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Spotlight

Nearing a decision on PAVE

Experts discuss new design of the Phase IIb PAVE 100 trial

It is not uncommon in the AIDS vaccine field for there to be some controversy about the conduct of large trials. Prior to the start of the first Phase III efficacy trial of an AIDS vaccine candidate known as AIDSVAX, there was extensive public discussion about whether or not the US National Institute of Allergy and Infectious Diseases (NIAID) should fund the trial. And before the now ongoing Phase III trial (RV 144) began in Thailand—testing a canarypox-based vaccine developed by Sanofi Pasteur in combination with AIDSVAX—there was public scrutiny over whether the trial should take place at all.

The latest debate centers around whether to conduct a Phase IIb test-of-concept trial, known as PAVE 100, which was on target to begin last year but was delayed when Merck's candidate vaccine MRKAd5 failed to show any efficacy in the STEP trial in either preventing HIV infection, or in lowering the amount of virus circulating in the blood of individuals who became HIV infected, despite vaccination, through natural exposure.

AIDS vaccine experts met on May 30 as part of the AIDS Vaccine Research Subcommittee (AVRS) to discuss the fate of the PAVE trial. After a day of discussion about the merits of the trial and the proposed design, a majority of committee members supported conducting the trial, albeit in a smaller form than originally planned. "The vast majority, it seemed, said to go ahead," said NIAID director Tony Fauci after the meeting, which took place in Bethesda, Maryland. After taking into account the committee's recommendations, Fauci will make the final decision.

The PAVE 100 trial would test a vaccine regimen developed by NIAID's Vaccine Research Center (VRC). This regimen bears some similarities to the MRKAd5 candidate—both use a cold virus called adenovirus serotype 5 (Ad5) as a vehicle to introduce HIV genes that will stimulate an immune response. The vaccination regimen evaluated in the STEP trial involved three vaccinations with the same Ad5 candidate. In contrast, the prime-boost vaccine regimen developed at the VRC involves three vaccinations with DNA encoding HIV fragments, followed by a vaccination with the Ad5 component of the vaccine regimen.

A wrinkle in the plans for the PAVE 100 trial came when researchers involved with the STEP trial subsequently observed a trend toward increased susceptibility to HIV infection among some sub-groups of trial volunteers who received the vaccine candidate. These volunteers were uncircumcised men who have sex with men (MSM) who had pre-existing immunity to the Ad5 vector from natural exposure to that cold virus.

As a result, the PAVE 100 trial would likely only involve volunteers who were circumcised MSM with no pre-existing Ad5 immunity, according to Scott Hammer of Columbia University, who chairs the trial's protocol team. Due to these restrictions, the size of the trial will likely be much smaller than originally planned. The original plans for PAVE 100 included 8,500 HIV-uninfected men and women from the Americas and southern and eastern Africa. But at the AVRS meeting Hammer suggested a much smaller trial called PAVE 100A that would enroll only 2,400 circumcised MSM in the US who have no pre-existing Ad5 immunity. Hammer said the other branch of the trial to be conducted in Africa, now known as PAVE 100B, is "deferred for now." "It is unlikely going to happen in any meaningful way for a considerable period of time," Fauci said.

PAVE 100A would be limited to the US because it would be easier to enroll circumcised volunteers without pre-existing Ad5 immunity. Prevalence of this serotype of cold virus is typically higher in developing countries—in South Africa, only about 20% of people are Ad5 seronegative, according to John Hural, associate director of laboratory operations at the HIV Vaccine Trials Network (HVTN). Still Hammer said it would be necessary to screen about 6,000 potential volunteers to successfully enroll the 2,400 proposed for the trial based on observations from the STEP trial in which 56% of the men screened for Ad5 in the US were seronegative and, of those, 83% were circumcised. "Screening and recruitment will be a challenge," Hammer said, "but definitely feasible."

In This Issue

Setting a new endpoint

Hammer also suggested that PAVE 100A should not focus on whether the vaccine candidates could prevent HIV infection altogether, but instead on their ability to lower the amount of virus circulating in people who become infected with HIV during the trial, despite vaccination. In the STEP trial, researchers looked at both of these endpoints and this was also the original plan for the PAVE trial. But Hammer noted that animal studies in nonhuman primates showed that versions of the VRC's DNA/Ad5 vaccine regimen carrying genes from simian immunodeficiency virus (SIV), the monkey equivalent of HIV, do not provide protection against infection. "That's what the science says," said Hammer.

