FACT SHEET
Office of Communications and Public Liaison
National Institute of Allergy and Infectious Diseases ▪ National Institutes of Health

Clinical Research on AIDS Vaccines

In partnership with volunteers nationwide, the National Institute of Allergy and Infectious Diseases (NIAID) supports clinical research to determine the best candidate vaccines to protect people from human immunodeficiency virus (HIV) infection (**preventive vaccine**) or from becoming ill after they acquire the virus (**therapeutic vaccine**). (Scientific terms common to vaccine research are printed in **bold-faced** type.)

To help design these vaccines, scientists have identified important immunologic targets on HIV and on infected cells. For example, they know the **glycoprotein 120 (gp120)** on the outer coat of the virus contains the **CD4 binding site**, the region that attaches to cells of the human host. Scientists also know that most **neutralizing antibodies** (proteins that block a virus from infecting cells) in HIV-infected people are directed against gp120. For these reasons, vaccines based on genetically engineered HIV **envelope proteins – gp160** and a smaller molecule, gp120 – have been the most well-studied to date.

Since the first HIV vaccine trial opened in 1987, more than 40 different preventive vaccine candidates have been studied in clinical trials worldwide, belying a misperception that few concepts have been examined. HIV vaccine research has progressed from its early focus on HIV envelope proteins and the role of antibodies to increased attention to the importance of **cytotoxic T cells (CTLs),** immune cells that kill HIV-infected cells. Many novel vaccine strategies to elicit anti-HIV antibodies and CTLs are now being pursued:

- ***subunit vaccine***: a piece of the outer surface of HIV, such as gp160 or gp120, produced by genetic engineering.
- ***live vector vaccine***: a live bacterium or virus such as vaccinia (used in the smallpox vaccine) modified so it cannot cause disease, but can transport into the body a gene or genes that makes one or more HIV proteins.
- ***vaccine combination***: for example, use of a recombinant vector vaccine to induce cellular immune responses followed by booster shots of a subunit vaccine to stimulate antibody production, referred to as a **prime-boost strategy**.
- ***peptide vaccine***: chemically synthesized pieces of HIV proteins (peptides) known to stimulate HIV-specific immunity.
- ***virus-like particle vaccine (pseudovirion vaccine)***: a non-infectious HIV look-alike that has one or more, but not all, HIV proteins.
- ***DNA vaccine***: direct injection of genes coding for HIV proteins.
- ***whole-killed virus vaccine***: HIV that has been inactivated by chemicals, irradiation or

other means so it is not infectious.

- ***live-attenuated virus vaccine***: live HIV from which one or more apparent disease-promoting genes of the virus have been deleted.

What are Clinical Trials?

After an experimental vaccine performs well in laboratory and animal studies designed to determine its safety and **immunogenicity** (ability to stimulate immune responses), it must successfully complete three stages of testing in people before being developed into a licensed product.

A **Phase 1** trial is the first setting in which an experimental HIV vaccine is given to people. Such a trial usually enrolls about 20 to 80 non-HIV-infected volunteers at apparent low risk of HIV infection. A Phase 1 trial primarily seeks information on safety, usually assessing any vaccine-related side effects by comparing the vaccine with an inactive **placebo** or **control** that looks like the test product. A Phase 1 trial also can provide data on the vaccine's immunogenicity, including the dose and administration schedule required to achieve optimal immune responses. If the vaccine elicits neutralizing antibodies, scientists can study how these react against HIV strains from the same or other HIV **subtypes** or **clades** to determine the potential breadth of protection. A Phase 1 trial may last one to two years.

Once Phase 1 trials show the experimental HIV vaccine is well-tolerated, it can advance into **Phase 2** trials. These trials enroll more people, up to a few hundred, and often include some volunteers at higher risk for acquiring HIV. Researchers gather data about safety and immune responses, asking more sophisticated questions that such larger trials allow. Optimally, the trials are **randomized** and **double-blind**, meaning that volunteers are assigned at random to a study group and that neither the health care workers nor the patients know what preparations the patients receive. Phase 2 trials usually last one to two years.

The most promising candidate vaccines then move into **Phase 3** or **efficacy** trials, enrolling large numbers of non-HIV-infected people at high risk for exposure to the virus. A Phase 3 trial usually is designed to ensure the collection of enough data on safety and effectiveness to support a license application, if warranted. The vaccine may be tested against a placebo or a vaccine such as hepatitis B of known potential benefit to the study population. An efficacy trial can involve thousands of volunteers and take at least four years to complete.

NIAID-supported investigators are also developing creative designs for intermediate studies that can provide preliminary answers about which products to move forward into efficacy trials. An intermediate trial design may be useful in quickly sorting out vaccines that clearly are efficacious from those that are not before initiating a large, expensive and resource-intensive efficacy trial.

Overview: Clinical Trials of Preventive HIV Vaccines

In August 1987, NIAID opened the first clinical trial of an experimental HIV vaccine at the NIH Clinical Center in Bethesda, Md. This Phase 1 trial eventually enrolled 138 non-infected healthy volunteers. The gp160 subunit candidate vaccine tested caused no serious adverse effects.

