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The Quest for an AIDS Vaccine

Robert T. Schooley, M.D.

More than fifty thousand cases of AIDS have been reported in the United States since the disease was first described in 1981. Many times this number of people are infected with human immunodeficiency virus (HIV), which has been identified as the agent responsible for the illness. The seriousness of the disease, coupled with the relatively rapid spread of HIV, has fueled the effort for development of an effective vaccine.

Much is now known about the life cycle of the virus, and about its structural components. This information, and information about methods of transmission of the virus, form the basis for a rational vaccine development program. A successful program depends both on technological advances and on the political will to create a climate in which interpretable vaccine trials can be undertaken. This review will focus on some of the impediments to rapid development and licensure of an AIDS vaccine.

Since the initial description of AIDS in 1981, and the initial definition of the human immunodeficiency virus (HIV) as the etiologic agent for the syndrome, much progress has been made in understanding the cell and molecular biology of HIV, and in defining the components of the immune response to the agent. In parallel with the growth in basic understanding of HIV, the agent has spread rapidly in the United States and worldwide, primarily through sexual, blood-borne, and perinatal exposure. It has been estimated that between 1 million and 3 million residents of the United States are currently infected with HIV, and that at least as many individuals are infected in other parts of the world. This relatively rapid spread of HIV, despite educational efforts aimed at interdicting spread of the agent, underscores the urgent need for development of an effective AIDS vaccine. This article will outline current prospects for development of an AIDS vaccine, and will delineate the steps required for the proof of efficacy in clinical trials.

Initial Infection and Spread of HIV

HIV gains access to the body either transmucosally (across mucous membranes) in sexual

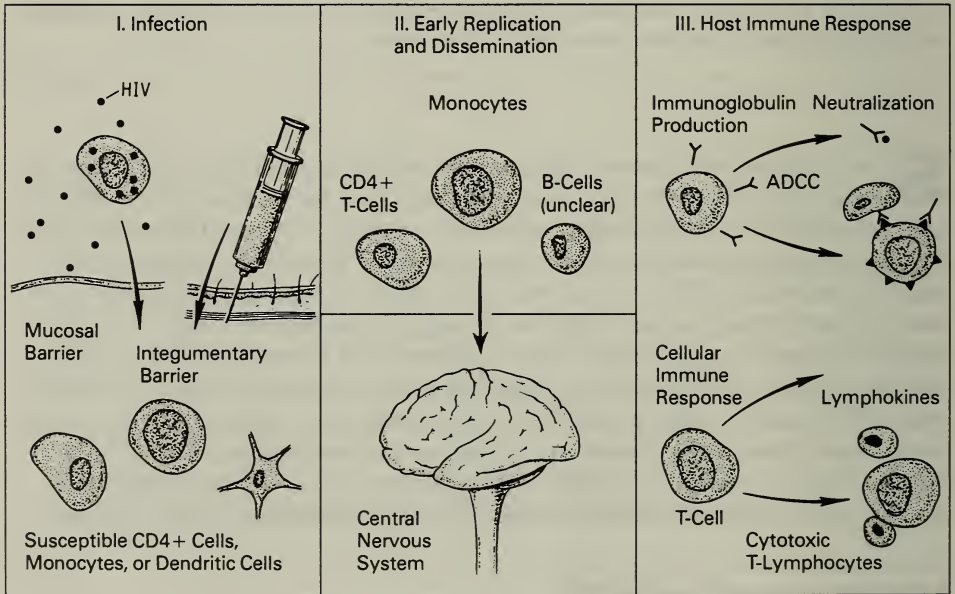
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transmission, or directly into the bloodstream or soft tissues with blood-borne (needle stick or transfusion) exposures (figure 1). In that the virus lives primarily within cells, it is not clear whether spread involves free virus or virus transmitted within cells. Once within the new host, the virus enters susceptible cells. The genetic material of the virus is acted upon by an enzyme known as reverse transcriptase, which is brought into the cell by the virus. The genetic material of the virus is then integrated into the host cell DNA. The virus may remain latent and be transmitted to any progeny of the infected host cell, or it may begin to reproduce and be transmitted to previously uninfected, susceptible cells. Although it is possible that a vaccine might slow secondary transmission of virus to uninfected cells, the primary goal in most vaccination programs involves prevention of establishment of the initial infection.

