PRIORITY:

Reducing New Infections

Vaccines

Microbicides

Behavioral and Social Science

Treatment as Prevention

AREA OF EMPHASIS

Vaccines

FY 2012 RESEARCH PRIORITIES

Research interest in HIV vaccines was re-energized at the beginning of FY 2010 with the report of limited efficacy to prevent infection that was observed in the HIV vaccine trial (RV 144) in Thailand. Major research efforts are being engaged to search for immune correlates of protection in samples derived from the 16,000 participants in the Thai trial. Teams have been developing new concepts for human HIV vaccine trials that either build on the RV 144 trial (of a pox virus vector to induce HIV-specific responses and a boost with envelope proteins) or substitute one or both components with newly designed candidate vaccines that might be even more effective. In addition, new data from the previous STEP trial that did not contain an envelope component and that failed to protect individuals from infection suggest that the HIV that infected some of the individuals was genetically different from the vaccine strain. Alternatively, the incoming virus is being rapidly modified by the vaccine-induced immune response in the individuals who became infected. This information added to the knowledge that the circumcised men who did not have high titers of antibody to adenovirus 5 also appeared to have a reduced risk of HIV infection.

The key priorities that were identified were the following.

- **KEEP THE BALANCE** *There is a strong sense that there still is much to learn about basic adaptive and innate immune mechanisms that might be triggered by HIV vaccines. Basic research on vaccine responses in animals must be complemented by basic research in human immunology to delineate the differences and similarities. Concerns have been expressed that the pipeline for new vaccine concepts and the availability of new candidate HIV vaccines for testing in humans will "dry up" if innovative research is not fostered at the same time that research is conducted on samples from large trials or nonhuman primate (NHP) studies. To this end, investigators should be encouraged to adapt and employ all of the new tools that might be appropriate for investigating immune responses and host defense mechanisms that are triggered by HIV vaccines.*

  In the past few years, several teams have defined new sites on the virus envelope that appear to render the virus susceptible to attack by antibodies that can block virus entry into cells or block virus replication. These have been defined by monoclonal antibodies, and it is postulated that antibodies that do not score as positive in virus-neutralizing assays may have been effective in the trial in Thailand. Studies to investigate passive transfer of different types of antibodies might reveal new mechanisms that have not been considered previously for protection.

  Information from potential vaccine cohorts around the world has confirmed findings from a number of years ago that the HIV that is transmitted from one individual to another is often very limited in its diversity—indicating that only one or a few virus particles are able to establish an infection in most people. However, the initial founder/transmitted HIV can change rapidly (within weeks) and become more complex as it tries to evade the response that the individual makes to keep it under control. The fact that only a limited amount of

virus is establishing infection has led HIV vaccine researchers to redesign the animal models, which are being used to evaluate vaccines, to more closely reflect the type of exposure that humans are encountering. These models also will be useful for microbicides and other prevention strategies.

- **BUILD MORE INTEGRATED, MULTIDISCIPLINARY HIV VACCINE CONSORTIA** Researchers are concerned that small groups of investigators have limited resources and lack sufficient interaction with others to develop products to the point where it is feasible to do definitive studies either in NHP or in human trials. Further, these small groups do not have the expertise to overcome in a timely fashion the barriers to vaccine development for clinical studies. *Consortia that engage multiple partners to test specific concepts and model challenges by different routes of exposure to HIV, especially when focused on mucosal transmission, may be the most efficient way to approach some of these questions.*

- **CONTINUE TO CONDUCT CLINICAL TRIALS OF HIV VACCINES** The combination of different candidate vaccines has indicated that unpredictable outcomes both in immune responses and in protection outcomes in humans can be observed. *The need for vaccine concepts to be more extensively studied in animal models that more closely mimic the transmission observed in human clinical studies has become evident from the efficacy trials that have been conducted thus far. Clinical vaccine trials need to be coupled with intensive and integrated immunological research to understand how the vaccines are working to prevent infection at the mucosal surfaces where humans are routinely exposed in the worldwide epidemic. The need to do this much more efficiently while retaining the ability to see benefit in different risk groups is a very high priority.*

OBJECTIVE–A: Host Defense Mechanisms

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 infection; 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 the HIV 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; conduct comparative translational research of 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 non-progressors) to define immune responses to HIV-1 and HIV-2, potential vaccine-inducible host immune responses, and viral factors (or viral attenuations) or host factors that enhance or 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.

  - Explore genome-wide association studies, in addition to targeted genetic analyses, to reveal novel viral protection/control mechanisms, particularly those that might be manipulated or inform HIV vaccine studies.

  - 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 NHPs.

- 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 the 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 genetic sequencing of selected regions of NHP genomes.
  - Create cryorepositories of cells isolated from NHP tissues (including blood, primary lymphoid organs, and mucosal specimens) from immune-naïve, HIV- or SIV-vaccinated, or SHIV- or SIV-infected animals to provide a resource for assay development in parallel with human studies.
  - Develop improved methodologies and assays to measure HIV neutralization; explore the mechanisms of virus neutralization and the reason(s) for the relative difficulty of neutralizing 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 clinical 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: Vaccine Design, Development, and Animal Testing

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 active and passive 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;
    - Antibodies or other virus-neutralizing molecules, delivered by passive transfer or by a recombinant vector; 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 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 candidates and other immune prevention strategies in NHP animal models of HIV and closely related lentiviruses by:
  - Testing HIV/SIV vaccine candidates 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 view 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 the 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 the potency of candidate HIV vaccines;
  - Standardizing and validating assays to be used as Phase III study endpoints; and
  - Developing novel endpoint assays under conditions of Good Laboratory Practice to support eventual 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 FDA regulations.
- Foster research on the safety and regulatory considerations of candidate HIV/AIDS vaccines in development:
  - That are produced utilizing 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;
  - That might have the ability to increase the risk of HIV infection through vector-specific activation of T cells or other vaccine-induced enhancement of infection; or
  - That express potentially harmful vector proteins.

