The Development of an AIDS Vaccine: Progress and Promise

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Synopsis

The development of a safe and effective vaccine against infection by the human immunodeficiency virus (HIV) is of paramount importance to the prevention of AIDS worldwide. Although a great deal has been learned about HIV in a few short years, the development of an AIDS vaccine has proved to be extremely difficult. The lack of an appropriate animal model for AIDS, the absence of a defined protective immune response in persons infected with HIV, the long latent period between initial infection and the development of symptoms, the existence of multiple strains of HIV, and the spread of HIV by way of cell-associated virus are issues that complicate the development of an effective AIDS vaccine.

Researchers are employing a multifaceted approach to the creation of a potential AIDS vaccine. These approaches include the use of killed or attenuated virus, purified natural or synthetic subunits of the virus, infectious recombinant viruses, and anti-idiotypes. The first clinical trial of a subunit AIDS vaccine began in September 1987 at the National Institutes of Health (NIH). Through support of basic research on AIDS vaccine development and the establishment of a mechanism for clinical trials of candidate vaccines, NIH is pursuing multiple approaches toward the goal of a vaccine against AIDS.

CONTROL OF HUMAN VIRAL DISEASES has thus far been achieved only by preventive measures such as vaccines or the elimination of vectors necessary for viral spread. The recent pandemic of AIDS due to infection with the human immunodeficiency virus (HIV) has led to an international consensus that the spread of the virus must be halted. The very long mean incubation period in adults—up to 7 years between initial infection with HIV and the development of clinical AIDS—and the known ability of HIV-infected, asymptomatic persons to transmit HIV, allow for the generation of an immense worldwide reservoir of infected people, many of whom will succumb to AIDS. Clearly, the development of a safe and effective vaccine to prevent HIV infection is of fundamental importance in the battle to halt the spread of AIDS.

This paper is a review of the research efforts that are currently underway to develop a safe and effective vaccine against AIDS. Although this review highlights many of the difficulties involved in generating an AIDS vaccine, it must be remembered that researchers have learned an enormous amount of critical information in a very short period while working to overcome those difficulties. The National Institutes of Health (NIH), in its role as the lead agency of the Public Health Service (PHS) responsible for AIDS vaccine research and development efforts, is committed to the goal of further expediting preclinical and clinical development of a safe and effective AIDS vaccine.

Preclinical Vaccine Development

General difficulties posed by HIV. Five of the key problem areas in devising a vaccine to prevent AIDS are

- The state of protective immunity in man is unknown.
- HIV mutates and many divergent strains exist.
- The virus can lie dormant in cells.
- Transmission is possible via HIV-infected cells.
- There is no perfect animal model for AIDS.

The conventional approach to developing a vaccine against an infectious pathogen is to examine people who have been infected with the

organism but have successfully contained the invader either by eliminating it from the body or by controlling it so that harmful sequelae do not result. The profiles of humoral and cellular immunity are then determined, and a vaccine preparation is designed so as to replicate the immune status of the "protected" individual. However, in the case of HIV infection, no individual in whom the infection has been controlled has been clearly identified. Therefore, the choice of what would constitute a protective vaccine has to be extrapolated from related animal models.

A critical problem in developing a vaccine against HIV is the existence of multiple strains of HIV and the potential for further rapid mutation (*1,2*). Extensive heterogeneity exists especially in the HIV envelope gene (*env*), which specifies the structure and the variable antigenicity of its external glycoproteins (g) (*3*). The existence of still another subfamily of HIV-like agents in man in western Africa, designated HIV-2, which may also cause an acquired immunodeficiency syndrome, further complicates the search for a broadly protective vaccine (*4*).

A third complicating feature of HIV is that it can infect several cell types in the body and, like several other retroviruses, can establish a state of dormancy during which the integrated DNA provirus expresses no RNA or proteins; that is, it presents no targets for an immune attack (*5,6*). The fact that HIV infection could occur efficiently by cell-to-cell contact further complicates vaccine development, since one component of a protective immune response must include a mechanism for eliminating HIV-infected cells.

