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# NIH NEWS RELEASE

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

FOR RELEASE
Tuesday, July 13, 1999
11:00 a.m. Eastern Time

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**Combination HIV Vaccine Induces Diverse Immune Responses**

Preliminary analysis of data from a clinical trial testing two candidate HIV vaccines given together shows that the combination is safe and can stimulate diverse immune responses against HIV. The findings will be discussed by the study's principal investigator, Robert Belshe, M.D., of Saint Louis University, on Tuesday morning, July 13, at the International Society for Sexually Transmitted Diseases Research meeting in Denver.

This is the second Phase 2 HIV vaccine trial, and the largest to date, sponsored by the National Institute of Allergy and Infectious Diseases (NIAID). The trial, known as AVEG 202/HIVNET 014, is being carried out at 14 sites nationwide by two NIAID-sponsored networks, the AIDS Vaccine Evaluation Group (AVEG) and the HIV Prevention Trials Network (HIVNET). Dr. Belshe heads the Saint Louis University AVEG site.

Earlier studies in volunteers at low risk of HIV infection showed this combined vaccine approach held promise for activating both components of the immune system. One vaccine, ALVAC-HIV vCP205, stimulates cellular immunity, resulting in cytotoxic T cells (CTLs) that can kill HIV-infected cells. The other vaccine, SF-2 rgp120, stimulates production of HIV neutralizing antibodies, which can stop HIV from infecting cells. The vaccines contain only selected HIV genes or proteins, and not the whole virus, so an individual cannot become infected from receiving the vaccines.

The current trial, which opened in May 1997, enrolled 435 healthy men and women not infected with HIV. Because the primary goal of this study is to assess the immune response and safety of the vaccine combination in individuals at increased risk of becoming infected with HIV, more than 80 percent of the participants had recent histories of injection drug use or high-

(more)

risk sexual behavior. All participants received extensive and repeated counseling on reducing high-risk behaviors.

Each participant was randomly assigned to one of three study groups. The first group received both vaccines; the second group received vCP205 and a placebo, or dummy vaccine; and the third group received two placebos. Volunteers received four doses spread out over six months; each time, they got one shot in each arm. By July 1998, all immunizations were completed. The participants will be followed for four years.

Dr. Belshe will report that the vaccines appear safe. Adverse side effects associated with either vaccine were generally mild.

The vaccines have induced anti-HIV immune responses in the majority of the volunteers. More than half of those individuals receiving vCP205 alone, and more than 90 percent of those receiving the vaccine combination, have developed antibodies that can inhibit HIV in a laboratory assay. So far, about one-third of the volunteers receiving either vCP205 alone or the combination vaccine have developed anti-HIV CTL responses. While the results are encouraging and support further evaluation of this vaccine strategy, the study was not designed to determine whether the vaccine combination can protect against AIDS.

Because vaccinated individuals may at times appear positive on a standard HIV antibody test, even though they are not infected, the research team was concerned that participation might put volunteers at risk of discrimination and other negative consequences. True infection, however, can be distinguished from vaccine-induced antibody responses by several tests. Encouragingly, the proportion of volunteers who reported that their participation resulted in a negative event with a major life impact was quite low.

Also reassuring was the fact that overall, participants reported a decrease in risky behaviors after one year in the study. These findings reflected the sustained efforts of the study team to counsel volunteers to practice safe sex and avoid high-risk behaviors.

During the course of the trial, 11 volunteers became infected with HIV as a result of high-risk behaviors: six in the placebo group, three in the group receiving vCP205 alone, and two in the group receiving the vaccine combination. Six of the 11 had received the full four-dose course of vaccine or placebo before becoming infected: three in the placebo group, two in

the group receiving vCP205 alone, and one in the group receiving the vaccine combination. However, the trial is neither large enough nor conducted over a long enough period of time to determine vaccine efficacy, says Dr. Belshe.

vCP205, made by Pasteur Merieux Connaught (Lyon, France) with support from the French ANRS (Agence National de Recherches sur le SIDA), consists of a weakened canarypox virus that has been genetically altered to contain a few selected HIV genes. The canarypox virus cannot grow or cause disease in humans. SF-2 rgp120, made by Chiron (Emeryville, CA), is a genetically engineered copy of the HIV surface protein, gp120. SF-2 is a laboratory-adapted HIV strain.

Additional NIAID-sponsored studies are gathering more data on this vaccination strategy before a large-scale efficacy trial is considered. For example, two newer canarypox HIV vaccines are undergoing a head-to-head evaluation. The current study adds compelling new evidence that large-scale efficacy trials using these or similar vaccines are feasible in communities at risk. At this time, the data needed to consider moving into the next phase of testing is expected to be available by late 2000.

For information about AIDS vaccine clinical trials, call the AIDS Clinical Trials Information Service (1-800-TRIALS-A) or visit their Web site at www.actis.org.

NIAID is a component of the National Institutes of Health (NIH). NIAID conducts and supports research to prevent, diagnose and treat illnesses such as HIV disease and other sexually transmitted diseases, tuberculosis, malaria, asthma and allergies. NIH is an agency of the U.S. Department of Health and Human Services.

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**Press releases, fact sheets and other NIAID-related materials are available on the NIAID Web site at www.niaid.nih.gov.**

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# FACSIMILE

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HIV Vaccine study - press release

4 **Pages [including this cover]**

# NIAID HIV/AIDS VACCINE RESEARCH AND DEVELOPMENT

# STRATEGY AND OPPORTUNITY

**National Institute of Allergy and Infectious Diseases**
**National Institutes of Health**

**November 1995**

# NIAID HIV/AIDS VACCINE RESEARCH AND DEVELOPMENT

# STRATEGY AND OPPORTUNITY

**November 30, 1995**

## INTRODUCTION

The identification of a safe and effective vaccine against the Human Immunodeficiency Virus (HIV) is of the highest priority to U.S. and worldwide efforts to control the epidemic. The National Institute of Allergy and Infectious Diseases (NIAID) has the lead responsibility at the National Institutes of Health (NIH) in the area of HIV vaccine research and development. In executing this mandate, the Institute has developed a comprehensive scientific research agenda implemented through an integrated program of fundamental and empiric research. The purpose of this paper is to describe the Institute's vision of the optimal strategic approach, including the spectrum of current scientific opportunity, which must be pursued to ensure success.

## BACKGROUND

Shortly after the discovery of HIV as the cause of AIDS over 10 years ago, it became apparent that the development of a safe and effective vaccine would pose unprecedented challenges. Many believed that the abilities of the virus to rapidly mutate, to evade strong humoral and cellular immune responses in the course of natural infection, and to produce a silent latent infection in lymphocytes and macrophages precluded the possibility of successful vaccination. As understanding of HIV pathogenesis has grown, additional scientific and logistical challenges have emerged. No clear correlate of immune protection has been identified, either in animal models where vaccine protection has been achieved or in studies of human cohorts at risk of infection. Because individuals at high risk for HIV infection are typically exposed many times over a period of years to multiple genetic variants of virus, it seems likely that successful vaccination will require a substantially longer and broader immune response than has been demonstrated in most animal models to date. The theoretical possibilities of vaccine-mediated enhancement or of misguided increases in risk-taking behavior among vaccine trial participants raise unusual degrees of concern. A number of social and ethical factors suggest that efficacy trials will be very difficult. Market forces do not foster a desirable level of private sector activity in vaccine research and development.

Despite these challenges, several factors contribute to a more optimistic outlook for HIV vaccine research and development today and set the stage for a number of important scientific opportunities.

- *Vaccine-induced protection is possible.* In 1989 a whole-killed SIV vaccine was shown to protect macaques from SIV infection, a finding which stimulated considerable enthusiasm for HIV vaccine research. Several years later, this result was largely discounted due to the presence of xenoantigens in the vaccine and challenge virus. More recent research with genetically and biologically attenuated strains of SIV, however, has demonstrated that long-lasting, broad protection from a highly virulent primate lentivirus can be achieved. Furthermore, vaccines that protect against several animal retroviruses have been licensed for veterinary use.

- *The immune system may be capable of complete control of HIV infection.* It is now well established that the initial immune response of the vast majority of infected individuals results in long-term but partial control of the disease. Animal model research has demonstrated that transient infection with highly pathogenic strains of SIV can occur in vaccinated animals. Evidence is also accumulating to suggest that transient infection may occur in some unvaccinated humans. Researchers are now investigating adults who have been repeatedly exposed to HIV but are not infected, as well as children born to HIV infected mothers who either remain uninfected or who are infected and subsequently appear to clear HIV. The goal of this research is to identify immune and other host factors and viral factors that can clear an incipient infection.

