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Current issues in developing a strategy for dealing with the acquired immunodeficiency syndrome

(retrovirus/immunopathogenesis/anti-viral/vaccine)

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ABSTRACT **A number of current issues exist that must be taken into account in the development of a strategy for dealing with the problem of the acquired immunodeficiency syndrome (AIDS) in the United States and throughout the world. Given the complexity of the problem and the fact that the epidemic is still in its evolving stages, such issues must be considered individually and as a group. The present discussion focuses on several of these critical issues and outlines approaches that might be useful in the formulation of basic scientific and public health strategies for dealing with the currently appreciated and projected problems in AIDS.**

There are a number of issues critical to the development of a strategy for dealing with the acquired immunodeficiency syndrome (AIDS). Foremost among these are the epidemiology and natural history of the disease, the etiologic agent and the role of cofactors, the immunopathogenesis of the syndrome, the immune response to the etiologic virus, antiretroviral therapy and immunologic reconstitution, and the development of a vaccine. Rather than describe in detail the multifaceted components of these issues, I will focus on the implications that arise from them with regard to the formulation of a strategy for dealing with AIDS.

Epidemiology and natural history of infection

Although an extraordinary amount is known about certain aspects of the epidemiology and natural history of infection with the causative retrovirus for AIDS, the human immunodeficiency virus (HIV), there are several important areas that have not yet been fully delineated. It is quite certain that the virus is spread through sexual contact, the sharing of needles for intravenous drug abuse, transfusion of blood or blood products that are contaminated with HIV, and from infected mother to infant perinatally (1–3). Although there has been much understandable public concern about the possibility of casual spread of the virus, compelling data from family studies in households with AIDS patients (4, 5) and from health care workers who work extensively with AIDS patients (6, 7) strongly indicate that the virus is not spread through casual (nonsexual, nonblood exchange) contact. Nonetheless, the prevalence of the infection among the groups at highest risk in the United States is extraordinary. An appreciation of the actual prevalence of infection at the present time and the relationship of this prevalence to the potential for further spread in the population are critical to the development of strategies for the implementation of public health measures such as educational campaigns designed to contain the infection. In this regard, it is important to understand the difference between infection with the AIDS retrovirus and the development of the full-blown disease called AIDS or AIDS-related conditions. The analogy of an iceberg is often used to explain this phenomenon (Fig. 1). As of October 13, 1986, there have been approximately 26,000

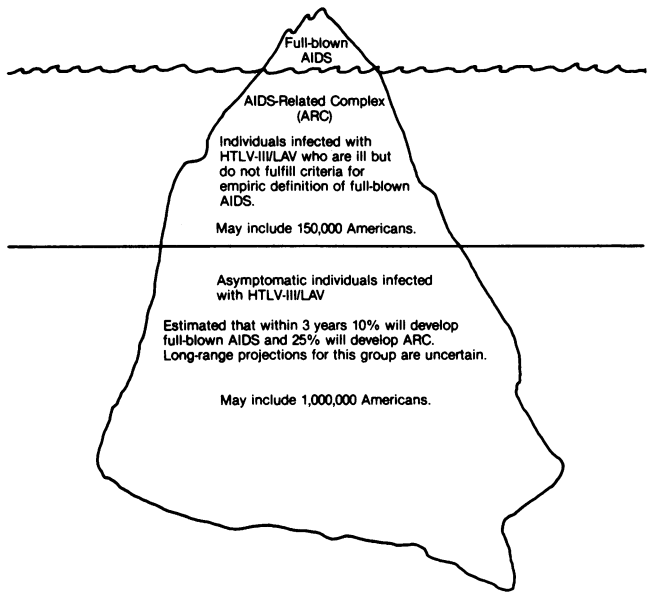

FIG. 1. The iceberg of HIV infection.

cases of AIDS according to the empirical criteria established by the Centers for Disease Control.* This is the "tip" of the iceberg since there are at least an additional 150,000 individuals in the United States who are infected with the virus, who do not fulfill the criteria for full-blown disease, but who have signs and symptoms such as malaise, fever, weight loss, and immunologic abnormalities. Of considerable importance with regard to further spread of the infection is the fact that 1–1.5 million individuals in the United States are infected with the AIDS retrovirus and are asymptomatic (8). The potential for spread of this infection by sexual contact in individuals, particularly those who are unaware that they are infected, is enormous. Spread via donated blood from this infected pool of individuals has been essentially eliminated with the advent of screening of all blood donors for antibody to HIV. Exceptions may occur with the rare blood donor who is infected but who tests negative for antibody to the virus (9).

