TOPICAL MICROBICIDES:
NEW HOPE FOR STI/HIV PREVENTION

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THE CENTER FOR HEALTH AND GENDER EQUITY (CHANGE) works to ensure that the health and population policies of international institutions supported by the United States government actively promote women’s reproductive and sexual health. We take our mandate from the Programme of Action of the 1994 International Conference on Population and Development (ICPD), and other relevant agreements that call on governments and international agencies to achieve these same objectives. Specifically, we seek to translate the language of these documents into practical, operational, and measurable changes in policy and program within and across the areas of family planning, sexually transmitted diseases, and gender violence, and to advocate for development policies that promote women’s rights and autonomy.
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Preface

This document is designed to provide answers to many of the questions that arise in the minds of individuals when they first encounter the notion of a “microbicide.”

When the concept was first introduced to me in 1990, it seemed almost too good to be true—a prevention option that women could use to protect themselves from sexually transmitted infections (STIs) without having to “negotiate” with their male partner. At the time, there was little consensus within the scientific community—or within the wider AIDS community—that such a method was either necessary or possible to develop.

This is changing, although there is still a remarkable degree of ambivalence in some quarters about the notion of a topical microbicide. This ambivalence derives from many sources, including the fear that adding a new prevention alternative to the current method mix might deflect attention away from the male condom and undermine the clarity of existing public health messages. Others are not fully convinced that we need a new alternative—they feel that most women and men could be helped to use condoms if only given proper support. Still others fear that by focusing on a technology, microbicide advocacy reinforces the tendency of medical science and public health to search for “silver bullet” cures rather than address the complex social and economic realities that condition people’s risk.

I am particularly sympathetic to the last concern. I think that there is a very real tendency in the health profession to prefer the “quick fix”—no matter how illusory—to longer-term social change strategies designed to address the underlying causes of people’s vulnerabilities. The roots of women’s vulnerability are complex: gender norms that give sexual license to men while constraining female sexuality; power inequities that leave women economically dependent on men; and social conventions that keep vital information about sexuality away from young people, especially girls. Our strategies must address these issues if our agenda is to have any integrity.

At the same time, women need and deserve access to a prevention method that is within their personal control. Women are the only group of people at risk who are expected to protect themselves without any tools to do so. We must commit ourselves to the type of fundamental social change that will reduce women’s risk of infection and disease. But this kind of change takes time—time that women at risk of HIV today do not have. The AIDS epidemic therefore creates two imperatives: to begin in earnest to address the underlying causes of women’s vulnerability, and to pursue vigorously every means possible to strengthen women’s immediate ability to protect themselves—including providing new woman-controlled technologies.

We invite you to add your energy and vision to this agenda.

Lori Heise
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**General Questions about Microbicides**

**What is a microbicide?**

A “microbicide” is any substance that can substantially reduce transmission of sexually transmitted infections (STIs) when applied either in the vagina or the rectum. A microbicide could be produced in many forms, including gels, creams, suppositories, films, sponges or vaginal rings. Some of these products may provide protection for several hours, or even days. As a woman-controlled prevention option, a microbicide would fill a critical gap in today’s STI/HIV prevention arsenal.

**Are such products currently available?**

No. Scientists are currently testing existing spermicides and other substances to see whether they help prevent the spread of HIV and/or other sexually transmitted infections. They are seriously pursuing more than 50 new product leads, including at least 20 compounds that have been tested in animals and are now being tested in people. With sufficient investment, a microbicide could be available to consumers within five years.

**How would a microbicide work?**

Scientists are presently exploring three different approaches to microbicide development. Among these are substances that:

1) kill or otherwise immobilize STI pathogens,

2) block infection by creating a barrier between the pathogen and the vagina or the rectum, or

3) prevent the virus from replicating once it has infected epithelial cells (the cells that line the vaginal wall).

**Would a microbicide eliminate the need for condoms?**

No. As with “combination” therapies, we must begin to think in terms of “combination prevention strategies.” Microbicides would be added to existing prevention options, namely male and female condoms. Condoms would remain the option of choice, because when used consistently and correctly, they will likely always provide better protection than a microbicide. But for people who cannot or will not use a condom, and particularly for women whose partners refuse to use condoms, microbicides will provide an important “fallback” that can save lives and have a substantial impact on the epidemic. Microbicides have the added advantage that they are within women’s control.

**Would a microbicide protect against all sexually transmitted infections?**

Since STIs are caused by different pathogens (some viral, some bacterial), a microbicide that works against one STI pathogen would not necessarily protect against another. But scientists are trying to develop products that would be effective against a wide range of pathogens, including HIV. This is important because in many parts of the world the health burden posed by “traditional STIs” still exceeds that posed by HIV (World Bank, 1993). STIs other than HIV can cause infertility, ectopic (tubal) pregnancy, cervical cancer, preg-
nancy complications, and infant death. Moreover, many STIs substantially increase a woman’s risk of contracting HIV.

**Would a microbicide also prevent pregnancy?**

Some of the microbicides being investigated prevent pregnancy and some do not. Women’s groups have argued persuasively that it is important to have a non-contraceptive microbicide in addition to one that prevents pregnancy, so that women and couples can protect themselves from infection, but still have children. A non-contraceptive microbicide is also important for individuals who may need to protect themselves but who object to contraceptive use on religious or cultural grounds.

**Would a microbicide be detectable to a woman’s partner?**

In theory, a microbicide could be developed that is undetectable to a woman’s partner—a significant advantage for women who would prefer to use a product secretly. Whether the first generation of microbicides proves to be detectable or not will largely depend on the product’s formulation. In early “acceptability” studies, many women have said that under most circumstances they would tell their partner about their microbicide use. Striving to develop an “undetectable” product is nonetheless important in order to meet the needs of those women who may need to keep their product use secret.

