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Scientific and Social Issues of Human Immunodeficiency Virus Vaccine Development

Barton F. Haynes

Development of a preventive immunogen for human immunodeficiency virus (HIV) infection is a national priority. The complexities associated with HIV host-virus interactions, coupled with the rapid progression of the HIV epidemic worldwide, have necessitated lowering expectations for an HIV vaccine that is 100 percent effective and have raised important scientific and nonscientific issues regarding development and use of preventive and therapeutic HIV vaccines.

HIV infection is preventable (*1*, *2*). In spite of this, HIV is spreading worldwide at an alarming rate, and projections of the magnitude of the pandemic by the year 2000 are staggering (*3*). The development of a preventive HIV vaccine (an immunogen administered to HIV-uninfected individuals to prevent infection) is a national priority. Efforts have also begun to develop therapeutic HIV vaccines, whereby HIV-infected individuals would be treated with immunogens designed to boost salutary anti-HIV immune responses, decrease virus-infected cells, and either eradicate HIV or prolong the time until development of acquired immunodeficiency syndrome (AIDS) (*4*–*6*).

HIV Preventive Vaccine Development

The difficult scientific issues before us underlie the fact that, as yet, there is no preventive HIV vaccine on the near horizon with clear prospects for clinical use. What has been developed are (i) promising experimental immunogens and (ii) clear ideas of what the central questions are that should be asked in ongoing and planned human clinical trials (*7*). Whereas traditional non-HIV vaccine development tracks have led to successful killed or attenuated immunogens in spite of lack of knowledge of pathogenic mechanisms or correlates of protective immunity (such as for the development of vaccines for smallpox or polio) (*8*), the emergent nature of the HIV pandemic, coupled with a plethora of critical unknowns, has forced investigators to pursue several vaccine tracks simultaneously in hope of the rapid development of a successful preventive HIV vaccine (*9*, *10*) (Fig. 1).

Scientific Problems of HIV Preventive Vaccine Development

Although more is known about HIV than almost any other infectious agent, scientific questions remain unanswered that are critical to development of an HIV preventive vaccine.

Optimal requirements for a preventive vaccine. A successful preventive HIV vaccine should be safe and effective for the prevention or quick eradication of initial HIV infection by multiple HIV strains, regardless of HIV exposure by mucosal or parenteral routes (*9*, *11*–*17*). It is important to emphasize, however, that most vaccines prevent disease, not infection. Thus, a successful HIV vaccine may not prevent establishment of infection but still may prevent the development of AIDS. For the

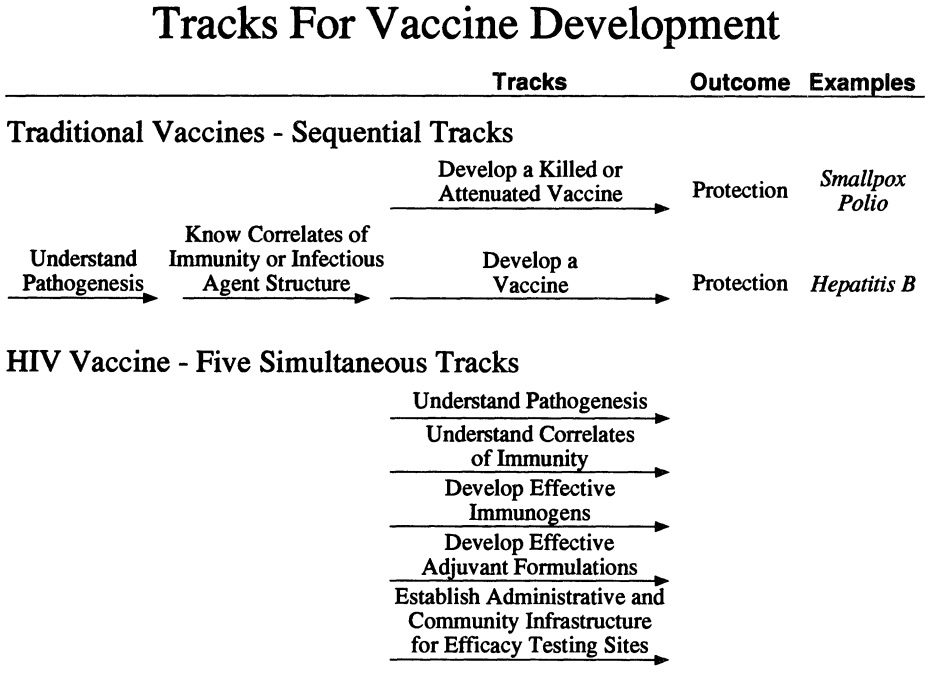

Fig. 1. Approaches to vaccine development. Traditional vaccines either use successful approaches without knowledge of pathogenesis or correlates of immunity (such as with the development of the smallpox and polio vaccines) or proceed in sequential tracks of understanding aspects of pathogenesis, correlates of immunity, or infectious agent structure before development of an effective immunogen (such as with the hepatitis B vaccine). In contrast, HIV vaccine development is proceeding along several simultaneous tracks to maximize the chances of rapidly developing a successful preventive vaccine.

