

Who's who in Microbicides?

What follows is a resumé of the main actors in microbicide research, development and advocacy;

- The Global Campaign for Microbicides (www.global-campaign.org) is a broad-based international effort to build support among policy-makers, opinion leaders and the general population for increased investment into microbicides and other user-controlled HIV and STI prevention methods.
- The Microbicide Development Programme is a UK funded research programme currently focussed on conducting a Phase 3 trial of Pro2000 in 5 African countries. It includes the UK and South African Medical Research Councils.
- The Alliance for Microbicide Development is a consortium of all the research bodies and biotech companies engaged in microbicide research, monitoring developments in the field and convening policy dialogues on critical issues. Progress reports on product trials are posted at www.microbicide.org
- Global Microbicides Project (www.gmp.org) is the Gates funded programme on microbicide research.
- The International Working Group on Microbicides (IWGM) is a voluntary network of individual researchers seeking to ensure closer coordination in the field and build consensus on requirements for testing.

- The International Partnership for Microbicides (www.ipm-microbicides.org) is a public-private partnership to accelerate microbicide research and development and ensure access to microbicides, their exclusive focus is on products for women in developing countries.

The microbicide challenge facing the Gay Men's Health Sector:

- be informed
- be active
- be supportive
- be prepared

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May 2005

Special thanks to Gus Cairns (UK Coalition), Julian Meldrum, Rebekah Webb (Global Campaign for Microbicides), Caroline Haworth (Interact Worldwide) and Kim Mulji (Naz Foundation) for their help in writing this report.

Notes

(1) Animal studies of pre-exposure prophylaxis using oral Tenofovir showed infection with the ape equivalent of HIV was delayed but not prevented. An earlier ape study showed that, when injected, Tenofovir protected against infection; details at <http://www.aidsmap.com/en/news/F4EFF025-193B-4459-B3FC-AA5BD7096C71.asp>

(2) **Watts C et al.** The public health and economic benefits of microbicide introduction: model projections. XVI International AIDS Conference, Barcelona, abstract TuPeF5307, 2002

(3) *ibid*

(4) **Hendrix CW et al.** Imagining the distribution of a rectal microbicide gel and semen surrogate in the lower GI tract. Microbicides 2004, London, oral abstract 02685

(5) **Michael Boyd** and colleagues at America's National Cancer Institute have isolated an anti-viral protein, cyanovirin-N (CV-N), which prevents HIV from binding to mucosal cell surfaces in the vagina and rectum. Researchers at the University of Washington have shown that a gel containing CV-N prevented rectal transmission in monkeys of the ape equivalent of HIV. Microbicide developers are following these leads and further testing on apes is planned.

(6) **Dr Robin Shattock** and team at St George's Hospital, London have done much work into developing tissue-culture systems for evaluating rectal and vaginal microbicides.

(7) **Hylton J et al.** An assessment of sexual practices affecting the feasibility of microbicide development among MSM. Microbicides 2004, London, poster 02667.

(8) **Carballo-Dieguez A et al.** Frequent use of lubricants for anal sex among men who have sex with men: the HIV prevention potential of a microbicide gel. American Journal of Public Health, 90:1117-1121, 1999

(9) After being told what they were 23.7% of gay men said they had already heard of microbicides and 93.4% said they would consider using a partially effective anti-HIV microbicide. Unpublished data from the National Gay Men's Sex Survey 2003

(10) This campaign can be viewed at www.advocacyonline.net/tht/22march/content_camp_micro.jsp

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Sector Summary Report: Microbicides

Microbicides offer the prospect of a much-needed additional HIV prevention option, especially for those unable or unwilling to use condoms. Microbicial products are currently undergoing clinical trials and the first microbicide could be on the market within the next 5–6 years. This report looks at what vaginal and rectal microbicides are, who they could benefit, the challenges in developing effective and safe products (especially ones suitable for anal sex) and the role of the gay men's health sector in preparing the ground for their arrival.

What are microbicides?

Microbicides are substances which protect against infection by microbes (such as viruses and bacteria). They would protect against such microbes by:

- killing them on contact
- stopping them from entering the body
- or, once in the body, stopping them reproducing within cells.

Ways in which microbicides might prevent infection include:

- interfering with the ability of HIV to bind onto the receptors on human cells
- creating an environment too hostile for HIV to survive in

Microbicides are not to be confused with 'spermicides', a similar concept but one that acts as a contraceptive by killing sperm. However, once developed some microbicides may also function as spermicides.

