Overview of Findings and Executive Summary

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OVERVIEW OF FINDINGS

Potential and Risks of HIV Vaccines

- Although the human immunodeficiency virus (HIV) that causes acquired immunodeficiency syndrome (AIDS) is the most intensively studied virus of all time, a successful preventive vaccine lies at least several years ahead. In addition, we have yet to define the immune response elements necessary for protection from HIV infection.
- HIV is endowed with an unusual set of capacities that enables it to evade or manipulate normal immune responses. Because of these unique capacities, a model for an effective HIV vaccine is much more complicated than the model for other vaccines.
- More than 1,400 volunteers have participated in U.S. trials of HIV vaccines since 1988. Most vaccinees have received envelope-based vaccines (proteins present on the surface of the virus). Adverse reactions following immunization with HIV vaccines have been minimal.
- Of the more than 1,400 individuals who have participated in U.S. trials, 17 have become infected with HIV. There is no evidence that the experimental vaccines increased susceptibility to HIV infection or increased the rate of disease progression in these individuals.
- A number of vaccines are being developed that use new strategies, and each of these strategies may carry special risks.

"Each of the HIV vaccine strategies may carry special risks."

1. Vaccines using *live vectors*, such as the vaccinia virus shown to be attenuated in laboratory animals, may prove to be inadequately attenuated, producing the disease caused by the unattenuated vector:
2. *Naked DNA* vaccines have been shown to create potent immune responses, but there are theoretical reasons to be concerned that they might produce tumors or autoimmune diseases, or be transmitted from mother to fetus.
3. Although *inactivated whole virus* vaccines have generally been successful in protecting from infection with other viral diseases, it would be difficult to assure that all HIV particles in such a vaccine were inactivated.
4. *Live attenuated virus* vaccines have also been successful in protecting from other viral diseases, but there is the potential for the viruses to be inadequately attenuated, for an adequately attenuated viral vaccine to cause disease in immunocompromised individuals, and for an adequately attenuated virus to revert to virulence. There is also concern that a live attenuated HIV vaccine could induce tumors.

- A number of *social harms*—nonmedical adverse consequences—may result from vaccination:

1. Vaccines may cause a false-positive HIV screening test, making the diagnosis of HIV infection more difficult. This vaccine-induced positivity on HIV screening tests may result in discrimination against vaccine recipients in, for example, military service, health insurance, life insurance, employment, and travel.
2. Participation in an HIV vaccine trial, in itself, may result in stigmatization, as others may assume that all vaccine trial participants are members of groups, such as injection drug users and men who have sex with men, who are at increased risk for HIV infection.
3. Vaccinees, relying on the protection afforded by an experimental vaccine, may engage in behaviors that increase their risk for HIV infection.

- In June 1994, the AIDS Research Advisory Committee (ARAC) of the National Institute of Allergy and Infectious Diseases (NIAID) recommended that Phase III clinical trials with envelope vaccines should not proceed in the United States. Factors contributing to the decision included scientific, political, and ethical issues, and the significant level of scientific uncertainty about the wisdom of immediate trials. Phase I and Phase II clinical trials of HIV vaccines will continue.

Ethical Issues in HIV Vaccine Development

- Procedures must be in place to ensure the confidential handling of research data, given the sensitive nature of the information collected in the trial.
- Community involvement with the trial is important to ensure sensitivity to trial participants concerns and to better protect the rights of trial participants.
- Pregnant women should not be excluded from HIV vaccine trials because the efficacy of vaccines to prevent transmission of HIV from an infected mother to her fetus can only be demonstrated in pregnant women.
- It may be ethically acceptable to recruit persons who have little control over their ability to avoid exposure to HIV, such as women whose high-risk male partners refuse to wear condoms, because such persons may be targeted for HIV vaccination, once it is approved.
- Vaccine efficacy trials will target for enrollment individuals from high-risk groups, many of whom may be involved in illegal behaviors (such as injection drug user, prostitution, and, in certain jurisdictions, male-to-male sex). These individuals may increase their risk of detection as a result of trial participation. Assurances of confidentiality are essential to ensure their participation.

- In addition to the general requirements for informed consent, potential subjects of HIV vaccine trials need to be informed of the potential social harms of participation.
- Investigators have an ethical obligation to ensure that research subjects are counseled about avoidance of risk behaviors because some subjects will be randomly assigned to receive placebo vaccine, there is no assurance that the experimental vaccine will be effective, and no vaccine is completely effective.
- If potential subjects are to be screened for HIV infection, there should be an informed consent process for this screening, in addition to the informed consent process for participation in the vaccine trial.
- Investigators have an ethical obligation to provide subjects with documentation of their trial participation, and to make available sophisticated tests necessary to distinguish vaccine-induced false positivity from true HIV infection.
- Trial participants should agree not to be tested for HIV outside of the study; participant's knowledge of their assignment may bias study results.
- Vaccine trials also need to be conducted in developing countries because AIDS is a devastating problem in these countries, and because the circulating strains in each part of the world differ, so that findings from vaccine trials in developed countries may not be generalizable to the developing world.
- Local representatives should be consulted at all stages of vaccine trials in developing countries. Both Western requirements and local requirements for informed consent must be met. Efforts must be made to ensure that potential subjects have an adequate understanding of the study's risks, and the importance of avoiding risk behaviors in order to provide informed consent, but potential subjects and investigators need not have a completely shared understanding of disease causation.
- Investigators have the ethical obligation to ensure that the trial does not interfere with other health care or public health efforts.
- To ensure fairness in the distribution of benefits and burdens, the vaccine must be made available to the communities where trials were conducted. In poorer communities, this may require that the vaccine be made available either at cost or free of charge.
- Although vaccine sponsors have no legal obligation to provide compensation to subjects for injuries incurred as a result of their participation, there is an ethical obligation to do so.

Liability and Compensation for Adverse Reactions

- Any system that limits compensation to injuries from one specific cause, like an HIV vaccine, raises questions of fairness to people with similar injuries from a different vaccine. A compensation system limited to persons with adverse reactions to an HIV vaccine invites the question why people living with injuries from other vaccines or from other causes should not be compensated as well.
- More companies are engaged in HIV vaccine research than in research for any other type of vaccine. Potential liability may have discouraged some companies, but it has not stopped HIV vaccine development.
- Some have argued that drug and vaccine makers should be exempt from liability because their products confer significant benefits and their designs and labeling are approved by the Food and Drug Administration (FDA). Supporters of liability argue that no exemption should be granted because not all drugs provide significant social benefits, and that manufacturers should be held to at least the same standards as manufacturers of ordinary consumer goods because consumers are vulnerable to undetectable risks in pharmaceutical and biological products.

- Physicians are more likely than vaccine manufacturers to be the target of complaints that patients were not informed of vaccine risks. The "learned intermediary" rule permits the maker of prescription drugs or vaccines to warn only the prescribing physician, and not the patient who receives the product. Physicians have an independent legal obligation to obtain their patients' informed consent to immunization.
- Although the legal basis for liability is the same, both the likelihood of claims and the probability that any such claims would succeed in practice is far lower with respect to investigational vaccines than with marketed vaccines.
- For a number of reasons, there has been little concern about liability for adverse reactions to therapeutic vaccines, in contrast to preventive vaccines.
- Liability claims based on low levels of effectiveness have not been brought against existing vaccines. The likelihood of success of a claim of lack of effectiveness of an HIV vaccine is speculative, but probably small as long as those who take the vaccine are warned of its limited efficacy and advised to take precautions against exposure to HIV infection.
- The likelihood of a successful claim of liability for enhanced susceptibility to infection of disease progression would depend upon whether the manufacturer knew or should have known that the vaccine was capable of causing the reaction, and whether the plaintiff could prove that the vaccine was the only cause of the reaction in his or her case.
- Given the need for an HIV vaccine, it appears unlikely that a manufacturer would be held responsible for distributing a vaccine with a risk of development of cancer that could not be verified at the time it was released.
- The decision whether or not to invest in the development of a vaccine depends on complex financial considerations of a number of factors, including the scientific obstacles to vaccine development, the potential market for the vaccine, the price at which the vaccine could be sold, and the potential liability for vaccines. The major factor influencing vaccine development is the expected return on investment or profitability, and the major obstacles to developing an HIV vaccine are scientific.
- Evidence that liability may deter some companies from developing an HIV vaccine comes from anecdotal reports that several companies interrupted HIV vaccine research or testing and sought immunity from liability before they would consider proceeding. Other factors, however, including scientific problems with the candidate vaccine, inadequate financing, poor market predictions, patent problems, and internal corporate restructuring, may also explain their decisions about whether to pursue testing.
- Nonrecombinant vaccines that use killed, inactivated, or attenuated virus may be unappealing to vaccine makers because of the consequences of the failure of the manufacturing process to inactivate a virus that could cause active infection. Companies may not wish to pursue a type of vaccine that might produce HIV infection, regardless of exposure to liability, especially if they believe that they cannot eliminate the risk of a manufacturing error.
- Vaccine manufacturers are not likely to be responsible for harms resulting from the bigotry of others. Physicians who administer HIV vaccines may be the more likely targets for any claim that a vaccine recipient was not adequately warned about possible discrimination.
- Preventive vaccines may be more susceptible to claims of liability than most drugs and biologics, primarily because they are used in large numbers of healthy people. The rate of actual liability, however, has been quite low.
- Since liability is so rarely imposed for vaccines, the fear of liability may be more accurately described as the fear of having to litigate at all. Complaints about the litigation process, however, are not limited to cases involving

HIV vaccines, so that any alternative that is intended to remedy tort litigation's inefficiencies would have application beyond HIV vaccines.

