vax

AN IAVI REPORT BULLETIN

www.iavi.org

*VAX* is a monthly bulletin featuring shorter, non-technical versions of articles from the *IAVI Report*, the newsletter on AIDS vaccine research published by the International AIDS Vaccine Initiative. *VAX* is currently available in English, French, German, Spanish and Portuguese as a pdf (www.iavi.org/iavireport) or an e-mail bulletin. If you would like to receive *VAX* by e-mail, please send a request including language preference to: VAX@iavi.org



MAY 2004
Vol.2 ■ Num.5

## In this issue



# RESEARCH & TRIALS

## ◆ US Army Begins Small Phase I Trial

In May the Walter Reed Army Institute of Research (WRAIR) began a US-based Phase I trial of a preventive AIDS vaccine candidate based on technology developed by Avant Immunotherapeutics. The vaccine, called LFn-p24, combines a small protein taken from the anthrax bacterium with an HIV protein (Gag). Although live anthrax bacterium and HIV can both cause serious illness and death, the small fragments used in this vaccine candidate cannot cause these infections or diseases. Both fragments were selected for their ability to stimulate immune responses that might possibly protect against HIV infection. The trial will enroll 18 healthy HIV-uninfected volunteers and is being conducted by WRAIR in collaboration with the US National Institute of Allergy and Infectious Diseases.

## ◆ Malawi to Launch Preventive AIDS Vaccine Trial

Malawi is scheduled to launch its first trial of a preventive AIDS vaccine in June 2004. A team of researchers from Malawi and the United States plans to evaluate a candidate called MRK-Ad5 in roughly 40 healthy HIV-uninfected volunteers. Malawi is one of six countries participating in an international Phase I safety study of the candidate; overall the study will enroll more than 400 volunteers. The trial is being conducted by the US HIV Vaccine Trials Network and Merck and Co.

# GLOBAL NEWS

## ◆ World AIDS Day Vaccine Observances

Events on the 7th annual World AIDS Vaccine Day on 18 May 2004 reflected the diversity of the countries and communities involved in AIDS vaccine research. In Nashville, Tennessee the local baseball team featured a program on AIDS vaccines at one of its games; in Entebbe, Uganda a marching band led a parade of 500 people in celebration of the country's ongoing commitment to AIDS vaccine research; IMPACTA, an AIDS vaccine trials unit in Lima, Peru held a contest for comic strips about AIDS vaccines and winning entries were widely published throughout th country (see the winning comics at www.impactapru.org/cedoc/concurso.htm).

AIDS organizations in Belgium, Brazil, France, Germany, Spain and many other countries marked the day with public calls for increased funding and support for the AIDS vaccine field. A coalition of Canadian AIDS NGOs and research groups issued a press statement calling on the Canadian government to fund the country's national AIDS vaccine plan (www.cdnaids.ca/web/pressreleases.nsf/cl/cas-news-0132).

World AIDS Vaccine Day was also the release date for the AIDS Vaccine Advocacy Coalition's annual report on the state of the field. The 2004 report (available at www.avac.org/reports.htm) focuses on gaps in "readiness" for the small-, mid-, and large-scale AIDS vaccine clinical trials, and proposes specific steps for addressing these needs. The report also highlights issues related to adolescent participation in AIDS vaccine trials, and discusses the ways in which research projects can leave communities better off.

World AIDS Vaccine Day marks the anniversary of a 1997 speech by then-US President Bill Clinton. At the time, he compared the search for an AIDS vaccine to a previous generation's quest to put a man on the moon, and challenged the world to develop a vaccine within the next ten years.

## ◆ Measuring AIDS Vaccine Efficacy: Intermediate- Versus Full-Scale Trials

The vast majority of preventive AIDS vaccine trials to date have been Phase I studies that enroll small numbers of volunteers and primarily measure the safety and **immunogenicity** of a vaccine .candidate. Studies with small numbers of volunteers cannot provide any information about whether or not the vaccine candidate prevents HIV infection or disease. This information can only be gathered in large-scale "efficacy" trials. Traditional efficacy trials are called Phase III trials. The three completed and ongoing Phase III efficacy trials of preventive AIDS vaccines all enrolled thousands of people and cost hundreds of millions of dollars.

