

Questions and Answers: HVTN 049 HIV Vaccine Trial

WHAT IS THE HVTN 049 VACCINE TRIAL?

HVTN 049 is a trial designed to look at the safety and immune response of a combination of two experimental HIV vaccines. The term 'HVTN 049' is the name that the HIV Vaccine Trials Network (HVTN) uses to refer to this particular trial. This trial will test both a DNA plasmid vaccine and a protein vaccine.

These vaccines are NOT produced from live virus or from HIV-infected human cells, so there is NO possibility that they contain live or killed HIV virus. Therefore, there is NO WAY to get HIV infection or AIDS by receiving these vaccines.

WHY IS THE TRIAL BEING DONE?

Scientists want to know more about these experimental vaccines because they seem to have the ability to make the immune system respond in ways that might help the body fight HIV. Once these responses are found in studies in the laboratory, scientists have to find out if the experimental vaccines work the same way in people. The HVTN 049 trial is a Phase I trial, which means that it will primarily test to see if the experimental vaccines are safe. This trial will also start gathering data to see if the vaccines have an effect on the human immune response.

The experimental vaccines being tested in this trial are engineered to produce both antibodies, the part of the immune system that fights off viruses, and killer T-cells, the part that fights cells infected with the virus.

WHAT EXPERIMENTAL VACCINES ARE BEING TESTED IN THIS TRIAL?

Two different types of experimental vaccines are being tested in this trial. One is a DNA plasmid vaccine that carries two synthetic (man-made) pieces of the HIV virus, the *gag* and the *env* genes. The second vaccine is a synthetic protein called oligomeric gp140. These experimental vaccines are being given together with an adjuvant, which is a substance meant to help the body respond to the vaccine.

- The first experimental vaccine is referred to as a Clade B *gag* DNA/PLG and *env* DNA/PLG microparticles vaccine.
- The second experimental vaccine is referred to as a Clade B recombinant, oligomeric gp140 boost given with an MF59 adjuvant. (further explanation is below)

HOW ARE THESE EXPERIMENTAL VACCINES SUPPOSED TO WORK?

This trial tests two vaccines joined together in what is called a 'prime-boost regimen'. The body will be 'primed' with the first vaccine approach, and then will be 'boosted' by a second, different vaccine. In a prime-boost vaccine, the two approaches are brought together with the hopes that they will maximize the immune response. In this case the goal is to get a response from both arms of the immune system, the antibodies that fight off the virus, and the T-cells that fight infected cells.

The base of the first experimental vaccine is DNA plasmid. Plasmids are biological structures made up of DNA. Plasmids are easy to work with, and scientists can put bits of genes from other cells into them. Plasmids then carry this new material inside their structure. It is the genetic material they are carrying, though, that does the real work.

In this experimental DNA vaccine, scientists use synthetic (man-made) HIV genes. Genes hold instructions for various functions of the body. These synthetic genes are put into the DNA plasmid, which carries the genes into the body. Once there, the genes produce proteins that are just like the ones that the HIV virus makes. Scientists think these proteins may teach the body how to defend itself against HIV. The immune system may learn to recognize these proteins, which could trigger the body's T-cells to fight HIV infection.

The second experimental vaccine uses a man-made version of one of the many proteins that HIV produces. The protein is engineered so that a particular piece of the protein is missing. By leaving out this piece, the part of the protein that is then 'seen' by the immune system closely resembles the structure that occurs when the immune system responds to HIV. By mimicking this structure, the vaccine may teach the body's antibodies exactly what part of the HIV virus to attack.

WHAT DO THE HVTN 049 VACCINES CONTAIN?

The DNA plasmid vaccine carries two synthetic (man-made) genes. These genes will produce two different proteins normally made by HIV, Gag and Env. These genes were made based on Clade B HIV, a particular subtype of HIV. The first experimental vaccine also uses something called PLG microparticles. PLG (polyactide coglycolide) is a biodegradable polymer --- a man-made structure that the body easily gets rid of. These are attached to the DNA plasmids, and they help to carry the vaccine into the body.

The protein used in the second experimental vaccine is called oligomeric gp140. The gp140 in this experimental vaccine is made in a laboratory, based on the protein gp140, which is found on the outside surface of HIV. *Oligomeric* means that several versions of the same protein are attached together. Live HIV produces many proteins, and this one protein by itself cannot cause HIV or AIDS. Researchers think that it may be enough, however, to teach the body's immune system to react to HIV.

The second experimental vaccine also includes an adjuvant called MF59. A vaccine adjuvant is any substance given along with a vaccine that helps the body respond. This adjuvant is used in an influenza vaccine licensed in Europe.

Some groups within the trial will receive a control, or inactive substance. The control used in this trial is sterile salt water (sodium chloride).