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vaccine to be practical, protective anti-HIV immunity should be induced after one or two immunizations, although booster immunizations may be required to provide long-lasting immunity. In children, three to four immunizations may be feasible, as they could be given with other scheduled immunizations. For optimum availability and ease of use, the vaccine should be heat-stable and not require sophisticated measures of preservation. Finally, a successful preventive HIV vaccine should be simple to administer, affordable for all countries, and compatible with other vaccines being administered (*8, 18*).

Animal models. In spite of an extraordinary amount of work in search of an animal model for human AIDS, no animal model exactly mirrors human HIV infection (*19*). In general, current animal models of HIV or simian immunodeficiency virus (SIV) infection either do not develop AIDS symptoms, do not develop immune responses analogous to human anti-HIV T and B cell responses, or involve the use of endangered species such as chimpanzees (*19*). Thus, many important scientific questions of HIV vaccine development must be answered in human clinical trials.

Correlates of protective immunity against HIV. Because of a lack of an animal model of human AIDS and because a cohort of individuals naturally resistant to HIV infection is not available, the immune correlates of protection against HIV are not known (*9, 11–17*). For those working on a preventive HIV vaccine, lack of these critical data has forced the design of experimental immunogens that induce some or all of the types of immune responses that are surmised, but not yet known, to be protective against HIV (Table 1). Studies are ongoing to define the types of immune responses that decrease HIV plasma viremia in acute and chronic HIV infection (*20*), that are responsible for the lack of development of AIDS in chimpanzees (*21*), and that are present in HIV seropositive long-term survivors (*22*). In the National Institute of Allergy and Infectious Diseases (NIAID) Multicenter AIDS Cohort Study, HIV seronegative men with recent multiple exposures to HIV, but possibly immune to HIV, have been identified who have T cell (interleukin-2 release) but not B cell (no HIV antibody) responses to HIV proteins (*22*). These data have suggested that cellular immune responses may be protective against HIV infection (*22*).

Pathogenesis of HIV infection. In order to design effective HIV immunogens, researchers must learn about the pathogenesis of HIV. Many investigators have suggested that destruction of the immune system in AIDS is mediated in part by direct pathogenic effects of HIV (*23*) or by HIV-induced immune cell apoptosis, or programmed cell death (*24*). Although neutralizing antibody responses are important for protection against many viral diseases, nonneutralizing HIV envelope antibodies can enhance HIV growth in vitro and might promote progression of HIV infection in vivo (*25*). Molecular mimicry of host proteins such as the major histocompatibility complex (MHC) class I and class II molecules by HIV proteins may be one cause of some or all of the clinical manifestations of AIDS (*26*). Peptides from the HIV gp41 envelope protein suppress immune cell function (*27*) and in some cases induce immunological tolerance to HIV proteins (*28*). Thus, care must be taken that the immunogen selected for an HIV vaccine will induce salutary and not pathogenic immune responses (*29, 30*).

HIV protein sequence variation. The mutation rate of HIV-1 in HIV-infected patients is estimated to be between 0.1 and 1% per year (*31, 32*). HIV variability promotes the emergence of neutralization-resistant variants that may be relevant to the persistence of HIV infection (*32, 33*). Such mutations have been observed in the principal neutralizing determinant [the third variable (V3) region of HIV gp120 envelope protein (*34*)] and at non-V3 loop regions of gp120 as well (*33, 35*). HIV core protein variants that can escape cytotoxic T cell recognition by similar mechanisms have also been reported to arise in vivo over time (*36*).

This variation means that in every individual there is not just one virus but a swarm of HIV variants, each with different pathogenic properties, growth rates, and varying transmission potential (*33*). Current data suggest that only one variant or group of related variants is passed from host to host, although the factors that determine which HIV variants are passed are not known (*33*). Extensive sequence analyses of DNA of HIV variants worldwide have demonstrated the existence of five subtypes of HIV, with different HIV subtypes found in different geographic locations (*37*). A recent analysis of the eight amino acids at the center of the gp120 V3 neutralizing antibody binding region in 147 variants of the HIV subtype most often present in the United States and Western Europe found 61 unique V3 region sequences in 147 HIV isolates (*37, 38*). Fortunately, eight sequence motifs accounted for 50% of the HIV isolates analyzed (*38*). An important question is whether it will be feasible to prepare multivalent mixtures of peptides or recombinant proteins that reflect the variable sequences of HIV isolates in particular geographic locations. If an immunogen is to be based on HIV variable sequences, the likelihood for 100% efficacy of a preventive HIV vaccine is small.

A major question is whether it is possible to immunize patients with recombinant envelope proteins that express the conserved (nonvariable), conformation-dependent CD4 binding site and induce broadly reactive neutralizing antibodies that inhibit gp120-CD4 interactions (*39, 40*). In HIV-infected individuals, the initial neutralizing antibody responses are directed against the viral gp120 neutralizing determinants in the V3 region and neutralize only those HIV isolates with V3 sequences similar to the infecting HIV variant (type-specific antibodies) (*12, 33*). Broadly reactive neutralizing antibodies arise later that are directed against the site on the gp120 envelope that binds to the HIV receptor on immune cells, the CD4 molecule (*12, 33*). To date, immunization of HIV seronegative individuals with recombinant envelope proteins has induced primarily type-specific HIV neutralizing antibodies (*40*). A current challenge is to develop new formulations of recombinant envelope proteins that can enhance the induction of broadly reactive HIV neutralizing antibodies.