- *Mucosal transmission is relatively inefficient.* Reported rates of transmission of HIV across human mucosal surfaces have ranged between 0.001 and 0.03. Reproducible transmission of SIV across rectal mucosa in monkeys occurs only with amounts of virus at least 1,000-fold higher than that required for intravenous transmission.

- *Candidate HIV vaccines have proven safe and immunogenic.* NIAID initiated the first clinical trial of an HIV candidate vaccine in collaboration with MicroGeneSys, demonstrating interest and commitment on the part of government and the private sector to pursue vaccine research and development. To date, about 20 different candidates have been tested in human trials involving over 2,000 uninfected adult volunteers. Based on over 2,000 person years of follow-up in NIAID-supported trials, all candidate vaccines tested appear to be free of serious harmful side-effects. Concerns about vaccine-induced harmful immune responses have not been realized. Strong cellular and humoral immune responses, with memory, have been induced. More detailed summaries of these responses can be found elsewhere.

- *Efficacy trials among high-risk volunteers appear feasible.* Data from studies conducted in both the U.S. and in developing countries indicate that cohorts of people at high risk of HIV transmission through sexual or needle sharing behavior can be recruited and retained in follow-up. Furthermore, data from an anonymous survey of participants in a phase II preventive vaccine study indicate that, in the aggregate, volunteers do not increase their risk behavior and understand key aspects of trial design.

## THE GOAL

The ideal HIV vaccine will be safe, produce no serious side effects, and protect against chronic infection and/or disease upon subsequent exposure to all virus subtypes. This protection will be sustainable throughout the period of potential exposure to HIV, regardless of the route of exposure. In the long term, the vaccine will be inexpensive to manufacture and easy to store and administer anywhere in the world, including developing countries.
It must be noted that a less-than-ideal vaccine could have a substantial positive public health impact. Furthermore, it is very likely that progress toward the ultimate goal will occur in incremental steps in which vital lessons are learned from less-than-ideal vaccines.

## NIAID'S HIV VACCINE RESEARCH AND DEVELOPMENT STRATEGY

NIAID's strategy to identify a safe and effective HIV vaccine contains four elements:

I. Maintain a program of scientific inquiry that integrates fundamental research and empiric development to advance a broad front of critical knowledge and a variety of vaccine designs through laboratory, animal, and human research.

II. Develop more and better-defined partnerships between NIAID and industry sponsors of vaccine development.

III. Identify scientific opportunities that will accelerate HIV vaccine research and development and determine resource requirements to fully exploit them.

IV. Strengthen linkages with communities and other public or private organizations working in the field.

### I. MAINTAIN A PROGRAM OF SCIENTIFIC INQUIRY THAT INTEGRATES FUNDAMENTAL RESEARCH AND EMPIRIC DEVELOPMENT TO ADVANCE A BROAD FRONT OF CRITICAL KNOWLEDGE AND A VARIETY OF VACCINE DESIGNS THROUGH LABORATORY, ANIMAL, AND HUMAN RESEARCH.

There are many opinions on the best approach to identifying a safe and effective vaccine. At one extreme are those who favor basic research and the accumulation of much more fundamental knowledge before proceeding to large clinical trials. At the other are those who favor a more empiric approach of traditional vaccinology, arguing that products must be quickly evaluated in human efficacy trials to obtain the best information on how to improve vaccine designs. These points of view frame a much larger continuum of relevant scientific activity that is neither purely "fundamental" nor "empiric," and that contributes to the advancement of both approaches.

NIAID believes that success in identifying a safe and effective HIV vaccine will require progress across this continuum. Its program is, therefore, designed to capitalize on the most important and promising scientific opportunities regardless of their place in the fundamental-empiric spectrum. Priorities for allocating resources are based on this comprehensive view and implemented through flexible mechanisms that provide for the integration of fundamental research and empiric development. Acknowledging the limitations of the terminology, fundamental research will generate the knowledge needed to design and study promising vaccine concepts, and empiric development will characterize the clinical usefulness of those concepts and generate new insights of fundamental knowledge. NIAID's current program and its specific priorities and plans are described in detail in the NIAID HIV/AIDS Research Agenda.

Toward the fundamental end of the spectrum, NIAID's program is aimed at improving our understanding of HIV and related retroviruses and of immune responses to those viruses. In keeping with its traditional role, the Institute supports research to address a broad array of very basic questions about HIV pathogenesis, the host immune response to HIV, and the mechanisms by which HIV infection persists. In addition, NIAID supports more applied, obstacle-oriented research to identify the correlates of immune protection; develop animal models that more closely mimic HIV transmission, infection, and disease; evaluate novel antigen presentation methods, including new adjuvants; improve understanding of the role of mucosal immune responses to HIV; and, obtain a clearer understanding of the behavioral determinants of risk taking behavior and factors that correlate with willingness to participate in vaccine trials. NIAID relies predominantly, although not exclusively, on investigator-initiated grants to advance knowledge across this broad front of fundamental research. *In toto,* this knowledge forms the basis of most public and private sector efforts to identify promising vaccine designs.

Given the urgent need for a safe and effective HIV vaccine, the past successes of empiric vaccine development for other infectious diseases, and limited private sector involvement in the field, NIAID also supports considerable activity of a more empiric nature. This effort is intended to ensure that a number of promising vaccine designs are pursued in parallel. NIAID believes that this is important for two reasons. First, fundamental knowledge regarding optimal presentation of HIV antigens to the human immune system is presently insufficient to predict which approach will be successful. Second, most of the successful vaccines against viral diseases in current use are based on the whole-killed or the attenuated virus concept. Furthermore, the most successful design in the SIV-macaque model (the model most closely resembling HIV disease in humans) has been live-attenuated SIV. The potential use of whole-killed or live-attenuated HIV in humans, however, raises complex technological and safety concerns. Advances in biotechnology have made it feasible to design less problematic, novel vaccine prototypes, including recombinant proteins, viral and bacterial vectors, virus-like particles, synthetic peptides, and nucleic acid immunogens. These, as well as the more classical vaccine designs, are in NIAID-supported preclinical, animal model, and human trials. These studies are also designed to maximize the potential contribution to fundamental research.

## II. DEVELOP MORE AND BETTER PARTNERSHIPS BETWEEN NIAID AND INDUSTRY SPONSORS OF VACCINE DEVELOPMENT.

NIAID believes that private-public sector partnership and a vigorous level of industrial activity are pivotal to progress in this field. The Institute is, therefore, placing considerable effort on strengthening ties between the two sectors. A number of the Institute's activities, which are intended to serve the general scientific community, have particular relevance to needs of the private sector. The cornerstone, of course, is NIAID's commitment to and support of fundamental research, which leads to information that will diminish, or at least clarify, the scientific risks involved in HIV vaccine development, and facilitate the design of prototype vaccines. Second, NIAID develops and provides viral challenge stocks, important reagents, and access to animal models for evaluating novel designs and delivery methods (including adjuvants) to the scientific community. Third, in collaboration with the World Health Organization and United Nations AIDS Program (WHO/UNAIDS) and other international organizations, NIAID has established a global, basic, and clinical research network that includes specimen repositories, viral characterization laboratories, and multidisciplinary clinical research sites. Fourth, NIAID has established vital links with various communities of potential trial participants by involving representatives in all phases of trial design, implementation, and analysis. Fifth, the Institute has implemented research to address questions related to behavior, attitudes, counselling, informed consent, recruitment, and retention, all of which will play a key role in the ultimate success of efficacy trials and in building productive research-community partnerships. Sixth, NIAID-funded researchers and staff have developed alternative designs for efficacy trials that will expedite "proof of concept" efficacy trials to identify vaccine designs that have a promising level of efficacy.

### Industry-NIAID development plans

In order to implement its overall strategy of evaluating a variety of possible vaccine designs, NIAID must establish collaborative partnerships with private sector sponsors that have vaccine products in development. These partnerships must, in turn, also contribute to industry's goals by facilitating progress toward product licensure. Recognizing industry's need for precise planning in the face of this field's substantial scientific and economic uncertainty, NIAID has recently begun formulating joint development plans with its partners. These plans, negotiated between industry sponsors and NIAID, are specifically intended to encourage private sector collaboration with the Institute. They outline the laboratory, animal model, and human research and development path that will lead to a clinical trial designed to determine whether the specific vaccine design affords protection from HIV. They define each partner's responsibilities in areas where private sector and NIAID interests and priorities coincide. (Ideally, activities directed specifically toward licensure will be carried out with substantial private sector support, while NIAID resources will be directed toward test-of-concept and related fundamental research. These plans will not, of course, preclude other research independently supported by the company.)

