



HIV VACCINE
TRIALS NETWORK

Questions and answers: HVTN 064 vaccine trial

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1. What is the HVTN 064 trial?

HVTN 064 is the name of a clinical trial to test the safety and immune response of two experimental HIV vaccines. The trial will be run by the HIV Vaccine Trials Network (HVTN). The study vaccines are described in Question 5 below.

This trial will test whether the study vaccines (which are designed to be used together) are well tolerated, and whether they cause an immune response in people.

The products in this trial are not produced from live virus or from HIV-infected human cells. There is no possibility that they contain live (or killed) HIV virus. ***There is no possible way that the products in this trial can cause HIV infection.***

2. What is a vaccine trial?

Currently there is no vaccine against HIV. Part of finding an effective HIV vaccine involves testing the experimental vaccines that seem most likely to help the body fight HIV. A vaccine trial is a way to test an experimental vaccine to see if it is safe to give to people, and if it stimulates the immune system in ways that suggest it might help prevent or fight HIV. The people who participate in vaccine trials play an important part in the scientific research that may lead to an HIV vaccine.

3. Who are the people who participate in HIV vaccine trials?

Many types of people participate in HIV vaccine trials. All participants must be generally healthy and HIV-negative (free of HIV infection). People volunteer for these trials for a variety of different reasons. An important motivation for many people is altruism, the desire to help others. Before deciding to enter the trial, potential participants are provided with information about HIV and AIDS, about the reasons for the trial, about possible risks and benefits of participation, and about trial procedures.

4. Can these study vaccines cause HIV infection?

It is ***impossible*** to get HIV infection or AIDS from these study vaccines. They are not made from live HIV, killed HIV, or HIV-infected cells.

There is no possible way that these experimental vaccines can cause HIV infection.

5. What kinds of vaccines are being tested?

This study tests two different products, given alone or together. None of the products used in this study can cause HIV or AIDS.

The first study vaccine, *EP-1043*, is a protein vaccine. It is composed of 18 HIV *epitopes* — unique shapes on the surface of HIV that stimulate the immune system.

The other study vaccine, *EP HIV-1090*, is a DNA vaccine. It encodes the genetic information needed to produce 21 HIV epitopes that may help the immune system to produce infection-fighting white blood cells.

6. Why is this trial being done?

This is a Phase I trial, meaning its main purpose is to test if the study vaccines are *safe* to give to people. A secondary purpose is to test for certain types of immune response to the vaccines, given separately or in combination.

After testing the study vaccines in the laboratory, in animals, and (in the case of the DNA vaccine) in some people, researchers are interested in finding out more about the potential of the vaccines.

7. How could the study vaccines help prevent HIV/AIDS?

The idea behind both study vaccines is to train the immune system to kill cells that show signs of HIV infection, thus reducing the damage that HIV can do to the body. In theory, if a person later becomes exposed to HIV, the immune system could be prepared.

When the protein vaccine is given to a person, the protein (designed to resemble certain parts of HIV) can move into cells of the body. Once there, it is altered somewhat and taken to the surface of the cell, where it acts like a flag to catch the attention of the immune system. The immune system responds by producing white blood cells, called “helper” cells, that allow the growth of other, infection-fighting blood cells.

When the DNA vaccine is given to a person, the DNA in the vaccine instructs the body to make a protein resembling certain parts of HIV, different from the parts in the other vaccine. This protein can also act like a flag for the immune system, which sends infection-fighting blood cells to kill the “infected” cells.

8. What do the study vaccines contain?

In addition to protein or DNA, each of the study vaccines contains an *adjuvant*, a substance added to a vaccine to increase the immune response. The protein vaccine includes Alhydrogel[®], containing aluminum hydroxide. Aluminum hydroxide is commonly mixed with vaccines and is contained in several vaccines approved by the FDA.

The adjuvant for the DNA vaccine is polyvinylpyrrolidone (PVP), a chemical that improves solubility. Although PVP is used as a “wrapper” in many FDA-approved drugs taken by people, including antibiotics, cancer drugs, eye drops and hormones, it has not yet been approved by the FDA for use as a vaccine adjuvant. Since the researchers are testing PVP as a vaccine adjuvant, its use in this study is experimental.

In summary:

- The protein vaccine contains a recombinant (man-made) protein, the aluminum hydroxide adjuvant, and a saline (salt water) solution.
- The DNA vaccine contains a recombinant plasmid (piece of DNA), the PVP adjuvant, and a saline solution.

The *controls* for these vaccines (see Question 13) are the adjuvants alone. The control for the protein vaccine is the aluminum hydroxide adjuvant in a saline solution; the control for the DNA vaccine is PVP in a saline solution.

