



**Microbicides
for HIV prevention**



**UNAIDS
technical update**



April 1998

At a Glance

- Microbicides are products intended for vaginal or rectal administration that can decrease the transmission of HIV and other micro-organisms causing STDs. Discovery of an effective microbicide would be of enormous benefit and it would empower women to contribute more to the fight against HIV infection.
- Expanding the prevention options, in particular for heterosexual HIV transmission is more urgent than ever because of the rapidly expanding heterosexual HIV epidemic. In 1992, it was estimated that 25% of people living with HIV were women. By 1996, this proportion had increased to 42%. Today 85% of all instances of HIV transmission involve sexual intercourse, and heterosexual transmission accounts for more than 90% of all instances of sexual transmission (*Report on the Global HIV/AIDS Epidemic, UNAIDS/WHO, December 1997*).
- In recent years, it was suggested that spermicides might have microbicidal properties. However to date, two trials have failed to show that the spermicide nonoxynol-9 is effective against the transmission of HIV or other STDs, and it is clear that non-spermicidal microbicides will be needed. It is encouraging that the number of microbicides in development has increased significantly in the past few years. Between 1994 and 1996, the number of products known to be in pre-clinical evaluation increased from 12 to 20, products in early clinical development increased from 9 to 13, and products in advanced clinical development from 0 to 2.
- In spite of this progress there is still much more room for improvement. Basic scientific questions, such as a better understanding of how HIV is transmitted during sexual intercourse, need to be resolved to help researchers target microbicide development. Technical problems, such as the choice of appropriate study populations and the strengthening of research capacity of study centres for the clinical trials, have to be thoroughly addressed. Ethical issues, such as the validity of informed consent when underprivileged and undereducated women at high risk of HIV infection are asked to participate in microbicide efficacy studies, have to be resolved.
- In order to overcome these challenges, the development of microbicides requires the active commitment of both the private and public sectors. Advocacy must be strengthened, public sector support increased, the commitment of industry obtained, scientists attracted and the efforts coordinated. We shall only succeed if we form a true "partnership for prevention".

UNAIDS Best Practice materials

The Joint United Nations Programme on HIV/AIDS (UNAIDS) is preparing materials on subjects of relevance to HIV infection and AIDS, the causes and consequences of the epidemic, and best practices in AIDS prevention, care and support. A *Best Practice* Collection on any one subject typically includes a short publication for journalists and community leaders (Point of View); a technical summary of the issues, challenges and solutions (Technical Update); case studies from around the world (*Best Practice Case Studies*); a set of presentation graphics; and a listing of key materials (reports, articles, books, audiovisuals, etc.) on the subject. These documents are updated as necessary.

Technical Updates and Points of View are being published in English, French, Russian and Spanish. Single copies of Best Practice materials are available free from UNAIDS Information Centres. To find the closest one, visit UNAIDS on the Internet (<http://www.unaids.org>), contact UNAIDS by email (unaids@unaids.org) or telephone (+41 22 791 4651), or write to the UNAIDS Information Centre, 20 Avenue Appia, 1211 Geneva 27, Switzerland.

Microbicides for HIV prevention: UNAIDS Technical Update (UNAIDS Best Practice Collection: Technical Update). Geneva: UNAIDS, April 1998.

1. Acquired immunodeficiency syndrome—prevention and control
2. Anti-infective agents
3. Acquired immunodeficiency syndrome—transmission

WC 503.2

Background

In the absence of a cure for HIV infection, no potentially useful avenue for HIV prevention should be ignored. Microbicides are products intended for vaginal or rectal administration that can decrease the transmission of HIV and other micro-organisms causing STDs. The development of microbicides is a potential option for prevention of HIV and should therefore be pursued energetically.