The plans will contain the **concept-specific milestones, options, and decision-making criteria** to be applied at each major decision point. These milestones and criteria will be individualized, based on the general considerations outlined in the next section, the specific vaccine design in question, and the best available scientific information at the time they are determined. They will, of course, be evaluated and assessed by the partnership on an ongoing basis for their continued validity and usefulness. The plan, with its milestones and criteria, implies a commitment of resources and energy on the part of the collaborators to proceed accordingly, barring new important scientific information, opportunities, or unforeseen business/fiscal considerations on the part of either partner.

**General Considerations on Developmental Milestones and Criteria - NIAID Perspective**

Earlier attempts to define and utilize generic decision-making criteria applicable to all potential vaccine designs and circumstances proved extremely frustrating to investigators, vaccine manufacturers, and NIAID. The following discussion, therefore, outlines general principles of NIAID's current approach to the negotiation of the more specific criteria to be contained in these development plans.

- **Animal Models**: While animal model evaluations may provide an indication of clinical efficacy of a candidate vaccine, there is currently no ideal model of HIV disease in animals and, thus, no ideal or standard animal model experiment. The specific animal model experiments and the criteria of safety and efficacy needed to advance a given candidate at various stages of its development will, therefore, require careful consideration, planning, and agreement. They should, however, be based on consideration of the likely mechanism(s) of action, safety and immunogenicity data from earlier studies, and other relevant considerations. Specific details in this regard will be an important component of each prospectively negotiated development plan.

- **Phase I**: Phase I testing provides a first opportunity to explore the normal volunteer's immune response to HIV antigens presented in the particular vaccine design. In general, NIAID is most interested in working with partners to initiate phase I studies of promising examples (candidates) of vaccine designs that have not previously been evaluated. There should be a plausible scientific rationale supported by basic and preclinical research, as well as evidence that the vaccine candidate is safe in small animals and, usually, nonhuman primates. (NIAID maintains limited resources to assist in generating these data.)

- **Phase II**: Phase II trials, which enroll a larger number of individuals (including some with a history of high-risk behavior) will provide additional information on safety and immunogenicity in persons similar to those who will be entered into efficacy trials and who, presumably, would use the licensed vaccine. The development plan will outline the specific criteria of immunogenicity and safety, which must be met in phase I trials in order to proceed into phase II.

- **Determination of Efficacy**: The decision to proceed to a clinical trial of efficacy determination is a major one. The development plan will define specific criteria of efficacy and safety data from phase II and animal model experiments that must be met in order to proceed to further studies of efficacy. These criteria will be design-specific and will have been developed **by the partnership** in the course of earlier studies on the basis of the accumulated experience with the particular candidate. The criteria and modifications to them will be as objective and as specific as possible, may specify various contingencies depending on outcome, and will be agreeable to the partnership.

  The development plan will also describe the scientific and logistical plans for potential efficacy trial(s), including the degree of certainty with which efficacy would be measured. The proposed trial(s) may provide a relatively precise measure of efficacy or, alternatively, may be designed to estimate the vaccine's effect within a broader range (e.g., a so-called intermediate or test-of-concept trial). While the latter approach may not necessarily lead to licensure of a specific vaccine product, it may be appropriate for the accumulation of preliminary data about the usefulness of the vaccine design and its worthiness for additional development. Furthermore, the fundamental knowledge gained from such trials will be important in making incremental progress toward the ultimate goal. The development plan may also specify several contingency options, depending on the outcome of phase II trials.

## III. IDENTIFY SCIENTIFIC OPPORTUNITIES THAT WILL ACCELERATE HIV VACCINE RESEARCH AND DEVELOPMENT AND DETERMINE RESOURCE REQUIREMENTS TO FULLY EXPLOIT THEM.

NIAID believes that HIV vaccine research and development should be specifically identified as the highest AIDS-related biomedical research priority of the NIH for the following reasons:

- *The worldwide need to develop an effective HIV vaccine is more urgent than ever.* There are approximately 20 million individuals infected with HIV and 4.5 million AIDS cases worldwide. The African epidemic has cost over $30 billion and the United Nations estimates that AIDS will reduce Africa's overall labor force by as much as 25 percent by the year 2010. At the current rate, the impact on the world wide economy is estimated to reach $514 billion by the year 2000, and, in a worst case scenario, will rob the world of 1.4 percent of its gross product.

- *Identification of a safe and effective HIV vaccine will result in both financial and health benefits to the people of the U.S.* It costs approximately $119,000 to care for each HIV-infected individual over his or her lifetime. The disease has already cost $75 billion, with $3 to $6 billion being spent on new HIV infections each year. Costs to life and health insurance industries were nearly $1.6 billion in 1994; claims since 1986 total an estimated $9.4 billion. Furthermore, it has been estimated that AIDS will have cost the U.S. economy $81 to $107 billion by the year 2000.

- *It is in the long range health interests of the U.S. to take a worldwide perspective on the need for an effective HIV vaccine.* The dynamics of the epidemic in several developing countries provide opportunities to expedite progress in HIV vaccine research and development. The knowledge gained from such studies will benefit the entire world. Furthermore, new strains of HIV have now been documented.

- *Market forces do not currently foster an adequate level of private sector activity in empiric research; an increased commitment by the NIH may help boost investor confidence.* Empiric research and development have traditionally been left to the private sector, which generally produces the products and contributes development expertise. In the case of HIV vaccines, however, the market forces that drive private sector investment decisions are not favorable. At the present time, private sector activity is skewed heavily toward smaller, less well-capitalized biotechnology companies that have insufficient resources to accomplish their goals. Most of the larger pharmaceutical companies are concentrating their efforts on potentially less risky and/or more profitable pursuits. Many companies involved in HIV vaccine research and development have either terminated their programs or cut back on their investment over the past 2 to 3 years. One international company with considerable experience in vaccine research and development maintains one of the world's largest and most active HIV vaccine programs with only substantial foreign government support.

- *There are a number of scientific opportunities beyond the limits of current resources that, if pursued, would significantly accelerate progress toward an HIV vaccine.*

  Basic and applied research

  Advances in a number of areas of fundamental research could greatly facilitate the design and evaluation of potential HIV vaccines. In particular, research on correlates of immune protection, animal models, mucosal immunity, and HIV diversity are of the highest priority. The following summarizes a more detailed accounting of the key research needs and gaps described in the NIAID HIV/AIDS Research Agenda.

  Correlates. There are currently several lines of research that could help identify the correlates of immune protection. Reports of adults and infants who have been exposed to HIV but are not infected have suggested that some individuals may be relatively resistant to HIV infection and/or have the capacity to clear the virus during the early stage of infection. A better system to identify and thoroughly evaluate exposed/uninfected individuals is needed. Recent reports of individuals in the earliest/acute stage of HIV infection have helped elucidate immune mechanisms that may play a role in the initial control of HIV infection. Most of these individuals have been identified because they experienced an acute viral syndrome. Methods to identify additional individuals in the acute stage, including those who do not experience symptoms, are needed. This should include the development of improved assays for

viral detection and seroconversion, more frequent screening of individuals at high risk for infection, and referral of newly infected individuals to laboratories and clinics that can evaluate them and determine the impact of early therapeutic intervention. In addition, elucidating important host factors, particularly immune responses that predict outcome, would greatly facilitate the conduct of vaccine efficacy trials.

Animal Models. Animal model research and the development of better animal models are two major areas of scientific opportunity. Additional work in animal models could expedite understanding of the correlates of immune protection. There is a pressing need for animal models that more accurately reflect human HIV disease and routes of exposure, particularly mucosal exposure, in order to improve the relevance of preclinical vaccine evaluation. Recent exciting data on pathogenic chimeric SHIV in monkeys and a report of HIV disease in a chimpanzee suggest that improved models can be developed. In addition, development of methods to obtain twin macaques could lead to extremely valuable experiments that define the immune correlates of protection from SIV infection/disease. Increased evaluation of promising vaccine candidates in standardized, comparative studies will facilitate advances in fundamental knowledge, as well as the selection of the most promising candidates for further study.

Mucosal Immunity. While most vaccine concepts have focused on induction of systemic immune responses, candidate vaccines capable of inducing mucosal responses are being explored in several laboratories. Additional research on the role of mucosal immunity in the control of HIV infection and methods to induce mucosal immunity are needed.