The need for anti-HIV mucosal immunity. Because a major HIV transmission route is via HIV-infected cells at mucosal surfaces, a successful preventive HIV vaccine should induce both systemic and mucosal protective immunity. Very little is known about the nature of mucosal immunity required

Table 1. Possible correlates of protective immunity for HIV infection.

Immune response	Rationale
HIV neutralizing antibodies	HIV neutralizing antibodies to gp120 protect against an intravenous HIV challenge in vivo (*14, 42*); neutralizing antibody levels fall as HIV infection progresses (*85*).
$CD8^+$ T cell responses that kill HIV-infected cells or suppress HIV infectivity	$CD8^+$ MHC class I–restricted cytotoxic T cells are important for the control of other viruses such as Epstein-Barr virus, cytomegalovirus, and influenza. Human cytotoxic T cells partially protect SCID-hu mice from HIV challenge in vivo (*86*); $CD8^+$ T cells can inhibit HIV and SIV infectivity in vitro (*30*); cytotoxic T cell activity decreases as HIV infection progresses (*30*).
Anti-HIV T helper cell responses	T helper cell responses are critical for the induction of anti-viral antibodies and for in vivo priming of anti-HIV cytotoxic T cell generation (*87*).

for protection from HIV, whether protection from HIV at mucosal sites is possible at all, or if any systemically administered HIV immunogens induce mucosal immunity. In the SIV model, protection from SIV mucosal challenge has recently been achieved with macaques previously immunized systemically with killed SIV (*41*).

Scientific Problems of HIV Therapeutic Vaccine Development

A hallmark of HIV infection is the persistence of HIV in the host, either in a latent or nonexpressed form, or in peripheral lymph organs in an expressed form (*23*). Treatment of SIV-infected monkeys with killed SIV has resulted in no decrease in viral load and has not delayed the onset of AIDS (*42*). In infected humans, host proteins (recombinant CD4), killed HIV, and recombinant HIV envelope proteins have been used to boost salutary anti-HIV host immune responses (*40*). Although administration of soluble CD4 into HIV-infected seropositive patients was safe, no lasting salutary therapeutic effects were seen (*6*). Immunization of HIV seropositive patients with killed HIV has been safe and in some patients appeared to stabilize immune cell numbers (*6, 43*). The use of the recombinant HIV envelope protein from viral strain LAI ($gp160_{LAI}$) in HIV seropositive patients has also been safe and induced antibody and T cell responses to $gp160_{LAI}$ (*5*). The effect of any experimental HIV immunogen on HIV viral load and CD4 levels in HIV seropositive patients remains to be determined. These early HIV therapeutic vaccine studies, like the early preventive HIV vaccine trials, have used killed HIV or recombinant envelope proteins of the HIV_{LAI} variant—a variant now known to be reflective of only a minority of HIV isolates worldwide (*37*). Prophylactic and therapeutic vaccine trials are now ongoing or planned with envelope proteins from strains MN and SF2 that are more representative of HIV isolates in the United States and Western Europe (*10, 40*).

Many of the immunogens that induce excellent cellular anti-HIV immune responses are live non-HIV vectors (nonpathogenic replicating viral or bacterial agents) containing HIV proteins (*40*). However, the use of live vectors as therapeutic vaccines is not advisable for fear of vector-induced disease, as HIV seropositive patients have compromised immune systems (*44*). Because immunization of animals in-

Table 2. Types of experimental immunogens for HIV vaccine development.