The existence of an animal model for AIDS that exactly mimics the disease in man would be advantageous. Currently, the only animal that can be readily infected by HIV is the chimpanzee (*7*). This species is susceptible to HIV infection, and a chronic state of infection and immune response similar to that in man has been achieved in every infected chimpanzee tested (*8*). Of note is the fact that—with the exception of rare, self-limited lymphadenopathy—no disease has occurred in these animals in more than 3 years since they were infected. Accordingly, the chimpanzee is very amenable as a model for the development of an AIDS vaccine that prevents primary infection by HIV. This species cannot be used to predict whether an AIDS vaccine could reduce or eliminate clinical disease in HIV-infected persons who receive the vaccine.

HIV is a retrovirus that is most clearly related to the subgroup of animal lentiviruses (*9*). Although experimental vaccines exist for some animal retroviruses, several attempts at preventing lentivirus infection by vaccines in domestic animals have not been successful. In fact, in some cases, vaccinated animals experienced an exacerbated course of disease compared with unvaccinated controls when challenged (*10–12*).

Vaccine approaches and preparations. A number of conventional and specialized approaches to the development of an AIDS vaccine can be considered and prioritized. Two of the most obvious approaches, the use of a killed or nonpathogenic HIV, may pose intrinsic dangers. Theoretically, a nonpathogenic virus could be engineered; however, there is always the possibility that it could revert to virulence. Furthermore, the powerful molecular "switches" or gene controls in integrated proviral DNA from either killed or attenuated HIV have the potential to adversely affect contiguous cellular genes such as oncogenes, which could result in cancer (*13*).

To ensure greatest safety, only purified HIV proteins or glycoproteins should be used in vaccine preparations. Current genetic engineering technology allows for essentially unlimited supplies of such material from a variety of bacterial, yeast, insect, or mammalian vector systems (*14*). Knowing the complete genetic sequence of a number of HIVs also permits the construction and synthesis of specific peptides that constitute the critical antigenic sites. Such peptides are simple to prepare, are stable, can be made against many divergent variants, and represent epitopes needed for stimulating both B- and T-cell responses (*15*).

An alternative approach is the use of an infectious recombinant virus—a process that entails taking a large virus of known safety such as vaccinia, removing a nonessential gene, and substituting a HIV gene of interest (*16*). This approach is attractive because both the vaccinia and HIV proteins would be made, and presumably a protective immune response would result against both viruses.

Another approach to making a vaccine, the anti-idiotype approach, does not involve any viral product. To produce an anti-idiotype vaccine, antibodies (idiotypes) to a HIV protein are injected into animals to produce a second antibody response (anti-idiotype). The anti-idiotype resembles the original HIV protein and can be used as a vaccine to generate an immune response to the HIV protein. Theoretically, this vaccine is safe

Table 1. Viral and nonviral antigens considered as vaccines against AIDS

Antigen	*Type*	*Structure*
HIV external glycoproteins or peptides	*env*	(gp160), gp120, gp41
HIV core structures or peptides	*gag, pol*	(p55), p24, p17, p9, p7, p66, p51, p32-endonuclease
HIV nonstructural proteins	*protease, tat, trs, sor, 3' orf, R*	Various medium-sized to small proteins
Antibody against HIV receptor	Antibody to CD4a	Mimics the attaching epitope on HIV gp120
Anti-idiotypic antibody to HIV	Antibody to HIV neutralizing monoclonal	Anti-idiotype "looks" like the antigen

NOTE: Structure in parenthesis denotes the size of the entire uncleaved gene product that can also be used as an antigen; gp means glycoprotein; *env* means HIV envelope; *gag*, group specific antigen; *pol*, polymerase; *tat*, trans-activating transcriptional gene; *trs*, transacting regulator of splicing; *sor*, short open-reading; *3' orf*, 3' open-reading frame; *R*, reading frame; CD4a, receptor for HIV.

Table 2. Outcome of HIV challenge in vaccinated chimpanzees

Vaccine	*Response*	*Challenge*	*Outcome*
Native gp120 from HIV-IIIb	Group reactive precipitating and type specific neutralizing antibody. Group reactive cellular immunity	HIV-IIIb 100 percent *in vivo* infective titer	HIV reisolated in 4-6 weeks; boost in immunity
Vaccinia infectious recombinant *env* gene	Group reactive precipitating antibody and cellular immunity	HIV-LAV high titer, not assessed *in vivo*	HIV reisolated rapidly; enhanced HIV-LAV immunity

because it contains no HIV antigens (*17*). Another variation would be to use as a vaccine a monoclonal antibody to the CD4a molecule, the receptor for HIV for all variants of HIV.