- Tort reform proposals have sought to change the substantive grounds for liability, the procedures or evidence used in litigation, or the amount of compensation payable. Similar proposals to reform the law of medical malpractice and product liability have been the subject of considerable debate. If considered for HIV vaccines, they may have to be considered for other types of injuries.
- Voluntary agreements between companies and individuals to provide compensation for an adverse reaction without the necessity of litigation reduce the time and expense of resolving claims. Voluntary agreements are unlikely to work well with new HIV vaccines, because the company and the vaccinee do not have the relationship necessary for contract, and because there are likely to be substantial unresolved issues about whether the injury was caused by the vaccine.
- Government-funded excess insurance would limit the amount of financial exposure companies face from liability payments, but the primary difficulties are in estimating the amount of excess insurance needed for a new vaccine and determining the amount of liability expenditures that should be considered excessive for manufacturers. In addition, an excess insurance program might set a precedent for government reinsurance of liability expenses for other types of tort claims.
- Vaccine-related injuries could be compensated through government disability insurance programs. A more general expansion of disability insurance to cover injuries regardless of cause avoids questions of justice to persons with injuries from other causes and the costs of such a program would be more predictable than the costs of a program that compensates only those injuries caused by new HIV vaccines. But a government disability insurance program would be costly.
- No-fault compensation programs eliminate the need to prove negligence or legal responsibility for injury, so that administrative costs can be lower than those of litigation. No-fault compensation systems that are limited to injuries from a specific cause, like adverse reactions to vaccines, require proof of causation, which is often difficult, time-consuming, and expensive, especially where the scientific evidence is uncertain or conflicting. No-fault compensation programs also have the disadvantage of treating one group of people differently from others with similar injuries or needs. Also, no-fault compensation systems may generate more, rather than less, costs and typically compensate more people than would recover compensation in tort law.
- The National Vaccine Injury Compensation Program may provide a model for a no-fault system of compensation for adverse reactions to HIV vaccines. Adding HIV vaccines to the program would expand its scope beyond children's vaccines, but it would also avoid the need for creating a new administrative structure to provide compensation.
- By themselves, compensation programs cannot guarantee that any vaccine is developed. Alternative methods of encouraging vaccine development may be necessary, including tax incentives, expedited FDA review, purchase guarantees, expanded patent protection, and facilitation of collaborative efforts.

EXECUTIVE SUMMARY

AIDS researchers are investigating new vaccines that would prevent HIV infection and reduce the spread of AIDS. Some have claimed that potentially promising approaches to developing a vaccine against HIV have been deferred due to concerns about liability of vaccine manufacturers, and have urged legislation that would limit the liability of manufacturers of HIV vaccines. This study examines the current state of HIV vaccine development, the adverse reactions that may be associated with HIV vaccines, and proposals to re-

form product liability to encourage the development of an HIV vaccine. The findings of this study may be used in considering legislation that addresses HIV vaccine liability, and also have important implications for the reform of product liability in general.

The next three chapters address the medical, ethical, and legal issues in the development and marketing of an HIV vaccine. Chapter 2 addresses the potential safety problems that may emerge from vaccines for the prevention of HIV infection.[1] The chapter reviews the biological basis for development of a vaccine to prevent AIDS, the difficulties that must be overcome in developing an effective HIV vaccine, and the unique features of the virus and disease it produces that elude vaccine control. The chapter also reviews the adverse events that have occurred to date in clinical trials of HIV vaccines. The chapter explains the difficulties in predicting the types and rates of adverse reactions that may occur with HIV vaccines; this uncertainty has important implications for the design of a compensation scheme. The chapter concludes with a discussion of the important adverse social consequences of being vaccinated for HIV.

Chapter 3 provides an overview of the basic ethical principles that guide human subjects research, and shows how these ethical issues apply to each stage of HIV vaccine development. The chapter discusses ethical issues in the design of clinical trials, selection of research subjects, the informed consent process, compensation for trial-related injuries, and incorporation of HIV vaccines into clinical practice. The chapter also addresses special ethical issues that arise in clinical trials in developing countries.

Chapter 4 summarizes existing product liability law and relevant literature on liability for vaccine-related injury and analyzes how that law might apply to vaccines to prevent HIV infection or progression to AIDS. To gauge how liability might affect the vaccine industry's ability or willingness to develop and market new HIV vaccines, the report reviews other factors that influence such decisions, such as the feasibility of identifying an effective HIV vaccine and the attractiveness of the potential market. Although there is little basis for assuming that liability itself will halt HIV vaccine development, some highly risk-averse companies may avoid specific types of vaccine products that they fear may induce severe adverse reactions. Whether such products should be encouraged depends upon their safety and effectiveness compared with available alternatives.

Liability's effect on vaccine development does not answer the question whether society should endorse compensation for vaccine-related injuries, which may be desirable to achieve other social goals. For this reason, chapter 4 begins with a brief description of common reasons for compensating injuries and assigning responsibility (liability) to different entities for paying compensation. Finally, the chapter summarizes several types of compensation systems as a guide to issues that should be considered in any debate on the desirability of establishing a new compensation system for HIV vaccine-related injuries.

Appendix A provides a detailed technical discussion of adverse reactions that may, in theory, be predicted to occur. These include late-occurring reactions and rare adverse reactions that may not be detected until after an HIV vaccine has been approved for marketing. The appendix also assesses the strength of the support for these potential harms from HIV vaccines.

POTENTIAL FOR ADVERSE REACTIONS TO HIV VACCINES

Role of Vaccines in Control of Disease

One way to control the spread of AIDS is to vaccinate individuals against HIV infection. Vaccines have been credited with eliminating smallpox and of reducing the number of cases of measles, mumps, rubella, diphtheria, pertussis, tetanus, and other infectious diseases. Vaccines consist of

[1] In this report, the term HIV will refer to human immunodeficiency virus type 1 (HIV-1), unless otherwise indicated.

a microorganism or its components, in a safe form, which are administered to stimulate, or "prime," the body's immune system to generate protective defenses specifically directed against the microorganism. The portions of the microorganism that stimulate the body's immune system are called antigens.

The immune system has three response components: 1) antibody circulating in the bloodstream (humoral immunity); 2) a network of immune white cells in the blood and tissues (cellular immunity); and 3) a specialized system of antibody and immune cells located at mucous membranes (mucosal immunity), such as those covering the surface of the vagina, anus, and penile urethra (the routes of sexual transmission of HIV infection). Antibodies are produced by immune white cells called B lymphocytes. Each antibody is antigen-specific, and can neutralize virus particles that are free in the circulation, but cannot inactivate virus that is located inside infected cells. Another type of white cell, the T lymphocyte, participates in cellular immunity. Among the types of T lymphocytes are the CD4+ "helper" T lymphocytes, which are necessary for the development of mature functional lymphocytes, and the CD8+ "cytotoxic" T lymphocytes, which can kill cells undergoing active viral infection.

Vaccines in use today follow only a few basic designs. Most common are live attenuated vaccines, which are composed of a live virus or other pathogenic organism that has been altered to reduce or eliminate its potential to produce disease. Also common are inactivated virus vaccines, which use virus that has been killed (i.e., rendered unable to replicate). Two are protein subunit vaccines, which are composed of antigenic proteins from the pathogenic organism. And one vaccine, Hepatitis B, is prepared by recombinant biotechnology. The number of infectious agents for which we have failed to develop a satisfactory vaccine, however, is far greater than the number of those that have been successful.

Unique Features of HIV

Although HIV is the most intensively studied virus of all time, a successful vaccine lies several years ahead. Because of several unique features of HIV, a model for an effective HIV vaccine is much more complicated than the model for contemporary vaccines. HIV is endowed with an unusual set of capacities that enables it to evade or manipulate normal immune responses. These include the following:

- HIV is a "retrovirus" that integrates its genome into the human genome through a process called "reverse transcription." Once this happens, it cannot be detected and eliminated by the immune system.
- HIV is able to evade immune recognition through a process of rapid genetic mutation and selection.
- The virus selectively invades and can injure CD4+ lymphocytes and macrophages, the very cells that play central roles in immune defenses.
- The virus can spread through direct cell-to-cell contact, avoiding immune activation.
- During the years of apparent clinical wellness before the onset of HIV-related symptoms, the virus continues to multiply to high concentrations in lymphoid tissues of the body, and is silently transmissible.
- HIV is transmissible by three different routes (through sexual contact with mucous membranes, by direct inoculation into the bloodstream, or by transfer from mother to fetus or infant), which, in itself, can complicate the task of developing a vaccine that mounts an effective immune blockade.
- HIV can be transmitted as free virus as well as virus inside cells; it is more difficult to block the transmission of virus inside cells.
- Unlike other viral infections that are self-limited, there are few, if any, instances of recovery

from HIV infection to offer clues for understanding the key immune response elements necessary for protection from the virus.

