

NATIONAL INSTITUTES OF HEALTH
FISCAL YEAR 2003
PLAN FOR HIV-RELATED RESEARCH

V: VACCINES

PREPARED BY THE OFFICE OF AIDS RESEARCH

AREA OF EMPHASIS:

Vaccines

SCIENTIFIC ISSUES

Recent progress in HIV/AIDS vaccine research in animal models has provided strong scientific motivation to further explore and develop several vaccine concepts, and to move additional candidate vaccines into clinical testing. As a result of increased funding from NIH in the area of HIV vaccines, many new approaches to HIV vaccines are being pursued from basic research in vaccine design and studies of immune responses in small animals through vaccine product development. At least 10 new candidate vaccines will enter Phase I trials in the next 2 years. Over the past several years, investigators have determined that a number of AIDS vaccine strategies have been able to decrease the initial peak of virus and/or the level of the virus that was established within a few months after challenge in animal models. All of these vaccine strategies appear to have a common ability to induce, at least to some level, cytotoxic T lymphocytes (CTL) specific for viral antigens and parallel T helper cell (Th) responses. Even though vaccines in the animal models have not been effective in preventing virus infection, the ability to control viral load early in the course of virus infection may be an equally important vaccine outcome. This is true for two reasons: First, cohort studies with large numbers of infected individuals indicate that the ability to control viral load is correlated with good prognosis and delayed progression to AIDS. Second, several studies recently have demonstrated that uninfected partners of HIV-infected subjects become infected far less frequently when there is a reduced level of HIV in the blood. Transmission is also reduced for infants born to HIV-infected mothers whose viral load is low. If HIV vaccines are

**SCIENTIFIC ISSUES
IMPACTING BASIC
RESEARCH IN
VACCINE DESIGN
AND TESTING**

able to reduce transmission, they could have a profound impact on the epidemic, particularly if these vaccines can be delivered to individuals with high-risk behaviors including youth and infants that are breast-feeding.

Animal Model Development

HIV-1 does not infect and cause sustained high levels of replication with disease development in any species of nonhuman primate (NHP) without alterations in its genome and adaptation to the host. Several chimeric viruses constructed with the envelope gene of HIV and the core and replication genes of simian immunodeficiency virus (SIV) (i.e., SHIV viruses), have been produced and adapted for growth in macaque models with differential pathogenicity. A SHIV chimeric virus (SHIV 89.6) that can readily infect both macrophages and T cells is highly pathogenic for peripheral T cells and now has been used to evaluate a number of vaccine approaches. The SHIV-SF162 is a selectively macrophage-tropic virus, that utilizes CCR5 co-receptor, which has shown a pathogenicity reflecting a rapid loss of T cells in the gastrointestinal tract with a slower loss of peripheral CD4 T cells. Like SHIV 89.6P, several other SHIV chimeras with a strong T cell tropism result in a dramatic and rapid depletion of peripheral T cells. Attempts to create new SHIV viruses that can express the envelope gene from HIV isolates of different genetic clades are being developed for the evaluation of vaccines that are based on envelope products from different regions of the world. Several Clade C SHIV constructs based on African or Chinese isolates are being tested in macaques.

Structure of the HIV Envelope

Continued studies of the structure and function of the HIV envelope have led several groups of researchers to pursue vaccine designs that remove the carbohydrate sites from HIV envelope protein. Deglycosylated envelope gp120 and 140 proteins are currently under study in macaques where these modified proteins appear to be more immunogenic and induce high titers of antibody that can at least neutralize a range of primary HIV isolates. With this same goal in mind, new approaches to configure fully native trimeric gp160 or partially truncated gp140 proteins are also underway. Many of these and other new approaches to seek more immunogenic forms of HIV envelope are using envelope genes that are derived from CCR5-using nonsyncytium-inducing isolates that appear to have some early outgrowth advantage in HIV-infected individuals.

Correlates of Immune Protection

Exposed individuals that have remained seronegative despite high risk of HIV exposure have been documented in groups of individuals that have been studied in various parts of the world and in the United States. Opposing concerns have been raised about the possibility of a hidden virus infection or partially attenuated virus that may become apparent if the repeated exposure either continues so that a pathogenic recombinant forms, or a protective immune state wanes so that individual is no longer protected.

Individuals and animals treated with antiretroviral therapy within days to weeks after infection and long-term survivors of HIV infection have contributed important information about the complexity of the immune response that may be needed for effective vaccine protection. Studies within the past few years have indicated that T cell help for maintenance of HIV-specific CTLs, CTLs themselves, and chemokines generated by T cells may be extremely important for effective control of viral load. Parallel assessment in animals models has indicated that a complex of these adaptive immune responses will be important immunological endpoints for HIV vaccines.

Targeting Antigen Presentation with Vectors and DNA Approaches

Several newer vaccine strategies are targeting the dendritic cells either through vaccine delivery or the use of viral vectors that do so naturally. The alphavirus family, which includes Venezuelan equine encephalitis virus (VEE), Sindbis virus, and Semliki Forest virus, may have a natural propensity to move to antigen-presenting cells, macrophages, or dendritic cells. Making a vaccine that uses the outer coat of the alphavirus to carry copies of HIV protein genes, in a product called VEE replicons, has been shown to induce immune responses and effect reduced virus load in macaques challenged with pathogenic virus. Other investigators have developed DNA vaccines that have incorporated nonmethylated CpG motifs that appear to also target dendritic cells through cytokine stimulation. In addition, vaccines containing cytokines or other immune stimulators have been shown to reduce viral load after challenge.

Vaccine Designs

Vaccine approaches that will focus on non-envelope proteins, in particular, the exploration of HIV gag and pol as genetically conserved proteins and tat or nef proteins as targets for early immune intervention, are under investigation at several research centers. Generally the approaches seek to achieve expression or presentation of multiple HIV antigens to maximally stimulate the immune response.

