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MICROBICIDES FOR HIV PREVENTION

This issue describes efforts to develop a safe, effective, and acceptable vaginal microbicide to prevent HIV.

Scientists around the world are working diligently to develop new ways to prevent HIV, including vaccines, pre-exposure prophylaxis (when drugs normally used to *treat* HIV are used for prevention), and topical microbicides. South Africa is at the forefront of prevention research, with studies under way from Durban to Cape Town. Advocacy and support for this research are strong, and the availability of an effective product—although likely years away—could help alleviate the HIV epidemic in South Africa and worldwide.

The Joint United Nations Programme on HIV/AIDS recently reported that the prevalence of HIV has stabilized or declined in

many countries in sub-Saharan Africa. Nevertheless, of all the countries in the world, South Africa remains the hardest hit by the epidemic. According to data from 2007, about 18 percent of South African adults (approximately 5.5 million people) are living with HIV. Women, who are disproportionately affected, make up 90 percent of the HIV-infected population of 15- to 24-year-olds.

Women are at especially high risk of HIV infection because of biologic susceptibility, economic dependence on men, and inability to negotiate condom use with all their partners. A method of HIV prevention that a woman could control, such as a vaginal microbicide, could help overcome some of these inequities and save many lives.

An effective microbicide could be a powerful addition to current efforts to protect against HIV, including abstinence, mutual monogamy with uninfected partners, condom use, treatment of sexually transmitted infections, and male circumcision.

CLINICAL RESEARCH UPDATE

KEYPOINTS

- An effective vaginal microbicide has not yet been identified.
- Three products are being studied in large-scale effectiveness trials.
- The newest candidates are designed to stop HIV from replicating.

The research pipeline is filled with hopeful microbicide candidates.

Research to develop an effective vaginal microbicide began nearly three decades ago. Today, more than 60 different products are in some stage of laboratory or clinical development. Eleven of these products are in human clinical trials, and three are in large-scale effectiveness trials. However, no candidate microbicide has yet been shown to prevent HIV or other sexually transmitted infections (STIs) in humans.

“The process of product development is long, but the HIV-prevention community is hopeful that an effective topical agent will be identified within the next decade,” says Dr. Willard Cates, president of research at FHI.

Types of products

The “first generation” of microbicide candidates are typically formulated as gels, which are applied to the vagina before each act of sexual intercourse. These candidates employ one of three mechanisms that should theoretically prevent HIV and other STI pathogens from infecting cells. Some are surfactants (agents that reduce the surface tension of a liquid) that inactivate a bacterium or virus by damaging its surface membrane. Others enhance the vagina’s natural defenses against pathogens, for example by maintaining the natural acidity of the vagina in the presence of semen, which is alkaline. Still others block viruses from attaching to healthy cells.

The next generation of microbicide candidates is based on antiretroviral drugs. These products specifically target HIV, acting later in the viral life cycle to prevent HIV from replicating once it has entered the body. Although some are formulated as gels, others may be released through vaginal rings. And, unlike the first-generation candidates, some of the newer products may be delivered on a daily or monthly basis (such as through a vaginal ring) regardless of the timing of intercourse.

Eventually, a combination of different products with more than one mechanism of action may be the most effective way to prevent a wide range of STIs. Products with a contraceptive ability will also be important for meeting diverse reproductive health needs.

Research process

After a microbicide candidate is identified, its safety and effectiveness is first assessed in test tubes and animal models. If the product passes this stage of testing, it enters human clinical trials.

In Phase I microbicide trials, scientists assess the safety of the product, determine its acceptability among potential users, and identify its appropriate dose and formulation. In Phase II trials, scientists again assess safety and acceptability, but among more participants and for a longer period.