HIV prevention by women

Women throughout the world face a growing risk of HIV infection. In 1992, it was estimated that 25% of people living with HIV (PLWH) were women. By 1996, 42% of people living with HIV/AIDS were women and by the end of the century, women living with HIV infection will likely outnumber men living with HIV because of shifts in the predominant modes of HIV transmission (*Report on the Global HIV/AIDS Epidemic*, UNAIDS, December 1997).

At the same time, women's options for prevention are very limited. Women also often have little power to refuse or leave relationships that put them at risk. The use of male or female condoms requires the consent and cooperation of the partner, which would not be the case with microbicides. Negotiating

consistent condom use is not always feasible for many women. A microbicide offers the potential for a preventive option that women can more easily control and would not require negotiation, consent or even knowledge of the partner.

However women are not the only stakeholders in microbicide development: an effective microbicide would protect both partners. Microbicides are not just about HIV prevention for women but about HIV prevention by women.

Ideally, microbicides should be effective against HIV and other STDs. STDs not only cause considerable morbidity but are also associated with an increased risk of HIV infection. Microbicides may or may not have spermicidal properties. A microbicide that is not also a spermicide may prevent disease but not pregnancy, an

option that is not available to condom users.

In addition, a microbicide developed for vaginal use can be adapted for rectal use, like the female condom, which is now also being used rectally. Men who have sex with men have demanded that their need for expanded options of prevention be considered too, and have succeeded in getting their gender perspective introduced in the microbicide research agenda.

A disadvantage of microbicides is that, like condoms, they represent a recurring expense for people who may be unwilling or unable to purchase them. However, a reasonably priced microbicide that is at least as effective as a condom could be subsidized by donors and distributed through social marketing programmes.

The ideal microbicide should be...

Effective against HIV and all other STDs (when used either before or after intercourse)
Active as it is inserted, and for a long time
Safe
Inexpensive
Available without prescription
Colourless, odourless, tasteless, invisible
Stable
Easy to store
Pleasure enhancing
It may have or lack contraceptive properties

The ideal microbicide may never be found. Fortunately, in formulation-preferences studies conducted by The Population Council in five countries, participants indicated that they would use a messy and unpleasant product if its efficacy against HIV were proven.

Background

Steps for developing a microbicide

In vitro, animal and human data will all be needed for a microbicide to be licensed.

Laboratory studies (*in vitro*) on microbicides should evaluate:

- their activity against HIV and other STDs
- whether a microbicide has spermicidal activity
- their impact on embryogenesis and teratogenicity
- the interactions with latex and polyurethane condoms.

Animal studies should next:

- assess the product's safety,
- predict its dosing regimen,
- confirm its activity against the transmission of HIV or other organisms,
- assess the product's carcinogenic potential and reproductive toxicity.

Studies in humans should comprise:

- small Phase I clinical studies

to gather initial information on safety and pharmacokinetics,

- Phase II studies to confirm the product's safety,
- Phase III studies to determine whether the product prevents sexual transmission of HIV and other STDs.

For the assessment of local safety, it is recommended that colposcopy be performed in phase II studies and on a relatively small number of female participants in phase III studies (see Global Programme on AIDS, World Health Organization. *Manual for the standardization of colposcopy for the evaluation of vaginally administered products* in the Key Materials).

Status of microbicide development

The shortest path to introduction of an effective microbicide is to prove in well-controlled clinical trials that the over-the-counter spermicides (i.e. available without prescription), intended for contraception, are also

active against HIV transmission. All available spermicides, including nonoxynol-9 (N-9), octoxynol-9, benzalkonium chloride and chlorhexidine, are biodegradants (surfactants) that disrupt cell membranes. This property results in their spermicidal activity and their *in vitro* activity against HIV and STDs. Unfortunately, in high doses, biodegradants also cause genital tract ulcers, possibly increasing the risk of HIV transmission (see Niruthisard *et al.*, 1991, Roddy *et al.*, 1993 and Goeman *et al.*, 1995, in Key Materials).

