March 2008 • Vol.6 • No.3

VAX

AIDS VACCINE BULLETIN • WWW.IAVIREPORT.ORG

## Spotlight

# When it rains… it pours

*A flurry of results from clinical trials of new HIV prevention strategies headline recent conferences*

Following on the heels of the STEP trial, which showed that Merck's AIDS vaccine candidate (widely considered the most promising in clinical trials) was not effective, several other trials of novel HIV prevention methods have culminated. Unfortunately, many also ended with disappointing results.

The final data from two of these trials—one testing the effect of adult male circumcision on HIV transmission to women and another testing whether or not treatment of herpes simplex virus (HSV)-2, a common sexually-transmitted infection that causes genital warts, could reduce the risk of HIV infection—were presented at this year's Conference on Retroviruses and Opportunistic Infections (CROI), held in Boston from February 3-6. Additionally, results from another circumcision study, which looked at the protective effect circumcision may offer against HSV-2 infection, were also presented.

Soon after, final results from the Phase III efficacy trial of a candidate microbicide gel known as Carraguard were released just prior to the opening of the Microbicides 2008 Meeting, which took place from February 24-27, in New Delhi, India. During the biannual conference, several updates on other trials and candidates were presented.

## Extended benefits of circumcision

In heterosexual men, the protective effect of circumcision against HIV infection has been firmly established by three randomized, controlled clinical trials, showing that surgical removal of the foreskin reduces the risk of HIV acquisition by approximately 60% (see *VAX* January 2008 *Global News*). Additional studies presented at CROI looked at the effect of male circumcision on the acquisition of HSV-2, which is thought to increase the risk of HIV infection, and on transmission of HIV from infected men to their female partners.

Aaron Tobian of Johns Hopkins University reported results from a randomized trial conducted in Rakai, Uganda that enrolled over 3,500 uncircumcised men who were not infected with HIV or HSV-2. Half of them were randomly assigned to immediate circumcision, while the other half were offered circumcision at the conclusion of the trial. After two years, researchers observed that the risk of HSV-2 infection was reduced by almost 25% in circumcised men. "This might be part of the reason male circumcision decreases HIV acquisition," says Tobian. Several observational studies have supported the role of HSV-2 infection in aiding HIV transmission (see *VAX* November 2005 *Spotlight* article, *HIV prevention in a pill?*). Infection with HSV-2 causes inflammation or, even worse, ulceration at the genitals, which is believed to make it easier for HIV to establish an infection.

While all of the male circumcision studies done so far were in HIV-uninfected men, Maria Wawer of Johns Hopkins University says that knowing the effects of circumcision in HIV-infected men is also important. After all the news about circumcision's protective effects, Wawer says that in some communities, being uncircumcised may stigmatize men as being HIV infected. To avoid this, some HIV-infected men may seek circumcision.

This led Wawer and her colleagues to conduct another randomized trial in Rakai, Uganda that enrolled discordant couples—HIV-infected men with uninfected female partners. This allowed researchers to study both the safety and benefits of circumcision in HIV-infected men, as well as how circumcision impacts HIV transmission rates to female sexual partners. In this trial, 93 couples were enrolled in the intervention group, in which the male received immediate circumcision, and 68 couples were enrolled in the control group. Men in this second group were offered circumcision after the trial was complete.

After two years, researchers found that circumcision did offer some benefit to HIV-infected men—rates of genital ulcers were reduced by about 50% in circumcised trial participants compared to men in the control group. But circumcision had no effect on HIV transmission rates to the female partners of HIV-infected, circumcised participants. That result was "unexpected and disappointing," Wawer says. "In previous observational data we had seen lower HIV rates in women married to HIV-positive circumcised men compared with HIV-positive uncircumcised men."

Researchers suggest that one reason the female partners were not protected from HIV was because the couples resumed sex too soon after surgery. "If the males resume intercourse early after

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circumcision, before the wound is fully healed, there might be increased transmission," says Wawer. Among 18 couples who reported resuming sex before the wound healed completely, 27% of the female partners were infected with HIV in the first six months of the study, compared to only 9.5% of female partners who became HIV infected after waiting to resume sexual activity. Wawer says it is very important that people not resume sex in the early postoperative period, even if they are not HIV infected. "In our trial of negative men the protective effects of circumcision became significant and apparent only after the six-month follow-up period," she adds, referring to an earlier trial of male circumcision.

