CHAPTER 2

Prevention Research

Microbicides

Vaccines

Behavioral and Social Science

Microbicides

AREA OF EMPHASIS
Microbicides

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A

Elucidate basic mechanisms of HIV transmission (virus and host factors) at mucosal/epithelial surfaces that are important for the development of a microbicide-focused prevention strategy in diverse populations.

STRATEGIES

Basic Biological and Physiological Research Related to Microbicides

- Search for and characterize new and understudied viral and host targets and kinetic sequencing of infection important for transmission and early dissemination of HIV in the female and male genital tracts and the rectal (lower gastrointestinal [GI] tract) and oral (upper GI tract) mucosal/epithelial sites that are relevant for microbicide discovery and development.
- Investigate the importance of innate and adaptive host defenses in protecting against HIV transmission and acquisition, and explore strategies to harness these host defenses to protect against HIV acquisition in the female and male genital tracts and the rectum (lower GI tract).
- Determine the impact of microbicides on innate and adaptive mucosal/epithelial defense mechanisms in the female and male genital tracts.
- Study the impact of microbicides on microbial ecology, population dynamics of the microbial biome, and their effects on mucosal/epithelial secretions and surfaces.
- Study the physiologic changes that occur during intercourse and discern how they relate to transmission or acquisition of HIV and the safety, efficacy, and acceptability of microbicides.
- Determine the cells and/or tissue types that serve as portals of entry and support subsequent spread and dissemination of HIV/SIV (simian immunodeficiency virus) to the lymphoid tissue.
- Determine the role of viral phenotype/genotype/clade/resistance patterns in microbicide activity and delineate their relative effect on the efficiency of transmission of cell-free and cell-associated virus in secretions and tissues in the female and male genital tracts.
- Determine the mechanisms by which genital tract inflammation and/or infections (including sexually transmitted infections [STIs]) may influence HIV transmission and early propagation and dissemination of virus to lymphoid tissue.

- Investigate the effect of endogenous hormonal states (puberty, pregnancy, menopause, lactation-induced hypoestrogenic states, and menstrual cycles) and exogenous hormonal states (including oral and injectable contraceptives and hormonal replacement therapy) on the susceptibility of the female and male genital tracts and the rectum (lower GI tract) to infection with HIV.
- Evaluate the effect of intravaginal and intrarectal practices and products (hygiene, etc.) on HIV transmission and/or microbicide effectiveness.

OBJECTIVE–B

Support the discovery, development, and preclinical evaluation of topical microbicides alone and/or in combination.

STRATEGIES

Microbicide Development and Preclinical Studies

- Support the development, validation, and standardization of specific, sensitive, and reproducible methods for assessing the antiretroviral activities of microbicide candidates.
- Support the development, validation, and standardization of specific, sensitive, and reproducible methods for assessing and quantifying innate and adaptive responses in mucosal/epithelial tissues and secretions before and after use of microbicides.
- Support the development, validation, and standardization of *ex vivo* cervicovaginal, rectal, penile, and foreskin explant models of human or nonhuman primate tissue that might provide a useful approach to: (1) investigate the very early events in HIV or SIV/SHIV (chimeric simian/human immunodeficiency virus) transmission and (2) evaluate the activity and toxicity of topical microbicide candidates.
- Validate and standardize existing (nonhuman primate SIV/SHIV) microbicide efficacy and safety models.
- Support the development, validation, and standardization of new animal models that closely reflect the dynamics of sexual transmission of HIV in humans.
- Promote the development of new models and assays to discover and evaluate microbicide candidates, acknowledging that most assays used for microbicide development are adaptations of those used for development of systemic antivirals and may not be appropriate.
- Develop exploratory techniques such as genomics and proteomics to identify novel candidate agents or targets for microbicide strategies.
- Facilitate the study of potential microbicide candidates for their effect(s) on innate and adaptive immunologic and inflammatory parameters associated with HIV acquisition and replication.
- Support preclinical, pharmacokinetic, pharmacodynamic, and acute and chronic toxicity testing, including genotoxicity, reproductive toxicology, and carcinogenicity studies, of topical microbicide candidates. This may include the development of new methodologies and technologies to accomplish product concentration measurements *in vivo*.
- Investigate the effect of endogenous hormonal states (puberty, pregnancy, menopause, and menstrual cycles) and exogenous hormonal states (including oral and injectable contraceptives and hormonal replacement therapy) on the safety and efficacy of microbicides.

- Foster methods and approaches for solving manufacturing and synthesis hurdles that may prevent the advancement of microbicides through the preclinical pathway, by providing support for early Good Manufacturing Practice (GMP) manufacturing design and scale-up.

OBJECTIVE–C

Develop and assess acceptable formulations and modes of delivery for microbicides, bridging knowledge and applications from the chemical, pharmaceutical, physical, bioengineering, and social sciences.

STRATEGIES

Microbicide Formulations and Modes of Delivery

- Develop formulations, dosage, and delivery systems suitable for the genital and GI tracts, so that toxicity and trauma to the tissue are reduced or eliminated, while maintaining product acceptability.
- Develop formulations to serve as placebos with rheological, physical, and chemical properties that are identical to their microbicide-containing counterparts.
- Identify and validate methods that improve the understanding of bioadhesion, biodispersion, retention, and distribution of microbicide formulations prior to, during, and after intercourse in male and female genital compartments.
- Develop methods to measure local tissue and systemic absorption following topical microbicide use, and relate this to microbicide efficacy and potency.
- Develop and incorporate culturally sensitive measures and mechanisms to assess microbicide and delivery mode acceptability in diverse populations of men and women that are and may be used in exploratory clinical studies as well as phased clinical trials.
- Understand the biologic mechanisms and physiologic changes that contribute to safety, efficacy, and acceptability of microbicide formulations, including, but not limited to, hormonal status, age, menstrual cycle, nature of intercourse, pregnancy, frequency of use, sexual arousal, and concomitant STIs.
- Develop, validate, and standardize methodologies to analyze the physical and chemical properties of individual microbicides, formulated microbicides, and combinations of microbicides.
- Develop methodology and supportive studies to evaluate product characteristics of microbicides (such as taste, smell, color, lubricity, and texture) that may affect acceptability and adoption/use of microbicides in diverse populations and for different types of sexual acts.
- Promote the discovery and application of the new sustained-release and solid-phase formulations technologies for the development of microbicides that will enable product use independent of coitus.
- Support the development of reference formulations with known acceptability profiles that can be used as a starting point for optimization of microbicides. Support the development of alternative formulation strategies and approaches, such as films and rings.

