

AIDS RESEARCH

Promising Prevention Interventions Perform Poorly in Trials

Adding to a long list of letdowns for AIDS prevention research, two promising approaches to thwarting HIV infection have both failed in their first real-world trials. One intervention attempted to lower people's risk of becoming infected with HIV by treating their existing herpes simplex virus-2 (HSV-2) infections. Several studies have shown that HSV-2 eases entry of HIV. The second approach investigated whether using a latex diaphragm that covers the infection-vulnerable cervix could present a barrier to HIV. Researchers reported disappointing results from the trials this week at the 4th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention in Sydney, Australia, 22 to 25 July, where they stressed that the interventions may have failed because trial participants did not use them consistently.



Risky business. Tanzanian women who participated in the HSV-2 treatment study worked in establishments such as this one that put them at high risk of HIV infection.

The HSV-2 study followed 651 Tanzanian women for up to 30 months who at the trial's start were infected with that virus but not HIV. The women worked in places like bars and guesthouses that put them at high risk of becoming infected with HIV. Other epidemiological studies have shown that HSV-2, which causes genital ulcers, triples a person's risk of becoming infected with HIV. Half the participants were assigned to take the HSV-2 drug acyclovir twice a day, whereas the other half received a placebo.

Clinical epidemiologist Deborah Watson-Jones of the London School of Hygiene and Tropical Medicine, the study's lead investigator, reported that they found no difference in HIV acquisition between the two groups. "We

were very disappointed," Watson-Jones told *Science* in an interview.

Watson-Jones said many women did not take acyclovir as instructed, which may explain the dispiriting results. Researchers assessed adherence by tallying unused tablets returned at each study visit. Although no one knows precisely how many doses can be missed without undermining effectiveness, only half of the women managed to take the drug 90% of the time.

Biological analyses provide additional evidence that adherence issues clouded the results: The researchers found only a modest decrease in HSV-2 shedding in the vagina and on the cervix in women on acyclovir. "I know of no study that's been published with acyclovir at this dosing that did not have a very substantive effect on HSV-2 itself,"

says Lawrence Corey, an HSV-2 and HIV researcher at the University of Washington (UW), Seattle, who was not involved with the study. "We're left with [lack of] adherence being the best explanation of why you don't see much of an anti-HIV effect."

In the women who did take 90% or more of the tablets, the study found a trend toward efficacy, but it did not reach statistical significance. "The suggestion of an effect

for women who had good adherence is encouraging," says Watson-Jones, but if strict adherence is so critical, "it begs the question of how feasible this is."

Two large, multicountry studies of acyclovir to prevent HIV transmission now under way should have results in the next year, says epidemiologist Connie Celum, a UW epidemiologist who is heading those trials. "I don't think at this point that the Tanzania study disproved the hypothesis that HSV-2 is an important cofactor in acquisition or transmission of HIV," says Celum. "We need to understand the issues around adherence."

The two studies involve 10,000 people in Africa, Latin America, India, and the United States. One trial will have a similar design to

the Tanzania study—although it also involves men who have sex with men. The other tests whether people dually infected with HSV-2 and HIV can take acyclovir to lower the risk of transmitting the AIDS virus to their uninfected regular partners. In the first study, which is further along, Celum says they have seen about 90% adherence. She notes that they have much more frequent study visits than in the Tanzania trial, and they also distribute weekly pillboxes to help people remember to take their medication. "There may be tools that really enhance adherence," says Celum.

Adherence issues may also have undermined a trial testing whether a latex diaphragm can protect women from HIV infection. More than 5,000 women participated in the trial, held in South Africa and Zimbabwe, which had a control group use condoms alone whereas the experimental group used condoms and the diaphragm. At the end of the 2-year study, HIV infection rates were about 4% per year in both groups, reported epidemiologist Nancy Padian of the University of California, San Francisco. "It's terribly disappointing not to be able to add this to our armamentarium of prevention strategies," said Padian.

Padian and co-workers, who published their results online 13 July in *The Lancet*, noted that the diaphragm group reported using it only 73% of the time; they also reported using condoms much less frequently than the control group. Although this might indicate that the diaphragm compensated for the lack of condom use and did offer some protection from HIV, Padian and co-authors stress that it's equally plausible that the control group over-reported its condom use. "This is an area where doing more research on adherence is every bit as important as testing new biological prevention methods," says Padian.

In the *Lancet* report, Padian and co-authors note that of the 25 carefully done HIV-prevention trials to date, all but four have failed. She suspects that some of these apparently failed interventions may actually have had a small protective effect, which was difficult to detect. And she worries that this accumulated failure obscures the fact that many proven prevention interventions exist. "There's still quite a bit we can do with regard to HIV prevention that we know does make a difference," says Padian. "Why aren't we scaling those up?"

—JON COHEN