OBJECTIVE–C: Active and Passive Pediatric Vaccines

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 should 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 the preclinical safety and immunogenicity of various HIV vaccines and adjuvants, particularly in pregnant and newborn primates;
    - Determine the 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 NHP infant cellular and humoral immunity to HIV or SIV in the context of breastfeeding from a SHIV- or SIV-infected mother, and determine immune correlates of protection for potential exploitation in vaccine strategies;
    - Evaluate the 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; 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, particularly in breastfeeding 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 feasibility and 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 or adults.

  - 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 or passive antibodies administered 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, II, and III Vaccine Trials

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 candidates, and address questions about optimal vaccine strain/gene insert selection (i.e., the properties of a strain [immunologic, genotypic, or phenotypic]) that make it optimal for use in a selected population. The feasibility of trials to test concepts of immune prevention and control by antibodies may be explored via passive administration of antibodies. Vaccine trials should include an appropriate representation of the general population (gender, age, and ethnic and racial minorities), 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 that might 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, detailed 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 the 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-uninfected 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 vaccine 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 all 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: Research and Preparation for HIV Vaccine Trials

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, including women and adolescents; 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 clinical 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 clinical 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 setpoint, 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-positive and HIV-negative 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 clinical trials might be conducted to optimize education, recruitment, and followup activities; consider 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 clinical trials, enlist participation of local representatives or community advisory boards (CABs) in the development of appropriate clinical 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, the Joint United Nations Programme on HIV/AIDS, and the Global HIV Vaccine Enterprise 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, pre- or postexposure prophylaxis, anti-herpes simplex virus treatment, HPV vaccine, and breastfeeding strategies) that might have a substantial impact on either the design or the conduct of an HIV vaccine clinical 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, and rapid testing), 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 agencies and community-based organizations to develop education programs to facilitate the conduct of Phase III HIV vaccine clinical trials in hard-to-reach populations in domestic sites; collaborate with the U.S. Military HIV Research Program, the Centers for Disease Control and Prevention, the U.S. Agency for International Development, and other organizations to develop vaccine clinical trial sites in international settings.

  - Evaluate the impact of community-based participatory research in the acceptability of HIV vaccine clinical 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 clinical trials are conducted.

- Determine possible adverse social, economic, behavioral, or legal consequences of participation in vaccine clinical trials; develop broadly applicable strategies for mitigating potential harm.
- Determine optimal methods of achieving informed consent for HIV vaccine efficacy trials.
- Design comparative effectiveness research to compare effective vaccine candidates with other various biomedical and behavioral interventions.

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

AREA OF EMPHASIS

Microbicides

FY 2012 RESEARCH PRIORITIES

- Develop and test animal models that are predictive of microbicide safety and efficacy.
- Design and conduct microbicide studies that integrate the biological, behavioral, and social sciences.
- Develop, test, and standardize assays to assess the safety of microbicide candidates.
- Develop a robust pipeline of microbicide candidates and a standardized method for efficiently advancing candidates through the pipeline.
- Define and analyze normal and abnormal male and female genital tract and anal/rectal immune function and their impact on HIV risk and acquisition.

OBJECTIVE–A: Basic Mechanisms of Mucosal Transmission

Elucidate basic mechanisms of HIV transmission (virus and host factors) at mucosal surfaces that are important for the development of topical and oral microbicide prevention strategies in diverse populations.

STRATEGIES

Basic Biological and Physiological Research Related to Topical and Oral Microbicides

- Identify, investigate, and characterize new and understudied viral and host targets and kinetic sequencing of infection important for the transmission and early dissemination of HIV in the upper and lower female and male genital tracts and the anus/rectum.
- Develop and study exploratory techniques such as genomics and proteomics and other systems biology approaches to better characterize the functions and secretomes of female and male genital and anus/rectum immune and mucosal/epithelial cells.
- Investigate the importance of innate, adaptive, and maladaptive host defenses that protect against HIV transmission and acquisition or enhance susceptibility. Explore strategies to harness these defenses to protect against HIV acquisition in the upper and lower female and male genital tracts and in the anus/rectum.
- Study the impact of oral and topical microbicides on innate and adaptive mucosal/epithelial defense mechanisms and integrity in the female and male genital tracts and in the anus/rectum.
- Study the interactions between oral and topical candidate microbicides and genital tract physiology, microbiology, viral population dynamics, and mucosal/epithelial secretions and surfaces.
- Study the impact of normal and abnormal microflora on innate and adaptive mucosal/epithelial defenses in the upper and lower female and male genital tracts, in the anus/rectum, and on HIV susceptibility, transmission, and acquisition.
- Study the physiology, immunology, microbiology, and physical changes that occur during intercourse and discern how they affect HIV transmission, acquisition, and susceptibility and the safety, efficacy, and acceptability of, and adherence to, microbicides.
- Study the effect of semen on the immunology, physiology, microbiology, and structural integrity of the female and male upper and lower genital tracts and anus/rectum in the presence or absence of candidate oral and topical microbicides, and the impact of semen on HIV transmission and acquisition.
- Determine the cells, secretions, and/or tissue types that serve as portals of entry and/or facilitate transport processes that support the subsequent spread to and dissemination of HIV in humans, simian immunodeficiency virus (SIV) in small animals, and SIV or chimeric simian/human immunodeficiency virus (SHIV) in the lymphoid and other reservoir tissue in nonhuman primate models of infection.
- Determine the role of viral phenotype, genotype, clade, and resistance patterns on oral and topical microbicide activity. Delineate the relative impact of these factors on the efficiency of transmission of cell-free and cell-associated virus in secretions and tissues in the upper and lower female and male genital tracts and in the anus/rectum.
- Determine the mechanisms by which genital tract and anus/rectum inflammation, adaptive and maladaptive immune responses, and infections (including sexually transmitted infections [STIs]) influence HIV transmission and early propagation and dissemination of virus to lymphoid and other tissue reservoirs.
- Investigate the effect of variations in male and female endogenous hormonal status, including puberty, pregnancy, and menopause and

