

vax

The Bulletin on AIDS Vaccine Research

[SPOTLIGHT]

PrEP Work

If effective, PrEP will offer many opportunities, as well as numerous challenges *By Regina McEnergy*

MORE THAN A DECADE AGO, highly active antiretroviral therapy (HAART), the combination of multiple antiretrovirals (ARVs) to treat HIV infection, began rescuing HIV-infected individuals from the brink of death. Yet this is only part of the critical role ARVs, either alone or in combination, have played in the battle against HIV.

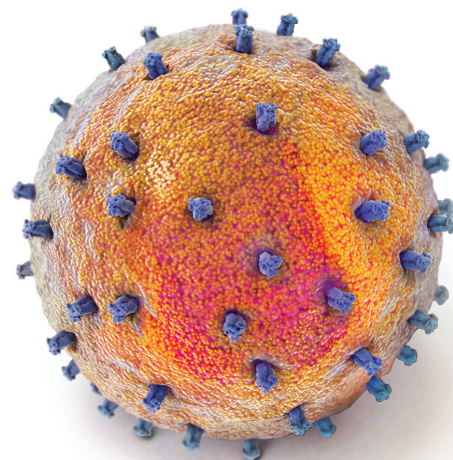
Routine and timely delivery of ARV therapy to HIV-infected pregnant women and their babies is highly effective at preventing infants from contracting HIV, and ARVs are also thought to possibly block infection in adults when taken for a short time very soon after known exposure to HIV, a concept called post-exposure prophylaxis (PEP).

Considering this, it's not surprising that researchers are investigating whether delivering ARVs prior to exposure to HIV, an idea known as pre-exposure prophylaxis (PrEP), can also be turned into an effective prevention tool. A growing body of preclinical data shows that administration of certain ARVs can effectively block infection in animal models. This has sparked a lot of excitement about the potential for PrEP and there are now several large clinical trials, either in process or planning, to test whether this strategy can also work in humans.

If these trials yield promising results, PrEP could be added to the stockpile of existing HIV prevention strategies that

despite years of research still largely revolve around condom use, sexual abstinence, and syringe-exchange. Male circumcision, the latest biomedical intervention against HIV, was found to reduce HIV acquisition by as much as 65% in heterosexual men, but because of logistical, cultural, and religious considerations, only a handful of countries so far have adopted policies recommending the surgical procedure for HIV prevention.

To ensure that PrEP, if found effective, doesn't face a similar fate, HIV prevention advocates are starting to consider the weighty challenges, both medical and logistical, that will need to be overcome to successfully implement PrEP. Governments and public health agencies, like the World Health Organization (WHO) that usually make recommendations that many developing countries adopt, will have to tackle a myriad of questions, including identifying who should be the recipients of PrEP and the best systems for distributing ARVs to healthy yet high-risk individuals. Systems will also have to be established to continuously test PrEP users for HIV infection and monitor them for any long-term side effects from the drugs. Massive public education campaigns will also be required to explain PrEP and to counter any behavior change that might occur as a result of its use. All of this could add considerably to the already staggering costs of HIV/AIDS prevention, treatment, and care.



Yet if it works, PrEP will also bring unprecedented opportunities. Despite achievements in treating HIV/AIDS, 2.7 million new HIV infections occurred just last year.

Awaiting human data

The first preclinical evidence to indicate that PrEP might be effective came from nonhuman primate studies conducted in 1995. Subsequent studies in nonhuman primates have provided additional data showing that ARVs administered prior to exposure to simian immunodeficiency virus (SIV), the monkey equivalent of HIV, can prevent infection. However, the success of the intervention seems to vary based on the animal model and the ARVs used.

There are now seven planned or ongoing clinical trials of PrEP evaluating the efficacy of the ARV drug tenofovir (Viread),

ALSO IN THIS ISSUE

GLOBAL NEWS

- ▶ IAVI Opens AIDS Vaccine Laboratory in New York City

PRIMER

- ▶ Understanding Approaches to Inducing Neutralizing Antibodies

MANAGING EDITOR

Kristen Jill Kresge

SENIOR SCIENCE WRITER

Andreas von Bubnoff, PhD

SCIENCE WRITER

Regina McEney

PRODUCTION MANAGER

Nicole Sender

EDITOR AT LARGE

Simon Noble, PhD

FREE SUBSCRIPTIONS:

To obtain a FREE subscription to VAX by e-mail, or to change your subscription details, please go to www.iavireport.org and click on the appropriate link in the yellow box at the top left. If you would like to receive multiple print copies of VAX to distribute and/or use in your programs, you may enter your request using those same subscription links. For more information, go to www.iavireport.org.