There are now several AIDS vaccine candidates completing early phases of testing and moving towards large-scale efficacy trials. This is a promising development, but it also raises new challenges since many sponsors feel that it may not be possible to test every AIDS vaccine candidate in a Phase III trial.

One reason for this is that the field has limited financial and human resources for clinical trials. Time is another factor. It can take two or more years to prepare for such a large-scale trial and then up to five years to get an answer about vaccine efficacy.

Given the urgent need for an AIDS vaccine, sponsors are considering testing some candidates in intermediate-size efficacy trials, also known as Phase IIb trials. These studies are smaller and less expensive than Phase III trials and could still provide some preliminary indication of a candidate's efficacy.

Intermediate-size trials have been used to test many other types of medicines and vaccines, including cancer drugs and, recently, an experimental vaccine against human papillomavirus (HPV) which causes genital warts and cervical cancer. However Phase IIbs have not yet been used to test AIDS vaccine candidates.

This could change in the next few years. The International AIDS Vaccine Initiative, the HIV Vaccine Trials Network and Merck and Co. are all currently considering Phase IIb trials. As plans for these trials advance it will be important for communities and AIDS vaccine advocates to understand the strengths and limitations of this approach to evaluating AIDS vaccine candidates.

### *Comparing Phase IIb and Phase III trials*

Phase IIb and Phase III trials take the same overall approach to measuring vaccine efficacy. Both trials divide volunteers into two groups: volunteers in one group receive the experimental vaccine, and volunteers in the other group receive an inactive substance called a placebo. Neither the trial staff nor the volunteers know who has been assigned to receive the vaccine or the placebo until the study is over. This is called a double-blinded, placebo-controlled study.

All volunteers in both types of trials are regularly tested for HIV and receive condoms and risk reduction counseling which emphasizes that volunteers should not assume that they have received, or are protected by, the experimental vaccine. However some volunteers still become infected with HIV despite these services. It is important to remember that the vaccine cannot cause HIV and that no volunteers in these trials are ever intentionally exposed to HIV.

The number of volunteers and the duration of both Phase IIb and Phase III trials are determined by the rate of HIV infections or "incidence" in the community where the trial is going to take place. The higher the incidence, the fewer volunteers and/or shorter the follow-up period required. A Phase IIb trial would enroll fewer volunteers than a Phase III trial done in the same population. In general, Phase IIb trials are likely to be about half the size of a Phase III trial.

At the end of the study, researchers "unblind" the study, which means that they learn who received the vaccine and who received the placebo. They then look for evidence that the vaccine helped protect against HIV infection, or helped to reduce the severity of disease in people who became HIV-infected. (See *Primer* to learn more about the different types of AIDS vaccine efficacy.) To do this, researchers compare the number of new HIV infections in the vaccine and placebo groups. They also look at markers of HIV disease including viral load and $CD4^+$ cell counts in volunteers who became infected with HIV. If differences are detected, statistical tests are performed to determine whether they are due to the vaccine or just a coincidence.

The main difference between Phase IIb and Phase III trials lies in the precision of the conclusions that can be drawn from a trial. A Phase III trial can make more accurate estimates of vaccine efficacy than a Phase IIb trial done in the same population. Phase III trials can also detect lower levels of efficacy than Phase IIb trials. This is because accuracy is directly related to the number of people studied in a trial. When there are more volunteers, there are likely to be more people who become infected through blood or sexual exposure. These infections are the key "endpoints" for an AIDS vaccine trial. The more endpoints there are, the more confident sponsors can be that a possible vaccine effect is real and not a coincidence.

Phase IIb trials are not as precise. A Phase IIb trial would only be able to tell if a vaccine candidate was very effective or not effective at all, and could not reliably detect moderate or low levels of efficacy. Instead, a Phase IIb trial might provide "inconclusive" data about a candidate with moderate efficacy,

*immunogenicity: The strength of the immune responses produced by a vaccine; these immune responses are measured through laboratory tests on a sample of the volunteer's blood.*

meaning that it wouldn't be known for certain if it had any beneficial effects.