OBJECTIVE–D

Conduct clinical studies of candidate microbicides to assess safety, acceptability, and effectiveness in reducing sexual transmission of HIV in diverse populations in domestic and international settings.

STRATEGIES

Clinical Trials of Microbicide Products

- Design, implement, and conduct pre-Phase I and accessory clinical trials designed to explore, identify, and develop procedures, methodologies, or approaches to address microbicide safety, effectiveness, and acceptability as a means to inform on the design of Phase I, II, and III clinical microbicide trials.
- Develop and evaluate improved culturally informed methods to recruit and retain participants for Phase I, II, and III microbicide studies at domestic and international sites.
- Conduct research on mechanisms to improve clinical trial adherence and compliance with use requirements of products under study.
- Identify, develop, and validate behavioral markers to evaluate safety, effectiveness, and adherence to microbicides, including designing, developing, and evaluating tools to measure product use and acceptability both within and outside the clinical trial environment.
- Identify, develop, and validate biological markers of safety, effectiveness, and acceptability to microbicides, both within and outside the clinical trial environment.
- Address ethical issues in the design and conduct of microbicide trials, including communication with community stakeholders and the informed consent process for participants.
- Conduct research on the acceptability and effectiveness of microbicides relative to and in combination with other behavioral, preventive, and therapeutic methods.
- Identify and develop improved relevant techniques to evaluate safety of microbicides when applied to genital mucosal/epithelial surfaces during clinical trials.
- Follow up seroconverters in clinical trials to assess the impact of long-term product use and to assess the specific effect of these products on other STIs, contraception, and pregnancy.
- Study microbicide products in HIV-infected people to determine their impact on the development of drug resistance, drug-to-drug interactions, and the potential for other adverse events.
- Design, implement, and evaluate Phase IV postmarketing surveillance studies once an effective and safe microbicide has been identified in Phase III trials.

OBJECTIVE–E

Conduct basic and applied behavioral and social science research to inform and optimize microbicide development, testing, acceptability, and use domestically and internationally.

STRATEGIES

Social Science Research Related to Microbicides

- Support theory-building and the development of behavior epidemiological models of risk and protection in the context of microbicide research, development, and rollout. Conduct research on how microbicide use affects and is affected by psychological and social factors, incorporating a developmental perspective on individual, partner, and social influences.
- Develop and evaluate the efficacy of behavioral interventions to enhance correct and consistent use of microbicide products in diverse populations in different settings.
- Support health services/operations research on the implementation and costs of interventions using microbicides, including studies of dissemination, sustainability, acceptance, and adoption of microbicide interventions by health care providers.
- Improve methods and develop focused new and improved tools for microbicide research, including enhancing survey methods and tools, collecting valid self-report data, collecting behavioral and disease outcomes, measuring change over time, and recruiting and retaining subjects in clinical trials.
- Conduct research on optimal counseling approaches to enhance health decisionmaking around partially efficacious microbicides and the implications for HIV prevention.
- Use the tools and measures of behavioral and social science to predict potential trends in microbicide use and sustainability in at-risk populations, including adolescents and young adults.

OBJECTIVE–F

Establish and maintain the appropriate infrastructure (including training) needed to conduct microbicide basic and clinical research domestically and internationally.

STRATEGIES

Infrastructure

- Establish and strengthen training and infrastructure for the development of national and international institutional capacity for basic microbicide research, including the discovery and development of new microbicide candidates, assays for discovery and testing, and the infrastructure, training, and capacity required to advance microbicide candidates from discovery to initial clinical testing.
- Establish clinical trial sites and the infrastructure required for Phase I, II, and III studies domestically and internationally, and coordinate with efforts of other organizations to optimize available resources and encourage harmonization.
- Identify site-specific gaps in biomedical, behavioral, ethical, clinical, regulatory, and administrative training in national and international microbicide research sites, and design strategies that respond to these needs.
- Provide microbicide research training activities to foster and develop the acumen of national and international independent investigators (including development of mentor relationships and grant and protocol writing skills).
- Foster the dissemination of microbicide-related discovery and development strategies, including assay standardization and validation, to international investigators.
- Strengthen training and infrastructure for the development of national and international institutional capacity for microbicide research, including the enhancement of laboratory capability, data management/analysis, population-based research, high standards of conduct for clinical research, operational support, and physical infrastructure.
- Ensure the involvement of national and international communities in the planning and undertaking of international microbicide research.
- Foster and support the development of pilot and large-scale GMP production systems for the manufacture of microbicide active agents and their formulations.
- Develop strategies to promote the involvement of local governments, communities, and advocacy groups in the identification of priorities for and development of clinical protocols, and to sustain these efforts during the conduct of clinical trials.
- Foster interactions in the form of public and private partnerships aimed at integration of NIH microbicide activities with external organizations to accelerate microbicide development.

