

Each day, over 15,000 people become newly infected with HIV — 90% of them through sexual contact. While condoms remain the only widely available means of preventing the sexual transmission of HIV, many individuals do not have the power to avoid sex with partners who may be HIV-infected or to ensure condom use. Along with continued education and other harm reduction efforts, topical microbicides that can kill HIV and be applied by the vulnerable partner prior to sex have the potential to empower millions of people to protect themselves against HIV/AIDS.

Microbicides: A New Weapon Against HIV

A microbicide (mi-CRO-bi-cide) is a synthetic or natural substance in the form of a gel, cream, suppository, or film that can kill or neutralize viruses and bacteria. When applied directly in the vagina or rectum before sexual intercourse, a microbicide would neutralize HIV or microbes that cause other sexually transmitted diseases (STDs) and facilitate HIV infection. Unlike other barrier methods, a microbicide could be used without the cooperation or even the knowledge of one's sexual partner. A safe, effective, and affordable microbicide could save many millions of lives. Scientists agree that such a product is within reach, yet neither private industry nor government-funded researchers are devoting adequate resources to this promising approach to prevention. To help address this need, the American Foundation for AIDS Research (amfAR) has launched a new targeted grants initiative to speed the development of microbicides that could play a critical role in reducing HIV transmission rates worldwide.

The HIV/AIDS Catastrophe

The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that nearly 34 million people worldwide are now infected with HIV (human immunodeficiency virus) or living with AIDS (acquired immunodeficiency syndrome). Ten new infections occur every minute — over 15,000 each day. An estimated one out of every ten people is HIV-positive in the Central African Republic, Côte d'Ivoire, Djibouti, and Kenya. The rate is closer to one in four in Botswana, Namibia,

South Africa, Swaziland, and Zimbabwe. Here in the United States, there are close to one million people living with HIV/AIDS, and 40,000 new infections occur each year. Globally, AIDS has already killed over 16 million people.

In recent years, the number of women infected with HIV has increased dramatically. Worldwide, women accounted for 44% of all people living with HIV/AIDS in 1999, as compared to 25% in 1992. In sub-Saharan Africa, the epicenter of the global epidemic, fully 55% of adults living with HIV/AIDS are women. In the U.S., women accounted for only 7% of AIDS cases in 1985. Today, one-third of all new infections in the U.S. occur among women, and this number is growing.

The best current treatment for HIV/AIDS is highly active antiretroviral therapy (HAART), a complex regimen of potent anti-HIV drugs that has been available to some HIV-positive people in the developed world since the end of 1995. HAART can prolong life by reducing the amount of HIV in the body, thus delaying the onset of AIDS. But it is not a cure. And it is much too expensive to be used in the developing countries that account for over 90% of all AIDS cases.

There is an urgent need for more methods to prevent HIV infection, especially those that put women in control.

***— Peter Piot, M.D., Ph.D.,
UNAIDS Executive Director***

The Need for New Prevention Methods

Ultimately, vaccination to protect against HIV infection will be the surest means of stopping the spread of AIDS, and intensive vaccine research funded by amfAR and others has resulted in some promising advances. But even optimists predict that we will not see an effective AIDS vaccine for at least a decade, at which point a daunting worldwide vaccination program would have to begin. In the case of polio, we have had a vaccine for 45 years, but only now is the polio virus close to eradication. Clearly, even after an AIDS vaccine is found, other HIV prevention methods will remain needed for decades to come.

Preventing the sexual transmission of HIV is essential to slowing the AIDS epidemic. Worldwide, fully 90% of all instances of HIV transmission involve sexual intercourse — 85% through heterosexual contact and 5% among men who have sex with men. In the U.S., sexual contact accounts for 53% of all new infections. Current efforts to reduce sexual transmission rates focus on minimizing high-risk behavior. However, this approach does not adequately take into account the social contexts in which sexual intercourse occurs. In fact, an analysis of 27 published studies incorporating some 20,000 participants recently established that HIV counseling and testing alone was not an effective primary prevention strategy for uninfected people.

Currently, the male condom remains the only widely available barrier against sexual transmission of HIV. When used properly and systematically, condoms can achieve prevention rates close to 99%. But evidence suggests that even intensive education and distribution efforts fail to promote consistent condom use. Obstacles include a low sense of risk for HIV/STDs, the condom's impact on sensation, its contraceptive effect, religious teachings and

cultural attitudes, and concerns about raising suspicions of promiscuity or infidelity. Most important, condom use requires the active cooperation of the insertive male partner. Female condoms offer one alternative, but they are costly, awkward, and still not widely available. Also, like male condoms, they usually cannot be used without the male partner's knowledge and consent. Far too many individuals do not have the power either to avoid sex with partners who may be HIV-infected or to ensure the use of condoms.

