

## Spotlight

### HIV prevention in a pill?

*Drugs that treat herpes may help reduce HIV transmission.*

If ongoing clinical trials pan out, it's possible that one day people could be cutting their risk of HIV infection simply by popping a couple of pills per day. The pills are cheap, safe, and have been around for years. The catch? These drugs don't target HIV, they fight off herpes.

Simply suppressing genital herpes could be enough to substantially reduce an individual's risk of acquiring and transmitting HIV. Researchers have long known that sexually transmitted infections (STIs) play a role in HIV transmission. Now nearly a dozen clinical trials are investigating whether drugs that suppress a type of herpes virus (herpes simplex virus-2 or HSV-2) that causes genital herpes can reduce HIV transmission.

Approaches to HIV prevention that aim to modify behavior are yielding only modest gains against HIV transmission, so many researchers are now looking into strategies that focus on biology rather than behavior. For example, earlier this year a clinical trial in South Africa found that male circumcision could reduce the risk of men acquiring HIV.

Ideally strategies that combine biology and behavior may provide greater gains in prevention than either would alone. "Aside from individual behavior change, we don't really have ways to prevent HIV transmission," says Anna Wald, an epidemiologist at the

University of Washington School of Public Health and Community Medicine in Seattle. "That is the starting point of why we are looking at herpes."

The current trials will test whether drugs to suppress herpes can actually reduce HIV transmission in real world settings, says Jairam Lingappa, medical director of one of the studies organized by the University of Washington. "While epidemiologic studies show a relationship between HIV and genital herpes," he says, "we don't yet have a clear demonstration of the public health benefit."

### Partners in crime

Herpes is a lifelong infection that causes recurring outbreaks of painful ulcers at the surface tissues (or mucosae) of the genitals. During the course of infection the virus moves between periods of latency and reactivation, when the ulcers appear. Numerous studies have found a strong association between herpes or other genital ulcer diseases and an increased risk of HIV transmission. An analysis of previously completed studies conducted by Esther Freeman and colleagues at the London School of Hygiene and Tropical Medicine (LSHTM) found that men and women with genital herpes are at three times greater risk of acquiring HIV.

Genital ulcers can help HIV establish an infection by disrupting the physical barrier of the skin and enabling the virus to more easily enter the body. Genital herpes also causes inflammation of the genital tissues, which in turn recruits activated CD4<sup>+</sup> T cells, the primary cells infected by HIV, to the site. Dendritic cells are also recruited and can entrap HIV particles and carry them to CD4<sup>+</sup> T cells in other areas

of the body.

The elevated risk of acquiring HIV may be greatest in the first few months following infection with HSV-2, when severe outbreaks of genital ulcers are most common. So controlling these ulcers should reduce HIV transmission, especially in sub-Saharan Africa where genital herpes is the most widespread STI. In some regions of Africa about 80% of the population has acquired HSV-2 by age 35.

There are also other ways that herpes could increase the risk of becoming HIV infected. Even if actual genital sores are not present, HSV-2 can increase the risk of HIV transmission because the two viruses can interact in complicated ways that aggravate the effects of both diseases.

People infected with HIV and HSV-2 will often have frequent and prolonged outbreaks of genital ulcers because herpes takes advantage of HIV's ability to weaken the immune system. This increased expression of the herpes virus in turn allows for an increase in HIV replication. This vicious cycle between HIV and HSV-2 means that suppressing herpes could reduce both the risk of acquiring HIV (acquisition) and the risk of transmitting it to a sexual partner (infectiousness).

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## Herpes suppression on trial

To demonstrate the possible public health benefit of knocking down herpes, researchers are running a number of clinical trials to evaluate if two types of treatments can reduce HIV transmission. One type will assess the benefit of giving a drug to treat HSV-2 only during outbreaks of genital herpes when genital ulcers are present. The other will evaluate the benefits of suppressing the herpes virus by continuous administration of the drug in order to keep it latent. All of these trials are using the drug acyclovir, an affordable, safe, and proven anti-herpes medication efficient at blocking HSV-2.

Some researchers, including Philippe Mayaud of the LSHTM, think providing acyclovir just when herpes flares up and ulcers appear could have a significant effect on HIV transmission. He is currently involved in three studies, one of which is looking at HIV transmission after acyclovir is given to women in Ghana and the Central African Republic who come to clinics seeking treatment for genital herpes. Women who consent to be in the study are HIV tested and offered acyclovir three times a day for five days or an inactive substance called placebo. Mayaud and his colleagues will take genital samples from all women and will monitor the interactions between the two viruses in women that are also HIV infected.