**Would men benefit from a microbicide as well?**

There is every reason to believe that men would also be protected from infection if a woman used a vaginal microbicide.

**Would a microbicide be effective for anal sex?**

Microbicides may work for rectal use, but the safety and effectiveness of microbicides for rectal use must be established separately. The anal environment is completely different from the vagina: it is not a closed cavity; it has an alkaline pH; its endogenous flora are different; its epithelial cells are more fragile than those of the vagina; and it has more cells with CD4 receptors—the receptors that facilitate HIV transmission.

It is important that any candidate microbicide be shown to be safe for rectal use—even if its effectiveness is unclear—because products available on the market will be used rectally, even if not approved for that purpose. Rectal safety studies of some potential microbicides are just beginning.

**Would such products be safe?**

Any new product must go through rigorous safety testing before it can be made available to consumers. Fortunately, many of the substances being investigated have been around for a long time, and some are even commonly used as food additives. Scientists are seeking to develop a product that would be so safe that it could be made available “over the counter” at drugstores and supermarkets and through community distribution networks.

**What are examples of some of the products under development?**

One of the attractive features of microbicide research is that many of the avenues being pursued build on the natural defense mechanisms of the body.

**Buffer Gel:** One product being pursued is a substance called “Buffer Gel” that works by maintaining the natural acidity of the vagina in the presence of semen. The healthy vagina is normally about pH 4.2, an environment too acidic for HIV to survive. Semen, however, is alkaline (basic) and during intercourse the pH of the vagina becomes basic, allowing HIV to survive. Buffer Gel keeps the vagina acidic even during intercourse and creates a physical barrier that inhibits the passage of pathogens into the vaginal and cervical epithelium.

**Carageenan:** A second substance being tested as a microbicide is carageenan, an inexpensive substance derived from seaweed that is widely used as a food additive (for example, to thicken ice cream). Carageenan forms a tasteless gel that coats the vagina, possibly preventing HIV from entering the vaginal epithelium.
Antibiotic peptides: A third approach marshals the natural bacteria-fighting properties of antibiotic peptides, the small protein molecules that form the body's first line of defense against infection. These peptides line every surface of the body—eyes, skin, lungs, tongue, and intestinal tract—and kill bacteria within minutes of contact. If applied in concentrated quantities at the site of potential infection, these peptides may kill off pathogens before they infect the body.

Detergents and surfactants: Detergents work by disrupting the outer membranes of cells and the envelopes (outer shell) of viruses. This is the mechanism of action of Nonoxynol-9, the active ingredient in most spermicides sold in the United States. Other detergents being explored as potential microbicides include octoxynol-9 (a compound used in some U.S. spermicides), sodium dodecyl sulfate (common in shampoos and toothpastes), and benzalkonium chloride (frequently used in contact lens solution to prevent the growth of bacteria).

“Plantibodies”: Another innovative approach to microbicide development uses genetically engineered plants to produce human antibodies active against HIV and other STIs. Antibodies are one of the body's main defense systems, and the basis for vaccine technology. Scientists have found ways to isolate the particular antibodies that counteract HIV and other STIs and to mass produce them using genetically engineered plants. This raises the possibility of delivering anti-HIV antibodies directly to the vagina, allowing them to combat pathogens before actual infection occurs.

Lactobacillus Crispatus (LB) suppository: The LB suppository works by recolonizing the vagina with hydrogen-peroxide producing Lactobacillus organisms. Lactobacillus crispatus is one of many naturally occurring bacteria that live in the healthy vagina (a sister species of lactobaccilli is found in yogurt). LB helps keep the vagina free from infection by producing hydrogen peroxide, a substance that is highly acidic. When the ecology of the vagina is somehow disrupted—through infection, douching, or poor hygiene—the LB bacteria can die off, leading to a condition known as bacterial vaginosis (BV). BV has been linked to increased risk of HIV infection. One research team is presently exploring the effectiveness of adding “good” LB microbes to the vagina via a suppository as a way to boost the vagina's natural defenses.

PMPA Gel: PMPA gel works in the same way as some of the anti-retroviral drugs currently used for therapy: it interrupts the replication of the virus once it enters cells. Scientists hope that PMPA could be absorbed by cells in the vaginal epithelium and then stop the virus in its tracks once it enters the outer cells of the vaginal wall. Many anti-retroviral drugs that were initially explored as potential AIDS therapies were later abandoned because they were not easily absorbed into the bloodstream; these same compounds might be perfect candidates for a vaginal microbicide because they could be topically applied and not absorbed systemically.

For more information and descriptions of other products, see the Alliance for Microbicide Development web site, http://members.aol.com/ggkidder/alliance.html.
Questions of Special Relevance to Policymakers

**How might microbicides fit into an overall program of STI/HIV prevention?**

Topical microbicides could play a variety of roles in an overall program of STI/HIV prevention. They could be used as an adjunct to condom use during vaginal or anal intercourse to provide added protection in case of condom failure. They could also be promoted as a “fallback” option for those encounters during which condom use is not possible. For individuals who are totally unwilling or unable to use the male or female condom, microbicides could be promoted as an alternative form of protection that, while not as effective as consistent condom use, is definitely better than nothing.

There are also some potentially novel uses for microbicides, depending on their ultimate mechanism of action. It is conceivable, for example, that scientists could develop a substance that would also provide some protection against STIs and HIV during oral sex. The epithelium in the mouth is part of the same mucosal system found in the vagina; thus, a substance that works in one place has a chance of working in the other. Such a product could be produced either as a mouth rinse or a sexual lubricant that would coat the mouth during oral sex.