Attenuated Vaccines

Serious concerns have been raised from the recent evidence of CD4 loss in the rare individuals who had received attenuated forms of HIV and late disease progression observed in nonhuman primates that have received attenuated virus with nef gene alterations reveals that many have progressed to disease years after infection leading to increasing concern as to whether an attenuated vaccine for HIV will be possible. Investigators have continued to evaluate new mutations that might cripple the virus in ways that make defective proteins or substitute nonpathogenic genetic variants for both structural and other regulatory genes. Also new approaches to look at whole killed virus that has been genetically and/or chemically inactivated have also been linked with the concept that presentation of the immune system with an appropriately configured virus particle and multiple structural proteins could present a better surface to induce neutralizing antibody.

In summary, many new vaccine concepts are being explored at the basic research level that are bolstered by new scientific findings on the immune response to HIV and new insights that have been revealed from the structure and function relationships of the HIV virion itself. To be certain that this kind of scientific base continues to fill the gaps in HIV/AIDS vaccine research, the following priority for AIDS-related research was identified.

FY 2003 PRIORITIES

In considering the various obstacles and the priorities for HIV/AIDS vaccine development, one of the foremost priorities for testing candidate vaccines is a resolution of the crisis in the supply of monkeys available for HIV/AIDS vaccine studies. To properly test vaccines and to do comparative analysis of candidate vaccines requires larger numbers of animals than those that have been available to most HIV/AIDS vaccine research investigators. The shortage of rhesus macaques, particularly the limited availability of genetically-defined and/or pedigreed, specific pathogen-free (SPF) rhesus macaques of Indian origin, previously was identified in the FY 2002 NIH Plan for HIV-Related Research. This has not been adequately addressed by several grants that were funded in FY 2000. This problem is not restricted to HIV/AIDS vaccine research and other areas of HIV-related research, including etiology and pathogenesis, therapeutics, and microbicide development, but it also is a problem that must be addressed by the larger biomedical community.

PRIORITY FOR FUTURE RESEARCH:

- **To resolve the current crisis in the supply of macaques for HIV/AIDS vaccine research, NIH should develop innovative and creative ways to work with suppliers of both not-for-profit and for-profit organizations to immediately build the breeding capacity of these animals. NIH should develop and implement a long-term plan to ensure the future supply of macaques for HIV/AIDS-related research and other areas of NIH-funded biomedical research.**

A second, linked obstacle that is impeding HIV/AIDS vaccine research is the availability of appropriate facilities for vaccinated animals after they are tested with infectious virus. As more HIV/AIDS candidate vaccines and combination approaches are moved into preclinical testing in animals, the biosafety level (BSL) 2/3 housing for SIV- or SHIV-infected nonhuman primates is becoming increasingly limited. This is complicated by the fact that a number of the vaccine concepts now being tested do not prevent infection with SIV or SHIV, but decrease the viral load in the animals for months to years. To evaluate vaccinated animals and determine the potential for long-term benefit of candidate vaccines, animals will need to be maintained and monitored with intensive immunological and virological studies over longer periods of time to determine the relative beneficial effects of different vaccine approaches for preventing disease and potentially transmission. This will further exacerbate the current existing shortage of BSL 2/3 facilities that are available at nonhuman primate facilities in the United States.

PRIORITY FOR FUTURE RESEARCH:

- **NIH should ensure that resources are available domestically and, where appropriate, at international sites, as soon as possible for the expansion of appropriate space, in particular BSL 2/3 housing to maintain animals that are being studied for outcomes of vaccine experiments. Funding must not be restricted to Regional Primate Research Centers (RPRC) to satisfy this need.**

One of the major scientific hurdles that is still impeding the development of highly effective HIV vaccines is the failure of current candidate vaccines to induce high levels of functional or neutralizing antibodies against a broad spectrum of HIV isolates with genetically variant envelope proteins. A number of vaccine approaches that have been tested in animal models have been demonstrated to induce virus-specific, cytotoxic T lymphocytes (CTL) that are correlated with the ability to control virus after pathogenic virus challenge. However, none of the candidate vaccines currently under

study in clinical trials have been shown to have a broad range of neutralizing antibody reactivity. Several attempts to design new immunogens, which employ the relatively conserved internal structures of the envelope proteins, envelope proteins with reduced glycosylation, selected epitopes that are able to mimic complex neutralization epitopes, or cocktails of immunogens, are ongoing. However, further exploration of innovative vaccine approaches to induce antibodies with a wide breadth of reactivity against primary HIV isolates is essential. In addition, approaches that optimally prime both T cell helper and B-cell memory cells for improved duration of antibody responses are likely to be essential for highly effective vaccines and should be entered into clinical trials as rapidly as possible. In conjunction, additional approaches that will be effective in optimizing the priming and maintenance of cytotoxic T cells to multiple epitopes in conserved proteins of HIV or conserved regions of highly variable proteins should be undertaken.

PRIORITY FOR FUTURE RESEARCH:

- **NIH should continue to support innovative efforts to design and test vaccines that can induce antibody responses to HIV envelope capable of neutralizing a large array of HIV isolates. Resources should continue to be available and expanded whenever necessary to rapidly move any promising vaccine approach through safety and preclinical studies to testing in human volunteers as quickly as possible.**

One of the most immediate priorities for vaccine development is the standardization and validation of newly developed assays for assessment of immune responses at all levels of vaccine testing. To date, evaluation by rapidly developing research level assays has constituted most of the evaluation of the immune responses in human vaccinees. These assessments have been performed in one or two central laboratories in the AIDS Vaccine Evaluation Group/HIV Vaccine Trials Network (AVEG/HVTN). This now constitutes an increasing commitment of the immunological laboratories in the HVTN. As we move from testing of HIV vaccine candidates in laboratory animals to the clinic, the characterization of immune responses by more sensitive and more specific assays needs to be refined so that assays are more reproducible and more consistent. Immunogenicity assays will be important for potency testing of different lots of candidate vaccines in addition to assays that are able to measure the levels of gene expression of different vectors. Assays also need to be expanded to assess the potential breadth of the immune response. In addition, resources to perform epitope mapping to evaluate nondominant immune responses needs to be expanded. Systems of proficiency testing

for quality assurance of immunological assays with standardized reagents also need to be developed. Coordination should be supported between different networks so that standardized protocols, which are checked between laboratories, as well as protocols that are parallel and consistent between animal testing and testing of human volunteers are instituted. Training should be planned to assure that this is achieved.

