



Information Regarding Trials using the MRK Ad5 gag/pol/nef Vaccine

"We are enormously grateful to the investigators and participants who have dedicated so much of their time and their energy to these trials. We know the STEP Study results are of great importance to our participants and to our network of investigators around the world. We may not be able to fully understand the results of STEP until more research is conducted. We are optimistic that this work will provide insight into how to advance the search for an effective HIV vaccine."

Larry Corey, M.D., Principal Investigator of the HVTN.

What does the information from the STEP Study announced in November 2007 show?

The STEP Study is one of two Phase IIb trials of Merck & Co., Inc.'s investigational HIV vaccine (V520). The results showed that the vaccine did not work. It did not prevent HIV infection. It also did not reduce the amount of virus in those study participants who became infected with HIV during the trial. **The current STEP results suggest that people who got the vaccine might get infected with HIV more easily if they are exposed to it.** We saw this trend toward more infections especially in the group of participants who had pre-existing immunity (antibodies) to adenovirus type 5 (Ad5), a cold virus. (The Ad5 virus was used as a part of the vaccine.)

We still don't know if the HIV vaccine actually increased the risk of HIV infections, and if it did, if it applies to all study participants or only to some. We also don't know how long this effect may last. However, no one is getting any more vaccinations. We are also talking with all participants to tell them whether they received vaccine or placebo, and their level of pre-existing antibodies to Ad5. We are counseling all participants to lower their risk of HIV infection.

The infections were mostly in men who have sex with men. So far, only one woman has become infected with HIV during the trial, and only one heterosexual man.

This means that we don't know about the effects of the vaccine in women or in heterosexual men.

Because almost all HIV infections were in men, our latest information is about men in the study who have sex with other men. This table shows you the numbers of men in each group and the number of HIV infections. It also shows you the number of HIV infections in relation to pre-existing Ad5 immunity.

	No immunity to Ad5 (< 18 units)	Medium immunity to Ad5 (18-200 units)	High immunity to Ad5 (201-1000 units)	Very high immunity to Ad5 (> 1000 units)
Vaccine	20 infected out of 382 total	8 infected out of 140 total	14 infected out of 229 total	7 infected out of 163 total
Placebo	20 infected out of 394 total	4 infected out of 142 total	7 infected out of 229 total	2 infected out of 157 total

Did the study vaccine give people HIV?

No. It is impossible to get HIV from any HIV vaccine being studied. The vaccine only used small parts of HIV, and these parts were made in a laboratory. These small parts are not able to create a whole HIV virus, which means there is no way they can cause infection. Participants in the STEP Study got their HIV infection from another HIV infected person.

How were the trial results determined?

We reviewed all of the information collected during the trial. This is called "data analysis." We are continuing to do more analyses to explore what happened. These extra analyses were not originally planned as part of the trial. This means that the answers we get may be hard to interpret, since the study was not designed to give clear answers to these new questions.

We want to know what really caused the results. For example, it could be that the vaccine made some people more easily infected with HIV when they were later exposed to it. It is also possible that the differences in HIV infection were due to differences between groups of study participants, not related to the vaccine. The results could also be due to chance.

What did we learn about viral loads and Ad5?

Viral load levels tell us how much HIV is in the blood of a person who is infected with HIV. In the STEP Study, we looked at the viral load of every study participant who got infected with HIV while in the study. The study vaccine did not have any impact on the viral load of those participants who became HIV infected, measured in the few months after infection. We will continue to follow study participants who became HIV infected to see if there are any differences in viral load over time between those who got the vaccine and those who got the placebo.

What kind of follow-up is happening for participants in the STEP Study?

Although vaccination has been discontinued, all STEP Study participants (both those who remain HIV uninfected as well as those who are HIV infected) are still being asked to return to the clinical trial sites for all of the visits scheduled in the trial. They are being told whether they received vaccine or placebo. They are also being told their level of pre-existing Ad5 immunity.

We do not know whether the participants who got the study vaccine will continue to have an increased number of infections over those who got the placebo. This will be very important to answer. That is why we are asking all study participants, including those who got the placebo, to stay in the study. The only way we can truly understand what is happening with study participants who got the vaccine is to compare them with study participants who got the placebo. We will continue to provide regular HIV counseling and testing. We will measure the immune responses in the blood, to see if they change over time. The frequency of study visits, the study procedures, and the length of follow-up are being discussed by study investigators, staff, and community members.

Will participants in the STEP Study and other studies using the vaccine be told what level of pre-existing immunity they have to adenovirus type 5 (Ad5)?

Yes. But, we are telling all study participants that the vaccine could increase susceptibility to HIV infection, regardless of their Ad5 status. Participants should do everything possible to avoid exposure to HIV.

How can I get more information about the STEP Study and any further analyses that will be done?

New analyses of the data from the entire study population were presented on November 7 at a special open scientific meeting of the HVTN. Presentations on the STEP Study from the HVTN meeting are available at www.hvtn.org. Additional analyses are underway. We will share the information as it becomes available.

What is the history of the STEP Study? Is the product that was used in the STEP Study used in any other HIV vaccine trials?

Merck has studied this vaccine or one very similar to it in at least nine trials. These trials were to establish safety for use in humans and the proper amount of vaccine to give in larger, Phase IIb trials. Vaccinations in all trials except one were completed by the time the STEP Study vaccinations were stopped. When the STEP Study vaccinations were stopped, vaccinations in any study using the same product were stopped also.

The Merck HIV vaccine was being studied in two Phase IIb clinical trials, STEP and Phambili. In both studies, half the study participants received three doses of the vaccine over six months, and half were given three doses of a placebo (the injection without the vaccine). All participants were counseled on ways to reduce their risk of exposure to HIV at every study visit throughout the trial.

