

## QUESTIONS AND ANSWERS

### On the decision to stop vaccinations with the Merck HIV vaccine

#### 1. Why were vaccinations in the Step Study stopped?

On September 18, 2007, the Data & Safety Monitoring Board (DSMB) reviewed unblinded interim data and recommended that vaccinations in the trial should be discontinued because of lack of efficacy. This decision has nothing to do with vaccine safety. The DSMB concluded that this vaccine will not meet the efficacy objectives defined in the protocol. There is no evidence of a protective effect from the vaccine (the numbers of people who became infected after vaccination were about the same as the number of people who became infected after receiving the placebo), and there is no difference in the viral load of those people who became infected after receiving placebo or vaccine. While vaccinations will be discontinued, follow-up of Step study participants will continue.

#### 2. What is the Data & Safety Monitoring Board, and how does it monitor this study?

The Data & Safety Monitoring Board (DSMB) is an independent committee composed of clinical research experts, statisticians, and ethicists to provide additional oversight of the study. It is a regular component of all clinical trials. The DSMB regularly reviews data while a clinical trial is in progress to ensure the safety of participants and that any benefits shown in the study are quickly made available to all participants. A DSMB may recommend that a trial, or part of a trial, be stopped if there are safety concerns or if the trial objectives have either been achieved or are unlikely to be achieved. The DSMB looks at unblinded analyses, which are not available to the investigators or to anyone else.

#### 3. Was this the first review of Step study data by the DSMB?

The DSMB had met on a regular schedule during the conduct of the Step trial to review data on participant safety and trial conduct. After each review the monitoring board had concluded that there were no safety or operational concerns and recommended that the trial proceed. The schedule of DSMB meetings included two meetings to review interim efficacy data, and the review on September 18 was the first review of interim efficacy data. At that meeting the DSMB reviewed unblinded data on efficacy and concluded that the vaccine did not prevent HIV acquisition and did not result in a lower HIV viral load among vaccinated participants who later became infected.

**The Hope Clinic**  
603 Church Street  
Decatur, Georgia 30030

Tel 404.377.3719  
Fax 404.377.6962  
[www.hopeclinic.emory.edu](http://www.hopeclinic.emory.edu)

**The Robert W. Woodruff Health Sciences Center**  
*An equal opportunity, affirmative action university*

**4. Were there safety issues that contributed to this decision?**

The decision to stop the trial was made because the study would not meet the study endpoints (i.e., it would not show that the vaccine could protect against infection or control viral load). Merck's HIV vaccine candidate has been generally well tolerated in studies to date, which involve over 2,500 people who have received at least one injection of the adenovirus based vaccine. Reported adverse events appear to be dose related and include mild/moderate injection site pain and swelling, headache, fatigue and fever. Adverse events appear to be most common within the first few days after the first vaccination.

**5. Will the Step study be stopped?**

Although vaccinations have been stopped, the Step study will continue and follow-up of Step study participants is ongoing. There is still much to be learned from this trial that will inform and improve future efforts to develop a successful vaccine to prevent HIV infection and HIV disease progression.

**6. What do these results mean for the field?**

While disappointing, the results from this trial will add to the body of scientific knowledge about HIV and inform future clinical programs. In depth analysis of the data is ongoing and the investigators are committed to sharing this information with scientists and the community in the upcoming months. This trial was also the first "test of concept" HIV vaccine trial and demonstrated that this trial design can provide information more quickly and efficiently than with a traditional Phase III design.

**7. Given that the Step study has shown no impact on acquisition of HIV infection or on reduction of HIV viral load after infection, will it impact any other HVTN HIV vaccine trials?**

We will make data from the Step study available to the independent DSMB overseeing the Phambili trial (also known as HVTN 503 or Merck V520-026) which was initiated in 2007 to explore possible efficacy of the vaccine in a clade C region. Vaccinations in Phambili have been put on hold until the DSMB overseeing that study can review the data and, in conjunction with other South African partners, make a recommendation on that trial. Similarly, the data will be shared with the DSMB for the HVTN 071 trial, which examines the same Merck vaccine in a trial designed to study correlates of vaccine efficacy. As with Phambili, vaccinations in 071 are on hold until that DSMB can review the data and make a recommendation.