The studies in monkeys did show, however, that there was some impact on viral load. Some researchers are also intrigued by data from a very small group of volunteers in the STEP trial. Julie McElrath, director of laboratories at the HVTN and a professor of medicine at the University of Washington, presented preliminary data from the STEP trial looking at a small group of volunteers who were infected but had low levels of HIV in their blood. In about a dozen such volunteers who were Ad5 seronegative, those with higher T-cell immune responses to the MRKAd5 vaccine had lower viral loads. However, this analysis was in a tiny subgroup of the 3,000 volunteers who participated in the STEP trial and interpretation of this observation is severely limited, not only by the small number of people, but also because this analysis was not part of the original trial design. "We call that sort of the glimmer of hope," Hural said.

Jerald Sadoff, who heads the AERAS Global TB Vaccine Foundation, supports conducting PAVE 100A in order to confirm this possible correlation between viral load and T-cell responses. "It's the only positive finding of vaccine-induced protection in the entire field of HIV vaccine research," said Sadoff, adding that the STEP trial analysis is only a preliminary finding. "[We need to] repeat the study to show that that's correct."

But others questioned whether the VRC vaccine regimen is sufficiently different from MRKAd5 to learn anything beyond what was observed in the STEP trial. To address this issue, McElrath presented a preliminary comparison of human immune response data collected from the STEP trial to data from a Phase II trial (HVTN 204) of the VRC vaccine regimen. While the VRC's DNA/Ad5 combination showed stronger $CD4^+$ T-cell responses, both the $CD8^+$ T-cell responses and the breadth of responses appeared to be similar for the DNA/Ad5 and MRKAd5 candidates except the predominant responses were to different HIV proteins for the two regimens.

Not everyone agreed as to whether these differences were enough to justify conducting PAVE 100A. "There is a lot of subjectivity in how you view the lab data," said Hural.

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>
> **Barton Haynes**

"I was impressed by the difference in the immune responses," said committee member Deborah Birx of the US Centers for Disease Control and Prevention. "I am strongly supportive of PAVE 100A proceeding." But others disagreed. "The data look more similar than different," said Jeffrey Lifson, head of retroviral pathogenesis at the National Cancer Institute. He suggested that PAVE 100A may not provide any additional insights beyond the STEP trial.

Sadoff argued that the similarity between the two vaccines was actually a good thing because it will make it possible to confirm the preliminary observation from the STEP trial that immune responses induced by this type of Ad5-based vaccine candidate may impact viral load. He said that in vaccine development it is not unusual to conduct a trial to confirm preliminary results from a previous trial. "This is normal vaccine development," he said.

Limitations

Confirming results or providing insight into future development of AIDS vaccine candidates would be the main objective of the newly-proposed PAVE 100A trial. As a result of the restrictive trial design, it won't be possible to generalize the results of PAVE 100A to the general population, said Hammer, and the purpose of the trial would not be identifying a candidate vaccine. Rather, it would be to test the hypothesis of whether this kind of vaccine is safe and can lower viral load in individuals who become HIV infected. "We have to be very clear about this as we reach out to potential participants," said Hammer.

That may be not easy, said Mitchell Warren, executive director of the AIDS Vaccine Advocacy Coalition (AVAC). "[This] will be the most complicated AIDS vaccine trial any of us will ever have to explain," Warren told the committee. Others expressed concern as to what would happen if the PAVE 100A vaccine, like the STEP candidate, also failed to have any effect. "What if another trial fails? Do you risk losing the trust and support of this community for future trials?" asked Enid Moore, associate director for community education at the HVTN, which would provide clinical sites for the PAVE 100A trial. But even a negative result would move the field forward, said Barton Haynes of Duke University and director of the Center for HIV-AIDS Vaccine Immunology (CHAVI). "If it doesn't show any control of viral load, it will empty out a large number of the trials in the pipeline," said Haynes, since several candidates are based on similar approaches.

Stacey Little, senior program officer of the Academy for Educational Development, which works to educate the community about AIDS vaccine research, pointed out another community concern—the exclusion of women from the PAVE 100A trial. But Fauci said that eventually, such a trial will move the entire field forward and that would benefit everyone.