HIV Diversity. The genetic diversity of HIV is now well described and several laboratories are maintaining active surveillance in this country and in selected populations in other countries. Additional molecular characterization of HIV around the world would lead to a better understanding of the extent of genetic diversity. Equally important is accelerating research on the immunologic significance of this genetic diversity and the characterization of HIV serotypes. Research to identify common neutralizing antibodies and CTL epitopes should facilitate design of vaccines with broad protective ability. This can best be accomplished through improvement of humoral and cellular assays. In particular, improvements in standardization and quantification of CTL assays would facilitate study of the impact of genetic diversity on CTL activity.

Vaccine concept evaluation

There are also important opportunities to help ensure that innovative HIV vaccine approaches are pursued in preclinical and clinical evaluation in adequate number and in a timely manner.

The NIAID's AIDS Vaccine Evaluation Group is a comprehensive phase I/II clinical trials network. Most of what we know about existing vaccine candidates has come from work done by this group of outstanding investigators. The group's overall productivity and contributions to the field would be greatly augmented by the addition of a contract laboratory for performance of some routine immunologic and virologic assays needed to meet the milestones and timelines called for in the collaborative development plans. This would permit existing core and mucosal immunology laboratory investigators to expand research on innovative assays that require a centralized but creative academic research laboratory, and to devote greater attention to research dissecting human immune responses elicited by various vaccine approaches.

NIAID's Strategic Programs for Innovative Research on AIDS Treatment offers a model for innovative bench to clinic, multidisciplinary collaborations, which should be implemented to advance creative vaccine approaches. In these programs, groups of investigators would pursue iterative laboratory, animal model, and early clinical research on a particular novel vaccine design.

It is difficult for academic investigators to obtain funding for certain animal model, immunology, and toxicology studies needed to move a vaccine design from concept to early clinical product. Supplemental support for such work would help elicit greater private sector interest in and sponsorship of novel vaccine designs. Other important opportunities are discussed in the earlier section on animal models.

Finally, evaluation of vaccines to prevent perinatal transmission and pediatric AIDS offers opportunities to expedite the study of some promising approaches in humans and to develop more practical and cost-effective alternatives to zidovudine. To facilitate this research, NIAID has proposed the establishment of an international pediatric prevention trials network, which will require additional resources to implement.

Other opportunities

It would be desirable to attract more talented researchers, particularly immunologists, to the field of HIV vaccine research and development. Funding levels have not permitted the award of all high quality grant applications. Some more empiric vaccine research has been regarded as "too applied" within the current NIH system of peer review.

These problems would be helped by additional resources. Even within existing resources, however, progress could be made if HIV vaccine research and development were explicitly identified as the NIH's highest AIDS research priority. This would facilitate: 1) funding of more "pilot" or short-term/high-risk projects under a variety of administrative mechanisms of grant and contract supplementation; 2) use of set-aside funds targeted towards awarding high priority and high quality investigator-initiated

grants submitted in response to a broad vaccine-related program announcement; 3) changes in the emphasis of the NIH peer review system to place greater weight on programmatic relevance and applied research and development.

Finally, rapid mobilization of resources in response to pressing scientific need, implementation of new or expanded programs, facilitation of collaboration between researchers and across international borders, and provision of assistance, reagents, and other resources, could be greatly enhanced. This would best be accomplished through a master contractor that has science management expertise and the ability to quickly fund essential research under the direction of NIAID staff and as recommended by NIAID advisors.

## IV. STRENGTHEN LINKAGES WITH COMMUNITIES AND OTHER PUBLIC OR PRIVATE ORGANIZATIONS WORKING IN THE FIELD

Success in carrying out the research needed to reach the ultimate goal will require a partnership between scientists and the communities of individuals who are asked to participate in this research. Efforts are already underway to strengthen linkages with domestic and foreign communities of individuals at increased risk of infection and are described in some detail in the NIAID HIV/AIDS Research Agenda.

The likelihood of success will be increased by close coordination of NIH with private and public sector organizations that share its interest in HIV vaccine research and development. Both for-profit and non-profit organizations bring their own unique resources and skills to the overall endeavor. Like all public agencies, the NIH must (and should) operate under regulations and policies mandating peer review and competitive procurement. It is, as a matter of course, answerable to diverse constituencies that have conflicting visions of priorities and the government's role. Privately funded organizations, on the other hand, have fewer checks on spending, more sharply focused missions, and smaller and less diverse constituencies. They are, by definition and design, able to move more quickly, assume similar levels of risk more easily, and address certain pressing needs more rapidly. However, they lack the level, breadth, and stability of government/NIH resources. A more closely integrated effort, capitalizing upon the strengths of private and public efforts, could provide synergistic, complementary mechanisms of support and increase efficiency, productivity, and incentives for private sector investment in HIV vaccine development. The NIAID intends to devote considerable energy to strengthening collaborative interactions with other public and private organizations (e.g., the Department of Defense, the Agence Nationale de Reserches sur le SIDA, Medical Research Council, UNAIDS [United Nations AIDS Program], International AIDS Vaccine Initiative [Rockefeller Institute], the Sabin Foundation).

Finally, NIAID proposes changes in its mechanisms for obtaining independent advice and guidance. We believe that this effort should involve a small group of widely respected and committed individuals with extensive relevant laboratory and field experience. They will meet

regularly and will provide detailed guidance concerning NIAID's efforts, with special focus on those activities aimed at the empiric components of the Institute's program. The group will also have a key role in coordination beyond NIAID, where most efforts are directed to more empiric activities. This group will work with and/or through various other working groups of actively involved scientists and community representatives focused on more specific areas of basic or clinical research, such as the existing Vaccine Design Focus Group, the Correlates of Human Immune Protection Focus Group, the AIDS Vaccine Evaluation Group and HIV Vaccine Efficacy Trials Network (HIVNET) Executive Committees. In addition, the National Advisory Allergy and Infectious Diseases Council, and the AIDS Research Advisory Committee (ARAC) will continue to provide broad program oversight and advice, including review of concepts for new vaccine initiatives.

## CONCLUSION

The challenges confronting the identification of a safe and effective HIV vaccine are enormous. The NIAID believes that the optimal strategy to achieving this goal involves four components: 1) maintenance of a program of scientific inquiry that advances a broad front of critical knowledge and a variety of vaccine designs through laboratory, animal and human research, which integrates fundamental research and empiric development; 2) encouragement of pharmaceutical/biotechnology industry collaboration; 3) identification of scientific opportunities and the resources required to exploit them; and 4) strengthening of relationships with other public and private organizations and communities at risk.

National Institute of Allergy and Infectious Diseases

National Institutes of Health

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# HIV/AIDS Vaccine and Prevention Strategies: NIAID Resources for Research and Development

Developing safe and effective prevention strategies to curb the human and economic costs of the HIV/AIDS pandemic has become an international health priority. Toward this end, NIAID, which spearheads federal funding for biomedical research on HIV/AIDS for the National Institutes of Health (NIH), supports a broad-based HIV vaccine and prevention research program.

NIAID's Division of AIDS (DAIDS) directs this program. Institute staff meet regularly with scientific, public health and community advisors to review the priorities and operation of the program.

The program has two main thrusts:

- to foster basic research on the structure and function of HIV, vaccine formulations, vaccine delivery systems, laboratory studies of vaccine performance and microbicides, and

- to promptly evaluate promising candidate vaccines, microbicides and other intervention strategies in animal models and, if warranted, in humans.

Traditional investigator-initiated research forms the foundation for HIV/AIDS vaccine research. NIAID supports several special collaborative and interdisciplinary initiatives to accomplish specific research objectives.

- ***National Cooperative Vaccine Development Groups (NCVDGs)*** constitute the core of preclinical HIV vaccine design and evaluation efforts sponsored by NIAID. Teams of scientists from industry, academia and government collaborate to develop and test novel experimental HIV vaccine concepts in the laboratory and in animal models.

- The ***Cooperative Mucosal Immunology Group for Investigations on AIDS Vaccines*** supports research on methods to stimulate and evaluate mucosal immune responses to HIV and its monkey counterpart, simian immunodeficiency virus (SIV). Investigators use this information to design new vaccines that will protect against mucosal exposure to HIV.

- The ***Antibody Serologic Project*** identifies and standardizes panels of monoclonal antibodies to characterize the antigenic components of HIV and SIV. This collaborative project involves investigators from around the world.