exogenous hormonal exposure, throughout the life cycle on HIV susceptibility, transmission, and acquisition in the female and male upper and lower genital tracts and anus/rectum.

- Study the impact of male circumcision and female genital cutting on HIV mucosal transmission mechanisms in the presence and absence of oral and topical microbicides.

- Investigate the effect of aging on the innate and adaptive immunity of the male and female genital tract and anus/rectum.

OBJECTIVE–B: Discovery, Development, and Preclinical Testing

Support the discovery, development, and preclinical evaluation of oral and topical microbicide candidates, including probiotics and recombinant live microbicides used as single or multi-drug combinations and used alone and as oral/topical combinations.

STRATEGIES

Topical and Oral Microbicide Development and Preclinical Studies

- Support the development, validation, and standardization of specific, sensitive, reproducible methods and algorithms to assess the antimicrobial and contraceptive activity of microbicide candidates.
- Support the development, validation, and standardization of specific, sensitive, and reproducible methods and biomarkers for assessing and quantifying innate, adaptive, and maladaptive responses in mucosal/epithelial tissues, semen, and other secretions before and after the use of microbicides.
- Develop and validate biomarkers and other methods to assess the safety, efficacy, and genital pharmacodynamics of oral and topical microbicide candidates, determine adherence to product usage, and document the sexual activity and viral exposure of female and male participants in clinical studies.
- Support the development, validation, and standardization of upper and lower genital tract, anus/rectum, and foreskin explant and cell culture models of human and nonhuman primate tissue to investigate the very early events in HIV or SIV/SHIV transmission.
- Support the development, validation, and standardization of *ex vivo* upper and lower genital tract, anus/rectum, and foreskin explant and cell culture models of human or nonhuman primate tissue that facilitate the evaluation of the activity and toxicity of microbicide candidates and the determination of safety profiles, including the impact on susceptibility to HIV and STI infection.
- Support the development, validation, and standardization of new cellular and animal models, including primate and small animal transgenic and humanized models, for HIV susceptibility that closely reflect the dynamics of sexual transmission of HIV, and the potential safety and efficacy of oral and topical microbicide use in humans.
- Support the development of animal models of HIV transmission in the presence of other STIs that may affect the safety and efficacy of oral and topical microbicide products.
- Support and promote the development of novel models, technologies, and assays to discover, develop, and evaluate oral and topical microbicide candidates.
- Evaluate the efficacy of oral and topical microbicides against a variety of HIV viral resistance types, subtypes, and clades.
- Develop exploratory techniques such as genomics and proteomics and other systems biology approaches to identify novel candidate agents or targets for microbicide strategies.
- Facilitate the study of potential microbicide candidates for their effect(s) on innate, adaptive, and maladaptive immunologic, microbiologic, and inflammatory parameters associated with HIV susceptibility, acquisition, transmission, and replication.
- Study the effect of microbicides used before, during, and after intercourse on the structural integrity of the upper and lower genital tract and anus/rectum, and the impact on the risk for HIV susceptibility, transmission, and acquisition.
- Support the study of preclinical, pharmacokinetic, pharmacogenetic, pharmacodynamic, and acute, chronic, and extended exposure toxicity testing of oral and topical microbicide candidates. This should include, but not be limited to, genotoxicity, reproductive toxicology, and carcinogenicity studies. This may include the development of new methodologies and technologies to measure product concentration and activity *in vivo*.

- Investigate the potential interactions between microbicides and the use of alternative, complementary, and nutritional therapies.
- Investigate the effect of variations in female and male endogenous and exogenous hormonal status across the life cycle on the innate and adaptive and maladaptive immunity of the female and male genital tracts, and the anus/rectum, and on oral and topical microbicide safety and efficacy.
- Develop methods to solve manufacturing and synthesis hurdles that may prevent the advancement of microbicides through the preclinical pathway, by providing support for early Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP), manufacturing design, and scale-up.
- Collaborate with the Food and Drug Administration to accelerate the pace of development of combination topical and oral microbicide strategies.
- Develop and test specific assays that will inform which candidate microbicides should be advanced through the pipeline.
- Devise and test safety and pharmacokinetic algorithms that can determine which candidate microbicides should advance through the pipeline.

OBJECTIVE–C: Formulations and Modes of Delivery

Develop and evaluate safe and acceptable topical and oral microbicide formulations and modes of delivery, bridging knowledge and applications from the chemical, pharmaceutical, physical, bioengineering, biologic, social, and behavioral sciences.