Vaccines

AREA OF EMPHASIS

Vaccines

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A

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 closely related lentiviruses by pursuing research in models that will provide information directly relevant to HIV infections; this 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 (adaptive) and antigen-nonspecific (innate) 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 envelope proteins, including transient or intermediate and conformational domains induced by virus interacting with CD4, chemokine, dendritic cell (DC) surface proteins and adhesion molecules, and other cellular receptors to improve vaccine designs to more effectively induce immune responses to block infection by active T-cell immunity and protective antibody.
  - Define and characterize viral B-cell and T-cell epitopes that induce protective immunity in HIV or AIDS-related disease; utilize structural analysis of envelope to determine whether and how their immunogenicity can be improved and exploited in vaccine development.
    - Determine the mechanism of how HIV and closely related lentiviruses evade or escape from humoral and cellular immune responses; 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 major histocompatibility complex (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 the role of DCs in the induction of immunological memory and long-term protective function of different subsets of human lymphocytes 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 viral antigens of closely related lentiviruses, and development of long-term protective immunity, particularly in human subjects.

- Study the mechanism of action of vaccine adjuvants for HIV immunogens that enhance HIV/SIV (simian immunodeficiency virus) antigen presentation to induce different cytokine or chemokine responses, innate immunity, and host factors; carry out comparative translational research in nonhuman primate (NHP) and human vaccines.

- Determine how chronic infection with one strain of HIV or closely 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 responses that are responsible for lack of disease induction by attenuated viruses and/or protection from challenge with related pathogenic virus, and determine the protective mechanism, duration, and extent of cross-protection.

- Define the heterogeneity of specific responses to vaccine immunogens, specifically those derived from HIV, SIV, and SHIV (chimeric simian/human immunodeficiency virus), 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 anti-HIV effector cell types, promote production of antiviral substances including chemokines, or enhance non-antigen-specific innate 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); study clinical samples from human volunteers participating in HIV vaccine trials to determine the extent of cross-reactive immune responses that can be achieved with different candidate vaccines.

- 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 and vaccine design by studying HIV-infected or highly exposed but seronegative individuals, across the lifespan, and SIV or SHIV NHP lentivirus models by conducting the following research:
  - Study acutely HIV-infected individuals, exposed/seronegative, or possibly transiently infected humans (including uninfected children born to or breastfed by 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, SIV, and SHIV, including identification of specific responses by passive transfer of antibody or immune cells and deletion of selected immune subsets in NHP models.
  - Investigate the sequence of events required for mucosal transmission/infection of HIV, SIV, or SHIV 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 HIV and SIV antigens and other infectious pathogens being used as HIV vaccine vectors in relevant animal models and humans to develop optimal vaccine strategies for HIV antigen delivery and effective immune-based prevention of HIV transmission.
  - Acquire clinical specimens from populations relevant to HIV vaccine trials for laboratory studies; explore the molecular epidemiology, humoral, and cell-mediated immune responses to HIV-1 and their relationship to class I and class II MHC alleles; and define constraints on HIV evolution under immune selection pressure so as to guide vaccine development. Acquire appropriate, linked, epidemiological information to optimize interpretation of these analyses.
  - Monitor the effects on immune activation with intercurrent sexually transmitted diseases (STDs), malaria, tuberculosis (TB), hepatitis B and C, human papillomavirus (HPV), and other infectious diseases, and with administration of drugs of abuse or effects of antiretroviral therapy (ART) on HIV shedding in vaccinated subjects. Model these confounding elements in NHP.
- Develop *in vitro* experimental approaches for analysis of HIV 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 lifespan) and animals protected against SIV or SHIV by undertaking the following research activities:

- Develop and improve NHP 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 NHP 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 HIV neutralization; explore the mechanisms of virus neutralization and the reason(s) for the relative difficulty to neutralize primary HIV isolates.

- Develop and standardize immunological reagents for HIV vaccine trials; 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, storage, recovery, viability, shipping, and tracking of samples that will be essential in large-scale HIV vaccine trials.

- Study the function of HIV/SIV-specific CD4 T cells, CD8 T cells, and viral suppressive immune responses; develop and adapt high-throughput assays with specificity for primary HIV isolates; and make available those reagents required for HIV 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–B

Design HIV 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, nongovernmental 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 such as breastfeeding infants, adolescents, and women.

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 immunogen strategies designed to target DCs;
    - Recombinant HIV envelope protein subunits produced by a variety of methods, with an emphasis on retention or exposure (e.g., through deglycosylation) of critical nonlinear or conformational structural epitopes for induction of effective antibody responses;
    - Structurally constrained HIV envelope 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, the NIH, the 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 HIV vaccine candidates for testing in NHPs and human subjects. Where necessary, the NIH will provide products produced under clinical grade Good Manufacturing Practices (cGMP) and ensure that products meet these standards;
  - 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 among, academic investigators, industry, affected communities and populations, and other agencies in the research, development, production, and clinical testing of candidate vaccines.
- Foster the development of HIV 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 arms of the immune response; and
  - Multivalent vaccine candidates incorporating different genetic clades and/or antigenic types to increase the breadth of immune responses.
- Support HIV vaccine design and development, incorporating methods to improve or modulate vaccine-elicited immune responses (qualitatively or quantitatively), including:
  - Novel adjuvants and delivery methods that might enhance effective DC presentation of HIV/SIV antigens;
  - Agents that stimulate or modulate mucosal immune responses to HIV or other host defenses, including cytokines or chemokines;
  - HIV/SIV vaccines formulated with cytokines or incorporating cytokine genes or other biologically active molecules in vectors to improve the avidity of T cells and/or the functional activity of antigen-specific T cells; and
  - Other novel strategies, including nutritional supplementation and treatment of underlying infections and/or diseases that might have an impact on HIV vaccine responses.

