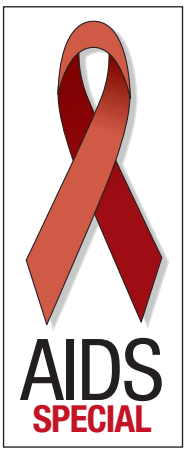
Starting to gel

In sub-Saharan Africa, there's an urgent need for creams or gels that can protect women from infection with HIV. Now the first large-scale trials are getting under way. Helen Pilcher reports.

F. HERHOLDT/MDP



Martha is a fairly typical South African teenager. At 15, she lost her virginity to a man ten years her senior. But he refused to wear a condom, and now Martha is HIV positive.

Martha's is a familiar story in a country where HIV is rife and women bear the brunt of the epidemic. Young women account for nearly 60% of all adult HIV/AIDS cases in sub-Saharan Africa[1]. Many find it hard to negotiate safe sex and so cannot protect themselves against the virus. But a new type of drug is being developed to help put women in control.

Microbicides are creams or gels that can be applied to the vagina before sex to help prevent HIV infection. It is hoped that they will be undetectable to male partners, so that women will be able to protect themselves discreetly. With condom use patchy and any successful vaccine some way off, hopes are pinned on these compounds' prophylactic powers.

Women are especially vulnerable in some African cultures, where they are not expected to answer back or to make decisions about their sex lives. It is often hard for them to enforce condom use and difficult to refuse intercourse. Those who do may risk violence. And some impoverished African women have little choice but to exchange sex for material favours, such as shelter, food or school fees.

"I don't think people have an understanding of the enormity of the problem here in Africa," says Ingrid Kelters, an HIV health worker in Tanzania who runs a tiny health centre on the main road to Zambia, near the stop where long-distance truck drivers break their journeys to buy sex from local barmaids. "You can almost see the HIV flying around at night," she says.

Women are being infected at an early age. In South Africa, one in four women aged 20 to 24 are HIV positive, compared with just one in fourteen men[2]. The epidemic trickles down through the generations as older, sexually experienced men have sex with naive young girls. "This speaks volumes for the need to target therapies at young women," says Helen Rees, executive director of the Reproductive Health Research Unit at the University of the Witwatersrand in Johannesburg.

Shaky start

Microbicides could meet this need. But so far, only one has been fully tested in people, and that proved to be a resounding flop. The detergent molecule nonoxynol-9 inactivates HIV in laboratory cultures[3] and prevents a similar virus, SIV, from infecting macaques[4]. In the United States, it has been sold over the counter as a spermicide since the 1960s, so researchers reasoned it should be safe to use.

But when women used it regularly, it damaged the vaginal lining, an important barrier to HIV infection. More than 400 sex workers from Benin, Côte d'Ivoire, South Africa and Thailand were enrolled in a clinical trial. Those who used the cream three times per day or more were almost twice as likely to become infected with HIV as those who used a placebo product[5].

Researchers are now working on gentler microbicides. These include dextrin sulphate and PRO 2000, gels in which large, negatively charged carbohydrate molecules bind to positively charged groups on the surface of HIV, preventing the virus from entering cells lining the vagina. Another microbicide, known as BufferGel, inactivates HIV by lowering vaginal pH.

Six large clinical trials using microbicides have started or are about to begin later this year (see Table, overleaf). The largest, backed by Britain's Medical Research Council and the Department for International Development, will test the ability of dextrin sulphate and PRO 2000 to prevent HIV infection. Over the next few years, 12,000 women in five African countries who are currently free from HIV will apply one of the microbicides or a placebo gel each time before they have sex. They will also receive ongoing HIV counselling and healthcare. Nine months after their treatment begins, the women will be tested to see if they have become HIV positive. "There's a lot of excitement about it," says Rees, who is helping to coordinate the South African arm of the trial.

No one is sure how the gels will perform,

although laboratory and animal studies of dextrin sulphate and PRO 2000 look promising. Dextrin sulphate and related compounds stop HIV from entering host cells in culture[6]. And both PRO 2000 and dextrin sulphate provide partial protection from infection by a related virus in female monkeys, who had the gel placed in their vaginas[7]. But it is difficult to extrapolate from monkeys to people — human transmission of HIV is predominantly through sex, whereas monkeys normally transmit SIV by biting and scratching.

