



## Spotlight

### Capping infection

*Can the diaphragm help lower women's risk of HIV infection?*

On a recent afternoon at a health clinic in Epworth, a densely-populated suburb of Harare, Zimbabwe, a dozen or so women arrived for their final visit of a year-long study to see if a small, round disc of latex known as a diaphragm can protect them from sexually contracting HIV. Researchers from the University of California at San Francisco (UCSF), University of Zimbabwe, and Ibis Reproductive Health have enrolled 2503 women aged 19-49 for a randomized, controlled trial. If the diaphragm is found effective the researchers hope that this old-fashioned birth control method could soon make a comeback as a woman-controlled HIV prevention method.

"Biologically, it's very plausible that it will work," says Nancy Padian, a researcher at UCSF and principal investigator of the study. Contraceptive diaphragms are designed to cover a woman's cervix, the lower opening of the uterus, and prevent access to the upper genital tract. Both of these sites, the cervix and the uterus, are thought to be important target tissues for the sexual transmission of HIV.

One reason for this is that the tissues of the cervix are much thinner than those that line the vagina. Observational studies suggest that other sexually-transmitted pathogens, including those causing gonorrhea and chlamydia, preferen-

tially infect cervical as opposed to vaginal cells. Diaphragms have been shown to prevent the transmission of some sexually-transmitted infections (STIs), when used along with contraceptive spermicidal gels. The cervix also contains some of the same target cells for HIV that are found within the foreskin of the penis; a recent prospective study in South Africa showed that male circumcision, which involves removing the foreskin, may significantly reduce a man's chances of acquiring HIV.

Together, these findings suggest that shielding the cervix with a diaphragm might lower the risk of a woman contracting the virus. It is unlikely that this simple female-controlled device will offer complete protection since other studies have shown that even women who have undergone hysterectomies (where the cervix and uterus are removed) can still become HIV infected. But even if diaphragms offer only partial protection against HIV, Padian is hopeful that they can have a powerful effect on the epidemic. "None of the methods we are looking at are 100% effective," she says. "Even though it's not perfect, it's better than nothing, especially when women can't negotiate male condom use."

#### Current methods fall short

With effective AIDS vaccines and microbicides still years away from practical use, male and female condoms remain the most reliable method for HIV prevention. Yet condom use remains extremely low. Female condoms, comparable in efficacy to the male condom in preventing STIs other than HIV and on the market for more than a decade, have been

inadequately supplied and adopted—in 2005, only 14 million female condoms were available worldwide, compared with 6 to 9 billion male condoms.

Male circumcision is showing some promise in trials as a way for men to reduce their risk of HIV infection. But female-initiated HIV prevention methods are still urgently needed. Young married women are the fastest-growing group of new HIV infections in many countries and they often have difficulty negotiating condom use. The diaphragm, which can be inserted by a woman and used without her partner's knowledge, is also already an approved device. If the current ongoing Bill & Melinda Gates Foundation-funded trials in Zimbabwe and in Durban and Johannesburg, South Africa show that the diaphragm is effective at protecting women against HIV infection, the approach could be implemented nearly immediately. This makes it particularly attractive to prevention researchers.

Diaphragm use as a birth-control method has mostly fallen out of favor in countries like the US where oral hormonal contraceptives are affordable and widely available, and researchers wondered if this device would be accepted by women as an HIV prevention method in developing countries. So before starting the HIV prevention studies Padian launched a six-month diaphragm acceptability study in Zimbabwe. She found that nearly all of

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the 186 participants reported trying the diaphragm during the study period.

In the ongoing diaphragm trials in Zimbabwe and South Africa, women are randomized into two groups or arms; both are given condoms and HIV education but only one group receives the diaphragm. At the conclusion of the trial all women are offered a diaphragm. "Most women are accepting it," says Project Director Agnes Chidanyika. "They look forward to using it, especially those in the condom arm who haven't used it."

In the Zimbabwe study Chidanyika says the diaphragms were acceptable among the male partners of most women, who were happy to let their female partners use a potential HIV prevention method that their partners were responsible for and they could not feel. However, this sentiment was not universal, she says. "The problem we did have with some women is the partner would say if she can use it without me knowing, then she can be unfaithful."