But even if circumcision does not offer a direct protective benefit to women, there are still benefits on the population level—if fewer men are HIV infected, overall infection rates in women will also be lower.

## Stopping HSV doesn't stop HIV

More news on the HIV prevention front came from Connie Celum of the University of Washington in Seattle, who reported the results at CROI of a randomized clinical trial (HPTN 039) assessing whether or not administering an antiviral drug used to treat HSV-2 infection would decrease risk of HIV infection.

The trial enrolled 3,277 volunteers who were infected with HSV-2 but not HIV. Volunteers included men who have sex with men in the US and Peru, and heterosexual women at sites in Zimbabwe, Zambia, and South Africa. All participants randomly assigned to the intervention group received a twice-daily dose of an antiviral drug known as acyclovir that suppresses HSV-2. Volunteers in the control group received an inactive placebo. After 18 months, there was no difference in the number of new HIV infections between the two groups.

This came as a surprise to researchers. "Many people thought this would be a slam dunk," says Celum. Although this was the first randomized, controlled trial to be conducted, several studies have suggested that HSV-2 infection increases susceptibility to HIV by two to three times, and therefore suppressing HSV-2 should have lowered the chance that volunteers would become HIV infected. The incidence of genital ulcers was reduced by 37% among volunteers who received acyclovir, but even this was much lower than what was observed in previous studies.

For now, it is still unclear why this trial led to such unanticipated results. "Why didn't we have an effect on HIV at all?" Celum asks. She thinks it is unlikely that HSV-2 is not a risk factor for HIV, given the mounds of observed data that suggest otherwise, and instead suggests that adherence may be one factor that could have influenced the results. Volunteers in the study reported high levels of adherence—taking the medication as prescribed—but Celum said it could have been overestimated since it was all based on self-reported behavior. The less-than-expected reduction in occurrence of genital ulcers also varied geographically, suggesting biological reasons may also account for why researchers did not see any effect on HIV infection rates, says Celum. For example, there may be differences in how the drug was metabolized or in how susceptible HSV-2 was to the drug, based on the background characteristics of the population in which it was tested.

> ***Many people thought this would be a slam dunk.***
>
> **Connie Celum**

## Microbicide results aren't gelling

In February, the Population Council announced the results of a Phase III trial of Carraguard, a microbicide gel containing the compound carrageenan, which is a seaweed derivative used as a stabilizer and thickening agent in food and cosmetics. This randomized, double-blind, placebo-controlled trial was conducted at three sites in South Africa and involved 6,202 women between the ages of 16 and 72. Last year a Phase III trial with another candidate, known as cellulose sulfate, was terminated early by the trial's data safety monitoring board (DSMB) because a higher number of HIV infections occurred among microbicide recipients than in those receiving a placebo gel (see *VAX* June 2007 *Primer* on *Understanding Data Safety Monitoring Boards*).

Data collected in the Carraguard trial showed that 134 individuals who received the microbicide candidate became HIV infected, compared to 151 individuals who received an inactive placebo gel. The difference was not deemed statistically significant and researchers concluded that Carraguard was not effective at protecting women from HIV (see *VAX* February 2008 *Primer* on *Understanding Biostatistics and the STEP Trial*).

## Measuring usage

Similarly to the HSV suppression study, a critical aspect of the Carraguard trial was women's adherence to the product being tested. Women were counseled to apply the microbicide before every sex act, and although the self-reported adherence rates were 96%, researchers estimate that the actual adherence was much lower. To measure adherence to the gel, researchers collected behavioral information directly from participants and also conducted an applicator test. All applicators used to apply the gel were treated with a compound that, when subjected later to a stain, would change colors if it had been exposed to vaginal mucous. The results of these tests showed women used the gel in only 44% of sex acts, and only 10% of women were estimated to have used it during every sex act.

An applicator test is one method researchers are using to better estimate adherence, but even this approach is complicated. Barbara Friedland of the Population Council says it was difficult to determine the effectiveness of the applicator test. "All we can tell is whether the applicator was inserted in the vagina or not," she says. "We don't know when in relation to the sex act the applicator was inserted into the vagina."

"It's possible that low levels of adherence in the trial were responsible for why the product didn't show an effect," Friedland notes. "It's also possible that there was a biological reason—it worked in the lab but it didn't have the same effect in humans." Researchers conducted tests of the microbicide in human cell cultures but did not conduct preclinical studies in nonhuman primates with the monkey equivalent of HIV, known as simian immunodeficiency virus (SIV), to gauge the efficacy of the product. Prior

to initiating the Phase III trial, the Population Council conducted two Phase II safety studies of Carraguard in South Africa and Thailand, involving a total of 565 HIV-uninfected women.

