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Spotlight

Treatment as prevention

Researchers are studying the use of licensed drugs to prevent—rather than treat—HIV infection

When AIDS was first described in the medical literature 25 years ago, there was not a single medicine to treat people infected with this new human virus. Since then more than 20 antiretrovirals (ARVs) have been licensed by the US Food and Drug Administration for the treatment of HIV/AIDS. These drugs have dramatically improved the health of millions of HIV-infected people around the globe and are now becoming increasingly available in developing countries where the need is still the greatest.

But with 4.9 million new HIV infections last year alone, new ways to stem the spread of HIV are more urgent than ever. In response researchers have turned their attention to novel approaches to HIV prevention. One of these involves giving the ARVs usually used to treat HIV infection to try to protect people from contracting the virus in the first place. The idea of healthy people popping pills to stay HIV free may seem strange, but it isn't without precedent. Travelers headed to countries where malaria is endemic will often take drugs to protect them from becoming infected with this parasitic disease. Researchers hope that giving ARVs to individuals at high risk of HIV infection could have the same effect. This idea is known as pre-exposure prophylaxis, or PrEP, and is being tested in five ongoing clinical trials. "We urgently need new types of prevention tools and PrEP is one of many promising strategies, like microbicides and vaccines," says Albert Liu, an investigator for one of the PrEP trials in the US.

Researchers first thought that PrEP might be an effective approach more than a decade ago but the complexities of conducting clinical trials to test the idea has placed them at the forefront of debate. Many researchers harbor concerns that giving drugs that are known to be effective for treating the disease could encourage people to participate in more risk behavior, an idea known as behavioral disinhibition, which could lead to a higher risk of infection. But investigators involved in clinical trials insist that measures are in place to limit this effect. And if found effective PrEP may have the greatest benefit for people who are unable to negotiate use of traditional barrier methods and therefore have few options when it comes to HIV prevention. "We desperately need PrEP to protect women in resource-poor settings," says Joep Lange of the University of Amsterdam.

If the idea of PrEP is borne out in clinical trials, many other questions may arise about implementing this strategy on a global basis. Researchers will confront issues of long-term drug toxicity when ARVs are taken outside the controlled environment of a clinical trial. Other issues like drug pricing and the community outreach and educational campaigns needed to introduce this concept to communities may present further obstacles. "PrEP is not a universal panacea," says Lange, who emphasizes that an AIDS vaccine is "still an absolute priority" since its impact will be far greater.

Preparing for PrEP

The concept of PrEP is not altogether new. "The concept of using an antiretroviral as a preventive has been tested and proven successful in preventing mother-to-child transmission of HIV," says Jim Rooney of Gilead Sciences, the company that manufactures both drugs currently being tested in PrEP trials. Over the last 12 years countless children have been spared from HIV infection because mothers and babies received ARVs during labor or for a short time following birth (see *VAX* February 2005 *Spotlight* article, *Preventing mother-to-child transmission*).

Administering ARVs to laboratory or healthcare workers after accidental needle-stick exposure to HIV is also a common practice, known as post-exposure prophylaxis (PEP). But in both of these situations the window of exposure to the virus is known and healthy individuals only need to take ARVs for a limited time. The premise of PrEP is that ARVs could be taken on a daily (possibly less frequent) basis for years in order to protect against the possibility of multiple exposures to the virus either

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through sexual activity or injection drug use. Giving ARVs, even if their toxic effects are minimal, to otherwise healthy people over a long period raises safety concerns.

The choice of ARV is therefore paramount. Tenofovir, licensed for the treatment of HIV infection, was the first drug that researchers considered for PrEP. Tenofovir has been on the market since 2001 and has a relatively good safety profile. It also has several other characteristics that make it favorable for PrEP, including once-daily dosing.

An initial study by Gilead showed that tenofovir was able to protect macaques from infection with simian immunodeficiency virus (SIV) when given just before or after exposure to the virus. However in subsequent studies when animals were treated with tenofovir and exposed repeatedly to a similar virus, the results weren't as promising.