Mayaud and other research teams are also exploring providing volunteers with a continuous, suppressive regimen of acyclovir therapy. One study is testing this concept in female bar- and hotel-workers in Tanzania. Either acyclovir or placebo is being given to 1,000 HIV-infected and uninfected women in a trial led by Debby Watson-Jones at the LSHTM. The women that are HIV uninfected at the start of the trial are being monitored for HIV infection, while the HIV-infected women are being monitored to see if the suppressive acyclovir regimen decreases the amounts of HSV-2 and HIV present at the genital mucosae.

But researchers also want to know if giving continuous acyclovir to people with HSV-2 can reduce HIV acquisition. A large scale study to answer that question is being conducted by Wald and Connie Celum, also of the University of Washington. The study is following

women in three African nations (South Africa, Zambia and Zimbabwe) and men who have sex with men (MSM) in the US and Peru to see if acyclovir can reduce their risk of becoming HIV infected. The researchers will also be looking at how well the drug controls the occurrence and frequency of genital ulcers and whether the participants can adhere to the regimen of two pills daily. “The trial of 3,200 women and men is over 80% enrolled with excellent retention and adherence, so we are optimistic that we will get an answer about the degree to which genital herpes increases HIV susceptibility,” says Celum.

### Stopping transmission

Researchers are also interested in studying how continuous HSV-2 suppression can limit the risk of an HIV-

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## *Aside from individual behavior change, we don't really have ways to prevent HIV transmission*

Anna Wald

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infected person transmitting the virus to their sexual partners. This question is being studied in a cohort of “HIV discordant” couples, where one partner is infected with both HIV and HSV-2 and the other partner is not infected with HIV. Nearly 3,000 HIV discordant couples will participate in such a study at twelve sites in seven African countries. The HIV-infected, HSV-2-infected partner will be given either acyclovir or a placebo to see if they are at reduced risk of passing HIV to their non-infected partner, in the context of couples' counseling (see October *Primer on Understanding Couples Voluntary Counseling and Testing*), treatment of bacterial STIs, and condom provision.

If acyclovir proves capable of reducing HIV transmission, the trial results will benefit everyone—but none so much as the discordant couples them-

selves. HSV-2 is the leading cause of genital ulcers in married couples, says Susan Allen, a professor at Emory University's Rollins School of Public Health and a pioneer in studying HIV-discordant couples. “This time period [when one partner is infected and the other is not] is a critical window in which to implement a public health strategy to reduce transmission,” says Lingappa. “If we can enhance the number of families that maintain one healthy parent or adult, that is one of the things we should promote.”

While well-designed, no study can answer every question about HSV suppression. The couples study is meant to examine acyclovir's role in preventing HIV transmission to the non-infected partner, but it does not test whether a greater reduction in intra-couple transmission could result if both members of the couple took acyclovir. By studying acquisition and transmission of HIV in two separate trials, the researchers run the risk of finding only weak associations in both. But Celum says the team carefully considered combining the trials and decided it would be better to separate the studies to determine the relative impact of acyclovir.

### A medicine for the masses?

If Mayaud's trials are successful, he hopes that acyclovir will be offered as a standard treatment for genital ulcers when people seek treatment at a clinic. But providing a suppressive therapy regimen—that is, a 400 mg pill of acyclovir twice a day for years—will be expensive and may be difficult to distribute. Although a year's course of generically-produced acyclovir could cost as little as US\$40 per year in Africa, it could still be prohibitive in most settings. Valacyclovir, the newer form of the drug that can be taken just once a day, is not yet manufactured generically.

Despite these concerns most researchers argue that if there is a remedy on the shelf that can be used to reduce HIV transmission it should be made available. “Until the day comes when an effective AIDS vaccine is developed,” says Pat Fast, medical director at the International AIDS Vaccine Initiative, “researchers must try everything they can to stem the spread of HIV.”

## Global News

### Phase II AIDS vaccine trial begins in South Africa

A clinical trial evaluating the safety and immune responses generated by a candidate AIDS vaccine known as tgAAC09 recently began at three sites in South Africa, including clinics in Soweto, Cape Town, and Medunsa. This is the country's first Phase II AIDS vaccine trial and investigators will enroll and follow 78 volunteers over a period of 18 months.

The vaccine candidate uses an adeno-associated virus vector to deliver HIV fragments from subtype C, the most common subtype of HIV in southern and eastern Africa, into the body. Phase I trials with tgAAC09 were conducted in Belgium, Germany, and India. Other arms of this Phase II trial will occur in Zambia and Uganda, after receiving regulatory approval in these countries.