Over the past few years, the relative percentages of cases of AIDS among various groups considered to be at high risk for infection have remained constant (Table 1). With regard to the 1–1.5 million asymptomatic infected individuals mentioned above, these are contained largely in the groups that

Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

*AIDS Program, Center for Infectious Diseases (1986) Acquired Immunodeficiency Syndrome (AIDS) Weekly Surveillance Report—United States (Centers for Disease Control, Atlanta), October 13.

Table 1. AIDS cases in adults and adolescents in the United States as of August 25, 1986

Transmission category	Cumulative number
Homosexual/bisexual males	15,595
Intravenous drug abusers	4,088
Homosexual males and intravenous drug abusers	1,877
Hemophilia/coagulation disorder	196
Heterosexual cases	918
Transfusion, blood/blood components	411
None of the above	759
Subtotal: Adults/adolescents	23,844

Data are from ref. 8.

reflect the incidence of established disease. For example, it is estimated that the prevalence of HIV infection in male homosexuals in the United States is 20–70% depending on location, with an incidence of 2–5% infection per year. The prevalence of infection among intravenous drug abusers is estimated at 5–75% with an annual incidence of 1–10% (J. Curran, personal communication). In contrast, the prevalence among prescreened blood donors, which for the most part reflect the adult, heterosexual, nondrug abuser population in the United States, is less than 0.03% (10).

A major unknown is the degree to which the infection will spread heterosexually among the general population in the coming years. At present, the disease itself is spread by heterosexual contact in 4% of the cases reported in the United States (Table 1). The evidence that the infection is spread from man to woman is clear, and there is a prevalence of infection of 10–60% and an annual incidence of 3–10% among the spouses of infected men. However, there is no question that the infection can be spread heterosexually from women to men as well as from men to women. The firmest data that the infection can be spread heterosexually in a bidirectional manner come from epidemiologic studies in central Africa where the male to female ratio of disease is approximately 1:1 (11). The three major factors that must be considered in any projections as to the degree to which the infection will spread heterosexually into the general population in the United States are the prevalence factor, the degree of sexual "promiscuity" within the general population, and the potential roles of cofactors in infection susceptibility. At present, the prevalence factor in the heterosexual population in the United States would militate against the dramatic spread that is seen among male homosexuals. As mentioned above, the prevalence of seropositivity among prescreened blood donors in the United States is less than 0.03%. In contrast, in certain central African countries with high incidence of disease, up to 10% of the general population is infected (12). Thus, the chances of being exposed to the virus in a sexual encounter with someone in the general population in the United States is extremely small, while the chance of such exposure in certain central African countries is much greater. However, recent data collected from the screening of military recruits for antibody to HIV indicate that among young sexually active people, the prevalence of infection may be much higher. Among over 300,000 military recruits who were screened for antibody to HIV from October 1985 through March 1986, 1.5 per 1000 were positive (0.15%), which is 5 times the prevalence in the "general" population (13). The ratio of seroprevalence between male and female recruit applicants was 3:1, much lower than the 13:1 observed among all AIDS cases in the United States. Seroprevalence rates were highest in the regions of the country with the highest incidence of AIDS cases and the rates were 4–5 times higher among Blacks than Whites. In fact, in high incidence cities such as New York, the prevalence among Black recruit applicants was 1 per 100. Since Blacks comprise the majority of AIDS cases among intravenous drug abusers from whom heterosexual spread would be expected to emanate, the implications for an expanding pool of infected heterosexuals are considerable. As with any sexually transmitted infection, as the pool of infected individuals increases, so too does the chance of becoming infected upon sexual contact with someone in the group in question. Clearly, the up to 10% prevalence of infection among certain populations in central Africa plays a major role in the rapid heterosexual spread in these populations. Closely connected with the prevalence factor is the degree of heterosexual promiscuity within the general population. In this regard, AIDS among males in Africa is associated with a history of frequent sex with prostitutes and there is an increased prevalence of HIV infection in male heterosexuals who are patients in sexually transmitted disease clinics (12). Obviously, high prevalence and high rate of exposure will play a major role in the spread of a sexually transmitted disease such as AIDS.