In the case of HIV, this initial interception of virus by the immune response might be complicated by the ability of the virus to spread directly from infected to uninfected lymphocytes through cell-to-cell spread, and by the possibility that the initial infection of host cells might occur at mucosal surfaces such as vaginal and rectal linings. Initial infection at these sites might significantly limit the effectiveness of immune response induced by traditional vaccines.

Figure 1

HIV Pathogenesis



The figure describes interaction between HIV and the infected individual. The virus gains entry to the body through mucous membranes with sexual exposure, or more directly through blood-borne exposure. After entry, the virus infects certain cells of the immune system and the brain. The immune response that is evoked by the virus is multifaceted and probably slows the rate at which the virus causes illness. Greater knowledge about the characteristics of this immune response will be useful in vaccine development.

Host Immune Response to HIV

Once the virus is within an individual, replication of HIV proceeds at a rate that may be dependent on a number of factors, including the state of activation of host cells; the HIV-specific host immune response; and, possibly, virus-specific strain differences. As the initial cycles of viral replication proceed, a vigorous antibody and cellular immune response to the virus is developed. The antibody response to HIV is directed to a number of viral components. These antibodies are useful diagnostically in the identification of HIV-infected individuals, but, more important, they provide insight into the components of the virus recognized by the host as being foreign.

Antibody activity can be measured in functional assays that measure biologic effects of the antibodies. The functional assay that has been most extensively studied for the purpose of vaccine strategy is the neutralization assay. In this assay, dilutions of sera to be tested are mixed with a known amount of virus. After exposure of the virus to serum for a defined length of time, the ability of the serum-exposed virus to infect susceptible cells is tested. If protection of susceptible cells by a given dilution of serum is demonstrated, the serum is said to contain neutralizing activity at that dilution. Neutralizing activity appears within the serum of most HIV-infected individuals within the first several months following infection. These assays are useful in planning vaccine approaches because they permit investigators to determine which parts of the virus are able to elicit antibodies that cripple its ability to infect host cells. In the case of HIV-1 (the most common AIDS virus type in the United States), this neutralizing activity is most easily demonstrated in antibodies that react with the envelope (surface) of the virus.

Although one can demonstrate neutralizing activity specific for the envelope of HIV-1, such knowledge is far from sufficient for providing an effective vaccine. As noted above, such antibodies must be present at the site of initial infection, such as the rectal or vaginal mucosa. Furthermore, HIV possesses an envelope that varies significantly from strain to strain. In addition to the two currently known types of HIV, within each type there are many, many strains. Thus, an antibody that is able to neutralize one strain of virus may be less able to neutralize other strains of virus, or may be incapable of doing so. In addition, with the description of a second type of HIV, now termed HIV-2, which was initially isolated in west Africa, vaccine development is faced with the need to deal with at least two types of HIV.

Although the antibody response to HIV is the aspect of the immune response which has been most intensively studied, it is clear that neutralizing antibodies represent only one component of a multifaceted response. In addition to antibodies that neutralize the virus, cytotoxic (killer) T-cells are induced by HIV infection. These cells are capable of seeking out and killing HIV-infected cells. They, thus, form a second impediment to uncontrolled replication of the virus, and may play an important role in slowing the rate at which HIV causes symptoms in infected individuals. These cytotoxic T-cells are directed at the envelope of HIV, but, in addition, cells with activity against other components of HIV are present. The other components of HIV tend to vary less from strain to strain and thus are more conserved. These observations are of importance in AIDS vaccine development in that inclusion of more strictly conserved components might allow development of vaccines that have activity against a wider variety of strains.

Because of the relentless progress of infection in most individuals, the effectiveness of the HIV-specific immune response that can be detected within the first several months of infection has been called into question. Despite this consideration, it should be noted that

individuals, once infected with one strain of virus, are rarely, if ever, infected by other strains, even when repeated exposure to other strains occurs frequently. This suggests that although the naturally occurring immune response might fail to prevent onset of disease following infection, it is at least capable of preventing infection with additional strains of virus. Thus, if an immune response that closely mimics the response following natural infection can be elicited by an AIDS vaccine, subsequent infection with live virus might well be preventable.