- Evaluate the efficacy of HIV/SIV vaccine and other immune prevention strategies in NHP animal models of HIV and closely related lentiviruses by:
  - Testing HIV/SIV 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 generated by HIV/SIV vaccines;
  - Determining the effect of HIV/SIV vaccine formulation, site of delivery, and regimen, as well as the nature, timing, phenotype, and route of infectious SIV or SHIV challenge on the effectiveness of the vaccine-induced immunity;
  - Defining the impact of different HIV/SIV vaccine approaches on the kinetics of immune responses, kinetics and localization of viral replication, including long-term followup of disease progression in the presence of low-level chronic infection and concomitant diseases (e.g., TB, hepatitis, or autoimmune diseases), and biologic characteristics of breakthrough virus including transmissibility;
  - Determining the impact of genetic factors, age, and concurrent prophylactic antiretroviral therapy or topical microbicides on HIV/SIV vaccine responses and on protection against virus at various challenge sites; and
  - Studying the efficacy of the HIV/SIV immune response in the face of viral variation.
- Investigate HIV/SIV vaccines and other biomedical prevention strategies with attention to potential factors such as integrity of the mucosal surface, changes in vaginal/cervical epithelium during puberty, hormonal changes during pregnancy, use of contraceptives or hormone replacement therapy, and presence of STDs; wherever possible, study potential concomitant effects on the genital tract immune responses and how inflammatory activity might compromise integrity of the mucosal surface or the inductive ability of HIV vaccines.
- Support development of reagents and standardized methods to assess specific HIV or SIV vaccine-induced immune responses in NHP 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 versus those due to HIV, SIV, or SHIV infection;
  - Characterizing and evaluating potential negative side effects of candidate HIV/SIV vaccine designs, including the potential to increase the susceptibility to infection or the rate of disease progression in NHP animal models;
  - Standardizing and validating assays to assess potency of candidate HIV vaccines;

- Standardizing and validating assays to be used as Phase III study endpoints; and
- Abiding by Good Laboratory Practice (GLP) regulations to perform endpoint assays in support of product licensure and instituting quality assurance programs to assure sponsors and vaccine manufacturers that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with regulations stated in 21 CFR Part 58 and Part 11.

- 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 suppression of immunity, or to generate highly immunogenic antivector responses; or
  - That express potentially harmful vector proteins.

OBJECTIVE–C

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 NHP animal models of maternal-fetal and maternal-infant perinatal transmission of HIV/SIV/SHIV that can:
    - Determine preclinical safety and immunogenicity of various HIV vaccines and adjuvants, particularly in pregnant and newborn primates;
    - Determine safety of various monoclonal and polyclonal antibody preparations against HIV;
    - Determine the best immunization routes or protocols to induce antibodies to HIV in milk and other secretions;
    - Evaluate infant cellular and humoral immunity to HIV in the context of breastfeeding from an HIV-infected mother, and determine immune correlates of protection for potential exploitation in vaccine strategies;
    - Evaluate efficacy of vaccines and passive immunotherapy for prevention of perinatal or breastfeeding HIV 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 ART in combination with immune and behavioral prevention strategies.
  - Determine virologic and nonimmunologic/genetic 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 additional viral factors are associated with differences in perinatal transmissibility;

- Developing standardized methods to collect specimens and to detect, characterize, and quantify HIV in cervicovaginal secretions and in breast milk to determine their potential relevance in mother-to-child transmission (MTCT); and

- Determining if HIV 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 HIV 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/SIV 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/SIV with its receptors and coreceptors and/or that targets infected cells.

  - Characterize the transmitted viral strains and monitor changes that may occur in proposed HIV vaccine 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 *in utero* and intrapartum to HIV (born to HIV-infected women) as well as breastfeeding infants.

- 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 HIV 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 may 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 HIV vaccines, passive immunity, and other perinatal interventions with prospective long-term followup. For vaccines, this should include the assessment both 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 HIV 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 HIV infection status as a perinatal intervention trial endpoint in countries where breastfeeding is recommended despite maternal infection status, including type of diagnostic tests, timing of the tests, length of followup, and adherence to followup visits.
- Study HIV 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 ART interventions and HIV vaccines given while on effective ART, on the maintenance or regeneration of naïve T cells and antiviral immune responses in HIV-infected infants.

OBJECTIVE–D

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

STRATEGIES

- Support the conduct of Phase I, II, and III HIV vaccine clinical trials that will determine short- and long-term safety; immunologic responses measured by a broad range of humoral, cell-mediated, and mucosal immune parameters; and the efficacy of different preventive vaccine candidates. This includes the following:
  - Develop and implement strategies to coordinate studies in NHP with clinical trials so that data from NHP studies inform decisions about clinical trials and data from clinical trials can be used to improve NHP animal models.
  - Design and conduct Phase I and Phase II trials using promising HIV vaccine candidates. Trials should determine safety, 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 the general populations (gender, age, ethnic and racial minority), particularly including understudied populations affected by HIV such as women and adolescents, and should 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 test-of-concept (TOC) or efficacy trials.
- Develop a comprehensive plan for conducting HIV vaccine trials with rapid accrual, high retention, and adequate long-term followup of vaccinees to reach predefined endpoints, as follows:
  - Conduct research into methods to effectively recruit and retain diverse populations into HIV vaccine trials.
  - Prepare for adequate long-term followup of volunteers in HIV vaccine clinical trials to determine the durability of immune responses and protection, the immune correlates of protection, long-term safety, behavioral factors to influence adherence of followup visits, the impact of participation on risk-taking behavior, and vaccine-related reduction (or enhancement) of disease progression and HIV transmission.
  - Conduct collaborative large-scale efficacy trials of preventive HIV 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 HIV infection, disease progression, and/or transmission;

- Evaluating additional virologic, immunologic, and behavioral outcomes, particularly potential correlates of protective immunity against HIV;
- Ensuring that HIV vaccine trials are conducted with the highest regard for social, legal, and ethical standards and in populations that reflect the racial and ethnic burden of HIV disease, also including women and adolescents;
- 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, age (adolescents), 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.

- Explore innovative trial designs to improve efficiency of HIV 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 HIV-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, clinical outcomes, and the benefit of long-term followup.
  - Encourage linkage between vaccine preparedness studies in high-risk populations and other research activities, including research on TB and STDs.
  - Utilize information from trials of other biomedical and behavioral interventions to consider novel trial designs (including, but not limited to, factorial designs and cluster-randomized designs), and the timing and impact of data from other trials on HIV vaccine trial design and conduct.
  - Consider the impact of early ART on HIV infections in complex trial designs.
  - 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 HIV vaccine trials, particularly to vulnerable populations of women and adolescents, and assist in providing solutions.