Microbicides could also play a role in helping to prevent the transmission of HIV and other STIs during childbirth in settings where even a short-course regimen of AZT is not feasible or affordable. Scientists now believe that most perinatal HIV transmissions happen during birth as the baby passes through the birth canal. It is conceivable that vaginal washing with a topical microbicide prior to birth could help prevent perinatal transmission. Vaginal washing with the antiseptic chlorehexidine has already been shown to reduce maternal sepsis (blood poisoning in the mother) and to improve a variety of neonatal outcomes.

**Why bother developing a microbicide if we will have an HIV vaccine in several years?**

The recent success of combination anti-retroviral therapy underscores the importance of attacking HIV on a variety of fronts simultaneously. Like AIDS therapies, prevention strategies increasingly must rely on novel combinations of interventions rather than on one “silver bullet.” Prevention techniques have different advantages and disadvantages, and no one approach will be ideal for all people at risk. Microbicides would fill a unique gap in the HIV prevention arsenal even if and when a safe and effective vaccine is developed.

An ideal microbicide will be available over-the-counter, like condoms, in stores, kiosks, and pharmacies. This offers an advantage of accessibility over vaccines, which will have to be administered by trained health personnel—a rarity in many parts of the developing world. As the history of the Hepatitis B vaccine demonstrates, developing a vaccine is only half the battle. Getting it into the hands of those at risk, especially in resource-poor settings, remains a challenge. Because of the expense and logistics involved, even an effective vaccine would have to be part of a multipronged effort to control HIV.
Second, a microbicide would likely offer protection against a range of STIs, whereas an HIV vaccine would only be effective against HIV. The health burden from traditional STIs in many developing countries is greater than HIV, and in the industrial world STIs continue to have both short-term and long-term health effects.

Several scientific challenges mean that a vaccine may still be years away, and that the protection it conveys may be imperfect. For example, it is not certain that an HIV vaccine would be effective against all strains of the virus or all routes of transmission. Almost all candidate vaccines being pursued today are designed to combat the “B” clade of HIV, the variant of the virus prevalent in the industrial world. It is not yet clear whether a vaccine active against this strain would necessarily protect individuals infected with one of the other strains dominant elsewhere in the world.

Likewise, it is unclear whether a vaccine that works to prevent blood-borne infection (e.g., via sharing of needles) will be equally effective against virus transmitted sexually. Since the vagina is part of the body’s “mucosal immune system,” it might be necessary to have a vaccine that can mount a mucosal immune response in addition to a systemic immune response. It is conceivable that scientists would develop a vaccine that is partially protective against infections caused by blood transfusions or sharing needles, but ineffective at preventing sexual transmission.

Finally, despite our best efforts, it may not be possible to develop a vaccine that fully and permanently prevents infection. (Decades of research and millions of dollars have yet to yield an effective vaccine against any STI except hepatitis B). Far more likely will be a vaccine that permits infection but helps postpone or avoid the development of disease. Because of the complexities involved, scientists are now pursuing vaccines that would be only 40-60 percent effective rather than the near-100-percent effectiveness the public commonly associates with the word “vaccine.” Although scientists would clearly prefer a “one shot” vaccine, it is highly likely that individuals will need multiple shots throughout their lives in order to maintain immunity.

Until these scientific barriers are overcome, microbicides represent a more immediate prevention option. Scientists predict that a range of safe and effective microbicide products could be available within five years, since the number of candidate products currently ready for testing is greater. It is important to simultaneously pursue all promising methods of prevention.

Why should we believe that women would be better able to use microbicides than condoms?

There are a variety of reasons to believe that women would have an easier time using microbicides than the male condom. First, women do not use male condoms—their partners do. One of the enormous advantages of microbicides is that women do not have to “negotiate” their use. The fact that microbicides are within women’s personal control helps compensate for power imbalances between women and men.

Moreover, the fact that microbicidal use does not need to be discussed and that women do not have to admit (either to themselves or their partners) that they may be at risk reduces an enormous psychological barrier to protection. If women had something that was easy to use, that did not require negotiation—in fact did not even require talking about sex or the relationship—they might be more likely to act on any lingering doubts they may have about their risk. Right now, acknowledging that doubt requires women to openly discuss their concerns and to risk alienating their partners.

Microbicides also have an enormous advantage in that they allow skin-to-skin contact, increasing both pleasure and intimacy. Research indicates that as relationships deepen, couples become less willing to use condoms, partly because “physical” barriers interrupt closeness. Throughout the world, skin-to-skin contact is interpreted as a cultural icon of intimacy.

Finally, women in many parts of the world are
already acculturated to using a wide variety of vaginal products, from tampons and douches to herbs and other substances to treat infections or increase sexual pleasure. In fact, there are many cultures where women are far more accustomed to using vaginal substances than women are in the United States or Europe.

**Why is government support for microbicide development so important?**

Pharmaceutical companies—the entities arguably best positioned to bring a microbicide to market—have been reluctant to invest in this area due to concern over liability exposure (marketing a product that gives an implied protection against a fatal disease), an uncertain regulatory environment, and the perception that the potential microbicide market is not sufficiently lucrative. As a result, the public sector (government and foundations) will have to take the lead in this area, encouraging microbicide development via research grants directed toward product development and forming partnerships with small biotech companies to help evaluate their products. While there are many small companies interested in microbicide development, they generally do not have the money necessary to take compounds through expensive clinical trials.