At the conclusion of the day-long meeting, some argued that nothing is more valuable than human data. "Man is the measure of all things," said Stanley Plotkin, an advisor to Sanofi Pasteur. "We have to do this clinical trial." *–Andreas von Bubnoff*

Global News

Coordinated action on TB and HIV

Jorge Sampaio, the United Nations (UN) Secretary-General's Special Envoy to Stop Tuberculosis (TB), convened a meeting on June 9 in New York City at which activists and researchers called for integrated health services for people infected with HIV and TB in order to prevent TB from undermining the advances made in providing life-saving antiretroviral (ARV) treatment to more HIV-infected people, especially in Africa. Representatives at the meeting issued a "call for action" to the global community to better prevent, diagnose, and treat TB in HIV-infected individuals.

HIV and TB are a deadly combination (see *Deadly Duo: Joining forces to fight TB and HIV*, *IAVI Report*, Nov.-Dec. 2006). TB is the number one cause of death among HIV-infected individuals in Africa. This bacterial infection also contributes to the death of one-third of the people who die of AIDS in low- and middle-income countries, said Kevin De Cock, director of the World Health Organization's (WHO) HIV/AIDS department.

This HIV/TB meeting preceded a UN General Assembly High-Level Meeting on HIV/AIDS, which was held on June 10-11, also in New York City. The focus of this meeting was to review progress toward reaching the goal of achieving universal access to HIV prevention and treatment by 2010. On that front, UN Secretary-General Ban Ki-moon reported significant progress. At the end of 2007, three million people in low- and middle-income countries were receiving ARV therapy, a 42% increase over the previous year.

But even with this progress, there is still a long way to go in meeting the goal of universal access—only one-third of individuals currently in need are now receiving ARV therapy, according to the Secretary-General's report on progress in the response to HIV. "There must be better access to prevention, treatment, and support services, especially for those populations at most risk," said H.E. Srgjan Kerim, President of the UN General Assembly, in his closing statement to the High-Level Meeting. "We must not lose the momentum of our global response. For every two people that begin HIV treatment there are five new HIV/AIDS infections," he added.

De Cock said progress toward universal access to ARV therapy should also involve access to TB prevention, treatment, and care since even individuals on ARV therapy are more vulnerable to TB. This requires successfully diagnosing TB in HIV-infected people, said Lucy Chesire, an HIV/TB activist. "We need to ensure that every person with HIV [is] screened for TB," added Chesire. "We know that that's not the case now. That's why we [had] over 700,000 new HIV-associated TB cases in the last year."

There are already examples of how coordinated HIV/TB efforts can make a difference, according to Mario Raviglione, director of the WHO's Stop TB Department. In Kenya, for example, only 19% of individuals diagnosed with TB were also tested for HIV in 2004. This went up to 70% in 2007, he said, largely due to funding from the US President's Emergency Plan for AIDS Relief (PEPFAR). "These are very good signs that this funding is being used properly to implement activities," added Raviglione.

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The "call for action" issued at the HIV/TB meeting requests that the global community mobilize an estimated US$19 billion to halve, by 2015, the number of HIV-infected people who die each year of TB, compared with 1990 levels. Of this, $14 billion would be spent on TB prevention and $5 billion on research, said Chesire. Part of the funding for research would go into developing better treatments for TB. There is an urgent need for better tools, such as drugs, said Raviglione. *–Andreas von Bubnoff*

Be sure to check out the July 2008 Special Issue of *VAX*, featuring a three-page graphic explaining immune responses to HIV and how a vaccine works, as well as a vaccine-specific roadmap for the upcoming XVII International AIDS Conference that will take place August 3-8 in Mexico City.

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What can AIDS vaccine researchers learn from live-attenuated SIV vaccines?

Researchers have drawn on a number of different strategies in the pursuit of a safe and effective AIDS vaccine. Among the approaches that have been tested are using non-infectious viruses such as the cold virus as vectors to transport HIV fragments into cells to try to induce immune responses against HIV that will subsequently protect against infection. This was the strategy tested in Merck's recently conducted STEP and Phambili trials.

