

# NIH Vaccine Meeting: HIV Vaccine Trial to Have Substantial Design Changes

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June 2, 2008 (Bethesda, Maryland) — Discussions at last week's National Institute of AIDS and Infectious Diseases (NIAID) AIDS Vaccine Research Subcommittee (AVRS) meeting may have substantial implications for the next HIV vaccine trial, on hold since last fall. It is likely to move forward with substantial changes in the scientific questions asked, the endpoints measured, and the number and type of participants.

The Partnership for AIDS Vaccine Evaluation (PAVE) 100 trial as initially conceived was an ambitious phase 2b trial of about 8500 participants in 13 countries on 3 continents. Using a DNA prime made up of 6 plasmid constructs (gag, pol, and nef, plus env from clade A, B, and C virus), patients would receive 3 injections (at baseline, 1, and 2 months) followed by an adenovirus vector 5 (Ad5) booster at 6 months. The product was developed by the NIAID Vaccine Research Center (VRC).

But in September 2007, investigators learned that more participants in Merck's phase 2b STEP vaccine trial were becoming infected with HIV than were those who had received the placebo. Nor was there any evidence of support in the secondary endpoint, an immune response that resulted in a lower viral load set point that might slow the course of disease progression. That trial was stopped and all other vaccine trials were placed on hold until researchers could figure out why.

Two factors emerged as associated with higher risk for infection in subsequent analysis: one was being uncircumcised, the other was higher titers of antibody to Ad5 from previous natural exposure to the virus. The former presumably increased the risk of HIV acquisition through sexual activity while the latter resulted in a blunted response to the vaccine.

A central question became whether the PAVE 100 trial was sufficiently different from STEP for it to move forward. At an AVRS meeting in December, supporters made the case that it was, but the committee wanted to see further post-hoc analysis of the STEP trial, particularly analysis of immune function generated by both vaccines as measured by the same assays. Prior studies had been conducted using different assays and methodologies, making head-to-head comparisons difficult.

## What's New

At last week's committee meeting, M. Juliana McElrath, MD, PhD, from the University of Washington in Seattle, presented an impressive amount of new data and analysis that the AVRS had requested. It showed that the 2 vaccines generated somewhat different immune responses, as would be expected given the somewhat different constructs used in each. STEP generated stronger responses in some areas, and PAVE in others. Analysis of proliferation and neutralization remains to be performed.

Those differences may have been statistically significant in some instances, but there was little reason to believe that they might be clinically significant. There are no established correlates of protection in humans, but animals that naturally control SIV infection exhibit an immune response that is many times broader in terms of the number of epitopes recognized, and the immune response was of greater magnitude than either of the vaccines generated in humans.

Dr. McElrath did point out that a few vaccinated individuals in the STEP trial appeared to have an association between a higher response to gag and a lower viral set point. The analysis was post hoc and offered a clue as to where future investigation might focus.

## PAVE Revamped

The PAVE 100 sponsors substantially revised the trial in light of issues raised by the STEP trial and recommendations by the AVRS. Principal investigator Scott Hammer, MD, professor of medicine at Columbia University in New York City, presented the current iteration. The product and its administration would remain the same, but the study population would be greatly restricted, they would be studied much more intensely, and the emphasis would shift from product development toward basic research.

The study would shrink to 2400 participants; the international groups would disappear; and enrollees would be exclusively men who have sex with men (MSM) who are both circumcised and have no measurable antibodies to Ad5 at screening. It assumes a 3% incidence of HIV infection within the study population, a conservative projection given the 4.6% incidence that actually occurred in a similar population in the STEP trial.

The new primary endpoints are (1) effect on viral set point among those who become infected and (2) safety of the product. The secondary objectives are to determine:

- efficacy at preventing infection
- predictive value of early specific CD8+ T-cell response to a lower viral set point or protection from infection
- immunogenicity of the product
- effect on disease progression

Additional study of viral isolates and immune response will may enable a better understanding of the basic science of early infection and development of better tools to measure response.

### **Community Perspective**

Several community advocacy organizations in their oral and written testimony focused on how the revised PAVE 100 differs from a traditional vaccine trial. The revisions will require a substantial educational effort to ensure informed consent from those participating in it.

Martin Delaney with Project Inform was not convinced that trial should move forward. He called the data "singularly unconvincing." After hearing the comparative analysis presented for the first time, he concluded, "There was really no pattern of superiority, only patterns of differences. That is a word of caution as to whether these vaccines are really different."

He added, "We are asking so little in this trial. It is not going to protect people, it very likely is not going to affect viral load. And if it fails to meet even those endpoints, it is going to have a very hard time with the media and in Congress 3 years from now."