**How much will it cost to develop a microbicide?**

Drug development is a costly endeavor. The pharmaceutical industry recently cited $350-500 million as an estimate of what it costs to bring a new product to market—although this number includes the basic research costs of discovering new product concepts, including leads that do not pan out. Biotech companies involved with microbicide development estimate that it costs roughly $20 million to take an identified compound through animal and human safety testing. Phase III efficacy trials cost an additional $17-30 million.

**How much money is the U.S. government currently investing?**

At the Vancouver AIDS Conference in 1996, U.S. Secretary of Health Donna Shalala announced to great fanfare that the U.S. government would invest $100 million in microbicide development over four years ($25 million a year). Rather than a dedication of new money, however, this commitment turned out to be a “repackaging” of research already under way—some only marginally related to microbicides.

In FY1998, the National Institutes of Health invested only $21 million in microbicide-related research, a mere 1 percent of its AIDS research budget. For every dollar that NIH invested in microbicide-related research, it invested more than $7 in HIV vaccines and $22 on developing new HIV-related therapies. Given the dramatic rise of HIV infection among women, more money and energy should be dedicated to developing microbicides as one of the only new female-controlled methods of protection on the horizon. NIH recently received a 15-percent increase in its appropriations from Congress, adding more than $2 billion in new money for medical research. Women’s health and HIV advocates are calling for the Public Health Service (PHS) to triple its investment in microbicide research to $75 million a year.

**Wouldn’t we be better off investing in more and better condom promotion programs?**

Much more can and should be done to increase the availability of condoms and to help individuals use them. But there are individuals for whom condoms will never be a viable option (e.g., women living in abusive relationships) and others who have proved resistant to using condoms despite being exposed to intensive condom promotion. Women and men in primary partnerships are one such group. For all the reasons cited above, individuals the world over have been resistant to

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1 In FY1998, the U.S. government invested more than $3.8 billion in HIV treatment and care via the Ryan White Care Act and various other governmental initiatives. The National Institutes of Health (NIH)—the main research apparatus of the federal government—invested $153 million in HIV vaccine-related research, $458 million in new therapies, and $21 million in microbicide-related research. NIH’s total HIV/AIDS research budget for FY98 was $1.6 billion.
### Table 1: Levels of consistent condom use achieved among heterosexual women, post-intervention

<table>
<thead>
<tr>
<th>STUDY</th>
<th>DESCRIPTION</th>
<th>SAMPLE</th>
<th>FOLLOW-UP</th>
<th>TYPE</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pauw et al., 1996 Nicaragua</td>
<td>Community-wide AIDS education and outreach campaign</td>
<td>2,160 residents at baseline; 2,271 at follow-up</td>
<td>12 months</td>
<td>Intervention Study</td>
<td>Sometimes condom use increased from 9 to 16% (p=0.003) among intervention women but only from 9% to 11% (p=0.5) in control women. Consistent condom use increased from 3% to 7% in the intervention community</td>
</tr>
<tr>
<td>Allen et al., 1992 Rwanda</td>
<td>Video, HIV testing, and counseling of women and partner</td>
<td>1,458 childbearing women</td>
<td>12 months</td>
<td>Prospective Cohort</td>
<td>Percentage of women using condoms increased from &lt; 7% who had ever tried condoms to 22% using condoms regularly at one year. HIV+ women were more likely to adopt condom use than HIV- women (36% vs. 16%; P&lt;0.5)</td>
</tr>
<tr>
<td>CDC AIDS Community Demonstration Projects, 1999 USA</td>
<td>Community-level intervention involving small media &amp; peer educators</td>
<td>High-risk individuals in five U.S. cities (CSWs, IVDUs, their sexual partners, etc)</td>
<td>3 Years</td>
<td>Prospective Community Trial</td>
<td>Consistent condom use with main partners increased from 8.5% at baseline to 17% at 3 years. The percentage using condoms with nonmain partners increased from 25% to 33%</td>
</tr>
<tr>
<td>DiClemente &amp; Winwood, 1995 California</td>
<td>Five sessions; social skills intervention; wait-list control</td>
<td>128 low SES women 18–29 years old</td>
<td>3 months</td>
<td>Randomized Control Trial</td>
<td>Percentage of women achieving consistent condom use went from 45.3% at baseline to 48.9% at follow-up in the social skills intervention group (adjusted O.R. 2.1; 95% CI, 1.03-4.15; P=.04)</td>
</tr>
<tr>
<td>Kamb et al., 1998 USA</td>
<td>Four sessions; client-centered HIV counselling</td>
<td>5,758 STD patients at five publicly funded STD clinics</td>
<td>6 &amp; 12 month</td>
<td>Randomized Control Trial</td>
<td>Percentage of times condoms were used 100% of the time increased from 17% at baseline to 39% at 6 months and 12 months</td>
</tr>
<tr>
<td>Moore et al., 1998 USA</td>
<td>HIV counselling and testing repeated every six months</td>
<td>871 HIV women and 439 HIV- women in four U.S. cities</td>
<td>12 months</td>
<td>Prospective Cohort</td>
<td>Consistent condom use achieved at 1 year among HIV+ women was 37% and 15% among HIV-. Consistent use among HIV- women with partners of unknown status was only 11%</td>
</tr>
<tr>
<td>Sikkema et al., 1998 USA</td>
<td>Risk reduction workshops and on-going community campaign</td>
<td>690 women in 18 low-income housing developments in five U.S. cities</td>
<td>12 months</td>
<td>Quasi Experimental 9x9</td>
<td>Percentage of women in intervention communities who did not have unprotected sex in the last two months increased from 50% to 73% (p=.03); percentage of intercourse occasions protected increased from 30.2% to 47.2% (p=.007)</td>
</tr>
</tbody>
</table>
introducing and sustaining condom use with their primary partners. Condoms are seen as something “of the street,” for “casual encounters,” or for use with prostitutes. Even sex workers who routinely use condoms with their clients refuse to do so with their lovers or husbands (see Gardner, 1999).

