



HIV VACCINE TRIALS NETWORK

Questions and Answers: HVTN 040 Vaccine Trial

WHAT IS THE HVTN 040 AVX101 VACCINE TRIAL?

HVTN 040 is a trial to look at the safety and immune response of an experimental HIV vaccine. The term 'HVTN 040' is the name that the HIV Vaccine Trials Network (HVTN) uses to refer to this particular trial. The vaccine candidate is called AVX101, and it is known as an alphavirus replicon vaccine. Scientists designed this vaccine candidate to teach the human body how to fight off HIV infection. The hope is that a vaccine can eventually keep people from becoming infected with HIV.

This vaccine is NOT produced from live virus or from HIV-infected human cells, so there is NO possibility that it contains live or killed HIV virus. Therefore, it is NOT possible that you can get HIV infection or AIDS by receiving this vaccine.

WHY IS THE TRIAL BEING DONE?

Scientists want to know more about this candidate vaccine because it seems to have the ability to make the immune system respond in ways that could help the body fight HIV. Once these responses have been found in studies in the lab, scientists have to find out if the candidate vaccine works the same way in people. This trial is called a Phase I trial, which means that it will test to see if the vaccine candidate is safe in varying dose amounts, and if it has an effect on the human immune response.

WHAT KIND OF VACCINE CANDIDATE IS BEING TESTED IN HVTN 040?

A genetically altered form of Venezuelan Equine Encephalitis virus containing the *gag* gene from HIV-1 subtype C.

WHAT DOES THE HVTN 040 VACCINE CONTAIN?

This vaccine candidate is made from a genetically altered virus known as the VEE (Venezuelan Equine Encephalitis) virus. This virus carries in it a synthetic piece of the HIV virus called the *gag* gene. The *gag* gene is the working part of the vaccine candidate, the part that should make the immune response specifically tailored to fight HIV. The vaccine candidate also contains a saline solution and a cryopreservative, which helps the vaccine candidate stay stable when it is in frozen for storage before it is used.

The wild VEE virus typically infects horses, although occasional human infections occur. In these cases the VEE virus usually produces flu-like symptoms. To use this virus in vaccines without causing infections of VEE, the VEE virus has been genetically altered so that it cannot reproduce itself. When a virus cannot reproduce it no longer can cause

an infection, and therefore this vaccine candidate is not expected to cause VEE infections. As a further safety measure, the type of VEE virus used has been changed so that it is weakened, thus attenuating, or lessening, its ability to cause harm.

The altered VEE virus is the carrier, called a vector, for a particular piece of HIV. The *gag* gene of HIV is put into the RNA of the VEE virus through genetic engineering. This gene is synthetically made, it is only a small part of the HIV virus, and it cannot cause any HIV infection. The VEE virus vector carries the *gag* gene into the cells, where it will cause the cells to make *gag* proteins. These proteins might be part of what would one day help the body fight off real HIV.

HOW COULD THIS VACCINE CANDIDATE HELP PREVENT HIV/AIDS?

The *gag* gene that has been inserted into the vaccine candidate produces a protein. This protein is the same as one that live HIV would produce. The protein serves as a kind of flag to show the body's immune system how and what to fight. The hope is that if the body's immune system can fight off this particular protein, a vaccine can then be developed that will teach the body how to fight off real HIV.

The possible benefit with this particular vaccine candidate is that it seems to produce several different kinds of immune system responses. Two of these are the antibody response and the cellular response. In the antibody response the immune system fights off any invading force before it has a chance to infect the body's cells. In the cellular response the body fights the cells that have already become infected. If this vaccine candidate does indeed produce multiple kinds of immune responses that may mean that it has the potential to be a broadly effective vaccine.

CAN THIS VACCINE CANDIDATE CAUSE HIV INFECTION?

No. This vaccine candidate does not use live or killed HIV virus, so there is NO possibility of HIV infection or AIDS from the vaccine. A particular HIV gene is used in this vaccine candidate, but without the rest of the virus it has not ability to cause HIV infection.

THERE IS NO POSSIBLE WAY THAT THIS HIV VACCINE CANDIDATE CAN CAUSE HIV INFECTION.

HAS THIS VACCINE CANDIDATE BEEN STUDIED BEFORE?

