



HIV vaccine trial no longer PAVEs the way

The National Institute of Allergy and Infectious Diseases (NIAID) decided recently to cancel plans for a large clinical trial of a candidate vaccine against HIV.

The canceled clinical trial, known as PAVE 100, was originally proposed in January 2007 and designed to test whether the vaccine, which was developed by the NIAID's Vaccine Research Center (VRC), could reduce acquisition of HIV infection and reduce viral load in those who became infected. However, PAVE 100 was put on hold even before it began enrolling volunteers and was then redesigned in May 2008 to reduce its scope after the failure of a similar vaccine made by Merck in a smaller clinical trial. Now Anthony Fauci, director of the NIAID, has decided to cancel the clinical trial altogether, saying that it was becoming clearer that more fundamental research and animal testing would be needed before an HIV vaccine was ever marketed (1).

The candidate vaccine was to be administered using a prime-boost strategy, whereby individuals would be immunized three times with a priming DNA vaccine containing synthetic versions of four HIV genes (*gag*, *pol*, *nef*, and *env*) followed by a vaccine boost in the form of a weakened common cold virus (specifically adenovirus type 5 [Ad5]) carrying the same HIV genes. The vaccine boost element is similar to the vaccine developed by Merck, which was tested

in a phase IIb clinical trial known as STEP — a multicenter, randomized, double-blind, placebo-controlled trial in which 3,000 participants in North America, South America, the Caribbean, and Australia received three doses of either vaccine (a mixture of three components, each consisting of a replication-defective Ad5 carrying a synthetic form of either *gag*, *pol*, or *nef*) or placebo.

The STEP clinical trial was halted in September 2007 after interim analysis indicated that the vaccine did not work — it failed to reduce both acquisition of HIV infection and viral load in those who became infected. Subsequent analyses indicated that the vaccine made some individuals more susceptible to infection with HIV: more individuals who received the vaccine became infected with HIV than did recipients of the placebo. Although the vaccine itself was not responsible for the increased acquisition of HIV infection, it particularly increased the risk of infection in males who were both uncircumcised and had preexisting antibodies specific for Ad5.

Given the similarity between the Merck vaccine and the vaccine boost portion of the VRC vaccine regimen, the original design of the PAVE 100 trial came under intense scrutiny from the AIDS Vaccine Research Subcommittee (AVRS), the group assisting the NIH in developing a comprehensive research program aimed at expediting the discovery and development of an HIV/AIDS vaccine. However, the scientists involved in PAVE 100 argued that much could still be learned from a clinical trial with their vaccine, and they scaled down the scope of their trial from 8,500 individuals in multiple international locations to 2,400 individuals in the United States. Furthermore, the redesigned PAVE 100 trial was to enroll just men who have sex with men, and only those both circumcised and with no measurable Ad5-specific antibodies at screening, and to focus on determining whether any immune correlates of decreased viral load could be detected in those who became infected during the course of the trial.

When the redesigned PAVE 100 clinical trial was outlined at the May 2008 meeting of the AVRS, most members expressed support for the scaled-back trial (2). However, in announcing his decision, Fauci said that after meeting with scientists try-

ing to understand why the Merck vaccine failed, he concluded that doing a large trial was not justified because scientists still do not understand many fundamental facts, such as which immune reactions are the most important in preventing infection with HIV (1).

The NIAID will consider a much smaller and more focused trial designed to test whether the vaccine can markedly decrease viral load in individuals who become infected. "Show me that the vaccine works by lowering the amount of HIV in the blood," said Fauci. "Then we will move to a larger trial that will document the link with a particular immune response" (1).

A minority of researchers at the May 2008 meeting of the AVRS expressed concern that the VRC vaccine to be tested in the PAVE 100 clinical trial performed very similarly to the Merck vaccine in immunogenicity assays; one of the minority, John Moore (an HIV researcher at Weill Cornell Medical College), told the *JCI* that he agreed with the decision of the NIAID to cancel the vaccine trial. Other vaccine advocates, such as Seth Berkley, president and CEO of International AIDS Vaccine Initiative (IAVI), were quick to stress that "The decision by NIAID does not reflect paralysis in the AIDS vaccine field, or a lack of direction forward. In fact, it reflects the opposite. It reflects the dynamic learning that is the scientific process, that is pharmaceutical product development. The decision reflects leadership on the part of NIAID" (3).

Berkley continued, "The AIDS vaccine field does not suffer from a lack of ideas about how to move forward . . . There's a lot of work going on and a lot more that needs to get done. We're not at our destination, but we know the paths to follow" (3).

Karen Honey

1. Altman, L.K. 2008 July 18. Trial for vaccine against H.I.V. is canceled. *The New York Times*. <http://www.nytimes.com/2008/07/18/health/18vaccine.html?hp>.
2. National Institute of Allergy and Infectious Diseases. 2008 May 30. AIDS Vaccine Research Subcommittee Meeting. http://www3.niaid.nih.gov/research/topics/HIV/vaccines/advisory/avrs/avrs_may08.htm.
3. International AIDS Vaccine Initiative. 2008 July 17. IAVI Statement in response to NIAID decision not to move forward with PAVE 100 HIV vaccine trial. <http://www.iavi.org/viewfile.cfm?fid=49062>.



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