- Primate models of human HIV infection have not yielded definitive guidance to the immune elements necessary for protection.

Animal Models of HIV Infection and Disease

Animal models of infection historically have contributed to the development of vaccines by helping to define the immune responses associated with control of infection, and to predict the behavior of a candidate vaccine in man. The chimpanzee is the only animal in which HIV will replicate. But in the chimpanzee, the virus causes a minimal persistent infection, waning over time, with no disease manifestations. Macaque monkeys can become infected with simian immunodeficiency virus (SIV), a retrovirus that is closely related to HIV. SIV is highly virulent in macaques, and causes a persistent infection leading to an AIDS-like syndrome within 6 to 24 months after infection. Thus, the HIV/chimpanzee system models HIV infection in humans, while the SIV/macaque system parallels HIV disease progression in humans.

There are examples of vaccine protection or partial protection in primates, largely under conditions that are optimal for protection, but do not mirror typical conditions. Also, large doses of antibody administered to the chimpanzee provide passive protection to infection with HIV for several hours, but no longer. Live attenuated vaccines show a high level of protection against SIV infection in macaques, but there are safety concerns that may have inhibited the development of live attenuated HIV vaccines for human use.

Development and Clinical Evaluation of HIV Vaccines

The U.S. Public Health Service has established a program of basic science and clinical research toward the development of a safe and effective preventive HIV vaccine. The effort is centered at the National Institutes of Health (NIH), with the National Institute of Allergy and Infectious Diseases as the lead institute. The NIAID Division of AIDS (DAIDS) has created an AIDS Vaccine Clinical Trial Network (AVCTN), which has several components. The AIDS Vaccine Evaluation Group (AVEG) includes six AIDS Vaccine Evaluation Unit (AVEU) trial sites at university research centers. Each unit has an associated Community Advisory Board. Other AVCTN elements include a Central Immunology Laboratory, a Mucosal Immunology Laboratory, a Data Coordinating and Analysis Center, and a Data and Safety Monitoring Board.

The process of testing a candidate vaccine in clinical trials is initiated by a sponsor, which presents preclinical data for review by the Food and Drug Administration's Center for Biologicals, Evaluation and Research (CBER). The FDA is also responsible for approval and oversight of experimental protocols as vaccines progress through clinical trials. The AIDS Vaccine Selection Group determines whether a vaccine will be entered into federally funded AVEG trials. Other major participants in HIV vaccine development include the National Cancer Institute, the Center for Disease Control and Prevention (CDC), vaccine manufacturers, the World Health Organization (WHO), and the Department of Defense, with capacities for research, product development, and conduct of clinical trials in the developed and developing world.

Promising candidate vaccines are selected for initial assessment of immune responses and safety in carefully monitored, randomized, controlled trials. The first phase (Phase I) of clinical trials of vaccine focuses on the safety and immunogenicity of the vaccine. The Phase I protocol involves 25 to 100 individuals at low risk for HIV infection, assigned to one or more experimental groups and to a placebo group for comparison. If immune responses and safety warrant further studies, the vaccine may undergo Phase II trials involving up to several hundred individuals. Phase II studies refine and enlarge on the database, may directly compare vaccine products or sequences, or may include individuals at higher risk of acquiring infection.

HIV vaccine sponsors have been, to a large extent, small biotechnology companies, private research institutions, and universities; some of the large pharmaceutical manufacturers in the United States are not represented among vaccine sponsors. A number of considerations influence corporate decisions to enter into the development of an HIV vaccine, including the opportunity costs of vaccine development relative to development of drugs, potential markets for HIV vaccines, the scientific feasibility of vaccine development, and the potential for liability for adverse reactions to HIV vaccines. Because of concerns about vaccine safety, manufacturers have primarily pursued the development of HIV vaccines composed of envelope protein subunits, proteins present on the surface of the virus, which have inherently more limited immune capability, but have fewer inherent safety risks, than vaccines composed of inactivated or live attenuated virus.

Adverse Reactions to HIV Vaccines

The standard of safety applied to preventive vaccines has been extremely high; even the rare occurrence of significant injuries to uninfected, healthy individuals has been considered unacceptable. Despite the inherent potential for injury from vaccines, currently licensed vaccines have been extremely safe, and have provided a highly cost-effective method for disease prevention.

Initial approaches to HIV vaccines have concentrated on gp120 and gp160, glycoproteins that are present in the membrane or "envelope" of the virus. Purified envelope proteins have been produced using recombinant biotechnology. A second method of immunization uses live vaccinia virus (derived from the strain used to prevent smallpox) as a delivery "vector, which has been genetically altered to express HIV gp160 on its surface. From the initiation of the AVEG program in 1988, more than 1,400 volunteers have participated in trials. Twelve envelope-based vaccine products have been used, prepared by five manufacturers, using three different strains of HIV.

Envelope vaccines have induced neutralizing antibody against strains of HIV that are homologous (identical) to strains used in vaccine preparation. The titers (concentrations) of antibody induced by envelope vaccines have been 5- to 10-fold lower than titers of antibody seen in HIV-infected individuals, and have fallen rapidly after each vaccine dose. Heterologous (nonidentical) strains of HIV were neutralized less well, and strains of HIV that were recently isolated in the community were entirely resistant to the vaccine. Envelope vaccines failed to generate cytotoxic T lymphocyte responses (cellular immunity).

Adverse reactions following immunization with envelope products have been minimal. Sequential measurements of biochemical, blood, and immune status, and kidney and liver function tests have shown no significant vaccine-related abnormal findings. Importantly, there has been no evidence of adverse effects on immune function.

Envelope vaccines that were combined with alum "adjuvant" (a substance used to enhance the vaccine's immunogenicity) were accompanied by local reactions at the injection site, consisting of mild pain, tenderness, redness, and swelling for 1 to 2 days after injection. Vaccinations with some of the newer adjuvants were accompanied by transient moderate to severe local reactions and febrile flu-like illnesses for one to three days after injection in a number of recipients.

Ten vaccinees developed a rash to several products, and one also developed joint pain. A few individuals developed a positive antinuclear antibody (ANA) test (which may at times be associated with autoimmune disease, such as rheumatoid arthritis). However, further testing ruled out any vaccine-related diseases. Despite careful screening and counseling, 14 pregnancies occurred during these trials. There was no evidence of vaccine-related adverse events to the fetus.

The trials permitted comparison of the side effects of an attenuated vaccinia/gp160 vector with the commercial vaccinia virus strain used to prevent smallpox. Reactions to the vaccine re-

sembled those seen following classical smallpox vaccination. There were no differences in the development of pustules at the inoculation site, regional lymph node swelling, or level of systemic symptoms. The vaccinia virus vector did not appear to be adequately attenuated and thus could carry the risk of vaccinia complications known to occur with classical vaccination. With broad use of an HIV vaccine, substitution of a more attenuated virus vector, such as canarypox, is preferable.

As of May 1994, 10 neoplasms (tumors) were observed among participants in 9 vaccine trial protocols. One of the neoplasms was benign. Cases of malignancy tended to occur among older participants. Analysis by the Data Safety and Monitoring Board and an ad hoc expert committee found no evidence that the neoplasms were linked with any vaccine products. Because of the wide variety of tumor types, it was judged to be biologically implausible that the tumors had a causal relationship to the vaccine.

To date, 12 of the 1,400 individuals in AVEG trials since 1988 have become infected with HIV. Of the 12 infected vaccinees, three received a placebo vaccine, eight received an envelope protein vaccine, and one received a vaccinia/gp160 vaccine. Five of the infected vaccinees received one or two doses of vaccine, and only four infected vaccinees received an adequate series of three to four doses. Three additional "breakthrough cases" occurred in an intramural NIAID trial, and two others occurred in non-NIAID trials, so that a total of 17 infections have occurred in all HIV vaccine trials to date. Envelope vaccines of all participating manufacturers were involved. A number of breakthrough infections was to be expected because some volunteers received placebo, some volunteers had not completed a full dosage schedule, and the protective efficacy of the vaccines being tested is not known.

Envelope vaccines, in themselves, cannot cause HIV infection. The possibility that the vaccine may increase susceptibility to HIV infection or may increase the rate of disease progression (a phenomenon called "antibody-dependent enhancement") must be considered and investigated. Although there is laboratory evidence of an increase in growth of virus in cell cultures in the presence of antibodies from the serum of vaccinees, there is no evidence of enhancement with SIV or HIV in primate experiments.

There is concern that HIV vaccines have the potential to cause autoimmunity (an immune reaction against the bodies own tissues), because HIV shares several envelope proteins that are identical to proteins on human tissues. For example, there is a similarity between one HIV envelope protein region and a normal human blood-type protein. Autoimmunity has not been observed among vaccine recipients to date, although in theory, autoimmune phenomena could first appear months to years after vaccination.

New Generation Vaccines: Implications for Safety

Because of HIV's unique abilities to evade immune controls, all immune response elements may need to be invoked to provide protection, including humoral immunity, cellular immunity, and mucosal immunity. Vaccines using new strategies may be needed to fulfill these immune requirements for protection. Each vaccine formulation or variation on a formulation is regarded as a new product by the FDA and requires a separate evaluation. Each new approach may carry special risks, some unique to that strategy.