9. Have these vaccines been studied before?

The protein vaccine and DNA vaccine have been tested together in animals, with no serious side effects. Animal testing, however, does not always show what will happen in people. In HVTN 064 the protein vaccine is being tested in people for the first time.

The DNA vaccine is being tested in people in another trial, HVTN 048. The only severe side effects reported during this trial (two people with a temporary change in blood chemistry and one person with severe back pain) were considered unrelated to the DNA vaccine.

10. Who is eligible to participate in this trial?

Participants must be healthy adults between 18 and 50 years old and HIV-negative (free of HIV infection). All participants must meet certain medical and non-medical criteria for eligibility. Volunteers are carefully screened to make sure they meet the eligibility requirements.

11. How can people find out if they are qualified to join this trial?

Potential participants are asked about their medical history and given a physical examination. They then have blood and urine samples taken for routine analysis, and are asked a series of personal questions about sexual activity and drug use.

Women who want to join the trial will be given a pregnancy test. Pregnant or breastfeeding women, or women planning a pregnancy in the next year, are not allowed to join.

All volunteers are tested to ensure that they are HIV-negative (free of HIV infection). A volunteer who is HIV-positive at screening cannot enroll in the trial.

Information about participants will be kept confidential and will be used only for trial purposes.

12. When and where is this trial being conducted?

HVTN 064 is an international trial, and research sites are located in two countries. The trial is expected to begin enrolling participants around November 2005. It will be conducted in three US cities: Baltimore, MD; Rochester, NY; and San Francisco, CA. It will also be conducted in Lima and Iquitos, Perú.

13. What is the design of this trial?

The trial will enroll about 120 people. It has two parts, Part A (24 people) and Part B (96 people).

Part A is evenly divided into two groups (Groups 1 and 2) of 12 people each. Over the course of six months, these groups will receive four injections of protein vaccine, Group 1 at a dose of 0.05mg and Group 2 at a dose of 0.2mg. The researchers will determine whether the lower dose is safe and well tolerated before escalating to the higher dose. (Participant safety is monitored very carefully; any dose that does not appear safe will be stopped.) For comparison, a few people in each group are given a *control*, an injection which lacks the active protein or DNA of the study vaccines. The control for the protein vaccine is the aluminum hydroxide adjuvant in a saline solution; the control for the DNA vaccine is PVP in a saline solution.

DESIGN OF PART A

Group	# of people	First day	+1 month	+3 months	+6 months
1	10	Protein vaccine 0.05 mg	Protein vaccine 0.05 mg	Protein vaccine 0.05 mg	Protein vaccine 0.05 mg
	2	Control: Alhydrogel	Alhydrogel	Alhydrogel	Alhydrogel
2	10	Protein vaccine 0.2 mg	Protein vaccine 0.2 mg	Protein vaccine 0.2 mg	Protein vaccine 0.2 mg
	2	Control: Alhydrogel	Alhydrogel	Alhydrogel	Alhydrogel

Part B will begin two weeks after the last person in Part A has received the second injection, if there have been no severe side effects due to the study vaccine. Part B is divided into three groups, one group of 24 people (Group 3) and two groups of 36 people (Groups 4 and 5). Over the course of six months, Group 3 will receive four injections of protein vaccine at the highest dose from Part A that the researchers consider suitable to give to more people. Group 4 will receive four injections of DNA vaccine, and Group 5 will receive four injections of both vaccines. As in Part A, some people will be given a control instead of vaccine.

DESIGN OF PART B

(Note: Part B will begin only after data are available about the protein doses given in Part A.)

Group	# of people	First day	+1 month	+3 months	+6 months
3	20	Protein vaccine	Protein vaccine	Protein vaccine	Protein vaccine
	4	Control: Alhydrogel	Alhydrogel	Alhydrogel	Alhydrogel
4	30	DNA vaccine 4 mg	DNA vaccine 4 mg	DNA vaccine 4 mg	DNA vaccine 4 mg
	6	Control: PVP	PVP	PVP	PVP
5	30	Protein + DNA vaccines	Protein + DNA vaccines	Protein + DNA vaccines	Protein + DNA vaccines
	6	Controls: Alhydrogel + PVP	Alhydrogel + PVP	Alhydrogel + PVP	Alhydrogel + PVP

HVTN 064 is a multicenter, randomized, controlled, double-blind trial. ‘Multicenter’ means the trial is being conducted in more than one research site. ‘Randomized’ means that participants are assigned by chance to get either the study vaccine or the control at all their injection visits. ‘Controlled’ means that some people are given a neutral substance for comparison, so the researchers can tell if the study vaccine makes a difference (in HVTN 064 the neutral substances are Alhydrogel and PVP). ‘Double-blind’ means that neither the participants nor the scientists know who is getting the study vaccines and who is getting the controls until after the trial is over.

