

MICROBICIDES

This *Making it Count* briefing sheet provides an overview on the current status of research towards the development of microbicides for sexual health promoters working with gay men, bisexual men and other men that have sex with men (MSM). Microbicides offer the prospect of a much-needed additional HIV prevention option. A vaginal microbicide containing an antiretroviral drug has already been shown to reduce women's risk of HIV infection but rectal microbicides are at a much earlier stage of development.

WHAT ARE MICROBICIDES?

In terms of HIV prevention, a microbicide is a product which is designed to be applied to the vagina or the rectum, in order to reduce the user's risk of HIV infection when HIV exposure occurs.

While potential microbicides have most often been developed as gels or creams (similar to a lubricant), they could be developed in a number of different formulations. For example, work is currently underway on microbicides in the form of:

- vaginal rings which slowly release the product (similar devices are used for hormonal contraception);
- tablets or pieces of film which are placed in the vagina or rectum, where they dissolve and cover the mucosal surface;
- anal douches or enemas;
- a coating for a condom.

In each case, the product is applied to a specific, localised part of the body – this is sometimes referred to as 'topical application'.

The most promising microbicide products are all formulations of anti-retroviral (ARV) drugs. The idea is that an ARV applied in the vagina or rectum might be able to block HIV activity at the site of exposure, thereby preventing infection. Different ARVs work in different ways:

- targeting the virus and preventing it from attaching and entering white blood cells (the cells that HIV must infect in order to reproduce);
- blocking entry by targeting receptors on the outside of the white blood cell itself;
- preventing HIV from making more copies of itself (replicating) once it has entered a white blood cell.

The use of ARVs means that there are important similarities between pre-exposure prophylaxis (PrEP) and microbicides

for HIV prevention. For PrEP, the ARVs are taken in tablet form and the drug spreads throughout the body. In the case of a microbicide, the ARV is applied to the vagina or rectum and should only spread through local tissues.

Before the development of ARV microbicides, researchers had investigated a wide variety of substances with varying modes of action. For example, some substances interfered with the ability of HIV to bind onto the receptors of cells; others created an environment too hostile for HIV to survive in; others boosted the vagina's natural defences. However these substances (eg. Carraguard, BufferGel, Pro2000) turned out to be ineffective and for a number of years, the results of microbicide trials were consistently disappointing.

In July 2010, the first large trial of a microbicide containing an anti-retroviral drug (tenofovir) found that it reduced women's risk of HIV infection by 39%. (For more information, see *What research has been conducted into vaginal microbicides?* below).

THE POTENTIAL BENEFITS OF MICROBICIDES

The number of new HIV infections and diagnoses each year – both in men who have sex with men and in other groups – demonstrate that the current provision of condoms and of behaviour change interventions to support their use is insufficient to prevent the HIV epidemic from continuing.

Condoms rely on the willingness of both partners to use them and a degree of negotiation skills on the part of either partner to ensure they are used. Condoms have to be put on when sex happens (making adherence to their use difficult) and they can fail, are intrusive and often unpopular.

Existing HIV prevention methods have limitations and a wider variety of methods would be welcome to many people. Alternative methods which are cheap, long-lasting, without side-effects, discreet, controlled by the receptive

MAKING IT COUNT

Making it Count is the strategic planning framework that guides HIV prevention for MSM across the CHAPS partnership. Although earlier editions of *Making it Count* argued that the government, researchers and HIV organisations should take action to encourage the development of microbicides (and vaccines), the topic does not figure in the fourth edition of the framework which is much more concerned with current direct contact interventions for gay men and other MSM.

However, the CHAPS partnership remains committed to policy and advocacy work to ensure that the development of rectal microbicides is a priority for governments, researchers and their funders, and HIV organisations. Future editions of MiC will address the issue of microbicides, as and when they become a more tangible possible intervention.

partner, easy to adhere to, and not requiring substantial attention at the time of sex (similar to most contraceptives) would be particularly welcome.

However no single HIV prevention solution is likely to be sufficient on its own. An approach of 'combination prevention' is more likely to be effective. This requires biomedical interventions (such as condoms or microbicides) to be provided alongside: behaviour change programmes to support their consistent use; treatment of HIV and sexually transmitted infections; and social justice and human rights.

