



*Advocacy to accelerate ethical research & global delivery of AIDS vaccines and other new prevention technologies*

*November 7, 2007*

**The following is a preliminary question and answer document that AVAC has prepared for advocates to understand the new STEP study data that were made public at the HIV Vaccine Trials Network full group meeting on November 7, 2007. We will continue to expand on and update our analyses in the weeks to come, and urge advocates to refer to the additional documents prepared by trial sponsors [see [http://avac.org/pr\\_step\\_study.htm](http://avac.org/pr_step_study.htm)]. As always, please send us any questions at [avac@avac.org](mailto:avac@avac.org)**

**1. What did we learn from the new STEP study data that were presented at the November 7<sup>th</sup> meeting of the HIV Vaccine Trials Network?**

One important and, at this stage, confusing finding was that there were more infections among male volunteers (see questions 4 and 5 below) who received the vaccine, as compared to male volunteers who received the placebo. This trend was more pronounced in volunteers who had high adenovirus titers (this is a measure of pre-existing immunity—those with high titers had naturally high levels of antibody to adenovirus type 5 at the time that they enrolled in the study, before they received the vaccine).

**2. Is there anything that we know for sure?**

We know that the vaccine itself **did not** cause HIV. It was constructed with synthetic fragments of genetic material which cannot, themselves, cause HIV infection.

We know that the vaccine did not provide protection against infection or a reduction in viral load among the male volunteers who received it.

We know that when there is any doubt about vaccine safety, it is imperative to err on the side of caution, and that volunteer safety is of the utmost importance.

We cannot say for certain that the vaccine itself increased risk of acquiring HIV. We also cannot say that it did not. Under these circumstances, AVAC feels that the field should slow down and take as much time as it needs to explore the underlying causes of the observed trend before launching trials of similar candidates.

We know that this is not the end of AIDS vaccine research. While these data are disappointing and deeply concerning, they should not be taken as a sign that the search for an AIDS vaccine is over.

### **3. Which study volunteers were included in the analysis?**

The meeting focused on data from the 1850 men in the trial. These were primarily men who had sex with men, and whose risk factors included high numbers of sex partners, partners with known HIV status, and unprotected anal sex.

Data on the 1150 women volunteers were not included in the analysis. As of October 17, 2007, there had been only one infection in a woman volunteer in the placebo arm. This does not mean that the vaccine protected women. Instead, the low rate of infections suggests that the women who were recruited were not at high risk for HIV infection.

### **4. Does this mean that the vaccine increased men's risk of acquiring HIV?**

It is possible. But based on the current data, it is impossible to say for sure. Presenters at the November 7<sup>th</sup> meeting described some of the analyses they had conducted to try to find other explanations. None of these analyses provided an alternative explanation, however here are some of the issues discussed:

- **The small number of total infections (n=82) in the trial.** While this number is relatively small, it does allow the trial team to draw strong conclusions that the vaccine did not protect against HIV and did not have an impact on viral load in men who received the vaccine and went on to become infected. These were the questions the study was originally designed to answer. Now scientists are analyzing these data to attempt to answer a question that the study was not designed to answer—namely whether the vaccine increased risk. Some of the ways that they are looking at this question involve segmenting the data into even smaller groups. In some cases, these subgroup analyses involve very small numbers of people, making it difficult to draw firm conclusions. While we must be cautious about drawing conclusions, we must also act on the data we have.
- **Differences in the populations of men with high and low Ad5 titers.** There were significant differences in some of the demographic characteristics of men in the high and low Ad5 titer groups. There were significantly more non-white, non-US men in the high Ad5 titer group. This group also had significantly more uncircumcised men and more men under the age of 30. However, in the analyses that have been conducted to date, none of these demographic differences account for the observed trend towards increased rates of infection in vaccine recipients.

### **5. Is there a compelling alternative explanation for the trend towards increased susceptibility in men who received the vaccine?**

No, not at this time. The November 7<sup>th</sup> presentations included preliminary analysis of a variety of variables. These included demographic characteristics, like the ones described above, as well as analyses of patterns of risk behavior reported by participants. In addition, researchers presented a limited amount of data on participant assumptions about whether they had received the vaccine or the placebo. These data helped to address questions about whether volunteers who assumed correctly that they had received the vaccine—i.e., after side effects or local reactions to the immunizations—took more risks than volunteers who received the placebo.

Researchers have also looked at preliminary immunology data and compared immune responses among vaccine recipients who became infected and those who did not. There were no significant differences in immune responses to the vaccines in any of the analyses reported.

Overall, none of these analyses provided a compelling alternative explanation for the observed trend.

## **6. Why did the study enroll people with high and low titers of Ad5 antibody?**

The vaccine candidate MRK-Ad5 used a disabled form of a common cold virus, known as adenovirus type 5, as the vector, or carrier, for synthetic fragments of HIV genetic material.

Viral vectors like adenovirus have been used in many HIV vaccine candidates. They are selected for their ability to stimulate a strong immune response to the HIV antigen included in the vaccine. It is hoped that these vaccine-induced immune responses will provide protection against HIV infection or disease if a person who received the vaccine is exposed to the virus through risk behavior later on.

Since adenovirus is a common virus, some people have been exposed to it and have had immune responses to it.

Early immunogenicity studies showed that people with high levels of pre-existing immunity to adenovirus had different levels of immune responses to the vaccine as compared to people with low or no pre-existing immunity. The first population enrolled in the study had low pre-existing immunity. Trial sponsors assumed that the vaccine had the best possibility of working in this population. However, while there were differences, research showed that people with pre-existing immunity also had significant responses to the vaccine. Sponsors recognized the need to get answers about how the vaccine worked in this population as well, and expanded enrollment STEP to include people with higher adenovirus antibody levels. The South African Phambili trial also enrolled a significant proportion of such volunteers.

## **7. What happens now?**

The trial scientists and their collaborators will continue to analyze the data that are available to try to understand what the results are really telling us. They will look at the types of viruses that people were infected with and probe possible differences in the high- and low-Ad5 groups that might have led to the perceived trend. They will also continue to look at immune markers in the samples taken from volunteers in order to understand if and how the vaccine might have increased the risk of infection.

## **8. What is the role for advocates?**

It is of the utmost importance that we all work together to communicate what is known and what is not known at this time. The over-riding priority is the safety of the volunteers. We must work together to ensure that the open questions are clearly explained to a wide variety of audiences. We must also ensure that decisions about future trials are made with caution and over a time period that allows us to learn as much as we can from the STEP data. At the same time, we must prepare for moving forward—as we must—even if some questions remain unanswered over the long term.