Since protection in other retrovirus systems has been achieved using the major external viral glycoprotein as antigen (*10,11*), most of the current strategies are based on various permutations of the HIV counterpart, the total *env* gene product gp160 (160,000 dalton sized glycoprotein) or its natural cleavage products, gp120 and gp41 (*18,19*). Several dozen versions of the entire gene product, its pieces, or selected peptides have been used as antigens. The viruses initially used have been HIV-IIIb and its close relative HIV-LAV. More recently, a number of products from other HIV types have also been made.

Vaccines may also be made from internal core structural proteins of HIV, the group specific (*gag*) antigens, or from the reverse transcriptase or polymerase (*pol*) antigens. Immune responses to these proteins have been detected during infection, with a variable degree of response found in different persons. Analogues of these core antigens have been able to elicit protection in recipient hosts in at least the most widely studied murine leukemia retrovirus system. Some internal antigens could appear on the cell surface during processing, and at least one of these could induce cytotoxic antibody to virus-infected cells (*20*). Because lentiviruses have additional functional genes that control the rate of HIV replication, the products of those genes represent yet another category of antigens. These groups of viral gene products and their "internal images" represented by anti-idiotypes are schematically grouped in table 1.

Immunity induced by HIV antigen preparations. Immunity to HIV antigens has generally been measured in various tests as an antibody response. Specifically, researchers have focused on the ability

of these antibodies to neutralize, that is, kill the virus. During infection by HIV in man, group specific (reacting with multiple isolates) neutralizing antibodies have been observed. However, the reactivity was unpredictable in that some HIV types, but not others, were neutralized by antibodies from a single infected person (*21*).

To date, immunization with HIV gp160 or gp120, either native or genetically engineered, has resulted, with few exceptions, in a poor to moderate immune reaction in a number of species. Relatively low to moderate levels of neutralizing antibody were induced, but these were strictly type specific (that is, they would not inactivate less related HIV types in cell culture systems or in chimpanzees) (*14*). The gp41 and the core p17 proteins have been reported to induce neutralizing antibody, but this response has not been generally confirmed. Other antigens have not been known to yield neutralizing antibodies.

In addition to the neutralization of free virus, the killing of HIV-infected cells may be critical to slowing the infection. Both antibody and complement mediated cell-killing and antibody and cell dependent cytotoxicity have been described under various situations in hosts vaccinated against other infectious organisms (*14*). Induction of T-cell responses that help to enhance antibody levels to HIV has also been achieved by conserved peptides from HIV gp120 (*15*). In addition, measures of more typical cell mediated cytotoxicity have been described after immunization with HIV *env* gene products in several species including primates (*22*). These latter responses were interesting in that the reactivity extended even to less related HIV types. At this time, the use of either the purified viral subunits or their expression in the infectious recombinant vaccinia virus has given roughly equal results.

Outcome of challenge experiments in vaccinated chimpanzees. As summarized in table 2, chimpanzees vaccinated either with the native gp120 from HIV-IIIb or with a vaccinia-HIV-LAV *env* gene recombinant responded to the antigen. In the former case, the immunizations resulted in low level neutralizing antibody that could kill only HIV-IIIb but not less related HIV types. Cell mediated immunity was detected in both sets of animals (*23,24*). Each group was challenged only with the exact HIV type from which the vaccine was derived. Because virus titers measured in tissue cultures are not accurate indicators of the potential infectiousness *in vivo*, a titration of a given virus stock of HIV-IIIb in the animal was performed to determine the minimal 100 percent infectious dose. The amount needed to infect a chimpanzee is very low, and the time to detect infection in a chimpanzee inoculated intravenously was only 6 weeks, using the lowest dose of virus.

In the case of the native gp120 immunized animals, a 100 percent infectious dose and 10 times that dose were used. In each challenged vaccinated animal, HIV was recovered by 4 weeks after infection—similar to the time of isolation of HIV from nonvaccinated control animals. When HIV-LAV was used to infect the animals vaccinated with the vaccinia recombinant containing the HIV-LAV *env* gene, rapid breakthrough by the virus was also observed. In the HIV-IIIb experiment, the reisolated virus from the vaccinated animals was already altered in its capacity to be neutralized by the standard typing serum, suggesting that a variant virus type(s) appeared rapidly.