- The ***HIV Variation Project*** examines the rates and magnitudes of genetic and immunologic changes in HIV and related retroviruses and their consequences for vaccine design. The project includes a laboratory that determines the genetic sequences of large

numbers of viral isolates (Genetic Variation Contract), a laboratory to assess the immunologic significance of genetic variation (Antigenic Variation Contract), and the **HIV Sequence Database and Analysis Unit** at the Los Alamos National Laboratory, which compiles and analyzes genomic sequences contributed by sequence laboratories. The HIV Variation Project is carried out in collaboration with the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO).

- ***Primate Research Laboratories*** answer HIV-vaccine-related questions by testing HIV and HIV-like vaccines in chimpanzees and monkeys. The **Simian Vaccine Evaluation Units (S-VEUs)** evaluate vaccine concepts in the macaque model and compare immunologic and protection data, permitting standardized and directly comparable evaluations of various vaccine candidates. Substantial effort is being made to develop the chimeric SIV-HIV (SHIV) model for use in challenge studies. The **Chimpanzee Unit**, operated through an interagency agreement with the National Cancer Institute, has been used to prepare chimpanzee stocks and to evaluate candidate vaccine concepts and products in chimpanzees. The **Immunology Laboratory Support for Assessment of AIDS Vaccines in Primates** (which includes several contracts) develops, standardizes and performs cellular and serologic immune assays to assess responses to SIV and HIV vaccines in the S-VEUs, and is also available to NCVDG laboratories. This permits the direct comparison of candidate vaccines evaluated in independent laboratories and facilitates selection of the most promising vaccine designs.

- The ***Reagent/Resource AIDS Vaccine Project*** acquires or produces biological and chemical substances for comparative immunologic analyses, preclinical vaccine development, adjuvant development and standardized immunologic assessments of clinical samples from volunteers in vaccine trials.

- The ***Master Agreement for Preclinical HIV Vaccine Development*** provides flexible resources for the preclinical evaluation of the most promising HIV vaccine candidates. These resources include preclinical evaluation of vaccines in nonhuman primates, vaccine production and the development of reagents for preclinical and clinical vaccine studies.

- The ***AIDS Vaccine Evaluation Group (AVEG)*** conducts **Phase I** and **Phase II** trials in humans to evaluate the safety of and immune responses stimulated by experimental HIV vaccines. AVEG includes the following:

  - A **Vaccine Selection Group** independently evaluates the rationale and preclinical safety and immunogenicity data of candidate vaccines prior to their study in AVEG trials.

  - Six **AIDS Vaccine Evaluation Units (AVEUs)**, located at research centers throughout the United States, conduct Phase I and II clinical trials of candidate HIV vaccines in volunteers who are not infected with HIV.

  - A **Central Immunology Laboratory** provides state-of-the-art evaluation of antibody and cellular immune responses of vaccinated volunteers in AVEG trials. Laboratory scientists evaluate samples from the AVEUs using standardized assays, permitting the comparison of responses in volunteers who receive different candidate vaccines at different AVEUs.

- A **Mucosal Immunology Laboratory** evaluates human mucosal immune responses to candidate vaccines in standardized assays, permitting the comparison of responses in volunteers who receive different candidate vaccines at different AVEUs.

- A **Data Coordinating and Analysis Center** provides a central facility for collecting and analyzing data from the trials conducted by the AVEUs.

- A **Data and Safety Monitoring Board** periodically reviews data from AVEG studies.

## Planning for Efficacy Trials

NIAID is laying the groundwork for large-scale Phase III efficacy trials of candidate HIV vaccines and other prevention strategies to ensure that such trials begin promptly once suitable candidates are identified.

To assess the feasibility of conducting vaccine trials in the United States, NIAID initially provided supplemental funds to help support ongoing studies sponsored by the Centers for Disease Control and Prevention and the National Institute on Drug Abuse, and to other investigators working with populations at high risk of HIV infection.

To determine the feasibility of and develop the capability for conducting such trials abroad, NIAID in 1992 awarded eight two-year ***Preparation for AIDS/HIV Vaccine Evaluations (PAVE)*** grants to U.S. researchers and their international collaborators.

In 1993 the NIAID unified and extended these efforts by establishing the ***HIV Network for Prevention Trials (HIVNET)***. HIVNET is charged with preparing for and conducting large-scale, randomized, controlled trials to evaluate the efficacy of vaccines and other strategies to prevent sexual, parenteral and perinatal transmission of HIV. In addition, HIVNET provides a unique opportunity to study the epidemiology of HIV transmission in different populations, and to examine the natural history and pathogenesis of early HIV infection and disease. HIVNET consists of five contracts:

- A **domestic master contractor** subcontracts with clinical sites to conduct activities in preparation for efficacy trials. These sites will evaluate the efficacy of HIV vaccines and other prevention strategies in U.S. populations once suitable candidates are identified.

- An **international master contractor** subcontracts with clinical sites to prepare for efficacy trials and to evaluate prevention strategies in international populations.

- A **statistical and data coordinating center** provides statistical and data management support for the domestic and international trials.

- A **central laboratory** provides quality assurance and specialized testing for the domestic and international trials, and preparatory research trials.

- A **specimen repository** collects, stores and distributes samples from the domestic and international clinical sites.

HIVNET investigators are collecting baseline data on virus strains being transmitted, rates of new HIV infections and the prevalence of other sexually transmitted diseases and other potential cofactors of HIV transmission from various populations at high risk for HIV infection. They also are collecting data on the willingness of high-risk individuals to enroll in vaccine trials.

Several of the HIVNET sites are conducting randomized controlled trials of various methods to prevent sexual and perinatal HIV infection. These interventions include microbicides to prevent sexual transmission, and antiretroviral drugs and HIV immune globulin to prevent perinatal transmission. Behavioral interventions also are being evaluated.

Institute staff assist public health and government officials, community members, scientists and others affiliated with potential trial sites to resolve legal, practical and ethical issues involved in planning for vaccine efficacy trials. These concerns include vaccine cost and delivery, liability issues, training of medical personnel and conduct of trials at potential overseas sites.

NIAID, a component of the National Institutes of Health (NIH), supports research on AIDS, tuberculosis and other infectious diseases, as well as allergies and immunology. NIH is an agency of the U.S. Department of Health and Human Services.

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# Clinical Research on HIV/AIDS Vaccines

The National Institute of Allergy and Infectious Diseases (NIAID) conducts clinical trials of candidate vaccines to discover which might most successfully protect people from human immunodeficiency virus (HIV) infection (**preventive vaccine**) or from becoming ill after they acquire the virus (**therapeutic vaccine**). (Throughout this fact sheet scientific terms common to vaccine research have been printed in **bold-faced** type and defined.)

Scientists have identified important immunologic targets on HIV and on infected cells. For example, they know that the glycoprotein 120 (gp120) on the outer coat of the virus contains the region that attaches to cells of the host, the **CD4 binding site**. Scientists also know that most **neutralizing antibodies** (proteins that block a virus from infecting cells) in HIV-infected people are directed against gp120. For these reasons, vaccines based on genetically engineered HIV **envelope proteins**--gp160 and one of its cleavage products, gp120--have been the most well-studied to date.

More than 40 experimental HIV vaccines have been tested in humans worldwide. Vaccine approaches in development or in clinical trials include the following:

- ***subunit vaccine***: a piece of the outer surface of HIV, such as gp160 or gp120, produced by genetic engineering.

- ***recombinant vector vaccine***: a live bacterium or virus such as vaccinia (used in the smallpox vaccine) modified to transport into the body a gene that makes one or more HIV proteins.

- ***vaccine combination***: for example, use of a recombinant vector vaccine to induce cellular immune responses followed by booster shots of a subunit vaccine to stimulate antibody production, referred to as a **prime-boost strategy**.

- ***peptide vaccine***: chemically synthesized pieces of HIV proteins (peptides) known to stimulate HIV-specific immunity.

- ***virus-like particle vaccine (pseudovirion vaccine)***: a non-infectious HIV look-alike that has one or more, but not all, HIV proteins.

- ***anti-idiotype vaccine***: antibodies generated against antibodies to the virus.

- ***plasmid DNA vaccine (nucleic acid vaccine)***: direct injection of genes coding for HIV proteins.

- ***whole-inactivated virus vaccine***: HIV that has been inactivated by chemicals, irradiation or other means so it is not infectious.

- ***live-attenuated virus vaccine***: live HIV from which one or more apparent disease-promoting genes of the virus have been deleted.

## Clinical Trials Background

After an experimental vaccine performs well in preclinical safety and immunogenicity tests, it must successfully complete three stages of testing in people before development into a licensed product.