PRIORITY FOR FUTURE RESEARCH:

- **NIH should commit the support needed to develop a coordinated program of quality control and quality assurance for testing in both macaques and human studies for assays that now are being developed and evaluated so that assays essential for evaluation of clinical trial endpoints are in place when large efficacy trials are undertaken.**

The evidence continues to indicate that youth, particularly adolescents and young adults in domestic minority communities, are one of the highest risk groups for acquisition of HIV. As NIH moves forward to investigate efficacy of HIV vaccines in high-risk populations, adolescents and young people in culturally diverse populations should not be overlooked for logistical reasons or for perceived notions that it is simply “too hard” to include them. Vaccine researchers should look at the balance sheet and take into account the ethical considerations and the increased risk, as well as the idealism and altruism, and the willingness of some adolescents to participate in complicated studies when fully informed. The explicit goal of such efforts should be licensure of successful HIV/AIDS vaccines in adolescents at the same time as or shortly after licensure for vaccines for adults is obtained in the United States.

PRIORITY FOR FUTURE RESEARCH:

- **NIH should develop a strategy to ensure licensure of HIV vaccines for adolescents, including linking adolescent cohorts to networks that are anticipating vaccine and prevention efficacy trials as soon as possible. It is essential to ensure community outreach and education and enable participation of adolescents in appropriately designed clinical trials of candidate HIV vaccines and other prevention strategies that are reasonably likely to be licensed in the United States.**

In addition, the final FY 2003 priority for HIV/AIDS vaccines is to continue to address all of the priorities identified in the Vaccines Plan for FY 2002.

PRIORITY FOR FUTURE RESEARCH:

- **Continue to expand core programs in HIV/AIDS vaccine research and development to ensure that the research pipeline for vaccine research and development is robust.**
 - **Encourage studies that will identify immunotypes, define the significance of genetic variation, and assist in selection of products that may induce broadly protective immune responses.**
 - **Continue to explore different combinations of vaccine products and schemes of priming and boosting with different products to optimize both quality and duration of the immune responses.**
 - **Enable testing in the most relevant animal models (e.g., that reflect kinetics of human HIV infection).**

PRIORITY FOR FUTURE RESEARCH:

- **Conducting clinical trials of promising vaccine candidates in both domestic and international settings is a top priority for the vaccine field. Current plans for expanded trials required an initial expansion for the vaccine trials network in FY 2001, and this effort will need to be further expanded in FY 2002 to conduct efficacy trials. Clinical trials are expected to be iterative and allow for comparison of vaccine candidates.**
 - **Conduct Phase I and II trials of products moving new concepts and products into human testing as rapidly as possible.**
 - **Enable the conduct of efficacy trials with sufficient lab support to define correlates of immunity.**

PRIORITY FOR FUTURE RESEARCH:

- **Expand immunological assessment of vaccines. This priority is deemed to be a critical element that underlies the evaluation of vaccines at multiple levels and is reflected in the following initiatives.**
 - **Ensure that standardized assays with high throughput for both animal and human studies are developed that are precise, sensitive, and practical. Develop and provide resources and appropriate reagents for these assays to enable a number of**

laboratories to work in parallel, in different animal models as well as clinical trials.

- ▶ **Strengthen the immunological assessment of clinical vaccine trials, including therapeutic vaccines trials and ensure linkage with development of the therapy aspects to understand principles and mechanisms of priming and boosting of the immune response.**
- ▶ **Study the immune responses in neonates and infants as a special case to assure development of appropriate vaccine products for breastfeeding populations where safe alternatives to breastfeeding are not readily available.**

PRIORITY FOR FUTURE RESEARCH:

- **Increase AIDS-dedicated nonhuman primate resources for breeding and holding. NIH should immediately initiate a survey to define the extent of needs for nonhuman primates. A major program to assure the availability of pedigreed, SPF nonhuman primates designated for AIDS-related research that deals with several specific aspects relevant to vaccines should be ramped up as quickly as possible.**
 - ▶ **Because of the impact of major histocompatibility complex (MHC) genes on immune responses to vaccines, this program should incorporate characterization of the MHC haplotypes in macaques and other nonhuman primates that will permit functional programs for genetic typing of animals assigned to vaccine studies.**
 - ▶ **Increase availability of neonatal as well as adult animal for vaccine studies.**

PRIORITY FOR FUTURE RESEARCH:

- **Invest in the development of critical vaccine research capabilities, information dissemination, and education to conduct vaccine trials in populations with a high incidence of HIV infection. As HIV infections continue to move deeper into minority populations, adolescents, and women in the United States, who often do not perceive risk, new efforts must be developed for enabling partnerships and full participation of volunteers from these groups. Similarly, in international settings, increased attention must be paid to building the capability and infrastructure in populations in the sites identified for future efficacy trials; to provide a solid scientific**

knowledge base (incidence, viral subtypes, MHC types, natural history) to justify clinical trials; and to conduct vaccine trials in these sites and communities according to the highest clinical and ethical standards. This includes a broad range of activities that include:

- ▶ **The transfer of information, development of scientific expertise, and training in all aspects of clinical trials to individuals in the populations identified for potential vaccine trials.**
- ▶ **To enable full participation for long-term trials and for international vaccine studies, especially in developing countries, this may require development of information and skills that will contribute to infrastructure development that will be required.**

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE:

Increase scientific knowledge through basic research on protective immune responses and host defenses against HIV to facilitate the development of vaccines and other biomedical intervention strategies to prevent and/or control HIV infection.