- Conduct behavioral risk assessment research in appropriate subgroups during HIV vaccine trials, particularly with Phase II, TOC, and Phase III trial participants, to identify and evaluate any changes in risk behavior as a result of participation in an HIV 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 vaccine research and HIV immunotherapeutic interventions to facilitate and expedite translation of basic research to clinical practice.

OBJECTIVE–E

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 HIV 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 or populations.

STRATEGIES

- Identify and develop potential domestic and foreign sites with a high HIV seroincidence and improve 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 applying newer epidemiologic tools for estimating the HIV incidence in various populations with documented high-risk behaviors 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 able participants in HIV vaccine trials.
  - Identify and address barriers to participation in clinical trials among all at-risk groups, so that all relevant populations, especially women and adolescents, are included in HIV vaccine trials.
  - Develop and apply new laboratory diagnostic tools, including rapid, point-of-care tools, that can be adapted for high throughput to detect, characterize, and amplify virus in blood and mucosal fluids from individuals with new HIV infections and allow distinction between vaccinees and infected individuals.
  - 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 virus peak and set point, and disease progression.
  - Acquire and analyze HIV isolates from mucosal sites, as well as blood from recently infected people 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 HIV vaccine efficacy trials. This includes education and training of personnel from international sites hosting vaccine trials; development of laboratory infrastructure; standardization of assays and development of panels of geographic-specific reagents composed of local, indigenous HIV+ and HIV- samples as well as peptide reagents to serve as controls when validating and standardizing assays that will

be used in support of clinical trials in that region; 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 HIV/AIDS vaccine efficacy trials. This includes the following:
  - For all HIV 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 and public health need for the study.
  - Develop mechanisms (including CABs) to engage in collaboration and to provide education and the means to inform communities about HIV vaccines on a continuing basis so that social as well as medical concerns are addressed; work to establish trust in the community 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), the World Health Organization (WHO), the Joint United Nations Programme on HIV/AIDS (UNAIDS), and the Global HIV/AIDS Vaccine Enterprise (GHAVE) to prepare for, plan, and conduct HIV vaccine trials adhering to the highest ethical and scientific standards.
  - Support the education of local CABs and local institutional review boards on issues concerning the conduct of HIV vaccine clinical trials in their communities.
- In collaboration with Government agencies, institutions, NGOs, and communities being identified as potential collaborators, explore behavioral and social issues and prevention activities (e.g., circumcision, microbicides, anti-HSV treatment, HPV vaccine, breastfeeding strategies) that might have a substantial impact on either the design or the conduct of an HIV vaccine 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 one or more populations identified for future vaccine efficacy trials; address their potential impact on the evaluation of HIV 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 vaccine efficacy trial, especially for populations that have been historically underrepresented in clinical trials and where the HIV epidemic is expanding disproportionately.

- Identify and develop strategies to involve the populations with highest risk for HIV transmission in different communities; particular attention should be given to high-incidence populations of adolescents and young persons.
- Develop research that anticipates and addresses effectively the potential adverse or unintentional effects of biomedical advances in HIV prevention (e.g., vaccines, microbicides, rapid testing, etc.), including behavioral disinhibition or increases in risk behavior such as failure to use condoms in sexual encounters, which may offset gains in prevention.
- Collaborate with other U.S. Department of Health and Human Services (DHHS) agencies and community-based organizations to develop education programs to facilitate the conduct of Phase III HIV vaccine trials in hard-to-reach populations in domestic sites; collaborate with the U.S. Military HIV Research Program (USMHRP), the Centers for Disease Control and Prevention (CDC), the U.S. Agency for International Development (USAID), and other organizations to develop vaccine trial sites in international settings.
- Evaluate the impact of community-based participatory research in the acceptability of HIV vaccine trials.
- Develop appropriate communication strategies involving affected communities in the process of testing HIV vaccines and prepare for the eventual integration of preventive vaccines into comprehensive prevention and care programs in the United States and in countries where HIV vaccine trials are conducted.
- 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 HIV vaccine efficacy trials.

- Develop tools to enhance recruitment, training, and retention of new investigators and staff involved in conducting HIV vaccine research globally.

Behavioral and Social Science

AREA OF EMPHASIS

Behavioral and Social Science

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A

Develop, evaluate, and advance prevention interventions: Support research to develop, evaluate, and diffuse effective behavioral, social, environmental, and economic interventions to prevent HIV transmission and acquisition by reducing HIV-related risk behaviors and increasing protective behaviors, including studies of "scaling up" effective interventions.

STRATEGIES

- Develop and evaluate the efficacy, effectiveness, and cost-effectiveness of demographically and culturally appropriate behavioral, social, and structural interventions in different domestic and international settings and populations to reduce high-risk HIV-related sexual and drug-use behaviors and HIV transmission.
- Translate and apply basic behavioral and social science research to optimize the development of innovative and effective intervention strategies.
- Support new research to identify or adapt the active ingredients of efficacious, theory-based interventions for broader adaptation and uptake.
- Modify, adapt, or refine existing efficacious HIV prevention interventions to increase their potency, and also to make them more easily administered and used in the community.

Populations and Contexts

- Develop and test interventions targeted at HIV-infected persons to reduce sexual and drug-use transmission risk behaviors.
- Support intervention research that addresses the impact of alcohol and/or drugs on sexual encounters that may contribute to HIV transmission and acquisition.
- Continue development of interventions targeting at-risk populations (e.g., injection drug users [IDUs], other drug users, partners of drug users, street children, and men who have sex with men [MSM]), with particular emphasis on drug-use and sex-related risks.

