

With no vaccine in sight, AIDS researchers are testing a range of surprising biomedical interventions

Prevention Cocktails: Combining Tools To Stop HIV's Spread

If AIDS researchers reported that a vaccine protected 65% of the participants in an efficacy trial, the news would be trumpeted across the globe. Two weeks ago at an AIDS meeting in Brazil, a study revealed that male circumcision produced that level of protection in South Africa. Many major media did not even mention this advance.

True, male circumcision as an HIV prevention strategy pales in comparison to a vaccine, a few shots of which theoretically could train the immune system of both genders to ward off HIV for decades. But the search for a safe and effective vaccine has stumbled repeatedly, and fundamental questions remain about whether a vaccine is even feasible, much less how it would work. These frustrations have prodded researchers to explore other, decidedly more mundane, alternatives like circumcision.

Nearly a dozen potential preventives are now under study that have a refreshing simplicity to them. They include drugs already on the market, existing devices such as the female diaphragm, and such basic concepts as improving genital hygiene. The hope is that these could work together with condoms and behavior change to help communities slow AIDS epidemics. "We all know that abstinence and couples being mutually faithful would be great if they were applicable to everybody's lives, but they're not," says Helene Gayle, who directs the HIV, TB, and Reproductive Health program for the Bill and Melinda Gates Foundation. "These more short-term endeavors are giving people

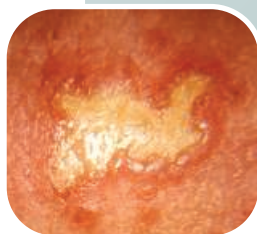
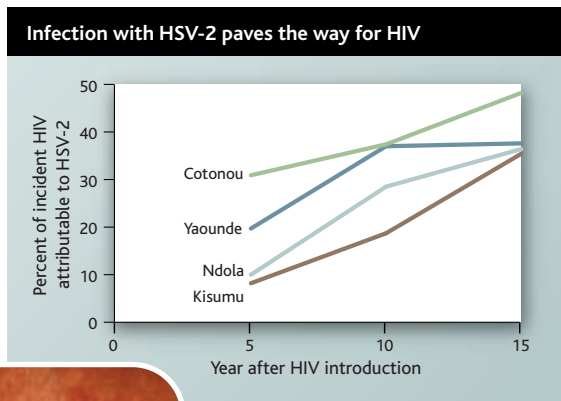
hope. We know that's its going to take at least decade to get to a vaccine." Adds psychologist Thomas Coates, who does prevention research at the University of California, Los Angeles (UCLA): "It's a new era of prevention."

Each of these interventions, circumcision included, has serious limitations. They

factors most responsible for HIV transmission. "There are interesting scientific data that support development of very tightly reasoned biological hypotheses that are not just relying on a vaccine," says Kenneth Mayer, director of the Brown University AIDS Program in Providence, Rhode Island, who does prevention studies in several countries. Roughly 5 years ago, two large observational studies began to yield several overlapping insights.

One, the so-called Study Group on the Heterogeneity of HIV Epidemics in African Cities, looked at 8000 men and women from four locales, two of which had much higher HIV prevalence than the others. Anne Buvé, an epidemiologist at the Institute of Tropical Medicine in Antwerp, Belgium, and her colleagues found that circumcision and pre-existing infection with herpes simplex virus-2 (HSV-2), which causes genital ulcers, seemed to account for much of the difference in prevalence. The second study, led by Ronald Gray of Johns Hopkins University in Baltimore, Maryland, and Maria Wawer of Columbia University in New York City, followed 15,000 adults in the Rakai District in Uganda. The researchers found that in "discordant" couples in which only the woman was infected with HIV, if the male partner was circumcised, which occurred in 50 cases, she never transmitted the virus; nearly 17% of the uncircumcised men did acquire the virus from their infected partners. In these same initially discordant couples, people with higher HIV levels—or viral loads—more readily spread their infection. And the researchers later found that HSV-2 infection strongly increased the likelihood of transmission.

