



HIV VACCINE  
TRIALS NETWORK

## **HVTN HIVNET 026 Caribbean and South American HIV Vaccine Trial Questions and Answers (Long version)**

### **What is HIVNET 026?**

HIVNET 026 is a clinical research study that will examine whether two experimental HIV vaccines— ALVAC-HIV vCP1452 and rgp120 MN – stimulate immune responses against HIV. The main purpose of the study is to test how the immune system responds to the vaccines and to confirm that the investigational vaccines are safe when given alone and when given together. HIVNET 026 is a Phase II study, meaning that it is a medium-size trial built upon the results of previous smaller trials of these vaccines.

The study will be carried out in Brazil, Haiti, and Trinidad and Tobago. The trial includes HIV-negative volunteers at low risk of contracting HIV and is not large enough to determine if the vaccines tested can prevent HIV infection. That will require studying a few thousand individuals in a Phase III trial.

### **Why is the trial being done?**

This trial is being conducted so that additional data can be obtained about the safety of and immune responses to this combination vaccine approach. Depending on the results of this study, this vaccine combination might be considered for evaluation in a large-scale (Phase III) trial in people at higher risk of HIV infection. Phase III trials would be necessary to determine if the combination of these vaccines is effective in preventing HIV/AIDS.

Ultimately, the goal of all studies such as this is to obtain information that can be used to help develop a preventive HIV vaccine – a vaccine that can prevent HIV/AIDS.

### **What vaccines are being tested in HIVNET 026?**

The ALVAC-HIV vCP1452 vaccine uses the canarypox virus, a virus that cannot infect or harm humans, to carry select HIV genes - but not the whole virus - into the body. The vaccine is provided by its manufacturer – Aventis Pasteur of Lyon, France. The rgp120 MN vaccine is a subunit vaccine, a synthetic HIV protein, provided by its manufacturer, VaxGen of San Francisco, California, USA. Both vaccines are made according to guidelines reviewed by the U.S. Food and Drug Administration (FDA).

Some people in the trial will receive a placebo instead of a vaccine. A placebo is an inactive substance that has no vaccine or medicine in it. The responses of volunteers who receive the placebo will be compared with those who receive the ALVAC-HIV vCP1452 and the combination of ALVAC-HIV vCP1452 and rgp120 MN.

### **Have these vaccines been studied before?**

Yes. More than 800 volunteers in France, Uganda and the United States have received canarypox-based HIV vaccines, and no serious side effects attributable to the vaccines have been reported. ALVAC-HIV vCP1452 is the most advanced ALVAC-HIV vaccine and has recently been administered to more than 75 participants in a U.S. trial.

The rgp120 MN vaccine has been extensively studied in the U.S. and in Thailand. Although other rgp120 vaccines have been evaluated in combination with several other ALVAC-HIV vaccines, this is the first clinical study to use ALVAC-HIV vCP1452 and rgp120 MN together. This trial will help to provide information to determine if the vaccine combination warrants further testing of its effectiveness in preventing HIV infection.

### **What does the ALVAC-HIV vCP1452 vaccine contain?**

ALVAC-HIV vCP1452 is made from a vaccine used to protect canaries against the canarypox virus. In making the vaccine, the canarypox virus is attenuated, or weakened. ALVAC-HIV vCP1452 uses the weakened canarypox virus to carry copies of HIV genes coding for the HIV envelope, core and a regulatory protein. ALVAC-HIV vCP1452 contains additional genes that may help stimulate the immune response to the vaccine.

When injected into the body, the canarypox virus can enter some human cells, but does NOT multiply in them. However, it directs the cell to make the HIV proteins encoded in the genes that are inside the canarypox virus. These proteins trick the immune system into thinking that the host is infected with HIV. The immune system of the host may then make specialized immune cells called cytotoxic T lymphocytes (CTLs) that can kill HIV-infected cells - just as if it were fighting an actual HIV infection.

Scientists chose canarypox to make ALVAC-HIV vaccines such as vCP1452 because: (1) research has shown that the virus appears to be safe to use in humans, (2) canarypox does not multiply in human cells, and (3) it carries the vaccine genes into the body's cells.

### **What does rgp 120 MN vaccine contain?**

The rgp120 MN vaccine is a synthetic copy of an HIV surface protein made in the laboratory. Because most neutralizing antibodies in HIV-infected people are directed against the HIV envelope, vaccines based on gp120 were among the first developed and are the most well-studied. The vaccine is made from MN, a laboratory-adapted strain of HIV that is representative of the subtype of the HIV in the United States and Europe. The vaccine is formulated with alum, an adjuvant, or substance that enhances the immune response.

Over the last six years, rgp120 MN has been given to more than 1,000 adults, children, and newborns in Phase I (small), Phase II (medium), and Phase III (large) studies, alone or in combination with a similar ALVAC-HIV vaccine. The vaccine appears to be very safe and is generally well-tolerated. The rgp 120 MN vaccine may stimulate the production of HIV neutralizing antibodies, proteins that may be able to stop HIV from infecting cells.