Another important factor to consider in projections concerning the degree of heterosexual spread is the potential role of cofactors in the spread of infection as well as in the productivity of infection. In a recent comparative serologic survey among different groups of individuals in the United States and the central African country of Zaire, it was found that the prevalence of infection with viral agents such as cytomegalovirus, Epstein–Barr virus, and hepatitis B was comparable between heterosexual men in Zaire and homosexual men in the United States. Between 90 and 100% of individuals in both groups showed evidence of infection with these agents. In contrast, heterosexuals in the United States had a significantly lower prevalence of infection with these agents. AIDS patients from both countries had a 90–100% prevalence of infections with the agents (T. C. Quinn and A.S.F., unpublished observations). Since it is speculated that activation of the immune system may enhance the efficiency and productivity of infection with HIV (14, 15) and since the above-mentioned infections can activate the immune system, it is quite conceivable that prior or ongoing infection with these agents may enhance the chances of HIV developing into a productive infection in an exposed individual.

A major consideration in projecting the magnitude of the problem of AIDS in the United States and worldwide is the determination of the proportion of individuals who are infected with the virus who will go on to develop full-blown AIDS. A recent projection by the U.S. Public Health Service is that over a 5-year period 20–30% of HIV-infected individuals will develop AIDS (8). Thus, by the year 1991, it is projected that approximately 270,000 individuals will have developed AIDS in the United States. The vast majority of these cases will have come from individuals who are already infected. The projected medical care costs for this group is up to $16 billion (8). Any strategy for dealing with the AIDS problem now and into the next decade must take into account this issue of staggering health care costs.

The etiologic agent of AIDS and the role of cofactors

It has been clearly established that the etiologic agent of AIDS is a human retrovirus that has been termed human T-lymphotropic virus type III (HTLV)-III (16), lymphadenopathy-associated virus (LAV) (17), and AIDS-associated retrovirus (ARV) (18). Recently, a subcommittee of the Committee on the Taxonomy of Viruses has renamed the virus human immunodeficiency virus (HIV) for purposes of uniformity (19). Of importance is the fact that these various isolates are essentially the same virus and cause the same disease. However, heterogeneity exists among various iso-

lates and the implications of this heterogeneity for vaccine development (see below) are unclear at present.

An extraordinary amount is known about HIV. It is a retrovirus most closely resembling the previously described lentivirus group of retroviruses (20). In this regard it is an RNA virus that replicates following infection of the target cell by making a DNA copy of its genomic RNA via the enzyme reverse transcriptase. The DNA can exist either in an unintegrated form or can integrate a copy of its DNA (proviral DNA) into the DNA of its host cell. It can persist here in a latent form (see below) or it can code for genomic and messenger RNA to assemble, package, and replicate as a free virion (21).

The molecular biology of HIV has been studied extensively (22, 23). However, it is relevant to point out here that multiple isolates of the virus have been cloned, their amino acid sequences have been determined, mutagenized strains have been made, and the functions of several of the viral genes have been determined. Briefly, the virus has the flanking long terminal repeats typical of retroviruses as well as the *pol*, *gag*, and *env* genes coding for the polymerases such as reverse transcriptase, the core proteins, and the envelope, respectively (21–23). A trans-acting transcriptional activating (*tat*) gene has been described that plays an important role in the amplification of virus replication (24, 25). In addition, a gene that has been termed the anti-repression trans-activator gene has also been described (26). Moreover, there are two open reading frames termed short *orf* and 3′*orf*, whose functions are unknown (27).

A more precise delineation of the biology and the molecular biology of the AIDS retrovirus will be critical in the development of strategies for virtually every area of AIDS activities, particularly the design and implementation of therapies and the development of vaccines. Also, an understanding of the factors involved in the conversion of a latent to a productive infection and an understanding of the mechanisms whereby the virus destroys its target cells will require further intensive study of the biology and molecular biology of the virus.