Both the four-city and Rakai studies have become landmarks in the field, and clinical trials are now building on those observations. A lead investigator in the four-city study, Bertran Auvert of the Uni-



Co-factor. Infection with herpes simplex virus 2 (left) in four African cities is estimated to have accounted for more than 30% of new HIV infections.

also could do more harm than good if they lull people into taking more sexual risks. That's just one of several vexing ethical dilemmas that prevention researchers are facing. But Gayle, who has helped steer the Gates Foundation's funding of many of these projects, says the promise is undeniable. "People are energized in ways that they weren't before," says Gayle. "People have gotten jazzed."

Beyond observation

In addition to the vaccine field's travails, the impetus for many of the new interventions being tested comes from observational studies that have highlighted the co-

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◀ **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.

tute of Allergy and Infectious Diseases (NIAID) in Bethesda, Maryland, recently launched an ambitious antiretroviral treatment study led by Myron Cohen of the University of North Carolina (UNC) in Chapel Hill; it ultimately hopes to enroll 1750 discordant couples on four continents. Columbia's Wawer is also examining the role of

lenge" have dodged the infection. Although enthusiasm dampened for this approach when a recent study from the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, showed that tenofovir-treated monkeys eventually did become infected after repeated challenges, many researchers suspect PrEP will work to some

works, it offers clear advantages over some other prevention strategies. "The idea of doing circumcision on a mass scale is kind of daunting," says Coates. "Providing pills is a lot simpler." Tenofovir PrEP might also work equally well in both sexes and isn't limited to people who already have another infection, like HSV-2.

Researchers have also begun to incorporate tenofovir and other antiretrovirals into microbicides, gels or creams that are put into the vagina—or, in one new study, the rectum. The five efficacy trials now underway with vaginal microbicides all rely on nonspecific formulations such as buffering agents and detergents; as a result, many researchers question whether any will have much success. These non-specific compounds must also be used about one hour before intercourse. "Maybe the deck is stacked against them," says Zeda Rosenberg, a virologist who heads the International Partnership for Microbicides in Silver Spring, Maryland.

In contrast, tenofovir and some other anti-HIV drugs—including one being developed by Rosenberg's nonprofit—remain active longer and may only need to be used once a day. And ideally, she says, microbicides will take a page from the treatment world and use a cocktail of anti-HIV drugs to attack the incoming virus from many angles at once.

Early containment

Very early detection of HIV infection may also offer an opportunity to prevent transmission when the risk is highest—which typically occurs before people even know they are infected.

The Rakai study and several since then have reported that people have the highest viral loads, and are most infectious, right after they become infected—and before infections show up in antibody tests. "You're never going to be able to deal with the epidemic until you deal with those acutely infected people," explains UNC's Cohen.

He and Christopher Pilcher have pioneered a strategy to better identify acutely infected people. They have used the polymerase chain reaction (PCR) to detect HIV in blood that has been pooled from thousands of people visiting STD clinics and the like. If they detect the virus, they break the pool into smaller and smaller pools for retesting, eventually identifying the individual patients who harbor the virus. As the researchers explained in the 5 May *New England Journal of Medicine*, they used this technique, which cost less than \$4 per blood donor, in North Carolina to identify 23 acutely infected people. They and 48 of their sexual partners were notified and given counseling about how to