- Continue development of interventions for persons with multiple mental and physical disorders.
- Support domestic and international intervention research on the HIV prevention role of programs designed to enhance healthy sexual development and protective behaviors (including avoidance of too-early or nonconsensual sex, abstinence from unsafe sexual behavior, and access to and use of barrier methods) throughout one's lifetime.
- Support interventions for populations that are currently at low risk or that perceive themselves to be at low risk for HIV infection, but that may be susceptible to engaging in high-risk behaviors (e.g., non-sexually active, non-drug-using adolescents; subpopulations of heterosexual men and women; and certain middle-aged and older populations).
- Support intervention research that addresses important contextual risk factors for disproportionately affected groups that continue to demonstrate high-risk behaviors. This research also should identify which public health applications most effectively attend to cultural contexts.
- Develop, test, and evaluate interventions that target individuals both within prisons and returning to society from correctional settings; strategies include increasing access to education, information, therapeutic care, substance abuse treatment, prevention services, and clinical trials.
- Develop, test, and evaluate interventions that make use of existing systems of care that serve at-risk populations but do not routinely provide HIV prevention services (e.g., primary care or mental health settings) or address limited aspects of HIV prevention (e.g., sexually transmitted infection [STI] clinics that address sexual, but not drug use, risks).
- Develop, test, and evaluate interventions that target individuals both within the military and returning to society from the military; strategies include increasing access to education, information, therapeutic care, substance abuse treatment, prevention services, and clinical trials.
- Support the capacity to develop rapidly domestic and international intervention studies in response to changes in the epidemic.

Effectiveness

- Develop, test, and evaluate interventions that target a range or combination of levels of social organization (i.e., individual, dyad, family, network, community, institution, and society) and that examine how these levels interact to affect HIV risk and protective behavior and HIV transmission in different cultural contexts.
- Support research to increase the effectiveness, as strategies of HIV prevention, of interventions already used in service delivery systems for high-risk populations, such as family planning interventions; drug and alcohol abuse prevention; and treatments for STIs, drug and alcohol abuse, and mental disorder.

- Conduct studies to identify key components of efficacious interventions to facilitate transfer, adaptation, and application of them.
- Support research in the United States and abroad to improve the transfer of effective HIV interventions among communities, particularly research on the adoption and adaptation of efficacious HIV interventions by communities (including studies of diffusion processes and the exchange of knowledge between service providers and researchers); this research includes study of the maintenance of effective interventions and assessment of the generalizability of interventions with diverse populations.
- Evaluate novel interventions identified as high priority by HIV community planning groups and other service providers.
- Support research on the long-term impact of HIV prevention interventions on individuals and communities (i.e., 5 or more years postintervention).
- Develop and test the efficacy of adaptive preventive interventions, in which different dosages of certain prevention components are assigned to different individuals, or within individuals across time, with dosage varying in response to the intervention needs of the individuals.

Systems

- Support research to understand and improve the organization, financing, management, access, delivery, cost-effectiveness, and cost-utility of health care (including care for substance abuse and other psychiatric disorders), family planning, and other social services that reduce HIV risk behaviors and HIV transmission.
- Support research to understand and improve prevention services' linkages, coordination, and integration with primary medical and dental care; drug, alcohol, and mental health treatment; STI treatment; reproductive health and family planning services; services for orphans and vulnerable children; and other social services.
- Support research on integrating HIV prevention interventions into addiction treatment settings, with emphasis on behavioral treatments, alone or in combination with pharmacotherapies, for both HIV-positive and HIV-negative patients.
- Support intervention research on strategies for improving the willingness and capacity of communities to adopt and sustain primary prevention interventions.

Methods

- Design and test behavioral interventions for relevant populations to increase recruitment, retention, and adherence to protocols for HIV prevention research, including trials studying prophy-

lactic vaccines, access and use of HIV testing, microbicides, and other biomedical prevention methods.

- Encourage, where appropriate, the use of quasi-experimental designs and the evaluation of natural experiments in domestic and international HIV intervention research.
- Integrate behavioral, social, and biological measures to improve sampling, measurement of risk factors, and evaluation of outcomes, including measures of substance use, recent HIV infection, population-based outcomes (e.g., seroepidemiology), recent sexual exposure, and STIs, with the overall goal of increasing the reliability and validity of measurement and sampling in prevention research.
- Support behavioral intervention studies that include HIV seroincidence data and other biologic markers as outcome measures.
- Support development of new approaches for addressing "hidden" or "difficult to reach" populations in intervention studies.

OBJECTIVE–B

Conduct basic social and behavioral research on factors influencing HIV risk behaviors and on the consequences of HIV disease: Support basic social and behavioral research to strengthen understanding of the determinants, processes, and cultural and contextual issues influencing HIV-related risk and protective behaviors and the consequences and impact of HIV disease, including treatment for and management of HIV infection. This includes domestic and international research that examines the societal, community, organizational, social network, dyadic, and individual barriers to and facilitators of the adoption and utilization of effective preventive and treatment interventions across the life course.

STRATEGIES

Continuing Critical Areas

- Conduct basic research to understand better the impact of HIV therapeutic regimens on adherence to treatment for HIV and cooccurring infections, sexual risk behaviors, drug-related risk behaviors, and psychosocial adaptation (i.e., improved quality of life).
- Examine neurobiological mechanisms of motivation that underlie HIV risk behaviors.
- Define the applicability and limits of rational models of behavior versus models that address states such as sexual arousal or drug- or alcohol-altered cognitive processing that do not conform well to existing models.
- Develop new models of behavioral change that integrate biological, psychological, and social perspectives to explain and predict the adoption and maintenance of HIV risk and HIV protective behaviors among vulnerable individuals and understudied groups, both domestically and internationally.
- Support theory-building studies developed in the context of HIV prevention research, as well as study theories developed for other areas (e.g., drug and alcohol abuse prevention, family planning, sexual development, and interpersonal social skill development) to see how they inform HIV prevention research.
- Support research that can more closely monitor the HIV/AIDS epidemic and associated risk behaviors so that emerging needs for basic behavioral and intervention research can be identified.