Injections of protein vaccine or Alhydrogel are given in a deltoid (upper arm muscle). Injections of DNA vaccine or PVP, which have a slightly larger volume, are given in a thigh muscle.

14. How will the safety and rights of participants be protected?

Trial participants play a very important role in the search for an HIV vaccine, and the HVTN works hard to make sure that the safety and rights of the participants are given the highest priority. There are several ways that the HVTN works to make its trials as safe and convenient as possible, but it is important for participants to realize that any new, experimental vaccine may have both medical and non-medical risks.

Before they join the trial, volunteers are provided with information about HIV and AIDS, about the reasons for the trial, about possible risks and benefits, and about trial procedures. Clinic staff allow ample time to talk with volunteers and answer their questions, and information is also provided in writing.

After the trial has been fully explained, volunteers are asked to sign an *informed consent* form before enrolling. This form will help ensure that participants have been given all the information they need. Volunteers will be given plenty of time to consider whether or not they want to join the trial. They may decide not to enroll as participants. If they do enroll, they may still leave the trial at any time without losing the benefits of their standard medical care.

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

Participants are reminded frequently that being part of a vaccine trial does not mean they are protected from HIV infection. They are counseled at each clinic visit on ways to avoid HIV infection (including, for example, correct and consistent condom use).

15. Are these study vaccines safe?

Evaluating the safety of the study vaccines is the main purpose of HVTN 064. The study vaccines have been tested in animals with no serious side effects, although animal testing does not necessarily predict results in humans. (The DNA vaccine has been tested in some people, with no serious vaccine-related side effects.) Based on the data now available, scientists believe that the study vaccines are suitable for use in this trial.

While scientists believe that there are no serious safety risks with the study vaccines, there is always the possibility that there could be problems that no one expected. This is why these study vaccines, like any new drug or vaccine, need to be tested in participants in a controlled clinical setting. Participants' health and safety will be closely monitored throughout the trial.

The study vaccines do not contain live HIV virus, and therefore there is no way for the study vaccines to cause HIV infection.

16. How is the safety of the study 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 HVTN itself. In addition, the researchers at each study site have an obligation to report to their local Institutional Review Board every year, and more often if necessary.

Physicians and nurses on the team that designed HVTN 064 will monitor the safety of the trial. This team carefully considered the available information to decide if the study vaccines were suitable for use in a human trial. The HVTN also has a Safety Monitoring Board not affiliated with this particular trial. Both of these groups will carefully monitor the safety of the participants. If there appear to be problems involving participant safety, the trial will be put on hold. After additional review by independent monitors, the trial can be modified, or stopped if necessary.

17. Are there non-medical risks?

Participants are asked to carefully consider all risks before joining a trial. Some risks are medical (related to health and safety), but there are also non-medical, or social, risks. Trial participation takes time and commitment. It can also lead to complications with others who do not agree with the participant's choice, or who do not have enough information about HIV vaccines. For example, some people have reported that being in a trial has upset their spouse, friends, or family members.

Participating in a trial also restricts the volunteer's behavior. For instance, participants are asked not to donate blood, and women must avoid pregnancy during the trial.

Participants may experience discrimination when they tell people they are taking part in clinical research for an HIV vaccine. In the case of discrimination, study staff can (at a participant's request and with their permission) talk to insurance companies, employers, and others to explain a participant's involvement in the trial.

In the unlikely event that the study vaccines cause a false positive result on a standard HIV test (see Question 18), such a result may lead to being treated unfairly by others.

It is important to remember that being given a study vaccine does not mean the participant is protected from HIV infection. Trial participants will also not know whether they have received a study vaccine or a control, which has no protective properties. Participants are therefore counseled to avoid behavior that will put them at risk of HIV infection.

To help avoid problems that could come from participating in a trial, participants will be offered an identification card that shows that they joined an HIV vaccine study. A number will be listed on the card that may be called for information or for help to resolve problems.

18. Could the study vaccines cause a "false positive" result on an HIV antibody test?

Some experimental vaccines may cause a trial participant to have an HIV test that appears HIV positive. Standard HIV tests look for antibodies (a part of the immune system) that recognize HIV. If an experimental vaccine has caused the body to produce these antibodies, the standard HIV test could show a positive result. This is called a "false positive" result because the test may make a person *appear* infected, even when they are not infected.