A **Phase I** trial is the first setting in which an experimental HIV vaccine is given to people. Such a trial enrolls about 20 to 80 non-HIV-infected volunteers at apparent low risk of HIV infection. A Phase I trial primarily seeks information on safety, usually assessing any vaccine-related side effects by comparing the vaccine with an inactive **placebo** or **control** that looks like the test product. A Phase I trial also can provide data on the vaccine's immunogenicity, including the dose and administration schedule required to achieve optimal immune responses. If the vaccine elicits neutralizing antibodies, scientists can study how these react against HIV strains from the same or other clades to determine the potential breadth of protection. A Phase I trial may last one to two years.

Once Phase I trials show that the experimental HIV vaccine is well-tolerated, it can advance into **Phase II** trials. These trials enroll more people, up to a few hundred, and often include some volunteers at higher risk for acquiring HIV. Researchers gather data about safety and immune responses, asking more sophisticated questions that such larger trials allow. Optimally, the trials are **randomized** and **double-blind**, meaning that volunteers are assigned at random to a study group and that neither the health care workers nor the patients know what preparations the patients receive. Phase II trials usually last one to two years.

The most promising candidate vaccines move into **Phase III** or **efficacy** trials, enrolling large numbers of non-HIV-infected people at high risk for exposure to the virus. A Phase III trial usually is designed to ensure the collection of enough data on safety and effectiveness to support a license application, if warranted. The vaccine may be tested against a placebo or a vaccine such as hepatitis B of known potential benefit to the study population. An efficacy trial can involve thousands of volunteers and therefore takes much longer, at least four years, to complete.

## Clinical Trials of Preventive Vaccines

In August 1987, NIAID opened the first clinical trial of an experimental HIV vaccine at the NIH Clinical Center in Bethesda, Md. This safety trial eventually enrolled 138 non-infected healthy volunteers. The gp160 subunit candidate vaccine tested caused no serious adverse effects.

Since the first trial, more than 40 preventive HIV vaccine trials have been initiated worldwide. These Phase I/II trials examine the vaccine's safety and provide preliminary information on its ability to stimulate immune responses.

The NIAID ***AIDS Vaccine Evaluation Group (AVEG)*** is the largest U.S. cooperative HIV vaccine clinical trials group. The AVEG, which began enrolling volunteers in February 1988, includes the following:

- The ***AIDS Vaccine Evaluation Units (AVEUs)***, located at six U.S. research centers, conduct phase I and II clinical trials of candidate HIV vaccines in low-risk and high-risk HIV-seronegative volunteers.

- The ***Central Immunology Laboratory*** provides state-of-the-art evaluation of humoral and cellular immune responses of vaccinees in AVEG trials. The evaluations use standardized tests, permitting comparison of responses in different individuals and to different candidate vaccines.

- The ***Data Coordinating and Analysis Center*** provides a central facility for collecting and analyzing data from the trials conducted by the AVEUs.

- The ***Immunology Laboratory Support for Assessment of Mucosal Immune Responses Induced by AIDS Vaccines*** evaluates human mucosal immune responses to candidate vaccines in standardized tests, permitting the comparison of responses in volunteers at different AVEUs and in volunteers who receive different candidate vaccines.

- The ***Specimen Repository*** collects and maintains blood samples and other specimens from volunteers in AVEG trials for use in current and future studies.

- A ***Data and Safety Monitoring Board*** periodically reviews data from AVEG studies.

As of January 1997, more than 2,000 men and women have participated in preventive HIV vaccine trials conducted at six medical center AVEU sites located in Baltimore, Nashville, Seattle, St. Louis, Birmingham and Rochester, N.Y.

To date, all the vaccine candidates tested have been well-tolerated, generally producing only mild side effects typical of most vaccines. The first candidates tested stimulated production of antibodies, although levels decreased within a relatively short period of time. Initial formulations and dosages of these vaccines produced few or low levels of neutralizing antibodies and rarely elicited **cytotoxic T cells**, which are invoked through cell-mediated immunity to kill HIV-infected cells.

With newer protocols, using increased vaccine dosages, different immunization schedules, experimental adjuvants and new recombinant proteins, more promising data regarding the induction of neutralizing antibodies and cytotoxic T cells have emerged.

In December 1992, NIAID launched the first Phase II HIV vaccine clinical trial. Earlier trials enrolled noninfected people at low risk of HIV infection and primarily sought data on safety. This trial includes noninfected volunteers with a history of high-risk behavior--injection drug use, multiple sex partners or sexually transmitted diseases. Participants are counseled repeatedly to avoid any behavior that puts them at risk of HIV infection. Follow-up for this trial has been extended to four years.

The trial will help determine if these distinct populations, representative of people likely to be enrolled in large-scale efficacy trials, respond differently to vaccines. The trial also will provide more detailed data on the safety and ability of vaccines to stimulate immune responses.

A second Phase II HIV vaccine clinical trial is now under way at AVEU sites and in the HIV Network for Prevention Trials (HIVNET).

Experimental HIV vaccines are growing in number and kind. Clinical trials will yield valuable information about the relative effects on immune response of different formulations and delivery methods.

## Future Directions

Although the challenges are daunting, scientists remain optimistic that safe and effective HIV vaccines can be developed. Novel ways to present HIV proteins to the immune system continue to be designed and tested, as do new antigen/adjuvant vaccine formulations. A growing number and variety of experimental vaccines are entering clinical tests in primates and humans, and more trials are exploring whether changing immunization schedules, increasing booster doses or using a combination vaccine strategy can stimulate stronger, more durable immune responses. Together, progress in basic and clinical research is moving scientists closer toward identifying products suitable for large-scale HIV vaccine efficacy trials.

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# Challenges in Designing HIV Vaccines

Designing an effective vaccine to protect people from infection with the human immunodeficiency virus (HIV) or from becoming ill if already exposed to the virus is a high priority of worldwide efforts to control the epidemic.

The ideal HIV vaccine would be inexpensive, easy to store and administer and would elicit strong, appropriate immune responses that confer long-lasting protection against both bloodborne and mucosal (sexual) exposure to many HIV subtypes. The following describes why this ideal has not been easily achieved.

(Throughout the fact sheet scientific terms common to vaccine research have been printed in **bold-faced** type and defined.)

## What Constitutes Immune Protection?

Researchers face unprecedented scientific challenges in trying to develop vaccines for HIV. The easiest way to design an effective vaccine is to know what immune responses protect against the specific infection and construct a vaccine that stimulates those responses. Although scientists have found clues about these so-called **correlates of immunity** or **correlates of protection** for HIV, these factors have not been precisely identified.

Unlike other viral diseases for which successful vaccines have been made, complete recovery from HIV infection has not been documented. Therefore, HIV vaccine researchers have no human model of protection to guide them. *Indeed, whether a natural protective state against HIV can exist remains unknown.*

However, now that the pandemic has matured, **long-term survivors**--those who remain clinically asymptomatic and maintain a CD4+ T cell count greater than 200 for at least 10 years following infection--provide ample evidence that some people appear better able than others to resist progression of HIV infection or the development of AIDS. Long-term survivors can be divided into two groups: (1) **long-term nonprogressors**, those who maintain healthy or steady levels of CD4+ T cells despite many years of infection, and (2) HIV-infected individuals who lose a significant proportion of CD4+ T cells but still remain healthy.

Recent attention also has been directed to those people who remain uninfected despite repeated exposure to HIV. If these **multiply exposed but uninfected individuals** can be proven to have resisted HIV by an active immune mechanism, they would represent the *natural protective state* upon which a vaccine could be modeled.

Another clue to why some people resist HIV infection has come from studies of recently identified co-receptors for HIV. Scientists have found that individuals who have inherited two copies of a mutated gene coding for one of these co-receptors, CCKR5, appear to be protected from HIV infection. This suggests that a single targeted intervention may be capable of preventing HIV infection.

To determine the factors that influence the body's response to HIV exposure and infection, investigators are comparing long-term HIV survivors with people who quickly became infected or sick. Leading areas of research include genetics, individual variations in the immune response and exposure to or infection by less deadly HIV variants. Such studies will help clarify what contributes to protective immunity against HIV.

## Immune Responses

The ability to stimulate immune responses is called **immunogenicity**. Two main types of immunity exist: humoral immunity and cellular immunity. **Humoral (antibody-mediated) immunity** refers to protection provided by the secreted products of one type of white blood cell called a **B lymphocyte**. These products, custom-made proteins known as **antibodies**, circulate in body fluids, primarily blood and lymph. B lymphocytes (**B cells**) produce antibodies in response to a specific foreign invader like HIV or a vaccine.