The candidate was developed and manufactured by Targeted Genetics Corporation in Seattle based on work by Philip Johnson when he was a researcher at the Children's Hospital in Ohio. The South African trial is a collaboration between Targeted Genetics and IAVI and is an important advancement in a country where 25 million people are estimated to be HIV infected.

South Africa is also hosting another important HIV prevention trial involving the microbicide candidate PRO 2000, a vaginal gel consisting of a synthetic compound that binds to HIV and may prevent it from infecting target cells. This Phase III trial will enroll over 10,000 women volunteers in South Africa, Uganda, Tanzania, and Zambia, making it the largest microbicide trial to date. This trial is being coordinated by the UK Medical Research Council.

### First AIDS vaccine trial starts in Rwanda

A Phase I vaccine trial of a two-part vaccine developed by the Vaccine Research Center (VRC) of the US National Institutes of Health (NIH) recently began enrolling volunteers at a site in Kigali, Rwanda. This is the first AIDS vaccine trial to take place in the country and is being conducted by the NIH, IAVI, and Project San Francisco, a research organization that has been working in Kigali for almost 20 years.

The trial will test a two-part vaccine that

first uses a DNA vaccination to 'prime' the immune system. The DNA fragment carries several HIV proteins from subtypes A, B, and C, the most common in Africa and parts of Asia. This is followed by a 'boost' vaccination with an adenovirus serotype 5 (Ad5) vector carrying several HIV genes. The vaccine candidates can not cause infection with either HIV or adenovirus.

The candidates were developed at the VRC and yielded promising results in Phase I trials in the US. Several other Phase I and II trials testing the DNA/Ad5 candidates are either ongoing or expected to soon begin in several other countries, including HVTN sites in North and South America, southern Africa, and the Caribbean. The prime-boost approach will also be tested at other clinical trials sites in partnership with IAVI and the US Military HIV Research Program.

"I'm really excited and pleased that these groups have taken the considerable effort to harmonize their trial plans," says Gary Nabel, director of the VRC. "Each of these organizations has a special strength," he adds, allowing the vaccine to be tested in different communities.

### Merck's HPV vaccine shines in Phase III efficacy trials

A vaccine to protect women from infection with human papillomavirus (HPV)—a virus that causes cervical cancer and genital warts—was found to be 100% effective at preventing pre-cancerous lesions associated with the strains of the virus that are contained in the vaccine. This is the first report from a large-scale efficacy trial with Merck's HPV vaccine, known as Gardasil.

In this Phase III trial (FUTURE II), 12,167 women aged 16-26 were inoculated at 90 sites in Brazil, Colombia, Denmark, Finland, Iceland, Mexico, Norway, Peru, Poland, Singapore, Sweden, the UK, and the US. Women in the trial received up to three injections. Gardasil is a virus-like particle (VLP) vaccine consisting of a single HPV protein that self-assembles into an empty shell and closely resembles a virus particle. Proteins from 4 strains of HPV are included; strains 16 and 18 are responsible for over 70% of cervical cancer cases worldwide, while 6 and 11 cause more than 90% of genital warts. The vaccine can not cause HPV infection because the whole virus is not included in the vaccine.

Merck is now in the process of preparing its application to the US Food and Drug Administration for approval and licensure to

market and sell the first cervical cancer vaccine. Cervical cancer is one of the leading cancers among women and there are more than 290,000 mortalities associated with it annually. Many of these deaths occur in developing countries where there are few screening programs to provide women with regular Pap tests that can detect cervical lesions caused by the virus.

"Where the vaccine is really needed is in developing countries," says Jessica Kahn, of the Cincinnati Children's Hospital. "It could have a tremendous impact there on mortality rates." Another HPV vaccine, developed by GlaxoSmithKline Biologicals in Rixensart, Belgium is also in Phase III clinical trials.



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IAVI is a global not-for-profit organization working to speed the search for a vaccine to prevent HIV infection and AIDS. Founded in 1996 and operational in 23 countries, IAVI and its network of partners research and develop vaccine candidates. IAVI also advocates for a vaccine to be a global priority and works to assure that a future vaccine will be accessible to all who need it.

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## How can participation in an AIDS vaccine trial affect HIV test results?

