

Summary report of the December 12, 2007 meeting of the AIDS Vaccine Research Subcommittee



This report provides summary coverage of the December 12 meeting of the AIDS Vaccine Research Subcommittee (AVRS) of the NIH AIDS Research Advisory Committee. The AVRS met to discuss STEP and future HIV vaccine trials. This committee is in a position to make a recommendation about NIH-funded vaccine trials.

In a heavily-attended session which was open to the public, the AVRS met and reviewed data analysis to date on the STEP trial and discussed possible ways forward for the PAVE 100 trial, a planned efficacy study of a combination strategy (including a DNA prime and an adenovirus-vectored boost) developed by the US Vaccine Research Center (VRC).

Update: STEP Data Analysis

During the first part of the meeting, presenters reviewed and committee members discussed the ongoing efforts to understand the STEP study data. Here, there are two central questions:

- 1) Why did the vaccine fail to reduce viral load setpoint or to reduce the risk of infection?
- 2) What is the explanation for the apparent increase in susceptibility to HIV infection that was observed in male vaccinees with high Ad5 titers (>200)?

There are no clear answers to either question at this time. The following brief summary aims to capture some of the most salient points from the discussions and presentations.

Understanding vaccine failure

In the Sherlock Holmes mystery, *The Hound of the Baskervilles*, one of the central clues is an absence: the hound that did *not* bark in the night. Similarly, with the STEP data, the absence of protective benefit is of the utmost importance for our next steps. As committee members discussed, the field must look closely at the tests that were used to evaluate Merck's vaccine candidate, MRK-Ad5. Using this information, we can seek to draw conclusions about improving the "assays" or tests used to evaluate future vaccines in pre-clinical, animal models and early clinical trials.

For example, MRK-Ad5, like all candidate vaccines, was advanced into human trials after extensive pre-clinical testing and studies in non-human primates. In the primary non-human primate study that showed vaccine-related benefit, monkeys were given a candidate vaccine closely resembling MRK-Ad5 and challenged with a viral strain called SHIV 89.6p. Monkeys that received the vaccine had lower viral loads than those that did not get the vaccine. Based on the subsequent failure of the candidate in human clinical trials, there is a strong sense, voiced by several AVRS members, that animal model challenge experiments using SHIV 89.6p should not be used as the basis for advancing candidates.

At the meeting, there was more discussion, and less consensus, on how to use immunogenicity assays (measures of vaccine-induced immune responses) to predict whether or not a vaccine will have a protective benefit in humans. In the very simplest terms, the consensus from the committee appeared to be that immunogenicity measures need to move well beyond ELISPOT assays that measure interferon-gamma production. There are several additional assays that can be

used to provide a clearer picture of vaccine-induced immune responses. These include: proliferative ability, polyfunctionality (ability to produce more than one cytokine, i.e., interferon gamma, TNF-alpha, IL-2, etc), and phenotype (effector or memory cell). (For more information on assays [click here.](#))

One of the critical questions is whether or not to advance the VRC candidate strategy (DNA prime plus adenovirus boost). Immune responses induced by MRK-Ad5 and VRC candidates have not been analyzed using identical methods. This makes it difficult to draw firm conclusions about how the candidates compare to one another. There was a strong feeling at the committee that these comparisons (which might potentially be done with stored samples) should be done to provide additional insights into how different the VRC strategy is from MRK-Ad5. AVAC fully endorses this suggestion.

Understanding the STEP data

There are, at this time, only the faintest of clues about whether there are biological factors underlying the STEP data—specifically the greater number of infections in men with pre-existing Ad immunity who got the vaccine as compared to men with preexisting immunity who received placebo. The crucial question to attempt to answer is whether and how the Merck vaccine might have increased susceptibility to HIV infection among these volunteers. Julie McElrath of the University of Washington and the HVTN reviewed the analyses that have been completed to date. She reported on several analyses which did not find differences in the quality or duration of vaccine-induced immune responses in the high versus low Ad5 groups. She noted that at week 30, after volunteers had received all three immunizations, men in the high Ad5 group had greater numbers of activated T-cells expressing CCR5 than individuals with low Ad5 titers. CCR5 is a cell-surface receptor that HIV uses to infect cells. However, there were no differences in overall numbers of activated cells between the groups. This increased expression of CCR5 may or may not be relevant to the observed vaccine effect.