A vaccine candidate using this technology has never been given to humans before. The vaccine was tested extensively in monkeys, mice and rabbits, with no harmful side effects or evidence of toxicity. Lab tests also show that the vaccine candidate produced potentially promising immune system responses in these animals. Based on this information, scientists believe that the vaccine candidate looks safe, and that it causes enough of an immune response to be worth studying in humans.

IS THIS VACCINE CANDIDATE SAFE?

A different weakened (attenuated) strain of VEE has been used in another vaccine product in humans for decades. Vaccine candidates using VEE have been tested extensively in experimental animals without causing any significant side effects or infection. There is a remote possibility that the vaccine candidate contains a very tiny amount of live carrier VEE virus that was not detected in the safety test. To protect against this, the virus has been altered to be extremely weak, but there is still a very

small possibility that it might cause an infection, which would most probably be flu-like. It is not possible for the vaccine candidate to contain live HIV virus, and therefore there is no way for the vaccine candidate to cause HIV infection.

This vaccine candidate has never been tested in humans before. While scientists believe that there are no serious safety risks, there is always the possibility that there could be problems that no one expected. This is why this vaccine candidate, like any new drug or vaccine, needs to be tested for the first time in a few volunteers in a controlled clinical setting.

HOW IS THE SAFETY OF THE VACCINE CANDIDATE MONITORED?

Many people, from scientists and doctors to community members, looked carefully at the information about the candidate vaccine to make sure that they thought it was safe enough to begin the trial. In addition to the protocol team, the HVTN has a Safety Monitoring Board, which will carefully watch to make sure nothing goes wrong. If there seem to be any problems, the trial will be put on hold. After additional review by those independent of the study the trial can be stopped, if necessary.

WHEN AND WHERE IS THE STUDY BEING CONDUCTED?

This trial is planned to begin in June, 2003 in the United States and South Africa. The U.S. clinical trial sites are Columbia University in New York City, New York; the University of Rochester, Rochester, New York; Johns Hopkins University, Baltimore, Maryland; and Vanderbilt University, Nashville, Tennessee. The South African sites are the Medical Research Council (MRC) in Durban and the Chris Hani Baragwanath Hospital in Soweto, South Africa.

WHY IS THIS VACCINE BEING TESTED IN THE UNITED STATES AND IN SOUTH AFRICA?

This vaccine candidate has been developed based on HIV subtype C, which is the strain of the HIV virus most prevalent in southern Africa. KwaZulu-Natal sex workers who are HIV-positive gave blood samples, which were used to help develop the vaccine candidate. Scientists do not know if a vaccine might work better if it is matched to a local clade or virus type, so they are studying different variations to further understand the issue. This vaccine candidate allows scientists to establish baseline safety information that could lead to answering this important question.

Vaccine candidates designed using HIV subtype B, the type of virus common in the U.S., have been tested in the U.S. and Africa for the same safety profiles. There was no significant difference found between the volunteers' responses in the two regions.

WHAT IS THE DESIGN OF THIS TRIAL?

Ninety-six people will be enrolled in the trial, 48 in South Africa and 48 in the U.S. These people will randomly be divided into eight groups of 12 people each. Ten of these people will receive the vaccine candidate and two will receive the placebo. The groups of twelve, four in each country, will receive increasingly higher dosages of the vaccine candidate. The trial will last two years, with one year of participation expected from each volunteer. Participation will include nine clinic visits, three injection dates, and seven blood draws.

This is a multi-center, randomized, placebo-controlled, double-blinded study. It is multi-center because there are several 'centers,' or sites, where people are being given the candidate vaccine. It is called 'randomized' because the trial participants are assigned to get either one of the four dosages of the candidate vaccine or the placebo randomly. 'Placebo-controlled' means that some volunteers are given an inactive substance so that scientists can tell if there is a difference between those who get the vaccine candidate and those who do not. Neither the participants nor the doctors and scientists know who gets the vaccine candidate and who gets the placebo, and that makes the trial 'double-blinded'.

WHEN WILL THIS VACCINE CANDIDATE MOVE ON TO A BIGGER TRIAL?

This study is an important step in understanding many of the questions about the safety of the vaccine candidate, what the best dose is, and how much the immune system responds. Depending on the results of this trial, this vaccine candidate might be considered for a larger Phase II trial. If the vaccine candidate moves into a Phase II trial scientists will be looking to find out more about how to use this drug safely and in a way that helps people's bodies fight off HIV. There would likely be some changes to the vaccine candidate, based on information learned from this first trial. Participants in this Phase I trial will not be eligible for participation in any future trial of this product.