Steps in the Development of an AIDS Vaccine

As basic understanding of the HIV-specific immune response is developed, application of this information to the technical aspects of vaccine development will be increasingly effective. Induction of an effective immune response requires delivery of an appropriate stimulus (termed *antigen*) to the immune system prior to exposure to the natural agent. Antigen delivery may be achieved through the use of either living or nonliving material (table 1). One of the oldest approaches to vaccines has involved growing the agent itself in the laboratory, then purifying and killing it by chemical means. The purified, killed material is then injected into the individual being vaccinated and, thus, is presented to the immune response. The magnitude of the immune response is highly dependent on how a vaccine is delivered (that is, whether it is injected or given by other routes) and on carrier or other materials (termed *adjuvants*) that may be added to the killed virus. Killed virus approaches have the advantage that they are technologically straightforward, but the disadvantage that most of the material injected consists of portions of the infectious agent that are irrelevant to the immune response in developing protective immunity. Thus, the theoretical possibility exists that undesired vaccine side effects may be induced by the presence of unnecessary vaccine components. Finally, there is the unlikely possibility that the inactivation procedure may be incomplete. If the vaccine preparation steps do not completely kill the virus, infection with the agent for which the vaccine is intended in the first place could occur. In addition, there has been at least one instance in which killed vaccine was contaminated with a virus of a different type (in the case of an early lot of polio vaccine) which was not killed by the inactivation procedure. Although these two latter possibilities are increasingly unlikely with modern technology, they are not totally outside the realm of possibility.

Table 1

Antigen Delivery Systems

- A. Nonliving antigen delivery systems
 - 1. Killed whole virus
 - 2. Viral components
 - a. Purified from whole virus
 - b. Prepared by recombinant DNA technology
- B. Live antigen delivery systems
 - 1. Attenuated virus
 - 2. Viral components carried by a nonpathogenic (or minimally pathogenic) unrelated virus

A second approach to vaccine preparation using nonliving material involves use of viral components, termed *subunits*. These subunits can be purified from whole, killed virus, or they can be prepared with DNA technology. This approach involves introduction of a selected portion of the viral genetic information into the genetic material of another living organism, such as a bacterium or a yeast. The material normally encoded by the viral gene selected is then made by the new host. When the new host is grown in the laboratory, large amounts of the HIV component are also produced. This material can then be purified and utilized as a vaccine. The advantage of this approach is that it has the potential to produce well-characterized portions of the virus at great purity. By selecting a portion of the viral genetic material which encodes for portions of the virus which appear to be targets of the protective component(s) of the immune response, one can avoid introduction of deleterious or irrelevant viral components. Thus, one could include only selected portions of the viral envelope or other components. Recombinant DNA technology has the disadvantage, however, of producing material that might be more likely to induce an immune response that is specific only for the strain (or closely related strains) from which the initial genetic information was procured. Recombinant DNA technology also runs the risk of producing material that will be slightly different from the material encoded by the native gene, owing to events that occur within cells following initial protein production. These events relate mainly to the way in which the proteins are folded after production, and to the addition of sugar molecules. Newer developments in molecular biology have circumvented some, but not all, of these problems.

Live virus approaches have several potential advantages over those utilizing nonliving material. These include the fact that vaccine delivery may be achieved without injection (for example, through oral or aerosol routes). It has also been said that live agent approaches may be more likely to stimulate a more global immune response, both in terms of the viral components recognized and in terms of the development of immunity at likely sites of infection, such as mucosal surfaces. The live virus approach that is used most frequently involves the introduction of changes (termed *attenuation markers*) in the normal viral genetic material which make the agent less likely to cause disease. A virus that has been modified by addition of these attenuation markers is termed an *attenuated virus*. Once the host has dealt with the attenuated virus, the immune response developed during this interaction is capable of preventing infection with the natural (wild) virus. This approach is the one that was used in the production of the Sabin vaccine for polio.