Consequences

- Support research on the decisionmaking processes and behaviors of health care workers regarding the offering of HIV counseling, testing, and other prevention services, as well as the prescription of HIV disease treatments, to those in need of HIV services and care; investigate the

relationships between the health care workers' decisions and those of patients, family members, and community members.

- Conduct research concerning the health and life course of children, including orphans, affected by HIV. This research should include early identification and assessment of affected children for physical, psychological, and social consequences.
- Identify the neurobiological, behavioral, cognitive, social, and economic consequences of HIV disease for HIV-seropositive individuals (including children), their support systems (e.g., partners, family members, and other caregivers), health care systems, and communities.
- Support research on the economic and social implications for retired and older individuals who provide support and care to younger family members or friends with HIV/AIDS and their dependents, including studies of the support systems that may be in place for such individuals.
- Support behavioral research to study end-of-life transition strategies for patients with AIDS and their caregivers.
- Support interdisciplinary research, involving behavioral and biomedical scientists, to determine the relationships among stress, mood disorders, immune system functioning, and HIV infection, and to examine the psychosocial and physiological factors affecting those relationships.
- Support studies on animal models of behavior and behavioral change relevant to HIV infection and prevention; in particular, conduct behavioral neuroscience and neuropsychological research to determine the brain/behavior changes associated with exposure to HIV, the effects of HIV exposure on social behaviors (e.g., mother-infant attachment and peer interactions), and behavioral changes in relation to comorbidities of HIV and substance use and addiction.

Prevention

- Study the acquisition and maintenance of HIV-related risk and protective behaviors associated with HIV transmission or progression in specific social and cultural contexts, such as the sexual dyad, peer groups, social and substance-using networks, families, and communities. This would include studies of HIV risk, transmission, and progression as related to cultural norms that affect disempowerment of and violence toward women.
- Study how HIV risk changes over time as a function of developmental and life-course events, such as adolescence, childbearing, marriage or entry into other committed partnership, divorce and separation, and aging.
- Conduct research on decisionmaking processes that relate to sexual and drug-related risk-taking across the life course.

- Support multidisciplinary research that investigates the biobehavioral and sociobehavioral determinants of sexuality, including processes of sexual and gender identity formation, as they relate to HIV risk.

- Conduct research on partner selection and relationship dynamics, including how partner choice, partner formation, relationship development, and partner stability change over the life course and affect HIV risk and HIV-related behavior; studies should examine psychological, cultural, and social factors that influence these phenomena. Interactions of alcohol/drug use with partner selection and demographic trends in partnering, as related to HIV risk, should also be addressed.

- Support multidisciplinary research that investigates biobehavioral and sociobehavioral determinants of injection drug use and the transition from noninjection to injection drug use as they relate to HIV transmission; such research may also include studies that investigate the relationship between any drug use and sexual risk behaviors.

- Conduct research on individual social and cultural differences in human sexuality that have an impact on the sexual transmission of HIV; such research may include studies that examine how sexual behavior is affected by substance use and abuse, sexual abuse or coercion, developmental processes, and the formation and dissolution of intimate relationships.

- Study the social, structural, cultural, and demographic factors (e.g., socioeconomic status, marital status, ethnicity, sexual identification, age, and gender) that influence HIV-related behavior.

- Support research to understand how and whether communities engage in HIV preventive interventions, including studies to determine how to better ensure the use of prevention research by communities and public health entities in the United States and abroad.

- Support research that investigates the impact of laws and policies on behaviors associated with HIV transmission and acquisition.

- Conduct research that identifies the social and behavioral factors affecting recruitment, retention, and adherence to prevention and treatment interventions, including clinical trials of HIV-related vaccines, microbicides, and therapeutics.

- Support behavioral and social research on the acceptability, initiation, and use of biomedical and barrier HIV prevention methods (e.g., condoms, microbicides, rapid tests, and vaccines), and determine their impact on adherence to risk-reduction guidelines.

- Support behavioral and social research on the acceptability, initiation, and use of methods for HIV screening, counseling, and testing, and determine their impact on adherence to risk-reduction guidelines.

- Support basic and preintervention research on behavior modification and maintenance of new behavioral patterns for developing prevention and intervention strategies.

- Support behavioral surveillance research that measures changes, especially as a function of the diffusion of information and Internet use, in norms, attitudes, and expectancies regarding behaviors associated with HIV transmission and acquisition.
- Support research to identify how alcohol use (e.g., binge drinking trends) affects HIV risk among selected age groups.
- Study factors that enhance or preclude partner notification and the impact of partner notification on HIV testing and risk reduction.

OBJECTIVE–C

Conduct treatment, health, and social services research for people infected and affected by HIV: Support research into the development, evaluation, diffusion, and adoption of strategies to increase early identification of HIV infection; to improve treatment adherence; and to prevent or minimize the negative physical, psychological, cognitive, and social consequences of HIV infection, including stigmatization of persons with or at risk for HIV infection. Support research strategies for promoting effective health care utilization among all persons with HIV infection and for promoting modifications in the health care delivery system to develop more effective, socially appropriate, and culturally sensitive methods to better serve treatment needs of infected populations, both domestically and internationally.