The final stages of microbicide trials (Phase IIb and Phase III trials) are used to evaluate a product’s effectiveness in preventing HIV and other STIs. Phase IIb trials are typically smaller than Phase III trials, giving some indication of effectiveness and helping scientists decide whether a larger Phase III trial is necessary. Lasting up to four years, Phase III trials enroll thousands of participants who are at risk of HIV, such as those living in communities with a relatively high incidence of HIV.

Although all participants in microbicide trials are regularly counseled on how to reduce their risks of acquiring HIV and other STIs, prior experience has shown that even with optimal counseling and free access to condoms, most women are not able to negotiate condom use every time they have sex. The effectiveness of a candidate microbicide is tested in those sex acts in which women are not able to use condoms.

Ruling out candidates

Three first-generation products—SAVVY, cellulose sulfate, and Carraguard—were ruled out as effective microbicides in advanced clinical trials.

In 2005, FHI closed its Phase III trial of SAVVY (a surfactant) in Ghana when an independent data monitoring committee determined that



A counselor explains condom use to a woman participating in a microbicide trial.

the incidence of HIV was so low that the study would not be able to determine whether SAVVY could prevent HIV. FHI closed its parallel Phase III trial of SAVVY in Nigeria in 2006, after a similar committee concluded that the trial was unlikely to find a protective effect if it continued. Earlier studies had shown that spermicides containing another surfactant, nonoxynol-9, may actually increase the risk of HIV infection when women at high risk of infection use them frequently.

In 2007, CONRAD closed its Phase III trial of cellulose sulfate (an inhibitor of viral attachment and entry) in South Africa, Benin, Uganda, and India after a planned interim analysis suggested that the product might contribute to an increased risk of HIV. Because of these safety concerns, FHI simultaneously closed its Phase III trial of cellulose sulfate in Nigeria. However, the final data from both trials showed that cellulose sulfate had not significantly affected the risk of HIV infection either positively or negatively.

Most recently, the Population Council completed a Phase III trial of Carraguard (another inhibitor of viral attachment and entry) in

South Africa. Results, released in 2008, showed that the Carraguard gel was safe and acceptable. However, it did not reduce the risk of acquiring HIV. Although these results were disappointing, the Carraguard trial was the first effectiveness trial to be completed as planned for a product that was developed specifically as a microbicide—an historic accomplishment in the eyes of many microbicide advocates.

More effectiveness trials

Three microbicide candidates—BufferGel, PRO 2000, and tenofovir—are currently in large-scale effectiveness trials. Three additional products—ACIDFORM, the invisible condom, and dapivirine—will enter the advanced stages of clinical trials soon (see table).

“As with all other HIV-prevention approaches, no vaginal product is expected to offer 100 percent protection against HIV or other STIs,” says Dr. Cates. “At best, an effective product would prevent infection perhaps half the time. But even a partially effective microbicide could help women who might otherwise not be able to protect themselves at all.”

MICROBICIDE EFFECTIVENESS TRIALS

Mechanism of action	Microbicide	Trial status
Enhances vaginal defenses against pathogens	BufferGel*	The Microbicide Trials Network is conducting a Phase II/IIb trial of BufferGel vs. 0.5% PRO 2000 gel vs. a placebo vs. no intervention (condoms only) in Malawi, South Africa, Zambia, Zimbabwe, and the United States. Results of the trial, begun under the HIV Prevention Trials Network, are expected in 2009.
	ACIDFORM*	CONRAD and partners are planning a Phase III trial of a diaphragm with ACIDFORM gel in Madagascar (for the prevention of STIs other than HIV).
Inhibits viral attachment and entry	PRO 2000*	The Microbicides Development Programme is conducting a Phase III trial of 0.5% PRO 2000 gel vs. a placebo in Zambia, Tanzania, and South Africa. Results are expected in 2009. See “BufferGel” above for information on a second trial involving PRO 2000.
	Invisible condom*	Scientists at Laval University and partners are planning a Phase III trial of the invisible condom (a gel containing sodium lauryl sulfate, a common ingredient in soap). Sites are to be determined.
Inhibits viral replication	Tenofovir	The Centre for the AIDS Programme of Research in South Africa (CAPRISA) and partners are conducting a Phase IIb trial of 1 percent tenofovir gel vs. a placebo in South Africa. Results are expected in 2010. The Microbicide Trials Network is planning a Phase IIb study of tenofovir gel vs. oral tenofovir vs. oral Truvada (a combination of tenofovir and a second antiretroviral drug, emtricitabine) vs. a placebo gel vs. an oral placebo in South Africa, Malawi, Uganda, Zambia, and Zimbabwe.
	Dapivirine	The International Partnership for Microbicides is planning a Phase III trial of dapivirine gel. Sites are to be determined.