A significant degree of heterogeneity exists among HIV isolates (28, 29). It is unclear at present whether this variability from strain to strain, which in fact constitutes a spectrum of restriction site differences among isolates ranging from only 1 site in 23 to at least 16 sites in 31 (28), will be a major prohibitive factor in development of a vaccine with a broad range of protection against the diversity of wild-type strains.

The development of antiviral agents has relied heavily on an understanding of the biology and molecular biology of the virus. For example, several antiretroviral agents that are currently undergoing clinical trials in AIDS patients exert their antiviral effects by blocking the reverse transcriptase of HIV (30). In addition, understanding the function of the various genes of HIV will guide strategies for targeted antiviral research. The *tat* gene has recently been shown to be essential for the replication of HIV (31, 32). An agent specifically directed at the *tat* gene product might prove effective and specific in blocking replication of HIV *in vivo*.

Naturally occurring viral mutants or constructs with altered functional capability have potential in influencing strategies for vaccine development. Two recent reports exemplify this potential. A cellular clone (8E5) was recently isolated by limiting dilution of a culture of cells that had survived infection with HIV (33). The clone was found to contain a single, integrated provirus that was constitutively expressed. This single integrated copy of proviral DNA directed the synthesis of all major viral structural proteins except p64, which is the reverse transcriptase. These expressed viral structural proteins could potentially be used as immunogens in experimental vaccine studies without danger of infection of the host. Another potential approach in vaccine development is the use of viral mutants that are infectious but have markedly reduced or absent cytopathic effects. A variant of HIV termed X10-1 has recently been described that was derived from the genome of a cytopathic HIV clone by excision of a 200-base-pair segment in the 3′ region of the virus spanning the *env* and 3′*orf* genes (34). The variant replicated but did not kill normal human T cells *in vitro*, raising the possibility of the ultimate use of such variants as "attenuated" whole virus vaccines.

The role of cofactors both in the initial infection with HIV as well as in the conversion of a latent or low-level infection to a productive infection resulting in full-blown disease is a subject of great interest. As discussed above, it is felt that any factor that activates the immune system, be it a drug, microbe, or environmental antigen, has the potential of amplifying the infection or disease-producing capability of the AIDS retrovirus. Since it is now clear that the *tat* gene is responsible for the amplification of viral replication (24, 25), it is possible that any of the above factors that activates the *tat* gene might contribute to the conversion of latency to productivity of viral infection. The issue of cofactors remains of major importance in developing strategies for treatment as well as prevention of HIV infection.

Immunopathogenesis of HIV infection

The phenomenology of the immune defect in AIDS as well as the recognized mechanisms of the immunopathogenesis of AIDS have been described in detail (35, 36). However, a number of unresolved issues remain that have important implications in our understanding of the pathogenesis of the disease as well as in any strategies that will be developed concerning antiretroviral therapy, immunologic reconstitution, and vaccine development.

Briefly, the predominant target cell for the AIDS retrovirus is the helper/inducer subset of T lymphocytes phenotypically defined by the CD4 surface marker (37). This T-cell subset is commonly referred to as the T4 cell. It is responsible for the induction directly or indirectly of most, if not all, of the functions of the human immune system (35, 36). HIV selectively binds to the T4 cell by virtue of an epitope on the surface of the cell that is either part of or closely associated with the CD4 molecule (38, 39). Following binding, the virus enters the cell and exerts a cytopathic effect. Given the critical role that the T4 cell plays in the orchestration of the entire human immune system, it becomes clear how an infection that is relatively selective (see below) for a subset of T cells can have such profound and global effects on the entire immune system (35, 36). However, there are certain issues that have not been fully explained with regard to the immunopathogenesis of HIV infection.