Proteins that duplicate viral antigenic proteins may be artificially synthesized. These "synthetic peptides" have been shown to induce cytotoxic T lymphocyte responses to SIV in macaques. In clinical trials, reactions to synthetic peptide vaccines have been benign.

Vaccines using a number of vectors (e.g., canarypox virus, adenovirus, Salmonella, Shigella, and attenuated poliovirus) are being studied. These live vectors are better able to induce cytotoxic T lymphocyte responses, and vectors that grow on body surfaces (e.g., adenovirus and Shigella) are better able to induce mucosal immune responses to HIV. Live vectors, however, carry inherent safety concerns. If they are inadequately or unstably attenuated, they may produce the disease

caused by the unattenuated vector. They may result in unwanted spread to contacts and the community at large. And even an adequately attenuated vector may cause disease in individuals with impaired immunity.

Some new vaccines are composed of "naked DNA," pure viral genetic material. Persistent antibody and cytotoxic T lymphocyte responses have been induced in laboratory animals immunized with naked DNA. The mechanisms leading to the potent immune responses are not understood. Concerns about naked DNA involve the theoretical possibilities of tumor formation, production of autoimmune disease, or the transmission of DNA to the fetus.

Development of inactivated whole virus vaccines against HIV was seriously considered in early deliberations. Although inactivated whole virus vaccines have generally been successful in protecting from infection with other viruses, this strategy has not been applied to HIV by vaccine manufacturers because of inherent risks. The primary concern with these vaccines is the difficulty in assuring inactivation of all HIV particles. Of particular concern is whether cell cultures or animal models are sufficiently sensitive to detect minimal amounts of residual live virus capable of infecting humans.

Vaccines using live attenuated viruses have also been successful in protecting from other viral diseases. Live attenuated vaccines are capable of inducing a vigorous and broad antibody response, as well as inducing cellular immunity and mucosal immunity. Live attenuated SIV vaccines were able to protect monkeys against challenge with large doses of virulent virus. In addition, the attenuated virus used in these vaccines was shown to be stable, not reverting to a virulent form over an observation period of several years.

However, there are a number of concerns about the safety of attenuated viral vaccines. First, there is the potential for the viruses used to be inadequately attenuated, resulting in the induction of the disease that the vaccine was designed to prevent. By contrast, viruses that are overattenuated may not be able to induce protective immune responses. Second, even an adequately attenuated virus may be virulent in individuals whose immune system is impaired by immunosuppressive drugs, cancers, or other causes.

Third, there is concern about the "stability" of attenuation of the virus—the potential for an attenuated strain of virus to undergo genetic reversion to a more virulent form during replication in the vaccinee. Spread of the attenuated virus to contacts (secondary spread) provides the virus with further opportunities to revert to virulence. Fourth, live attenuated HIV may induce tumors. Other retroviruses have been shown to produce tumors, and in theory, the prolonged residence of an attenuated HIV strain in humans could allow the production of tumors. There is recent evidence that HIV has a direct role in the etiology of some T-cell lymphomas, a type of immune cell cancer.

Social Harms as Adverse Reactions to HIV Vaccines

Individuals may suffer social harms—non-medical adverse consequences—as a result of HIV vaccination. Vaccines may cause a "false-positive" screening test for HIV infection. The false-positive tests from envelope vaccines can only be distinguished from HIV infection by the Western blot test, which is widely used to confirm the results of positive screening tests. These false-positive screening tests could potentially result in discrimination against false-positive individuals, for example, in eligibility for military service, employment, health or life insurance, or restriction of travel. Volunteers in NIAID-sponsored trials have received identification documents certifying their participation in these trials, although AVEG personnel have had to provide validation of confounding Western blot confirmatory tests. This problem may be greater with new generation vaccines that include many more types of antigenic proteins than are currently used, which may render the Western blot tests incapable of distinguishing false-positive screening tests from HIV infection. Reliance must then be placed on more expensive and time-consuming polymerase chain reaction (PCR) tests and viral cultures.

Participation in an HIV vaccine trial, in itself, may engender social harms. Others may perceive that trial participation implies that the volunteer is a member of a group at special risk for acquiring HIV infection, resulting in stigmatization of that volunteer. Furthermore, volunteers immunized with one vaccine may be precluded from participation in clinical trials of subsequent, possibly more effective, vaccines. Also, trial participants, assuming that the vaccine protects them from infection, may increase their risk-taking behaviors. This may occur despite intensive counseling about the possibility of assignment to placebo vaccine and about the unknown efficacy of the experimental vaccine.

Clinical Trials in HIV-Infected Individuals

A number of vaccines to prevent transmission of HIV from an infected mother to her fetus or infant (maternal-fetal transmission) are being developed. Although pregnancy had been a cause for exclusion from Phase I and II clinical trials of HIV vaccines, Phase I clinical trials of HIV envelope vaccines, involving 23 infected pregnant women, are now in progress. Such trials are specifically designed to study safety and possible efficacy of vaccines in prevention of infection in the infant. No significant vaccine-related adverse events have occurred in the mothers or in the 20 infants that have been delivered thus far.

A number of vaccines are being developed to treat individuals with established HIV infection. Approximately 35 Phase I and Phase II trials of therapeutic HIV vaccines are being conducted in the United States and abroad. Thus far, there has been no clear evidence that these vaccines have delayed or prevented disease progression in infected individuals. Conversely, there is no evidence that these vaccines have accelerated or enhanced HIV infection in vaccinees.

Phase III Efficacy Trials

The purpose of Phase III efficacy trials of HIV vaccine is to determine its capability to protect against infection, and to provide a more definitive assessment of vaccine safety. Efficacy trials of HIV vaccines will be large, complex, lengthy, and expensive, involving several thousand volunteers per experimental group. Trials will be conducted among groups with a high incidence of HIV infection, such as injection drug users and men who have sex with men; members of these groups may feel disenfranchised and socially stigmatized, and may distrust government and scientific experimentation.

In anticipation of these large-scale efficacy trials, preparatory studies involving several thousand injection drug users and men who have sex with men with high HIV incidence are under study by the HIV Evaluation Network (HIVNET), sponsored by the NIAID, the CDC, and the National Institute of Drug Abuse. The purposes of these trials are multiple: to study the social and cultural factors affecting trial recruitment and retention; to measure the effect of trial participation, counseling, and unblinding on risk behaviors; to determine the basis for attitudes toward vaccine acceptance; to develop educational strategies and consent forms appropriate to the groups that will be targeted; and to study the dynamics of trial acceptance and feasibility. Information derived from such studies will help to prepare for full-scale HIV vaccine efficacy trials in the United States.

A number of criteria may be used to select vaccine candidates for Phase III efficacy trials: 1) evidence of the vaccine's safety and immunogenicity in Phase I and Phase II trials; 2) the ability of the vaccine to induce high and sustained titers of broadly reactive antibody capable of neutralizing strains circulating in the community; 3) the ability of the vaccine to induce cytotoxic T lymphocyte responses; 4) evidence of vaccine protection in primate models. Because of the scientific uncertainty, the relative emphasis given to each of these criteria have varied.

Two vaccines, Biocine SF2 with MF59 and Genentech MN with alum adjuvant, have completed Phase II efficacy trials. In June 1994, the NIAIDS AIDS Subcommittee and the AIDS Research Advisory Committee recommended that Phase III clinical trials with the envelope vaccines should

not proceed in the United States at this time. Factors contributing to the decision included scientific, political, and ethical issues, as well as the significant level of scientific uncertainty about the wisdom of immediate efficacy trials. Phase I and Phase II clinical trials of HIV vaccines, however, will continue. New products recently entered into Phase I trials or in preclinical testing are designed to increase and improve the quality of the protective immune response to the vaccine. Additional vaccines should be available for consideration for Phase III trials within two to three years.

Long-term followup of large numbers of vaccine trial participants and controls allows for surveillance of events that are infrequent or occur after an interval of years. The trial participants constitute prospectively defined cohorts that are not easily duplicated once controlled efficacy trials are completed. Vaccinated cohorts from efficacy trials could be compared with unvaccinated cohorts currently under epidemiologic and virologic surveillance. Provision for long-term followup should be an integral part of trial efficacy design to allow surveillance for adverse events, such as enhanced infection, autoimmune disease, tumors, or reversion to virulence.

The NIAID and U.S. military are working with governments in the Americas, Africa, and Asia to establish sites for HIV vaccine trials. Trials of HIV vaccine in developing countries provide opportunities to study diverse population groups in highly endemic areas, including heterosexual and maternal-fetal transmission of HIV and a variety of cultural and health settings, and to test vaccines targeting a multiplicity of HIV subtypes.

ETHICAL ISSUES IN HIV VACCINE TRIALS

Ethical issues arise in all stages of vaccine development and marketing. A prophylactic vaccine for HIV infection raises some unique ethical issues.

Principles of Research Ethics

All biomedical research should be conducted in a manner that seeks not to violate three primary ethical principles: beneficence, respect for autonomy, and justice.