Trials and tribulations

Still, researchers knew the ultimate answers on the efficacy of this approach will come from studying tenofovir PrEP in humans and clinical trials are now underway. The CDC started a Phase II safety study in February last year in the US with tenofovir in 400 men who have sex with men (MSM) and two larger Phase IIb/III trials with tenofovir PrEP with 1600 injection drug users (IDUs) in Thailand and 1200 heterosexual volunteers in Botswana.

Family Health International, a US-based nonprofit public health organization, also launched a series of tenofovir PrEP trials in Malawi, Nigeria, Cameroon, Cambodia, and Ghana, with funding from the Bill & Melinda Gates Foundation, but only the Ghana trial is still ongoing. Some of the trials were stopped or suspended after activist protests regarding the lifetime provision of ARV treatment for volunteers who become infected during the trial. Others were halted for concerns about the ethical or biological parameters of these trials. In Malawi the government halted the trial due to concerns that it would foster HIV resistance to tenofovir, which they are now using in treatment. In response to these events the International AIDS Society held a global consultation on PrEP research last year where researchers and activists discussed the issues regarding these trials (http://www.iasociety.org/images/upload/1025.pdf).

Another PrEP trial, conducted by the US National Institutes of Health (NIH) and the University of California, San Francisco (UCSF) is in the process of getting approval from local institutional review boards to begin recruiting 1400 MSM in Peru. This study is expected to start later this year, according to IMPACTA, a Peruvian non-governmental organization.

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>
> **Albert Liu**

Questions linger about why PrEP is just now entering clinical trials, but disinhibition was one concern that kept researchers away from these studies. Many hesitated to dive into PrEP research because of fear it could actually encourage volunteers to abandon other proven methods of HIV prevention like condoms or increase their number of sexual partners.

Others like Lange are not as concerned about disinhibition. As in any clinical trial, volunteers in PrEP trials will be tested frequently for HIV infection and counseled on how they can reduce their risk. "Usually people are better off in a clinical trial than on the outside," he says. Volunteers will also have easy access to condoms. "We want to test the efficacy of PrEP on top of what we know already works," Liu adds.

Several studies have analyzed the behaviors of volunteers during prevention trials and the results have been mixed. During the Phase III AIDS vaccine trial run by VAXGEN, researchers found that injection drug users did not increase their risk behavior during the trial. But Mayer warns that this may not be a fair comparison. "We can't say that what happened in a vaccine trial will happen with PrEP." Volunteers in vaccine trials may receive at most three inoculations. "It's very different taking a pill every day," he adds, which researchers fear could reinforce a false sense of protection among volunteers on a regular basis.

All of the ongoing clinical trials are placebo controlled so that researchers can be sure to detect any protective effect the drug may offer. The trial Liu is coordinating in San Francisco is also attempting to evaluate the effects of disinhibition by staggering when volunteers start receiving pills. Only half of the volunteers will receive a daily pill of either tenofovir or placebo for the first nine months of the study, while the others receive nothing. This will allow the study investigators to compare the reported behaviors of volunteers who are taking pills and those who aren't. This information will be valuable to researchers, but the true impact of disinhibition isn't likely to be realized until PrEP is administered widely. Then educational campaigns will be critical in describing both the promise and limitations of this approach.

One is the loneliest number

Researchers have always speculated that a combination of ARVs, like that used for HIV treatment, may work even better for PrEP. At a major scientific meeting in the US earlier this year, researchers from the CDC presented results from an animal study with the drug Truvada, a single pill containing tenofovir and another drug called FTC, which supports this hypothesis. This idea, now being called combo-PrEP, may be even better at fending off infection than tenofovir alone and sparked great interest among prevention researchers. In response, some of the ongoing or planned PrEP trials have been modified to test Truvada.

The NIH/UCSF trial that will start later this year has been altered to include combo-PrEP instead of tenofovir alone

and the CDC plans to add an additional site to the US safety trial where volunteers will receive Truvada rather than tenofovir. New volunteers in the CDC trial in Botswana will also receive Truvada, while the 70 who were already enrolled will continue on tenofovir.

Non-viral challenges

Results from these trials are still several years away but some investigators are already considering the next steps. All of the current trials are testing daily doses of drug but the next round of studies will evaluate more sporadic use of PrEP drugs, according to Lynn Paxton who is running the PrEP trials at the CDC.

