

◀ **Testing patience.** A social worker (red sweater) in Kolkata, India, takes a group of people to the city's busy HIV testing clinic at the School of Tropical Medicine.

versity of Versailles in Saint-Quentin, France, headed the South African trial that found 65% protection from circumcision. Gray and Wawer are currently running a similar circumcision study in HIV-uninfected men in Rakai, as well as a second trial that asks whether circumcising HIV-infected men in discordant couples might reduce transmission. (Yet another circumcision study underway in Kisumu, Kenya, run by Robert Bailey from the University of Illinois at Chicago School of Public Health, is also evaluating circumcision of HIV-uninfected men.)

A model based on data from the four-city study underscores circumcision's potential to alter AIDS epidemics. As Kate Orroth from the London School of Hygiene and Tropical Medicine reported last month at an Amsterdam conference on sexually transmitted diseases (STDs), her preliminary data suggest that if circumcision rates jumped from 10% to 100% in the Zambian city of Ndola, the prevalence of HIV in adults would drop from 27% to 7% in little more than a decade—and that's assuming circumcision offers only 50% protection.

Following up on the HSV-2 lead, epidemiologist Connie Celum from the University of Washington in Seattle is heading two multisite, international trials of daily acyclovir, which is licensed to treat herpes infections, to see whether suppressing that virus can reduce the incidence of HIV transmission. "These trials have a reasonable chance of providing some data that will reshape our focus on HIV and sexually transmitted diseases," says Celum. One trial will include some 3000 HIV-uninfected people. The other, building on evidence that HSV-2 reactivation helps HIV copy itself—and thus makes a person more infectious—is recruiting 3600 couples who are discordant for the AIDS virus.

Acyclovir is ideal for this type of study because it "has virtually no toxicity except in really high doses," says Celum, and there's little danger that daily doses will lead to the emergence of drug-resistant strains. For HSV-2 to become resistant to acyclovir, it must mutate a key enzyme used by the virus, which reduces its "fitness," Celum explains. She knows of only two cases in which people transmitted such resistant strains.

If acyclovir treatment of HSV-2 works as an HIV prevention strategy, it too could greatly affect AIDS epidemics. HSV-2 infects from 22% of adults in the United

States to a staggering 70% of women in southern Africa. And that's in HIV-uninfected people; more than 80% of HIV-infected adults are co-infected with HSV-2. Again, models offer provocative predictions. At the Amsterdam STD meeting, Esther Freeman, a grad student who works with Orroth and Richard Hayes at the London School of Hygiene, used the four-city data to show that 15 years after HIV was introduced to those locales, HSV-2 accounted for more than one-third of the new infections with the AIDS virus (see graph, p. 1002). "It's a huge effect," Freeman says.

Direct hit

Other prevention trials underway use anti-HIV drugs to attack the virus directly.

Antiretrovirals lower viral loads, and given the Rakai data showing that people with less virus are less infectious, this strongly suggests that anti-HIV drugs might work as both a treatment and prevention tool—but that remains to be proved. "Knowing whether they have some benefit in prevention is a really important question," says Brown University's Mayer.

To specifically address this question, the HIV Prevention Trials Network (HPTN), sponsored by the National Insti-

Hedged Bet: An Unusual AIDS Vaccine Trial

Even the AIDS vaccine world has jumped on the simplicity bandwagon. To many AIDS vaccine researchers, the key obstacle is that no one has yet found a vaccine that can trigger effective antibodies against the surface protein of the virus. So Merck has constructed a vaccine that abandons antibodies altogether, and the company is testing it in a fast-tracked study to determine whether it's worth pursuing the approach.

Although antibodies prevent cells from becoming infected, the Merck vaccine attempts to train the cell-mediated arm of the immune system, which eliminates cells that HIV has infected. The vaccine uses adenovirus to carry three HIV genes, but, in a marked difference from almost every other vaccine under development, not the gene for the surface protein.

Working with the National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Maryland, Merck has launched a study in 3000 people at high risk of becoming infected. This unusual study is essentially a hedge bet: it will not have the statistical power of the typical Phase 3 efficacy trial that leads to licensure, so researchers are calling it a Phase 2b. "What do you do if you want to know if something works, and the only way to do it is humans, and you don't have enough confidence to do a Phase 3 study?" asks Peggy Johnston, who heads NIAID's AIDS vaccine program. "You do an overpowered Phase 2."

The trial aims to answer two discrete questions. First, most people have been infected with the adenovirus subtype (called Ad5) that Merck uses, and their antibodies against this "vector" could prevent it from producing the HIV proteins needed to stimulate a robust immune response. So half the people recruited for the international study, called Step, will have low levels of antibodies to Ad5. If the vaccine works, researchers then can evaluate whether the Ad5 antibody levels have any impact. Secondly, if it produces robust cell-mediated immunity, they'll know once and for all whether that response by itself can protect against HIV. "The Step trial is a good name for it," says Johnston. "I see it as a step forward. But it's not the final step."

—J.C.



Fight on. The San Francisco Department of Public Health uses this ad to recruit for the Step study.