To date, one trial assessing the efficacy of a vaginal sponge with N-9, and one assessing the efficacy of a vaginal film with N-9 have been completed. Both trials failed to show protection against HIV or other STDs (see Table 1). One trial assessing the efficacy of a gel with N-9 has recently been stopped prematurely, without the results being released, and another—sponsored by UNAIDS—is ongoing.

Table 1: Results of two studies investigating the efficacy of N-9 products against HIV and other pathogens

| Study | Product | Target organism or disease | Incidence in active product group | Incidence in control group |
|---------------------------|-----------------------------|----------------------------|-----------------------------------|-------------------------------|
| Kreiss <i>et al.</i> 1992 | Vaginal sponge, 1000 mg N-9 | HIV | 45% of 60 women | 36% of 56 women |
| Roddy <i>et al.</i> 1997 | Vaginal film, 75 mg N-9 | HIV | 6.7% per year among 478 women | 6.6% per year among 463 women |
| | | Chlamydia | 20.6% per year | 22.2% per year |
| | | Gonorrhoea | 33.3% per year | 31.1% per year |
| | | Genital lesions | 42.2% per year | 33.5% per year |

None of the differences between the N-9 and control product study groups was statistically significant.

Background

New products that might be more active against HIV than existing spermicides, and less toxic, are required and it is encouraging that increasing numbers of candidate products are under evaluation. Product concepts include new spermicides, inhibitors of viral attachment and/or entry, antiretroviral

products, and vaginal buffers (Table 2).

Between 1994 and 1996, the number of products known to be in pre-clinical evaluation increased from 12 to 20, products in early clinical development increased from 9 to 13, and products in advanced clinical development

increased from 0 to 2 (see Elias and Coggins, 1996 in the Key Materials). One of the products in advanced clinical development failed to show efficacy in 1997, and one remains under investigation. At least two newly designed microbicides will likely be ready to start efficacy testing in humans within the next two years.

Table 2: Microbicide product concepts

| Concept | Examples of products |
|---|---|
| Surfactants | Nonoxynol-9; octoxynol-9; benzalkonium chloride; chlorhexidine; C31G. |
| Acid buffering gels | Acid-gel; Buffergel. |
| Natural products | <i>Lactobacillus crispatus</i> suppository; antimicrobial peptides (protegrins); magainins (e.g. squalamine); plant extracts (gossypol, praneem). |
| Inhibitors of viral entry | N-Docosanol; sulfated and sulfonated polymers (e.g. dextrin sulfate, carageenans; chemically modified proteins (B69)) |
| Post-binding fusion inhibitors | Bicyclams |
| Reverse transcriptase inhibitors | PMPA, PMEA, non-nucleotide inhibitors |

The Challenges

Commitment and support

The development of microbicides requires the active commitment of both the private and public sectors.

Major research-based pharmaceutical companies have not invested significantly in microbicide research and development. Enthusiasm is limited by the perception that the product might be comparatively unprofitable. In developing countries, where microbicides are badly needed because of the high risk of HIV transmission, buying power is limited. Even in developed countries, a microbicide should rapidly become an over-the-counter product, which typically has a lower profit margin than prescription drugs. Companies are also concerned about regulatory uncertainties and the potential for unreasonable liability claims.

In industrialized countries, the public sector spends much more on therapeutic research than on prevention research, including microbicides.

In developing countries, where most of the HIV epidemic is concentrated, there is little activism to press for vaginal microbicides (or other parts of the HIV agenda) because the economic situation is not very conducive for it. Women's health activists, who must also deal with maternal mortality, abortion, education for women, and discrimination against women, have up to now not argued strongly for microbicides.

Lastly, in the scientific community, the perception is that therapeutic research is more innovative and attractive than microbicide research.

Scientific questions

Some scientific issues remain unresolved. Scientists do not know

- which cells in the mucosa are most susceptible to HIV infection,
- whether HIV is transmitted as free virus or as cell-associated virus or both, or
- whether infectivity or the target cells differ by viral subtype.