Several different antibodies can be generated. So-called **binding antibodies** simply attach to part of HIV and may or may not have antiviral effects. **Functional antibodies** are binding antibodies that actually do something more. For example--**neutralizing antibodies**--inactivate HIV or prevent it from infecting cells.

Scientists have identified the outer envelope of HIV as important for stimulating neutralizing antibodies. A major protein, **gp120** (glycoprotein 120), is found on the surface or **envelope** of HIV. Together with its parent protein **gp160**, gp120 forms the basis of many **recombinant subunit vaccines,** so-called because each is genetically engineered to contain only one small piece of the virus.

The second type of immunity, **cellular (cell-mediated) immunity**, refers to activities of **T lymphocytes**. **Cytotoxic T lymphocytes (CTLs)**, nicknamed **killer T cells,** directly destroy HIV-infected cells. A subset called **CD8+ CTLs (CD8+ T cells)** bear **CD8 receptors** on their surfaces and kill cells that are producing HIV. Other CD8+ T cells can suppress HIV replication without necessarily killing the infected cell. CD8+ T cells may be critical to resisting HIV infection.

**Regulatory T cells**, another component of cellular immunity, direct antibody- and cell-mediated immune responses, like a conductor leading a symphony orchestra. The chief regulatory T cell, the **helper T cell**, also is HIV's main target. The virus attaches to the cell through a **receptor** on the cell's surface called **CD4**. Hence, helper T cells are called **CD4+ T cells**.

A subset of helper T cells, **memory T cells**, are evoked on first exposure to an invading organism. The name "memory" reflects their function, which is to create a criminal record file

on that virus or microorganism. If the virus enters the body again, memory T cells will quickly stir the immune system into action. The most common way to measure memory T cells is by a test called the **T lymphocyte proliferation assay**, which indicates the strength of such cellular responses to HIV.

To be effective, an HIV vaccine may have to stimulate a third type of immunity, **mucosal immunity**. Immune cells lining the mucous membranes of the genital tract and other HIV portals into the body produce different responses that are not well understood.

## HIV Strain Variation

*HIV continually evolves as a result of genetic mutation and recombination.* Thus, researchers must estimate the significance of **strain variation** within individuals and among populations when developing AIDS vaccines. Usually a person does not appear to be infected with more than one HIV **variant**. But once HIV infection becomes established, the virus continually undergoes changes, and many variants may arise within an infected person.

Whenever a drug or immune response destroys one variant, a distinct but related one can emerge. Also, certain variants may thrive in specific tissues or become dominant in an individual because they replicate faster than others. Any of these changes may yield a virus that can escape immune detection.

The envelope and core genes of many HIV **isolates**, the viruses taken from patients, have been analyzed and compared. On this basis, scientists have grouped HIV isolates worldwide into two groups, M and O. At least nine **subtypes** or **clades** have been identified in group M, and only a few in group O. Each subtype within a group is about 30 percent different from any of the others. In contrast, successful vaccines for other viruses have only had to protect against one or a limited number of virus strains.

The first AIDS vaccines made were based on the **LAI** strain (also known as **IIIB** and **LAV**). Subsequently, LAI has been shown to differ from most strains found in infected people. Newer vaccines have been based on the **SF-2** and **MN** isolates, which belong to the same subtype as LAI but better represent HIV strains isolated from North Americans and Europeans.

*A preventive vaccine will need to generate immune responses that protect uninfected individuals from all the different HIV subtypes to which they may be exposed.*

Scientists are looking for **conserved regions** of HIV genes, those that produce proteins common to all or most subtypes. If such common proteins are not found, a cocktail vaccine comprising several proteins or peptides from different HIV strains may be necessary to invoke broad-based immunity.

## HIV Transmission is Complex

Unlike some other viruses, *HIV can be transmitted and can exist in the body not only as free virus but also within infected cells.* Thus, a vaccine against HIV may be required to stimulate the

two main types of immunity. Humoral immunity uses antibodies to defend against free virus. Cellular immunity directly or indirectly results in the killing of infected cells by immune cells. A major unanswered question is how important each type of immunity is for protection from HIV. Data from animal models and long-term HIV survivors, and human clinical trials of experimental HIV vaccines, may offer clues to the answer.

Another factor complicates the attempt to define HIV protection. According to WHO, 80 percent of all HIV transmission worldwide occurs sexually. *Thus, to be effective, an HIV vaccine also may need to stimulate mucosal immunity.* Mucosal immune cells that line the respiratory, digestive and reproductive tracts and those found in nearby lymph nodes are the first line of defense against infectious organisms. Unfortunately, relatively little is known about how the mucosal immune system protects against viral infection.

## Immune System Breakdown

Perhaps the most difficult challenge for vaccine researchers is that *the major target of HIV is the immune system itself.* HIV infects the key CD4+ T cells that regulate the immune response, modifying or destroying their ability to function.

After infection, HIV incorporates its genetic material into that of the host cell. If the cell reproduces itself, each new cell also contains the HIV genes. There the virus can hide its genetic material for prolonged periods of time until the cell is activated and makes new viruses. Other cells act as HIV reservoirs, harboring intact viruses that may remain undetected by the immune system.

Understanding how HIV disease evolves, especially during early infection, is a high priority for the Institute. Scientists at NIAID and elsewhere have shown that no true period of biological latency exists in HIV infection. After entering the body, the virus rapidly disseminates, homing to the lymph nodes and related organs where it replicates and accumulates in large quantities. Paradoxically, the filtering system in these lymphoid organs, so effective at trapping pathogens and initiating an immune response, may help destroy the immune system: HIV infects the steady stream of CD4+ T cells that travel to the lymph organs in response to HIV infection.

Basic research in immunology, epidemiology studies of long-term survivors, and vaccine trials in animal models and humans all contribute to a greater understanding of the immune system breakdown and ways vaccines may be designed to prevent or slow down the progress of HIV disease.

## Adjuvants, Other Immune Enhancers

Because of safety concerns, most candidate HIV/AIDS vaccines use one or more proteins of HIV, not the whole infectious virus. These *new generation vaccines contain no intact live virus and thus stimulate less potent immune responses than traditional vaccines* made from whole viruses that have been inactivated or **attenuated** (weakened).

To augment the immune responses elicited by these and other vaccines, scientists use immunologic **adjuvants**, which can increase the type, strength and durability of immune responses evoked by a vaccine. Some vaccine antigen/adjuvant combinations can induce cell-mediated immune responses in animals, even if the vaccine antigen by itself does not. Some adjuvants also stimulate mucosal immunity.

Currently, only one adjuvant--**alum**, first discovered in 1926--is incorporated into vaccines licensed for human use by the U.S. Food and Drug Administration (FDA). An adjuvant may work well with one experimental vaccine but not another. Therefore, the FDA licenses the vaccine formulation, or the antigen-adjuvant combination, rather than the adjuvant alone. Alum primarily increases the strength of antibody responses generated by the vaccine **antigen**. Because of alum's limited activity, other adjuvants now being evaluated in animal models and human studies may be better suited for the newer candidate HIV vaccines.

A different way to enhance immune responses to HIV is the **prime-boost** vaccine strategy. Researchers first prepare or prime the immune systems of volunteers with a **live vector vaccine**, a bacterium or virus that has been genetically engineered to contain a gene for an HIV protein such as gp160 but that cannot infect the person with HIV or cause disease.

The best studied vector is **vaccinia virus**, formerly used to immunize against smallpox. Vaccinia carries the foreign HIV gene into the body. There, the vaccine directs cells to make the HIV protein that the body perceives as foreign, stimulating production of protective antibodies. Later, the volunteers receive booster shots of a different vaccine made from the same HIV protein.

By itself, a gp160-containing vaccinia virus vaccine stimulates production of memory T cells but few antibodies. The prime-boost combination, however, can stimulate a strong cellular immune response--including persistent killer CD8+ T cells--as well as antibodies that neutralize the virus or inhibit formation of **syncytia**, giant cells formed when HIV-infected cells fuse with cells that are not infected.

Because of concerns that a vaccinia-based vaccine might cause serious vaccinia infection in some people with compromised immune systems, such as people with HIV who have not been exposed to either smallpox or the vaccine, other vector vaccines are being developed and evaluated.

Several experimental vector vaccines made from a **canarypox virus**, which closely resembles vaccinia, are in clinical trials. Canarypox virus infects but does not reproduce in human cells and therefore should be much safer. Another example of a vector under development for HIV vaccines is *Salmonella*, bacteria that infect the human gut.