* Also being evaluated for contraceptive ability.

EVALUATING TENOFVIR GEL IN SOUTH AFRICA

Community members play important role in trial.

The Centre for the AIDS Programme of Research in South Africa (CAPRISA) and its partners are testing the effectiveness of tenofovir gel—a promising antiretroviral-based microbicide—in two South African communities. The intense collaboration between CAPRISA and the community of Vulindlela demonstrates just how vital community involvement can be in the preparation and conduct of a microbicide trial.

“Vulindlela is one of many communities we have worked in,” says Dr. Quarraisha Abdool Karim, CAPRISA’s associate scientific director and one of the principal investigators of the tenofovir gel trial. “But our experience in Vulindlela has been unique.”



The semi-rural district of Vulindlela, shown here, is one of two communities participating in the trial.

A semi-rural district outside of Durban, Vulindlela is home to almost half a million people. For years, the residents of Vulindlela had experienced the effects of AIDS on their community, watching as family graveyards filled up at an astonishing pace. Finally, the traditional village chief, or *Inkosi*, was compelled to take an unusual step: He contacted a group of local scientists.

Dr. Abdool Karim was one of the scientists who met with the traditional leaders of Vulindlela one Saturday morning in 2001. After welcoming the visitors, the *Inkosi* apologized that he could not spend the entire day with the group, as planned. “He had several funerals to attend,” recalls Dr. Abdool Karim.

In response to the concerns of the traditional leaders, CAPRISA conducted extensive research on the nature of the HIV epidemic in the community. For two years, scientists hosted focus group discussions with local stakeholders, studied the HIV cases from local clinics, and conducted “verbal” autopsies to establish the main causes of death in the community. Armed with these data,

THE TRIAL . . .

- Phase IIb study evaluating the safety and effectiveness of tenofovir gel in preventing HIV infection
- Enrolling 980 sexually active, HIV-uninfected women, ages 18 to 40, who are at high risk of acquiring HIV
- Being conducted at clinical research sites in Vulindlela and Durban
- Study participants randomized to use either 1 percent tenofovir gel or a placebo gel
- Participants counseled to apply the gel via single-use, prefilled applicators before and after intercourse
- Participants given free condoms and counseled on reducing the risks of infection
- Participants and their partners provided with free screening and treatment for sexually transmitted infections
- Results expected in 2010

. . . AND WHY IT IS UNIQUE

- First effectiveness trial of an antiretroviral-based microbicide
- First microbicide trial that an institution in the developing world is leading
- First microbicide trial that a South African government agency is co-funding
- First time that South Africa has secured an up-front voluntary license to manufacture and distribute a microbicide if it is proven effective



they were able to secure funding to establish an AIDS treatment program. Today, the program cares for more than 5,000 patients, including 1,300 who are receiving antiretroviral treatment. As part of a community fellowship program, CAPRISA also trained 32 community members as HIV/AIDS educators.

Despite these accomplishments, the prevalence of HIV remained high in Vulindlela. At last measure, about 55 percent of women ages 20 to 24 were infected. This alarming statistic highlighted the importance of finding an effective HIV-prevention method that women could control. Ultimately, CAPRISA selected Vulindlela as one of the study sites for its tenofovir gel trial, which began in May 2007.