VAX is a monthly bulletin from IAVI Report, the publication on AIDS vaccine research published by the International AIDS Vaccine Initiative (IAVI). It is currently available in English, French, Spanish, and Portuguese as a downloadable PDF file or an e-mail bulletin.

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 24 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.



Printed with soy-based ink on FSC-certified paper. Copyright © 2008

or a combination pill of two ARVs—tenofovir and emtricitabine—known as Truvada, which will enroll upwards of 18,000 individuals. These trials are enrolling men who have sex with men (MSM) and injection drug users (IDUs) in Asia, the US, Latin America, and Africa, as well as heterosexual men and women from Africa. The first round of data—a safety study being conducted in 400 HIV-uninfected MSM in the US—is expected to be released next year, and results of the first efficacy trial involving 2,400 IDUs in Thailand will closely follow.

Researchers most closely involved in the study of PrEP, as well as HIV prevention advocates, agree that it is productive to start conversations about PrEP implementation while

clinical trials are still ongoing so that governments and public health agencies like the WHO are ready to act as soon as possible. But some also suggest that the discussions about this unproven strategy should proceed cautiously until some clinical data is collected.

“Countries hardest hit by the epidemic have a lot of other things going on,” says Lynn Paxton, the coordinator of PrEP studies with the US Centers for Disease Control and Prevention (CDC). “They don’t have much money and to ask them to start intensive preparation for something that might not have been shown to work yet is difficult.”

The AIDS Vaccine Advocacy Coalition (AVAC) has spearheaded many of the discussions about PrEP so far, even though its central mission has historically centered around AIDS vaccines. AVAC’s executive director Mitchell Warren says the group diversified its message for two reasons. “First, we are many years from vaccine efficacy,” he says. “We will begin to get answers about PrEP over the next two years and there has been pitifully little said about what we will do if it works.” Warren says response plans that are adequately funded and which correctly identify the high-risk uninfected individuals most likely to benefit from this intervention should be developed sooner rather than later.

Addressing the challenges

Some key concerns about the implementation of PrEP are access, adherence, and education. One challenge will be identifying the individuals who should receive PrEP. It is likely that PrEP programs will, at least initially, target high-risk individuals in communities in which the HIV infection rates are highest, but many stakeholders say that it is too premature to determine that now. “If a study shows it is highly effective then recommendations will be made on how best to use it and in what populations,” says James Rooney, vice president of medical affairs for Gilead, the company that developed and licensed tenofovir and Truvada. “In conjunction, there will also be discussions on whether the current infrastructure would allow for PrEP to be

provided, or whether there needs to be further discussions on how the drugs could be made available,” Rooney says.

Another key obstacle will be adherence to the prescribed regimen—all of the ongoing trials are testing a daily dose of either tenofovir or Truvada. While there are clear-cut medical reasons for HIV-infected individuals to stick to treatment—failure to do so could accelerate their progression to AIDS—motivating high-risk but uninfected individuals to take a daily dose of ARVs could prove difficult, like convincing men and women to use a condom every time they have sex or substance abusers to use clean needles every time they inject drugs. There are many challenges associated with ensuring consistent behavior change and some advocates see adherence as potentially the biggest barrier to PrEP’s effectiveness.

To avoid issues with daily adherence, some researchers are eyeing the possibility of testing intermittent PrEP use—such as before and after high-risk activity. “It will be important to understand if intermittent PrEP is feasible and effective,” says Timothy Mastro, senior director of research at Family Health International. “Taking the drug intermittently around the time one might be exposed is probably more feasible for many people in the world.” IAVI is considering utilizing excess clinical trial capacity to evaluate the feasibility of intermittent PrEP use, which could also provide insight into immunological questions that may be important for AIDS vaccine research.