STRATEGIES:

- Define the mechanisms underlying protective systemic and mucosal immunity to HIV and other lentiviruses by pursuing research that includes the following areas of interest:
 - ▶ Determine the mechanisms of immunologically mediated control of infection with HIV and other related lentiviruses, including the role of antigen-specific and antigen-nonspecific cellular and humoral immunity in inhibiting viral replication to provide a basis for optimal vaccine design.
 - ▶ Define the structure-function relationships and the antigenicity and immunogenicity of HIV proteins, including transient or intermediate and conformational domains induced by virus interacting with CD4, chemokine, dendritic cell (DC) SIGN, and other cellular receptors to improve vaccine designs to more effectively induce immune responses to block infection by active and passive immunity.
 - ▶ Define and characterize viral B-cell and T-cell epitopes that induce protective immunity in HIV or AIDS-related disease; utilize structure and antigenicity to determine whether and how their immunogenicity can be improved and exploited in vaccine development.
 - ▶ Determine the mechanism of how HIV and related lentiviruses evade or escape from humoral and cellular arms of the immune response; design vaccine approaches to prevent this; and define conserved epitopes in which genetic substitutions cannot be tolerated by the virus.
 - ▶ Characterize pathways of antigen processing of HIV proteins, including envelope glycoproteins, for presentation by MHC class I and class II molecules. Investigate the interaction of HIV proteins with antigen processing mechanisms that enhance or inhibit specific epitope presentation to the immune system.

- ▶ Study immunological memory and long-term protective function of different subsets of human lymphocytes and DCs in HIV-related disease and in response to vaccination; define factors that favor establishment and maintenance of memory cells able to generate effective recall to vaccine antigens, particularly HIV and related viral antigens, and development of long-term protective immunity, particularly in human subjects.
- ▶ Study the mechanism of action of vaccine adjuvants and enhanced modes of HIV and related lentivirus antigen presentation to induce different cytokine or chemokine responses, innate immunity, and host factors; carry out translational research in nonhuman primates and human vaccinees.
- ▶ Determine how chronic infection with one strain of HIV or related lentivirus, including attenuated viruses, confers protection against subsequent infection or reduces viral replication of a second pathogenic virus strain; define the properties of the virus and of the immune system that are responsible for lack of disease induction by attenuated viruses and protection from challenge with wild-type virus; and determine the protective mechanism, duration, and extent of cross-protection.
- ▶ Define the heterogeneity of specific responses to vaccine immunogens, particularly HIV, within diverse tissue compartments, and identify factors that confer protection from infection by various routes including vaginal, rectal, oral, and parenteral exposure.
- ▶ Determine which factors promote development of particular human effector cell types, promote production of antiviral substances including chemokines, or enhance non-antigen-specific protective mechanisms.
- ▶ Define the basis for adaptive, antigen-specific immune reactivity (humoral, cellular, and other) across divergent HIV types (clades and biological phenotypes or immunotypes).
- ▶ Determine whether HIV immune responses that can contribute to immune enhancement of viral replication *in vitro* can interfere with induction or propagation of vaccine-induced effector responses *in vivo*.
- Seek new clues for correlates of immune protection from HIV-infected or highly exposed but seronegative individuals, across the life span, and from lentivirus models that will provide the basis for further design of candidate vaccines by conducting the following research:

- ▶ Study acutely infected individuals, exposed/seronegative, or possibly transiently infected humans—including uninfected children born to HIV-infected mothers, individuals with controlled therapy interruptions, HIV-infected individuals vaccinated with therapeutic vaccines while on antiviral therapy, and nonprogressors—to define immune responses to HIV-1 and HIV-2, potential vaccine-inducible host immune responses, and viral factors (or viral attenuations) that reduce the amounts of circulating virus and influence disease course.
 - ▶ Elucidate the functional mechanisms for protective immunity against HIV, including identification of specific responses by passive transfer of antibody or immune cells and deletion of selected immune subsets in nonhuman primate models.
 - ▶ Investigate the sequence of events required for mucosal transmission/infection of HIV and other lentiviruses at different portals of entry to define how and where specific immune effector mechanisms can impede viral entry and/or prevent establishment of infection.
 - ▶ Study mucosal immunity to viral antigens and other infectious pathogens in relevant animal models and humans to develop optimal vaccine strategies for HIV antigen delivery and effective immune-based prevention of HIV transmission.
 - ▶ Explore the molecular epidemiology, humoral, and cell-mediated immune response to HIV-1; acquire clinical specimens from populations relevant to vaccine trials for laboratory studies; and acquire appropriate epidemiological information to enable interpretation of these analyses.
 - ▶ Monitor the effects on immune activation with intercurrent sexually transmitted diseases (STDs), malaria, TB, hepatitis B and C, other infectious diseases, and with administration of drugs of abuse or effects of antiretroviral therapy on viral shedding in vaccinated subjects. Model these confounding elements in nonhuman primates.
- Develop *in vitro* experimental approaches for analysis of vaccine responses that will combine sensitivity, specificity, high throughput, and the ability to use small sample volumes; develop *in vitro* and *in vivo* tools to study systemic and mucosal immune mechanisms of control of virus for analysis of vaccinated individuals (across life span) and protected animals by undertaking the following research activities:

- ▶ Develop and improve animal models of lentivirus infection that are practical and representative of the spectrum of HIV infections and development of AIDS, including use of appropriate HIV cellular receptors and different modes of transmission; develop genetically defined and histocompatible nonhuman primate models to facilitate immune cell transfer studies; in general, make models amenable to use in evaluating protection by vaccines and other biomedical interventions. This may be approached, in part, by a genetic sequencing, particularly of selected regions of the macaque genome.
- ▶ Develop improved methodologies and assays to measure viral neutralization; explore the mechanisms of virus neutralization and the reason(s) for the relative difficulty to neutralize primary isolates.
- ▶ Develop and standardize immunological reagents; standardize cell, fluid, and tissue processing to ensure viability and maintenance of functional capacity of cells and stability of factors in serum, plasma, and culture supernatants; and develop quality control procedures for collecting, processing, freezing, and shipping samples that will be essential in large-scale trials.
- ▶ Study the function of CD4, CD8 T cells, and viral suppressive immune responses; develop and adapt high-throughput assays with specificity for primary virus isolates; and make available those reagents required for vaccine-related studies.
- ▶ Develop or improve sensitive quantitative measures of HIV (and SIV) in body fluids and low-level tissue reservoirs, including genital secretions and breast milk, to assess the effectiveness of vaccines designed to lower viral load and interrupt transmission or prevent disease progression.