Together, the researchers and local traditional leaders established the Vulindlela Community Research Support Group to function as a liaison between the

community, study participants, and research team. The group is a mixture of community leaders, representatives from religious and women's organizations, young people, government health care providers, and other stakeholders who review study materials and provide advice on recruitment and retention. They also function as a conduit through which community members can voice any concerns about the trial or other research that CAPRISA is conducting.

So far, more than 3,000 women in Vulindlela have received general information about the tenofovir gel trial. Among these women, 800 volunteers have been screened, and 454 have been enrolled in the study. As a testament to CAPRISA's dedication to building research capacity in the region, all of the study staff—including the recruitment teams, community educators, and project managers—are South African.

CAPRISA

CAPRISA is a nonprofit organization dedicated to researching new ways to prevent and treat HIV and tuberculosis, and to building local research infrastructure and capacity. CAPRISA is collaborating with CONRAD, FHI, and the South African Ministry of Science and Technology (through LIFE/ab) on its effectiveness trial of tenofovir gel. More information about the trial is available at: <http://www.caprisa.org/Projects/microbicides.html#5>.

ADHERENCE

A participant's adherence to the study regimen is absolutely vital for valid results in a trial. Yet, unstable living conditions and other stressors sometimes make it difficult for women to follow the directions for using the study products.

The CAPRISA team has implemented an innovative Adherence Support Program to help increase adherence rates. The program is based on the intention-motivation-behavioral skills model of HIV prevention, which reduces the risk of infection through behavioral change.

Before enrolling in the trial, potential participants learn about using the gel applicators, possible side effects of the gel, the time required to participate in the trial, and the benefits and risks of participating. Once enrolled, each woman receives tailored counseling provided by a nurse using an approach called "motivational interviewing." Counselors use various teaching techniques to emphasize that the gel has to be inserted

within 12 hours before sex and again up to 12 hours after sex, no matter how many times a woman has sex within that period. This core message is summarized as BAT-24: a dose **B**efore sex, a dose **A**fter sex, and not more than **T**wo applications within **24** hours.

When a woman reports problems with adherence, the nurse helps her develop a plan to address them. The counselor also writes "adherence support prescriptions" that spell out practical, customized suggestions for each individual's situation.



Explicit instructions on using the gel applicators, combined with tailored counseling during the trial, help participants adhere to the study regimen.

PARTICIPATING IN MICROBICIDE TRIALS

KEYPOINTS

- The informed consent process aims to give participants a complete, continuing understanding of a trial.
- Community representatives can help researchers design trials that are acceptable, relevant, and ethical.
- Ensuring continuity of care for women who become infected with HIV during a trial is challenging.



Community nurses, shown here with FHI's Stella Kirkendale, are working closely with microbicide trial participants in Malili, Malawi, to address any concerns the women have about the trial.

Researchers use multiple strategies to protect participants.

Since 1996, more than 20,000 women have participated in clinical trials to help identify a safe and effective vaginal microbicide.

All of the women volunteered for the trials, knowing they were going to help answer a question about the safety, acceptability, and in some cases effectiveness of a study product. They agreed to return to their study sites every three months, or even monthly, to receive counseling, supplies of gel and condoms, and an HIV test.

Study staff also made a commitment to the women. In their study protocols, counseling messages, and educational materials, the staff outlined how they would protect the safety, confidentiality, and human rights of each study participant. Their experiences have shown just how complex—and critical—that commitment can be.

Truly informing women

First, researchers have an ethical responsibility to ensure that participation in a clinical trial is voluntary and that the women who enroll in a trial understand exactly what their participation means.

The women must understand that the researchers do not know whether the study product works, that a portion of the participants may be randomly assigned to use a placebo that contains no microbicide, and that all participants need to continue using condoms and other HIV-prevention measures throughout the study.