The hallmarks of the immune defect in AIDS are a quantitative and qualitative deficiency of T4 cells (35, 36). Although the T4 cells are depleted, the precise mechanisms of cytopathic effect have not been fully delineated. Another question that remains unanswered at present is whether the depletion of T4 cells is totally explained by a direct killing of the cells by the cytopathic virus. In this regard, the use of radioactive nucleotide probes to detect viral RNA in cells of infected individuals has revealed that only a small percentage of peripheral blood mononuclear cells (as low as 1 per 100,000 cells probed) express viral RNA (40). Although this technique detects only expressed virus and not latent virus such as a single copy of integrated provirus, it would seem that with the degree of lymphodepletion observed in AIDS patients a greater proportion of cells would express virus at any given time. This observation has led to speculation of alternative mechanisms of lymphodepletion in HIV infection. In addition to the direct cytopathic effect of HIV on T4 cells, several

other mechanisms have been suggested including the following: (*i*) selective depletion of a subset of T4 cells critical to the propagation of the entire T-cell pool resulting indirectly in attrition of the pool, (*ii*) induction by HIV of soluble substances with toxic effects on T4 lymphocytes, and (*iii*) autoimmune phenomena. Most recently, it has been suggested that the high-level expression of the HIV envelope gene in infected cells induces syncytia formation and cell death in neighboring T4 cells that are not directly infected with the virus (41).

Although the T4 cell is the major target cell of the AIDS retrovirus, it has been shown that other cell types can be infected with HIV. Of particular note is the fact that monocyte-macrophages have been shown to contain the virus and to be susceptible to infection with the virus *in vitro* (42–44). Also, macrophage-like cells have been shown to contain viral RNA by molecular probing of tissues from AIDS patients (45). There is considerable speculation that monocytes might be reservoirs for the virus and that they might serve to disseminate the virus throughout the body. The scope of HIV infectivity from human cells is an issue that must be clarified, particularly with regard to the formulation of strategies for antiretroviral therapy and immunologic reconstitution.

Other issues of interest and potential importance in HIV infection are the nature and cause of the B-cell defect and the relationship between the immune defect and the development of Kaposi sarcoma. Patients with AIDS have significant abnormalities of B-cell function, which is characterized by a polyclonal hyperactivity and a defective response to *de novo* antigen stimulation (46). It has been shown recently that HIV itself can activate human B cells without transforming them (47, 48). The precise role of HIV as well as the roles of other viruses such as cytomegalovirus, Epstein–Barr virus, and perhaps other agents in the activation of B cells are at present unresolved.

It is now well recognized that AIDS patients who have Kaposi sarcoma without opportunistic infections generally have a much more competent immune system than do patients with such infections (35, 36, 48). In fact, an occasional patient is noted who is positive for antibody to the virus and/or virus isolation, who has Kaposi sarcoma, but who has relatively normal immune function (H. C. Lane and A.S.F., unpublished observations). This raises the possibility that other as-yet-unidentified factors or even microbes may be involved in the etiology of Kaposi sarcoma. This possibility gains even more credence with the well-established observation that Kaposi sarcoma is vastly more common among male homosexuals with AIDS than among AIDS patients from other risk groups (1–3). Strategies aimed at antiretroviral therapy and immunologic reconstitution must take such issues into account.

Immune response to HIV infection

The scope of the immune response to HIV infection has not been fully delineated. Certainly, it has not been established what constitutes protective immunity against the virus. This is an issue that is of paramount importance in virtually any aspect of the AIDS problem, particularly immunologic reconstitution and vaccine development.

Neutralizing antibodies have been demonstrated in the sera of individuals infected with HIV (49, 50). However, there is no apparent distinction between individuals who are asymptomatic carriers of the virus and those with AIDS with regard to presence and titers of neutralizing antibodies. Thus, these antibodies do not appear to be protective and currently there are no immunologic parameters that indicate protection or prognostication for protection against development of AIDS following infection with HIV.

In addition to the neutralizing antibodies, it has been found that infected individuals possess serum antibodies that can effectively mediate antibody-dependent cellular cytotoxicity (ADCC) against virus-infected target cells (A. H. Rook, S. Koenig, H. C. Lane, and A.S.F., unpublished observation; ref. 51). Here again, there is no apparent relationship between the titers of neutralizing antibodies and the levels of ADCC. An interesting observation that requires further study is the finding that the sera of individuals who are asymptomatic carriers of HIV mediate high levels of ADCC and that these sera contain antibodies against both *gag*-encoded (p24) and *env*-encoded (gp120) proteins, whereas sera of individuals with AIDS mediate low levels of ADCC and these sera lack antibodies against *gag*-encoded but contain antibodies against *env*-encoded proteins (A.S.F., unpublished observations). It is uncertain at present whether antibodies against the *gag*-encoded proteins are protective or whether individuals lose their antibodies against these proteins later in the course of infection with HIV when they develop AIDS.