Immunogen	Advantages	Disadvantages or concerns
Live, attenuated HIV strains	SIV with *nef* deleted protects after one immunization; potent inducer of long-lived cellular and humoral immunity; attenuated live HIV could blunt the epidemic by conferring "herd immunity."	Serious concern regarding safety in normal and immunodeficient patients; concern about reversion to virulence; some HIV proteins remaining in the virus may be pathogenic; does not directly deal with variability of HIV strains unless multiple strains of HIV are used.
Inactivated HIV	Simple to prepare; mimics natural infection; inactivated SIV has protected against systemic and rectal SIV challenge.	Host cellular proteins are present in the immunogen; does not deal with variability of HIV strains unless multiple strains of HIV are used.
Protein subunit immunogens (individual HIV proteins such as gp120, gp160, or various types of synthetic peptides of HIV proteins)	Safety, purity; experimental immunogens can be designed that delete potentially pathogenic HIV epitopes; ease of production.	Immune responses to HIV subunit immunogens not long-lasting with current adjuvants; there may not be sufficient immunogenic T cell epitopes on small subunit immunogens to stimulate T cell responses in a cohort of individuals with disparate MHC types.
Multivalent HIV protein subunit immunogen mixtures	Rational strategy for dealing with HIV variability of neutralizing regions of gp120; mixtures can include sufficient T cell epitopes for most participants to respond to, including those with disparate MHC types.	Mixtures of peptides or recombinant gp120 must be based on variable neutralizing domain sequences present in HIV strains in different geographic locations; this necessitates having screening programs to initially define and then follow gp120 neutralizing domain sequences in specific locations.
Subunit immunogens in live vectors (vaccinia, Salmonella, Calmette-Guérin bacillus, poliovirus, rhinovirus, or adenovirus, for example)	Potent inducers of cellular immunity.	Concern for safety in immunocompromised patients; to date, HIV antibody responses induced by these vectors are not good; preexisting immunity to the vector prevents effective boosting by vector.
Anti-idiotypic antibody to CD4 or gp120	May overcome HIV variability problems by inducing broadly neutralizing antibodies.	Induces only antibody responses, not T cell responses; may induce antibodies that interfere with normal CD4 function.
Intracellular immunization (gene therapy)	Would make host $CD4^+$ cells resistant to HIV infection by introducing an HIV resistance gene into $CD4^+$ immune cells.	There are many $CD4^+$ cells in the body of disparate lineages, and the technology is too far underdeveloped to get protective genes in all $CD4^+$ cell lineages; once a protective gene is in cells, resistance may be overcome by HIV mutation; it is not known at present which genes to put in; gene therapy requires isolation of cells from each individual to be treated.
Direct immunization with complementary DNAs of HIV proteins	Promising results in animal protection studies against influenza.	Same concerns as for monovalent and multivalent subunit immunogens; in protection trials of influenza, complementary DNA infection did not protect against injection but protected only against severe disease.
Immunization with host proteins (CD4 or MHC molecules)	Immunogens are nonviral proteins; antibodies to human cellular proteins in SIV grown in human cells protected rhesus monkeys from intravenous SIV challenge; HIV incorporates host MHC proteins when budding from infected cells.	CD4 antibodies theoretically may interfere with CD4–MHC class II interactions and immunosuppress the host; immunization with MHC proteins may make the host resistant to organ transplantation; rhesus monkeys, immunized and challenged with SIV grown in autologous macaque cells, were not protected from SIV infection.

fected with other lentiviruses has, in some cases, led to enhanced disease (*45*), it is important to continue to carefully monitor the virologic and immunologic sequelae of therapeutic immunizations in future trials in HIV seropositive individuals.

Immunogens for HIV Preventive or Therapeutic Vaccine Development

Table 2 summarizes the types of HIV experimental immunogens currently being tested or being considered for testing in human clinical trials (*9–17, 40, 46*). Chimpanzees have been protected from HIV and rhesus monkeys from SIV when the challenge virus was given intravenously just at the time of peak neutralizing antibody response from boosting with either killed virus or subunit immunogens (*19*). The recent successful protection of rhesus monkeys by a single administration of an attenuated SIV strain 2 years before challenge with large amounts of pathogenic SIV has provided the strongest indication to date that a clinically useful preventive HIV immunogen is feasible (*47*). Although there is concern for the use of an attenuated HIV strain in humans for fear of reversion to virulence and induction of other diseases or conditions such as tumors, the development of an attenuated HIV strain and the demonstration of efficacy for protection against parenteral and mucosal challenge of chimpanzees with multiple HIV strains would provide a benchmark against which other HIV experimental immunogens could be compared. The goal is to design other, less potentially dangerous immunogens that would possess the same efficacy for protection as the attenuated HIV strain.

Currently, most of the immunogens being tested in clinical trials are subunits of HIV envelope proteins, such as gp120 or gp160 (*10, 40, 48*), or HIV core proteins, such as p17 (*10, 40*). To address the variable nature of HIV subtypes, researchers have developed mixtures of types of synthetic peptides of neutralizing regions of multiple HIV isolates (*40*). The ability of HIV and SIV synthetic peptides to prime for $CD8^+$ MHC-restricted cytotoxic T cells with antiviral activity has demonstrated the feasibility of multivalent peptide mixtures as candidates for trials of preventive or therapeutic HIV immunogens (*49*). However, to date all of the subunit HIV immunogens in animals and in humans induce HIV neutralizing antibodies that last for only several months at most after boosting (*40, 48, 50*), a feature that would necessitate repeated boosting yearly or more frequently.

Alum (aluminum hydroxide) is currently the only adjuvant formulation approved by the Food and Drug Administration for human use. An essential area of ongoing research is development of new adjuvants that can amplify immune responses to HIV immunogens (*51*).