Thus, both initial vaccination attempts with the use of viral antigens failed to prevent HIV infection against the homologous virus. Further, the presence of relatively good levels of immunity in the chimpanzee subsequent to infection could not prevent superinfection by a less related HIV type (*25*). Challenge of vaccinated chimpanzees with less related HIV types will be considered only if challenges with homologous HIV types are successful.

National Cooperative Vaccine Development Groups

The unique problems associated with the development of a vaccine for AIDS require the combination of creative talents and resources from a number of different scientific areas. To foster such collaborations, NIH has established the National Cooperative Vaccine Development Groups (NCVDGs). These groups are composed of Government-industry-academic participants with the diverse skills needed to explore different experimental approaches to the development of an AIDS vaccine. The investigators will approach the development of effective vaccines based on leads from basic studies in virology, molecular biology, genetics, and immunology.

By pooling the expertise of scientists from a variety of disciplines and institutions, and by interacting with scientists who are with the Federal Government, the NCVDGs will be able to generate new strategies for developing a vaccine and will have the capacity to move rapidly from the basic

research setting through the preclinical development process for candidate AIDS vaccines. These groups represent the first of what is anticipated to be an expanding network of scientists who are responsible for linking resources, reagents, and technology with the common goal of expediting AIDS vaccine development.

Vaccine Clinical Trials

The NIH has the capability to test candidate AIDS vaccines in humans through both its intramural and extramural programs. After a vaccine has been shown to be safe and immunogenic in laboratory and animal tests and has gained approval from the Food and Drug Administration (FDA), it undergoes clinical evaluation in humans. Vaccine testing proceeds in a step-by-step fashion: Phase 1 studies are conducted with limited numbers of volunteers to evaluate the safety and immunogenicity of the vaccine preparation and provide preliminary dosage information; phase 2 studies extend the examination of safety and immunogenicity to larger numbers of volunteers and establish proper dose levels and routes of administration of the vaccine; phase 3 studies are performed to test for efficacy, that is, whether the vaccine prevents disease. Phase 3 trials generally involve very large numbers of volunteers to provide the statistically significant data that are necessary before the vaccine can be made available for general use.

Phase 1 studies of the first AIDS vaccine to be given FDA approval began in September 1987 at NIH. The vaccine, which is manufactured by MicroGeneSys, Inc., consists of an envelope protein, gp160, derived from the genetic material of HIV and produced in a baculovirus-insect cell system. The total number of participants in this study is 81. Although it is too early to report on the results of the study, we can report that no significant toxic side effects have occurred at the doses tested thus far. A second AIDS vaccine was approved for phase 1 testing in November 1987. This vaccine, produced by Bristol-Meyers, is a recombinant product made by inserting the HIV gp160 gene into vaccinia virus. The phase 1 study will be a company-sponsored trial in Seattle, WA.

To facilitate the testing of AIDS vaccines, NIH has expanded its support of the six Vaccine Evaluation Units (VEUs) that have been used previously for the testing of other vaccines, including those for influenza, respiratory syncytia virus, and hemophilus influenzae B. The experience of the VEUs, their unique facilities, and their access to population groups represent a national resource for the early evaluation of AIDS vaccines in clinical trials. FDA's approval for the first trial of an AIDS vaccine to be conducted in these units was given in January 1988; this will be a phase 1 evaluation of the MicroGeneSys gp160 vaccine.

Many issues complicate the testing of candidate AIDS vaccines. One such issue, vaccine-induced seroconversion, negatively affects the recruitment of volunteers. Because persons immunized with candidate AIDS vaccines will probably test positive by HIV antibody ELISA (enzyme-linked immunosorbent assay), volunteers in the AIDS vaccine trials may be subjected to social discrimination such as difficulties in donating blood, obtaining life and health insurance, entering foreign countries, and joining the military or foreign service. NIH is addressing this issue by providing certificates that identify volunteers as participants in NIH-supported vaccine trials. In addition, NIH is contacting representative organizations, such as health and life insurance companies, and obtaining from them letters of understanding to demonstrate the companies' agreement that volunteers who seroconvert as a result of their participation in an AIDS vaccine trial should not face difficulty in applying for life, medical, or disability insurance.

Liability issues also complicate AIDS vaccine studies and can jeopardize the development of a safe and effective vaccine. The spectrum of participants concerned about vaccine liability includes the volunteers, investigators, and institutions carrying out clinical trials, vaccine manufacturers, interest groups, and the Federal Government. NIH has actively participated in meetings and workshops addressing this issue and will continue to explore potential solutions.