Unfortunately, the primary source of risk for many women is not their own behavior, but the sexual or drug-using behavior of their primary partner. For these women, protecting themselves means having to raise thorny issues of fidelity and trust by introducing condom use. As a result, doubts go unspoken and condoms go unused. Moreover, placing a physical barrier between yourself and someone you love is widely perceived as interrupting the intimacy associated with skin-to-skin contact.

These concerns partially account for the difficulty that prevention programs have had in increasing consistent condom use within primary partnerships. Globally, only about 4 percent of married women of reproductive age use condoms as their method of family planning and as many as 60 percent of all condoms are used outside of steady partnerships (Gardner, 1999). In the United States, a 1996 household survey revealed that only 18 percent of women aged 18-59 used a condom the last time they had intercourse with a steady partner (Anderson et al., 1999). Consistent condom use among these women is likely to be even lower.

Even with HIV counseling and community interventions, programs have had only limited success in raising consistent condom use within primary partnerships. Table 1 summarizes the results of some of the condom interventions used with heterosexual women that have been rigorously evaluated. Consistent condom use seldom exceeds 20-30 percent of women or intercourse occasions, even after a directed intervention. Where higher rates prevail, it is usually among women recruited from STD clinics, in which case some or all of the use may be among non-main partners.

What would the prevention message be if microbicides were available?

If microbicides were available, the public health message would shift from “Use a condom at every act of intercourse” to a hierarchical message that emphasized condom use but provided backup choices for those unable to follow the primary message. This is known as a “harm reduction” approach to public health. It recognizes that not everyone will be able to follow the “best” advice at all times, but that both individual and communal good can come from doing something, rather than nothing, to reduce HIV transmission.

A common example of this approach is the HIV prevention message given to individuals who use intravenous drugs. The number one message is “Don’t use drugs.” Recognizing that many people nonetheless will use drugs, harm reduction proponents advise users not to share needles. Recognizing further that this may be impossible for some, it gives backup advice about cleaning needles with bleach before reusing them.

Some jurisdictions—most notably New York State—have already moved to a hierarchical prevention message for sexual behavior that integrates male- and female-controlled methods. The New York Hierarchy recommends in descending preference: the male condom, the female condom, the diaphragm and jelly, and as a last resort spermicides containing Nonoxynol-9 (see the discussion below on research related to Nonoxynol-9).

Shouldn’t we be concerned about introducing a prevention method that is less effective than the male condom?

There is understandable concern that a shift from the simple message about condom use to a hierarchical message may undermine the clarity of HIV prevention efforts. The fear is that a hierarchical message might reduce confidence in the effectiveness of male condoms for HIV prevention, or that women would default to the microbicide and stop trying so hard to use condoms.
It is equally likely, however, that providing women with more options will actually increase the number of intercourse occasions that are protected. The literature from the contraceptive delivery field shows that adding a new contraceptive method to an existing method mix increases the overall percentage of individuals who are using modern contraception (Jain, 1989). It is quite possible that any substitution that occurs because of the availability of the new product is counterbalanced by the recruitment of new users who are taking protective action against STIs/HIV for the first time.

It is important to remember that the protection conferred by a method is a function of not only how good a method is at preventing transmission on a per intercourse basis, but also how consistently it is used. In fact, mathematical models demonstrate that efficacy and consistency of use are direct trade-offs (see box). A more efficacious method used inconsistently averts fewer infections over time than a less protective method used consistently.

Thus a 90-percent efficacious method used 20 percent of the time prevents fewer infections than:

- a 70-percent efficacious method used 30 percent of the time, or
- a 50-percent efficacious method used 40 percent of the time, or
- a 30-percent efficacious method used 60 percent of the time.


Questions of Special Relevance to Policymakers

The Prevention Equation

Level of protection conferred (the number of cases averted) depends on the product of three factors:

- efficacy of the method,
- consistency of use within a partnership, and
- extent of use in a sub-population (coverage).

A low-efficacy method used with high levels of consistency would offer the same protection as a high-efficacy method used less consistently.

Thus a 90-percent efficacious method used 20 percent of the time prevents fewer infections than:

- a 70-percent efficacious method used 30 percent of the time, or
- a 50-percent efficacious method used 40 percent of the time, or
- a 30-percent efficacious method used 60 percent of the time.
Questions Regarding the Clinical Testing of Topical Microbicides

How would you test whether a new microbicide reduces transmission of STIs/HIV?

Microbicides, like all new drugs, must go through rigorous testing before the U.S. Food and Drug Administration (FDA) will approve them for use. These tests include animal and human testing to determine both safety and effectiveness of any new device or compound.

Evaluation in human beings can only begin once the product sponsor proves to the FDA that the substance has been tested for probable safety and efficacy in a number of animal species.

Human testing proceeds via a series of staged “clinical trials” during which individuals are enrolled and followed extremely closely as they begin to use the experimental product.

The first set of trials is used to establish the safety of the substance for human use. The final large trial, known as a Phase III efficacy trial, is designed to establish whether or not the substance “works” for the purpose it is intended.

The clinical trial sequence is set up as follows:

Phase I:

In a Phase I trial, a small number of volunteers (usually 10-50) use the product for a short period of time just to see how their bodies react to it. In the case of microbicides, scientists will be looking to see whether the product causes irritation or negatively affects the vagina’s normal environment. Only women who are at no known risk of sexually transmitted infection are enrolled in Phase I.