OBJECTIVE:

Design viral antigens, adjuvants, immunomodulators, and vaccine delivery methods that elicit long-lasting protective immune responses against a broad range of HIV isolates by applying findings from basic, epidemiologic, and clinical research; facilitate development and preclinical evaluation of vaccine strategies in laboratory studies and animal models; and foster early and continued collaboration between academicians, other Government agencies, nongovernment organizations (NGOs), and industry in the research and development of candidate vaccines to test a broad array of vaccine concepts and combinations of different approaches for development of potential HIV vaccine products, including vaccines for particular populations.

STRATEGIES:

- Multiple parallel approaches to development and testing of candidate HIV/AIDS vaccines will be investigated to provide complementary and comparative preclinical data on safety and immunogenicity questions about HIV vaccines. Such studies should achieve the following:
 - Support the design, development, production, and testing of novel HIV/AIDS vaccine candidates for safety and for their ability to elicit appropriate antiviral immune responses. This may include, but is not limited to:
 - Virus-like particles containing one or more virus proteins, peptides, or antigens;
 - Whole-inactivated HIV rendered noninfectious by chemical and/or genetically engineered deletions of pathogenic viral elements;
 - Naturally occurring and genetically engineered, live-attenuated strains of HIV;
 - DNA or RNA coding for viral proteins;
 - Live, recombinant viral and bacterial vectors engineered to express one or more HIV proteins with attention to vectors that might provide dual benefit for HIV and some other pathogen or to vaccine vectors that target mucosal immune responses;
 - Viral replicons or other strategies to target dendritic cells;

- Recombinant HIV viral protein subunits produced by a variety of methods, with an emphasis on retention or exposure (e.g., through deglycosylation) of critical nonlinear structural epitopes for induction of effective antibody responses;
- Structurally constrained viral protein fragments, peptides, mimetopes, or complex peptides capable of inducing and boosting cellular or humoral immunity to HIV; and
- Cell surface components carried on the viral surface.
- ▶ Foster collaboration between academic investigators, industry sponsors, NIH, the U.S. Food and Drug Administration (FDA), other Government agencies, and NGOs on research and development of novel vaccine design concepts. These collaborations should
 - Enable production of pilot lots of vaccine candidates for testing in nonhuman primates and human subjects;
 - Develop programs to design and conduct comparative testing of vaccine approaches with industry and academic partners that will permit long-term followup to assess disease progression in animal models; and
 - Develop infrastructure; address scientific, legal, ethical, and regulatory issues to foster and encourage participation by, and collaboration between, academic investigators, industry, and other agencies in the research, development, production, and clinical testing of candidate vaccines.
- ▶ Foster the development of vaccines to optimize characteristics appropriate for broad international use, including designs exhibiting low cost with ease of production, stability, and ease of administration. This may include
 - Combined use of two or more vaccine strategies with mixed modalities to boost the same component and/or to engage different components of the immune response; and
 - Multivalent vaccine candidates incorporating different genetic clades and antigenic types to increase breadth of immune responses.
- ▶ Support design, development, and incorporation of methods to improve or modulate immune responses (qualitatively or quantitatively) in vaccine approaches, including

- Novel adjuvants and delivery methods that might enhance effective DC antigen presentation;
 - Agents that stimulate or modulate mucosal immune responses or other host defenses, including cytokines or chemokines;
 - Vaccines formulated with cytokines or incorporating cytokine genes in vectors or other biologically active molecules; and
 - Other novel strategies, including nutritional supplementation and treatment of underlying infections and/or diseases that might have an impact on vaccine responses.
- ▶ Evaluate the efficacy of vaccine and other immune prevention strategies in animal models of HIV and related lentiviruses by
- Testing vaccine and other biomedical prevention strategies in animal models that most closely mimic HIV infection in humans;
 - Determining *in vitro* correlates of an *in vivo* protective immune response;
 - Determining the effect of vaccine formulation, site of delivery, and regimen, as well as the nature, timing, phenotype, and route of infectious virus challenge on the effectiveness of the vaccine-induced immunity;
 - Defining the impact of different vaccine approaches on kinetics of immune responses, kinetics and localization of viral replication, long-term followup of disease progression with low-level chronic infection and concomitant diseases (e.g., tuberculosis, hepatitis, or autoimmune diseases), and biologic characteristics of breakthrough virus including transmissibility;
 - Determining the impact of genetic factors and age on vaccine responses and on protection against virus at various challenge sites;
 - Studying the efficacy of the immune response in the face of viral mutation and variation; and
 - Investigating vaccines and other biomedical prevention strategies with attention to potential cofactors such as integrity of the mucosal surface, changes in-vaginal/cervical epithelium during puberty, hormonal changes during pregnancy, use of contraceptives or hormonal replacement therapy, and presence

of STDs; wherever possible, study potential concomitant effects on the genital tract immune system and inflammatory activity that might compromise integrity of the mucosal surface or the inductive ability of vaccines.