Novel Prevention Studies

Intervention	HIV status	Product	Sponsors	Locations	Stage	Projected end
Pre-exposure prophylaxis	-	Tenofovir	CDC, Gates Foundation	Malawi, Ghana, Thailand, U.S., Peru	Safety-efficacy	2006–08
Circumcision	-	n/a	NIAID	Kenya, Uganda	Efficacy	2007
Circumcision	+	n/a	Gates Foundation	Uganda	Efficacy	2008
Treat HSV-2	-	Acyclovir	NIAID	Zambia, Zimbabwe, S. Africa, U.S., Peru	Efficacy	2007
Treat HSV-2 in discordant couple	+/-	Acyclovir	Gates Foundation	Kenya, Tanzania, Uganda, Zambia, Botswana, S. Africa	Efficacy	2008
Treat HIV in discordant couple	+/-	ARVs	NIAID	Malawi, India, Zimbabwe, Brazil, Thailand, U.S.	Pilot	2006
Diaphragm	-	n/a	Gates Foundation	S. Africa, Zimbabwe	Efficacy	2007
Topical penile microbicide	-	Ethanol based	NIAID	Kenya	Phase 2	Start in fall
Rectal microbicide	+/-	Biosyn UC-781 RT inhibitor	NIH	U.S.	n/a	Pending
Acute infection	+	PCR on pooled blood samples	NIH	Malawi, North Carolina	n/a	Pending
Vaginal microbicide	-	Tenofovir	NIAID	U.S., India	Safety	Start in fall
Treat depression	+/-	Bupropion	NIH	San Francisco	Phase 2	2006

antiretrovirals as a prevention strategy with a new, multiyear observational study in Rakai. Wawer essentially is taking advantage of the fact that the U.S. government is providing treatment to many HIV-infected Ugandans as part of the President's Emergency Plan for HIV/AIDS Relief.

The most advanced trials to test whether antiretrovirals can prevent infection involve giving a drug called tenofovir to uninfected people. Several monkey studies have shown that tenofovir—which cripples an enzyme that HIV needs to copy itself and has been on the market since 2001—works remarkably well at what's called pre-exposure prophylaxis (PrEP). In these experiments, researchers give animals the drug and then attempt to infect them with SIV, the simian relative of HIV. Monkeys that receive the drug up to 2 days before this SIV "chal-

degree in humans. "In the absence of a vaccine, it could be a very effective tool against HIV," says UCLA's Coates.

Seven clinical trials, funded separately by the Gates Foundation and CDC, are now evaluating the safety and efficacy of tenofovir PrEP. Two other tenofovir PrEP studies ended prematurely after activists raised ethical concerns—which had more to do with trial designs than the specific intervention—and a third closed up shop for technical reasons (*Science*, 18 March, p. 1708). In an unusual twist, tenofovir's maker—Gilead Sciences of Foster City, California—says it has no interest in pursuing PrEP because of fears that uninfected people who take tenofovir and still become infected might sue the company.

Tenofovir appears to be safer than most antiretrovirals on the market, and if it

lower their risks. Twenty of the acutely infected people also opted to start treatment, likely reducing their viral loads.

Low tech

In this new era of prevention, even the commonly used diaphragm and other simple approaches are playing a role.

“It took me over 10 years to get this funded,” says Nancy Padian, an epidemiologist at the University of California, San Francisco (UCSF), describing her study of the diaphragm and a lubricant as an HIV prevention device in Zimbabwe and South Africa. “People are interested in a new microbicide, a new vaccine. But the diaphragm? ‘No, no, no,’” says Padian, who finally received funding from Gates.

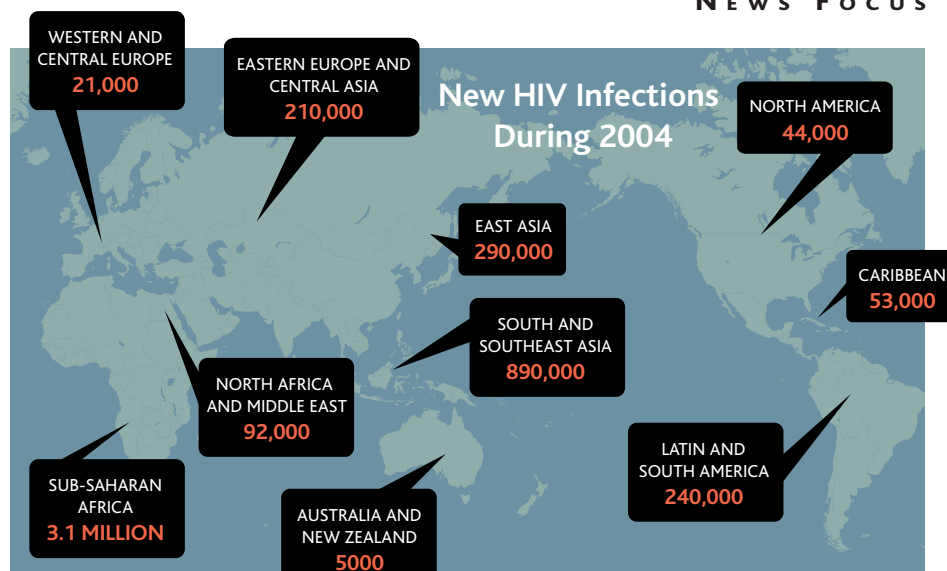
As Padian explains, the diaphragm should prevent HIV from reaching the cervix and endocervix, where most female infections occur. If it works, she says, the diaphragm will have a distinct advantage as it will enable a woman to protect herself without having to negotiate with a partner, as often happens with condoms.