Phase II:

If the Phase I trial shows that the product is safe among “low-risk” women, a slightly larger number of women (usually 50-200) at higher risk of STIs and HIV is enrolled and the product is tested again for safety. Safety must also be assessed in HIV+ women because many women will not know their HIV status when they use a microbicide.

Phase III:

In this trial, a large number of women (generally 500-5,000) are enrolled to establish whether the product works for the purpose intended—in this case, prevention of HIV and STIs. Phase III trials often go on for a year or more, and therefore also give more extended information on safety.

How would Phase III trials establish whether a microbicide reduces infection?

Phase III trials are essentially experiments during which researchers compare the clinical course of women who use an experimental product with those who do not. To make sure that any observed differences between the two groups are due to the experimental product and not other factors, scientists use a process called randomization that assigns women by chance to either an “experimental group” or a “control group.” Randomization ensures that any differences among women—other
than those that result from use of the product—are equally distributed between the two groups. In scientific language, this is called “eliminating bias.”

In microbicide trials, both the experimental and control groups would be given access to free condoms and actively encouraged to use them at every act of intercourse. Women in the experimental group would also be instructed to use the experimental microbicide in addition to condoms every time they had sex, or the experimental product alone if condom use was not possible. Women in the control group would receive the same instructions but would be given a placebo product, fashioned to look and feel like the experimental microbicide but without active ingredients. In a “blinded” controlled trial, neither the participants nor the scientists know which group is which until the end of the trial.

Scientists would follow the women over the course of the study, observing the number of STIs and HIV infections that developed in both groups. Using statistical techniques, researchers would then determine whether there were fewer infections among women who used the experimental product than among those who did not. If so, and if the result were greater than chance (i.e., statistically significant), the product could be said to reduce infection.

**Where would trials take place?**

Safety testing of new vaginal products (Phases I and II) can take place almost anywhere. The only requirement is that the investigator be able to enroll and follow women and/or couples who are healthy and at little or no risk of sexually transmitted diseases. Safety trials conducted in the United States will likely be repeated in developing countries to ensure that products under investigation are also safe for women to use in these settings. Women in developing countries may have different health and nutritional profiles and/or have different menstrual and sexual practices that could affect the safety of the product.

Phase III efficacy trials will likely involve multiple sites in both the industrial and developing world. By all accounts, the number of women required to mount a Phase III trial will be large—at least 4,000. The number of women that must be enrolled in a trial is a function of many factors, including the underlying rate of HIV transmission in the population and the effect size to be detected (i.e., it takes a bigger trial to detect a microbicide that is only 50-percent effective versus 70-percent effective.)

Chances are many of the sites that will become part of a multicenter trial on microbicides will be in the developing world. In order to distinguish the effectiveness of a product at preventing heterosexual transmission, women enrolled in the trial must be at risk of infection only from sexual intercourse, not from blood transfusions or IV drug use (otherwise researchers wouldn’t know if an infection in the experimental group occurred because the product failed or because the woman contracted the virus through receiving blood or sharing needles). For a trial to be feasible, the underlying rate of HIV infection in the population must exceed 2 percent a year. The number of trial participants required to detect a microbicide of 50-percent efficacy in a population with an underlying rate of infection of 3 percent a year is 4,847; this jumps to 14,736 participants when the infection rate is 1 percent a year.

Most of the sites that fit this profile are in the developing world. This means that effectiveness
trials of new microbicides would involve women from developing countries in addition to any women enrolled from the United States.

Isn’t that just another example of using Third World women as guinea pigs?

The potential exploitation of vulnerable women—whether from the South or the North—is an important and legitimate concern. To address issues raised by microbicide trials in developing countries, a group of scientists and advocates came together in 1997 and sponsored an international symposium at Airlie House in Warrenton, Virginia, on the Practical and Ethical Dilemmas of Microbicide Testing. This meeting brought together 55 scientists, advocates, and policymakers from 19 countries to debate key issues in the design and implementation of efficacy trials for topical microbicides.

Meeting participants were unanimous in the view that such testing should proceed, but only after consultation with the local community and due consideration of proper ethical precautions. Advocates from countries hard hit by the HIV epidemic expressed an urgency for alternative forms of STI/HIV protection, and concluded that an emphasis on developing country sites was justified in light of the limited number of U.S. and European sites in which a high enough seroincidence rate among non-IV drug-using women existed. The group nonetheless thought it was important that multicenter trials include at least one U.S. and/or European site so that women there would share in the burdens of research.

To limit opportunities for abuse, the group also recommended that trial sponsors consult with local community groups and potential trial participants prior to initiating trials. Community advisory boards can help identify and share community concerns and can help monitor the implementation of the trial. And as in all trials, proper informed consent procedures should be observed and monitored to ensure that women fully understand the trial and the risks and benefits involved.

Wouldn’t it be faster and easier to test a contraceptive microbicide than one that allows conception?

Some people have argued that researchers should focus exclusively on developing contraceptive microbicides because of the presumed costs and ethical difficulties of testing a microbicide that allows conception. They cite concern that a microbicidal product that is not contraceptive could potentially harm a developing fetus. In reality, researchers would need to conduct the same battery of reproductive toxicology tests for any microbicide, whether it is designed to be contraceptive or not. Because no spermicide is ever 100 percent effective, researchers need to establish the safety of the product for mother and fetus should the product fail. The Food and Drug Administration has established standard tests for this purpose.
What can women do today to help protect themselves from STIs and HIV?

As always, the best advice to women for HIV protection is to use a male or female condom every time they have sexual intercourse, whether it is vaginal, anal, or oral sex. There are workshops and skill-building materials that can help women learn creative ways to introduce and enforce condom use.

