



HIV VACCINE  
TRIALS NETWORK

## News Release

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### **Data from STEP Study Presented at Open Scientific Session Confirm Merck's Investigational HIV Vaccine was not Effective**

SEATTLE, Nov. 7, 2007 – In the STEP study, one of two phase II trials of Merck & Co., Inc.'s investigational HIV vaccine (V520), the vaccine was not effective at either preventing infection in volunteers not previously infected with HIV or at reducing viral loads in those study volunteers who became infected with HIV during the trial. Analyses presented today indicate that in those volunteers with pre-existing immunity to the cold virus used as a carrier for synthetic HIV genes in the vaccine, there were more infections in those volunteers who received the vaccine than in those who received placebo. Most of these analyses are considered exploratory in nature, and the reasons for this result are still being studied. The study was co-sponsored by Merck & Co., Inc.; the National Institute of Allergy and Infectious Diseases (NIAID), part of the U.S. National Institutes of Health; and the HIV Vaccine Trials Network (HVTN), which is funded by NIAID.

Data from the first, planned interim analysis of STEP in one study population were first reported on Sept. 21, 2007 by the three trial sponsors. New analyses of the data from the entire study population were presented today at a special open scientific meeting of the HVTN. These new analyses are summarized below, and will be available at [www.hvtn.org](http://www.hvtn.org) by Nov. 14, 2007. Additional analyses are underway and will be shared as more information becomes available.

The vaccine cannot cause HIV infection. The vaccine was created using a mixture of three components, each made with a replication-defective version of one of the common cold viruses, adenovirus type 5 (Ad5), which served as a carrier, or delivery vector, for three synthetically produced HIV genes.

The current STEP results suggest that those who received the vaccine might have an increased susceptibility to acquiring HIV infection, particularly those volunteers who had higher

levels of pre-existing immunity to Ad5 because of prior natural exposure to Ad5. However, there are a number of confounding factors that make it very difficult to draw conclusions about this finding.

All but one infection was in men, primarily in men who reported having sex with other men, so little information is available about the effects of the vaccine in women or in heterosexual men.

Study volunteers are being counseled about the possibility that those who received the vaccine may be more susceptible to developing HIV infection when exposed to HIV.

"The data from this trial are remarkably complex. We are analyzing the data to try to determine if the results are due to immune responses induced by the vaccine, differences in study populations, or some other biological phenomenon we don't yet understand, or simply due to chance," said Keith Gottesdiener, M.D., vice president, Vaccine and Infectious Disease Clinical Research, Merck Research Laboratories. "It will take some time before we understand why the vaccine did not work and why there was a trend toward more cases of infection in volunteers who received the vaccine. We recognize that understanding STEP is important for the study volunteers, investigators and for the entire field of HIV vaccine research, and we remain committed to continuing to thoroughly analyze the data and share it as broadly and as quickly as possible."

"We are enormously grateful to the investigators and volunteers who have dedicated so much of their time and their energy to these trials," said Larry Corey, M.D., principal investigator of the HVTN. "We know the STEP study results are of great importance to our volunteers 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."

Further analyses are being conducted. The trial partners will share the data as it becomes available with the broader scientific community at subsequent scientific meetings and in publications over the next several months. A presentation is scheduled at the Conference on Retroviruses and Opportunistic Infections in Boston in February, 2008.

**Summary of Data and Analyses of STEP Presented at HVTN meeting, Nov. 7, 2007**

STEP analyses will be available at [www.hvtn.org](http://www.hvtn.org) by Nov. 14, 2007.

**About STEP and Phambili, the Phase II studies of this vaccine**

The Merck vaccine candidate 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, while the other half were given three doses of a placebo. All volunteers were counseled on ways to reduce their risk of exposure to HIV at all study visits throughout the trial.