The principle of *beneficence* addresses one's obligations toward the well being of others. In clinical research, beneficence requires that the welfare of research subjects be protected. In vaccine trials, the investigators and vaccine sponsors are responsible for protecting research subjects from undue or excessive risks, and this responsibility cannot be avoided merely by informing subjects of those risks. There are certain risks that are too great for any altruistic volunteer to consent to, regardless of whether the volunteer understands the risks. In clinical trials, an external review board determines whether the risks of the trial are excessive.

Respect for autonomy obligates investigators to recognize research subjects as individuals who have the right to make their own decisions. The doctrine of informed consent is derived from this principle.

Justice requires fairness in the distribution of benefits and burdens. In research, this requires that no individuals or groups bear a disproportionate share of the risks of research without justification, and that all groups have equal access to the benefits of research participation.

Design of Clinical Trials

In designing clinical trials of HIV vaccines, a number of ethical issues should be addressed. First, investigators should determine whether a randomized trial is ethical. Random assignment to an experimental intervention is ethical only in cases of "clinical equipoise"—that is, where there is a lack of consensus in the medical or scientific community about whether the experimental intervention is beneficial. It is not ethical to randomly assign research subjects to vaccine and placebo control groups if there is consensus that the experimental vaccine is effective. Given the serious consequences of erroneous vaccine research findings, it is also unethical to base conclusions about vaccine efficacy on nonrandomized studies, because of the risk of bias. Thus, it is ethical to con-

duct randomized clinical trials to determine whether a vaccine is effective, but not to provide confirmatory data.

Second, investigators have an ethical obligation to ensure that research subjects are counseled about avoidance of risk behaviors. Behavioral counseling is ethically required in HIV vaccine trials because some subjects will be assigned to placebo vaccine, because there is no assurance that the experimental vaccine will be effective, and because no vaccine is completely efficacious. Also, it would be good to give research subjects some benefit in return for participation, if it can be provided at not at too great an expense.

Third, procedures should be in place to ensure the confidential handling of research data. Protection of confidentiality is important in any clinical research, but especially in HIV-related research, because of the sensitive nature of the information being collected. A number of practical measures should be taken to better ensure that confidentiality is maintained: each research subject should be assigned a unique identification number to be used, instead of full names, for labeling written forms, specimens, and any other information about the subject; all research data should be kept in locked storage cabinets or computer files with restricted access; only a select group of investigators should be allowed access to the "master key" that links subjects' names to their unique identifiers; all research staff should be educated in procedures that ensure the protection of research subjects' confidentiality.

Vaccine sponsors should pay for all trial-related medical procedures. Patient confidentiality may be threatened if investigators are allowed to bill the subject's insurer for medical procedures related to the trial.

Research subjects should be assured that they may have access to their own files upon completion of the trial, and that they may obtain documentation of their trial participation, even years later, if they need to demonstrate, for example, that the experimental vaccine was the source of a positive HIV antibody test.

Fourth, community involvement in the trial is important. A community board, usually composed of trial participants, meets with investigators periodically throughout the course of the trial to discuss plans, to review progress, and to make recommendations to the investigators. The community board can serve as a liaison between research subjects and investigators, and can help ensure that the rights of research subjects are protected. The research subjects' resultant greater involvement with and "ownership" of the research could improve retention and compliance.

Sample Selection

Research ethics has been concerned with protecting vulnerable populations from being enrolled in human subjects research without their (or their guardian's) knowledge and without adequate justification for their specific inclusion. More recently, there has also been a concern that vulnerable populations not be denied the benefit of participation in research.

Vulnerable" populations are those that are unable to provide valid informed consent, either because they do not have the mental capacity to provide consent (such as children or the mentally ill), or because they may not be able to provide consent voluntarily (such as prisoners or patients who are in a dependent relationship with the investigator). Such vulnerable populations should only be included if they will contribute knowledge that cannot be obtained from studying other, less vulnerable populations, and if the members of the vulnerable population (or their guardians) believe that the research will be beneficial.

Until recently, pregnant women have been excluded from trials of HIV vaccines because of concerns about harm to the fetus. However, the efficacy of vaccines to prevent transmission of HIV from an infected mother to her fetus can only be demonstrated in pregnant women. Three clinical trials of vaccines to prevent maternal-fetal HIV transmission have now enrolled infected pregnant women.

Certain populations targeted for vaccine trials may be considered vulnerable, not because they are unable to provide consent, but because they may be at greater risk of social harms as a result of their trial participation. Persons involved in illegal behaviors (such as injection drug user, prostitution, and, in certain jurisdictions, male-to-male sex) may increase their risk of detection as a consequence of trial participation. At the same time, it is important to include members of these groups in HIV vaccine trials, given the higher incidence of HIV infection in these groups, and given that members of these groups would be candidates for a vaccine once it is approved. Measures to protect their confidentiality are important to ensure their participation.

Members of racial minority groups are more highly represented among populations at increased risk of HIV infection, so they are more likely to participate in HIV vaccine trials. Members of racial minority groups may be less trustful of investigators, given the history of abuses of minorities in research, such as in the Tuskegee syphilis study. Community boards should be established to ensure that minority group participants' needs are addressed and that investigators are sensitive to cultural concerns.

Informed Consent

Rooted in the principle of respect for autonomy is the ethical obligation on the part of investigators to obtain informed consent from prospective research subjects. Federal law requires that all federally funded research be approved by external review boards, which have the responsibility to ensure that investigators have obtained informed consent. Virtually all academic institutions require that all research involving human subjects (not just that which is federally funded) secure such approval.

The process of informed consent requires the following: 1) prospective subjects must be provided with information relevant to their decision about participation; 2) they must understand that information; 3) they must provide consent voluntarily; 4) their consent must be documented. Prospective research subjects should be given the following information: a statement that explains that they are being asked to participate in research, not clinical care; the purpose of the research; the reason why they were selected; all procedures that are required, including the location, duration, and frequency of study visits; a description of foreseeable risks; the alternatives to the experimental intervention; a description about how confidentiality will be maintained; whether there will be compensation for injuries resulting from trial participation; information about who to contact for questions or problems; and a declaration that the subjects have both the right not to participate and to cease their participation at any time.

In addition to these general requirements, there are a number of special requirements for informed consent in HIV vaccine trials. If potential subjects are to be screened for HIV infection, they must provide informed consent for this screening. This is in addition to the informed consent that they must provide for participation in the trial. The informed consent process for HIV testing of potential research subjects should include the pre- and post-test counseling, as is required for HIV testing in other contexts, and referrals should be made available for those who test positive for HIV.

Potential subjects of HIV vaccine trials need to be informed of the following:

- The experimental vaccine has not been demonstrated to be effective, and it is unlikely that any HIV vaccine will be completely effective. In addition, the subject may be randomly assigned to a placebo vaccine. Compensation will not be provided for failure of the experimental vaccine to protect research subjects from HIV infection.
- Receipt of the experimental vaccine may complicate the diagnosis of HIV, because vaccinees may falsely test positive on conventional HIV screening tests. The investigators will make sure that more sophisticated tests are available to distinguish vaccine-induced positivity from true HIV infection.
- Trial participants should not be tested for HIV outside of the study, since knowledge of their

assignment could bias the study's results. They should also be told that investigators have made arrangements to provide trial participants with HIV testing, should they wish to be tested.

- Social harms may result from testing positive on an HIV screening test, such as problems with health or life insurance, employment, military service, and travel. All subjects will be provided with documentation of their trial participation.
- Anyone who participates in an HIV vaccine trial risks being socially stigmatized. Investigators also have the ethical obligation throughout the trial to provide subjects with any other information that might influence the subjects' continued willingness to participate in the trial.

Vaccine Trials in Developing Countries

Vaccine trials need to also be conducted in developing countries because AIDS is a devastating problem in these countries, and because the circulating HIV strains differ in each part of the world, so that findings from vaccine trials in developed countries may not be generalizable to developing countries. Local representative should be consulted at all stages of vaccine trials in developing countries.

Questions have been raised about whether it is ethically acceptable to recruit persons who have little control over their ability to avoid exposure to HIV, such as women whose male partners refuse to wear condoms. Such persons, however, may be targeted for vaccination, once an HIV vaccine is approved.

In developing countries, both local and Western requirements for informed consent should be met. In some societies, permission for trial participation is granted by some individual other than the potential research subject, such as a community leader or the female subject's husband. This does not abrogate the responsibility of the investigator to obtain consent from the potential subject as well.

Potential subjects should have an adequate understanding of the study and its risks in order to provide informed consent. If the potential subject is illiterate, investigators must provide information orally, using the local language or dialect.

In some societies, broad understandings about disease causation are completely different than Western understandings. Potential subjects and investigators need not have a completely shared understanding of disease causation, so long as no harmful consequences are likely to ensue.

In developing countries, there may not be available the more sophisticated tests that are necessary to distinguish vaccine-induced positivity from true HIV infection. In that case, investigators have the responsibility to make these sophisticated tests available to trial participants, should they need them.

Investigators also have the ethical obligation to ensure that the trial does not interfere with other health care or public health efforts. Finally, investigators and vaccine sponsors have an ethical obligation to make vaccine available to the communities where the trial was conducted; to ensure that vaccine is available to members of poor communities, they may have to provide it either at cost or free of charge.