### Why Phase IIb trials?

The risk of conducting a Phase IIb trial is that sponsors may end up with an inconclusive answer. The possible benefit is that sponsors may be able to find out relatively quickly whether or not a particular candidate shows signs of efficacy or has very high efficacy. This is sometimes called a "proof of concept" trial. Vaccine and drug developers sometimes test early versions of promising candidates in "proof of concept" trials before investing in design, testing and manufacturing of a final candidate in a large efficacy trial.

A Phase IIb trial that provided "proof of concept" for a particular candidate might also help suggest correlates of protection for preventive AIDS vaccines. A correlate of protection is an immune response that corresponds to a high degree of vaccine protection. For example, antibody against the hepatitis B virus is the correlate of protection for hepatitis B vaccine. Physicians can measure the level of anti-hepatitis B virus antibody in the blood of a vaccine recipient to confirm that he or she is likely to be protected from hepatitis B virus infection. This way, a vaccine recipient knows whether he or she is protected from hepatitis B virus without being exposed to the virus itself.

One of the major challenges in the AIDS vaccine field is that the correlates of protection are not well understood. At present, trial sponsors analyze the type and quantity of "vaccine-induced" immune responses in Phase I and II trial volunteers but it is not known for certain that the immune responses they are measuring will protect against HIV infection or disease.

Both Phase III and Phase IIb trials could help identify correlates of protection, but Phase IIb trials could potentially accelerate this process by providing rapid estimates of efficacy. Once a candidate shows efficacy, researchers can analyze immune responses to try to learn which immune responses are associated or "correlated" with vaccine protection. These correlates could then be used to help make decisions about whether or not future candidates should be tested in large-scale trials.

Phase IIb trials could also be used to gather information about partially effective vaccines (see *Primer*). The current generation of AIDS vaccines will be evaluated for their ability to reduce viral load and HIV disease in vaccine recipients who become HIV-infected. Scientists believe that a vaccine-induced reduction in viral load would be beneficial, but do not know how much the viral load would have to drop, or how long it would have to last, to have a health benefit for the volunteer.

Phase IIb trials could gather information on these types of questions, allowing the field to fine-tune its goals for partially effective candidates. These goals could then be used to shape the design of Phase III trials.

### New challenges

If Phase IIb trials move ahead, the AIDS vaccine field will have to do additional education and outreach to explain that some efficacy trials will be designed as information-gathering tools, and will not lead directly to a "license" for widespread use, even if that candidate appears effective. One reason for this is that sponsors may choose to conduct a Phase IIb trial of an earlier version of the candidate while they are developing manufacturing plans for their final product (see *Primer*, April 2004). In this case, another efficacy trial would be tested once the final product had been completed. Another reason is to gain more precise information, since Phase IIb trials usually provide a general idea of whether a candidate is effective or not.

Phase IIb trials are a new development in AIDS vaccine research and communities, researchers and sponsors will need to work together to find effective ways of explaining the contribution that these studies can make to the field.

vax
MAY 2004
3



The Spotlight in this issue of VAX is based on an article by Emily Bass which originally appeared in the Feb-Apr 2004 issue of the *IAVI Report*. All articles by Emily Bass.

*VAX* is a project managed by Emily Bass.


*VAX* is a monthly bulletin from the *IAVI Report*, the newsletter on AIDS vaccine research published by the International AIDS Vaccine Initiative (IAVI). It is currently available in English, French, German, Spanish and Portuguese as a pdf file (www.iavi.org/iavireport) or an as an email bulletin. If you would like to receive *VAX* by e-mail, please send a request including language preference to: vax@iavi.org

IAVI is a global organization working to speed the development and distribution of preventive AIDS vaccines—the world's best hope for ending the AIDS epidemic. IAVI focuses on four areas: mobilizing support through advocacy and education, accelerating scientific progress, encouraging industrial participation in AIDS vaccine development and assuring global access.

vax
MAY 2004
4

# WHAT IS A PARTIALLY EFFECTIVE VACCINE?

It is widely thought that receiving a vaccine against a particular disease-causing agent or "pathogen" provides life-long protection against that disease. Many vaccines do indeed provide high levels of long-lasting protection against disease caused by many pathogens. However, there is no such thing as a vaccine that provides 100% protection, 100% of the time. In this sense, all vaccines are "partially effective." It is important to remember that vaccines are still highly beneficial for individuals and communities. They are the most powerful tools we have for preventing disease worldwide. Understanding "partial efficacy" can help to understand current goals for AIDS vaccines.