STRATEGIES

Topical and Oral Microbicide Formulations and Modes of Delivery

- Develop microbicide formulations, and dosage and delivery systems suitable for the upper and lower female and male genital tracts and the anus/rectum, that reduce or eliminate tissue toxicity and trauma while maintaining product acceptability.
- Develop placebo formulations with rheological, physical, and chemical properties that are identical to their microbicide-containing counterparts.
- Study the impact of long-term oral and topical microbicide exposure on genital and anal/rectal mucosal immunology and integrity.
- Study the systemic- and tissue-level dose-response and bioavailability of oral and topical microbicides.
- Identify and validate methods that improve the understanding of rheological and physical properties and provide optimal bioadhesion, biodispersion, retention, distribution, and tissue concentration of candidate microbicide formulations before, during, and after intercourse in the female and male upper and lower genital tracts and anal/rectum compartments.
- Develop, standardize, and validate methods to measure local tissue, target cell, and systemic absorption and concentration following oral and topical microbicide use, and relate this to microbicide safety and efficacy.
- Develop and incorporate age-appropriate and culturally sensitive measures and mechanisms to assess the acceptability of microbicides and their mode of delivery in females and males, including adolescents and young and older-age adults, that can be used in exploratory clinical studies and phased clinical trials domestically and internationally.
- Develop and study methods to better understand the biological mechanisms and the physiologic and biological changes that contribute to the safety, efficacy, adherence, and acceptability of microbicide formulations. This includes, but is not limited to, the interaction between the rheological properties of the formulation and hormonal status, age, timing in the menstrual cycle, sexual practices, use of sexual enhancement products, vaginal and rectal practices, pregnancy, frequency of candidate microbicide product use, sexual arousal, and concomitant STIs.
- Develop, validate, and standardize methodologies to analyze the physical, biological, rheological, and chemical properties of microbicides, formulated as individual and combination products. Analyze the properties of candidate microbicide products that facilitate tissue safety, efficacy, and desirable biologic properties.
- Develop methodologies and supportive studies to evaluate product characteristics of microbicides (such as taste, smell, color, lubricity, texture, and other factors) that can affect acceptability and use of, and adherence to, microbicides in females and males across the life cycle, in varied communities and cultures, and for different sexual acts.
- Develop and study reference formulations of candidate microbicides with known safety and acceptability profiles that can be used as a starting point for optimization and production of microbicide delivery systems suitable for the upper and lower female and male genital tracts, the anus/rectum, and the oral cavity.
- Develop novel, alternative formulations for microbicide delivery systems such as microbicide rings, films, gels, and suppositories as coitally dependent and independent formulations with short-term and extended-delivery dosing.
- Evaluate the interaction of vaginal practices and rectal practices on the safety, efficacy, and rheologic properties of candidate microbicides.

OBJECTIVE–D: Conduct Topical and Oral Microbicide Clinical Trials

Conduct clinical studies of candidate topical and oral microbicides to assess safety, efficacy, acceptability, and adherence in the reduction of sexual transmission of HIV in at-risk female and male populations, including adolescents, young adults, pregnant women, and adults over the age of 50 in domestic and international settings.

STRATEGIES

Clinical Trials of Topical and Oral Microbicide Candidate Products

- Identify populations in domestic and international settings with sufficient size and current HIV sero-prevalence to meet the power threshold for the conduct of Phase I, II, III, IV, and accessory clinical studies.
- Design, implement, and evaluate novel testing assays and seroincidence assessments to provide current data that will identify appropriate communities for clinical trials implementation.
- Assess and integrate community-level cultural beliefs, behaviors, practices, and expectations in the design and conduct of microbicides clinical trials.
- Integrate and analyze the impact of behavioral and sociological HIV prevention interventions on community-level and individual risk behavior on microbicides trials over the course of trial implementation.
- Ensure the validity and comparability of study outcomes by optimizing all phases of microbicide clinical study design and evaluation, including the use of standardized measures.
- Conduct pre-Phase I and accessory clinical research to address the issues of safety, efficacy, and acceptability in microbicides clinical studies.
- Conduct and evaluate novel culturally appropriate strategies to recruit and retain female and male participants across the life cycle in Phase I, II, III, and IV microbicide clinical studies in domestic and international settings.
- Design and implement Phase I, II, III, and IV clinical studies within HIV at-risk and HIV-infected populations and during pregnancy to evaluate the safety, efficacy, and acceptability of, and adherence to, microbicide products.
- Design, develop, and implement Phase I, II, III, and IV microbicide clinical studies that address and evaluate the influence of variations in endogenous (including adolescence, pregnancy, menopause, and older age) and exogenous hormonal status in women and men on the pharmacokinetics, safety, efficacy, and acceptability of, adherence to, and usage of candidate microbicide products in females and males across the life cycle.
- Identify, develop, and validate behavioral markers to evaluate the safety, efficacy, acceptability of, adherence to, and use of microbicides.
- Design, develop, and evaluate culturally appropriate tools that measure product use and acceptability within and outside the clinical study environment. These tools should be adapted for applicability to female and male populations of varied ages.
- Address ethical issues in the design and conduct of microbicide clinical studies, including methods to enhance communication with community stakeholders and to evaluate and improve the informed consent process for participants, with emphasis on consent for minors.
- Address the ethical-legal challenges inherent in adolescent participation in HIV prevention intervention research, including community and geographic policy variation, comprehension of partial efficacy, age of consent/assent, decisionmaking capacity, right to autonomy, and local legal definitions of statutory rape.

- Conduct research on the acceptability and efficacy of microbicide candidates, used alone and in combination with other behavioral and therapeutic HIV prevention methods. Compare these outcomes to non-microbicide-based approaches to HIV prevention.

- Implement novel translational research strategies to develop criteria for the movement of microbicide agents from preclinical animal studies to Phase I human trials.