Women: A Population at Risk

Women are at disproportionate risk of contracting HIV/AIDS. In fact, females are four times more likely to contract HIV from infected males than vice versa, and young women are especially vulnerable. In some regions, HIV-infected females already outnumber infected males by as much as 16 to one in the younger age groups.

This biological vulnerability is compounded by a host of factors that put women at special risk and undermine their ability to define sexual practices and boundaries. Poverty, inequality, lack of educational and economic opportunities, social and cultural biases, and practices such as female genital mutilation exacerbate women's inability to control their sexual interactions with men. Rape is shockingly prevalent in many parts of the world; married women often risk violence and abandonment if they are not sexually compliant; and large numbers of women with few resources or skills are forced to support themselves and their children by becoming commercial sex-workers. A 19-country study conducted by the International Center for Research on Women found that the lower women's social status, the higher their rate of HIV infection. Even women who are monogamous are at risk if their partners are promiscuous. In many regions, a significant percentage of HIV-positive women were infected by their husbands.

Of course, HIV infection among women also impacts others. Each day 1,800 infants are born with HIV in the developing world, and UNAIDS estimates that there will be 13 million children orphaned by AIDS by 2001. Just as oral contraceptives dramatically enhanced the ability of women to avoid unwanted pregnancy, effective female-controlled prevention strategies are urgently needed to enable women worldwide to avoid HIV infection and other STDs.

In the developing world, basically every woman is at risk of acquiring HIV.

***— Zeda Rosenberg, Sc.D.,
Scientific Director, HIV/AIDS
Prevention Trials Network,
Family Health International***

In all the studies we supported, poor women in low-income communities — without knowing the term “microbicide” or understanding the science behind it — asked individually for a prevention technology that they could use without their male partners’ knowing. They are suffering because the technology doesn’t currently exist.

***— Geeta Rao Gupta, M.D., President,
International Center for Research on Women***

The Promise of Microbicides

Effective microbicides would revolutionize HIV prevention:

- Microbicides could be used without the cooperation or even the awareness of one's sexual partner.
- In addition to neutralizing HIV, microbicides could protect against other STDs that cause genital sores or inflammation that facilitate HIV transmission. In one study in Tanzania, improved treatment of STDs led to a 42% reduction in the incidence of HIV.
- Microbicides may also help prevent the transmission of HIV from pregnant women to their fetuses. In one study, the rate of mother-to-infant HIV transmission was significantly reduced by low-risk sexual behavior during pregnancy.
- Ideally, microbicides should be available in spermicidal and non-spermicidal formulations. The first would enable women to prevent both HIV infection and pregnancy, while the second would allow pregnancy while protecting both mother and child from HIV.
- Microbicides could be used anally, as well as vaginally. Men who have sex with men have a strong interest in new prevention methods (particularly ones that could be controlled by the receptive partner). And as many as one-quarter of sexually active women in the U.S. engage in anal intercourse at least occasionally.

Microbicide Products in Development

For many years, researchers had high hopes that the popular contraceptive nonoxynol-9 (N-9) and related biodegradable substances might also be effective against HIV.

Unfortunately, recent tests show that N-9 has no impact on HIV transmission. In addition, these harsh products can cause ulcerations that may actually increase the risk of HIV infection. In spite of this setback, research to develop anti-HIV microbicides is proceeding on a range of fronts, as reported recently in *USA Today* (10/28/99). Some of the major approaches include:

Physical barriers: These microbicides could safeguard against infection by preventing the virus from gaining access to vulnerable tissue. One such product is liquid at room temperature but quickly turns into an impermeable gel inside the body. This thermo-reversible gel, as with other products, could serve as an "invisible condom."

Agents that inhibit microbes and viruses: Such microbicide candidates include C31G, a synthetic molecule that is also spermicidal; antibodies to HIV produced by genetically-engineered corn; *Lactobacillus crispatus*, a harmless

bacterium that maintains a hostile environment for HIV; and BufferGel, a new compound that maintains vaginal acidity even after exposure to semen. Some researchers are also experimenting with gels containing derivatives of existing anti-HIV drugs, such as zidovudine (AZT), as well as other antiviral and antibacterial drugs. Other scientists are investigating carageenan, a natural seaweed-derived gel that can be combined with active agents, and similar products, such as PRO2000, are undergoing clinical trials. Still others are working with sodium dodecyl sulfate (SDS), a common detergent found in many shampoos and toothpastes, and with a cream containing cellulose acetate phthalate, which is used to coat pills to help them last longer inside the digestive system. Research also continues on developing microbicides based on N-9 in combination with other substances.