Additional research was also presented at both CROI and Microbicides 2008 on the previously-halted cellulose sulfate microbicide trial conducted by CONRAD, a US-based reproductive health organization. After the trial was stopped by the DSMB, researchers tried to find out if the microbicide gel was in any way enhancing the risk of HIV infection. Researchers from Albert Einstein College of Medicine in New York conducted laboratory studies with the candidate microbicide in vaginal tissues. They found that cellulose sulfate disrupts the proteins that help form tight junctions between the cells that comprise the vaginal tissue layers, which are the first line of defense against HIV. This disruption makes it easier for HIV to cross the mucosal barrier (see *VAX* January 2008 *Primer* on *Understanding HIV Transmission*). These findings provide a possible explanation for how cellulose sulfate may have increased women's vulnerability to HIV, and the researchers argue that this type of laboratory study should be conducted for all future microbicide candidates.

Together these results offer some sobering news for the HIV prevention field, but at the same time researchers also reported great progress in understanding basic scientific questions that open potential avenues of exploration for both HIV prevention and treatment.

## Global News

### Addressing the challenges of HIV prevention trials

The prestigious US Institute of Medicine (IOM), an independent advisory group on public health policy, convened a series of meetings last year on the methodological challenges of conducting non-vaccine HIV prevention trials. The final report based on these proceedings, as well as site visits by IOM committee members to clinical trial sites in Uganda and South Africa, was just issued in February (www.nap.edu/catalog/12056.html).

These meetings and the final report were commissioned by the Bill & Melinda Gates Foundation. The foundation requested that the IOM committee focus in particular on research involving microbicides and pre-exposure prophylaxis (PrEP; see *VAX* May 2006 *Spotlight* article, *Treatment as prevention*), and provide recommendations on how future trials could be conducted in a way that could increase the likelihood of success and enable donors to optimally invest their limited financial resources.

At the public meetings, committee members and leading researchers in the field discussed several of the most-pressing issues surrounding the design and conduct of large-scale HIV prevention trials (see *Advisory Panel considers complexities of HIV prevention trials*, *IAVI Report*, January-February 2007 and *Optimizing HIV prevention research*, *IAVI Report*, March-April 2007).

The final report outlines the recent spate of late-stage clinical trials in the HIV prevention field that have failed to provide any benefit in reducing the risk of HIV infection (see *Spotlight*, this issue), leading the authors to conclude that, "A near-perfect biomedical intervention for preventing HIV infection is unlikely to be available in the near future."

The importance of accurately estimating HIV incidence is among the main issues highlighted in the report. This became a concern when multiple prevention trials were stopped early because the HIV incidence observed during the trial was lower than initial estimates on which the trial was based (see *VAX* July 2007 *Primer* on *Understanding HIV Incidence*). The IOM committee recommends that all late-stage trials be designed based on incidence estimates collected through traditional cohort follow-up studies of HIV-uninfected individuals in the communities where the trial will occur. The authors also suggest that this estimate should be corroborated by at least one other source.

High pregnancy rates during HIV prevention trials, and the impact on retention of female volunteers, was another critical issue that was discussed at the committee meetings and is addressed in the report (see *Primer*, this issue). Female volunteers are typically not allowed to receive the experimental intervention during pregnancy because of potential safety risks to the fetus. But their exclusion from the trial can confound the results. On this issue, the authors suggest that researchers should try to determine the safety of the intervention in pregnant women to determine circumstances where women could potentially continue to participate in HIV prevention trials while pregnant.

The report also outlines several other ways that trials can be designed to more efficiently determine the influence of behavior and adherence on the final results.


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*VAX* is a monthly bulletin from *IAVI Report*, the publication on AIDS vaccine research published by the International AIDS Vaccine Initiative (IAVI). It is currently available in English, French, German, Spanish, and Portuguese as a downloadable pdf file (www.iavireport.org) or an e-mail bulletin.

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# Understanding the Recruitment and Retention of Women in Clinical Trials

## What are some of the considerations regarding recruitment and retention of women in AIDS vaccine clinical trials?

To determine the safety and efficacy of an AIDS vaccine candidate, it must be tested in populations that are most affected by the disease. This requires conducting AIDS vaccine clinical trials in developing countries in which there are the highest HIV infection rates.