- Identify and develop improved techniques to evaluate the safety and efficacy of microbicides applied to upper and lower female and male genital tract, anus/rectum, and other mucosal/epithelial surfaces.

- Conduct followup research with participants who have seroconverted during the course of microbicide clinical studies in order to assess the impact of long-term product use and the effect of the product on contraception, pregnancy, and the acquisition of STIs and other coinfections, and HIV resistance.

- Study microbicide candidates in HIV-infected participants to determine the impact of product use on the development of HIV progression, superinfections/reinfections, the progression of coinfections, and on drug resistance, drug interactions, and the potential for other adverse events.

- Design, implement, and evaluate Phase IV post-marketing surveillance studies on microbicides.

- Design, develop, and implement preclinical studies and Phase I and II clinical studies in pregnant women to assess the pharmacokinetics, safety, and acceptability of the agents likely to enter Phase IIB/III clinical trials.

- Study the contraceptive and non-contraceptive properties of microbicides *in vivo* and the impact of microbicides exposure on fertility, fetal development, maternal and infant pregnancy outcome, and childhood development.

- Investigate the development of HIV resistance when antiretroviral (ARV) and non-ARV-based microbicides are used alone or in combination in HIV-infected individuals and those who seroconvert while using microbicide products. Identify and study the correlates of increased risk for ARV resistance.

- Promote and support the rigorous use of comparative effectiveness research in evaluating various biomedical and behavioral interventions for HIV/AIDS.

OBJECTIVE–E: Conduct Topical and Oral Microbicide Behavioral and Social Science Research

Conduct basic and applied behavioral and social science research to inform and optimize topical and oral microbicide development, testing, acceptability, and use in domestic and international settings among female and male populations across the lifespan, including adolescents, young adults, pregnant women, and adults over the age of 50.

STRATEGIES

Social and Behavioral Science Research Related to Topical and Oral Microbicides

- Support the development and study of epidemiological models of risk and protection within community and population, social, and cultural contexts, to inform research on and the implementation and evaluation of microbicide use.
- Conduct behavioral and social science research on individuals, their partners, and communities at the onset of microbicide use targeting adolescents and individuals over the age of 50. Assess the influence of behavioral and social factors on the continuation or discontinuation of product usage.
- Conduct behavioral and social science research with individuals, their partners, and communities on methods to improve adherence to microbicide products with varied formulations and to research protocols during clinical studies.
- Develop and evaluate the efficacy of behavioral and social interventions to enhance correct and consistent use of microbicide products in diverse populations and in diverse settings.
- Develop and evaluate the efficacy of behavioral interventions aimed to reduce sexual risk behaviors among participants in microbicide studies.
- Support operations and cost analysis research on the implementation and costs of behavioral interventions designed to support microbicide intervention, implementation, acceptance, use, sustainability, and dissemination.
- Develop and improve methods and tools for measurement and analysis in behavioral and social science microbicide research.
- Develop and improve methods and tools for behavioral and social science research on microbicides, to inform techniques for the enhanced recruitment and retention of participants in all phases of clinical studies and the prediction of sustained microbicide use in female and male at-risk populations across the life cycle.
- Conduct behavioral and social science research on counseling strategies for females and males at varied ages, families, and communities that address the decisionmaking processes that determine use or nonuse of microbicides.
- Determine and study the optimal combination of biomedical and behavioral HIV prevention strategies that decrease risk for acquisition while using a microbicide that is known to have partial efficacy.
- Develop and test behavioral and social science research tools to predict and evaluate trends in microbicide use, adherence, sustainability, and pregnancy rates in at-risk populations of males and females, including, but not limited to, adolescents, young adults, pregnant women, and older age groups in clinical trials.
- Evaluate the effects of family and community pregnancy expectations on the use or nonuse of candidate microbicides in clinical studies.
- Evaluate the effect of vaginal, rectal, and other sexual practices, including the use of products for hygiene, lubrication, sexual enhancement, and prevention of HIV transmission, on the use and efficacy of microbicides.
- Evaluate the impact of microbicide clinical trials on individual and community-level HIV-risk behavior.

OBJECTIVE–F: Topical and Oral Microbicide Infrastructure

Establish and maintain the appropriate educational, physical, and human resource infrastructure needed to conduct basic, preclinical, clinical, behavioral, and social science topical and oral microbicide research domestically and internationally among HIV-uninfected and -infected females and males, including adolescents, young adults, and pregnant women.

STRATEGIES

Infrastructure

- Establish and strengthen training and infrastructure for the development of domestic and international institutional capacity for basic, translational, and preclinical microbicide research, including studies that facilitate the discovery and development of new microbicide candidates and assays for discovery, testing, and clinical evaluation and implementation.
- Establish clinical study sites and the infrastructure required for Phase I, II, III, and IV studies domestically and internationally: coordinate with other domestic and international organizations to optimize the availability of resources and encourage harmonization.
- Identify site-specific gaps in basic science, biomedical, behavioral, sociological, ethical, clinical, regulatory, and administrative training and support in national and international microbicide research sites, and design strategies that respond to those needs.
- Provide microbicide research training and career development opportunities to foster and develop the skills of new independent domestic and international investigators.
- Support and fund the dissemination of microbicide-related discovery and development strategies that will assist the research process, including assay standardization and validation, to domestic and international investigators.
- Strengthen training and infrastructure for the development of domestic and international institutional capacity for microbicides research, including laboratory capability, epidemiology and statistics expertise, data management/analysis, operational support, physical resources, human capacity, and the development of high standards of conduct for clinical research.
- Ensure the collaborative involvement of domestic and international community representatives and leaders in the planning and implementation of microbicide research.
- Foster and support the development of pilot and large-scale GLP and GMP production systems for the manufacture of microbicide agents and their formulations.
- Develop and evaluate strategies to promote and sustain the involvement of local governments, researchers, communities, and advocacy groups in the identification of priorities for the design and conduct of basic, translational, clinical, behavioral, and social science research strategies, and in the maintenance of participants in research projects.
- Develop and evaluate strategies to encourage community participation in research and facilitate community acceptance of microbicides. Develop and evaluate appropriate communication strategies for affected communities in which candidate microbicides are being tested, and prepare for the eventual integration of microbicides into domestic and international comprehensive prevention and care programs.
- Foster public–private partnerships to integrate NIH microbicide activities with external organizations to facilitate the cost-effective use of available resources and accelerate microbicide development.
- Foster domestic and international collaborative partnerships between established investigators and between established and young investigators for the conceptualization, design, and conduct of innovative microbicide research.