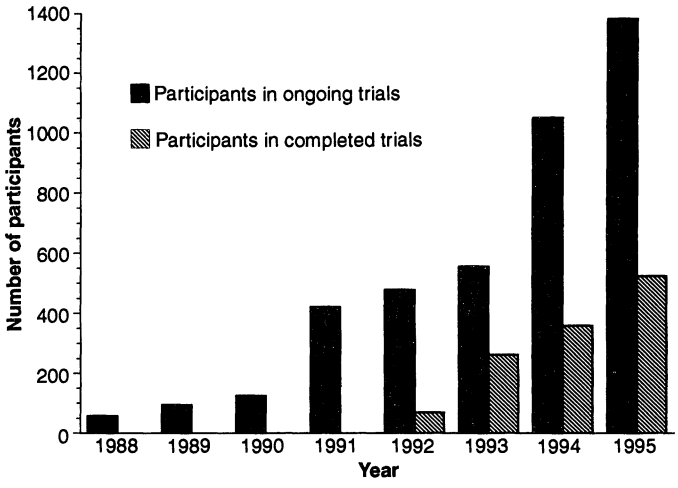

Fig. 2. Phase I and phase II NIAID-sponsored preventive HIV vaccine trials: actual and projected numbers of volunteers. Bars represent cumulative numbers of subjects in ongoing or completed clinical trials. Numbers up to 1992 are actual figures, and numbers after 1992 are projected figures. Source: Division of AIDS, NIAID, NIH.

HIV proteins in live vectors have the potential advantages of an attenuated HIV strain (Table 2) but less of the risk of reversion to virulence (*11, 14, 16, 40*). Other experimental strategies being considered are (i) immunization with antibodies against the CD4 HIV receptor or gp120 envelope to raise anti-idiotype antibodies that would react with gp120 or CD4 and block HIV infection (*52*); (ii) intracellular immunization, combining bone marrow transplantation with gene therapy to insert protective genes in immune cells to make cells resistant to HIV (*53*); and (iii) immunization with complementary DNAs, resulting in the expression of infectious agent proteins (*54*). This last strategy has resulted in protection of mice and chickens from challenge with influenza and has induced anti-HIV immune responses in mice (*54*). Finally, experimental immunogens of host proteins such as MHC and CD4 molecules are being considered for the production of an immune response against host molecules involved in HIV infectivity, which would prevent HIV infection (*40*). In the future, combination of two or more of these immunogen types (one to prime and others to boost) may prove to be superior to single immunogen types for preventive vaccine development. For example, immunogen combinations of live recombinant smallpox and canarypox vectors that express HIV proteins and purified recombinant HIV envelope proteins are being explored (*40*).

HIV Vaccine Clinical Trials

Phase I trials refer to the first test of a preventive HIV vaccine for safety and immunogenicity in small numbers of low-risk individuals. Phase II trials are additional safety and immunogenicity tests in greater numbers of individuals, with some phase II trials undertaken in high-risk populations. Phase III trials, or efficacy trials, involve large numbers of high-risk individuals; the number of individuals to be tested is determined by the HIV infection rate in the cohort studied, the duration of the follow-up period, the number of participants that do not complete the study, the time needed to achieve maximum protection with the vaccine, and the efficacy rate of the vaccine for prevention of HIV infection (*10, 40*). A series of phase I clinical trials of recombinant envelope immunogens has been completed (*10, 40*). A phase II trial including some adults at high risk for HIV infection has begun (*55*), and phase I trials are about to begin with the use of recombinant envelope proteins as a vaccine for infants born to HIV seropositive mothers (*56*). It is important to determine if immunization of neonates born to HIV-infected mothers can decrease the incidence of perinatal HIV infection, not only to decrease maternal-child HIV transmission, but also because immunogen efficacy may be easier to define in this setting compared with efficacy trials in adults (*56*). However, differences in HIV transmission routes between neonates and adults may limit extrapolation of the results of such trials to adults.

There are 16 candidate HIV vaccines in clinical trials in HIV seronegative subjects in the United States, Europe, and Africa, with 8 of these products in the U.S. phase I protocols evaluated by the National Institutes of Health (NIH) (Fig. 2) (*10, 40*). All together, there are more than 20 candidate HIV vaccines in either preclinical (animal) or phase I or phase II clinical studies (*10, 40*).

Social and Ethical Issues of Preventive HIV Vaccine Development

The problems of HIV immunology and virology have created a myriad of complex social and ethical issues (*46, 57–61*). Three

Table 3. Core guidelines for HIV vaccines with regard to future testing for efficacy (*88*). For use in a phase III trial, a candidate vaccine must satisfy condition 1 and at least two of three of conditions 2 through 4.

1. Demonstrated safety in phase I clinical trials.
2. Demonstrated efficacy in HIV-infected chimpanzees or SIV-infected monkeys (with the use of the SIV vaccine analog).
3. Ability to elicit neutralizing antibody that is long-lasting and broadly reactive against heterologous isolates in phase I clinical trials; this would be strengthened by similar induction of long-term and broadly reactive cellular immunity.
4. Demonstrated immunological and genetic similarity to HIV isolates from the proposed efficacy trial study site.

of the more critical areas are ethical design of HIV vaccine clinical trials, community issues related to clinical trials, and issues of clinical trials performed in developing countries.

Design of clinical trials. The design of HIV vaccine phase III efficacy trials has posed major social, ethical, and logistic problems (*10, 40, 62–65*). Although it is beyond the scope of this article to completely review HIV clinical trial design, five major issues of HIV vaccine clinical trials will be highlighted here.