It is also imperative that a vaccine candidate be tested in individuals and populations that would eventually benefit the most from a preventive AIDS vaccine. This includes groups that are at high risk of HIV infection, either through sexual contact or through blood-to-blood transmission, which occurs in injection-drug users. In many countries, women are at increasingly high risk of HIV infection. According to the latest report from the Joint United Nations Programme on HIV/AIDS (UNAIDS), released in November 2007, 68% of the world's HIV-infected individuals live in sub-Saharan Africa and the majority of them are women. It is therefore critical that AIDS vaccine candidates are evaluated in HIV-uninfected female volunteers.

### Reaching the target

Specific targets are often set for the number of women that will be enrolled in an AIDS vaccine clinical trial. If the percentage of women participating is too low, researchers may be unable to draw conclusions about the safety or efficacy of the vaccine candidate in women.

During an efficacy or preliminary efficacy trial, such as a Phase IIb test-of-concept trial, it is also important that the women are at risk of HIV infection (see *VAX* July 2007 *Primer* on *Understanding HIV Incidence*). This issue was highlighted in the recently-conducted STEP trial, testing Merck's AIDS vaccine candidate (see *VAX* October-November 2007 *Spotlight* article, *A STEP back?*). The majority of volunteers enrolled at sites in North and South America, Australia, and the Caribbean were men who have sex with men. One-third of the participants were women, but during the course of the trial only a single HIV infection occurred in a female volunteer. As a result, all of the women were excluded from the final data analysis. For the Phambili trial, a companion study to the STEP trial that was conducted in South Africa, investigators planned to enroll mostly women, but this study was stopped early by the trial's data safety monitoring board based on the results of the STEP trial.

### Recruiting women

Recruiting women for AIDS vaccine trials can be challenging. In some places it is difficult for women to participate because they are the sole caregivers for their families and are therefore unable to make regular trial site visits. To make it easier for women to participate, some clinical trial sites offer supervised child-care services and encourage women to bring their children along on clinic visits.

In other situations women are hesitant to participate without the permission of their husbands or male partners. One strategy used to encourage participation in this case is to offer couples voluntary counseling and testing for HIV (see *VAX* October 2005 *Primer* on *Understanding Couples Voluntary Counseling and Testing*). At many clinical trial sites where couples cohorts are established, researchers have been able to recruit higher numbers of HIV-uninfected female volunteers for AIDS vaccine trials.

### Pregnancy and participation

Women may also be unwilling to participate in a trial if they wish to become pregnant. Pregnant women are not allowed to enroll in AIDS vaccine clinical trials because of safety concerns regarding the effect of the product on the woman or the fetus. If a woman becomes pregnant during the course of an AIDS vaccine trial, she is not allowed to receive further vaccinations. Women who become pregnant during an AIDS vaccine trial, as well as their babies, are usually followed beyond the end of the trial to monitor any potential adverse effects of the vaccine. During microbicide or pre-exposure prophylaxis trials—where antiretrovirals are administered to women to try to prevent HIV infection—women must discontinue use of the product for the duration of their pregnancy.

In all HIV prevention trials, women are counseled to use some form of contraception to prevent pregnancy. Some trials require that women use hormonal contraception, either oral or injectable, in addition to a barrier method such as condoms to prevent pregnancy. But this is somewhat controversial—some studies have suggested that hormonal contraceptives can increase a woman's risk of HIV infection. However, this association has not been proven. Whether or not hormonal contraception is required, female volunteers are usually offered it free of charge. These services, however, are not always provided at the clinical trial sites. Instead women are given a referral to a clinic in the area that provides hormonal contraception.

Despite efforts to provide access to contraceptives, pregnancy rates during some HIV prevention trials have been quite high. All women are tested for HIV infection before enrollment and researchers speculate that women who find out they are not infected may choose that time to become pregnant. In a microbicide trial conducted in Nigeria, 7% of women who were screened for participation in the trial were already pregnant, and during the trial 30% of the participants became pregnant. In a trial testing pre-exposure prophylaxis, the total pregnancy rate at all sites in Cameroon, Nigeria, and Ghana was 56% during the trial. If such a high percentage of women are excluded from the trial for an extended period of time, the trial can lose its statistical power. This limits the ability of investigators to interpret the data and draw conclusions about the safety and efficacy of the intervention being tested.