CAN THESE EXPERIMENTAL VACCINES CAUSE HIV INFECTION?

It is impossible to get HIV infection or AIDS from this experimental vaccine. This experimental vaccine is made in a laboratory. It is not made from live HIV or from HIV-infected cells. It does not contain live or killed HIV.

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

HAVE THESE EXPERIMENTAL VACCINES BEEN STUDIED BEFORE?

These experimental vaccines have not been given to humans before. The PLG microparticles used in the experimental DNA vaccine have been given to humans in various trials and have also been used as a component of approved medical procedures. Other DNA vaccines have been given to humans in past trials, with no serious side effects observed to date. The adjuvant has been shown to be safe in a range of studies, and is used in an influenza vaccine in Europe. Based on laboratory research, scientists believe that the experimental vaccines look safe, and that they cause enough of an immune response to be worth studying in humans.

ARE THESE EXPERIMENTAL VACCINES SAFE?

DNA plasmid vaccines seem to be well-tolerated by the body. Other kinds of HIV-1 DNA vaccines have been given to over one hundred participants with no serious side effects. This experimental vaccine is new, however, and scientists do not yet know everything about its safety risks. Possible risks include autoimmune problems (where the body reacts against its own tissues) and incorporation of vaccine DNA into the body's DNA, which could cause cancer or other unknown results. Scientists have not seen any evidence of this happening in the laboratory, animals or people, but the possibility exists.

The PLG (polyactide coglycolide) used in the experimental DNA vaccine has been used in some suture materials, bone plates, and drug formulations. It has shown no indication of causing side effects.

The oligomeric gp140 vaccine has not been given to humans before. There is a similar vaccine approach that uses a closely related protein, gp120, and this has been given to over 1200 trial participants with no noticeable problems beyond temporary pain and tenderness at the injection site. This side effect is common to many vaccines.

The adjuvant used in the second experimental vaccine, MF59, has not been used in combination with this protein vaccine. It has been widely tested in studies and has been used in an influenza vaccine licensed in the European Union with no side effects beyond temporary flu-like symptoms common to injectable vaccines.

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 experimental vaccine, like any new drug or vaccine, needs to be tested in participants in a controlled clinical setting. Participants' health and safety will be closely monitored throughout the trial. If researchers learn of any new risks during the course of the trial, the participants will be informed.

It is not possible for the experimental vaccine to contain live HIV virus, and therefore there is no way for the experimental vaccine to cause HIV infection.

HOW IS THE SAFETY OF THESE EXPERIMENTAL VACCINES MONITORED?

Several groups monitor this trial for safety and to make sure it is being done according to appropriate scientific and ethical standards. These groups include the US Food and Drug Administration (FDA); the US National Institutes of Health (NIH); and the HIV Vaccine Trials Network (HVTN).

The team that designed the protocol will monitor the trial throughout its duration. This team includes a range of people, from scientists and doctors to community members. The protocol team looked carefully at the information about the experimental 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 or stopped, if necessary.

WHEN AND WHERE IS THE STUDY BEING CONDUCTED?

This trial began in December 2003 in St. Louis, MO, Nashville, TN, and Seattle, WA. Eventually all of the HVTN's continental U.S. HIV Vaccine Trials Units will be running the trial. The cities that will be participating are Boston, MA; Providence, RI; Rochester, NY; New York City, NY; Baltimore, MD (2 sites); St. Louis, MO; Nashville, TN; Birmingham, AL; San Francisco, CA; and Seattle, WA.

WHAT IS THE DESIGN OF THIS TRIAL?

This trial will enroll approximately 168 people, with approximately 17 people per site. There will be two parts to the trial. Part A will study varying the dosages of the DNA vaccine and will involve 36 participants. Part B will study different timing of administration of the experimental vaccines and will involve 132 participants. Part A will be divided into 3 groups, and part B into 4 groups.

Each participant will be involved in the trial for 15 months, and the whole trial will take place over approximately 2 years. There will be fifteen planned clinic visits. Injections will be given at either four or five of these visits, depending on the group the participants in. Participants from groups 5 or 6 in part B will have one visit on which participants will receive 2 injections. There will be 12 blood draws taken for each participant throughout the study.

This is an 11-site, randomized, placebo-controlled, double-blinded study. It is called 'randomized' because the trial participants are randomly assigned to a group. 'Placebo-controlled' means that some participants are given an inactive substance so that scientists can tell if there is a difference between those who get the experimental vaccine and those who do not. Neither the participants nor the doctors and scientists know who gets the experimental vaccine and who gets the placebo, and that makes the trial 'double-blinded'.

WHEN WILL THESE EXPERIMENTAL VACCINES MOVE ON TO A BIGGER TRIAL?