First, the term "vaccine" traditionally signifies safety and protection to many people (*60*). For the reasons mentioned above, it is highly likely that most HIV immunogens will be less than 100% efficacious (*10, 60*). A recent analysis of HIV preventive vaccine efficacy has suggested that earlier use of a 60% effective vaccine would prevent more new HIV infections than later use of a more efficacious vaccine (*10, 66*). Nonetheless, there is a possibility that participation in a phase III efficacy trial could induce more high-risk behavior by creating a false sense of security from the vaccination, thus negating any salutary effect of a partially effective HIV preventive vaccine (*10, 60*).

Any ethical HIV vaccine trial must include counseling to prevent high-risk behavior of vaccinated participants (*59*). Thus, studies need to be performed in the context of HIV vaccine efficacy trials to determine the most effective counseling and education protocols and to study the effect of entrance into the clinical trial on the risk behavior of trial participants (*10, 66, 67*). It is likely that HIV infection rates will fall as a result of counseling and education about how to avoid high-risk behavior (*10, 66, 67*), which could confound the evaluation of the efficacy of the vaccine. In this case, if risk behavior in the face of counseling is carefully monitored, then turning the analysis to look at those individuals who maintained high-risk behavior throughout the trial to evaluate vaccine efficacy might be possible (*10, 67, 68*). Behavioral research is also needed to evaluate incentives provided to enter HIV vaccine efficacy trials in order to prevent coercion of trial volunteers and to prevent giving false impressions of vaccine efficacy (*68*).

Second, immunization with experimental HIV immunogens converts clinical trial participants to varying degrees of seropositivity in HIV antibody tests. Each immunogen tested must have an associated method for distinguishing immunogen-induced seropositivity from HIV infection, and each trial must have a mechanism in place for identification of trial participants to protect insurance eligibility and travel privileges. This problem has been addressed in NIH HIV preventive vaccine trials by issuance of tamper-resistant, numbered identification cards (*10, 60*). However, as the number of HIV preventive vaccine trial participants rises (Fig. 2), protection of uninfected, HIV seropositive vaccine trial participants from discrimination may become more difficult.

Third, the possibility exists that vaccine trial participants will be discriminated against by individuals either afraid that the vaccine itself will cause AIDS or fearful that participation in HIV vaccine trials signifies high-risk behavior (*46, 69*). Although HIV vaccine recipients generally are regarded as altruistic individuals (*46*), strict confidentiality must be guaranteed for all trial participants.

Fourth, considerable debate and concern has been generated over what the entrance criteria should be for phase III efficacy testing of preventive HIV vaccine candidates (*10, 46, 60, 64, 70*). Over the past 1½ years, the Ad Hoc HIV Advisory Panel of NIAID formulated two sets of guidelines for the study of HIV vaccines with regard to future testing for efficacy (*71*). Optimal guidelines for the study of HIV vaccines are essentially the same as the optimal requirements for a successful preventive HIV vaccine. Because no candidate exists as yet that fulfills all of these criteria and because some of the requirements are not yet fully defined (that is, correlates of HIV protective immunity are not known), a second set of core guidelines has been proposed for the entry of experimental immunogens into phase III trials (Table 3). Decisions regarding the selection of individual candidate vaccines for testing in efficacy trials would be made on a case-by-case basis, relative to new information regarding the types of immunity induced by the experimental immunogens and state-of-the-art research on AIDS pathogenesis and clinical correlates of protective anti-HIV immunity (*71*). In light of current gaps in this knowledge, the Ad Hoc HIV Advisory Panel did not believe that sufficient data were available in September 1992 to support selection of HIV preventive vaccine candidates for efficacy trials (*71*). Rather, the panel recommended the formation of the NIAID HIV Vaccine Working Group whose purpose is (i) to lead a coordinated HIV vaccine research effort in the United States among government and nongovernment scientists with the participation of community representatives; (ii) to define critical scientific questions and other issues; and (iii) to help coordinate future studies (*72*).

The core guidelines for HIV vaccine study (Table 3) are the minimum requirements that must be considered before an immunogen is to be taken into efficacy testing. Core criteria may be used to justify entry of an experimental immunogen into a phase III efficacy trial to answer scientific and clinical questions necessary to direct research and future immunogen design (*10*). For example, studies of anti-HIV cytotoxic T cell activity and neutralizing HIV antibodies could be correlated with seroconversion events in a trial to determine the immune correlates of protection against HIV in humans (*10*). Another example of information that could come out of such an efficacy trial would result from genetic study of the HIV isolates from those infected in an otherwise unsuccessful HIV vaccine trial (*10*). If the immunogen tested in the trial was representative of only one HIV subtype and those participants infected during the trial were infected by HIV subtypes other than the subtype represented in the immunogen, then these data would suggest HIV subtype–specific protection and argue for development of a multivalent HIV preventive immunogen (*10*).

Fifth, because there are potential risks of HIV immunogen use (that is, enhancement of HIV infection or induction of autoimmunity) and the true risks of many of the immunogens are not known, obtaining informed consent is difficult (*46, 59, 60, 69*) and the issue of who will provide liability coverage for vaccine-induced injury is a major concern (*61*).