**8. Is it time to give up on HIV vaccines?**

Vaccines are essential to the control of infectious diseases. While these results are very disappointing, it does not diminish the importance of continuing the search for an HIV vaccine. New infections continue to outpace the ability to get infected people on anti-retroviral therapy, so we cannot rely on treatment alone to address the epidemic. It is important for research to continue in all relevant areas: vaccines, behavioral interventions and other prevention strategies, in order to reduce the impact of this devastating disease. While this vaccine has not shown efficacy, there were successes in this vaccine trial. It was designed as a test of concept study to answer to a scientific question in an efficient manner, conserving resources. From first participant enrolled to this DSMB meeting was about 33 months. In that short period of time we had the answer about the efficacy of the vaccine. Additionally, we confirmed that the strategy of test of concept studies works to give us answers in a more timely manner than other types of efficacy studies.

## **OPERATIONAL ISSUES**

### **1. Will the participants be told that study vaccinations are being stopped?**

Yes, each site will develop its own process for notifying all participants in a timely manner.

### **2. Will the participants continue to be seen?**

Participants will continue to be seen for follow up, but no additional vaccinations will be administered.

### **3. How many people had more vaccinations remaining?**

Most of Step participants had received the full complement of three vaccinations. There are only about 14 people still on the schedule to get their 3rd injection in Step; they will not receive this vaccination.

## **BACKGROUND INFORMATION ON THE STUDY**

### **1. What is the Step study?**

The Step study, also known as HVTN 502 or Merck V520-023, is a clinical trial to evaluate the safety and preliminary efficacy of an investigational HIV vaccine developed by Merck that induces HIV-specific cell-mediated immunity (CMI). CMI is a type of immune response that prompts the body to produce a type of white blood cell (T lymphocyte, T cells) that helps kill HIV-infected cells. The trial is designed to determine if the vaccine can prevent HIV infection in HIV-negative individuals exposed to HIV through their behaviors or modify the course of HIV infection for those infected during the study.

### **2. Who is sponsoring and conducting this trial?**

Merck & Co. Inc and NIAID are co-sponsoring this HIV vaccine trial. The study is being conducted by the HIV Vaccine Trials Network (HVTN) and Merck.

### **3. What is the investigational vaccine being tested?**

The study is testing the MRKAd5 HIV-1 *gag/pol/nef* trivalent vaccine. The vaccine is a mixture of three components, each with a common weakened version of a type 5 adenovirus that serves as a delivery vector or carrier and one of three different HIV genes known as *gag*, *pol* and *nef*.

The vaccine cannot cause an infection in any person, as the genes are synthetically produced. Additionally, volunteers cannot get infected from the vaccine vector. Although many types of adenoviruses are among the causes of upper respiratory ailments such as the common cold, the adenovirus used in the investigational vaccine has been modified so that it cannot multiply itself. This vaccine has been tested in close to 2500 people and has been found to be generally well-tolerated and capable of inducing CMI responses.

### **4. How many participants are involved and where is the study being conducted?**

The trial, which began in December 2004, enrolled 3,008 adult volunteers at sites around the world.

The study site locations include:

- North America: Boston; Birmingham, AL; Chicago; Decatur (Atlanta), GA; Denver; Houston; Los Angeles; Miami; New York; Newark, NJ; Philadelphia; Rochester, NY; St. Louis; San Francisco; Seattle; Toronto; Montreal; Vancouver, BC;

- South America: Iquitos and Lima, Peru; Rio de Janeiro and Sao Paulo, Brazil
- Caribbean: Santo Domingo, Dominican Republic; Port-au-Prince, Haiti; San Juan, Puerto Rico; Kingston, Jamaica.
- Australia: Sydney

## **5. What is the study design?**

The Step study is a multicenter, randomized, double-blind, placebo-controlled phase IIb "test-of-concept" clinical trial. The trial enrolled HIV-negative volunteers between 18 and 45 years of age at high risk of HIV infection and who met certain medical and non-medical criteria. After an initial HIV screening, confirmation of eligibility criteria, and thorough informed consent process, participants were randomly assigned to receive either the study vaccine or placebo.

Neither the study investigators nor the trial participants know who is getting the study vaccine or placebo until the trial is completed. All participants were to be followed for up to four years to check the HIV status of the volunteers during regular study visits.

All participants receive risk reduction counseling and condoms at each study visit as part of participation throughout the trial. Infected volunteers will be referred for HIV evaluation, treatment and care and offered continued immunological and virological follow-up assessment in this trial.

Initially, the study only enrolled individuals with low pre-existing antibodies to type 5 adenovirus but was later opened to anyone irrespective of pre-existing level of antibodies following an early data assessment from other studies.

###