This study is an important step in understanding many of the questions about the safety of the experimental vaccines, how the experimental vaccines and the adjuvant work together, and how much the immune system responds. Depending on the results of this and other trials, these experimental vaccines might be considered for a larger Phase II trial. If that happens, scientists will be looking to find out more about how to use this experimental vaccine safely and in a way that helps people's bodies fight off HIV. 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 scientists at the Chiron Corporation, a private biotechnology company based in Emeryville, California.

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 experimental vaccine is considered investigational, meaning that the U.S. Food and Drug Administration (FDA) will allow the use of this experimental vaccine only in research with a small number of participants. The experimental vaccine is made according to the guidelines established by the FDA, and has been reviewed by them.

Additionally, the trial and the participants' safety and rights are monitored by the local Institutional Bio-Safety Committees and the Institutional Review Boards (IRB) or Ethics Committees. The IRBs and Ethics Committees exist to oversee that participants' rights and needs are being met. All of these committees are local to the sites at which the trial is conducted. Community members are involved throughout the trial development in order to ensure that participants' rights and needs are being met.

WHO IS ELIGIBLE TO PARTICIPATE IN THIS STUDY?

Healthy, HIV-1-uninfected adults of either gender who meet certain criteria for eligibility. Participants in Part A will need to be between 18-40 years old; participants in part B will need to be between 18-50 years old.

HOW CAN A PERSON FIND OUT IF HE OR SHE IS QUALIFIED TO BE IN THE TRIAL?

Potential participants will be asked about their medical history and have a physical examination in order to determine if they qualify to take part in this trial. Potential participants will also have blood drawn for routine tests and to check the immune system. A urine sample will also be collected for routine urine analysis. There will be a

series of personal questions asked about sexual activity and drug use. Pregnancy tests will be administered to women who want to join the trial. Women who are pregnant or breast-feeding will not be allowed to participate in this trial. All potential trial participants are screened to ensure that they are HIV negative upon entering the trial.

HOW WILL THE PARTICIPANTS BE PROTECTED?

Before deciding to enter the trial, potential participants 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 personal problems (for example: discrimination, anger or worry from friends and family, problems with travel or getting new insurance policies) associated with taking part in HIV studies.

During the trial, the clinic staff will monitor the participants to make sure that the experimental vaccine is not causing problems. If researchers learn any new information about the safety of the trial, this information will be provided to study participants. Participants will be able to decide whether or not to stay in the study based on any new information they learn.

Participants will be reminded frequently that being part of this trial does not mean that they are less likely to become infected with HIV. Participants are provided with counseling at each visit, explaining current proven ways to avoid HIV infection (including, for instance, correct and consistent condom use).

Participants 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. Participants will be given plenty of time to consider whether or not they want to participate. Participants do not have to join the study. Participants can leave the study at any time without losing the benefits of their standard medical care.

ARE THERE NON-MEDICAL RISKS?

Yes. There are ways in which being a vaccine participant can cause personal problems. Spouses, friends, and family members can become upset when they learn about a volunteer's participation. Some people have experienced discrimination when they told others that they were participating in clinical research for an HIV vaccine. Participants are asked to carefully consider all the risks, physical and personal, before they decide to participate in a trial.

Some experimental vaccines may make certain tests for HIV read positive even when a participant is not infected with HIV. Standard HIV tests look for antibodies (cells in your immune system) that recognize HIV. The experimental vaccine may cause the body to produce these antibodies (which is a part of the body's immune response to the vaccine). In this case, the standard HIV test might show a positive result. If a participant gets this result, further tests will clarify if the participant has what is called a *false positive* or is really infected with HIV. If there is a false positive due to the experimental vaccine, the HVTN will offer retesting free of charge until the false positive result disappears.

Participants will be counseled to only get HIV testing at their trial site because the site will have specific tests which can differentiate between a false-positive HIV test result


and true HIV infection. No medical side effects or problems are associated with false-positive results. However, others may treat participants unfairly if the experimental vaccine causes the test results to appear HIV positive. Participants will not be able to donate blood and they may also have difficulties with: getting insurance, medical/dental care, traveling to other countries, employment, Military/Peace Corps service, or relationships with friends and family. There are existing services to help participants if they get a false positive-HIV result.

To help avoid these problems, the participants 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. There are people in the study who will be able to talk to insurance companies, employers, and others to explain a volunteer's participation in the study.

WHAT WILL HAPPEN TO PARTICIPANTS 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 experimental vaccine can protect against HIV infection. All participants must be HIV negative when they enroll in the trial. The experimental vaccine cannot cause infection with HIV. Being given the experimental vaccine does not mean that the participant is protected from HIV infection. Participants will be counseled to avoid behavior that would put them at risk for HIV infection. If a participant becomes HIV infected during the study he or she will not receive any additional injections. The participants 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 offered participation in these studies. The participant would then 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 vice (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.