Explaining technical terms and research concepts such as randomization and placebos to potential participants can be difficult. As a result, researchers have developed creative materials such as illustrated booklets, videos, and interactive computer-based educational programs to help explain them. Many trials

also use a questionnaire to assess a woman's understanding of a study before she signs an informed consent form agreeing to participate in the study.

However, researchers also recognize that informed consent should be a continuing process rather than a one-time event. In the two Phase III cellulose sulfate trials that have been conducted, for instance, the study staff administered this type of questionnaire both before and during the trials.

Involving communities

Researchers also have an increasing appreciation for the value of involving communities in decisions about how the trials are designed and implemented. Most trials have community liaison officers, and many have community advisory boards that serve as a link between researchers and the communities where the research is conducted. Some trials also train participants to educate their fellow participants and other community members about the study.

These community representatives help ensure that the trials are designed and implemented in an acceptable, relevant, and ethical way. The representatives review study protocols and informed consent forms, evaluate draft educational materials, relay community concerns to the study staff, refute rumors, and help disseminate study results. Such community involvement generates support for microbicide research and reduces the likelihood that a woman will be stigmatized because of her participation in a trial.

Ensuring access to care

One of the most complex issues facing microbicide researchers is how to provide access to treatment for the relatively small number of women who seroconvert (become infected with HIV) during a trial, as well as for the many more volunteers who are ineligible to participate because pretrial screening showed that they were already infected.

Funding for microbicide trials does not always include support for antiretroviral therapy (ART) or other services for people living with HIV. However, cost is not the only barrier to treatment. The complexity of ensuring

continuity of care over a person's lifetime is also a challenge for research organizations conducting short-term studies.

A 2006 study by the Global Campaign for Microbicides found that the standard of HIV care for participants who seroconvert during microbicide trials has varied. One trial set aside funds to support five years of ART for every woman who seroconverted during the trial. Others offered to enroll seroconverters into trials of ART regimens. Most referred the women to the closest source of HIV care, and many were able to establish written agreements with programs that provide free ART.¹ A study by FHI suggests that such referrals are acceptable to study participants.²

The Global Campaign for Microbicides recommends that microbicide trials be conducted at or in partnership with local HIV care centers, and that researchers use their trials as opportunities to strengthen local standards of care for people living with HIV.

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PROGRAM DISPATCH

PREPARING FOR MICROBICIDES

Introducing new products is complex.

As clinical trials continue, scientists and the broader microbicide community are also preparing for the complex process of introducing a vaginal product once it has been shown to be effective.

Foremost, scientists are evaluating whether women and men will actually use a microbicide if it becomes available. Qualitative research on a product's acceptability may help to inform the design and development of new products, estimate how well women will adhere to an eventual microbicide, and influence how microbicides might one day be marketed.

Most acceptability studies focus on product characteristics such as formulation, color, texture, and the type of application. Others have investigated the importance of contraceptive ability among potential consumers, the influence of sexual partners on product use, and other factors that could differ between individuals or communities.

Few studies have evaluated the role that health care providers would play in promoting microbicides.¹ Yet, if and when a vaginal

microbicide becomes available, health professionals would strongly influence whether women could access the product and how they would use it.

To help ensure the acceptability and use of microbicides outside of the research setting, the microbicide community is also:

- Considering the cost and affordability of products for potential consumers, reproductive health programs, and donors
- Identifying the most appropriate targets for initial introduction
- Developing counseling messages and deciding how microbicides would fit into a larger HIV-prevention strategy
- Determining appropriate service-delivery points and evaluating the capacity of service-delivery systems and health care providers to offer the products
- Collaborating with donors, regulatory bodies, and other stakeholders who could influence introduction, since most of the products would be manufactured and distributed in developing countries without the help of large pharmaceutical companies

Reference

- 1 Mantell JE, Myer L, Carballo-Diéguez A, et al. Microbicide acceptability research: current approaches and future directions. *Soc Sci Med* 2005;60(2):319–30.