## What could a partially effective AIDS vaccine do?

The phrase "partial efficacy" can be used in two different ways. The first definition describes a vaccine which does not completely prevent infection by a particular pathogen but does help reduce the severity of disease caused by the pathogen. An AIDS vaccine with this type of efficacy would reduce the severity of HIV disease in vaccinated people who later became HIV-infected through blood or sexual exposure.

PRIMER
UNDERSTANDING
partial
EFFICACY

The second definition of a partially effective vaccine is one that can protect some people in a population but not others. This is possible because a variety of factors affect our immune systems and, by extension, our ability to respond to a vaccine. Most licensed vaccines are actually partially effective, although they may work for 80 or 90% of a population. Others, like oral cholera vaccine and BCG (against tuberculosis) have lower levels of efficacy but are still beneficial.

It is the first type of partial efficacy—protection against disease, but not infection—that is receiving the most attention in the AIDS vaccine field today. This is because most of the candidates being tested in clinical trials are designed to produce cell-mediated immune defenses (see *Primer*, March 2004), which act against HIV only after the virus has entered the body and infected immune cells. Instead of preventing infection from happening at all, these "vaccine-induced" defenses are likely to improve the immune system's ability to fight HIV once infection has occurred. They would do this by helping to slow viral activity and protect immune cells, especially $CD4^+$ T cells, which are targets for HIV infection. These defenses could also help to control the amount of virus circulating in the body (viral load).

Such a vaccine could have several benefits for the individual. First, it could slow the rate of disease progression following HIV infection. By reducing viral load and helping people preserve their $CD4^+$ T cells the vaccine would allow people to live with HIV for longer periods of time without getting sick. It could also prolong the time until a person needed to start antiretroviral therapy (ARVs). ARVs are generally recommended for people with less than 200 $CD4^+$ T cells per $mm^3$ of blood . Each person reaches this point at a different time after infection; an AIDS vaccine could help extend this time period. ARV therapy must be taken every day for life and a vaccine that allowed people to remain healthy and off ARVs could simplify people's lives and avoid the side effects of daily therapy.

A vaccine that reduced the severity of HIV disease could also have positive effects at the community level. Studies have found that people with high viral loads are more likely to transmit the virus to their partners during unprotected sex or to their infants during pregnancy and childbirth. A partially effective vaccine that reduced viral load might reduce the likelihood that an HIV-infected person would pass the virus on. If enough people were vaccinated, this could help to slow the spread of an epidemic in a given country or community.

## How do we find a partially effective AIDS vaccine?

Even without a vaccine, people with HIV usually do not get sick for five to seven years after infection. So to directly observe whether an AIDS vaccine affects disease, studies would have to be conducted for ten years or even longer. To get a more rapid answer, vaccine trial sponsors can look at markers of disease progression like viral loads and $CD4^+$ T cell counts in vaccine and placebo recipients who become infected through high risk contact. They can use these data as an early indication of whether or not the vaccine will have a long-term impact on disease progression or infectiousness.

A vaccine that improved health for people who became HIV-infected would be a major breakthrough. It is possible that such a vaccine would be licensed for use outside of a clinical trial. However even after licensure researchers would continue studies to answer open questions including: How long would vaccine-induced protection last? How much of a reduction in viral load is needed to translate into long-term health benefits for the individual? How much of a reduction in viral load is needed to reduce the risk of transmitting to another person?

## Part of a comprehensive response

Once an effective AIDS vaccine has been developed, it will not replace or even reduce the need for comprehensive prevention and treatment programs for HIV. This will be particularly true for partially effective vaccines that reduce the severity of HIV disease in vaccinated people who later become HIV-infected. In fact an AIDS vaccine will be most effective when it is promoted as one of several strategies for fighting HIV. This can be compared to family planning methods such as condoms, hormonal contraceptives and diaphragms. No single method is 100% protective, but used in combination, these methods can provide very, very high levels of protection.

*This Primer was adapted from the AIDS Vaccine Advocacy Coalitions' forthcoming* AIDS Vaccine Handbook*; for more information or to order a copy: www.avac.org*