### **A look to the future**

At the Epworth study site, women arriving for their quarterly visit fill out computer surveys and meet with counselors and clinicians. In a counseling room at the clinic, a young woman in the diaphragm arm of the study demonstrated its use on a plastic pelvic model. She grasped the latex, cup-shaped diaphragm by its firm, springy lip, squeezed it in half, and inserted it easily into the model. This young woman said she found her own diaphragm comfortable and had used it throughout the study period except when she tried to get pregnant. As with all barrier methods, the importance of child-bearing in many societies may be an obstacle to widespread adoption of the diaphragm as an HIV prevention method.

Completing this large study in Zimbabwe has taken an immense commitment from both the study volunteers and the research staff. The country is currently experiencing epic inflation and unemployment. The Epworth study site sits just a few feet away from the rubble of countless shanties destroyed by order of the Zimbabwean government in the summer of 2005 in a campaign called Operation Murambatsvina or "Drive out Trash." According to a UN-Habitat study, an estimated 700,000 people lost their homes or businesses in

the campaign. Over a quarter of the trial participants in Zimbabwe were displaced by Operation Murambatsvina.

Yet researchers managed to retain a stunning 99% of the participants by visiting homes, villages, and displaced persons camps, reaching out to alternative contacts, and launching a radio and poster campaign. Chidanyika says the high retention rate also reflects the enthusiasm of the diaphragm study participants. "The participants themselves, they were very interested in participating in the study and coming back," she says.

Results from the study across sites in Zimbabwe and South Africa are not expected until 2007 but if diaphragms prove effective at lowering HIV transmission then those wishing to promote wide-scale adoption of the method will need to contend with several difficulties. The major fear is that diaphragms could potentially lead to lower condom usage. "I don't think anyone thinks diaphragms will be more effective than condoms," acknowledges Padian, "but we're doing the study in the situation where many women cannot use condoms." There is also a fear that behavioral disinhibition will encourage women to engage in riskier behavior because they wrongly believe they can stop worrying about contracting HIV if they are using a diaphragm.

Perhaps the most serious obstacle to future use of diaphragms is the possibility that they will be less acceptable in real settings than they are in the research environment. Over-optimism about the prospects of the female condom, another woman-controlled contraceptive and HIV prevention method, is a cautionary case. While evidence suggests that the female condom is effective and easy to use, it has taken a long time to increase its uptake. But the diaphragm does offer an economic advantage over the female condom; a single diaphragm, though initially more expensive than a female condom, may be used for several years.

The main problem with traditional diaphragms is the cumbersome way they are fitted. Standard diaphragms come in nine different sizes and women must be properly fitted before they can begin using one. In Padian's ongoing study all women start with one size of diaphragm and then try other sizes as necessary

after an examination. Even this simpler method, however, requires a visit to a health clinic, a potentially costly prospect if implemented broadly in developing countries. It may also make women vulnerable to stigma.

This limitation has led developers to pioneer alternate forms of cervical barriers. Maggie Kilbourne-Brook, program officer with the Program for Appropriate Technology in Health (PATH), says a one-size-fits-all device would be a major improvement. Researchers have also identified several other modifications that would make diaphragms much more acceptable. "What we need to be able to achieve is to make a device that is easier to insert and remove than standard products, and easier to use and learn to use than the currently available product," says Kilbourne-Brook. "It needs to be comfortable for both partners."

The PATH researchers used this information to develop an improved diaphragm, known as SILCS, which is a single-sized silicone diaphragm that fits most women. The researchers expect to begin testing the product for contraceptive effectiveness in late 2006.

A number of other cervical barriers are also in the process of being developed and approved. The single-sized Lea's Shield is a silicone cervical barrier contraceptive already approved by the US Food and Drug Administration for up to 48 hours of continuous use. Another product being tested, the BufferGel Duet, is a disposable, one-size diaphragm pre-filled with the candidate microbicide and contraceptive BufferGel.