Compensation for Adverse Reactions

There is general agreement that, although vaccine sponsors and investigators have no legal obligation to provide compensation to subjects for injuries incurred as a result of participation, there is an ethical obligation to do so. If compensation will not be provided, this should be explained to subjects as part of informed consent.

Incorporating an HIV Vaccine into Clinical Practice

In considering whether to incorporate a partially effective HIV vaccine into clinical practice, one should consider whether the benefits of a partially effective vaccine are outweighed by the harmful increase in risk behaviors that may result in reliance on the vaccine.

Less rigorous standards of informed consent are applied to clinical practice, even though the consequences of vaccination are just as important. There is no requirement for signed written con-

sent, except for certain types of medical interventions, typically surgery and uncommon procedures. For public health interventions, the requirements for informed consent have been limited (although the requirements for informed consent for HIV screening is an exception). The risk that confidentiality will be breached in the clinical setting is greater, because insurance companies and other outside parties have access to patients' medical information.

LIABILITY AND COMPENSATION FOR ADVERSE REACTIONS

Responsibility for Injury and Compensation

With every injury, the question arises whether its financial losses should be shifted to someone else, and if so, to whom. Although the injured person inevitably bears the physical and emotional consequences of injury, financial losses may be either: 1) left where they lie, with the injured person, or 2) transferred, in whole or in part, to someone else by requiring that party to compensate the injured person. There are no other options; the losses do not disappear. The threshold question, therefore, is whether it is necessary or desirable to compensate people who incur particular injuries.

Reasons for Compensating Injuries

Arguments for and against compensating people who are injured have been based on economic, ethical, and social policy grounds. Economic arguments tend to focus on total social costs of injuries and do not necessarily justify compensation for all injuries. Whether society believes it has a moral obligation to ensure that injured persons are compensated may depend upon how society perceives the injured person. In different circumstances, compensation can be: 1) morally required, because not providing it is unjust; 2) morally desirable, but not morally required; or 3) not morally required and possibly unjust. Compensation has also been viewed as a pragmatic means to provide for people in need.

Tort liability for adverse reactions to vaccines has been justified as a reasonable method of compensating people who are injured from specific causes, but more commonly as providing a deterrent to creating products that pose unreasonable risks of injury to others. Compensation and liability for injury appear to be linked in policy discussions of vaccine-related injury because of a general sense that injured vaccine recipients deserve compensation, but that vaccine producers should not be responsible for paying compensation for all the injuries that occur.

Social Goals of Allocating Responsibility for Injury

If injury compensation is desirable or morally required, responsibility for providing compensation may be allocated to the vaccine manufacturer, the person who prescribed or administered the vaccine, the government, or some other party, depending upon the goals to be achieved. Any of the following might serve as goals for allocating responsibility for adverse reactions to a future HIV vaccine to different parties:

1. The development of an effective vaccine to prevent HIV infection or AIDS.
2. The marketing and distribution of an HIV vaccine.
3. The marketing and distribution of an HIV vaccine at a reasonable cost to users.
4. The use of HIV vaccine to prevent HIV infection or progression to AIDS.
5. Compensating persons injured as a result of vaccination with an HIV vaccine.
6. Minimizing the total social cost of HIV vaccine development, marketing, and injury compensation.
7. Minimizing the total costs of HIV infection, including prevention and transaction costs.

None of these goals can be achieved solely by assigning responsibility (or liability) for injuries. Rather, by assigning responsibility to different parties, society may encourage or discourage progress toward specific goals. The choice of system depends upon the goals to be achieved by liability and compensation and how alternative sys-

tems affect the achievement of other important goals, such as prevention of disease, deterrence of injury-producing products and activities, and the just distribution of resources.

Systems that satisfy one goal may undermine another. For example, a system that minimized the costs of compensation to vaccine makers might encourage vaccine development, but also reduce incentives to limit potential safety risks. A system that required vaccine makers to provide generous financial assistance might achieve the goal of equitable compensation, but might be too expensive for many companies that society, for other reasons, wishes to attract to vaccine development. If government were to assume responsibility for compensation, the cost to government might conflict with other societal goals to minimize government expenditures or to fund other important programs. Any system that limits compensation to injuries from one specific cause, like an HIV vaccine, raises questions of fairness to people with similar injuries from a different cause. A compensation system limited to persons with adverse reactions to an HIV vaccine invites the question why people living with HIV infection or AIDS or other serious illnesses or injuries should not be compensated as well.

Potential Deterrents to HIV Vaccine Development

Companies in private industry necessarily make choices about what products to make. Because new biologic products require a substantial investment of both time and money, choices may have long-term consequences for a company's product line. Thus, the decision whether or not to invest in the production facilities and equipment, as well as human expertise, necessary to produce an HIV vaccine is a complicated business decision in which companies must weigh the financial risks against the financial rewards.

Scientific Obstacles

The major obstacles to developing an HIV vaccine are scientific. Unfortunately, too little is known about how to produce an immune response in human beings that would protect against infection or development of disease to be assured than an effective vaccine can be produced in the foreseeable future. The National Institute of Allergy and Infectious Disease's decision in June 1994 not to proceed with large Phase III field trials of the leading candidates, for lack of adequate promise of effectiveness, is indicative of the difficulty of surmounting scientific and technical obstacles.

Potential Market for HIV Vaccines

If scientific obstacles can be overcome and an HIV vaccine appears technically feasible, the major factor influencing vaccine development is its expected return on investment or profitability. Profitability depends on the size of the market for an HIV vaccine and the price at which it can be sold. Although the worldwide population at risk for HIV infection numbers in the millions, the relevant market for HIV vaccine sales consists of paying purchasers: individuals who can pay for vaccination either out-of-pocket or with insurance and government agencies that purchase vaccine for distribution to individuals.

Not everyone in the potential market may be willing to buy an HIV vaccine, either because they do not wish to be vaccinated or because they cannot afford the market price. The United States may be the most profitable market for HIV vaccines. The prices at which vaccines can be sold are limited in many foreign countries, either by government regulation or competition from foreign vaccine makers who may receive government subsidies. Many developing countries have severely limited budgets for vaccine purchases and are unable to pay in the hard currency demanded for most transnational sales. A disproportionate number of people at risk for HIV infection are unable to pay for vaccination and are not likely to obtain vaccines without government assistance. Government purchasers, however, may demand substantial discounts from market prices, as the U.S. federal government does for pediatric vaccines, which limits the potential revenues from vaccine sales.

Potential Liability

An HIV vaccine would have considerable appeal to companies that believe that market demand will be strong, the price will not be regulated, and users would pay the price. HIV vaccine development may appear unattractive to companies that perceive any of these factors to be absent. Liability for vaccine-related injuries may affect the profitability of vaccines. If the financial costs of defending and paying expected liability claims are predicted to be too large a proportion of expected revenues, then companies are likely to pursue more profitable lines of product development. Thus, liability may influence decisions about whether to develop a specific product, but it is weighed with other factors. If scientific and financial factors argue against pursuing HIV vaccine development, it is unlikely that changes in liability can outweigh them.

The evidence that liability may deter some companies from developing an HIV vaccine comes from anecdotal reports that several companies interrupted HIV vaccine research or testing and sought immunity from liability before they would consider proceeding. Other factors, however, including scientific problems with the candidate vaccine, inadequate financing, poor market predictions, patent problems, and internal corporate restructuring, may have influenced their decisions about whether to pursue testing. One company later developed a new candidate HIV vaccine. Another proceeded with testing after all. A third attempted to test its preventive vaccine candidate in a single location but enrolled only two subjects before the trial was closed after about a year. The same company actively pursued tests of a therapeutic vaccine. At the same time, other companies developed and tested their candidate vaccines without raising liability concerns. Almost 30 candidate vaccines have been in clinical trials.

In summary, decisions about whether to develop an HIV vaccine, or any other product, entail predictions about its scientific, technical, and financial feasibility and profitability compared with alternative investments. However, the number of companies engaged in HIV vaccine development and testing is encouraging. More companies are engaged in HIV vaccine research than in research for any other type of vaccine. Potential liability may have concerned a few companies, but it is not likely to stop HIV vaccine development.

Tort Liability for Adverse Reactions to Vaccines

Principles of Strict Liability and Negligence

Like manufacturers of all products, vaccine makers are responsible under state law for personal injuries caused by their own negligence or by a defect in their products. Negligence is conduct by the manufacturer that deviates from standards of acceptable conduct adhered to by the ordinary manufacturer of similar products and that causes harm to the product user. Strict liability holds the seller (including a manufacturer) responsible for physical harm caused by a product that is in a defective condition unreasonably dangerous to the user. As a practical matter, most people claiming vaccine-related injury assert several causes of action to avoid losing their claim because of a technical characterization. Thus, the distinction primarily determines the success of a specific cause of action, rather than whether a claim is brought at all.

Product defects

Traditionally, product defects have been divided into three categories: 1) manufacturing defects, 2) design defects, and 3) errors or omissions in warnings accompanying the product. Concern about liability for vaccine-related injuries tends to focus more on strict liability for design defects and inadequate warnings, and less, if at all, on liability for negligence or strict liability for manufacturing errors. Critics of the former two causes of action argue that drug and vaccine makers should be exempt from liability because their products confer significant benefits and their designs and labeling are approved by the FDA. Supporters of liability argue that no exemption should be granted because not all drugs provide significant social benefits, and that manufacturers should be held to at least the same standards as manufacturers of or-

dinary consumer goods because consumers are vulnerable to undetectable risks in pharmaceutical and biological products. Courts have upheld both positions.