AREA OF EMPHASIS

Behavioral and Social Science

FY 2012 RESEARCH PRIORITIES

- Develop further understanding of biological–behavioral interactions and social/environmental dynamics related to changes in transmission risks over the course of HIV infection and disease, such as those differentially associated with acute infection, recent diagnosis, chronic infection with or without antiretroviral treatment, and later-stage disease.

- Conduct translational research (i.e., dissemination, implementation, or operational research) to foster the scale-up and optimize the use of existing efficacious interventions to prevent and treat HIV infections. This research should address the processes of identifying, adapting, and disseminating interventions, as well as methods of providing technical assistance and ensuring quality control. Priority should also be given to developing methodologies needed for designing, analyzing, conducting, and interpreting such research, and to securing relevant participants' input into design, analysis, conduct, and interpretation of such research.

- Study the continued disparities in HIV infection that manifest themselves among racial and ethnic communities in the United States and among similarly disproportionately affected populations in international settings (e.g., mobile subpopulations; migrant workers; refugees; and persons subjected to discrimination on racial, ethnic, or religious grounds) in order to identify epidemiologic, sociocultural, psychosocial, and structural aspects of epidemics that are unique to these communities and that would explain the disparities in acquisition, transmission, prevention services, health equity (to encompass not only access to care but also the root causes of health disparities), treatment provision, and/or progression of HIV infection within these communities.

- Develop and test methods of intervening at structural, environmental, and community levels to reduce transmission and acquisition of HIV, especially focusing on early intervention methods that address structural factors that have promise for large, long-term impact. Focus attention on prevention strategies that could be implemented in specific communities with high needs for prevention interventions, such as racial and ethnic communities, men who have sex with men, youth, women, transgender individuals, young adults in high-prevalence or high-risk areas, and older adult populations engaging in risk behaviors. Ensure the most effective utilization of funds by developing methods of integrating HIV prevention approaches within the context of existing infrastructure to deliver medical services and care. Assess means of reducing stigma associated with HIV and the impact of these reductions on transmission. Where necessary, conduct research to develop the methodological and statistical approaches needed to develop, implement, and assess these structural, environmental, and community-level interventions.

- Evaluate innovative methods of intervening to reduce HIV acquisition and transmission associated with sexual behavior and with drug and alcohol use, using methods that recognize the interdependencies and interactions of sexual behavior and substance use variables at multiple levels (such as at the individual, dyadic, group, community, societal, or policy level), as well as advances in development of community-based participatory research that fosters the ecological validity of such complex research.

- Advance research on adolescents' development of healthy sexual and relationship functioning to elucidate factors reducing risk of HIV infection through fostering healthy relationships for persons of all genders and sexual orientations; integrate knowledge of healthy sexual functioning, understanding of gender identity development and management of gender issues, and approaches to reducing disparities related to gender and/or gender identity into the design and evaluation of HIV prevention and care interventions.

- Ensure the use of state-of-the art methods and findings from behavioral and social sciences in the conduct of domestic and international research into viral, host, and environmental factors that affect morbidity, mortality, and response to antiretroviral therapy, as well as ensure the use of state-of-the art behavioral and social science in clinical trials in order to assess adherence, behaviors (e.g., drug and alcohol use) affecting trial outcomes (and eventual implementation of interventions), changes in sexual behaviors, mental health symptoms, and related issues such as stigma, access to care, and impact on HIV-affected family and community members.

- Examine the use of research and design methodologies from a variety of disciplines (e.g., economics and political science), to better evaluate the relationships among HIV risk and structural and environmental factors; incorporate methods of intensively examining the natural course of behavior change caused by and associated with interventions to inform development of better interventions.

- Foster the use of laboratory-based behavioral and social methods with human participants to more intensively examine risk behaviors and HIV-related outcomes to elucidate antecedents and determinants of risk, to clarify behavioral topography, to rigorously examine the role of alcohol and other drugs in risk behaviors, and to understand social forces affecting risk; develop methods to improve the ecological validity of laboratory studies where needed.

- Examine and evaluate approaches to maintaining the highest ethical standards in the conduct of HIV prevention science in order to ensure meaningful informed consent processes, decrease misunderstandings of the implications of trial participation, minimize risk of inadvertent harm to participants, and promote justice in research through the inclusion of difficult-to-recruit but critical populations.

- Foster research that explicitly differentiates among approaches to HIV/AIDS epidemics of varying types and stages to define priority targets for intervention according to the type and stage.

OBJECTIVE–A: Preventive Intervention Research

Support research to develop, evaluate, and implement behavioral, social, structural, environmental, and economic interventions that prevent HIV transmission and acquisition by targeting at multiple levels factors known to drive the epidemic.