STEP (HVTN 502, Merck V520 Protocol 023) was a multi-center, randomized, double-blind, placebo-controlled phase II test-of-concept clinical trial. The 3,000 HIV-negative volunteers in this trial were between 18 and 45 years of age, from diverse backgrounds, and at risk of HIV infection based on behavioral practices. STEP included multiple clinical trial sites in North and South America, the Caribbean and Australia, where HIV subtype B, the subtype of HIV from which the HIV genes included in the vaccine, is predominant. Approximately 38 percent of study participants were women and 62 percent were men. The first volunteer enrolled in the study in December 2004, and enrollment was completed in March 2007. More than 2,500 participants (2,675) had received all three doses of vaccine or placebo.

STEP was initially designed to include only volunteers with low levels of Ad5 immunity (Ad5 antibody level less than or equal to 200 units), because these volunteers were expected to have the best response to the vaccine. Subsequently, volunteers with higher levels of immunity to Ad5 were also enrolled in the trial because new data became available indicating that the vaccine was immunogenic in individuals with high Ad5 immunity (Ad5 antibody levels more than 200 units) and because, if the vaccine had worked, global vaccination programs would have had to consider any potential effect of pre-existing immunity to Ad5 on the efficacy of the vaccine. (Frequency of prior natural infection with Ad5 varies in different regions of the world.)

The second phase II trial of this vaccine candidate, Phambili (HVTN 503, Merck V520 Protocol 026), was begun in 2007 in South Africa by the HVTN to explore whether Merck's vaccine would be effective at preventing infection, reducing viral levels, or both, from HIV subtype C, which is more common in southern Africa and many other parts of the world with the highest rates of new HIV infections. Because this study just started this year, only 801 volunteers had been enrolled and 58 volunteers had received three doses of the vaccine or placebo.

### **Primary efficacy analyses of STEP study volunteers with low Ad5 immunity**

STEP evaluated two primary efficacy endpoints: whether the vaccine prevented HIV infection in those who were HIV negative at the start of the study, and whether the vaccine reduced the amount of virus in those who became HIV infected during the course of the study. These primary efficacy analyses were based on volunteers who had low levels of pre-existing immunity to Ad5.

In the pre-specified analysis [conducted for the STEP trial Data and Safety Monitoring Board (DSMB) review on September 18] of volunteers who had received at least one dose of vaccine or placebo and were HIV negative at the start of the trial, called the "modified intent to treat" study population, 24 cases of HIV infection were observed in the 741 volunteers with low pre-existing Ad5 immunity who received vaccine and 21 cases of HIV infection were observed in the 762 participants in the placebo group. In the analysis of a subgroup of this study population, those who had received at least two vaccinations and who were HIV negative for at least the first 12 weeks of the trial, 19 cases of HIV infection were observed in the 672 volunteers who received vaccine and 11 cases were observed in the 691 volunteers who received placebo. (Most cases not included in this more stringent study population analysis but included in the "modified intent to treat" population were volunteers diagnosed as having acquired HIV at or before week 12.)

In addition, the vaccine was not effective based on the analysis of the second primary endpoint, viral load levels in study volunteers who became HIV infected. HIV RNA levels approximately eight to 12 weeks after diagnosis of infection were generally similar in the vaccine and the placebo arms in the modified intention to treat population. The geometric means of the HIV RNA levels in the blood of infected individuals, the standard measure of ongoing HIV replication, were approximately 40,000 copies/mL in the 24 volunteers in the vaccine group who developed HIV infection and approximately 26,000 copies/mL in the 21 volunteers in the placebo group who developed infection.

### **Post-hoc analyses of the total STEP population, including those with higher Ad5 levels**

Extensive additional analyses have been and continue to be done to better understand the results from STEP. These are post-hoc exploratory analyses and are subject to the statistical limitations inherent in such analyses.

Post-hoc analyses included all cases of HIV infection observed in the overall STEP study population through Oct. 17, 2007, including eight additional cases that have been observed since the initial interim analysis was reviewed by the STEP DSMB on September 18. Because all of the cases of infection except one were in males, the extensive post-hoc analyses on the "modified intent to treat" population were conducted only on males.