**Plasmid DNA vaccines**, direct injections of genes coding for HIV proteins, are a recent innovation that have shown good ability to induce cellular immune responses. When the DNA is

injected, the encoded viral proteins, e.g., HIV gp160, are produced, just as with live vectors. The potential of this vaccine concept is actively being pursued.

## Animal Model Studies

Animal model studies can answer critical questions that cannot be answered either in humans, because of undue risk, or by using computer modeling or laboratory tests. For example, animals can be inoculated with an experimental vaccine and then challenged with virus to test the vaccine's effectiveness--a study that would be unethical to conduct in humans. However, *AIDS researchers lack an ideal animal model.*

Although chimpanzees can be infected with HIV, only one chimpanzee has been observed to develop disease, making it difficult to extrapolate findings to humans. Moreover, chimpanzees are an endangered species and both difficult and expensive to maintain.

Most non-human primate AIDS research is conducted with macaque monkeys. They can be infected with SIV, a retrovirus similar to HIV that causes an AIDS-like disease. The genetic and physical structures of SIV differ enough from those of HIV, however, that the results of SIV experiments may not wholly apply to humans.

Nonetheless, important information has been obtained from both monkeys and chimpanzees. Experiments in both species have demonstrated the feasibility of developing a protective vaccine. Moreover, a new animal model--infection of macaques with a **chimeric virus (SHIV)** based on SIV but including the HIV envelope, with subsequent development of disease--may become extremely valuable for evaluating candidate HIV vaccines.

In late 1992, NIAID-funded investigators first reported results from their experiments with a live-attenuated SIV vaccine made by deleting the SIV *nef* gene. The vaccine demonstrated durable protection against high intravenous doses of a lethal SIV strain different from that used in the vaccine. These findings provide hope that safe and effective human HIV vaccines can be developed. Optimism for the live-attenuated approach itself, however, is tempered by concerns about its safety.

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# HIV Prevention Efficacy Trials

The National Institute of Allergy and Infectious Diseases (NIAID) is committed to developing and testing experimental vaccines and other interventions to prevent the transmission of HIV infection and disease progression.

To this end, NIAID established the **HIV Network for Prevention Trials (HIVNET)** in 1993 to conduct efficacy trials of promising HIV prevention strategies in both the United States and abroad.

HIVNET is a cooperative group of investigators who primarily evaluate the safety and efficacy of interventions to prevent the sexual, perinatal and parenteral transmission of HIV. HIVNET's main area of emphasis is vaccines but it also encompasses other interventions: topical microbicides, sexually transmitted disease (STD) treatment, prophylaxis to prevent mother-to-infant transmission and behavioral risk reduction strategies. To accomplish its main mission, HIVNET supports randomized, controlled clinical trials that use HIV seroincidence as the primary endpoint. HIVNET also conducts a range of other studies, such as baseline seroincidence surveys, that lead to or support prevention efficacy trials.

HIVNET has five parts:

- A **domestic master contractor,** awarded in October 1993 to ABT Associates of Cambridge, Mass. In September 1994, ABT awarded subcontracts to **eight field sites** to evaluate candidate interventions in U.S. populations.

- An **international master contractor,** awarded in October 1993 to Family Health International (FHI) of Research Triangle Park, N.C. In September 1994, FHI subcontracted with **nine field sites** to conduct trials in populations outside the United States.

- A **statistical and data coordinating center** provides statistical and data management support for the domestic and international trials. NIAID awarded this contract in March 1994 jointly to the Fred Hutchinson Cancer Research Center and the University of Washington.

- A **central laboratory contractor** provides laboratory support for specialized testing of populations in the domestic and international trials. NIAID awarded this contract in March 1994 to Public Health Enterprises of Los Angeles, Calif., with the California State Health Laboratory in Berkeley as a subcontractor.

- A **specimen repository** serves the domestic and international trials. NIAID renewed this contract with Biomedical Research, Inc., of Rockville, Md., in June 1994.

HIVNET studies often engage collaborators at other institutes within the National Institutes of Health and at the Centers for Disease Control and Prevention, the U.S. Army, and various national and international health organizations.

To foster trust and mutual understanding of clinical trial issues, and to ensure that the studies respect cultural and ethnic differences among participants, HIVNET has involved community members in all phases of the research process.

## Highlights of HIVNET Accomplishments and Future Plans

### Vaccine Preparedness Study

The eight domestic HIVNET sites have undertaken a multicenter Vaccine Preparedness Study (VPS), to be completed in April 1997, to determine the feasibility of conducting an HIV vaccine efficacy trial. Close to 4,900 participants at high risk for HIV infection (gay men, injection drug users and women at risk through heterosexual contact) are enrolled in the VPS, which simulates the size of a large-scale vaccine trial. Overall, HIV seroincidence in this cohort has been stable at 2 percent per year, with a 95 percent retention rate after one year of follow-up. Willingness to participate in vaccine trials has been high and is being monitored in response to new information about trials and vaccine products.

### International Cohort Study

HIVNET currently sponsors international projects in nine countries: five in Africa, two in Asia and two in the Americas. The sites have recruited and followed more than 12,000 people at high risk for HIV infection (female commercial sex workers, gay men, STD clinic patients, truck drivers, factory workers and pregnant women). The annual HIV seroincidence at these sites ranges from less than 1 percent to greater than 12 percent, with one-year follow-up rates ranging from 70 to 94 percent. HIV strains isolated from participants in the diverse cohorts represent all the major HIV subtypes.

### Vaccine Research

One promising vaccine concept, the ALVAC vcp205/gp120 combination, will soon be ready for expanded testing, and HIVNET will be evaluating this concept over the next few years. A series of trials of this vaccine candidate are in various stages of planning. A Phase II trial in the United States to assess the safety and immunogenicity of the ALVAC vcp205/gp120 combination—which HIVNET will conduct in collaboration with the AIDS Vaccine Evaluation Group—is now under way.

In addition to U.S. studies, HIVNET has designed a Phase I study to assess the safety and immunogenicity of the ALVAC vcp205 vaccine alone in African populations, scheduled to begin in the Spring of 1997 at the Uganda site. Data from this study will be used to develop an appropriate ALVAC HIV vaccine for East African countries.

HIVNET also is providing supplemental support for a community advisory board for an ongoing HIV gp120 vaccine trial in Thailand, sponsored by the Walter Reed Army Institute of Research.

**Perinatal Interventions**

An efficacy study in the Malawi site, which was jointly funded by the National Cancer Institute, evaluated the effect of chlorohexidine wash of the birth canal to prevent perinatal transmission of HIV. Although chlorohexidine had no effect on virus transmission, it produced a significant drop in the rate of neonatal sepsis. Another Phase III study is planned to begin at the proposed Dominican Republic site in June 1997 to examine the effect of HIV immunoglobulin on preventing perinatal transmission.

In November 1996, the Uganda site began a Phase I study of the safety of nevirapine in seropositive pregnant women and their newborns. If the study demonstrates no safety concerns, HIVNET will proceed with a Phase II/III trial in Uganda to evaluate peripartum use of nevirapine or zidovudine (AZT) compared with placebo in preventing perinatal transmission. HIVNET also will consider evaluating other promising antiretroviral drugs (e.g., PMPA, protease inhibitors) as soon as initial safety studies are completed in the United States.

**Microbicides**

After successfully completing a Phase II safety study of a nonoxynol-9 (N-9) vaginal microbicide gel in January 1996, the Kenya site began a Phase III efficacy trial of this product in July 1996 to determine if it can prevent sexual transmission of HIV among commercial sex workers.

To further clinical development of novel topical microbicide products for vaginal use, HIVNET has planned a series of Phase I/II trials to establish the safety and acceptability of new products in different populations. In December 1996, the Boston site began a study in Rhode Island examining the safety and acceptability of an acid buffer gel. If no safety concerns arise in U.S. participants, the trial will be extended to HIVNET sites in Thailand, India, Malawi and Zimbabwe.

Microbicide products such as N-9 have been used rectally, but it is not known if these products are safe or effective when used in this manner. Therefore, HIVNET is conducting a Phase I safety study of an N-9-containing gel for rectal use. HIVNET researchers also are searching for more acceptable and effective delivery systems for these products.

**Behavioral Interventions**

The Zimbabwe site is currently conducting a randomized community trial of peer counseling to prevent sexual transmission of HIV in factory workers. The sites in Thailand, India and Uganda are developing a joint Phase I study of condom promotion to prevent heterosexual HIV transmission among stable couples in which one partner is infected and the other is not.

The domestic sites also are planning a trial to evaluate individualized behavioral counseling as a way to reduce HIV and/or STD transmission in gay men.

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