- ▶ Support development of reagents and standardized methods to assess specific vaccine-induced immune responses in animal models and humans, including infants, for both humoral and cellular aspects of systemic and mucosal immunity. This includes:
 - Developing and refining assays to distinguish between serological and cellular responses due to immunization and those due to viral infection;
 - Characterizing and evaluating the potential negative side effects of candidate vaccine designs, including the potential to increase the susceptibility to infection or the rate of disease progression in animal models;
 - Standardizing and validating assays to assess vaccine potency; and
 - Standardizing and validating assays to be used as Phase III study endpoints.
- ▶ Foster research on the safety and regulatory considerations of candidate HIV/AIDS vaccines in development
 - Whose production utilizes human-derived tumor cell and other continuous cell lines;
 - That utilize vectors that have the potential to integrate into the host chromosome or have the potential for chronic expression;
 - That might have the ability to be generated as either replicating or nonreplicating vectors;
 - That have the potential to cause autoimmunity or highly immunogenic anti-vector responses; or
 - That over-express potentially deleterious vector proteins.

OBJECTIVE:

Identify mechanisms of protective immunity to HIV in newborns and infants, and support the development of distinct study designs for safe and effective vaccine strategies and passive immune interventions, alone or in combination with other interventions, for preventing or controlling HIV infection in this population worldwide.

STRATEGIES:

- Investigate the unique immune status and develop immune interventions in both pregnant women and infants to interrupt HIV transmission. Active and passive HIV vaccine strategies need to be modeled and evaluated, particularly in infants, in parallel to studies in uninfected adults. To accomplish this goal, it is important to develop research that will achieve the following:
 - ▶ Develop relevant animal models of maternal-fetal and maternal-infant perinatal transmission that can
 - Determine preclinical safety and immunogenicity of various HIV vaccines and adjuvants, particularly in primates;
 - Determine safety of various monoclonal and polyclonal antibody preparations;
 - Determine the best immunization routes or protocols to induce antibodies in milk and other secretions;
 - Evaluate efficacy of vaccines and passive immunotherapy for prevention of perinatal or breast-feeding transmission; determine whether there is attenuation of disease progression among neonatal animals that become infected despite immune intervention; determine correlates of protective immunity; and
 - Evaluate the effect of antiviral drugs in combination with immune and behavioral prevention strategies.
 - ▶ Determine virologic and nonimmunologic host factors that influence transmission of HIV-1 from mother to infant that would have an impact on selection of viral antigens for the design of an HIV vaccine or for identifying the target of immune-based intervention to prevent perinatal transmission. This includes
 - Determining the importance of viral load and viral phenotypes and genotypes in perinatal or early infant HIV transmission and what viral factors are associated with differences in perinatal transmissibility;

- Developing standardized methods to collect specimens and to detect, characterize, and quantify HIV in cervico-vaginal secretions and in breast milk to determine their potential relevance in mother-to-child transmission; and
- Determining if virus in maternal genital secretions or breast milk is distinguishable from virus found in blood and which type is transmitted from mother to fetus and mother to infant.
- ▶ Identify maternal and infant immune responses that might control viral replication in either the mother and/or the infant and prevent transmission of HIV or establishment of infection in infants.
- Define immune approaches that will provide specific and sustained protection against HIV transmission; develop the products necessary to achieve these goals; and develop the capacity to evaluate their safety in human subjects. This research includes the following activities:
 - ▶ Determine specific immune strategies for perinatal intervention that blocks interaction of HIV with its receptors and coreceptors and/or to target infected cells.
 - ▶ Characterize the transmitted viral strains and monitor changes that may occur in proposed trial sites; evaluate the impact that genetic polymorphism in different racial or ethnic backgrounds might have on receptor usage or immune responsiveness.
 - ▶ Evaluate, in Phase I and Phase II studies, the safety and immunogenicity of various HIV vaccines, adjuvants, vaccine administration regimens, and the pharmacokinetics of passive antibody preparations among both HIV-infected pregnant women and newborns exposed to HIV (born to HIV-infected women).
- Test the safety and efficacy of active and passive HIV vaccine interventions alone or in combination with other modes of intervention, particularly in international settings with high seroprevalence. This testing includes the following activities:
 - ▶ Identify and characterize the important issues to consider in the development of criteria for advancement of candidate vaccines, adjuvants, and passive antibody preparations from Phase I and Phase II to Phase III clinical trials in pregnant HIV-infected women and/or HIV-exposed children. These criteria should include evidence of therapeutic effectiveness in mothers in addition to prevention of infection in HIV-exposed children.

- ▶ Develop the capacity in domestic and foreign trial sites necessary to enroll mothers and infants in trials of both preventive and therapeutic vaccines, passive immunity, and other perinatal interventions with prospective long-term followup. For vaccines, this should include both the assessment of duration and breadth of detectable humoral immune responses and of memory or recall responses in the cellular immunity compartment(s).
- ▶ Conduct Phase III clinical trials for evaluation of efficacy of the most promising candidate vaccines and/or passive antibody preparations that meet established criteria in pregnant HIV-infected women and/or children exposed to HIV.
- ▶ Develop criteria to define infant infection status as a perinatal intervention trial endpoint in countries where breast-feeding is recommended despite maternal infection status, including type of diagnostic tests, timing of the tests, length of followup, and adherence to follow-up visits.
- ▶ Study viral isolates and the immune response in infants who become infected despite administration of active and/or passive immunization to evaluate the effects of immune intervention on the characteristics of transmitted (escape) virus and on the quality, quantity, and timing of the infected infant's antiviral responses.
- ▶ Study the impact of early antiviral therapy and HIV vaccines, given while on effective antiretroviral therapy, on the maintenance or regeneration of antiviral immune responses of HIV-infected infants.

OBJECTIVE:

Conduct Phase I, Phase II, and Phase III trials for safety, immunogenicity, and efficacy with suitable candidate vaccines or concepts in domestic and international settings.