A better understanding of how HIV is transmitted during sexual intercourse would help researchers target microbicide development. It also would enable the development of better *in vitro* and animal models to forecast the efficacy and safety of candidate products.

Good data on user preferences and painstaking pharmacological evaluation are needed to formulate a product that will deliver the active compound efficiently, and that will be widely accepted. Ultimately, a variety of formulations will be needed to serve the varying needs of users.

Conducting clinical trials

Clinical evaluation of the efficacy of a microbicide requires access to large populations of women at high risk of HIV infection. Cohorts with a high incidence of HIV and STDs are expensive, difficult to recruit and maintain,

and must be followed for long periods of time. For efficiency, these cohort studies will likely need to be conducted in developing countries where HIV incidence is high. This poses many technical challenges such as strengthening the research capacity of study centres, and requires that the ethical challenges be addressed.

Another challenge is to find the right population for efficacy trials. Female sex workers would look like the ideal participants for such studies, but female sex workers tend to differ in a number of important ways from other women: they have more partners, often have STDs, and clean the vagina frequently, influencing its physiology and colonization patterns. Other populations at risk of HIV infection, such as post-natal women, teenage girls or university students in high HIV prevalence countries and men having sex with men, should therefore also be considered.

The Responses

Strengthen advocacy

Increased advocacy by activists, public sector institutions and the private sector should help make microbicide research and development part of the mainstream HIV agenda. The UN's commitment to microbicide development began in 1993 (see Global Programme on AIDS, World Health Organization. *Report of a meeting on the development of vaginal microbicides for the prevention of heterosexual transmission of HIV in the Key Materials*). Global advocacy organizations, such as UNAIDS, have the responsibility to speak out for and support the voice of the underprivileged and women in developing countries. UNAIDS is doing so, along with other organizations that are members of the International Working Group on Microbicides such as the Centers for Disease Control and Prevention (CDC), the Commission of the European Community (CEC), Contraceptive Research Development (CONRAD), Family Health International (FHI), the Food and Drug Administration (FDA), the National Institute of Child Health and Human Development (NICHD), the National Institute of Allergy and Infectious Diseases (NIAID), the Medical Research Council (MRC), the Population Council, the Society for Women and AIDS in Africa (SWAA), and the World Health Organization (WHO). But more efforts by others are badly needed.

Increase public sector support

Advocates must call on governments for wider and stronger public sector support for microbicide development. Considering the enormous costs of clinical care once people are infected, a few million dollars spent on the development of an effective microbicide to prevent HIV seems a sound investment.

The public sector needs to be convinced that having a microbicide is important, even if an HIV vaccine were available, since different persons will be interested in different prevention options. *Moreover, as the development of both vaccines and microbicides is likely to use similar populations for efficacy trials, efforts in support of either prevention option are likely to benefit the development of the other.*

Gain industry commitment

Advocates should present industry with data to reverse the perception that a microbicide product would necessarily be unprofitable. The EC is conducting a survey of the potential size of the microbicide market, and CONRAD is conducting a similar exercise in the US market. Advocates should also emphasize that major companies must be involved in microbicide development if they want to be seen as good corporate citizens, especially if they have a significant HIV product portfolio.

Advocates should support the efforts of small companies who are moving into the microbicide area to the best of their abilities in concert with a few interested academic researchers and limited public funds. Advocates should assist small company efforts when appropriate, for example by lobbying for public action funding, when it is time to start phase III studies.

Attract scientists

Mainstream HIV researchers must be persuaded that it is critical to find a microbicide so that they will request funding for the research required to develop one. Researchers need to be encouraged to investigate the sexual transmission of HIV and methods to decrease it. Reports on such research should be given

visibility at all major HIV scientific meetings to demonstrate that academic success can be obtained in microbicide development.