Participants in the trial will be encouraged to use both gel and condoms. But it is unlikely that people will use condoms all the time, so the study has been designed to enable statisticians to tease out the effect of the gel alone.

A big difference

At best, microbicide gels are likely to be only partially effective. "But this could make a big difference in places such as Africa," says Charlotte Watts, who works on the epidemiology of HIV at the London School of Hygiene and Tropical Medicine. Her team has calculated that even a microbicide that was 60% effective could prevent 2.5 million infections worldwide over a three-year period[8]. As well as the obvious health benefits, this could translate into substantial savings for overstretched economies, recouping US$2.7 billion in healthcare costs and productivity over the same time period.

There could be other benefits too. Condoms provide a high level of HIV protection, but also prevent conception. If gels could be identified that were non-spermicidal, they could offer protection to women who want to conceive but protect themselves from HIV. Microbicides may also help to safeguard against other sexually transmitted infections, such as chlamydia, herpes simplex and syphilis. In turn, this could provide another layer of protection against HIV. Syphilis may cause ulcers inside the vagina, which make it easier for HIV to enter its target cells.

Any HIV-related trial also leaves behind a legacy of improved health education and changed behaviour. Rees's team has recently completed a feasibility study in which 1,000 South African women received healthcare and counselling on HIV and microbicides, but no cream. A year later, condom use had increased.

But hurdles remain, including the need to find microbicide formulations that will be culturally acceptable. In some parts of Africa, such as Zambia, creams may be shunned because vaginal moisture is perceived as a sign of witchcraft. The ideal product would

Bearing the brunt: young women in sub-Saharan Africa face a high risk of becoming HIV positive. Fieldworkers do their best to increase awareness (below) but cash shortfalls hamper progress.

F. HERHOLDT/MDP

be tasteless, odourless and undetectable to both partners. It should be easy to store and apply, and the applicator — similar to those used for tampons — should be discreet and disposable. Various formulations are in the pipeline. Researchers are testing gels, creams, pessaries and even a silicon-based vaginal ring that could be worn inconspicuously for many months and would slowly release its microbicide. This would free women from the hassle of having to apply a cream or gel each time before sex.

What	Dextrin sulphate and PRO 2000	BufferGel and PRO 2000	Carraguard	Cellulose sulphate	Cellulose sulphate	Saavy
How it works	Both products prevent HIV binding to host cells	BufferGel alters vaginal pH, inactivating HIV	Prevents HIV binding to host cells	Prevents HIV binding to host cells	Prevents HIV binding to host cells	Detergent, destroys HIV directly
Where	South Africa, Zambia, Tanzania, Uganda, Cameroon	India, Malawi, South Africa, Tanzania, Zambia, Zimbabwe, US	South Africa	Benin, Burkina Faso, Kenya, India, Uganda, South Africa	Nigeria	Ghana, Nigeria
Number of participants	12,000	3,100	6,300	2,500	2,200	4,600
Start date	Mid 2004	Late 2004	Late 2004	Late 2004	Late 2004	Early 2004
Expected finish date	2007	2007	2007	2007	2006	2006

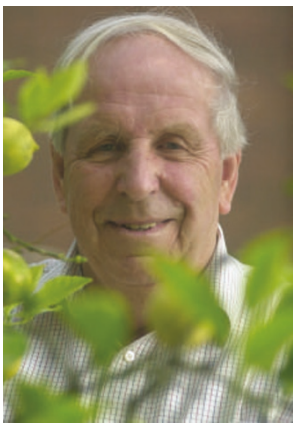
Trials and tribulations

Recruiting thousands of women into microbicide trials is far from trivial. In South Africa, organizers of the British-backed trial are using radio to get the message out. Mthoko Zisi, an HIV/AIDS counsellor for the project, gives talks on local stations to raise awareness. "We've already heard from a range of women who want to get involved," he says. These include rural villagers and city dwellers, some with their partner's support, some without. In turn, these women are being encouraged to talk to their friends in the hope of getting them involved. In Zambia, workers and families on a large sugar estate are being recruited. In Cameroon, prostitutes are being targeted.