But one approach used in many modern-day vaccines remains off limits to AIDS vaccine developers—using a weakened or attenuated version of HIV to stimulate protective immunity. This strategy has been used to develop several existing vaccines that are highly efficacious at preventing disease, including the measles and yellow fever vaccines. Although still a major killer of children in developing countries, measles deaths have dropped 91% in Africa and 68% globally, according to the World Health Organization, following introduction of the live-attenuated vaccine.

This strategy remains on the sidelines of AIDS vaccine development, however, because researchers are worried that live-attenuated HIV will revert to a disease-causing or pathogenic strain once inside the body, which could cause an HIV infection in the very people the vaccine is designed to protect.

Safety concerns

These safety concerns with live-attenuated HIV vaccines are not unfounded. A group of individuals in Australia were inadvertently infected with HIV after receiving tainted blood transfusions and, as researchers later discovered, the HIV they were exposed to was a live-attenuated version of the normally circulating virus. This group, which came to be known as the Sydney Blood Bank Cohort, was infected with HIV that lacked a critical gene known as nef that plays a key role in the virus's ability to replicate in human cells. The nef gene is also responsible for shutting down a class of molecules that would normally summon the immune system's killer T cells to attack and destroy HIV-infected cells. Despite being infected with an attenuated strain of HIV, several of the long-term survivors of this cohort have now developed damage to their immune systems. After living without any signs or symptoms for nearly two decades, three of the seven survivors now have declining $CD4^+$ T-cell counts, the key marker for progression of HIV infection and development of AIDS.

Researchers believe the nef-deficient HIV strain, which infected the individuals in the Sydney cohort, mutated to regain its ability to replicate rapidly, and therefore became pathogenic. For this reason, live-attenuated HIV vaccines are considered by many to be unsafe for study in humans.

Protection by live-attenuated vaccines

Live-attenuated vaccines are prepared by purposely removing critical pieces of the virus's genetic material that would normally allow them to wage war on their hosts. The attenuated virus strains are no longer pathogenic but they still pack enough punch to produce a strong immune response against the virus. Neutralizing antibodies, which bind to viruses and prevent them from infecting cells, are thought to be an important component of the protection generated by many of the currently available live-attenuated vaccines, including polio and measles.

In most situations where live-attenuated vaccines are employed, there is also ample evidence of natural immunity to support using an attenuated version of the actual disease-causing pathogen as a vaccine. Consider polio. Despite the recurring images of helpless victims in iron lungs, about 95% of people infected with polio either never get sick or display only mild symptoms. The live-attenuated polio vaccine merely replicated what occurred naturally. The opposite applies with HIV. Without treatment, over 95% of HIV-infected people will ultimately develop AIDS. An AIDS vaccine must therefore accomplish something that largely does not occur in natural infection.

Developing live-attenuated SIV vaccines

While safety concerns prevent the testing of live-attenuated HIV vaccines, the study of live-attenuated simian immunodeficiency virus (SIV) vaccines in nonhuman primates remains an important area of research. Although SIV is a different virus, nonhuman primate studies with SIV are the closest approximation researchers have for studying HIV. Experimental data collected from the study of SIV in non-human primate models can shed light on the development of future AIDS vaccine candidates.

To study the protection afforded by live-attenuated SIV vaccines in nonhuman primates researchers purposely handicap the virus by removing pieces of SIV's genetic material. One strain of live-attenuated SIV is developed by removing part of the virus's nef gene. There are also several other versions of live-attenuated SIV vaccines that are currently being studied in nonhuman primates. Generally, the virus becomes more compromised in its ability to replicate and cause an infection when more of its genetic material is removed. But as more genes or parts of genes are removed from SIV, the less effective the live-attenuated vaccine becomes at protecting against infection. Researchers must therefore develop an attenuated SIV strain that does not infect the animals, but is still close enough to the natural form to induce strong immune responses.

The crippled SIV strains are grown in a laboratory and are then used to vaccinate nonhuman primates. These animals are then purposely exposed to a naturally-circulating version of SIV so that researchers can see how well the immune responses induced by the vaccine are able to protect against infection.

Modeling protection

The live-attenuated SIV vaccine strategy has elicited some of the most impressive and consistent protection to date in nonhuman primate studies and can provide researchers with unique insights into the types of immune responses that might also provide some level of partial protection against HIV. Researchers are now developing a better understanding of how the spectrum of SIV-specific $CD8^+$ T-cell, $CD4^+$ T-cell, and antibody responses work together to provide protection against SIV.