WHO IS SPONSORING THIS TRIAL?

This trial is sponsored by the Division of AIDS (DAIDS), a subset of the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH), all of which are departments within the U.S. Department of Health and Human Services (DHHS). The product was created by AlphaVax, Inc.

WHO IS CONDUCTING THE TRIAL?

The trial will be run by the HIV Vaccine Trials Network (HVTN), a global partnership dedicated to conducting international clinical HIV vaccine trials. The HVTN is funded by the National Institutes of Health (NIH).

WHO REVIEWED AND APPROVED THE TRIAL?

The vaccine candidate is considered investigational, meaning that the U.S. Food and Drug Administration (FDA) and the South African Medicines Control Council (MCC) will allow the use of this experimental vaccine only in research with a small number of participants. The vaccine candidates are made according to the guidelines established by the FDA and MCC, and has been reviewed by both agencies. The United Nations AIDS (UNAIDS) Vaccine Committee of the World Health Organization provided an ethics review of the trial. Additionally, Institutional Review Boards and Institutional Bio-Safety Committees at each site have reviewed and approved the trial.

WHO IS ELIGIBLE TO PARTICIPATE IN THIS STUDY?

Healthy, HIV-1-uninfected adults of either gender between the ages of 18 and 60.

HOW WILL THE VOLUNTEERS BE PROTECTED?

Before deciding to enter the trial, potential volunteers are provided with the following: information about HIV and AIDS; the reasons for the trial; possible risks and benefits of

participation; and trial procedures. Any new, experimental vaccine may have unknown risks. These may include side effects due to injection into a muscle, and issues of social harm associated with taking part in HIV studies. Volunteers will be reminded frequently that being part of this trial does not mean that they are less likely to become infected with HIV. Volunteers are provided with counseling at each visit, explaining current proven ways to avoid HIV infection (including, for instance, consistent condom use).

Volunteers who are eligible and willing to participate after the study has been fully explained to them will be asked to sign an informed consent before they enroll in the study. Volunteers will be given plenty of time to consider whether or not they want to participate. Volunteers do not have to join the study. Volunteers can leave the study at any time without losing the benefits of their standard medical care.

ARE THERE NON-MEDICAL RISKS?

Yes. Some vaccine candidates may cause you to appear HIV positive. Volunteers will be counseled to only get HIV testing at the trial site because the site will have specific tests which can differentiate between appearing HIV positive and true HIV infection. No medical side effects or problems are associated with appearing HIV infected on certain tests. However, others may treat volunteers unfairly if the experimental vaccine causes them to appear HIV positive. Participants will not be able to donate blood and they may also have difficulties with: getting insurance, hospitalization, traveling to other countries, employment, Military/Peace Corps service, or relationships with friends and family.

Some people have experienced discrimination when they told others that they were participating in clinical research for an HIV vaccine.

To help avoid these problems, the participant will be offered an identification card that shows that he or she joined an HIV vaccine study. A number will be listed on the card and may be called for help or information.

WHAT WILL HAPPEN TO VOLUNTEERS IF THEY BECOME HIV-INFECTED FROM THEIR BEHAVIOR DURING THE COURSE OF THE TRIAL?

Since this is a phase I trial testing for safety and immune response, it is not intended to test whether the vaccine candidate can protect against HIV infection. All volunteers must be HIV negative when they enroll in the trial. The vaccine candidate cannot cause infection with HIV. If the volunteer becomes HIV infected during the study due to sexual contact or drug use, he or she will not receive any additional injections. The participant will be referred to an appropriate doctor for medical care, but the study staff will want to continue to monitor his or her health. If there are any other studies for which the participant is qualified and wants to join, he or she will be asked to provide an additional blood specimen and sign a new consent form that will explain the details of that study.

HOW CAN I OBTAIN MORE INFORMATION ABOUT THE TRIAL?

More information about AIDS vaccine clinical trials can be obtained by calling the AIDS Clinical Trials Information Service (1-800-TRIALS-A) from within the United States or by visiting their website at www.clinicaltrials.gov. More information about the HIV Vaccine Trials Network (HVTN) can be found on their website at www.hvtn.org.