STRATEGIES

Treatment and Care

- Develop and test interventions to modify the practice behaviors and decisionmaking processes of health care providers to improve the quality of screening, counseling, and treatment services for HIV-positive persons and persons at risk for HIV infection.
- Support research on adherence to treatment regimens, including studies on communication techniques to improve shared decisionmaking between health care providers and HIV-infected individuals, issues such as how and when to initiate, interrupt, or cease therapy, and behavioral strategies to manage symptoms secondary to treatment protocols.
- Promote research to identify and remove barriers to effective health care utilization among persons with or at risk of HIV infection, including barriers associated with fear and stigmatization that affect access, engagement, followup, and adherence to health and social services across the care continuum (e.g., early identification of HIV infection, testing and counseling, health-care-seeking behavior, adherence, case management, and home/hospice care) and across the life course (i.e., from childhood to old age).
- Develop and test interventions to increase recruitment, adherence, and retention in HIV/AIDS clinical trials and care by HIV-infected persons from all vulnerable populations, with special attention to developmental and life-course issues.
- Support health services research and evaluation research to determine the impact of changes in the health care delivery system on HIV/AIDS care.
- Support research to foster more effective participation in treatment planning, decisionmaking, and formulating advance directives by patients with HIV and their families.
- Support behavioral and social research on the acceptability, initiation, and use of methods for HIV screening, counseling, and testing directed toward seropositive persons, and determine their impact on adherence to risk-reduction guidelines and entry to and initiation of appropriate care and treatment.

- Support research on the special factors affecting adherence in older patients and medical decisionmaking in care of older patients.

Biopsychosocial Consequences

- Develop and evaluate interventions to prevent the adverse psychological and social consequences of HIV infection and to assist HIV-affected populations in coping with HIV infections, maintaining quality of life, and avoiding engagement in HIV-related risk behaviors.
- Test interventions to address the neuropsychological, neurodevelopmental, and psychiatric sequelae of HIV infection.
- Develop and evaluate interventions to minimize the impact of stigmatization on HIV-infected persons, including on their decisions regarding treatment and quality of life.
- Test interventions designed to support formal and informal caregivers and family members of HIV-infected persons in order to prevent, for example, depression and burnout.
- Support research to enhance the quality of life and minimize the impact of pain, fatigue, physical symptoms, and treatment side effects and to integrate effective palliative care throughout the course of treatment for all people living with HIV and AIDS.

OBJECTIVE–D

Improve the quality of behavioral and social science methodology in HIV research: Support research to advance innovative quantitative and qualitative methodologies to enhance behavioral and social science on HIV prevention and care, and to address pressing ethical issues in the conduct of such research.

STRATEGIES

Measurement

- Develop improved methodologies for collection and analysis of quantitative and qualitative data—including methods for obtaining and validating self-report data, culturally appropriate standardization of measurement tools for surveys, and the measurement of change over time—based on an assessment of the current status of qualitative and quantitative methodologies for studying behavioral and social factors associated with HIV and AIDS.
- Develop and strengthen research instruments that are culturally and linguistically appropriate for subpopulations (e.g., HIV-infected children, the elderly, and prisoners) and that reflect age-appropriate concerns.
- Develop and refine techniques for measuring social networks associated with HIV transmission.
- Develop and refine techniques for studying use of the Internet and its association with HIV transmission.
- Integrate behavioral, social, and biological measures to improve sampling, measurement of risk factors, and evaluation of outcomes, including measures of substance use, recent HIV infection, recent sexual exposure, and sexually transmitted disease.
- Develop improved methods for the reliable and valid collection of sensitive information regarding sexual and drug-use risk behaviors.
- Where appropriate, develop and/or adapt innovative substance abuse assessment approaches, such as biomarkers and passive alcohol sensors, ecological momentary assessment approaches, interactive voice response technology, personal data assistants (PDAs) to monitor substance use, wireless keypad surveys, Web-based surveys, cell phones, palmtop-assisted self-interviewing, and audio-enhanced PDAs.
- Assess new methodologies for testing efficacy of environmental-level (e.g., laws and policies) interventions for reducing HIV risk.
- Support research to determine under what circumstances each of the following outcome measures—alone or in combination—is appropriate to use: self-report measures, HIV infection, and other disease outcomes such as other STIs and blood-borne diseases.

- Develop improved qualitative approaches to theory building and to measurement of HIV-related behaviors, behavioral change, and factors that influence behavior and behavioral change.
- Develop improved approaches to formulate, integrate, and analyze theories founded on qualitative and quantitative observations.
- Develop and refine outcome measures and indicators appropriate for the evaluation of social policy and the societal impact of HIV prevention and treatment interventions.

Modeling

- Develop and refine mathematical models for linking behavioral change interventions with a reduction in HIV transmission at different levels of seroprevalence.
- Improve methods for forecasting and modeling AIDS caseloads, health care needs, and health care utilization under different treatment and survival scenarios and for forecasting and modeling prevention services needs.
- Develop and refine models of potential efficacy of environmental-level (e.g., laws and policies) interventions for reducing HIV risk.

Design and Statistical Analysis

- Develop improved methods for sampling subpopulations (e.g., children, homeless persons, drug users, the elderly, and gay men of color) and spatial units (e.g., migration routes, drug or human trafficking routes, and political jurisdictions of interest), with particular attention to "hidden" or "hard to reach" populations.
- Develop improved and innovative methods and techniques for conducting and analyzing longitudinal studies of HIV-vulnerable and HIV-infected populations, including improved participant retention strategies; statistical methods for dealing with participant attrition, missing data, and nonnormal distributions; and methods for measuring and analyzing nonlinear patterns of behavior change.
- Foster the development and dissemination of design alternatives to the randomized controlled trial that permit cost-effective evaluation of intervention strategies at the individual, group, and community levels.
- Foster the development, maintenance, and use of shared databases that will enhance the ability to identify and detect significant interactions between and within a variety of behavioral domains and also to identify the role of behavioral actions as mediators of biological outcomes of importance in HIV research.

Ethics and Other Issues

- Evaluate the effects of legal and ethical constraints on methods of HIV research and service delivery, particularly among vulnerable or special populations.
- Use behavioral and social research methods to investigate factors associated with particular ethical and legal principles in research design (e.g., competence to provide consent, prevalence of adverse events, and associated remedies).
- Develop and refine research techniques to advance multisite, intercultural, and international studies.
- Encourage secondary data analysis; develop approaches to protect and document confidentiality.
- Develop and evaluate mechanisms for dissemination of behavioral research findings to the HIV/AIDS research and service communities and for receiving and evaluating community or constituent feedback.