Mr. Delaney reminded the group, "The goal is not to create an HIV vaccine, the goal is to bring the HIV epidemic under control. A vaccine is a way to do that, but it is not the only way to do it, it is just one of them."

The Treatment Action Group (TAG) said in a submitted statement, "Based on the information that is currently available to us, we feel that the uncertainties argue against spending human and fiscal resources on PAVE 100 and instead suggest focusing on improving T cell–based immunogens so they can be studied in a broader population with a greater chance of success."

### **Skeptics Ask for Delay**

NIAID's Anthony Fauci, MD, PhD, posed the central question for the advisory committee: "Is there a reasonable chance that the field will gain from this in a way that is really discovery, as opposed to developing a product?"

The greatest reservations came from those working most closely with nonhuman primates. The University of Wisconsin's David Watkins, PhD, pointed out that the challenge in animals is autologous to the vaccine constructs, while the natural challenge to humans likely will be heterologous.

He added, "We need to remember that the number of epitopes induced by DNA/Ad in macaques far exceeds the 2 or 3 epitopes induced in humans. I have a hard time using the nonhuman primate data to support moving forward with this particular vaccine."

Bruce Walker, MD, from the Partners AIDS Research Center, thought the STEP and PAVE vaccines "are essentially indistinguishable." He saw little reason to proceed with the trial as a protective vaccine but did support it as a study to better understand vaccine-induced immune responses and perhaps identify correlates. But the study needs to be framed and explained to participants in those terms, he said.

Dennis R. Burton, PhD, from Scripps Research Institute, confessed to going back and forth as to whether the trial should proceed. He did not believe it to be a trial so much as "a human experiment." He suggested that in the lab, such an experiment would not move forward without greater rigor. "I'd be more in favor of taking a step back and thinking about what it is that we want to know from this experiment, and making sure that we have everything in place to do that."

Cornell University researcher John Moore, PhD, shared those concerns. "We have to define what we are going to learn and how we are going to learn it." He urged inclusion of a component on host genetics and correlates of immunogenicity.

### **Supporters Encourage Moving Forward**

Jerald C. Sadoff, MD, president of the Aeras Global TB Vaccine Foundation, was perhaps the most upbeat person on the panel. He saw the events as "a normal part of vaccine development" where failure is standard. He reminded the committee that a vaccine for malaria grew from identifying protection in a single individual and amplifying that into broader coverage and protection through the iterative process.

He focused on the weak inverse correlation between viral load and cellular immune responses that was found in the retrospective analysis. "It is the only positive finding of vaccine-induced protection in the entire field of HIV vaccine research. There is not another example in humans of such a finding, whether it is valid or not. There is no way to make it valid except to repeat it," Dr. Sadoff stressed.

"In my mind, the purpose of this experiment is to repeat that and find out if it is true. Everything else is gravy." From that perspective, Dr. Sadoff worried that the 2 vaccines might not be similar enough.

Lawrence Corey, MD, a researcher at the University of Washington in Seattle and principal investigator of the HIV Vaccine Trials Network (HVTN), argued that PAVE was necessary to establish whether the STEP trial was a failure of a product or of the T-cell vaccine concept in influencing acquisition and disease progression.

He downplayed the impact of another potential failure because that is several years away and the public can absorb it over time. Dr. Corey added that delay will only increase the size and cost of a trial because preexposure prophylaxis (PrEP) trials are likely to begin enrolling participants in 18 to 24 months. New, refined assays are most likely to be developed within the context of an ongoing trial.

"STEP was a landmark trial that wakened up from this blissful state of optimism of where we were in the vaccine field," Dr. Corey said. He said he thinks the field needed "the reality test" of other trials to move forward.

Susan Buchbinder, MD, from the San Francisco Department of Health, pointed to the 4.6% incidence of infection within the MSM participants in the STEP trial as a reason to proceed, particularly within the new target population of the PAVE trial.

Some questioned how using an Ad5 vector in persons who had not been previously exposed to that virus might be transferable to the broader world stage where levels of antibody to Ad5 are more common and higher than what is seen in the United States.

But the Gates Foundation's Margaret A. Liu, MD, saw this as "broadening the possible relevance of the results rather than narrowing it, because it is much more similar to [what would be seen with other vectors in development] where people do not have preexisting immunity."

## **Fauci's Dilemma**

Dr. Fauci has devoted an inordinate and intense amount of time to questions surrounding HIV vaccine development. In closing remarks he said we are in "a spectacularly unique position [in terms of] how little we know." We don't even know if immune protection is possible, he said.

In speaking with reporters he thought there was a broad consensus to move forward with the trial. He acknowledged that there may be additional minor modifications to the PAVE 100 protocol, and that outright cancellation would result in few net savings given the fixed costs already invested in the trial.

Dr. Fauci said he anticipates a fairly quick decision on whether the modified PAVE trial will move forward.