### **Are these vaccines safe?**

No serious side effects attributable to the vaccines have been reported in previous trials. The vaccine injections may cause a sore arm, headache, or a slight fever in some people for a few days. These symptoms have also been seen in placebo recipients. Additional information about the safety of these vaccines is collected during all similar studies; the volunteers have their blood drawn and urine checked for any reactions to the vaccines, and their immune responses to the vaccines are measured. These routine safety checks will be performed in HIVNET 026 as well.

However, for any experimental vaccine, the question of safety cannot be answered completely in advance, before it is tested in people. Scientists have wondered, for example, about the possibility that the vaccines may cause someone exposed to HIV to become infected with HIV more easily or cause the HIV infection to be worse. Although, so far, this has not been seen in any animals or people who have received the vaccines, participants will also be tested for HIV infection throughout the study.

The researchers conducting the study will watch the volunteers closely for any adverse effects of the vaccines. In addition, the study will be monitored by an independent group of experts known as the DAIDS Vaccine and Prevention Data and Safety Monitoring Board (VPDSMB) which will include a representative from each country in which the trial is being conducted. This group will review the information from the study and will pay close attention to any harmful reactions. If the Board decides that significant adverse events have occurred, it can recommend that further injections be delayed or the study be stopped.

### **Can these vaccines cause HIV infection?**

NO. The rgp120 MN vaccine is synthetic, it is NOT made directly from HIV, and cannot cause HIV infection. The ALVAC-HIV vCP1452 vaccine is made using synthetic copies of HIV genes. It is NOT made directly from HIV. The vCP1452 vaccine also lacks some very important genes that are absolutely necessary to make HIV. Volunteers cannot become infected with HIV from ALVAC-HIV vCP1452, nor can they pass the canarypox or the genes it carries onto anyone else.

### **What is known so far about how people in clinical trials respond to the ALVAC-HIV and rgp120 MN vaccines?**

In trials of ALVAC-HIV vaccines, some participants developed antibodies that neutralized the same strain of virus as that used in the vaccine. Some participants developed CTL responses against HIV.

**Who is sponsoring the study?**

This study is supported by the National Institute of Allergy and Infectious Diseases (NIAID), which is a part of the U.S. National Institutes of Health. The study was established through the HIV Network for Prevention Trials (HIVNET) and is now being conducted through the HIV Vaccine Trials Network (HVTN). Since 1987, NIAID has enrolled more than 3,300 men and women in 53 Phase I and II preventive vaccine trials involving 28 different experimental vaccines. This is only the third Phase II HIV vaccine trial sponsored by NIAID.

**Where will the study be conducted, and when will it start?**

HIVNET conducted domestic and international studies to evaluate the safety and efficacy of promising vaccine and non-vaccine interventions designed to prevent HIV infection. HIVNET 026 will be conducted at three sites located in the Caribbean: Rio de Janeiro, Brazil; Port of Spain, Trinidad and Tobago; and Port-au-Prince, Haiti. The study is being conducted at these sites because they have the necessary expertise, infrastructure and support to conduct high quality clinical trials; these sites have been preparing for vaccine trials for several years and have collected extensive data on their respective study populations. Researchers from these sites will carry out this study. The study will begin enrolling volunteers later this year.

**Who can participate in the study?**

The study will enroll a total of 120 healthy men and women not infected with HIV, 40 at each of the three sites. Participants will be between 18 and 60 years of age and at lower risk for acquiring HIV infection.

**What is the plan for the study?**

Participants will be randomly assigned (like flipping a coin) to one of three study groups: ALVAC-HIV vCP1452 plus rgp120 MN, vCP1452 alone, or placebo. All participants will receive immunizations at four time points during the study: 0, 1, 3, and 6 months. One group will receive ALVAC vCP1452 alone at 0 and 1 month and both vaccines at the 3- and 6-month visits and the second group will receive ALVAC-HIV vCP1452 alone at all four time points. The third group will receive a placebo at the same time points. When the two vaccines/placebos are given simultaneously, they are given separately in different arms.

This is a “double-blind” study, this means that no one directly involved in the trial, neither the volunteers nor the study investigators, knows which volunteers will get vaccine and which volunteers will get placebo until the study is completed.

**How do scientists think these vaccines could help prevent HIV/AIDS?**

The immune system fights viral infections with two major weapons: neutralizing antibodies and cytotoxic T lymphocytes (CTLs). Neutralizing antibodies are proteins that can block HIV from infecting cells. CTLs, also known as “killer T cells,” are white blood cells that can potentially kill cells infected with HIV.

The two vaccines are used to try to stimulate these two different parts of the immune system. ALVAC-HIV vCP1452 is given to stimulate the body's production of CTLs against HIV. The rgp120 MN is given to stimulate the production of neutralizing antibodies, proteins that kill free virus that is outside the cells.