There are other things, however, that women can do to help limit their risk. One is to reduce their frequency of sexual intercourse. There are any number of normal, satisfying, non-penetrative sexual behaviors—collectively known as “outer-course”—that carry little risk of HIV transmission (although behaviors such as mutual masturbation can transmit some STI pathogens, such as those that cause herpes).

Another line of defense against any sexually transmitted pathogen is a healthy vagina. Women should avoid any and all practices that can disrupt the natural ecology of the vagina, including:

- douching;
- placing any foreign substance in the vagina, including herbs, astringents, or sex toys; and
- using sprays or other products described as vaginal deodorants.

Both douching and vaginal substance use has been linked to increased risk of pelvic inflammatory disease and HIV (Zhang, 1997). If a woman feels she must wash after intercourse, she should wipe the inside of her vagina gently, using warm water only.

Women can also help protect themselves by seeking prompt treatment for all reproductive tract infections. Scientists have now shown definitively that a person's risk of contracting (and transmitting) HIV goes up if the individual has any of a number of other common reproductive tract infections, including gonorrhea, chlamydia, chancroid, bacterial vaginosis, and trichonomiasis.

REMEMBER: These infections do not necessarily have symptoms, especially in women. Women should seek testing from their physician if they think they may have been exposed.

Is it true that spermicides containing Nonoxynol-9 can help prevent some STIs?

Nonoxynol-9 (or N-9) is the active ingredient in most over-the-counter birth control products available in the United States, including diaphragm jelly, Conception suppositories, Delfin foam, the contraceptive film, Encare Oval, and the Today contraceptive sponge. These products work by disrupting the sperm’s outer membrane and thereby deactivating it.

Only a few well-controlled studies have been done to examine the effectiveness of these birth control products against sexually transmitted infections. It is difficult to establish exactly how good these
products are for preventing STIs because each of the studies tests different products, and some test the products with a diaphragm and some without. The consensus is that products that contain Nonoxynol-9 provide some protection against gonorrhea and chlamydia, but there is still disagreement about exactly how much.

The most conservative estimates put the protective effect of Nonoxynol-9 against gonorrhea, chlamydia, and trichomoniasis at roughly 15-25 percent—that is, of 100 women who would normally get an STI, 15-25 women would be protected if they used a spermicide (Roddy, Schulz, and Cates, 1998). Other researchers, however, concluded based on a review of the same data that there is “an appreciable” and “clearly protective effect” of N-9 on gonorrhea and chlamydia on the order of 40-50 percent (Cook and Rosenberg, 1998).

Thus, using a product containing Nonoxynol-9, with or without a diaphragm or cervical cap, can help reduce risk of bacterial STIs, but the protection is far from perfect and undoubtedly less than that provided by condoms. Recall, however, that the key to condoms’ effectiveness in such circumstances is CORRECT and CONSISTENT USE. Inconsistent condom use is LESS EFFECTIVE than consistent spermicide use in preventing bacterial STIs (Feldblum et al., 1995; Wittkowski, 1989).

At present, prevention options include outer-course (non-penetrative sex) or use of a male or female condom. During intercourse when condom use is not possible, women should use a spermicide, preferably with a diaphragm and/or a cervical cap. (Since many STI pathogens preferentially attack the cervix, it may be beneficial to have an added physical barrier in addition to a spermicide.)

Can N-9 products reduce HIV transmission?

This area of science is even more controversial than the issue of protection against bacterial STIs. It is clear that products containing Nonoxynol-9 easily kill HIV in a test tube and have offered some protection against HIV-like viruses in non-key models. The data on Nonoxynol-9’s protective effect against HIV in humans are mixed. As with STIs, it is difficult to interpret available studies because N-9 products vary dramatically by type (gel, film, foam, sponge, etc.) and by amount of active ingredient (from 52 mg to more than 1,000 mg), and it is now thought that formulation is key to N-9’s protective ability.

The first attempt to study the role of spermicides in HIV prevention was a randomized clinical trial among sex workers in Nairobi, half of whom used the spermicide-impregnated Today sponge, and half of whom used either a nonspermicidal cream or an insert. All women were also provided with male condoms (Kreiss et al., 1992).

The study found no protective effect against HIV from use of the Today sponge and a 60-percent reduced risk of contracting gonorrhea. In fact, the study showed that the women using the sponge had high levels of genital ulcers (mostly on the vulva), which the authors speculated may have been caused by irritation from the Nonoxynol-9 and/or reactivation of underlying genital herpes or chancroid infections.

Since it was published, the Today sponge study has been criticized on several grounds, including the fact that no sponges were used by the control group, making it impossible to measure the abrasive/drying effect that the sponge itself may have had on the vagina; the product contained 1,000 mg of N-9, a dose 10 times higher than the average N-9 product; women were exposed to even larger doses of N-9 because they were advised to change the sponge after every two to three customers and were seeing, on average, four to five customers per day; and the two groups of women were not equal at the study’s outset—sponge users had significantly more ulcers upon entering the study.

Other studies have come up with different results on N-9. In an observational study of a group of sex workers in Cameroon (having an average of 3.2 partners per week), researchers found that those who used 100 mg N-9 suppositories regularly (in addition to or in place of condoms) had 70-80 percent fewer new HIV infections than the women
who did not use the suppositories regularly. After adjusting for other risk factors, including concurrent condom use, consistent spermicide users had 90 percent fewer new HIV infections than less consistent users, and no more genital ulcers (Zeking et al, 1993).

A third study conducted by the Ministry of Health in Cameroon and Family Health International examined whether a vaginal contraceptive film containing 70 mg of N-9 helped prevent the transmission of sexually transmitted diseases, including HIV, when used in conjunction with condoms. The study found that the spermicidal film is safe to use but does not confer any additional protection from HIV, gonorrhea, or chlamydia infection beyond that provided by condoms.