WHY DO WE NEED RECTAL MICROBICIDES?

The main focus of microbicide development is on vaginal microbicides, which are seen by women's health advocates as female-controlled prevention methods which respond to the reality of power inequalities between men and women as well as to high infection rates among women in many parts of the world.

But there is pressure too for the development of rectal microbicides. HIV is transmitted about ten times more easily rectally as vaginally, with receptive anal intercourse being the main route of infection for men who have sex with men (MSM). MSM have a disproportionate burden of HIV infection, not only in the UK's 'concentrated' epidemic, but in many 'generalised' epidemics in sub-Saharan Africa and the Caribbean.

What's more, although anal intercourse is often a taboo topic for heterosexuals, there is evidence that a significant proportion of heterosexual men and women practice it. For example, in a large survey of South African young people, 5.3% of sexually experienced women and 5.5% of sexually experienced men reported having anal intercourse.

WHAT ARE THE CHALLENGES OF DEVELOPING MICROBICIDES?

Any microbicide should not irritate or harm the tissue it comes into contact with, should quickly spread throughout the area containing cells vulnerable to HIV infection and should stay in place for long enough in the face of

movement such as sexual intercourse or walking.

It needs to cross the protective barriers of the vagina or rectum, and penetrate the surrounding tissue and nearby lymph nodes. But ideally it would not be absorbed into the bloodstream and throughout the body – as this could lead to more side effects.

If an ARV-based microbicide were used by a person with undiagnosed HIV-infection, there is a theoretical possibility that this could lead to the development of drug-resistant HIV and limit future treatment options. An ideal ARV-based microbicide would use a drug which is not already used for HIV treatment. Nonetheless, there is less risk of resistance when only a limited amount of the drug is absorbed into the bloodstream – one advantage of a topical microbicide over oral pre-exposure prophylaxis.

To be acceptable to users, a microbicide needs to be easy to apply, unobtrusive to both the person using it and a sexual partner, and fit with sexual preferences (some people find extra lubrication pleasurable, others do not).

Most research has investigated products that are applied a few hours before sex and then again some time afterwards. A microbicide which is applied each day, rather than when sex is anticipated, might be easier for some people to use consistently.

Some women would prefer a dual-acting product that can protect against pregnancy and HIV at the same time. Other women have a need for a vaginal microbicide that will protect them from HIV but still allow conception. While an ideal product would be cheap to produce, require no prescription and be protective against other sexually transmitted infections, this may not be the case for ARV-containing microbicides.

One barrier to the development of microbicides has been limited investment in research. Most of the funding has come from American and European governments, while pharmaceutical companies – normally the engines of new drug research – have invested little. Microbicides (especially rectal microbicides) are thought unlikely to generate large profits.

International Rectal Microbicide Advocates and the Global

Campaign for Microbicides are two organisations advocating for more research and investment in microbicides. They would like more and more people to support and get involved in their activities.

WHAT ARE THE CHALLENGES OF DEVELOPING RECTAL MICROBICIDES?

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. Breaches of the rectal membrane, which increase the chance of HIV infection, are more likely. This means a rectal microbicide may need to offer a greater protective effect than one used vaginally.

Whereas the vagina is a small, enclosed cavity, the rectum is larger. Semen can travel up to 60 cm along the gut after anal intercourse, presenting a challenge to those creating a substance that will reach that far and stay there.

More of a microbicidal product might be needed for rectal use. 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.

Nonetheless, any vaginal microbicide needs to be tested for rectal safety, as people will experiment with rectal use of the first microbicides that become publicly available (as happened with condoms which were designed for vaginal use). There is a risk that a product that is safe in the vagina damages rectal tissue.

WHAT RESEARCH HAS BEEN CONDUCTED INTO VAGINAL MICROBICIDES?