STRATEGIES:

- Support the conduct of Phase I, II, and III clinical trials that will determine long-term and short-term safety, evaluate efficacy, and compare immunologic responses to different preventive vaccine candidates by evaluating a broad range of humoral, cell-mediated, and mucosal immune parameters. This includes the following tasks:
 - ▶ Design and conduct Phase I and Phase II trials using promising HIV vaccine candidates. Trials should test immunogenicity of vaccine concepts, and address questions about optimal vaccine strain selection, (i.e., the properties of a strain [immunologic, genotypic, or phenotypic]) that make it optimal for use in a selected population. Trials also should include an appropriate representation of ethnic and racial minority populations affected by HIV and be of an appropriate size to provide data on the frequency, magnitude and breadth of immune responses to facilitate decisions regarding initiation and evaluation of larger “proof of concept” or efficacy trials.
- Develop a comprehensive plan for conducting vaccine trials with a high level of retention and adequate followup of vaccinees to reach predefined endpoints, as follows:
 - ▶ Prepare for adequate long-term followup of volunteers in HIV vaccine clinical trials to determine the durability of immune responses and protection, the correlates of immune protection, long-term safety, behavioral factors to influence adherence of follow-up visits, the impact of participation on risk-taking behavior, and vaccine-related reduction (or enhancement) of disease progression and HIV transmission.
 - ▶ Conduct large-scale efficacy trials of preventive vaccine candidates that have proven promising, safe, and immunogenic in Phase II trials and that meet appropriate criteria by
 - Evaluating HIV vaccine candidate efficacy against infection, disease, and/or transmission;

- Evaluating additional virologic, immunologic, and behavioral outcomes, particularly potential correlates of protective immunity;
 - Ensuring that trials are conducted with the highest regard for social, legal, and ethical standards and in populations that reflect the racial and ethnic burden of the HIV disease;
 - Ensuring access to achievable, sustainable, and culturally appropriate best practices to prevent HIV exposure; and
 - Developing, adapting/modifying, and coordinating educational and information programs about HIV and HIV vaccines suitable for the individual participants and communities of different ethnic, racial, and cultural backgrounds that will be involved in trials.
- ▶ Characterize the clinical course, immune responses, and other characteristics of vaccinees (e.g., behavioral risk of infection) who become HIV-infected; isolate and characterize viral isolates from participants in vaccine trials with intercurrent HIV infections to explore the possible effects of vaccination on the characteristics of escape (transmitted) viruses.
 - ▶ Continue to use existing strategies to avert social harm and develop additional strategies to complement existing mechanisms at the local and national levels to reduce the risk of social and economic harm to volunteers in Phase I, II, and III trials and assist in providing solutions.
 - ▶ Conduct behavioral risk assessment research during vaccine trials, particularly with Phase II and Phase III trial participants, to identify and evaluate any changes in risk behavior as a result of participation in a vaccine trial; develop, test, and ensure access to interventions to prevent high-risk behaviors; conduct behavioral research with specific emphasis on individuals who become infected during trials to identify interventions that may prevent high-risk behaviors in future trials or application of HIV vaccines.
 - ▶ Closely coordinate the evaluation of research findings on prophylactic AIDS vaccines with preclinical research and immunotherapeutic interventions.

OBJECTIVE:

Develop strategies, infrastructure, and collaborations with researchers, communities, other U.S. Government agencies, other Governments, international and domestic NGOs, and industry that are necessary to ensure adequate performance of vaccine trials, while balancing the prevention needs of the at-risk populations; identify domestic and foreign populations; and perform necessary research to define seroincidence and viral subtypes and to determine and optimize feasibility of vaccine studies in appropriate cohorts.

STRATEGIES:

- Identify and develop potential domestic and foreign sites with a high seroincidence and access to populations at high risk for acquiring HIV infection, where vaccine or other prevention research activities may be feasible. This includes the following activities:
 - ▶ Track the course of the epidemic by studying HIV incidence in cohorts of individuals with high-risk behavior to identify and monitor changes in the risk profiles and infection rates (seroincidence) of various populations in the United States and worldwide; improve methods to identify and evaluate emerging risk groups and those groups most likely to be informed, willing, and capable participants in vaccine trials.
 - ▶ Analyze MHC genetic differences and other relevant genetic or medical factors of populations at potential trial sites that might affect the qualitative or quantitative levels of immune responses to candidate HIV vaccines, susceptibility to infection, control of viral load, and disease progression.
 - ▶ Acquire and analyze HIV isolates from mucosal sites, as well as blood from recently infected persons representative of potential efficacy trial populations, so that genetic and antigenic information about viruses being transmitted in the population can be obtained.
 - ▶ Develop and maintain the necessary immunology and virology laboratory infrastructure for conducting domestic and international vaccine efficacy trials. This includes education and training of personnel from international sites hosting vaccine trials, development of laboratory infrastructure, standardization of assays, and participation of trained personnel in studies related to the trial.

- Establish, build, and nurture linkages with communities and community organizations where vaccine trials might be conducted to optimize education, recruitment, and followup activities; listen to and address community concerns and social issues, and ensure ethical conduct of AIDS vaccine efficacy trials. This includes the following:
 - ▶ For all vaccine trials, enlist participation of local representatives or community advisory boards (CABs) in the development of appropriate trial protocols as well as responsive mechanisms to inform and educate the participating individuals; establish networks within the community that will effectively, and on a continuing basis, address the social and medical concerns of the participants; establish mechanisms to provide ongoing information and open discussions concerning the scientific rationale of the study.
 - ▶ Develop mechanisms to engage collaboration and to provide education and the means to inform communities, and particularly individuals participating in the trials through CABs, on a continuing basis so that social as well as medical concerns are addressed; work to establish trust through open discussions of scientific rationale, expectations, and concerns.
 - ▶ For international trials, in addition, work closely with national (host) governmental and regulatory authorities, collaborating institutions or agencies, local community representatives, vaccine manufacturer(s), and the World Health Organization (WHO)/Joint United Nations Programme on HIV/AIDS (UNAIDS) to prepare for, plan, and conduct vaccine trials adhering to the highest ethical and scientific standards.
- In collaboration with Government agencies, institutions, NGOs, and communities being identified as potential collaborators, explore behavioral and social issues and prevention activities that might have a substantial impact on either the design or the conduct of a research trial. This includes the following research:
 - ▶ Evaluate other biomedical and behavioral interventions that could prove of benefit in decreasing the incidence of HIV infection in the populations identified for future vaccine efficacy trials; address their potential impact on the evaluation of vaccine efficacy.
 - ▶ Conduct behavioral research in populations at high risk for HIV infection to determine, for example, appropriate risk-reduction interventions and to estimate risk behavior and recruitment,

adherence, unblinding, and retention strategies pertinent to the design and execution of a successful efficacy trial, especially for populations that have been historically underrepresented in clinical trials and where the epidemic is expanding disproportionately.