Another concern among researchers and advocates is that even though PrEP will unlikely be 100% effective at protecting against HIV, PrEP users may feel protected and therefore increase their risk behaviors, a phenomenon social scientists refer to as behavioral disinhibition. “If the public feels that they can take a pill and now have more sex, the effect of PrEP will go way down,” says John Mellors, a professor of medicine at the University of Pittsburgh who has done computer modeling studies to determine the influence behavioral inhibition could have on PrEP’s efficacy. To counteract any effects of such disinhibition, sustained education programs will be necessary.

We will begin to get answers about PrEP over the next two years and there has been pitifully little said about what we will do if it works. — Mitchell Warren

Resistance, safety, and cost

Another big concern is people who become unknowingly HIV infected despite taking PrEP, either because it is partially effective or due to poor adherence, and continue taking the ARVs. This could spur the development of HIV resistance to the PrEP drugs, which could in turn compromise an individual's treatment options over the long term. For this reason it will be imperative to regularly test PrEP users for HIV infection. "Any [PrEP] program [should] not make the mistake of giving PrEP to people who are already infected," says Mellors. While monitoring thousands of people in a three-year clinical trial is a manageable exercise, it would be much more difficult in the general population.

In addition to tracking HIV drug resistance, PrEP programs will also need to monitor individuals for any adverse effects due to the drugs. Although studies have found the drugs to be well-tolerated, tenofovir has been associated with renal toxicity, says Rooney.

Another lingering question about implementing PrEP will be its price tag. Gilead Sciences now charges developing countries about US\$17 and \$26 a month respectively for tenofovir and Truvada when used for HIV/AIDS treatment, and they plan to charge the same for PrEP, says Rooney.

PrEP, if safe and effective, could also influence the design of future AIDS vaccine trials. If more than one randomized controlled clinical trial shows PrEP is effective,

and government policies regarding this strategy are implemented, organizations conducting AIDS vaccine trials would likely be asked to provide PrEP or refer trial volunteers to a clinic in the community where it is available. Including enough volunteers in a trial to determine a vaccine's benefit on top of the protection afforded by PrEP and male circumcision would require substantially more volunteers, which would add significantly to the complexity and cost of conducting trials. ■

Find out more – For more information about PrEP, see "Anticipating the Results of PrEP Trials" at www.avac.org.

GLOBAL NEWS by Kristen Jill Kresge

IAVI Opens AIDS Vaccine Laboratory in New York City

ON NOVEMBER 12, IAVI CELEBRATED the opening of its AIDS Vaccine Design and Development Laboratory, the first research facility in the world dedicated exclusively to the research and development of an AIDS vaccine. The new lab is housed in an historic building in New York City known as the Brooklyn Army Terminal (BAT), at which the city and state governments, along with private entities, are developing a state-of-the-art bioscience center. New York City Mayor Michael Bloomberg, who spoke at the opening of the Design Lab, said investing in bioscience is a way to diversify the city's economy in troubling economic times. IAVI, the first research group to occupy the center, received US\$12 million from the New York City Economic Development Corporation to renovate the laboratory space. "The potential to change the world is right here in this building," said Bloomberg. "New York City is very glad to partner with IAVI in hastening the day to the development of a vaccine."

Scientists at the new Design Lab, working along with a broad network of researchers affiliated with IAVI's research consortia and partners in both academia and industry, are uniquely positioned to test and develop new vaccine candidates. There are many scientific challenges facing AIDS vaccine researchers and the Design Lab is meant "to focus on these challenges and solve them as quickly as possible," said Seth Berkley, founder and president of IAVI.

One key challenge is figuring out how to get the immune system to generate protective proteins, known as antibodies, against HIV. All vaccines that are used today induce antibodies, said Dennis Burton, a professor of immunology and molecular biology at the Scripps Research Institute and head of the HIV Neu-

tralizing Antibody Center, who spoke at the opening ceremony as well as a science symposium that was held earlier in the afternoon. Although antibodies against HIV can be found in HIV-infected individuals, "the problem is how to induce them," said Burton. "We have to get people to make these antibodies themselves, and that's the goal of vaccination." And while this has proven much more difficult for HIV than other viruses, "we're confident that in the end we will defeat this virus," Burton said.



Photo by Olga Shmaidenko

▲ **OPENING CEREMONY FOR THE DESIGN LAB** New York City Mayor Michael Bloomberg spoke about the city's commitment to HIV prevention, education, and treatment, but said, in the end "you have to have a vaccine."