In a post-hoc analysis of the overall study population, a total of 49 cases of HIV infection were seen among the 914 male volunteers in the vaccine group compared to 33 cases of HIV infection among the 922 male volunteers in the placebo group. Although the study was not designed to assess whether study volunteers with high Ad5 immunity who received vaccine were more likely to acquire HIV infection, the difference in the number of cases of HIV infection between the vaccine and placebo groups was more pronounced among volunteers with high Ad5 immunity. Among the 778 male volunteers who had high levels of pre-existing immunity to Ad5 (greater than 200 units), 21 cases of HIV infection were observed in those who had received vaccine and nine cases of HIV infection were observed in the volunteers who had received placebo.

To better understand this finding, additional post-hoc analyses were conducted based on levels of pre-existing immunity to Ad5:

- In volunteers who could be considered as having no pre-existing immunity to Ad5 at enrollment (baseline Ad5 titer less than 18 units), 20 cases of HIV infection were seen in the 382 volunteers in the vaccine group and 20 cases were seen in the 394 volunteers in the placebo group.
- In volunteers with immunity to Ad5 between 18 to 200 units, eight HIV infections were observed in the 140 volunteers in the vaccine group compared to four infections in the 142 volunteers in the placebo group.
- In volunteers with immunity to Ad5 between 200 to 1000 units, 14 cases were seen in the 229 volunteers in the vaccine group and seven cases were seen in the 229 volunteers in the placebo group.
- In volunteers with very high levels of immunity to Ad5, defined as greater than 1000 units, seven cases of HIV infection were observed in the 163 volunteers in the vaccine group and two cases were observed among the 157 in the placebo group.

Further analyses are ongoing, including extensive laboratory studies to define whether the genetic variation of the HIV virus contributed to the vaccine's lack of effectiveness. Additional analyses will help the research community understand the apparent association between levels of Ad5 immunity and risk for acquisition of infection, including whether level of Ad5 immunity is responsible for increased susceptibility or whether level of Ad5 immunity is an indirect marker for some other biological or behavioral factor.

Viral load levels were also evaluated across the total population, and there was no obvious correlation between levels of Ad5 immunity and viral load. In a post-hoc analysis of those male volunteers with high levels of immunity to Ad5 who developed HIV infection, the geometric means of HIV RNA levels were observed to be approximately 19,000 copies/mL in

the vaccine group (based on 21 infections) and 90,000 copies/mL in the placebo group (based on nine infections observed). In the total study population, including male volunteers with both low and high levels of immunity to Ad5, the geometric means of HIV RNA levels were approximately 29,000 copies/mL for the vaccine group (based on 46 infections) and approximately 38,000 copies/mL in the placebo group (based on 30 infections).

### **Confounding factors make reaching conclusions about the STEP data difficult**

There are a number of confounding factors that make it difficult to draw conclusions about why those who received the vaccine with higher levels of immunity to Ad5 developed more infections than those who received placebo. For example, on some measures, HIV infected volunteers in the vaccine group and the placebo group reported engaging in risk practices more frequently than uninfected volunteers in both groups, although these data are still being collected and analyzed. Also, fewer men in the study with higher levels of pre-existing immunity to Ad5 were circumcised than were men with lower levels of pre-existing immunity to Ad5. There were also geographic differences in the two study populations. More than 70 percent of the participants with lower levels of pre-existing immunity to Ad5 were from the United States, while approximately 41 percent of participants with higher levels of pre-existing immunity to Ad5 were from the U.S.

Demographic characteristics such as age and race, of the volunteers who received vaccine were similar to those who received placebo at each of the study sites, and there is no evidence to suggest that differences in demographics explain the differences in the number of infections in the vaccine and placebo groups.