The final potential advantage of live agent vaccines is that they might spread to unvaccinated contacts of the persons initially vaccinated. Thus, vaccinating one individual might lead to the protection of others, who become secondary vaccinees. Secondary vaccination may be good for the population, but the potential for harm exists, as well, if the attenuated agent is introduced into individuals whose immune responses are incapable of preventing morbidity even from the attenuated strain of virus used in the vaccination. The biggest drawback concerning the use of attenuated viruses as vaccines relates to uncertainty as to whether the changes introduced to include attenuation are stable. If these attenuation markers revert to the wild state after replication begins to occur in an individual receiving the vaccine, the deleterious effects are obvious.

An alternative to using attenuated virus involves the insertion of a portion of the viral genetic material important for induction of immunity into an agent that does not normally cause illness. As the agent of low pathogenicity replicates, the host immune response is also presented with the immunologically relevant portion(s) of the agent being vaccinated against. The resulting immune response then, in theory, prevents infection with the wild

agent if it is subsequently encountered. Although this approach shares many of the advantages of the attenuated virus approach, the possibility of inadvertently introducing wild virus is eliminated. One of the potential hazards, however, relates to concerns that while the carrier virus chosen might be unable to cause disease in individuals with intact immune responses, it might be capable of causing severe disease in individuals with immune dysfunction. In the case of the most intensively studied carrier virus (vaccinia), such concerns would exist in vaccination plans in which individuals who were already HIV-infected might be inadvertently vaccinated. This concern would include either direct or secondary vaccination, as discussed above.

Current Status of HIV Vaccine Research

At the time of this writing (March 1988), a large number of academic and industrial investigators have focused attention on AIDS vaccine research and production. Most of the scientific attention has centered on approaches that utilize the viral envelope or portions of the envelope as the primary component of candidate vaccines. Live and killed virus approaches have succeeded in producing immunogenes (vaccines) that induce neutralizing antibodies in laboratory animals ranging from mice to nonhuman primates. To date, most, if not all, of the animals vaccinated have produced antibodies that will neutralize only the strain or type of the virus from which the candidate vaccine was derived. Thus, attempts to produce a vaccine that might offer broad protection against a wide variety of strains or types have been unsuccessful. Vaccines useful in the United States may have limited utility in parts of the world where other viral strains are prevalent.

Only a handful of studies have progressed to the point that chimpanzees have been vaccinated with a candidate vaccine and then have been challenged with live virus. Most of these studies have not yet been reported in peer-reviewed scientific literature. In these studies, in general, although neutralizing antibodies have been elicited by the candidate vaccines, animals subsequently inoculated with live virus, even of the vaccine strains, have become infected. This failure to prevent infection might stem from any one of a number of factors. These include the inadequacy of the candidate vaccine and the probability that the live virus inoculation studies have used an excess amount of virus. In the chimpanzee challenge studies performed to date, most animals are challenged intravenously with many thousands of infectious virions. In human infection, it is clear that most sexual exposures do not result in transmission of virus. Those exposures which result in infection may do so because slightly more virus is present, or because of defects in the rectal or vaginal surfaces. Thus, in order for the chimpanzee challenges to accurately reflect human infection, it would be necessary to develop a model whereby animals were inoculated with much smaller amounts of virus, preferably administered to mucosal surfaces. In such inoculations, most animals would not become infected. In order to demonstrate protection, it would be necessary to vaccinate a large number of chimpanzees, and to then inoculate them with a small enough amount of virus that most of them would not become infected, even if unvaccinated. In such a study, one might immunize 100 animals with a test vaccine and another 100 with a sham (or fake) vaccine. One would then inoculate each animal with an amount of virus just in excess of what might infect a minority of unvaccinated animals. At the end of a study like this, a successful vaccine might reduce the number of infected animals from 8 of the 100 in the sham-vaccinated group to 2 of the 100 in the group receiving the active vaccine. Such studies would require tens to hundreds of chimpanzees per vaccine candidate. Given the short supply of chimpanzees, and the

cost of each animal (currently approximately \$70,000), it is unlikely that such studies are feasible.

Thus, at this point, a number of vaccine candidates have been developed. Many produce neutralizing antibodies in vaccinated animals. None has yet been demonstrated to protect animals from live virus challenge. Even if a vaccine demonstrated protection from infection in the chimpanzee model, it would not necessarily imply protection of humans in the real world setting. Therefore, even with all the knowledge theoretically available from animal studies, human vaccine studies will be required prior to licensure of an AIDS vaccine.