No proven safe and effective microbicides exist as yet but a range of products are possibilities, such as:

- gels/jellies
- foams
- creams
- films
- sponges
- vaginal suppositories
- slow-release internally fitted devices
- rectal enemas/vaginal douches.

Why do we need microbicides?

HIV incidence continues to rise, as do rates of sexually transmitted infections. Existing HIV prevention technologies are flawed and more user-friendly products would be very welcome.

Condoms rely on the willingness of the insertive partner to use them and a degree of negotiation skills on the part of either partner to ensure they are used. They can fail, are intrusive and often unpopular. Consistent condom usage among gay men appears to be declining and a significant number of men, with male or female partners, will never become consistent condom users.

Post-exposure prophylaxis is expensive, causes major side effects, can fail and, as it needs to be taken for four weeks after each exposure to HIV, is not for ongoing use.

Pre-exposure prophylaxis (taking antiviral drugs before sex to prevent HIV infection) is being investigated but may never become a reality.⁽¹⁾

A **vaccine**, the ultimate in HIV prevention, may never be found or may be many years away. Furthermore many experts believe the best we can hope for is a vaccine that is only partially effective.

Microbicides could offer the prospect of a cheap, easy to use prevention option controlled by the receptive partner – possibly inserted well before intercourse and without the insertive partner noticing it.

For those wanting children there are no options allowing contraception and HIV protection. For women for whom condom use is not an option for these reasons, microbicides could make a huge difference. These women account for a rapidly rising number of new infections globally.

It has been estimated that even an only partially effective microbicide, distributed in 73 low-income countries and used by 20% of those attending clinics in half the occasions that they have sex, could prevent 2.5 million HIV infections in a three year period.⁽²⁾ And it is estimated that in populations with low levels of condom use, such as in India or Africa, a partially effective microbicide could make a difference in reducing HIV transmission, even taking into account some people rejecting condoms in favour of microbicides.⁽³⁾

What are the challenges of developing microbicides?

Any microbicide would need ideally to be effective against not only HIV but other sexually transmitted infections (the great strength of the condom). It should not irritate or harm the tissue it comes into contact with, should quickly cover the area containing cells vulnerable to HIV infection and stay in place for long enough in the face of movement such as sexual intercourse and walking.

Prospects look good for microbicides with at least some efficacy against HIV when used vaginally

A microbicide may also need to be effective after HIV crosses the protective barriers of the vagina or rectum, so may need to reach effective levels of penetration in surrounding tissue and nearby lymph nodes.

The best microbicide, in addition to being effective and safe, would be cheap to produce and require no prescription or medical staff to apply. It should also be non-obtrusive to both wearer and their sexual partner. A vaginal microbicide would have to function in an acidic environment, remain stable in the face of vaginal fluids and enzymes and cope with the changes that accompany the menstrual cycle.

Ideally a microbicide would not be absorbed into the body, but instead be 'topical'. A product absorbed into the body risks more side effects and if so could take longer to get licensed. A product containing anti-HIV drugs might risk drug resistance if it were directly absorbed into the body of an HIV infected individual. For this reason careful screening to measure for absorption is being done on candidate microbicides that contain anti-retroviral medications.

A microbicide should be able to be used regardless of the HIV status of either sexual partner. Clinical microbicide trials currently enroll HIV positive women in safety studies. Ways need to be developed that test product effectiveness at preventing transmission in either direction when used by HIV positive individuals.

Could microbicides be used for rectal use?

There are specific challenges which face the development of a rectal microbicide. The lining of the rectum is more delicate than that of the vagina, with breaches of the rectal membrane increasing the chance of HIV infection. This means a rectal microbicide may need to offer a greater protective effect than one used vaginally – not only against HIV but other infections too.

Whereas the vagina is a small, enclosed cavity, the rectum is a much larger, more open space. Semen can travel up to 60 cm along the gut after anal sex,⁽⁴⁾ presenting a formidable challenge to those creating a substance that will reach that far and stay there.

Far more of a microbicidal product might be needed for rectal use, which could have cost implications. It may be that an enema-based product may be the best way of ensuring the required coverage. A rectal product may need to be an entirely different formulation than a vaginal one in order to be both effective and acceptable to users.