STRATEGIES

- Estimate the efficacy, effectiveness, and cost-effectiveness of tailored behavioral, social, and structural interventions in order to maximize their potential, when deployed singly or in combination, for stemming incident HIV infections. Apply basic behavioral and social science research to optimize intervention strategies.
- Support new research to identify the active components of efficacious, theory-based interventions for broader, sustainable implementation.
- Modify, adapt, or refine existing efficacious behavioral or social HIV prevention interventions to increase their impact and make them more easily administered to segments of the population most vulnerable to the epidemic.
- Study structural and systems-level interventions that seem likely to produce lasting impact over time by addressing the development of risk in youth.

Populations and Contexts

- Develop and test interventions targeted at HIV-infected persons to reduce sexual and drug-use behaviors that confer the greatest risk for HIV transmission.
- Support intervention research that addresses the impact of alcohol and/or drugs on sexual encounters that may contribute to HIV transmission and acquisition.
- Support research that addresses victimization history to reduce HIV transmission and acquisition.
- Develop interventions addressing modifiable determinants placing members of population subgroups at greatest risk for HIV transmission and acquisition (e.g., men who have sex with men [MSM], transgender individuals, ethnic minority heterosexuals, injection drug users, and migrants).
- Continue development of interventions for persons with comorbid psychiatric and physical disorders.
- Conduct studies on medication-assisted substance abuse treatment modalities and access to care (e.g., methadone maintenance, buprenorphine/naloxone, modafinil, naltrexone, and antabuse) alone or in combination with mental health and behavioral interventions, as HIV prevention interventions.
- Examine the impact of widespread antiretroviral therapy (ART) availability on willingness to be tested for HIV, willingness to provide HIV testing, and decreased stigma associated with HIV.
- Support research on populations in which epidemiological evidence suggests a need for more effective HIV prevention interventions.
- Support intervention research that addresses important determinants of risk among disproportionately affected groups that continue to demonstrate high-risk behaviors. Develop, test, and evaluate interventions that target individuals within prisons, jails, under justice system supervision, or returning to society from correctional settings.
- Develop, test, and evaluate interventions to improve linkage to existing systems of care that serve at-risk populations, including those that address single factors associated with incident HIV infections in isolation (e.g., sexually transmitted infection [STI] clinics) and those that do not routinely provide HIV prevention services (e.g., primary care or mental health clinics).
- Support the development of intervention strategies that adapt rapidly 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.
- Conduct studies to identify key components of efficacious interventions and processes that facilitate behavior change.
- Support research to improve the transfer of effective HIV interventions, particularly research on the diffusion, adoption, adaptation, and maintenance of efficacious HIV interventions. 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 levels of certain prevention components are assigned to different individuals, with levels varying in response to the intervention needs of the individuals.
- Study the impacts of multicomponent interventions that integrate behavioral and social approaches with other perspectives.
- Intensively investigate the outcomes of intervention studies, perhaps in select subjects, to fully understand the natural course of behavior change resulting from the intervention.

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 services that reduce HIV-risk behaviors and HIV transmission.
- Support research to understand and improve comprehensive care that reduces HIV transmission through reducing the fragmentation of HIV prevention, primary medical and dental care, drug and alcohol treatment, mental health treatment, STI treatment, reproductive health services, services for orphans and vulnerable children, and other care 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-infected and -uninfected patients.
- Support intervention research on strategies for improving the willingness and capacity of communities to adopt and sustain primary prevention interventions.
- Support research to develop flexible, pluripotent prevention intervention strategies for health care delivery systems providing prevention or treatment in other domains, such as family planning services, alcohol and substance use treatment, and psychiatric care.

Methods

- Design and test behavioral interventions for highly vulnerable segments of the population to increase recruitment, retention, and adherence to protocols for HIV prevention research, including trials studying prophylactic vaccines, access to 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, rigorous approaches for sampling "hidden" or "difficult to reach" populations in intervention studies.

OBJECTIVE–B: Basic Behavioral and Social Science Research

Conduct basic social and behavioral research on factors influencing HIV risk 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 better understand the impact of HIV preventive and therapeutic regimens on treatment adherence for HIV and co-occurring infections, sexual risk behaviors, drug-related risk behaviors, and psychosocial adaptation (i.e., improved quality of life).
- Examine neurobiological, cognitive, motivational, and other mechanisms that underlie HIV-risk behaviors and health decisionmaking.
- Develop new models of behavior 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 populations.
- Support theory-building studies developed in the context of HIV prevention research, as well as evaluation of theories originally developed for other contexts (e.g., drug and alcohol abuse prevention, family planning, and interpersonal social skill development) to see how they can inform HIV prevention research.
- Elucidate genetic and epigenetic factors associated with risk behaviors and behavior change.

Consequences of HIV Disease

- Support (non-intervention) 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.

- Support research on the impact of HIV and its clinical course on aging and adult development, with attention to the consequences of accelerated physical aging that may accompany HIV disease and its clinical course.

Prevention

- Study the acquisition and maintenance of HIV-related risk and protective behaviors associated with HIV transmission or disease progression in specific social and cultural contexts, such as the sexual dyad, peer groups, social and substance-using networks, families, and communities. This may include studies of HIV risk, transmission, and progression as related to cultural norms that affect disempowerment of and violence toward women.

- Study HIV risk changes over time as a function of changes in the perceived severity of or susceptibility to HIV disease and developmental and life-course events (e.g., 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, concurrency, serosorting, 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, gender 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 findings 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 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 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.

- Evaluate consequences of coercive sex, sexual violence, and interpersonal violence on concurrent and subsequent sexual and drug use risk behaviors, with consideration of how intervention can mitigate or prevent coercion, violence, and their consequences.