At least today, microbicide research is receiving relatively generous funding, after years of being the poor relative of vaccine studies. Over the past six years, the US government has quadrupled its microbicide expenditure and will spend a further $88 million this year. Worldwide, public- and private-sector spending on microbicides totalled $530 million over the same period. "But it's not enough," says Polly Harrison, director of the Alliance for Microbicide Development, an advocacy group based in Silver Spring, Maryland. It costs about $35 million to develop and test a single microbicide. And as new microbicides are developed and more clinical trials are planned, the coffers will need to be topped up.

The next generation of microbicides is already in development. More than 40 compounds are being tested in culture and animal models. It is already known that viral surface proteins, such as gp120, bind to the key receptors on host cells, triggering a wide range of cellular and molecular changes. So researchers are designing strategies that interfere with specific parts of this process. "We know what the targets of HIV are," says Robin Shattock, who works on microbicide development at St George's Hospital Medical School in London. "So we're moving to a phase of rational drug design based on this."

Another possibility is to develop gels containing existing drugs that are used to treat HIV infection. One such drug is tenofovir, which blocks the enzyme reverse transcriptase that is used to copy HIV's genetic material. Researchers hope that a gel containing tenofovir will last longer than those based on dextrin sulphate or PRO 2000 — it might need applying only once or twice per week, rather than every time before sex.



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Roger Short: believes citrus fruit may offer a cheap and convenient barrier to HIV infection.

When a product finally does make it to the market, it will have to be affordable. Dextrin sulphate and PRO 2000 are simple sugar polymers, whose manufacture should be cheap and easy to scale up. The World Bank may subsidize distribution costs, and the US Agency for International Development will help to negotiate low public-sector prices.

Even so, affordability is still a worry, says Rees. The female condom protects against HIV and costs about 70 cents. "But it's not controlling the epidemic because it's too expensive," she says. With 3 billion people living on less than $2 a day, microbicides will have to be a lot cheaper if they are to be effective.

Fruitful enquiry

Given these concerns, and the fact that the commercial microbicides won't be available until 2010 at the earliest, reproductive biologist Roger Short of the University of Melbourne, Australia, is looking for a cheaper, more readily available alternative. He thinks that the answer may grow on trees.

In a paper to be presented at next week's XV International AIDS Conference in Bangkok, Thailand, Short and his colleagues will report that a 20% solution of lemon juice takes just two minutes to achieve 90% inactivation of HIV in lab culture.

Historically, citrus fruit juices have been used as contraceptives. About 300 years ago, Mediterranean women used lemon juice in the vagina to help prevent pregnancy. Today, Nigerian prostitutes douche with dilute lemon juice in the hope that it will protect them against sexually transmitted diseases.

Short points out that in South Africa, five lemons can be bought for the price of one condom. And the juice of just one fruit goes a long way. A single lemon yields enough juice for ten sexual acts, and can be kept at room temperature for up to a month.

As long as the vagina is free of lesions, using lemon juice is virtually painless. It could also be applied to the foreskin after sex to help protect men from HIV infection. And because it's natural, it can't be patented. But the flipside is that with no profit motive for drug companies, funding for clinical trials is hard to come by.

Nevertheless, the Thai government recently agreed to launch an initial clinical study. Because limes — *manao* in Thai — grow widely in southeast Asia, the *manao* trial will focus on limes rather than lemons. The study, which should begin shortly, will assess the acceptability, safety and efficacy of lime juice against pregnancy and sexually transmitted infections, including HIV. "We've been looking for the microbicidal Cadillac," claims Short, "when all along we've been overlooking the humble push bike."

Whether the answer lies with Short's low-tech approach, gels such as dextrin sulphate, or advanced rational drug design won't be known until the results from clinical trials are in. But with no sign of an effective AIDS vaccine on the horizon, microbicides may offer the best hope for millions of African young women of avoiding Martha's fate. ■

Helen Pilcher works in *Nature*'s online news team.

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