It is not yet clear whether these negative results are because Nonoxynol-9 does not work to prevent HIV, or because there was not enough N-9 in this particular product, or because the “film” is not a good enough delivery device (i.e., it does not distribute in the vagina well enough to block infection). None of the above studies is adequate to fully evaluate whether Nonoxynol-9 works to prevent HIV.

The last study, however, is reassuring with respect to safety. Although participants in the experimental group had slightly higher rates of vulvar ulcers than in the control group (as in the sponge study), this did not translate into an increased risk of HIV transmission. Several additional studies have demonstrated that the disruptive effect of Nonoxynol-9 on the vaginal epithelium is dose-related, with lower dose products (52-150 mg) causing little or no disruption when used once a day or less (Niruthisard 1992; Roddy 1993; Stevens et al., 1996).

When will we know for sure whether N-9 works against HIV?

There is one study under way and one new study planned that should help resolve the current impasse. It is totally unconscionable that 20 years into the HIV epidemic we do not already have an answer to this simple question.

The current study is being conducted by UNAIDS and evaluates the efficacy of Advantage 24, an existing spermicidal product with 52 mg of Nonoxynol-9 in a “bio-adhesive” gel designed to coat the vaginal cavity. This study is being conducted in South Africa, Côte d’Ivoire, and Thailand.

The second study was due to begin in early 1999 and will evaluate the efficacy of a 100 mg N-9 gel.

Should women use N-9 products for HIV prevention when condoms are not possible?

The answer depends on whom you ask.

The U.S. government’s Centers for Disease Control and Prevention says that since N-9 has not been proven to be effective in preventing HIV transmission, and since it may irritate the vaginal lining, making it easier for HIV to get in, women should not be encouraged to use N-9 products for HIV prevention.

The New York State Health Department, on the other hand, developed a Hierarchical Method of Prevention in 1992 in which they recommend the use of moderate- to low-dose N-9 products, with a diaphragm if possible, as a way for women to reduce their risk of HIV infection when condom use is not possible.

Many women’s health advocates feel that women should be informed about all the methods that can, or possibly may, help prevent HIV transmission. That way, women can make their own fully informed decisions about how best to protect themselves. For an extra margin of safety, women should limit their spermicide use to once a day or less.


**ADDITIONAL RESOURCES**

**ORGANIZATIONS**

**Center for Health and Gender Equity (CHANGE)**
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**INTERNET SITES**

**Alliance for Microbicide Development**
http://members.aol.com/ggkidder/alliance.html

**Center for Health and Gender Equity (CHANGE)**
http://www.genderhealth.org

**Center for AIDS Prevention Studies (CAPS)**
http://www.caps.ucsf.edu/capsweb

**Family Health International**
http://www.fhi.org

**HIV Insite**
http://hivinsite.ucsf.edu/prevention

**International Center for Research on Women**
http://www.icrw.org

**Microbicides as an Alternative Solution (MAS)**
http://socrates.berkeley.edu/~sph/MAS

**National Institute of Allergy and Infectious Disease**
http://www.niaid.nih.gov

**The Alan Guttmacher Institute**
http://www.agi-usa.org

**The Body**
http://www.thebody.com

**The Population Council**
http://www.popcouncil.org

**UNAIDS**
http://www.unaids.org
The Global Campaign for STI/HIV Prevention Alternatives For Women is a broad-based effort to increase access to HIV and STI prevention technologies other than the male condom. This important educational and advocacy initiative is designed to raise awareness of the need for new technologies that women and men can use to protect themselves from infection, and to demonstrate popular demand for such alternatives.

Epidemiological, physiological and social science research has shown that women are increasingly vulnerable to infection from their male partners. However, traditional prevention efforts continue to focus on promoting male condoms, excluding many women who are unable or unwilling to insist that their partners always use a condom. Alternative prevention technologies that the user can control—such as topical microbicides and female condoms—could make people less vulnerable to infection by HIV or other sexually transmitted diseases.

However, political will and public funding are necessary to ensure access to alternative prevention technologies. Female condoms are prohibitively expensive for many people and research into new alternatives is grossly under-funded. Scientists believe that a topical microbicide could be available within five years with sufficient effort and investment by major research institutions in the United States and the European Union. Without a concerted demonstration of popular demand, women will continue to face high risks of infection without access to prevention tools they can control.

**GOALS OF THE CAMPAIGN:**
- To raise awareness of women’s risk of sexually transmitted infections and the need for new prevention alternatives.
- To educate the public about topical microbicides as a promising new prevention technology.
- To increase public investment in research and development of topical microbicides and access to female condoms, as part of a coordinated public health policy promoting women’s reproductive health.

**STRATEGIES:** The global campaign uses *education and awareness-raising* to help individuals understand their own risks for HIV and STIs, and to help policy makers understand the need for prevention alternatives. *Advocacy efforts* channel awareness and demand into concrete actions to increase global access to alternative prevention technologies. The Campaign has produced *Action Kits* and a *petition* for use by local organizers.

The Global Campaign for Microbicides and Woman-Controlled STI/HIV Prevention Alternatives represents the combined efforts of women's groups, HIV/AIDS activists, and reproductive health advocates from around the world. You or your organization can become co-sponsors by signing and distributing the petition, building public awareness, writing letters, or any other type of activity that increases public awareness of and demand for accessible, user-controlled prevention alternatives.

For more information contact Megan Gottemoeller at CHANGE, (301) 270-1182. mgottem@genderhealth.org.
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