

December 18, 2008

## **An Advocates' Guide to Recent Publications on STEP AIDS Vaccine Trial Data**

In September 2007, a scheduled interim data analysis of the STEP study by an independent committee found that MRK-Ad5 did not prevent infection or reduce viral load set point. The independent committee recommended that the STEP sites stop immunization, since it was clear that the vaccine would not have a benefit even if the trial ran to completion. Immunizations were also stopped in Phambili, a companion trial of MRK-Ad5 in South Africa.

Further analysis of STEP showed that men who got the vaccine and were uncircumcised and Ad5-seropositive (meaning they had pre-existing antibodies to adenovirus, the cold virus used as a vector in the vaccine) were more likely to become HIV infected than comparable men (uncircumcised and Ad5-seropositive) who received the placebo. A vector is a component of the vaccine that carries synthetic fragments of HIV into the body. It helps induce immune responses. There was no increased risk of infection among men who received the vaccine and were circumcised and Ad5-seronegative, compared to placebo recipients with the same characteristics.

The past fourteen months have seen a range of efforts to understand why MRK-Ad5 didn't have any benefit, and why it apparently increased risk of HIV infection in some volunteers. The articles that we review are the most current information—and we'll keep you updated as new insights and developments emerge.

### ***Some Key Messages:***

#### **1. Lack of male circumcision + Ad5 seropositivity + vaccine = Tangled risk factors (maybe).**

The [article by STEP principal investigator Susan Buchbinder and colleagues](#)<sup>1</sup> reviews all of the analyses completed so far to understand the differences in rates of infections among subgroups of STEP volunteers. This analysis focused on the male volunteers in the trial. STEP also enrolled women, but the rates of infection in both the vaccine and placebo arms were very low at the time that immunizations were stopped; subsequent analyses focused on the infections in men, the majority of whom were gay men.

As we've discussed in previous [Advocates' Network updates](#), the subsequent analyses of STEP also focused on analyses of various subgroups of volunteers, including men who were circumcised versus uncircumcised, and men who had high, moderate or no pre-existing levels of antibodies to the Ad5 vector. Statisticians had designed the study to look at some of these subgroups, but not all of them—since the finding that the vaccine may have increased risk was totally unanticipated.

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<sup>1</sup> The Lancet, Early Online Publication, 13 November 2008. doi:10.1016/S0140-6736(08)61591-3.

One question has been: were men who were either only uncircumcised *or* only Ad5-seropositive and got the vaccine at increased risk of HIV infection? The answer, unfortunately, is that we still don't know. The trial wasn't designed to measure whether circumcision status or Ad5 status affected risk of infection. The numbers of volunteers in these groups was too small to draw firm conclusions by post-hoc analysis. But while there wasn't evidence that either lack of circumcision or Ad5 seropositivity was an independent predictor of HIV-1 infection, the authors don't rule this out and state that, "these results should be interpreted with caution because the study did not randomly assign participants to Ad5 or circumcision groups, only to vaccine or placebo."

(The impact of male circumcision on HIV risk in MSM has not been studied in a randomized controlled trial, and the data that do exist are complex, contradictory, and ultimately inconclusive. For more information see a [previous Advocates' Network posting on the relationship between circumcision status and risk of HIV infection in gay men and other men who have sex with men](#).)

## **2. Male circumcision + Ad5 seronegativity + vaccine = no safety issue**

There was no difference in the rates of HIV infection in men who were circumcised and Ad5-seronegative, whether they received the vaccine or the placebo. This finding is the basis for the proposed inclusion criteria allowing only circumcised and Ad5-seronegative trial volunteers in HVTN 505, an exploratory AIDS vaccine trial with an Ad5-vectored component that is similar yet different from the STEP vaccine. This trial is being considered by the NIH. ([Click here for more information](#)).

## **3. No clear immunological explanation for why the vaccine failed, or for increased risk in some vaccine recipients**

The [article by Juliana McElrath et al.](#)<sup>2</sup> describes the range of immunological studies that have been done to try to understand why the vaccine failed to prevent infection and/or reduce viral load set point in those who became infected, and why some vaccine recipients were at increased risk of HIV. They conducted extensive analyses looking for potential explanations. As part of this approach, the team matched every "case" (an individual who got infected with HIV while in the STEP study) with two to four "non-cases" (comparable individuals who did not become infected with HIV while in the STEP study). None of these infections were caused by the vaccine itself; none of the AIDS vaccine candidates being studied in humans can cause HIV. McElrath and her team also went back to the data from the Phase I study of MRK-Ad5 and compared the immune responses from volunteers in this early study to those among STEP volunteers.

As extensive as it was, this analysis was by no means exhaustive. Immune responses can be found in the blood and in the body's mucosa, including the gut and the lining of the vagina and rectum. This

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<sup>2</sup> The Lancet, Early Online Publication, 13 November 2008. doi:10.1016/S0140-6736(08)61592-5.

particular analysis focused on what was detectable in the blood, and was conducted remarkably efficiently, in the compressed timeframe following the halting of STEP immunizations.