It has recently been reported that major histocompatibility complex-restricted T-cell-mediated cytotoxicity can be demonstrated against HIV-infected target cells (30). This was seen in AIDS patients who had received bone marrow transplants and lymphocyte transfusions from their identical twins (30). Since HIV clearly exists in a cell-associated form, the issue of the existence and protective efficacy of cell-mediated cytotoxicity is critical to any strategy concerning immunologic reconstitution and vaccine development, as well as to any prognostication concerning the conversion from the asymptomatic carrier state to full-blown disease.

Antiretroviral therapy

A great deal of effort and resources over the past year have been directed to the development and testing of agents with antiretroviral activity. The strategy that has been operative in this area has been to develop and/or select agents that can suppress HIV by any of a number of mechanisms. These have included agents that (*i*) block virus attachment to the target cell, (*ii*) inhibit reverse transcriptase, (*iii*) inhibit transcription of the virus, or (*iv*) block translation/assembly of viral proteins (30).

Effective treatment of a retroviral infection in man, or in any animal, is unprecedented. A number of antiretroviral agents are currently being tested and many others are undergoing preclinical testing. Of note is the fact that there are no agents that have been shown to be safe and effective in the treatment of HIV infection. Although several of these agents clearly have anti-HIV activity *in vitro*, either toxicity or *in vivo* ineffectiveness have precluded their use in AIDS patients (30, 52). Others still in clinical testing have shown some early promise but require more extensive, controlled clinical trials to establish their safety and efficacy over an extended period.

A compelling issue that must be addressed in the planning of any strategy related to antiretroviral therapy is the real possibility that no drug will be able to completely eliminate HIV from the body of an infected individual. This possibility certainly exists since it is well established that HIV can exist in a latent form in T4 lymphocytes and perhaps in other cell types (53, 54). As mentioned above, proviral DNA can exist as a single integrated copy in the DNA of the host cell. Activation of the host cell can result in the expression of the virus and the conversion of a latent to a productive infection. Thus, even if an antiretroviral agent could block replication or attachment of the virus, it may be completely ineffective in eliminating latent virus. If a safe and effective agent against replicating virus is found, it may have to be administered for the life of the patient to protect against any imminent conversion from latent to productive infection. Furthermore, given the nature of the immunopathogenesis of AIDS, it would be extremely difficult for an antiretroviral agent to eliminate HIV. In most other viral infections, the immune

response against the virus is intact and so any antiviral effect of a drug would likely synergize with the specific antiviral immunity present. Since HIV selectively eliminates that component of the immune response that recognizes antigen (56), the antiretroviral agent itself is required to exert the entire suppressive effect on the virus. In this regard, current strategies for treatment of AIDS include the combination of direct antiretroviral therapy and immunologic enhancement and/or reconstitution.

Immunologic reconstitution

The issues that impact the strategy for immunologic reconstitution are similar in some respects to those related to antiretroviral therapy. As long as the virus still exists in the host and is capable of exerting its destructive effects on the immune system, totally effective immunologic reconstitution is not feasible. This was clearly demonstrated in the case of an AIDS patient who received a bone marrow transplant and regularly administered lymphocyte transfusions from his identical twin brother (56). The study was performed prior to the availability of antiretroviral agents. The recipient experienced a modest but transient increase in immune competence that inexorably declined. It was highly likely that the HIV persisting in the AIDS patient ultimately destroyed the normal lymphocytes from the bone marrow transplant and lymphocyte transfusions. In this regard, another patient has received both a bone marrow transplant together with lymphocyte transfusions from his healthy identical twin and also the antiretroviral agent suramin. The suramin proved toxic and in other studies ineffective, and so it was discontinued. However, this patient has experienced immunologic reconstitution that persists 12 months after transplant (30). Obviously, the approach of combining antiretroviral therapy when an effective drug becomes available with identical twin bone marrow transplant will be pursued further.