Mike Robertson of Merck reviewed [the STEP data presented at the HVTN Full Group Meeting on November 7](#). He noted that men with high Ad5 titers were more likely to be from outside the US and Australia and more likely to be uncircumcised. The data are highly complex. For example, as Roberston discussed, among the high Ad5 titer group there were more infections in circumcised vaccinees than there were in circumcised placebo recipients. One committee member observed that perhaps some vaccine-related effect on susceptibility was overcoming the protective effect of circumcision. But these questions are, for now, speculative. As Robertson said, the data on herpes serology (whether participants had HSV-2, which has been linked to susceptibility) and more complex multivariate analyses are still being conducted. It also remains to be seen—and could never be clear—whether background immune activation (which could be due to different parasite and pathogen burdens in the environment) might also contribute to a biological explanation for the increased susceptibility.

Dr. McElrath outlined a range of additional analyses that will be conducted and emphasized that the trial sponsors were actively soliciting proposals from the broader scientific community. An independent committee, chaired by Bruce Walker, Director of the Partners AIDS Research Center at Massachusetts General Hospital, has been convened to review these proposals.

McElrath said that the full scientific agenda for STEP data analyses would be presented at the CROI meeting in early February in Boston. For more information about submitting proposals [click here](#).

Following the presentations by Robertson and McElrath, there was a general discussion of ways forward. The following is a partial list of the suggestions that were made about how additional questions might be answered:

- Use multivariate analyses and, possibly, case control methodology to analyze data on participants with the goal of better understanding the effects of various factors on susceptibility.
- Gather information on the immune responses to adenovirus that are generated by people who are naturally exposed: what is the nature of the T cell response? Is it biased towards memory or effector cells?
- Examine linkages between antibody levels and HIV susceptibility in STEP volunteers, in light of observations about antibody levels and rates of infection in participants in the failed VAXGEN trial. [Click here](#) for some background on the VAXGEN data.
- Try to determine how natural Ad5 immunity may compare to immunity induced by the viral vector.
- Gather information on if and how pre-existing antibodies affect how the vaccine is “taken up” and presented by immune cells.

Several subcommittee members emphasized that it is difficult to tell whether high Ad5 titers are causally-related to the apparent increased susceptibility, or whether they are an “epiphenomenon.” An epiphenomenon is something which happens alongside of, and secondary to, a primary phenomenon. In this case, it means that Ad5 titers could be secondary to some other, as-yet unidentified primary biological cause for increased susceptibility. Some of the panelists at the AVRS meeting referred to this as a “correlate of susceptibility.” Many also emphasized that the data analyses may not yield any definitive answers.

Update: Phambili

Larry Corey, of the HVTN, gave a brief update on the Phambili trial. He said that almost all of the volunteers have been unblinded at this time and follow-up is ongoing. Corey said that the data would be reviewed after 30 infections had taken place in the volunteer population. Since the study has been unblinded and both staff and volunteers know whether or not they received the vaccine, sites will also be able to keep an ongoing tally of infections in both arms. It is important to remember that all volunteers are receiving intensified risk-reduction counseling along with condoms and STD treatment at every follow-up study visit. Since the trial was halted early on, only 38 volunteers had received all three immunizations (either vaccine or placebo); 501 people received two immunizations (either vaccine or placebo); and 215 people received one immunization (either vaccine or placebo).

PAVE 100

Should the field move the VRC candidates (DNA prime and Adeno-vectored boost) into a redesigned PAVE 100 efficacy trial?

There was a robust discussion about moving the VRC candidates forward into an efficacy trial. The subcommittee grappled with two questions:

- 1) Is the VRC adeno-vectored candidate sufficiently different from MRK-Ad5 to warrant further testing?
- 2) Based on what we know now, could the trial be done? And, if so, how?