Continue efforts to develop guidelines

The International Working Group on Microbicides (IWGM) was formed in November 1993 at a meeting held at the World Health Organization in Geneva, Switzerland. The goal of the IWGM is to facilitate development, production and distribution of safe, acceptable, effective and affordable vaginal microbicides to prevent HIV and other STDs. Guidelines on how microbicides should be developed were published in 1996 by UNAIDS on behalf of the IWGM (see International Working Group on Vaginal Microbicides, *Recommendations for the development of vaginal microbicides in the Key Materials*). This document is likely to form the basis for future regulatory requirements for the development of vaginal microbicides. This effort should be continued and enlarged.

Exchange information and coordinate efforts

The public and private sectors need to reach consensus on an approach to microbicide development. With limited resources available for microbicide development, it is essential that agencies and companies cooperate with one another. As stated by Chris Elias, The Population Council:

"We (the public sector) must thus form strategic alliances: across disciplines within the scientific community, between scientists, advocates and communities at risk; with industrial partners who can mobilize needed resources and expertise; and with the community of women living with HIV infection. We will only succeed if we form a true 'partnership for prevention'."

Key Materials

Elias CJ, Coggins C. Female-controlled methods to prevent sexual transmission of HIV. *AIDS*, 1996; **10** (supplement 3): S43–S51. A state-of-the-art review on the development of female controlled methods to decrease HIV transmission.

The International Working Group on Vaginal Microbicides. Recommendations for the development of vaginal microbicides. *AIDS*, 1996; **10**: UNAIDS1–UNAIDS6. This document is likely to form the basis for future regulatory requirements for the development of vaginal microbicides.

Kreiss J, Ngugi E, Holmes K, *et al.* Efficacy of nonoxynol-9 contraceptive sponge in preventing heterosexual acquisition of HIV in Nairobi prostitutes. *Journal of the American Medical Association*, 1992, **268**: 477–82. This paper describes the results of the only clinical trial published to date about the efficacy of a vaginal microbicide in the prevention of HIV infection. HIV transmission was not prevented among women using an N-9 sponge. However, a number of design and implementation problems made its results and conclusions controversial and raised questions about the safety of the product. This led to the initiation of additional safety and efficacy studies on different formulations of N-9.

N-9 film fails to protect against HIV infection or STDs. Press release on a Family Health International study of a N-9 containing film among female sex workers in Cameroon, April 1997.

Global Programme on AIDS, World Health Organization. *Manual for the standardization of colposcopy for the evaluation of vaginally administered products.* Geneva, 1995. WHO/GPA/RID/CRD/95.10. WHO guidelines for the use of colposcopy in safety studies on microbicides, spermicides and vaginally administered products.

Global Programme on AIDS. World Health Organization. *Report of a meeting on the development of vaginal microbicides for the prevention of heterosexual transmission of HIV.* Geneva 11–13, 1993. WHO/GPA/RID/CRD/94.1. A state-of-the-art overview of microbicide development anno 1993, and is mainly important because it marks the beginning of the United Nations' commitment to vaginal microbicide development.

Niruthisard S, Roddy RE, Chutivongse S. The effects of frequent nonoxynol-9 use on the vaginal and cervical mucosa. *Sexually Transmitted Diseases*, 1991; **18**:176–9.

Roddy RE, Cordero M, Cordero C, Fortney JA. A dosing study of nonoxynol-9 genital irritation. *International Journal of STD & AIDS*, 1993; **4**:165–70.

Goeman J, Ndoye I, Sakho LM *et al.* Frequent use of Menfegol spermicidal vaginal foaming tablets associated with a high incidence of genital lesions. *Journal of Infectious Diseases*, 1995; **171**:1611–4. The three papers cited above describe a high incidence of genital lesions with frequent or high dose administration of surfactants.

Please note that clinical trial advice (protocols for Phase II and Phase III studies) can be obtained from UNAIDS. Please contact J. Perriens, at <perriensj@unaids.ch>.

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