Developing a microbicide for vaginal use is a more attractive research proposition because its anticipated market would be huge compared to that for a rectal microbicide. However, it is worth remembering that the vast majority of episodes of anal sex are between men and women, so any rectal microbicide would be used by both sexes – although men who have sex with men would probably be the most consistent users of a rectal microbicide as they have anal sex more often.⁽⁵⁾

Which vaginal microbicides are in the pipeline?

There are over 50 compounds being investigated for their potential microbicidal properties. Early phases of developing a product look at how it might work and its potential toxicity and include mathematical modelling of tissues exposed to HIV, experiments in cell cultures and then on small animals (who have had human vaginal tissue grafted onto them).

If early trials produce a promising candidate it goes forward to trials on hundreds or thousands of human subjects to gauge its efficacy and potential side effects. Five products (all in gel form) are undergoing such trials and are now being tested on tens of thousands of women. Further research will be needed to ascertain whether these will offer HIV protection if used rectally.

Prospects look good for microbicides with at least some efficacy against HIV when used vaginally. The first vaginal products could be available within 5–6 years. Although many compounds kill HIV in laboratory experiments, few expect the first generation of microbicides to be anything more than moderately effective. It is foreseen that they will be promoted as giving extra protection when used with condoms (in case of condom failure).

However, it is also assumed that microbicides will be used on their own. Although microbicides used on their own may prevent a significant number of infections on a population basis, for maximum protection an individual would need to use them with condoms.

The products in development fall into the following categories:

- **Sulphated and other charged polymers** – the products most advanced along the testing schedule (e.g. PRO2000[®] and seaweed-derived Carraguard[®])
- **Acid buffers** – these keep vaginal acidity in a range that kills HIV – and sperm (e.g. BufferGel[®])
- **Antivirals** – these are expensive to produce and would probably be added to other products to give extra protection against HIV. If absorbed into the body of an HIV positive individual drug resistance may become an issue (e.g. TMC120, UC-781 and SPL7013)
- **Naturally occurring antibiotics**
- **Antiseptics**
- **HIV-specific binding agents** (e.g. anti-HIV antibodies)
- **Hydrogen peroxide** – this natural disinfectant is produced by the 'friendly' bacteria lactobacilli found in the vagina
- **Surface active agents** – similar to spermicide Nonoxynol-9 with its well-known side effect of skin and mucous membrane irritation and ulceration (e.g. Savvy[®] aka C31G)
- **Porphyrins** – several of these proteins prevent HIV entering cells

What could be the role of health promoters in preparing for microbicides?

We have already seen how gay men adapt new technologies in ways not originally predicted. Post-exposure prophylaxis was not developed for use after sex and the 'female condom', used by some gay men (inserted anally or worn as an extra large condom), was never intended for such a purpose. The arrival of vaginal microbicides will no doubt see similar 'innovation'.

A microbicide with even partial HIV prevention potential during anal sex could be seen as useful by men who have sex with men, whatever their HIV status, especially if they will not use condoms or do not feel able to insist on their partners using them. Ideally they would be able to be inserted some time before sex occurs and with the insertive partner unaware of their use.

Very little has been done in Europe to advocate for a rectal microbicide, with few links between scientists/researchers and the gay men's health sector. Vaginal microbicide research is underfunded and funding for rectal products is almost non-existent.⁽⁶⁾

The first vaginal products could be available within 5–6 years.

The gay men's sector has potential to influence the following;

- involvement in more research into situations, relationships and populations (both heterosexually and homosexually active) where anal sex occurs – is necessary before there can be discussion of the potential value of any rectal microbicide
- advocacy for funding of rectal microbicide development
- involvement in research into the efficacy and safety of any licensed vaginal microbicides if used anally
- raising awareness of microbicides if shown to be useful during anal sex – or discouraging their use if shown to be ineffective.

Some research has already taken place to gauge gay men's attitudes to microbicides.^{(7) (8) (9)}

What's the latest on advocacy for microbicides?

Microbicides are increasingly on the agenda of the gay men's health sector. Past CHAPS conferences have highlighted the possibilities for microbicide development and their potential for gay men. March 2004 also saw Microbicides 2004 in London, following which a working group was established to advance rectal microbicide advocacy in the UK. This group now operates out of the UK Campaign for Microbicides hosted at Interact Worldwide. March 2005 saw Terrence Higgins Trust, Interact Worldwide and the National AIDS Trust together with the National Union of Students lobby MPs in an e-campaign for more European Union funding into microbicide research.⁽¹⁰⁾ Microbicides 2006 is scheduled to take place in South Africa.