Community involvement in HIV vaccine development. Two central issues are emerging regarding community needs and HIV vaccine trials (*57, 73–76*). First, lack of trust in the U.S. medical establishment has been voiced by both the African American (*73, 74*) and the gay communities (*60, 77*). Both cite multiple reasons for mistrust: lack of government assistance in dealing with the HIV crisis, recent cases of medical fraud, and past examples of unethical scientific behavior, as with the Tuskegee syphilis study (*60, 73, 74, 77*).

Second, there is a need for community involvement in all aspects of HIV clinical trial development efforts. Both NIAID and

the National Institute on Drug Abuse (NIDA) at NIH and the Centers for Disease Control and Prevention (CDC) are collaborating to establish phase III efficacy clinical trial sites in the United States at which there will be ongoing behavioral research (*78, 79*). Educational and counseling objectives will reflect the particular social, ethnic, and political complexities that affect HIV-AIDS research with culturally diverse minority groups (*78, 79*). The goals of the NIAID-NIDA-CDC vaccine preparedness efforts are listed in Table 4 (*78, 79*). Key among these are the initiation of community behavioral research projects and the establishment of community advisory boards to assist in the planning and development of the test sites and test protocols.

Table 4. Goals of the NIAID-NIDA-CDC vaccine preparedness studies. Source: Vaccine Trials and Epidemiology Branch, Division of AIDS, Clinical Research Program, NIAID, NIH, and the Division of HIV-AIDS, CDC (*78, 79*).

1. Development of newly recruited cohorts of individuals at high risk for acquiring HIV infection.
2. Measurement of HIV seroincidence among members of these cohorts.
3. Identification of appropriate but noncoercive incentives for recruitment and retention in phase III HIV vaccine trials.
4. Characterization of HIV virus strains in seroincident HIV infections.
5. Determination of recruitment and retention rates among study participants.
6. Development of a rapid risk assessment tool (questionnaire) that is a reliable and valid measure of behaviors that place persons at risk for acquiring HIV infection.
7. Assessment of attitudes toward participation in clinical trials of experimental immunogens with presumed varying levels of efficacy.
8. Development of a standard informed consent form that can be adapted by geographic sites and is known to be understood by volunteers.
9. Determination of the effects of HIV testing, counseling, and trial participation on behaviors that place individuals at risk for acquiring HIV infection.
10. Development of representative and active community advisory boards.

Research teams will need to work with community advisory boards to allay fears that vaccine trials for seronegative subjects might decrease funding and interest in developing immunotherapies for HIV-infected patients and to establish communication and coordinate referrals between HIV vaccine and HIV drug trials (*73, 74, 77–79*). Research teams must also allay fears of government involvement in trials by ensuring that minority participants in clinical trials will be neither excluded nor targeted and establish that the trials are nonexploitive, confidential, and in the best interest of the community (*78, 79*). The New York City Community Vaccine Working Group has outlined principles for community involvement in HIV vaccine trials (*80*). Community advocates already participate in HIV clinical trials planning at both the local and federal levels as members of the NIAID AIDS Clinical Trials Group and the NIAID AIDS Vaccine Evaluation Unit advisory groups. Minority community representatives also serve on the NIAID AIDS Clinical Drug Development Committee, the NIH AIDS Research Advisory Committee, the new NIAID HIV Vaccine Working Group, and the National Academy of Sciences Institute of Medicine Roundtable for the Development of Drugs and Vaccines Against AIDS. Continued involvement of community and patient advisory groups in the HIV vaccine development effort is essential for the HIV vaccine development effort to succeed (*73, 80*).

HIV phase III efficacy trials in developing countries. It is projected that over the next 10 years, the vast majority of new HIV cases will be in developing countries (*3, 81*). The Global Programme on AIDS of the World Health Organization (WHO) has recommended that phase I and phase II trials of HIV candidate vaccines be conducted initially in developed countries, where safety and immunogenicity can be carefully monitored, followed by repeat phase I and phase II trials of some of these vaccines in developing countries where nutritional status and background infections may alter vaccine safety and immunogenicity (*82*). The WHO also recommends that phase III efficacy trials be simultaneously conducted in both industrialized and developing countries, with cohorts with a high incidence of HIV infection (*82*). In addition to the NIH-CDC–sponsored U.S. phase III clinical trial infrastructure, NIAID will also establish HIV vaccine study sites in developing countries and will coordinate their efforts with those of the WHO (*83*). The WHO has selected four countries—Brazil, Rwanda, Thailand, and Uganda—to begin the process of establishing HIV-AIDS vaccine evaluation sites (*82*). The WHO will assist participating countries in providing a favorable environment for national and international collaborative HIV vaccine–related research. In turn, the countries with assistance from the WHO will provide an infrastructure for coordinating national and international collaborative HIV vaccine research (*82*). Work in establishing this infrastructure will include virologic studies to antigenically characterize HIV strains prevalent in the population, epidemiologic studies to quantify HIV incidence in potential groups for future efficacy trials, clinical studies (including repeat phase I and phase II studies of HIV candidate vaccines), and social and behavioral research to develop effective and culturally appropriate methods to educate and counsel vaccine trial volunteers and the general public regarding AIDS and HIV vaccine clinical trials (*82*).

