



## A Trial by Any Other Name: HVTN 505 and the VRC candidate

As *AVAC Report* went to press, the US Food and Drug Administration (FDA) had recently approved the protocol for HVTN 505, the test-of-concept study of the National Institutes of Health's Vaccine Research Center's (VRC) strategy that consists of three DNA "prime" immunizations and a single adenovirus 5–vectored "boost." (See timeline on page 37, and for more detailed information on the history of this candidate, please visit [www.avac.org/vax\\_update.htm](http://www.avac.org/vax_update.htm).)

At roughly the same time, some members of the scientific community were discussing newer animal data that had some relevance to HVTN 505. Much of the talk centered on the results of a study by Harvard's Dan Barouch and colleagues, in which animals received one of two variations on a DNA plus chimeric Ad (Ad5 plus an Ad48 hexon protein), or one of two variations on the chimeric Ad alone.<sup>5</sup> In that experiment, presented at this year's Keystone conference on HIV prevention, the animals that got the DNA plus chimeric Ad had survival rates and clinical outcomes comparable to the placebo group, while the chimeric Ad-alone animals had improved survival outcomes and, in an exploratory combined analysis, significantly lower viral loads. Barouch noted that his findings should be viewed as hypothesis-generating rather than conclusive.

Monkey studies are, by definition, small and inconclusive. Monkeys aren't humans; the numbers are too small to draw firm conclusions; and in the absence of a correlate of protection, it's difficult to know whether we're measuring the right things. What's more, the data concern a different vector; thus the strategy cannot be directly compared with the VRC strategy.

So why were Barouch's data of interest in the context of HVTN 505?

Primarily because monkey data considered relevant to the VRC vaccine strategy to be tested in HVTN 505 have been part of the scientific rationale for moving the trial forward.<sup>6,7,8</sup> Monkey data were cited extensively at the December 2007 meeting of the AIDS Vaccine Research Subcommittee (AVRS) of the NIH and mentioned in the fact sheet that the HVTN produced on 505 one year later. Over the past year, AVAC has voiced concern about the lack of clear materials to help lay audiences understand HVTN 505. These include the lack of clarity in explanations of both the scientific rationale and the ways that the trial

<sup>5</sup> DH Barouch. Novel Adenovirus Vector-based Vaccines for HIV-1 *Keystone Symposia Conference: Prevention of HIV/AIDS (X3)*. Keystone, Colorado, 2009 March 22-27. Abstract #017.

<sup>6</sup> Shiver JW, et al. Replication-incompetent adenoviral vaccine vector elicits effective anti-immunodeficiency-virus immunity. *Nature*. 2002 Jan 17;415(6869):331-5.

<sup>7</sup> Bolton DL, et al. Aerosol Adenovirus Immunization Controls Early Viremia. *Keystone Symposia Conference: HIV Immunobiology: From Infection to Immune Control (X4)*, Keystone, Colorado, 2009 March 22-27. Abstract #125.

<sup>8</sup> Casimiro DR, et al. Attenuation of simian immunodeficiency virus SIVmac239 infection by prophylactic immunization with DNA and recombinant adenoviral vaccine vectors expressing Gag. *J Virol*. 2005 Dec;79(24):15547-55.

was addressing the safety of participants—this in light of its use of an Ad5-vectored candidate that was similar to, though not identical to the candidate used in the Step trial.

Even though they're not directly related, the data presented by Barouch are still relevant to potential trial participants and communities as part of the broader body of knowledge around the proposed HVTN 505 trial, and they point to the unmet need for clear, simple statements of the rationale for the trial and how the varied body of non-human primate and human data have been analyzed to date.

These concerns aren't about whether HVTN 505 adequately addresses participants' safety in light of Step—we believe that this was addressed by the exclusion of Ad5-seropositive, uncircumcised men. The concerns are about the communication around these criteria and how the scientific rationale for the study is being explained to participants and engaged communities.

AVAC has followed and sometimes participated in many discussions about this candidate and whether it should be tested further. We feel that human trials are an invaluable part of the AIDS vaccine discovery process. The Step trial has provided a wealth of information that would never have been obtained otherwise. A trial of the VRC strategy could theoretically do the same. But, is such a trial possible? And have the NIH and the HIV Vaccine Trials Network (HVTN) taken the steps that would lead to such a trial? Here, the answers are more mixed.

