

Containment Strategy

HIV, like all viruses, spreads by entering a cell, commandeering the cell's reproductive machinery, and creating multiple copies of itself. Eventually, newly manufactured viral particles leave the infected cell and begin the cycle anew. Cell-to-cell transmission of HIV is still an area of much mystery, but advances in understanding are helping scientists to develop microbicides designed to slow or halt HIV's ability to replicate and spread.

One such replication inhibitor began life as a possible anti-HIV drug. The scientists who originally synthesized the compound, UC781, found that it has high antiviral activity and that it acts specifically against HIV. Investigators rejected UC781 as a drug because it is not well

absorbed and therefore cannot be taken as a pill. What is a defect in a candidate drug, however, is an advantage in a microbicide. If UC781 is not absorbed, it cannot cause unwanted effects elsewhere in the body. NIAID-supported researchers at the University of Pittsburgh are now conducting a series of basic and preclinical studies on UC781 to see if it has microbicidal properties. For example, the scientists are testing UC781, alone and in combination with other agents, to learn whether it works against multiple strains of HIV. Two other viral replication inhibitors, PMPA and dapivirine, have shown promise and are entering Phase I trials.

Crossing the Preclinical Bridge

Preclinical research links basic research and clinical trials. In this translational research—from lab to clinic and from clinic back to lab—what scientists learn about safety and acceptability of the test product informs the next round of microbicide formulation. Capacity for conducting preclinical assessments is limited, so scientists must have good ways to prioritize candidates. This has been difficult in microbicide research for several reasons. A key problem is determining correlates of protection. In other words, scientists must determine precisely which laboratory test results provide an accurate and genuine predictor that the test product will work in humans.

As in the discovery step, preclinical research is becoming more sophisticated. Relatively simple toxicity screens, for example, are being replaced by laboratory screening methods and animal models that more closely mimic the molecular and physiological characteristics of HIV infection in humans. NIAID supports two laboratories that use these more advanced screening techniques to identify compounds most likely to both inhibit HIV (or the genital herpes virus) and be effective in the vaginal environment. Both laboratories were operating at full capacity in early 2003.

An array of small animal and non-human primate models is now in use in preclinical microbicide development. Currently, it is not clear which model or combination of models will yield the most relevant information. Among the NIAID-

supported efforts toward improving animal models for microbicide preclinical testing is a project at Pennsylvania State University's Hershey Medical Center. Scientists there are refining a model in which human vaginal tissue is grafted into mice. Investigators will use the system to test compounds for their ability to kill STD organisms without harming vaginal tissue.

Preclinical research links basic research and clinical trials...from lab to clinic and from clinic back to lab...

Another mouse model, developed by NIAID-supported researchers at The Johns Hopkins University, will help scientists understand the details of how HIV travels (whether as a free virus or inside human cells) during sexual transmission from men to women.

Non-human primate models are being refined to simulate more closely human STD infection. The approaches include

- Delivering non-human primate forms of HIV along with other STD organisms
- Delivering virus in multiple, low doses to mimic HIV transmission through intercourse
- Using virus strains most commonly found in recently infected people

Proving Ground: Assuring Quality Trials

NIAID supports clinical trials of topical microbicide candidates through its HIV Prevention Trials Network (HPTN), a worldwide clinical research collaboration that conducts Phase I, II, and III trials of non-vaccine prevention strategies at multiple domestic and international sites. In 2002, two microbicide trials were underway in the HPTN.

Cultural, language, educational, and social status differences between trial officials and the participants must all be considered in achieving fully informed consent.

A planned trial comparing the microbicides PRO 2000/5 and BufferGel illustrates a basic conundrum in clinical testing of microbicides. The NIAID-sponsored trial will enroll 2,900 HIV-negative women at sites in India, several African nations, and the United States. Some of the women will use PRO 2000/5 gel while another group will test BufferGel. (Two additional groups will use either a non-microbicidal gel or condoms alone.) As required by basic ethical standards, all participants will be counseled on safe sex practices and will be advised to use condoms in every sexual encounter. If all trial participants and their sexual partners do indeed use condoms as directed, however, it will be impossible to distinguish protection, if any, conferred by the microbicide from that conferred by the condom. Advanced trials must therefore include very large numbers of volunteers so that evidence of

microbicide effectiveness emerges from the background of condom use by some, but not all, in the testing group.