Social and Ethical Issues of Therapeutic HIV Vaccine Trials

Many of the social issues of therapeutic HIV vaccine development are similar to those for preventive HIV vaccine development—community and patient involvement in trial advisory groups, full informed consent, confidentiality, and protection from discrimination for those participating in clinical trials. In addition, there is concern among patient advisory groups that preventive HIV vaccine development efforts will siphon away funds necessary for development of HIV therapeutics (*60, 77*). Clearly, information learned from preventive HIV vaccine trials will greatly assist development of successful therapeutic HIV immunogens by identification of the most protent immunogens and adjuvants. However, sufficient funds must be made available such that efforts to develop both preventive vaccines and therapeutic HIV immunogens can progress unimpeded. It should be emphasized that a far more scientific rationale exists for the feasible development of a preventive HIV vaccine than exists for the development of therapeutic HIV vaccines.

Another critical issue is who should decide what therapeutic HIV immunogens should go forward in clinical trials (*84*). Clearly, for both preventive and therapeutic HIV vaccine trials, rapid evaluation and approval of HIV immunogens by scientific review committees using peer review is essential, and this process should not be bypassed by legislation. The scientific peer-review process will protect patients, study volunteers, academic, industrial, and research communities, and taxpayers.

Conclusions

A lack of answers to key questions regarding HIV vaccine development has led to the need to proceed simultaneously along parallel developmental tracks to answer scientific questions and to establish the infrastructure for a series of clinical trials that will provide for future studies. What is needed now is unprecedented cooperation among U.S. and international academic scientists, government agencies, industry, communities, and patient advocacy groups to establish a comprehensive HIV preven-

tion program, a major component of which is an effort to develop a preventive immunogen for HIV infection (*1*, *2*). The U.S. government should take the lead in ensuring adequate funding for preventive and therapeutic HIV vaccine research, in providing funding for HIV behavioral research, in resolving HIV vaccine liability issues, and in implementing a comprehensive HIV preventive program for all Americans.

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Present Status and Future Prospects for HIV Therapies

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Since the discovery of human immunodeficiency virus (HIV) in 1983, significant progress has been made toward the discovery, development, and licensing of anti-HIV drugs. In vitro screens against whole virus are now being complemented by screens against specific viral targets, resulting in the development of clinical candidates acting at several critical stages of the viral life cycle. Despite these advances, clinical therapy remains largely palliative. In addition, it has recently been recognized that HIV resistance to most drugs may pose even greater obstacles. Moreover, emerging data on immunopathogenesis raise the possibility that even if virus was eliminated from an infected individual, the patient's immune system might not be capable of restoration to normal function. In the face of such obstacles, deeper insights into the pathogenic mechanisms of disease, aggressive exploitation of those mechanisms for therapeutic gain, and continued commitment of both public and private sectors to support and collaborate in this research are needed.

Introduction

In 1983, when HIV was discovered, the only antiviral agents licensed in the United States were amantadine, vidarabine, and acyclovir (*1*). Research was initially slow because only a limited number of facilities were willing to handle HIV, a new, lethal infectious agent. Fortunately, a significant body of information on the genomic structure and replication cycle of retroviruses had accumulated over the previous two decades (*2*) (Fig. 1).

Nucleoside analogs were a logical first place to search for anti-HIV agents because reverse transcriptase (RT) catalyzes a reaction not known to occur in humans and because several companies had libraries of nucleoside analogs synthesized in the search for anticancer or antiviral agents. In 1984, 3′-azidothymidine (AZT) was identified as active, first against murine retroviruses and then against HIV in cell culture (*3*). Clinical testing began in 1985. The phase II trial that conclusively showed a survival advantage for individuals with advanced disease taking AZT versus placebo was completed in September 1986, only 3 years after identification of HIV. The speed at which AZT was discovered, moved through clinical trials, and approved was unprecedented. Recognition that AZT did not completely suppress disease and had associated toxicities served as a stimulus for expanded research to identify additional agents.

The first inhibitors of HIV replication were discovered as a result of cell culture–based screening efforts, and such efforts continue to be valuable in identifying new agents that act at any step in the viral replication cycle. Recombinant DNA technology made possible the eventual cloning

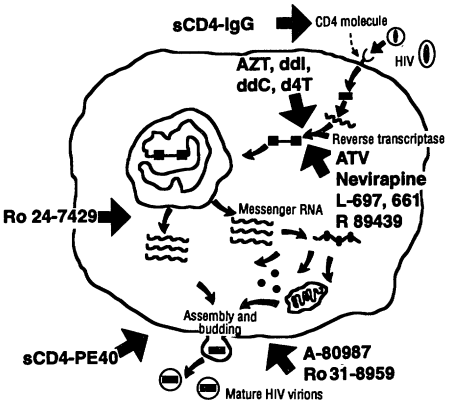

Fig. 1. Life cycle of HIV, showing the steps at which several anti-HIV agents act. Abbreviations are explained in the text.

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