Agents that prevent HIV from infecting cells: These products may block infection by interfering with HIV's surface protein and blocking attachment of the virus to its cellular receptors. They include the small protein cyanovirin (CV-N), a highly durable natural product. Some of the bioengineered antibody products may also act in this way.

Many experts believe that a successful microbicide will ultimately combine two or more of these approaches and require several active ingredients. There are currently 60 microbicidal products in development, many by nonprofit agencies, and 23 products have begun clinical testing. But the development pipeline is clogged. The best-studied compound, N-9, has not fared well in efficacy trials, and none of the major pharmaceutical companies is supporting microbicide research. Similarly, the government's investment in microbicides is minuscule; only 1% of the federal AIDS research budget goes toward microbicides. Why?

The ideal would be a microbicide that is safe and effective against HIV and other STDs; that allows women to become pregnant if they want to; is active as soon as it is applied and for a long time afterwards; is tasteless, odorless, and invisible; inexpensive and easy to store.

— Awa Marie Coll-Seck, M.D., Director, UNAIDS Department of Policy, Strategy and Research

First, there are a number of fundamental scientific questions that remain unresolved. Precisely how is HIV transmitted during sexual intercourse? Are free virus particles or virus-infected cells the major source of infectious HIV? A better understanding of sexual transmission will allow scientists to target microbicide research more effectively and develop better *in vitro* and animal models for microbicide testing.

The design and conduct of clinical trials in humans to test the safety and efficacy of microbicide candidates also present significant hurdles, such as choosing appropriate study populations, building local research capacity, and resolving ethical issues regarding the validity of informed consent given by underprivileged and poorly educated people at high risk of HIV infection.

Lastly, bringing a microbicide to market may require an investment of up to \$500 million. Yet pharmaceutical companies do not see a viable commercial market for microbicides in the developed world. What is more, the sponsor of an effective microbicide would be under strong pressure to distribute it cheaply in the developing world. And patents on many microbicide ingredients have expired, further narrowing profit margins. Companies are also concerned about regulatory uncertainties and the potential for unreasonable liability claims.

amfAR's New Targeted Microbicides Research Initiative

amfAR's new targeted grants initiative in microbicides research, launched in 1999, will award 100 one-year grants of between \$75,000 and \$90,000 over the next five years. In January 2000, after reviewing more than 60 proposals, the Foundation announced an initial \$875,000 in grants to ten U.S. and overseas researchers studying various approaches to microbicide development. These investigators are exploring a range of unresolved scientific issues, including:

- Which cells in the body's mucosal membranes — the thin, delicate tissues that line the vaginal and gastrointestinal (including oral and anal) tracts — are most susceptible to HIV infection?
- Is HIV transmitted as free-floating virus particles in blood and other body fluid or directly through cell-to-cell contact in either the mucosal linings of the vaginal or anal tracts, or both?
- What are the roles of mucosal antibody or cell-mediated immunity in blocking transmission of HIV, and what are the differences in mucosal immunity in intestinal vs. vaginal tissues?

- What are the physics of microbicides in the vagina? How would different product formulations distribute, and how long would they stay in place?
- Can natural products found in saliva that inhibit HIV work as microbicides?

Answers to these and other questions will be essential to accelerating the pace of microbicide research and product development. The American Foundation for AIDS Research is committed to a broad prevention agenda, including research to design a safe, effective AIDS vaccine, prevention education, and needle exchange programs to reduce HIV infections associated with injection drug use.

With the launch of its new targeted grants initiative in microbicides research, amfAR seeks to speed the development of a new prevention technology that can be broadly utilized by anyone at risk of acquiring HIV infection through sexual contact. Given the special vulnerability of women to HIV infection through vaginal intercourse and the increasing incidence of heterosexual HIV transmission, the need for microbicides is especially urgent. These biomedical prevention agents have the potential to save many millions of lives that will otherwise be lost to AIDS, and amfAR is determined to make the promise of safe, effective, and affordable microbicides a reality for men and women worldwide.

The issue of HIV prevention is not a gay issue or a women's issue — it's a human issue. We can make good, safe microbicides publicly available if we choose to. We have everything we need to make it happen — except the will and the money.

***— Sharon Hillier, Ph.D.,
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