### **Vaccination and enrollment have been discontinued in both studies**

As announced on Sept. 21, 2007 after study sites had been informed, vaccination was discontinued in trials of this vaccine candidate after the STEP DSMB reviewed an interim analysis of STEP data on Sept. 18, 2007. This pre-specified analysis of data from the low Ad5 population (the group expected to have the best response and the furthest along in the study) was designed to provide insight as soon as possible into whether the vaccine was likely to be effective. The results showed that the vaccine was highly unlikely to be effective, and that there were more cases of HIV infection in the vaccine group than in the placebo group.

In October, the Phambili DSMB reviewed the STEP data, and recommended that vaccination and enrollment in the Phambili trial be permanently suspended, that study volunteers be told whether they received vaccine or placebo, and that study volunteers be counseled on the possibility that those who received the vaccine might be more susceptible to developing HIV infection. This was announced on Oct. 23, 2007 after study investigators and volunteers had been contacted.

Although vaccination has been discontinued, STEP study volunteers are still being encouraged to return to the clinical trial sites for protocol-specified visits. Details of the alternative options for continued follow-up of STEP trial participants, and the timing of when they will be told whether they received the vaccine or placebo, will be discussed today following the presentation of the data at the open, scientific session of the HVTN meeting. This discussion will include clinical investigators and community representatives engaged in HIV vaccine efforts, and will provide the opportunity to gain input and advice from diverse interested constituencies. Based on this feedback, the trial co-sponsors will announce a decision on the future plans for STEP volunteers within a few days through the investigators in the trial.

### **About the vaccine**

The vaccine was created in Merck Research Laboratories and had been in development at Merck for more than a decade. The Merck adenovirus-based vaccine used a cell-mediated immune response approach; it was hypothesized that the HIV genes in the vaccine would stimulate the body to generate an HIV-specific immune response through the body's own CD8 T-cells, which become programmed to recognize and kill HIV infected cells. Because the vaccine did not contain live HIV and contained only three HIV genes, volunteers could not become infected with HIV from the vaccination. This vaccine had previously been tested in several smaller clinical trials and was found to be generally well tolerated and capable of inducing significant levels of HIV-specific cell-mediated immune responses.

### **About Merck's HIV research program**

Merck's efforts to develop investigational treatments and a vaccine against HIV/AIDS have been under way for more than 20 years and continue today; our HIV research program began in 1986. In the 1990s, Merck scientists discovered the protease inhibitor, CRIXIVAN<sup>®</sup> (indinavir sulfate), and the non-nucleoside reverse transcriptase inhibitor, STOCRIN<sup>®</sup> (efavirenz). In addition, in October, the Food and Drug Administration approved ISENTRESS<sup>™</sup> (raltegravir), Merck's integrase inhibitor.

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### **About the HIV Vaccine Trials Network**

The HVTN is an international collaboration of scientists and institutions whose goal is to accelerate the search for an HIV vaccine by sharing trial results and facilitating parallel, concurrent testing. The HVTN is a unique hybrid that combines the depth and diversity of the academic community and the flexibility of a commercial drug company. Working with industry and government, the HVTN seeks to expedite and coordinate the trial process, advancing vaccine candidates and building a body of knowledge about HIV vaccine trials.

The HVTN is supported through a cooperative agreement with the National Institute of Allergy and Infectious Diseases, which is a component of the U.S. National Institutes of Health. The Network and NIAID have a close, cooperative working relationship, with shared attention to the intellectual and scientific issues. The Network's headquarters are at Fred Hutchinson Cancer Research Center in Seattle.

### **Merck forward-looking statement**

This press release contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995. These statements are based on management's current expectations and involve risks and uncertainties, which may cause results to differ materially from those set forth in the statements. The forward-looking statements may include statements regarding product development, product potential or financial performance. No forward-looking statement can be guaranteed, and actual results may differ materially from those projected. Merck undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events, or otherwise. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Merck's business, particularly those mentioned in the risk factors and cautionary statements in Item 1A of Merck's Form 10-K for the year ended Dec. 31, 2006, and in its periodic reports on Form 10-Q and Form 8-K, which the company incorporates by reference.

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