Six months later, the NIAID ***AIDS Vaccine Evaluation Group (AVEG),*** the largest U.S. cooperative HIV vaccine clinical trials group, began enrolling volunteers in its first trial. AVEG includes the following:

- The ***AIDS Vaccine Evaluation Units (AVEUs)***, consisting of six clinical research centers nationwide, conduct Phase 1 and 2 clinical trials of candidate HIV vaccines in low-risk and high-risk HIV-negative volunteers. AVEG sites are located in Baltimore, Nashville, Seattle, St. Louis, Birmingham and Rochester, N.Y.
- The ***Central Immunology Laboratory*** provides state-of-the-art evaluation of antibody- and cell-mediated immune responses to vaccinees in AVEG trials. The evaluations use standardized tests, permitting comparison of responses in different individuals and to different candidate vaccines.
- The ***Data Coordinating and Analysis Center*** provides a central facility for collecting and analyzing data from the trials conducted by the AVEUs.
- The ***Immunology Laboratory Support for Assessment of Mucosal Immune Responses Induced by AIDS Vaccines*** evaluates human mucosal immune responses to candidate vaccines in standardized tests, permitting the comparison of responses in volunteers at different AVEUs and in volunteers who receive different candidate vaccines.
- The ***Specimen Repository*** collects and maintains blood samples and other specimens from volunteers in AVEG trials for use in current and future studies.
- A ***Data and Safety Monitoring Board*** periodically reviews data from AVEG studies.

Since 1987, more than 3,200 non-HIV-infected volunteers have enrolled in 52 NIAID-supported preventive HIV vaccine studies (50 Phase 1 and two Phase 2 studies) involving 27 vaccines. These trials have been conducted primarily through the AVEG. NIAID's HIV Prevention Trials Network (HIVNET), which includes international as well as U.S. sites, and NIAID investigators in Bethesda have also led or helped conduct some of these trials.

To date, all the vaccine candidates tested have been well-tolerated, generally producing only mild side effects typical of most vaccines. The first candidates tested stimulated production of antibodies, although levels decreased within a relatively short period of time. Initial formulations and dosages of these vaccines produced few or low levels of neutralizing antibodies and rarely elicited CTLs.

With newer protocols, using increased vaccine dosages, different immunization schedules, experimental adjuvants and new recombinant proteins, more promising data regarding the induction of neutralizing antibodies and cytotoxic T cells have emerged.

In December 1992, NIAID launched the first Phase 2 HIV vaccine clinical trial. Earlier trials enrolled non-infected people at low risk of HIV infection and primarily sought data on safety. This trial includes non-infected volunteers with a history of high-risk behavior – injection drug use, multiple sex partners or sexually transmitted diseases. Participants were counseled repeatedly to avoid any behavior that puts them at risk of HIV infection. Follow-up for this trial has been extended.

Highlights of Most Recent Trials

Recent studies supported by NIAID have examined canarypox vectors encoding multiple HIV gene products, administered with or without a gp120 subunit vaccine. Early results have been encouraging. CTLs have been detected in up to 70 percent of volunteers, and have persisted for up to two years following initial vaccination. In some patients, these immune responses also cross-react in laboratory experiments with subtypes of the virus different from that used in the vaccine, indicating the possibility of protection for lager, diverse populations. These findings provided the impetus for initiating the second Phase 2 HIV trial known as AVEG 202/HIVNET 014. This trial is testing a canarypox vector vaccine given in combination with a gp120 subunit vaccine.

A related study is evaluating three potential live canarypox vaccine vectors to determine which produces the most robust immune responses. Another trial will assess different HIV subunit vaccines given in conjunction with live vector vaccines. These studies, as well as additional data that emerge from basic research, will provide the information necessary to decide which products will advance into larger-scale testing.

In 1998, the company VaxGen began the first Phase 3 efficacy study of an AIDS vaccine. The three-year study of their subunit vaccine known as AIDSVAX will enroll 5,000 volunteers at clinical sites throughout the United States and in Canada and The Netherlands. In March 1999, the company opened a second efficacy trial in Thailand. NIAID is collaborating with VaxGen on assessing immune responses induced by AIDSVAX, and also is testing AIDSVAX in combination with other vaccines.

In February 1999, NIAID launched the first AIDS vaccine trial in Africa. The genes incorporated in the experimental canarypox vector vaccine used in this Phase 1 study come from only clade B viruses, the predominant subtype of HIV found in the United States and Europe. The researchers will see if the vaccine can also elicit immune responses to clade A and D viruses, the two subtypes that cause most HIV infections in Uganda. The study is designed to investigate how human differences influence the immune response to candidate vaccines. The outcome of this study will guide NIAID’s future HIV vaccine strategy and is an important step in a long process toward developing safe and effective HIV vaccines for worldwide use.

Future Directions

Although the challenges are daunting, scientists remain optimistic that safe and effective HIV vaccines can be developed. Novel ways to present HIV proteins to the immune system continue to be designed and tested, as do new antigen-adjuvant vaccine formulations. A growing number and variety of experimental vaccines are entering clinical tests in primates and humans, and more trials are exploring whether changing immunization schedules, increasing booster doses or using a combination vaccine strategy can stimulate stronger, more durable immune responses. Together, progress in basic and clinical research is moving scientists closer toward identifying products suitable for large-scale HIV vaccine efficacy trials.

NIAID, a component of the National Institutes of Health, supports research on AIDS, tuberculosis and other infectious diseases as well as allergies and immunology.

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Publications | Home