Human Studies with Candidate AIDS Vaccines

The human studies that must be undertaken in the evaluation process for AIDS vaccines will be patterned after such studies with other vaccines in the past. A logical sequence of studies progressing from simple dose-finding studies to larger-scale clinical trials will assure the most timely evolution of AIDS vaccine and will minimize the inherent risks to study subjects which are encountered with evaluation of any vaccine or drug product.

The process that is generally followed involves Phase I studies, in which the candidate vaccine is administered to a small group of healthy human volunteers who are at minimal risk for acquiring the agent being vaccinated against. In these studies, the primary goal is to determine whether any toxicities not anticipated from animal studies might be manifest in human subjects. In addition, through the use of several laboratory assays, these studies seek to measure the magnitude of the immune response induced by the vaccine. This endeavor will not necessarily identify adverse effects that might occur at a low frequency or that might occur in populations not included in the preliminary testing. The immunologic changes that are measured will be useful only in that they will indicate whether the immunologic impact of the vaccine in humans is similar to that experienced by animals in the prior studies.

The Phase I studies might involve several different vaccination schedules or doses of vaccine, and might compare the magnitude of the response encountered when the vaccine is given with various adjuvants (immune-enhancing materials). In some vaccine development programs, the Phase I studies are performed in several stages, in which adverse and immunologic effects are measured in a very small group of volunteers (five to ten persons) before they are repeated or modified for application to a larger number of volunteers.

After Phase I testing has been completed, information should be in hand about optimal dosing schedules and adverse effects of a vaccine. The next phase of the studies focuses on whether a vaccine actually prevents infection in the field. In such studies, members of a group or groups at risk for acquiring the agent are recruited and invited to participate in a placebo-controlled trial. In these studies, subjects are randomly allotted to one of two or three groups who will either receive the vaccine candidate or an identical-appearing placebo. Subjects are allotted by chance to these groups; neither the subject nor the investigator knows who receives the theoretically active material. Subjects are then followed to determine whether the group or groups receiving the vaccine are infected at a lower rate over time than those who receive the placebo. Only after such evidence is in hand is a vaccine considered safe and effective and is it offered for general use. Such information is mandatory, because premature licensure and use of an ineffective vaccine would give the public a false sense of security and would encourage behavior that would increase the rate

of infection. In general, most effective vaccines offer a significant degree of protection, but not complete protection. The speed with which a trial can demonstrate the effectiveness of a vaccine is directly related to the rate at which the study population acquires the agent being studied, and to the proportion of vaccinated individuals who are protected from infection by virtue of being vaccinated.

Although the need for such studies seems self-evident, in the case of AIDS vaccine studies practical and ethical concerns will make them extremely difficult to design. In the initial studies, it will be critically important to be certain that individuals who are already infected with HIV, or who are likely to become so in the ensuing several months, are excluded. This is important, since one would not wish to put a potentially useful vaccine at risk of being prematurely discarded because clinical manifestations of HIV infection are mistaken for untoward effects of the vaccine. In most vaccine studies in the past, these concerns have caused investigators to move totally out of "at risk" groups for the very early studies. Politically, this might prove to be difficult with respect to an AIDS vaccine, since individuals at risk for HIV infection have expressed a strong desire to be an integral part of any vaccine studies, from even the earliest phase through the finish. This consideration has caused some investigators to consider offering enrollment to HIV-seronegative homosexual men who have been abstinent for three months and who will guarantee abstinence during the period of the vaccine trial.