Understanding Approaches to Inducing Neutralizing Antibodies

What are some of the novel approaches researchers are exploring to induce broadly neutralizing antibodies against HIV?

By Regina McEnerly

WHEN VIRUSES AND BACTERIA invade the body, the human immune system fights back in two ways (see VAX July 2008 *Special Issue, Understanding the Immune System and AIDS Vaccine Strategies*). Initially, the innate immune responses are activated. These responses are always on standby and can act quickly against any pathogen to either eradicate or help limit an infection. The adaptive immune responses, which include both antibody and cellular immune responses, are the second line of defense.

Antibodies are Y-shaped proteins that work primarily by latching onto viruses, like HIV, and preventing them from infecting their target cells (see VAX February 2007 *Primer on Understanding Neutralizing Antibodies*). Antibodies that can effectively neutralize many different forms of HIV are referred to as broadly neutralizing antibodies. Cellular immune responses act against cells once they have already been infected by HIV (see VAX April 2008 *Primer on Understanding Cellular Immune Responses*).

Unfortunately, while several AIDS vaccine candidates are able to induce cellular immune responses against HIV, none of the candidates tested so far have been successful at inducing neutralizing antibody responses. This is one of the major scientific obstacles to the development of a preventive AIDS vaccine (see *Global News*, this issue).

Identifying neutralizing antibodies

To find broadly neutralizing antibodies against HIV, researchers closely study the immune responses in HIV-infected individuals.

Although most HIV-infected people do develop antibody re-

sponses against HIV, very few of them are actually capable of neutralizing or inactivating the virus. So far only about five broadly neutralizing antibodies against HIV have been identified. And even though these antibodies have been well studied and characterized, researchers still do not know how to induce them through vaccination. Solving this problem requires figuring out which non-infectious fragment of HIV, known as an immunogen, will stimulate the immune system in such a way that it produces one of these broadly neutralizing antibodies. But this has proven difficult. Designing immunogens that can induce neutralizing antibodies against HIV is a major area of focus in AIDS vaccine research.

A novel approach

Meanwhile, a subset of investigators are taking a different approach. Studies have shown that injecting large quantities of one of the already identified broadly neutralizing antibodies against HIV directly into nonhuman primates can protect them from infection with a virus that is a cross between HIV and simian immunodeficiency virus (SIV)—the monkey equivalent of HIV—known as SHIV. If the antibodies are present in a sufficient quantity when the animal is exposed to SHIV, they are capable of blocking an infection. Scientists have also observed that infusing antibodies into people infected with HIV temporarily suppresses their viral loads—the amount of HIV in the blood—when antiretroviral therapy is interrupted. This suggests that if broadly neutralizing antibodies were induced in humans at sufficient levels, they might be able to fend off an infection.

However, regularly administering enough of the broadly neutralizing anti-

body into humans to protect them against HIV would be impractical, both logistically and economically, over the long term. So rather than introducing the antibody itself, some researchers are instead trying to administer the gene that could direct the body to make the broadly neutralizing antibody. Within a cell, genes are responsible for overseeing the production of proteins, including antibodies. So by introducing the gene for a broadly neutralizing antibody into a cell, researchers are hopeful that the body's own cells would do the work, producing a continuous supply of antibody.

Like other vaccine strategies that use non-infectious viruses to deliver fragments of HIV to the immune system, researchers are using a crippled virus as a vector to chauffeur the antibody genes into human cells (see VAX September 2004 *Primer on Understanding Viral Vectors*).

So far this strategy has provided encouraging preclinical results. In studies with nonhuman primates, vaccination resulted in production of neutralizing antibodies that researchers could detect a year later. Even more encouraging, the antibody did appear to be effective at blocking infection against SIV in some of the vaccinated monkeys. Researchers are now conducting additional preclinical studies to try to determine what quantity of antibody needs to be produced to provide protection and whether the antibodies will be present in mucosal tissues, which are the primary entry point for HIV during sexual transmission.

After researchers adequately address any possible safety concerns with this approach, the goal is to conduct a clinical trial to see if this type of strategy could stimulate production of broadly neutralizing antibodies against HIV in humans. If so, it could potentially open the door to new strategies in both preventive and therapeutic AIDS vaccine research. ■

Researchers are using a crippled virus as a vector to chauffeur the antibody genes into human cells.