Indeed, if both microbicides and diaphragms prove to be partially effective at preventing HIV transmission then combining them could well offer higher protection. "We're interested in evaluating whether the use of a physical barrier like a diaphragm could advance the effectiveness of a microbicide," says Sharon Hillier, a microbicides researcher at the University of Pennsylvania. If the ongoing study indicates that traditional diaphragms are protective against HIV transmission, Padian believes there will be ways to extend the results to the new forms of cervical barriers that are being developed without doing large, time-consuming, and costly trials to prove their efficacy. "We'll be able to generalize somewhat," she says.

## Global News

### IAVI opens southern Africa regional office

IAVI recently launched a new program in Johannesburg, South Africa, to support expanding AIDS vaccine research, development, and advocacy efforts for southern Africa. The global public-private partnership already operates several regional offices worldwide in Nairobi, Kenya; New Delhi, India; Amsterdam, the Netherlands; and New York City where the headquarters is located. The Johannesburg offices will provide an opportunity for IAVI to work closely with existing partners and programs in southern Africa, including the South African AIDS Vaccine Initiative (SAVI), the Medical Research Council (MRC), the Desmond Tutu HIV

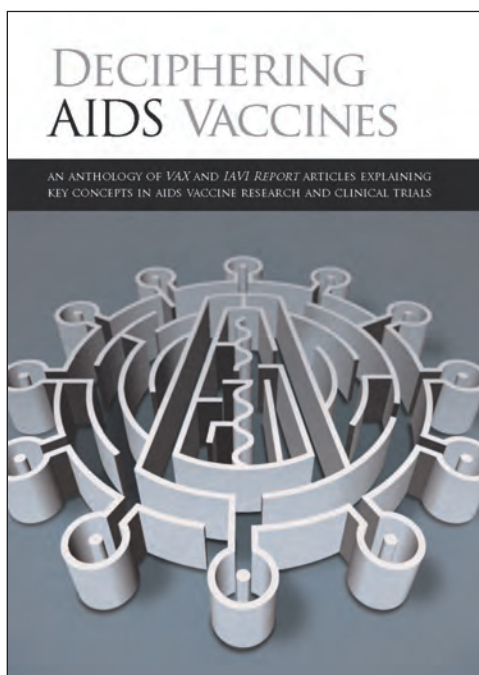
Foundation in Cape Town, the Zambia-Emory HIV Research Project, the Medical University of South Africa, the University of Limpopo, and the Perinatal HIV Research Unit at the University of Witwatersrand.

In an editorial published in South Africa's *Business Day*, Chief Executive Officer of IAVI Seth Berkley said that the new regional office will serve as a focal point for expanding AIDS vaccine programs and activities in southern Africa and will take advantage of the region's "growing biomedical capabilities, strong regulatory systems and manufacturing base" to build capacity to conduct clinical trials to the highest standards.

South Africa is already hosting several HIV prevention studies, including a large Phase III microbicide trial and multiple AIDS vaccine trials. Last year IAVI initiated a Phase II AIDS vaccine trial there and in Zambia with several

partner organizations to evaluate the safety and immunogenicity of an adeno-associated virus vaccine candidate known as tgAAC09 that is based on clade C HIV, which is the primary subtype of the virus circulating in the region (see [www.iavireport.org/trialsdb/](http://www.iavireport.org/trialsdb/) for more information). The Vaccine Research Center at the US National Institutes of Health, in collaboration with the HIV Vaccine Trials Network (HVTN), is also conducting a Phase II trial in South Africa with their DNA and adenovirus serotype-5 vaccine candidates. Merck and the HVTN will begin a Phase IIb AIDS vaccine trial there later this year with their lead adenovirus-based AIDS vaccine candidate.

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#### Editor

Simon Noble, PhD

#### Science Writer

Kristen Jill Kresge

#### Production Manager

Nicole Sender

All articles written by Kristen Jill Kresge.

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## How can researchers identify the correlates of protection for an AIDS vaccine?

An effective, preventive vaccine works by training the immune system to recognize and then eliminate a specific pathogen (either a virus or a bacterium) that a person may be exposed to in the future. So for a vaccine to work it must induce pathogen-specific immune responses—either antibodies, cellular (CD4<sup>+</sup> or CD8<sup>+</sup> T cell) responses, or other natural immune responses—that are capable of blocking a pathogen. Typically a subset of the immune responses induced by vaccination is what is actually required for a person to be protected against an infection. Researchers refer to these specific immune responses as the immune correlates of protection since without these particular responses a person is still susceptible to infection.