Design defects

An increasing number of states have held that makers of FDA-approved prescription drugs or vaccines are entirely exempt from strict liability for design defects, regardless of the product in question, largely for reasons of public policy. Other states have refused to grant a blanket exemption from liability for all drugs and vaccines. Instead they would exempt only those drugs and vaccines that are shown to be unavoidably unsafe, on a case-by-case basis.

Warnings of risks

In view of the impossibility of creating a risk-free vaccine, manufacturers have an obligation to provide a warning of the vaccine's inherent risks. The history of the legal doctrine and its application in litigated cases parallels that of the doctrine of informed consent to medical care.

A vaccine manufacturer's duty to warn differs from a physician's duty to obtain informed consent for medical care in one respect, however: who is entitled to receive the warning. The doctrine of informed consent to medical care requires a physician to tell his or her patient about the risks and benefits of taking a drug or vaccine, as well as any alternatives. Although the general rule is that all manufacturers have a duty to warn those who use their products of dangers that are not readily apparent, an exception, known as the "learned intermediary rule," permits the maker of prescription drugs or vaccines to warn only the prescribing physician, and not the patient who receives the product. This is because it is the physician—acting as a "learned intermediary" between the manufacturer and the patient—who ordinarily makes the medical judgment that a vaccine is appropriate to recommend for an individual patient.

Thus, vaccine manufacturers do not ordinarily have a duty to provide a warning directly to a vaccine recipient. Similarly, the National Childhood Vaccine Injury Act of 1986 barred any cause of action for a manufacturer's failure to warn a recipient (or a recipient's parent or guardian) about the risks of a childhood vaccine covered by the compensation program. It also created a rebuttable presumption that warnings approved by the FDA are adequate.

Under the learned intermediary rule, a warning is generally not considered inadequate unless the missing information would have caused a physician not to give the vaccine to the patient. A few reported cases have found specific warnings inadequate because they did not mention known risks of a vaccine. In most cases, warnings have been found adequate because they disclosed all reasonably known risks, or manufacturers have not been held liable because the warning would not alter the physician's decision to recommend the vaccine. Physicians have an independent obligation to obtain their patients' informed consent to immunization. This means that physicians are more likely than vaccine manufacturers to be the target of complaints that patients were not informed of vaccine risks.

Types or Uses of HIV Vaccines

The above principles of liability apply to manufacturers of all vaccines, regardless of whether they are preventive (intended to prevent) or therapeutic (intended to treat or cure infection or disease), and regardless of whether the vaccines are experimental (investigational) or approved and licensed. The likelihood of adverse reactions and liability claims occurring may differ, however, depending upon the way in which a vaccine is used.

Investigational Vaccines

The potential liability for adverse reactions to investigational preventive vaccines is less than that for marketed vaccines. Although the legal basis for liability is the same in both cases, both the likelihood of claims and the probability that any such claims would succeed in practice is far lower with respect to investigational vaccines than with marketed vaccines. Historically, there have been no

reported product liability cases involving vaccine research, probably because there has been a very low incidence of injury among research subjects in general. Claims of defective design are also minimized, if not precluded entirely, by the fact that the research is being conducted to find out whether the vaccine works and whether it has dangerous side effects.

Therapeutic Vaccines

Therapeutic HIV vaccines, which are used to treat people who are already infected with HIV, are more comparable to drugs than to preventive vaccines. Patients who take therapeutic vaccines may be willing to accept accompanying risks in order to receive any benefit the therapeutic vaccine might afford. Adverse reactions may be difficult to distinguish from other symptoms arising from existing illness. The potential for damages is also limited because of the perceived limited life expectancy of people with AIDS. Perhaps for these reasons, there has been little concern about liability for adverse reactions to therapeutic vaccines.

Potential Adverse Reactions to HIV Vaccines

In the absence of any approved HIV vaccine, predictions about adverse reactions are based on somewhat limited experience with the candidate vaccines in clinical trials, laboratory research, and theoretical hypotheses. The following are the most commonly mentioned hypotheses.

Low Levels of Effectiveness

There has been speculation among researchers that some candidate HIV vaccines now in clinical trials may ultimately prove effective in only a small percentage of the vaccinated population. If the vaccinated population is at risk for HIV infection, as anticipated, then some proportion may become infected after taking a vaccine of limited efficacy, even if the vaccine is not defective. Claims based on low levels (or lack) of effectiveness have not been brought against existing vaccines. The likelihood of success of a claim of lack of effectiveness of an HIV vaccine is speculative, but probably small as long as those who take the vaccine are warned of its limited efficacy and advised to take precautions against exposure to HIV infection.

Enhanced Susceptibility to Infection or Disease Progression

Researchers have theorized that candidate vaccines might have the potential to increase one's susceptibility to infection with HIV or other organisms, or to increase the rate of disease progression in people who become infected with HIV in spite of vaccination. Both hypotheses raise the possibility of a claim for defective design if they are not investigated, or a claim for inadequate warning if they are not disclosed. The likelihood of a successful claim would depend upon whether the manufacturer knew or should have known that the vaccine was capable of causing the reaction, and whether the plaintiff could prove that the vaccine did cause the reaction in his or her case.

Development of Cancer

There has been speculation that, because HIV is a retrovirus, an HIV vaccine might cause cancer many years after vaccination. Although a manufacturer is not liable for injuries caused by unforeseeable dangers in its products, there may be some question as to whether a manufacturer adequately investigated a suggested risk. Given the need for an HIV vaccine, it appears unlikely that a manufacturer would be held responsible for distributing a vaccine with a risk that could not be verified at the time it was released.

Vaccine-Induced HIV Infection

Non-recombinant vaccines that use killed, inactivated, or attenuated virus raise the possibility that the manufacturing process might inadvertently fail to remove or render harmless part of the virus that could actively infect a person. Although claims of vaccine manufacturing errors have been rare in the past, the consequences of a batch of vaccine accidentally escaping inactivation are sufficiently serious to make this type vaccine un-

appealing to many vaccine makers. However, companies may not wish to pursue a type of vaccine that might produce HIV infection, regardless of exposure to liability, especially if they believe that they cannot eliminate the risk of manufacturing error.

Social Harms

HIV vaccination may pose risks of social harm that are not adverse reactions to the vaccine itself. People who receive HIV vaccines may be especially vulnerable to denials of health or life insurance or permission to travel abroad, loss of employment or housing, segregation in institutions, or rejection by family and friends. Most such harms result from lawful conduct for which the vaccine recipient would have no legal recourse. Manufacturers are not ordinarily responsible for the bigotry of others. Physicians who administer HIV vaccines may be the more likely target for any claim that a vaccine recipient was not adequately warned about possible discrimination.

Susceptibility of HIV Vaccines to Liability Claims

Preventive vaccines may be more susceptible to claims of liability than most drugs and biologics, primarily because they are used in large numbers of healthy people. As with drugs, the majority of claims have affected only a few vaccines, and the number of reported cases that impose liability on the vaccine maker is very small. Thus, although the probability of *claims* of liability may be higher than that for drugs, the probability of actual *liability* is quite low.

Plaintiffs rarely succeed on a claim of design defect, probably because of the difficulty of proving that a safer, equally effective vaccine could have replaced a vaccine that was approved by the FDA. Although most states still permit claims that a vaccine was defectively designed, only one vaccine (Quadrigen) has been found to have a defective design (in a warranty, not product liability, action). No reported court decision after 1969 has held a vaccine maker liable for a design defect.

Few courts have found a vaccine maker liable for an inadequate warning of risks. More extensive and sophisticated warning statements may have increased manufacturers' protection against such liability. In addition, vaccine makers are largely exempt from any duty to warn vaccine recipients themselves of vaccine risks. Instead, manufacturers have a duty to warn the prescribing physician, who bears the responsibility for disclosing vaccine risks to patients. Thus, physicians may now be more vulnerable to claims (of lack of informed consent) than vaccine makers.

Fear of liability for adverse reactions to vaccines may have been based on a perception in the 1970s and early 1980s that courts were expanding the grounds for product liability. That expansion appears to have halted, although it cannot be assumed that it would never recur. Since liability itself is so rarely imposed, the fear of liability may be more accurately described as fear of having to litigate at all. This is understandable, given the time and expense of pursuing and defending claims. Complaints about the litigation process, however, are not limited to cases involving HIV vaccines (there have been none). Concerns about the efficiency and fairness of tort litigation as a means of resolving disputes are generic. This does not mean that an alternative means of allocating responsibility for injury and compensation is not warranted for other reasons. It does mean that any alternative that is intended to remedy tort litigation's inefficiencies would have application beyond HIV vaccines.

Alternative Compensation Options

The following outlines several major options for allocating responsibility for compensating adverse reactions to HIV vaccines.