HIV testing is an important first step for individuals interested in participating in an AIDS vaccine trial. All potential volunteers are tested for HIV infection because only HIV-uninfected individuals can join clinical trials of preventive vaccines. Eligible volunteers that choose to be in a vaccine trial will then be tested for HIV routinely throughout the study, which can last several years.

## How does an HIV test show if a person is infected?

There are several different types of HIV tests and the type used depends on the clinic or trial site. The traditional HIV test is called an antibody test because it detects antibodies against HIV that are circulating in the blood, saliva, or urine, without actually identifying the presence of the virus. Antibodies are proteins produced by the immune system that target pathogens like viruses or bacteria. The most common tests look for HIV-specific antibodies in the blood and are the EIA (enzyme-linked immunoassay) or ELISA (enzyme-linked immunosorbent assay). Different HIV testing kits are able to detect antibodies directed toward different parts of HIV. Traditional antibody tests require full blood samples and results are usually available in a few days or weeks.

If an antibody test indicates that a person is HIV infected then a more stringent test must also be performed. This confirmation test can either be a Western Blot or an indirect immunofluorescence assay (IFA). The combined results of both the antibody and Western Blot tests are over 99% accurate. This high level of accuracy means that there are few people who are not HIV infected that have a positive test result (false positive) and few people who are HIV infected that have a negative test result (false negative).

The antibody tests are highly sensitive and can detect very small quantities of antibodies but it can take anywhere from 14 days to 6 months after a person is infected with the virus for antibodies to appear. Because of this “window peri-

od” where a person can actually be HIV infected but not have sufficient antibodies to register on a test, it is important for volunteers in a vaccine trial to be tested at regular intervals.

Recently many trial sites worldwide have started using “rapid” HIV tests. These tests require only a drop of blood from a finger prick to detect antibodies to HIV and results are available in only 15-30 minutes. The rapid tests are 99.6% accurate so there are few false-positive or false-negative results. At many vaccine trial sites nurses will conduct 2 rapid tests simultaneously to determine if the volunteer is HIV infected. If both are negative then no confirmatory test is needed, but if at least one of the rapid tests is positive then a Western Blot is required to confirm infection. There are also rapid tests that use saliva samples gathered from a cotton pad placed in the mouth instead of blood. Saliva only contains antibodies to HIV, not HIV itself, so the virus can not be transmitted through this fluid.

## What if a vaccine candidate generates antibodies to HIV?

Many AIDS vaccines that are tested in clinical trials can make the immune system produce antibodies against multiple components of HIV. This is a sign that the vaccine candidate is inducing an immune response. Importantly, none of the vaccine candidates can cause HIV infection because they don't contain the whole virus but only parts of genes.

It is possible that a person who volunteers for an AIDS vaccine trial could produce antibodies against HIV that would be detectable by an HIV test, but without actually being HIV infected. If the antibodies are in response to the vaccine candidate then the test result is considered a false positive.

During a vaccine trial volunteers will be counseled to be HIV tested only at the study site. This is important because researchers at the study site can do specific tests to distinguish between a positive antibody test result from the vaccine candidate and one from an actual HIV infection obtained through exposure in the community. Most HIV tests are

designed to identify antibodies that target certain regions of the virus, so nurses at the site can use very specific tests that only detect antibodies towards components of HIV that are not included in the vaccine.

Researchers at the study site can also do other tests known as polymerase chain reaction (RNA or DNA PCR) or p24 antigen tests that actually detect the presence of the virus and not antibodies to confirm infection. These tests measure the amount of virus in the body and can help researchers easily determine if the person was infected through exposure to HIV in their community. Any volunteer that is tested away from the trial site should notify the clinic that they have participated in an AIDS vaccine trial so that the proper tests can be performed.

## What are the implications of false-positive HIV test results?

Researchers are unsure how long the antibodies generated from a vaccine candidate will last. Volunteers in vaccine trials that have positive test results, even if false, during routine testing could face potential discrimination when applying for insurance or future employment and could have difficulty with obtaining travel visas or going through immigration. People with a positive HIV test are also prohibited from donating blood and can face social stigmatization. These potential difficulties are discussed with each volunteer during the informed consent process before the vaccine trial begins. Investigators at trial sites can also provide volunteers with a letter, if requested, stating that they are participating in an AIDS vaccine trial and were not HIV infected as of a certain date.

Some organizations that are running vaccine trials will provide volunteers with a photo identification card and a contact they can call at anytime to help them to resolve conflicts over whether or not they are HIV infected. This process may not be sufficient when much larger numbers of people are participating in AIDS vaccine trials and then HIV testing policies will need to be revisited and possibly revised.