RV144: A Flawed Trial Falls Victim to Changing Circumstances
Treatment Action Group, Testimony to the FDA Vaccines and Related Biological Products Advisory Committee, September 23, 2004

The phase III trial currently before the committee has been a subject of controversy, as outlined in the background document prepared for this meeting by FDA. The Treatment Action Group (TAG) has serious reservations about RV144 and the decision by FDA to allow the trial to proceed as currently designed.

Can you prove the concept of the trial without an ALVAC only arm?

Perhaps the most significant concern regarding RV144 is the single arm design that will not allow the relative contributions of the two vaccine components (ALVAC vCP1521 and AIDSVAX B/E) to be evaluated. A previously planned trial, HVTN 501, would have compared the effects of a similar ALVAC vector alone to ALVAC+AIDSVAX. This trial was cancelled due to the poor immunogenicity of the ALVAC vector which would have prevented the study from achieving its main goal, which was to assess CTL responses (as measured by interferon-gamma ELISpot) as a correlate of protection. In the absence of HVTN 501, a successful outcome to RV144 would require additional phase III studies to tease apart the roles of the two vaccines in the observed protection. In other words, the concept that the trial is attempting to "prove" is that ALVAC-induced cellular immunity plus AIDSVAX-induced humoral immunity will be more protective against HIV infection than either approach alone, yet we have no idea whether ALVAC can offer any degree of protection against HIV infection (we do know that AIDSVAX alone – whether B/B or B/E - does not).

Lest it be assumed that the effect of adding AIDSVAX to ALVAC could only be additive, at least one study in macaques found that adding a gp120 protein boost to a vaccine designed to elicit cellular immunity resulted in a poorer outcome compared to the same regimen without the protein boost (S. L. Buge *et al.*, *AIDS Res. Hum. Retrovir.* 10:891, 2003).

To commit significant human and financial resources to a vaccine trial that cannot provide a definite answer to the question it purports to ask seems deeply foolish, particularly when there is widespread agreement that current funding for HIV vaccine research is inadequate. Based on this concern, TAG initially argued that the AIDSVAX boost should simply be dropped from RV144, allowing the study to definitively evaluate the protective efficacy of ALVAC vCP1521 (see *Science* 305;5681:180, 2004). However, once volunteers began to receive AIDSVAX immunizations this argument essentially became moot.

Ethical Considerations

The Helsinki Declaration states: "Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research."

TAG would argue that the benefits of participating in a phase III trial that can, at best, only lead to additional trials and cannot provide definitive answers as to the protective efficacy of the two vaccines involved are rather unclear. At the recent Bangkok meeting, it was stated that >70% of participants so far enrolled in RV144 cited "altruism" as their primary motivation, which leads to the question of whether the participants are aware that – even if successful – the trial will not be able to lead directly to the approval of an HIV vaccine for their population, or any other.

Politics & Science

TAG does not question the sincere and good-faith effort that many people (both in the US and Thailand) have put into RV144 since the idea was first proposed towards the end of the nineties. However, the failure of the leadership behind the trial to adapt to the changing circumstances surrounding it reflects poorly on trial's sponsors. The cancellation of HVTN 501 and the failure of the two AIDSVAX efficacy trials should have prompted a more thorough review of RV144 than seems to have occurred, and this review should have included input from NIAID's advisory body, the AIDS Vaccine Research Working Group (AVRWG) and FDA. Instead, input from the AVRWG was not solicited until after the study quietly began enrolling in October 2003. It is possible that this process was negatively affected by the politicking that surrounded the merging of the Military HIV Research Program back into the Division of AIDS at the National Institute for Allergy and Infectious Diseases (NIAID). TAG's understanding is that NIAID had to commit to supporting RV144 to completion as part of this merger, which presumably limits the ability of NIAID and its expert advisors to mandate substantive changes to the protocol.

AVRWG Recommendations

After a discussion at the January 2004 AVRWG meeting, a subcommittee chaired by Scott Hammer and comprising Larry Corey, Jerry Sadoff and ad hoc advisor Steve Self did review the RV144 protocol and made a series of recommendations aimed at improving the study, which were endorsed by the AVRWG as a whole. At the recent AVRWG meeting in Lausanne, Jorge Flores presented the response of the RV144 investigators to each of the recommendations. Below is TAG's summary of the recommendations and responses (any errors are ours and further information should be sought from the AVRWG):

- Recommendation: Making protection against HIV infection and reduction in post-infection viral load co-primary endpoints of the trial, thereby potentially reducing the total sample size from 16,000 to 8,000 or less.

    - Response: Yes to co-primary endpoints, no to any reduction in sample size (in case there is a decline in incidence).
- Recommendation: Clearly defining the criteria used for post-infection viral load analyses.
    - Response: Yes.
- Recommendation: Providing immunogenicity data from a subgroup of vaccinees and controls to the Data Safety Monitoring Board (DSMB) in real time.
    - Response: No, but will consider enrolling an extra 200 people in order to conduct an immunogenicity study.
- Recommendation: Framing a futility analysis for use by the DSMB in order to ensure that the trial can be stopped if it is not going to meet the primary goals (e.g. due to insufficient endpoints or inadequate enrollment).
    - Response: Criteria for stopping trial due to operational futility will be promulgated. Stopping rules based on scientific futility will not be developed.

In the apparent absence of any possibility of dropping the AIDSVAX component from RV144, TAG endorsed the original AVRWG recommendation as a reasonable attempt to address the shortcomings of a trial that was already underway. The fact that the RV144 investigators have chosen to only selectively adopt the recommendations is therefore profoundly disappointing. TAG encourages the committee to discuss these issues further with the AVRWG and the RV144 investigators.

Lessons for the Future

TAG strongly encourages the FDA to rigorously address the potential of any HIV vaccine efficacy trial to lead to licensure of a product (or products), regardless of the where the research is conducted. We also strongly believe that go/no go decisions on moving vaccines into efficacy trials need to be based on the best available scientific evidence; it is notable that the International AIDS Vaccine Initiative recently announced that they will likely not move their DNA/MVA HIV vaccine candidate into efficacy trials due to poor T cell immunogenicity, yet the levels of immunogenicity achieved with this approach are comparable to those seen with the ALVAC vector under discussion today.