Clinical trials of this size are difficult to conduct under any circumstance, but the problem is compounded for microbicides because many trials will be conducted in developing countries where infrastructure may not exist or is untested. Among the most pressing needs in the area of infrastructure development are

- Scientific training at all levels
- Community education efforts
- Adequate groundwork

Adequate groundwork will ensure that any eventual trial is capable of enrolling and maintaining large numbers of volunteers over time while adhering at all times to the highest ethical and data collection standards.

NIAID and other parts of NIH have several programs designed to ensure that host countries fully participate in this critical research. One is the Comprehensive International Program for Research on AIDS (CIPRA), funded by NIAID, which targets support to HIV prevention and treatment research priorities identified by the applicant country. Although specific CIPRA projects may not address microbicide research directly, they will nevertheless enhance the overall clinical research abilities in the recipient country.

Ethical considerations are addressed through the HPTN's ethics working group. Comprising experts in the fields of ethics, social science, and community relations, the group ensures sound ethical review at each stage of trial activity. A key task of the ethics working group is to put in place community-appropriate informed consent procedures. Informed consent (the free and full agreement to participate by a volunteer) poses distinct challenges in the setting of HPTN's trials. Cultural, language, educational, and social status differences between trial officials and the participants must all be considered in achieving fully informed consent.

A Pivotal Moment

The challenges facing developers of microbicides may seem daunting, but many in the field believe this is a pivotal moment. Scientific advances are yielding a better understanding of STDs, and the connections bridging basic and clinical research give cause for optimism. NIAID's strategy for microbicide development, with its emphasis on support for the full spectrum of research from laboratory to clinic, takes advantage of the opportunities in microbicide research. There is every reason to hope that an inexpensive, broadly acting, and highly effective microbicide is within view.

More Information

National Institute of Allergy and Infectious Diseases

31 Center Drive, MSC 2520
Bethesda, Maryland 20892-2520
<http://www.niaid.nih.gov>

The NIAID home page has links to the *NIAID Topical Microbicide Strategic Plan* and other reports and updates on microbicides as well as links to the HIV Prevention Trials Network (<http://www.hptn.org>).

National Institutes of Health Office of AIDS Research

Two Center Drive
Bethesda, Maryland 20814
<http://www.nih.gov/od/oar>

The NIH Office of AIDS Research (OAR) developed a strategic plan for microbicide research, which is on the Web site.

National Library of Medicine

MEDLINEplus

8600 Rockville Pike
Bethesda, Maryland 20894
1-800-338-7657
<http://medlineplus.gov>

MEDLINEplus has extensive information from NIH and other trusted sources on more than 600 diseases and conditions.

Centers for Disease Control and Prevention

National Center for HIV, STD and AIDS Prevention
Division of HIV/AIDS Prevention
Mail Stop E-49
Atlanta, Georgia 30333
<http://www.cdc.gov/hiv/dhap.htm>

This Division provides information on HIV biology, statistics on HIV/AIDS prevalence, and details of various prevention projects.

Global Campaign for Microbicides

c/o Program for Appropriate Technology in Health
1800 K Street NW, Suite 800
Washington, D.C. 20006
202-822-0033
<http://www.global-campaign.org>

A report on the projected benefits of marketed microbicides, *Mobilization for Microbicides*, is on the Web site.

Population Council

One Dag Hammarskjold Plaza
New York, New York 10017
212-339-0500
<http://www.popcouncil.org>

The council's report, *The Case for Microbicides*, is on the Web site.

International Partnership for Microbicides

1010 Wayne Avenue, Suite 510
Silver Spring, Maryland 20910
301-608-2221
<http://www.ipm-microbicides.org>

Alliance for Microbicide Development

8484 Georgia Avenue, Suite 940
Silver Spring, MD 20910
301-587-3302
<http://www.microbicide.org>

The Alliance for Microbicide Development is a global, non-profit organization whose sole mission is to speed the development of safe, effective, and affordable microbicides to prevent sexually transmitted infections, most critically HIV/AIDS.

The Rockefeller Foundation

420 5th Avenue
New York, NY 10018
212-869-8500
<http://www.rockfound.org>

Information on The Rockefeller Foundation Microbicide Initiative is available on the Web site.

U.S. Agency for International Development (USAID)

Information Center
Ronald Reagan Building
Washington, DC 20523-1000
202-712-4810
<http://www.usaid.gov>

The USAID Report to Congress, *Microbicide and Vaccine Research Program*, is available on the Web site.

National Institute of Child Health and Human Development

31 Center Drive
Bethesda, MD 20892-2425
1-800-370-2943
<http://www.nichd.nih.gov>

The 2001 report, *Contraceptive Microbicide Research and Development Program: A Vision of the Future*, is available on the Web site.



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