- ▶ Determine possible adverse social, economic, behavioral, or legal consequences of participation in clinical trials; develop broadly applicable strategies for mitigating potential harm.

Determine optimal methods of achieving informed consent for vaccine efficacy trials.

- Explore innovative trial designs to improve efficiency of vaccine efficacy studies (e.g., determine the impact of HIV vaccines on subsequent transmission from vaccinated individuals who become infected after administration of the trial vaccine or utilizing initially concordant negative couples at high risk or discordant couples). This includes the following areas of trial design research:
 - ▶ Consider the use of secondary endpoints, particularly immune correlates of protection, surrogates of disease progression and clinical outcomes, and the benefit of long-term followup.
 - ▶ Consider the impact of early antiretroviral therapy on HIV infections in complex trial designs.
 - ▶ Encourage linkage between vaccine preparedness studies in high-risk populations and other research activities, including research on tuberculosis and STDs; integrate research on vaccines against opportunistic infections, as appropriate.

APPENDIX A:

NIH Institutes and Centers

NIH INSTITUTES AND CENTERS

NCI	National Cancer Institute
NEI	National Eye Institute
NHLBI	National Heart, Lung, and Blood Institute
NHGRI	National Human Genome Research Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NICHD	National Institute of Child Health and Human Development
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NINDS	National Institute of Neurological Disorders and Stroke
NIDA	National Institute on Drug Abuse
NIHES	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIMH	National Institute of Mental Health
NINR	National Institute of Nursing Research
NLM	National Library of Medicine
CC	Warren Grant Magnuson Clinical Center
CIT	Center for Information Technology
NCCAM	National Center for Complementary and Alternative Medicine
NCRR	National Center for Research Resources
FIC	Fogarty International Center
CSR	Center for Scientific Review
NCMHD	National Center on Minority Health and Health Disparities
NIBIB	National Institute of Biomedical Imaging and Bioengineering

APPENDIX B:

FY 2003 OAR

Planning Group for Vaccines

FY 2003 VACCINES PLANNING GROUP

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APPENDIX C:

List of Acronyms

LIST OF ACRONYMS

ART	antiretroviral therapy
ACTIS	AIDS Clinical Trials Information Service
AIDS	acquired immunodeficiency syndrome
AITRP	AIDS International Training and Research Program, FIC
ATI	Analytic Treatment Interruption
ATIS	HIV/AIDS Treatment Information Service
AVEG/HVTN	AIDS Vaccine Evaluation Group/HIV Vaccine Trials Network
BSL	biosafety level
B/START	Behavioral Science Track Award for Rapid Transition
CAB	community advisory board
CBO	community-based organizations
CDC	Centers for Disease Control and Prevention
CFAR	Centers for AIDS Research
CIPRA	Comprehensive International Programs in Research on AIDS
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
CTL	cytotoxic T lymphocytes
DC	dendritic cell
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOT	directly observed therapy
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
FIRCA	Fogarty International Research Collaboration Award, FIC
GCP	Good Clinical Practices
GCRC	General Clinical Research Center
GI	gastrointestinal

GLP/GMP	good laboratory practices/good manufacturing production
HAART	highly active antiretroviral therapy
HBCU	Historically Black Colleges and Universities
HBV	hepatitis B virus
HCFA	Health Care Financing Administration
HCV	hepatitis C virus
HERS	HIV Epidemiology Research Study
HHV	human herpes virus
HIV	human immunodeficiency virus
HPTN	HIV Prevention Trial Network
HPV	human papillomavirus
HRSA	Health Resources and Services Administration
HVTN	HIV Vaccine Trials Network
IC	Institute and Center
ICC	invasive cervical cancer
IDU	injecting drug user
IHS	Indian Health Service
IUD	intrauterine device
JCV	JC virus
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma herpes virus
LRP	Loan Repayment Program, NIH
MAC	<i>Mycobacterium avium</i> complex
MCT	mother-to-child transmission
MDR-TB	multiple drug-resistant tuberculosis
MHC	major histocompatibility complex
MSM	men who have sex with men
N9	nonoxynol
NAFEO	National Association for Equal Opportunity in Higher Education
NGO	nongovernment organizations

NHL	non-Hodgkin's lymphoma
NHP	non-human primate
NIH	National Institutes of Health
NRTIs	nucleoside reverse transcriptase inhibitors
OAR	Office of AIDS Research, NIH
OARAC	Office of AIDS Research Advisory Council
OD	Office of the Director, NIH
OI	opportunistic infection
PHS	Public Health Service
PML	progressive multifocal leukoencephalopathy
RCMI	Research Center in Minority Institution
RCT	randomized clinical trials
RFIP	Research Facilities Infrastructure Program
RNA	ribonucleic acid
RPRC	Regional Primate Research Center
SAMHSA	Substance Abuse and Mental Health Services Administration
SCID	severe combined immunodeficiency
SHIV	chimeric simian/human immunodeficiency virus
SIT	scheduled intermittent therapy
SIV	simian immunodeficiency virus
SPF	specific pathogen-free
STD	sexually transmitted disease
STI	Structured Treatment Interruption
TB	tuberculosis
TI	treatment interruption
UNAIDS	United Nations Joint Programme on AIDS
VEE	Venezuelan equine encephalitis virus
VRC	Vaccine Research Center
WHO	World Health Organization
WIHS	Women's Interagency HIV Study

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