Others are considering how this approach could be implemented if found effective and one of the first considerations on everyone's mind is cost. "The access question is very important to start thinking about now," says Liu. Both drugs are only available from Gilead and a year's supply costs on average US$4800 for tenofovir and $7800 for Truvada. Gilead has provided free drugs for all of the trials but otherwise has stayed out of PrEP research altogether.

The company does have an access program for treatment, offering the drug at no-profit pricing in 97 developing countries. But even at this drastically reduced price of about a dollar a day it is expensive for governments struggling to treat those already HIV infected. The company does seem willing to negotiate. "If data suggest that tenofovir or Truvada is safe and effective in preventing transmission of HIV, we would continue to work to ensure access at the lowest feasible cost," says Rooney.

Distributing drugs to those most in need would be another challenge for PrEP programs. In developing countries it may be more difficult to educate communities on PrEP and to give out drugs to healthy individuals who are at high-risk for HIV infection if they aren't accustomed to seeking medical care. "This is going to have to be a team effort," says Paxton, "but there's no reason to think that it couldn't be done with proper planning."

Regardless of these questions, researchers and activists alike eagerly await the results of the ongoing PrEP trials and the public health opportunities this prevention strategy may hold.

Global News

Two AIDS vaccine trials begin

GeoVax, a US-based biotechnology company, recently began enrolling volunteers for a Phase I trial to evaluate the safety and immunogenicity of the company's AIDS vaccine candidates at four sites in the US.

The volunteers will receive two doses of a DNA vaccine candidate followed by two doses of a modified vaccinia Ankara (MVA) candidate over two months. The vaccine candidates were developed by Harriet Robinson at Emory University's Yerkes National Primate Research Center in Atlanta and neither can cause HIV infection. The DNA candidate was tested in a previous safety trial in three US cities. GeoVax is also planning an additional trial with a higher dose of this vaccine candidate in the coming months.

A second trial began recently in Zambia to evaluate the safety and immunogenicity of an AIDS vaccine candidate that uses an adeno-associated virus (AAV) vector to deliver pieces of HIV's genetic material to the immune system. This Phase II trial is the first AIDS vaccine trial to take place in the country and is being conducted by IAVI in collaboration with the Zambia Emory HIV Research Project.

The vaccine candidate, tgAAC09, was developed by US-based biotechnology company Targeted Genetics and was tested at a lower dose in Phase I trials in Belgium, Germany, and India. This Phase II study is a multi-center trial and volunteers are also being enrolled at sites in South Africa and Uganda.

World AIDS Vaccine Day observed

On May 18th communities around the world are planning events to commemorate an annual day dedicated to the development of a safe and effective AIDS vaccine. IAVI-sponsored events are planned in India and Kenya, including the screening of the documentary *Ending AIDS: The Search for a Vaccine* to raise awareness and highlight advances in the field. The US National Institutes of Health is also sponsoring several community events throughout the US.

This day was chosen as a reminder of the urgent need for an AIDS vaccine after US President Bill Clinton called for a renewed commitment toward the development of a vaccine by saying "only a truly effective, preventive HIV vaccine can limit and eventually eliminate the threat of AIDS."

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Editor
Simon Noble, PhD

Science Writer
Kristen Jill Kresge

Production Manager
Nicole Sender

All articles written by Kristen Jill Kresge.
VAX is a project managed by Kristen Jill Kresge.

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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. For more information, go to www.iavi.org.

What is the process for referring volunteers in vaccine trials for treatment and care?

To participate in clinical trials of preventive AIDS vaccine candidates, volunteers must not be HIV infected at the start of the trial. This allows researchers to determine the safety of the vaccine candidate in healthy individuals and, in larger Phase IIb or III trials, its efficacy at preventing HIV infection.

During the course of the trial volunteers receive counseling on how they can reduce their risk of HIV infection and have access to proven prevention methods like condoms (see *VAX* August 2005 *Primer* on *Understanding Risk Reduction Counseling*). None of the AIDS vaccine candidates being evaluated in clinical trials can cause HIV infection, yet some volunteers may still become HIV infected during the course of the trial through risk behaviors such as sexual activity or injection drug use. These volunteers may therefore need antiretrovirals (ARVs) to treat their HIV infection at some point in the future. The provision of this treatment to trial volunteers has been an important subject for organizations that conduct AIDS vaccine research and the communities where this work occurs.