The Step results brought an unprecedented dialogue involving NIAID, its Vaccine Research Program, and the broader community of HIV prevention advocates like AVAC who are not part of trial site communities. In the aftermath of the Step finding, there was a high level of information and materials sharing and constructive dialogue about how to craft messages that were accurate and moved the field ahead. This held true around PAVE 100 as well. But with the advent of 505, the gap has increased between the broader community (advocacy groups working on and impacted by HIV prevention research) and the trial sponsors, which has impeded community stakeholders from getting involved. The publicly available materials and consultations have fallen short in explaining such a complex undertaking. Specific concerns include:

- A series of calls held by the NIH allowed community members to hear a description of the trial and to pose questions to investigators in real time. Such forums are important and should be continued. But it's unrealistic to expect anyone to absorb the information for such a complex trial in a single conference call and to formulate the right questions. NIAID and HVTN representatives have made themselves available on an ongoing basis to answer questions. However, there's still a shortfall in terms of community-oriented materials that provide critical information in an easy-to-digest written format, such as a protocol summary, or a more detailed fact sheet addressing questions raised on the calls or

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other topics. Such written materials are key to helping communities navigate the complexities of this proposed trial.

- Confusion and concerns about whether the proposed strategy is safe to test—and how HIV prevention advocates could responsibly represent the trial to their friends, colleagues, and allies—have not been adequately addressed in the forums where AVAC has heard them raised. These are difficult questions to be sure. And the investigators and staff involved have the best intentions. The current fact sheet outlines the safety issues but does not provide a detailed, coherent explanation that can be used as the basis for community-led discussions.
- The public information sheet distributed by HVTN instructed individuals who were interested in learning more about the trial protocol to join community advisory boards (CABs). However, because no details were listed regarding sites or cities where the trials would take place, individuals couldn't easily decide whether the effort was worthwhile. Moreover, the link to the HVTN site led to a map of HVTN sites' own home pages. Some of the links on the individual sites' websites were to staff people who no longer worked there; on others it was difficult to figure out how to join. A far better approach would be to create a link to a page that includes (1) the list of trial sites (or likely trial sites, with a proviso that the protocol is in formation); (2) a list of contacts for these sites; and (3) some explanatory text about what CABs do and what membership entails. As it is, individuals who may have wished to be involved in protocol review had slim chances of accomplishing that.
- Discussions of the scientific rationale for the trial have focused on the data from monkey studies that show a different quality of immune responses in animals that receive the DNA plus Ad5 combination versus Ad5 alone. Several of those studies show no difference in clinical outcomes of viral load or survival in animals that received DNA plus an adenovirus-vectored candidate versus the adenovirus-vectored candidate alone. There are numerous variables in each of these studies as well as others that preclude drawing one over-arching conclusion. This complexity doesn't mean communities can't hear a more detailed explanation of the scientific rationale than they have to date, including the following statement:

*There are data suggesting a possible benefit from a DNA + adenovirus-vectored prime-boost strategy, and there are also data suggesting that this is not an optimal strategy to evaluate.*

On the positive side, in March 2009 in Philadelphia, HVTN started a series of town hall meetings for community discussion about HVTN 505 and vaccine research in general. These are not recruitment events but discussion sessions that will happen in each city that's home to a site. This is an excellent initiative, and we look forward to learning from these discussions and hope that the questions generated will be documented and shared in broader forums. Principal investigators Scott Hammer and Magda Sobieszczyk have been unfailingly open to conversations, requests for information, and presentations, as have other staff members at the NIAID and the HVTN.

A social science, psychosocial, and behavioral research working group has been convened to look at additional questions that could be posed and possibly answered through HVTN 505. Some of these questions concern data gathering to support trial data analysis. Others are aimed at some of the gaps that have been articulated in the Black Gay Men's Research Agenda, the research agenda articulated at the Gay Men's Health Summit, and similar documents. This approach adds value to the communities involved in the study. Whether there's a direct clinical benefit from the VRC vaccine strategy, there could be useful information gleaned to help communities advocate and implement different types of programs and research.

With FDA approval in place, we're one step closer to posing the question about what the VRC strategy does in humans. Whether that question gets answered depends on how the trial happens. We at AVAC have long argued that this will likely be one of the most complex trials to explain and in which to enroll participants, making the collaborative work that should be in place for any trial all the more important.