In males, basic hygiene of the penis may prevent transmission. King Holmes from the University of Washington in Seattle, working with Elizabeth Bukusi at the Kenya Medical Research Institute, is studying whether wiping the penis with an ethanol-based gel—similar to the commercially available Purell—can thwart transmission of HIV, HSV-2, and other sexually transmitted microbes. “There was a long history of men using topical prophylactics, but with advent of antimicrobials around World War II, these basically stopped,” says Holmes.

One of the most provocative, low tech prevention studies focuses on the master organ that makes people vulnerable to HIV: the brain. Grant Colfax at the San Francisco Department of Public Health studies the link between methamphetamine use in gay men and HIV transmission. Meth users have decreased dopamine levels in the brain, which can lead to depression. Because studies have shown strong links between depression in gay men and sexual risk-taking, Colfax explains, he plans to launch a study this fall that will assess the impact of an antidepressant, bupropion (trade name Wellbutrin), which acts by indirectly increasing dopamine levels.

Real world

Researchers concede that it’s difficult to envision how these myriad prevention



World of trouble. HIV infects nearly 5 million people each year.

interventions will play out in the real world. After all, the benefits of condoms have been widely known for years. In addition, clinical trials often fail to reflect how a drug is actually used. The tenofovir PrEP and acyclovir studies evaluate daily dosing, for instance, but if they work, people might take the drugs intermittently. More troubling still, investigators worry that the benefits of most prevention inter-

ventions, then ethics demand that everyone in any prevention study be offered the drug. “It could have a major impact on vaccine studies,” says Peggy Johnston, who heads AIDS vaccine research for NIAID. “Each prevention tool that’s added makes it harder for the next one to prove efficacious. But that’s not necessarily a bad thing. It means we’re getting better prevention tools.”

And in prevention, as in treatment, combining interventions appears to be the name of the game. “We need to really look at how we put together a combination of options that fit people’s lifestyles,” says the Gates Foundation’s Gayle. Ideally, prevention campaigns also will promote these options to the high-risk groups most likely to become infected and spread the virus (a concept that has far less importance in the many sub-Saharan locales that have double-digit prevalence, which makes all sexually active adults vulnerable).

UCSF’s Padian contends that a cocktail of the various prevention interventions now in trials could be “extraordinarily successful,” but she notes that other than circumcision, each one requires that people repeatedly take actions to protect themselves. Which means that a safe and effective AIDS vaccine will remain an urgent need. But in the meantime, if more of these unflashy biomedical alternatives prove their worth, they could powerfully slow HIV, which now infects another 14,000 people—half of them between 15 and 24 years old—each day.

—JON COHEN



Changing behavior? Limited success with prevention campaigns like this one being designed in Kunming, China, have fueled the search for new biomedical interventions.

ventions could be undermined by what psychologists call behavioral disinhibition. Specifically, if an intervention—whether it’s proven to work or still in trials—leads people to think they are protected and thus can safely have more sexual partners or unsafe sex, the risk of becoming infected could increase.

Another untidy dilemma is that success comes at a cost. If, say, tenofovir PrEP