Establishing the efficacy of an AIDS vaccine will also be difficult. Because of the low rate of HIV infection in the United States at present, phase 3 vaccine efficacy trials will require the participation of thousands of persons and may extend over several years. In addition, because behavior has a predominant role in the spread of HIV, and participants in a vaccine trial must, on ethical grounds, be instructed on how to avoid infection, the exposure to HIV among vaccine recipients as well as placebo groups will be very low. This condition is in contrast to the circumstances of the trials for a number of vaccines, in which it is difficult, if not impossible, to have patients avoid initial exposure to the infectious agent in question.

One of the ways that the trial size and duration can be reduced is to test the vaccine in phase 3 trials in countries where the HIV infection rate is higher than in the United States. However, variations in strains of HIV, as well as sociopolitical difficulties associated with testing vaccines in other countries, might present additional obstacles to efficacy trials.

Another approach to vaccine testing would be to immunize persons who are already infected with HIV for the purpose of preventing the onset of disease. The rationale for this approach is to boost the body's immune system against the virus even though the individual has already been infected with HIV, and the immune system has apparently not contained it successfully. There are specific safety constraints in this approach, since it is unclear whether attempts at boosting immunity with viral products in someone already infected would be detrimental. Because of the long incubation period for the disease's expression, any vaccine that did not prevent initial infection with HIV would require several years to demonstrate efficacy. Thus, such studies will require enormous resources. Therefore, it is imperative that the decision-making process for endpoint criteria and movement of candidate vaccines into phase 2 and phase 3 trials be expedited in a coordinated manner.

Conclusion

The development of a safe and effective vaccine against AIDS is a difficult endeavor that requires coordination of the input from numerous investigators from academia, industry, and the Government. Since HIV was isolated—less than 5 years ago—the research efforts of scientists from many institutions have resulted in significant progress toward the development of an AIDS vaccine. But we have only begun; much more research needs to be done. An understanding of the basic mechanisms of immunopathogenesis of HIV infection and a more precise delineation of the nature of the immune response to HIV are essential components of a sound approach to the development of a vaccine against AIDS.

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The Effects of the AIDS Epidemic on the Safety of the Nation's Blood Supply

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Synopsis

Present safeguards for the blood supply consist of three tiers of protection: donor deferral based on a donor's history of risk factors, confidential exclusion of blood units from donors with self-admitted risk factors, and testing of the blood itself.

Before the discovery of the AIDS virus in 1983 and 1984, there was no specific test relevant to AIDS that could be used to help improve the safety of the blood supply. The first step was intensified efforts, based on what was then known of the epidemiology of the disease, to take donor histories to identify risk factors. The first specific tests were for the detection of antibodies to the virus and came into use in 1985.

The general features of AIDS are described, together with the scientific rationale for the various types of laboratory tests, those for the virus itself, antigens, antibodies, the genetic material of the virus, and T4 lymphocytes. General characteristics of the tests are reviewed.

Since testing began, about 30 million units each of blood and plasma have been screened. More than 3,000 infected persons in the blood donor group have been identified as HIV-antibody positive. Thirteen cases of transfusion-associated infection have been documented. They are believed to have occurred because a detectable level of antibodies had not yet formed in the infected donors. Currently, such transmission is thought to occur once in about 40,000 to 250,000 donations, a dramatic improvement from 1983.

WITHIN A YEAR after acquired immunodeficiency syndrome (AIDS) was identified as a new clinical condition in 1981, accumulating evidence showed that the infectious agent could be transmitted from an infected blood donor to a transfusion recipient through the transfusion of blood, or certain products derived from blood, such as red cells, platelets, and antihemophilic factors, notably Factor VIII (*1*).

Because the AIDS virus had not been identified, there was no possibility at that time of a specific test to identify infected blood. However, in 1983, steps were taken to improve the situation by educating potential donors about AIDS and by asking persons who might be at risk for infection not to donate.

An indirect screening procedure was put in place in response to growing awareness of the need to protect the blood supply. Based upon what was then known of the epidemiology of the disease, the Food and Drug Administration (FDA) and the blood and plasma collecting organizations agreed to intensify and expand efforts to screen prospective donors by taking detailed personal histories.