Determining the precise correlates of protection for a certain pathogen is difficult. For some viruses a single type of antibody is enough to protect someone against future infection, but often it is a combination of immune responses. Identifying this exact combination of antibody and/or quality of cellular response that confers protection can be like finding a needle in a haystack.

This is especially true for HIV. Since the virus actually attacks the immune system itself, it is more complicated for researchers to tease out the HIV-specific immune responses in infected individuals. It is still unclear what immune responses are necessary to protect against infection with HIV, but researchers are using several different human and animal models to try to determine the correlates of protection and to use this information to design a preventive AIDS vaccine.

### Problematic for HIV

For most infectious diseases the simplest way to identify the immune correlates of protection is to study someone who has recovered from a natural infection because their immune system was able to defeat the pathogen. Although this is an imperfect model—it is likely that the immune responses necessary to prevent infection will not be exactly the same as those pres-

ent after a person has cleared an infection—it can still provide researchers with invaluable guidance on the types of immune responses that a vaccine should induce. This information could help them design a vaccine to mimic these responses. Unfortunately this is not possible for an AIDS vaccine because there is not a single documented case of a person who was able to clear an established HIV infection.

Another way to identify the immune correlates of protection is to already have an effective vaccine. Historically when researchers set out to develop vaccines against pathogens, they haven't known exactly what types of immune responses would be protective and so have experimented by trial and error, sometimes called the empirical approach. Researchers typically constructed vaccines using either a killed version of the specific virus or bacteria or a live, but attenuated, version that would cause at most a mild infection in humans. Often this approach induced robust immune responses specific to the pathogen that could protect against infection for many years after immunization. Researchers could then closely study these immune responses to identify exactly which ones were necessary for protection. However using a live-attenuated or whole-killed vaccine for HIV is not possible because of safety concerns. Researchers fear that the virus could mutate and become virulent.

Sometimes the correlates of protection are difficult to identify even with an effective vaccine. Two recently developed vaccines for rotavirus and human papillomavirus are highly effective but the precise immune responses that confer protection are still unknown (see *VAX* July and February 2006 *Spotlight* articles, *Vaccines enter battle against intestinal virus* and *Cervical cancer vaccines*). But in the absence of an effective AIDS vaccine, researchers often talk about the correlates of protection as an important way to guide them in the design of improved candidates.

### Models to study correlates of protection

Researchers have identified individuals who remain uninfected by HIV despite repeat exposure to the virus.

These individuals, known as exposed seronegatives (ESNs), may hold important clues. For several years researchers have been studying groups of sex workers in Kenya and the Gambia who are considered ESNs to try to identify just what makes them able to fend off HIV infection. There are several possible reasons for their apparent resistance to HIV infection, including the properties of the virus they are exposed to, their own genetic makeup, or that they are generating immune responses that are able to keep HIV at bay. If researchers can identify the HIV-specific immune responses in these individuals they can then use this information to design AIDS vaccine candidates.

Another group of individuals that could provide important clues are long-term nonprogressors (see *VAX* September 2006 *Primer* on *Understanding Long-term Nonprogressors*). These are HIV-infected individuals who are successfully controlling their infection without antiretrovirals, and the types of immune responses that they generate may also be informative to researchers developing preventive vaccines.

Also, if a vaccine candidate shows any efficacy in a Phase III trial it will likely give researchers an idea about the immune responses necessary for protection against HIV infection and could help them develop improved candidates that will be even more effective. Designing a Phase III vaccine trial to try to determine both the vaccine's efficacy and the correlates of immunity, however, may require an even larger number of volunteers as well as more sophisticated laboratory tests. This will make these already expensive and time-consuming trials even more complex.

AIDS vaccine researchers are also using animal models to try to identify the correlates of protection (see next month's *VAX Primer*). Researchers are hopeful that studying the correlates of protection in non-human primates, as well as in humans, will provide even more information that can aid the development of an effective vaccine.