Resources

Informed Consent in HIV Prevention Trials: Report of an International Workshop.
www.popcouncil.org/pdfs/ICWorkshop.pdf

Partnering for Care in HIV/AIDS Clinical Trials: A How-To Manual.
Order a copy of this soon-to-be-released publication by writing to publications@fhi.org.

WHO NEEDS TO BE READY

- Consumers
- Health professionals
- Reproductive health programs
- Service-delivery systems

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Managing Editor:
Kerry Wright Aradhya

Writers:
Kathleen Henry Shears, Jill Moffett
Art and Production Editor:
Karen Dickerson

Photos:
Cover: Karen Tweedy-Holmes/
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Page 2: Bev Symmonds/
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Elizabeth T. Robinson/FHI

Page 5: Elizabeth T. Robinson/FHI

Page 6: Michael Szpir/FHI

Page 8: CAPRISA

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USAID
FROM THE AMERICAN PEOPLE



FHI South Africa

Sonja Pilusa, Country Director
PO Box 12854
Queenswood, Pretoria 0121
South Africa
Tel: 27.12.342.0047

FHI Headquarters

PO Box 13950
Research Triangle Park, NC 27709
USA
Tel: 1.919.544.7040
www.fhi.org

Send comments to:
familyhealthresearch@fhi.org

INTERVIEW

MICROBICIDE RESEARCH IN SOUTH AFRICA

Dr. Salim Abdool Karim is pro vice-chancellor (research) at the University of KwaZulu-Natal, director of the Centre for the AIDS Programme of Research in South Africa (CAPRISA), and co-principal investigator for the CAPRISA 004 trial evaluating the safety and effectiveness of tenofovir gel (see page 4).

Q: Why is the search for a microbicide particularly important in South Africa?

A: What you see in South Africa, and in southern Africa, are epidemic curves that are unparalleled in the history of humankind. We've never had a disease that is able to grow at such a rapid rate and devastate so many people. If we want to make an impact, we need to understand the factors that have allowed the epidemic to flourish here. The first is the migrant labor system, which created family instability and kept men and women apart. The second is the status of women, who do not always have the power to implement prevention measures. And the third is poorly developed health care services that are not able to adequately implement public health measures.

Q: Why is so much microbicide research conducted in South Africa?

A: The South African epidemic is characterized by a high incidence of HIV in young women, so a microbicide could have a huge impact on the epidemic in South Africa. Further, South Africa has both suitable conditions for testing such an intervention, and the potential to benefit the most from an effective product.

Q: Several large-scale trials have been completed now, but we haven't identified an effective microbicide. Why do you think we should continue looking?

A: In scientific research, we almost never hit the jackpot on the first few attempts. The reality is that each attempt is a learning



Dr. Salim Abdool Karim

experience—when you fail, you learn from that failure to do better next time. We could not have discovered many of the great therapies, such as penicillin or the smallpox vaccine, were it not for the fact that we learned from failures along the way. Microbicides are no different.

Q: What have we learned from the trials so far?

A: We have learned an enormous amount. We've learned, for example, that one of the great challenges in these trials is to enable women to use the product in a way that ensures high levels of adherence. We have also learned the importance of the women using the gels even when they are not using condoms. And we've learned the importance of maintaining low pregnancy rates within the trials. Once a woman becomes pregnant during a trial, we stop the product use because we do not yet know if these products are safe for use during pregnancy. If the women aren't using the product, it is difficult to test whether it works.

Q: What can we expect from the results of the CAPRISA 004 study?

A: The CAPRISA 004 study will not lead, in all likelihood, to a product becoming readily available in the clinic. It is designed as a proof-of-concept study. If it shows that tenofovir gel prevents HIV infection, it would be the basis for a large Phase III trial, which would be necessary before the product could be licensed.