Ethical guidance

According to two landmark documents that serve as the basis for the conduct of medical research (the Declaration of Helsinki and the Council for International Organizations of Medical Sciences guidelines), sponsors of vaccine trials are not ethically required to provide volunteers with treatment for a disease that is contracted during the vaccine trial. The World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) issued guidelines in 2000 specifically for AIDS vaccine trials stating that volunteers should receive, at a minimum, the highest level of care attainable in the country where the trial is taking place and, ideally, the best proven therapy (http://data.unaids.org/Publications/IRC-pub01/JC072-EthicalCons_en.pdf). However several questions remained about who would pay for this treatment. As importantly, researchers had to consider how offering treatment only to those taking part in the trial could unfairly influence people's decision to participate, an idea known as undue inducement.

But the landscape of HIV treatment in developing countries has changed dramatically in recent years, and sponsors are now asking how—not if—treatment should be provided to volunteers. More people have access to life-saving ARVs because of significantly lower treatment costs and programs launched by the WHO; the Global Fund to Fight AIDS, Tuberculosis, and Malaria; the President's Emergency Plan for AIDS Relief (PEPFAR); and the Clinton Foundation, among others. Although the WHO's plan to put 3 million people on HIV treatment by 2005 did not meet its goal, it did substantially improve the systems for distributing ARVs to HIV-infected people in many developing countries. This, along with the other programs, has affected the way AIDS vaccine trial sponsors are approaching the issue of providing treatment to volunteers who happen to become HIV infected during a vaccine trial through exposure in their community.

Tapping into existing networks

Now many organizations that conduct AIDS vaccine research are working together with existing treatment programs provided either by national governments or by outside organizations to ensure that volunteers have access to ARVs. Before a trial even begins sponsors will map out the treatment services that are already available in the community and then investigators at the trial site can refer individuals that become HIV infected during the trial to one of these clinics for treatment.

This process can vary among the different organizations that are conducting AIDS vaccine trials and may even be different for each trial site. Some countries have created their own policies regarding treatment of volunteers. In Uganda the government has said that volunteers in HIV prevention research that become HIV infected will be a priority for receiving ARVs through their national treatment programs. In South Africa volunteers in AIDS vaccine trials are provided with an identification card that they can present at any government clinic to get treatment. Volunteers that may become HIV infected in any of the ongoing AIDS vaccine trials conducted by the Walter Reed Army Institute of Research (WRAIR) are guaranteed to receive ARVs directly through PEPFAR grants.

The WHO and UNAIDS recommend that an agreement is reached in writing before the trial starts about the systems for providing treatment and that the sponsors, researchers, host governments, and communities are included in this process.

Preparing for the future

In all communities where treatment is available there are still obstacles to getting infected volunteers into these programs. One of these obstacles is the distance volunteers have to travel to the clinic. Participation in a vaccine trial requires regular visits to the trial site for HIV testing and counseling and even those that become HIV infected will still be followed for the remainder of the trial because researchers want to study how the vaccine might affect disease progression. Making several trips to both the trial site and to the clinic for treatment may be difficult for some volunteers and could present a barrier to them accessing ARVs.

Another complication is following up on volunteers to ensure that they receive treatment and care. In Phase I or II trials, where investigators anticipate only a very small number of volunteers will be incidentally infected and need treatment, it is possible for the trial site staff to follow up on individuals who are referred to outside clinics to make sure they are actually accessing treatment. But this will be difficult in Phase III efficacy trials when several thousand volunteers are enrolled and significantly more infections occur through exposure in the community. Trial sponsors are concerned that trial sites may be referring people to already over-burdened clinics, which may have waiting lists for ARV treatment.

To combat this problem several organizations, like IAVI and the HIV Vaccine Trials Network, are now optimizing these referral networks so that they can be prepared for large-scale trials. Other trial sponsors are working to develop new funding mechanisms to provide treatment for volunteers in the future.