In a straw poll of committee members, the majority said that the candidate was sufficiently different from MRK-Ad5 to warrant further testing. There was less clarity when it came to the important and largely-unspoken question: how different is different enough? Here, some subcommittee members raised concerns about the breadth of the immune responses induced by the VRC strategies, while others raised broader questions about how the potential failure of a PAVE efficacy trial would impact the field and, specifically, future T-cell vaccine strategies.

There was general consensus that a redesigned PAVE 100 test-of-concept trial could be done. But there was substantial discussion and no resolution about the optimal design for this study.

Unanswered questions include:

- Should a redesigned PAVE trial focus on a single population with a high incidence rate that can give a relatively quick answer—e.g., men who have sex with men? Or should it seek to enroll a diverse cohort in order to address questions about whether the vaccine works differently depending on route of transmission (e.g., vaginal versus anal intercourse) or other factors?
- If the trial were to go the route of a diverse and international cohort, how would the sponsors avoid a time lag between start up in developing and developed world sites?

There was strong consensus that a redesigned PAVE 100 could only enroll Ad5-seronegative individuals. This is an essential precaution based on the possibility of enhancement observed in male STEP volunteers with pre-existing immunity to adenovirus. In its initial design, the STEP study stratified its volunteers into high and low Ad5 groups based on titers of above or below 200. However as Larry Corey presented, when volunteers are grouped according to the presence of *any* pre-existing Ad5 antibody (the assay cut-off is 18), the enhancement effect is still seen. Therefore, any study of an Ad-vectored HIV vaccine would only enroll Ad5-seronegative (<18) individuals.

Adding Ad5 seronegativity as an enrollment criterion would have dramatic effects on trial design. Ad5 seroprevalence varies throughout Africa but, as we heard at the meeting, by some rough estimates, up to 90% of the cohorts that had been preparing for PAVE 100 would be ineligible based on this criterion.

A presentation by Magdalene Sobieszcyk from Columbia University gave an initial review of potential trial designs. This review did not explore details of how community acceptance might affect enrollment rates, or of the feasibility and potential concerns raised by regulatory and ethics authorities in participating countries. Exploring these and other factors, including resources and time needed for community outreach and education is an essential prerequisite to any decision about a redesigned PAVE efficacy trial.

Summary of AVAC views

- Decisions about a redesigned PAVE 100 trial cannot be made hastily and must involve a more diverse array of stakeholders, including scientists, regulatory authorities, and advocates from regions of the world where there is high pre-existing immunity to Ad5—e.g., countries in Africa and Latin America. By the same token, there is a need for clear, global communication about the possibility that a redesigned PAVE could go forward.
- Samples of vaccine-induced immune responses from MRK-Ad5 and the VRC strategies should be analyzed using identical assays. This head-to-head comparison is needed and should be a priority.
- Critical details about the feasibility and potential design of a PAVE efficacy trial remain unclear and must be carefully explored.
- In the absence of a clear explanation for the STEP data, the field must err on the side of caution and assume that there may be a safety issue with Ad5-vectored AIDS vaccines in people with pre-existing adenovirus immunity. Based on what we know now, this means that the VRC candidates might not be suitable for licensure trials (due to safety concerns). While this could change, we must acknowledge the many unknowns that surround the STEP data and all Ad5-vectored candidates at this time. It is essential that the VRC develop a clear product development pathway should a redesigned PAVE 100 study given an indication of benefit.
- The field as a whole must articulate a clear scientific agenda for next steps; this agenda should consider the next steps should a redesigned PAVE 100 fail to show efficacy or show safety issues like those seen in STEP.

The AIDS Vaccine Advocacy Coalition (AVAC) is a non-profit, community- and consumer-based organization that uses public education, policy analysis, advocacy and community mobilization to accelerate the ethical development and global delivery of AIDS vaccines and other HIV prevention options. For additional information and up-to-date resources, please visit www.avac.org or e-mail avac@avac.org.