The authors looked at immune responses in the blood of people who got the vaccine and went on to get infected and people who got the vaccine and remained HIV uninfected. They looked at things like whether there was a difference in the quantity or breadth (the range of HIV epitopes or proteins targeted) by the vaccine-induced immune responses in these two groups. There were no stark differences that explained why the vaccine failed to protect, or why some individuals were at increased risk. In the conclusion, the authors do raise some interesting questions for further exploration (see below).

One of the positive outcomes of the STEP trial has been a triggering of a wide array of scientific inquiries and discussions that relate to the disappointing results, and aim to explain them and chart a way forward. This includes the *Lancet* papers discussed above, as well as work by other investigators in a range of disciplines.

For example, another [recent paper by Perreau et al. in \*The Journal of Experimental Medicine\*](#)<sup>3</sup> proposes an explanation that hinges on the effects Ad5 immunity has on dendritic cells, which play a key role in triggering the body's immune responses. People who have been exposed to the natural form of Ad5 have Ad5 antibodies in their blood. When they get the vaccine, these antibodies target and form complexes with the disabled version of Ad5 used in the vector. Perreau and colleagues showed that—in petri dishes, not humans—these immune complexes triggered activity in other cell types, including dendritic cells, which are targets for HIV infection. They suggest that this cascade of responses increased the number of target cells in people with pre-existing immunity, and may have made them more vulnerable to HIV infection. However, this proposed explanation doesn't account for all of the data observed in STEP, since Ad5-seronegative volunteers who got the vaccine, and then developed antibodies to the vector were not at increased risk.

#### **4. Open questions about mucosal immunity and optimal characteristics of vaccine-induced immune responses**

Within hours, if not minutes, of the public announcement of the STEP data in September 2007, stakeholders in the AIDS vaccine field were warning that we might never understand what happened in the trial. If the recent publications affirm this—in the sense that they do not provide clear or complete explanations—then they also give a sense of the ways that STEP and its aftermath *have* crystallized and clarified some of the things we don't know.

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<sup>3</sup> The Journal of Experimental Medicine, 3 November 2008. doi:10.1084/jem.20081786.

Much of the discussion in the articles (and in the immediate aftermath of STEP) hinges on what was expected of vaccines that induce T-cell based, or cell-mediated immunity before STEP, and how these expectations shifted when the STEP results came out.

Briefly, cell-mediated immunity is one “arm” or set of defenses of the body’s immune system. (Humoral immunity, which includes antibodies, is another.) MRK-Ad5 was designed to induce cell-mediated immunity, including HIV-specific CD4 and CD8 T-cells that would target and kill cells in the body that had been infected by HIV. (There are T-cells against many different types of invaders; HIV-specific refers to the fleet of T cells that recognize specific protein fragments, or epitopes, that are part of HIV.) CD4 and CD8 are receptors that sit on the surface of different kinds of T-cells; and CD4 and CD8 T-cells play different roles in cell-mediated immunity. Based on everything that’s known to date, both CD4 and CD8 cells are needed to mount an effective cell-mediated response against HIV.

McElrath and her colleagues sliced and diced the cell-mediated immune responses in several different ways, to try to get at which cells those were and what they did—or did not do. The authors point out that MRK-Ad5 led to a higher CD8 T-cell response than any vaccine candidate tested in the past 15 years. Yet this response had no beneficial effect overall. The authors explore some of the ways that this response may have been lacking: Perhaps more CD4 T-helper cells are needed? (Fewer than one third of volunteers had detectable HIV-specific CD4 responses.) Perhaps both CD8 and CD4 T cells need to recognize and target a broader range of HIV-specific epitopes; perhaps the response rate needs to be even higher?

The data from STEP raise, but do not answer these questions—that can only happen through further research including both “basic science” or discovery work that takes place in laboratories and what Merlin Robb in his *Lancet* comment describes as “efficient and focused efficacy trials.”<sup>4</sup>

McElrath et al. single out the role of mucosal immune responses as one very important but difficult area warranting further study. As noted above, all of the immune analyses reported in the *Lancet* article looked at responses in the blood. Immune cells, including CD4 T cells and CD8 T cells, two components of vaccine-induced cellular immunity, move between the blood and the body’s mucosa. Cells that are in the mucosa can’t be measured in blood samples, but they would be the first ones to encounter HIV when it is transmitted sexually. So the authors point out that there may have been different numbers of cells in the mucosa in the male vaccine recipients who became HIV infected versus those who did not. (One of the reasons they raise this suggestion is because the vaccinated men who became infected had fewer Ad5-specific T cells in their blood, compared to the vaccinated men who did not get infected. Perhaps, the authors suggest, these men had fewer Ad5-specific T cells in their blood because they had more of them in their mucosa, where the cells would be targets for HIV infection.) There will be future analysis

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<sup>4</sup> The Lancet, Early Online Publication, 13 November 2008. doi:10.1016/S0140-6736(08)61593-7.

of mucosal samples from STEP volunteers that will help address this suggestion. And regardless, the need to look more closely at vaccine responses in the mucosa as well as the blood in future studies is crystal clear.

It's also clear how much we still don't know about the kinds of vaccine-induced immune responses that are needed to control the virus or prevent infection. This leads us to believe that many more vaccine efficacy trials will be needed to shed light on how to make a useful and licensable vaccine.

While a trial like STEP cannot tell us what will work, these articles remind us that a close study of an AIDS vaccine that did not work is also a valuable guide for the field as it decides what to do next.