STEP (HVTN 502, Merck V520/Protocol 023) was a multi-center, randomized, double-blind, placebo-controlled phase IIb test-of-concept clinical trial. The 3,000 HIV-negative participants in this trial were between 18 and 45 years old. They were from diverse backgrounds and were at risk of HIV infection based on their sexual practices. STEP included 34 clinical trial sites in North and South America, the Caribbean and Australia. In all of these locations, HIV subtype B is most common. The synthetic HIV pieces in the vaccine are made to look like pieces of HIV subtype B. Approximately 38 percent of study participants were women and 62 percent were men. The first participant enrolled in the study in December 2004, and enrollment was completed in March 2007. Of the 3000 participants, 2675 had received all three planned doses of vaccine or placebo.

The second phase II trial of this study vaccine, Phambili (HVTN 503, Merck V520 Protocol 026), began in 2007 in South Africa. It was conducted by the HVTN, working with the South African AIDS Vaccine Initiative (SAAVI). The goal of Phambili was to see if the study vaccine used in STEP would prevent infection or reduce viral loads in an area where HIV subtype C is common. When the decision was made to stop

vaccinations in the STEP Study, the Phambili protocol team also stopped vaccinations. The study planned to enroll 3000 participants, but only 801 had been enrolled so far. Only 58 participants had received all three doses of the vaccine or placebo. Participants in the Phambili trial have been told whether they received vaccine or placebo. They are continuing to get HIV risk-reduction counseling. As with the STEP Study, participants continue to be seen for all of their scheduled clinic visits, but no more vaccinations are being given.

There was also a Phase I trial using this study vaccine called HVTN 071. This trial was conducted only in the U.S. The trial planned to enroll 60 people, and only 35 people had been enrolled so far. Vaccinations were stopped in this trial as well. Participants are being told whether they received vaccine or placebo and are continuing to get risk-reduction counseling. Participants are still being followed in the study. This trial was designed to collect larger volumes of blood in order to learn more about what immune responses might protect against HIV infection and which lab tests are most helpful for HIV vaccine trials.

Why does Ad5 immunity matter--and what is it?

The Merck vaccine was made using a weakened form of a common cold virus called Adenovirus 5, or Ad5 for short. Pieces of laboratory-made HIV were put in the weakened Ad5 to help carry those pieces into the body. Because the Ad5 was weakened, it could not cause a cold in the study participants. And because there were only pieces of HIV in the Ad5, these pieces could never turn into the entire HIV to cause an HIV infection.

Adenovirus 5 is one of many viruses that can cause a cold. Some people are already exposed to this virus naturally. When exposed to Ad5, your immune system learns how to fight it, and you develop antibodies against Ad5. This is known as “Ad5 immunity”. Having Ad5 immunity means that either you had a cold caused by Ad5, or you were exposed to another person who had a cold caused by Ad5. Doctors can measure the level of your Ad5 immunity in your blood. When it started, the STEP study was designed to only include participants with low levels of Ad5 immunity. These participants were expected to have the best response to the study vaccine. Later on, testing in other independent studies showed that people with a high level of Ad5 immunity could have an immune response to the Ad5 vaccine. Because of these results, participants with higher levels of immunity to Ad5 were enrolled in the STEP Study.

When did vaccinations stop in the STEP Study?

On September 21st, 2007, Merck and the HVTN announced that vaccinations had been stopped in the STEP Study and the two other trials in which the same study vaccine was being tested. The STEP Study was monitored by an independent group. At one of the planned times for monitoring the study, called an interim analysis, the independent group reviewed the study data and determined that the study vaccine was not effective. The study had been designed so that researchers would be able to use the results from this interim analysis to find out quickly if the study vaccine either worked really well or was really unlikely to ever work. In this case, they found that it was really unlikely to ever work. Getting early information on the study results allows researchers to limit the number of people who might get a product that does not work. It also allows researchers to begin exploring why this approach didn't work, and to use the information to try to design an effective study vaccine for use in future trials.

Since the findings from the STEP Study relate to men who have sex with men, should women or heterosexual men who got the study vaccine be concerned? What about participants with low pre-existing immunity to adenovirus type 5?

The safety of participants is our highest concern. Because we have so little information right now, we need to make sure everyone is counseled to reduce their risk of HIV infection. This includes women or heterosexual men who got the study vaccine. Because we don't have data, we are telling women and heterosexual men in the trial that the vaccine could increase their risk of HIV infection. Even though we did not see an increased risk of HIV infection in vaccine recipients who had low pre-existing immunity to Ad5, we are also encouraging them to reduce their risk of exposure to HIV.

All participants who received the study vaccine are being counseled about the potential increased risk of getting HIV. Study staff members are working with all participants to help them understand ways to reduce their risk of exposure.

Whom can I contact for more information?

If you are a STEP Study participant, you can contact your study site with any questions or concerns. If you have questions about your rights as a trial participant or feel you have not been treated well by the study staff and are not comfortable talking to

them, check your study consent form for an ethics committee contact. A phone number should be listed there for you to call.

If you are in another HVTN trial and have concerns about the vaccine you may have received or may be receiving, contact your study site staff. They are happy to talk to you about the STEP Study results and how those results relate to the HIV vaccine trial you are (or were) in.

If you are a member of the press, see the contact information below.

Merck Contact:	Mary Elizabeth Blake (215) 652-5558 maryelizabeth_blake@merck.com	Merck Investor Contact:	Graeme Bell (908) 423- 5185
HVTN Contact:	Sarah Alexander (206) 910-3801 Dean Forbes (206) 667-2896		