The combination of these two different types of vaccines appears to show the most promise among HIV vaccine strategies tested to date for stimulating a broad immune response because each vaccine stimulates a different arm of the immune system.

### **Are there non-medical risks?**

The ALVAC-HIV vCP1452/rgp120 MN vaccine combination may cause some people to transiently make antibodies to HIV. These people may test positive on a standard HIV antibody test (ELISA) and appear to be HIV-infected, even if they are not. This could cause some problems to the volunteer if they were tested for HIV outside of the trial.

During the study, participants will be tested to determine if they are making antibodies in response to the vaccines or if they are making antibodies due to HIV infection. If the antibody tests seem to indicate HIV infection, the participant will undergo additional testing using a polymerase chain reaction (PCR) test that can detect tiny amounts of HIV genetic material. This test can show if the volunteer is truly infected with HIV.

All volunteers will be offered an identification card indicating that they are participating in a vaccine trial. The card will provide information on whom the participant may contact for help in resolving any problems related to HIV testing, such as difficulties with employment, insurance, or foreign travel.

### **What ethical procedures and safeguards are in place for protecting the volunteers?**

First, before deciding about entering the trial, potential volunteers are provided information about HIV and AIDS, about the intent of the study, about possible risks and benefits of participation and about the study procedures. In addition to the unknown, long-term risks associated with any new, experimental vaccine, potential risks include side effects due to injection into a muscle and social risks associated with testing HIV positive. That is, as a result of receiving the HIV vaccine, some volunteers will likely test positive for HIV infection on standard HIV screening tests for some period of time. Several tests will be used during the study to distinguish "true" HIV infection from vaccination-induced immune responses. Volunteers will receive extensive counseling about risk reduction throughout the study.

A two-part informed consent process is in place for this study. If interested in joining the study, volunteers must first sign a consent form to begin screening tests to determine if they are eligible to participate. If these tests show that they meet eligibility criteria (study volunteers must be HIV negative with no recent history of sexually transmitted diseases), they will be thoroughly counseled about the study. If they are eligible and willing to participate after the study has been fully explained to them and they have been allowed to ask questions, they will be asked to sign a second consent to enroll in the study. Volunteers will be given plenty of time to consider

whether they want to participate. Informed consent will be an ongoing process from initial screening through trial enrollment. Volunteers are free to refuse to join the study or to leave the study at any time without losing the benefits of their standard medical care.

### **Who reviewed the study?**

Plans for the study, including the informed consent and protocol, have been reviewed and approved by an established Institutional Review Board (IRB) responsible for overseeing HIV-related research at the performance site in each country. Each country also has additional review steps. For example, in Trinidad, the Ministry of Health has established a special committee to review HIV vaccine trials. In addition, the implementing institution in each country is associated with an U.S.-based collaborating university (the University of Pittsburgh and University of Rochester for Brazil, Cornell and Vanderbilt Universities for Haiti and the University of Maryland for Trinidad and Tobago). The IRBs at each of these institutions must also review and approve the study. The Ethics Committee of the Joint United Nations Programme on AIDS (UNAIDS), the U.S. National Institutes of Health (NIH), and the U.S. Food and Drug Administration (FDA) must all review and approve the study. In addition, the Office for Protection from Research Risks under the U.S. Department of Health and Human Services must also provide final approval for the trial at each site prior to implementation.

In addition, while it is underway the study will be monitored by an independent group of experts known as the DAIDS Vaccine and Prevention Data and Safety Monitoring Board which will include a representative from each country in which the trial is being conducted. This group will review the information from the study and will pay close attention to any harmful reactions. If the Board decides that significant adverse events have occurred, it can recommend that further injections be delayed or the study be stopped.

UNAIDS assisted in preparations for HIV vaccine research in each of the countries, participating in and leading preparatory workshops and meetings with government and community leaders and providing independent advice to and support for the Ministries of Health. The Pan American Health Organization (PAHO), as part of the World Health Organization (WHO) has also had a role in supporting this research.

### **If in years to come the vaccines in this study are shown to be effective, will the countries that participated in the trials of these products have access to the vaccines at a reduced cost?**

This is an important issue that has been raised since the beginning of the first vaccine trials. It is currently impossible to predict the cost of an effective vaccine since we are still in the early stages of vaccine development and evaluation. A solution will need to be found through a partnership between the pharmaceutical industry, international donor agencies such as UNAIDS, and the countries involved.

### **How can I obtain more information about the study?**

Further information about this trial is available from the investigators conducting the study.

- Haiti: Jean W. Pape, MD, Institut National de Laboratoire et de Recherches, Port-au-Prince,

509-22-0031

- Trinidad and Tobago: Courtenay Barthomew, MD, Medical Research Foundation of Trinidad, Port of Spain, 868-623-5834
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