The same problems exist with regard to immunoenhancing agents such as interleukin 2. AIDS patients who have received interleukin 2 have experienced transient increases in immune function that returned to the abnormal baseline on discontinuation of the drug (30). The same holds true for other immunoenhancing agents. These experiences fortify the opinion discussed above that any strategy for treatment of AIDS must take into account the dual approach of antiretroviral therapy together with some form of immunologic reconstitution.

Vaccine development

The development of a safe and effective vaccine against infection with HIV is one of the highest priorities of public health officials and biomedical researchers in the field of AIDS. However, with vaccine development as much as or more than with any other area, there are a number of critical issues that must be addressed in the development of a strategy to approach this problem. One of the most important issues is whether or not an effective vaccine is even possible. As mentioned above, it is uncertain what constitutes protective immunity against HIV. Neutralizing antibodies have been found in infected individuals and in patients who have developed AIDS (49, 50). Their protective capability is totally unknown at present. In addition, the role of cell-mediated immunity against HIV such as cell-mediated cytotoxicity against virus-infected cells is unclear. Thus, the immunologic endpoint of a vaccine is only speculative at this point. More precise delineation of the nature of the immune response to the virus and a correlation if any between a certain immunologic profile and protective immunity is essential. Furthermore, it is almost certain that the virus exists in the body in both the cell-free and the cell-bound form. Induced immunity must be able to protect against both forms of the virus.

The lack of a convenient animal model for infection with HIV poses a significant problem in the area of vaccine development. Currently, the only animal that can be infected with HIV besides man is the chimpanzee (57). Given the inherent difficulties in working with chimpanzees such as expense, unavailability, and other constraints, immunogenicity studies have been performed in smaller animals such as rodents and efficacy studies must follow the common denominator of challenge in chimpanzees.

Another important issue in the "race" to develop a vaccine is the type of vaccine preparation that should be developed and tested. There is an understandable reluctance to use inactivated or killed whole virus preparations because of the possibility that nucleic acid of the killed virus could still be integrated into the genome of the host's cells with the possibility of ensuing viral replication. Virus subunits and synthetic polypeptides are currently being examined for immunogenicity in smaller animals and several will be advanced to testing in chimpanzees for virus challenge studies. However, there is concern that even the glycosylated recombinant subunits produced from mammalian vectors will not present antigenic determinants to the immune system in a manner which would elicit effective immunity.

The use of virus vectors such as vaccinia to express HIV proteins is an interesting approach with significant potential (58, 59). The obvious problem with the vaccinia vector is the possibility that the vaccine, even if proven effective, would likely be used in certain populations of individuals who might tend to have compromised immune systems such as male homosexuals who are immunosuppressed to variable degrees because of infections with other non-HIV microbes such as Epstein–Barr virus and cytomegalovirus. It is well recognized that live vaccinia vaccines are contraindicated in immunosuppressed individuals. Anti-idiotype vaccines have potential in that the recipient would never have to be deliberately exposed to any viral component. However, this approach to vaccine although of theoretical importance has not yet been used with success in any human disease. Finally, the recent description of an apparently nonpathogenic retrovirus called human T-lymphotropic virus (HTLV-IV) that is related to simian T-lymphotropic virus type III and infects humans without causing disease (60) may have implications for the use of nonpathogenic strains of human retroviruses as vaccines against HIV infection. Noninfectious virus mutants (33) or infectious, noncytopathic mutants (34) also have theoretical potential as vaccine candidates.

A major issue centers about in whom to test the vaccine candidate and whom to vaccinate if a candidate proves safe and effective. Certainly, any vaccine candidate would need to be tested in individuals who might be at risk for infection or else efficacy could never be established. Since the highest risk groups, such as male homosexuals in the United States, already have such a high prevalence of infection, vaccine studies in this group would be difficult but still feasible.

Finally, decisions regarding whom to vaccinate will have to take several issues into consideration. Certainly individuals in high-risk categories such as male homosexuals, intravenous drug abusers, hemophiliacs, prostitutes, and sexual partners of persons in high-risk categories should be vaccinated. It is likely that future decisions concerning whether the general population, or at least heterosexually active persons, should be vaccinated must take into account the degree to which the infection is spreading in the general population as well as the precise level of safety and efficacy of such a vaccine.

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