Tort Liability Reform

Tort liability imposes legal responsibility for compensating injuries. Tort reform proposals seek to change the substantive grounds for liability, the procedures or evidence used in litigation, or the amount of compensation payable. Any single reform can only be unidirectional: it either increases

or decreases the opportunity for a plaintiff to bring or succeed on a claim.

Currently, most tort reform proposals seek to limit the liability of potential defendants. By themselves, limitations on liability are cost control measures, not compensation mechanisms. Such limitations are best suited to circumstances in which the primary goal is to save potential defendants money and where providing compensation to those who would not qualify under the reform is not relevant or desirable.

Reforms expanding plaintiffs' opportunities to recover compensation would further a goal of increased compensation, but are likely to increase total costs. Reforms such as scheduling compensation are intended to make compensation more consistent across different claimants with similar injuries, without necessarily altering the grounds for recovery.

Other reforms are intended to reduce the time and expense of litigation and the possibility of inconsistent results, without changing the bases for liability. Similar proposals to reform the law of medical malpractice and product liability have been the subject of considerable debate. If considered for HIV vaccines, they may have to be considered for other types of injuries.

Voluntary Contractual Arrangements

Private companies and individuals are free to reduce the time and expense of resolving claims by voluntarily agreeing to provide compensation without the necessity of litigation or legislation. The voluntary contract model, exemplified by the Moore-Gephardt bill introduced in Congress (99th Congress, 1st Session, 1985) but never passed, would permit a vaccine maker or administering physician to agree, at the time of vaccination, to pay the vaccine recipient compensation for out-of-pocket expenses promptly if an adverse reaction occurred. Such contracts may encourage compensation even in cases in which the vaccine recipient would have no recourse in tort law. They may work reasonably well in circumstances in which the payor and payee know each other and where the cause of injury is relatively easy to establish. Neither circumstance is likely to apply to new HIV vaccines. The process of deciding how much, if any, compensation to offer resembles the process of settling a claim in litigation, and may be equally difficult in many cases.

Government-Funded Insurance Arrangements

Government-funded excess insurance

Government-financed insurance programs can fund compensation for injuries. Government might purchase private excess insurance or reinsurance or use its own revenues to finance compensation awards that exceed a predetermined amount. This would limit the amount of financial exposure private companies face from liability payments, and lower premiums for basic liability insurance. The primary disadvantage of government-funded excess insurance is the difficulty of estimating the amount of excess insurance needed for a new vaccine, and the amount of liability expenditures that should be considered excessive for manufacturers. Reinsurance systems do not alter the legal bases for liability and would not remedy concerns about inefficiencies of tort litigation and inconsistent awards. In addition, an excess insurance program might set a precedent for government reinsurance of liability expenses for other tort claims, from medical malpractice to automobile accidents.

Government-funded disability insurance

Vaccine-related injuries could be compensated through government disability insurance programs. For example, the Social Security program could be amended to specifically include coverage of injuries resulting from HIV vaccines. A more general expansion of disability insurance to cover injuries regardless of cause would be more in keeping with the general function of Social Security, which already covers AIDS-related disability. A general disability insurance program avoids hard questions of horizontal justice about why injuries resulting from one cause should be compensated while others are not. The cost of such a program may require new government revenues, but,

because the costs of disability for the entire national population are relatively consistent over time, they are more predictable than the costs of compensating injuries caused by new HIV vaccines.

If the health care system is reformed to ensure universal coverage, a significant expense of injury would be covered outside the disability insurance program. In the absence of universal insurance coverage, continued pressure for financial assistance to pay for medical care may be expected.

Public No-Fault Compensation Systems

Federal and state governments have created several publicly administered injury compensation programs, such as state workers compensation programs, the Federal Black Lung Benefits Act, the Radiation Exposure Compensation Act, Virginia and Florida's Birth-Related Neurological Injury Compensation acts, and the National Vaccine Injury Compensation Program.

Most such programs provide compensation on a no-fault basis for specific injuries from specific causes. As long as the injury is demonstrated to result from the specified cause, compensation is granted without the need to prove negligence or legal responsibility for the injury. Parties that might be liable for the injury typically need not participate in the claims determination process. Administrative costs can be less than those of litigation. Compensation can be funded from different sources to achieve different goals.

No-fault compensation programs have the disadvantage of treating one group of people differently from others with similar injuries or needs. Those who do not qualify for compensation may object to such special treatment or demand equivalent treatment themselves as a matter of horizontal justice. The more programs that exist for specific causes, the more difficult it becomes to defend excluding the remaining injuries from a no-fault system.

No-fault systems that are limited to injuries from a specific cause, like adverse reactions to vaccines, require proving that an injury resulted from that specific cause. Determining causation is often difficult, time-consuming, and expensive, especially where the scientific evidence is uncertain or conflicting. Yet no-fault systems are often recommended in order to provide desired compensation in circumstances where causation is unclear or controversial. Thus, many of the complexities that make litigation frustrating and expensive are often necessarily part of cause-based, no-fault compensation proceedings.

No-fault compensation systems may sometimes generate more, rather than less, cost, depending upon the level of compensation to be awarded and the scope of eligibility for compensation. No-fault systems typically compensate more people than would recover compensation (or even file a claim) in tort law. In the absence of reliable estimates of the number and type of compensable injuries, it may be difficult to predict system costs.

The National Vaccine Injury Compensation Program may provide a model for compensating adverse reactions to HIV vaccines. A no-fault system funded by federal revenues (for administration) and surtaxes on vaccines (for compensation), it provides compensation for adverse reactions that are caused by specific vaccines. Although the program was originally intended to cover only vaccines required by state law for children before they enter school or day care, it has been amended to permit coverage of vaccines that are recommended for children. Adding HIV vaccines to the program would expand its scope beyond children's vaccines, but it would also avoid the need for creating a new administrative structure to provide compensation.

Table 1-1 lists the basic elements of a no-fault compensation program and key questions that must be answered in constructing a suitable system.

Alternative Incentives for HIV Vaccine Development

By themselves, compensation programs cannot guarantee that any vaccine is developed. If HIV vaccines are not sufficiently attractive to private industry for reasons of the difficulty and expense of research compared with the expected financial

TABLE 1-1: ELEMENTS OF A COMPENSATION PROGRAM

Eligibility
- Who should be eligible for compensation?
- U.S. citizens, U.S. residents, nonresidents?
- What, if any, time period should be the limit for bringing claims?

Covered vaccines
- Should the program cover all or only some vaccines? Investigational vaccines?

Compensable injuries
- Should all injuries be covered, or only Injuries at a minimum level of severity (in either physical or financial terms)?
- Should injuries include HIV infection? Social harms?

Causation
- How is causation to be determined?
- Is causation understood well enough to permit a list of compensable injuries?
- Who has the burden of proving causation?
- What kind of evidence should be required to prove causation?

Compensation benefits
- Is compensation to be calculated on the basis of actual losses, a fixed schedule of injuries, a fixed amount per person or injury, or some other basis?
- Which, if any, actual expenses will be compensated?

Payment mechanisms
- Should payment of compensation be made in a lump sum, periodic payments, by an annuity providing periodic income, or a health Insurance policy providing coverage for medical expenses?

Decisionmaking authority and procedures
- What entity is authorized to make decisions about eligibility and compensation?
- Should any third party be required or permitted to participate in the decisionmaking process?
- What, if any, type of review or appeal should be available?

Relationship to tort law
- Should the compensation system be an optional alternate to the tort system or the exclusive source of compensation for claimants?
- Should people who have filed claims in court be eligible for compensation?
- If the program ceases operation or is repealed, what, if any, rights should the claimants have?

Financing
- What should be the source of funding for the compensation and administration? Government revenues? Taxes on products or manufacturers? Private insurance?

Period of operation
- Should the program's continuance be contingent upon future events, such as the development of a vaccine the sale of a vaccine at a specified price, the disposition of a maximum number of claims, adequate funding or some other event?

SOURCE Office of Technology Assessment, 1995

return, then other initiatives will be necessary to encourage vaccine development. Among the types of initiatives that might foster increased attention to HIV vaccine development are:

- Tax incentives for investment in vaccine development.
- Mechanisms for increased collaboration and in- formation-sharing among vaccine researchers to increase productivity and expedite research.
- Simplification of collaborative arrangements between government and industry researchers.
- Expanded access to preclinical nonhuman animal models for testing investigational vaccines.
- Expedited review by the FDA of applications for vaccine licensing.

- International harmonization of national vaccine licensing standards.
- Guaranteed purchase of vaccine supplies by government.
- Expanded patent protection for approved vaccines.
- National coordination of vaccine research and distribution policies.
- Creation of a National Vaccine Authority to foster research and product development by providing grants, facilities, and consultation, as well as arranging procurement contracts.

Social goals for HIV vaccines go beyond mere development and marketing of a vaccine. The vaccines developed should be reasonably safe and effective to prevent the continued expansion of a devastating epidemic. FDA regulation is one mechanism to assess the safety and effectiveness of vaccines. One of tort law's objectives is to provide additional incentives to produce safe and effective products. Whatever one's view of the FDA or tort law's effectiveness in this respect, some mechanism to ensure adequate quality in vaccines is necessary. In addition, effective mechanisms for distributing and encouraging the use of vaccines, especially by those unable to buy them, will be required if the benefit of HIV vaccines is to be realized.