In the field of vaginal microbicides, the most important and encouraging study findings were released in July 2010. The CAPRISA 004 study took place in South Africa, where 889 sexually active women were randomised to receive a microbicide gel containing 1% tenofovir (a nucleotide reverse transcriptase inhibitor) or a gel containing a placebo. During the trial, neither the women nor the researchers knew which product they were receiving.

The women taking part were at high risk of HIV infection, reflected in the annual incidence of 9.1% in the placebo group. However among women receiving the microbicide, annual incidence was 5.6% – in other words, 39% lower.

When women did use the microbicide consistently, results were better. Among women who used it on at least 80% of the days they had sex, their risk of infection was 54% lower than the placebo group. However the fact that many women's adherence was poor highlights the possibility that

consistent microbicide use may be as challenging as consistent condom use.

This study is extremely encouraging, but needs to have its results confirmed by further studies. Another South African study, known as VOICE, is likely to report results in 2011. It is comparing HIV infection rates in women using a tenofovir microbicide, pre-exposure prophylaxis and a placebo.

A third efficacy trial is called IPM 009 and will produce results in 2015. This trial will test the effectiveness of dapivirine (a non-nucleoside reverse transcriptase inhibitor), either as a gel or as a vaginal ring.

In addition, many more preliminary studies (for example, in animals or to test safety in humans) are underway. At least 13 different ARV-based microbicides have demonstrated efficacy in blocking HIV infection in monkeys. Some of these ARVs are also used for HIV treatment, while others such as dapivirine have anti-HIV activity but are not licensed for HIV treatment.

It is possible that a microbicide containing more than one ARV would be more effective than one containing a single drug.

WHAT RESEARCH HAS BEEN CONDUCTED INTO RECTAL MICROBICIDES?

Rectal microbicide research is at a much earlier stage than achieved for vaginal microbicides. There have been no phase 3 efficacy studies such as CAPRISA 004 conducted yet and it is unlikely that a rectal microbicide product will be ready for that kind of research in the next few years.

Research that is underway includes:

- Investigations of the safety of tenofovir gel (which has been formulated for vaginal use) when used in the rectum.
- Research into the safety of lubricants which are already used during anal intercourse.
- Studies assessing which gels or fluids could safely be used to 'carry' an ARV and which would effectively cover the rectal mucosa.
- Studies showing whether rectal microbicides protect against HIV infection in monkeys and other animals.

As well as investigation into the possible rectal use of tenofovir, some studies are looking into the use of UC-781, a non-nucleoside reverse transcriptase inhibitor rejected as an oral drug to treat HIV infection because of its poor absorption throughout the body. A phase I study looking into the safety of UC-781 asked 36 men and women to insert a measured dose of the gel with a rectal applicator. A range of tests for harm to the mucosal surface found that it was as safe as a placebo. Moreover, trial participants reported no problems with its colour, smell and consistency.

The researchers also used an innovative method to assess the ability of the microbicide to inhibit HIV infection. Soon after applying the microbicide, biopsies (small sections of rectal tissue) were taken. They were kept alive in a lab and then incubated with HIV. Whereas HIV took hold in almost all biopsies from the placebo group, infection rates were much lower in biopsies from people who had received the microbicide.

The fact that this study, whose results came out in 2009, was the first ever phase I human study of a rectal microbicide, gives an indication of the low priority accorded to rectal microbicides by the majority of funding agencies and scientists.

FURTHER READING

Abdool Karim Q *et al.* (2010) Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science* 329(5996): 1168-74.

Global Campaign for Microbicides: www.global-campaign.org

International Rectal Microbicide Advocates:
www.rectalmicrobicides.org

Aidsmap: www.aidsmap.com/Microbicides/page/1065777/

FIVE KEY POINTS

- A microbicide is a product which is applied to the vagina or the rectum and which reduces the user's risk of HIV infection.
- A microbicide could provide an alternative precautionary choice for people who have difficulty reducing HIV transmission risk in other ways.
- Following disappointing results with microbicides with other modes of action, the focus of microbicide research is now on products containing anti-retroviral drugs.
- A vaginal microbicide containing the drug tenofovir has been shown to reduce women's HIV infection risk by 39%.
- Rectal microbicide research is at a much earlier stage, and lacks substantial investment or champions.

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