The study vaccines used in HVTN 064 are not designed to produce antibodies. Nevertheless, participants are counseled to get HIV testing done only at their trial site. The site has specific tests which look for the presence of the virus itself, and thus can distinguish between false positives and true HIV infection. These tests will be available at no charge to the participant—even after the study ends.

No medical side effects or health problems are associated with a false positive HIV test result. But such a result may lead to being treated unfairly by others. People with a positive HIV test, even a false positive, are not allowed to donate blood. They may also have difficulties getting insurance or medical/dental care, traveling to other countries, obtaining employment, serving in the military or Peace Corps, or with their relationships with friends and family. Clinic staff are available to help with any difficulty, and services exist to help any study participant with a false positive HIV result.

19. What will be done with a participant's trial records?

Any information collected about a trial participant will be kept as private as possible. Most records have only a participant ID number, not a name. Samples used for tests are identified by number only, not by name. Any test results are confidential, and will not be made part of participants' medical

records. Information about trial participants will be used only for research related to HIV vaccines or vaccine trials.

Still, we cannot guarantee absolute privacy. For example, certain information about trial participants may be released if required by law. In addition, most groups that review the safety of and conduct the trials will be able to review the records—but all the members of these groups are obligated to keep any information confidential.

A *Certificate of Confidentiality* from the US Department of Health and Human Services helps protect participant confidentiality in the US. This certificate means that researchers and clinicians cannot be forced to give identifiable information to anyone not connected to the study, even in court proceedings. There are some exceptions to the Certificate of Confidentiality, such as in the case of government audit. These exceptions will be explained to volunteers at the trial sites.

20. What will happen to participants if they become HIV-infected from their behavior during this trial?

The study vaccines cannot *cause* HIV infection, but at this point we do not know if they *prevent* HIV infection. Participants can still get infected with HIV through sexual contact, sharing of injection drug equipment, or any other exchange of blood or bodily fluids, even if they are receiving a study vaccine.

All participants must be HIV negative when they enroll in the trial. Once in the trial, they are counseled to avoid behavior that would put them at risk of HIV infection. Anyone who becomes infected during the trial will stop receiving injections, but clinic staff will ask to continue monitoring their health for the rest of their scheduled time in the trial, and the researchers will provide blood testing to see how the body controls HIV infection.

There are many drugs that can be used to treat HIV infection, but none of these drugs can cure HIV infection. These drugs are not provided as part of this trial. Participants who become infected during the trial will be referred to an appropriate doctor for medical care and counseling.

21. How long will it take to find out if the study vaccines work?

Depending on the results of HVTN 064 and other trials, these experimental vaccines might be tested further in a larger Phase II trial. Such a trial would test safety in more people, adjust dosing, and give a better idea of whether the immune system responds to these vaccines. If results remain promising, more trials would be planned to see if the study vaccines help prevent HIV infection. Participants in HVTN 064 will probably not be eligible for any future trial of these products.

22. Who is sponsoring this trial?

This trial is sponsored by the Division of AIDS (DAIDS), within the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH), an agency of the US Department of Health and Human Services (DHHS), Bethesda, MD.

The study vaccines, EP-1043 and EP HIV-1090, were made by Epimmune, Inc. (now IDM Pharma, Inc.), San Diego, CA.

23. Who is conducting this trial?

The HIV Vaccine Trials Network (HVTN) will run the trial. The HVTN is a global partnership of researchers, government, pharmaceutical companies, academic institutions, and community members. The HVTN is dedicated to conducting international clinical HIV vaccine trials in the safest, most

efficient, and scientifically most rigorous way possible. The HVTN is funded and supported by the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH), an agency of the US Department of Health and Human Services (DHHS).

24. Who reviewed and approved this trial?

The study vaccines are considered investigational, meaning the FDA allows their use only in research. They have been made according to FDA guidelines.

HVTN 064 has been reviewed by numerous people within the HIV Vaccine Trials Network, and by the Prevention Sciences Review Committee and the Regulatory Affairs Branch of the Division of AIDS at the National Institutes of Health. It has also been reviewed by the FDA Center for Biologics Evaluation and Research.

In addition, the safety and rights of participants in HVTN 064 are monitored by Institutional Biosafety Committees (IBC) and Institutional Review Boards (IRB) local to each research center. Community members are involved throughout the trial to ensure that the rights and needs of participants are being met.

25. For more information

About AIDS vaccine clinical trials: AIDS Clinical Trials Information Service, 1-800-TRIALS-A (USA only); **www.clinicaltrials.gov**

About the HIV Vaccine Trials Network: **www.hvtn.org**