In the placebo-controlled trial, in which participants will be at risk of HIV infection, other ethical considerations are operative. Subjects must understand the study design in terms of the placebo inclusion. They must be told that even if they receive active material, the vaccine may not work. Finally, participants must be counseled about modes of infection and must be advised not to put themselves at risk of infection. To the extent that the counseling is effective, it will be increasingly difficult to demonstrate a protective effect of the vaccine. This is related to the fact that in order for a vaccine to demonstrate protection from infection, vaccine recipients and control subjects need to have a significant exposure rate. If trial members receive vaccine or placebo, and then are never exposed to the virus, it will not be possible to determine whether the vaccine is protective. An additional consideration relates to the need to protect the confidentiality of study subjects. This extends beyond usual concerns for such studies, because vaccinees will likely be designated HIV-seropositive by the standard HIV serologic screening tests. To the extent that widespread mandatory testing is employed or appears to be on the horizon, potential vaccine study participants will have a strong disincentive to take part in such vitally important trials. It has been proposed that vaccine trial participants be given certificates indicating participation in HIV vaccine trials in order to indemnify them from retribution from insurance companies and others. These certificates might or might not be useful to

Table 2

Attributes of an Ideal AIDS Vaccine

1. Effective against a wide variety of HIV strains and types
2. Lacking immunopathogenic or other untoward effects
3. Effective against genital, blood-borne, or percutaneous exposure
4. Inexpensive to prepare
5. Easy to administer
6. Stable upon storage

participants, and would certainly expose them to a loss of confidentiality in terms of risk group behavior if they were utilized.

A final consideration relates to the fact that successful completion of placebo-controlled vaccine studies in one risk group will not assure protection to persons in other risk groups. In the case of sexual exposure, it is likely that less virus is presented than with intravenous exposure with intravenous drug use and in transfusion-associated HIV transmission. In addition, in that intravenous drug users and hemophiliacs not infected by HIV are frequently immunosuppressed by drugs and clotting factors, respectively, the immunologic response to a candidate vaccine might be less vigorous than that in healthy homosexual men. Thus, it will be necessary to carry out vaccine trials in several different risk group populations (for example, homosexual men, intravenous drug users, heterosexuals, and hemophiliacs).

The Ideal Vaccine

The ideal AIDS vaccine must satisfy several requirements (table 2). Development of such a vaccine requires a thorough understanding of the modes of transmission of HIV, of the mechanisms by which the virus causes illness and death, and of strain variability among HIV isolates. The ideal vaccine must be safe; effective against a variety of HIV isolates; protective against either sexual or blood-borne exposure through needle sticks; inexpensive to produce; easy to administer; and stable in storage for prolonged periods. Technological progress in basic vaccine design over the past decade makes it likely that such a vaccine will ultimately be produced. However, the impediments to development of such a vaccine are substantial and are unlikely to be overcome in the near future. Although any timetable must be viewed as highly speculative, a possible one is presented in table 3. The vaccine development process is already well under way, having begun with the initial description of the syndrome in 1981. As outlined in the table, vaccine development should be viewed as an orderly process that consists of a series of temporally overlapping but discrete phases. At the present time, limited dose-finding studies have begun. These studies seek to determine whether vaccine preparations are safe to administer, and what dosing schedule induces the most potent immune response. Once an optimal dosing regimen has been established, larger, more elaborate trials will be required to determine whether the vaccine or vaccines actually prevent infection. Following this demonstration in several risk groups, the vaccine will be made available for commercial production. Although it is extremely difficult to make such predictions with precision, it seems unlikely to this author that AIDS vaccines will be widely available until at least 1994 or 1995.

Table 3

Timetable, Past and Potential, in the Development of an AIDS Vaccine

1981	Clinical recognition of acquired immunodeficiency syndrome
1983-84	Identification of HIV as etiologic agent for AIDS
1984-87	Delineation of components of HIV recognized by host immune response
1987-88	Phase I human studies (safety and dose finding)
1989-93	Phase II and Phase III human studies (controlled larger-scale clinical trials with vaccine candidates)
1994-95	AIDS vaccine licensure

Conclusion

In summary, much is now known about the immune response to HIV. This basic knowledge has formed the framework for initial plans for developing AIDS vaccines. AIDS vaccine studies have progressed to the point that portions of the virus have been identified which are capable of generating neutralizing activity in animals. To date, however, no vaccine preparation has been shown to prevent infection with live HIV following a challenge with the pathogenic virus. Human studies are in the earliest phase at this writing, but are both technically and ethically highly complex. It is likely that a vaccine or vaccines that offer a degree of protection, if not full protection, will be developed. It is the opinion of this investigator that such a development is at least five years away. 🐾