- Evaluate the impact of assortative and dissortative mixing on HIV transmission rates, and identify modifiable factors related to these patterns of mixing.

- Support clinical studies on the role of alcohol in risk for HIV, including studies that provide evidence on the ecological validity of various experimental designs.

- Utilize clinical studies to better define risk behaviors and to inform prevention studies regarding points of intervention or measurement of variables (e.g., cues) associated with risk behaviors.

OBJECTIVE–C: Consequences of HIV Infection

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-infected persons.
- 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 HIV infection, including barriers associated with fear and stigmatization that affect access, linkage, 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 research on the special factors affecting adherence in older seropositive persons and medical decisionmaking in care of older seropositives.

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: Research Methods

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, sexual minorities, the elderly, and incarcerated populations) and that reflect age-appropriate concerns.
- Develop and refine techniques for measuring social networks associated with HIV transmission.
- Develop and refine techniques for studying the use of digital technology, social media, and other innovations and their 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 diseases.
- Develop improved methods for the reliable and valid collection of sensitive information regarding sexual and drug-use risk behaviors.
- Develop and/or adapt innovative substance abuse assessment approaches.
- Assess new methodologies for testing the 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. Greater consideration needs to be given to probabilistic relationships among risk factors and other contributing variables, as well as practical constraints in the implementation and uptake of interventions.

- Develop and refine models of potential efficacy of environmental-level (e.g., laws and policies) interventions for reducing HIV risk.

- Develop and refine models of potential efficacy of network and dyad-level interventions for reducing HIV risk.

Design and Statistical Analysis

- Develop improved methods for sampling subpopulations (e.g., children, homeless persons, drug users, the elderly, sexual minorities, adolescents, and MSM 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.

- Research means of recruiting difficult-to-reach but critical populations, such as MSM, racial and ethnic populations, transgenders, women, adolescents, and other underaddressed or insufficiently understood groups in order to better understand how to involve these in relevant research projects.

- Develop improved and innovative methods and techniques for conducting and analyzing longitudinal studies of at-risk and HIV-infected populations, including improved participant retention strategies; statistical methods for dealing with participant attrition, missing data, and non-normal 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 combination intervention strategies that simultaneously target factors that increase risk for HIV transmission or acquisition.

- 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 new studies as required by epidemiologic findings on HIV transmission. Encourage secondary data analysis; develop approaches to protect and document confidentiality.

- Develop and test an ethical framework for the use of biomedical interventions (e.g., ART) for HIV prevention that encompasses such issues as misconceptions of the preventive efficacy of experimental products, ensuring informed consent over the course of longitudinal studies, and the provision of products for HIV prevention that may not be available to persons living with HIV.

- Foster research designs that will be able to uncover the mechanisms of action in successful interventions that may be transferred and applied elsewhere.

AREA OF EMPHASIS

Treatment as Prevention

FY 2012 RESEARCH PRIORITIES

- Develop safe, effective, feasible, and conveniently administered strategies for the prevention of mother-to-child transmission of HIV, with a focus on resource-limited settings and a special emphasis on breastfeeding transmission.

- Evaluate the mechanisms of treatment failure and develop strategies to maintain long-term undetectable viral load in HIV-infected individuals in domestic and international settings and to assess the impact of these strategies on the prevention of HIV transmission.

OBJECTIVE–A: Approaches to Interrupt Vertical Transmission

Develop and assess strategies to prevent mother-to-child transmission (MTCT), applicable to resource-limited and -rich countries, with emphasis on strategies to prevent transmission through breastfeeding; the short- and long-term effects of interventions for preventing MTCT on the health of women and infants; and the development of drug resistance after antiretroviral (ARV) MTCT prophylaxis and its association with the efficacy of subsequent antiretroviral therapy (ART) in future pregnancies.

STRATEGIES

Mechanisms of Transmission

- Investigate the mechanisms and timing of MTCT to facilitate and develop targeted drugs/strategies to further decrease MTCT or provide alternatives to currently identified effective strategies, including genomic studies.
- Evaluate the effects of acute HIV infection on MTCT.
- Investigate risk factors (e.g., immune, viral, and host-related, including infant microbiome) associated with transmission of HIV *in utero* and through breast milk.
- Develop reproducible, sensitive, and specific assays to detect and quantitate the amount of cell-free and cell-associated virus in breast milk and in genital fluids.

Interventions and Trials to Evaluate Interventions to Prevent Transmission

- Develop and evaluate strategies for preventing transmission of HIV from pregnant women to their offspring, and evaluate the impact of those strategies on maternal health treatment options; such strategies may include antiviral agents, anti-HIV immunoglobulin, monoclonal antibodies, agents targeted to cellular targets (e.g., blocking cytokine receptors), cell- and gene-based strategies, HIV vaccines, and adjuvants, alone or in combination.
- Develop safe and conveniently administered strategies to prevent MTCT using interventions that are affordable in resource-limited nations, including specific strategies to prevent postnatal transmission of HIV through breast milk by providing prophylaxis to the infant, mother, or both during the lactational period.
- Evaluate approaches to maintain HIV-free survival of HIV-uninfected babies who are breastfed.
- Evaluate the pharmacokinetics and safety of ARV drugs in pregnant women and their fetuses/infants, and the penetration of ARV drugs into breast milk and genital fluids.
- Encourage development of novel delivery methods to both enhance the efficacy and decrease the toxicity of existing and future drugs used for the prevention of MTCT, particularly agents with long half-lives in formulations able to be used in neonates and infants.
- Evaluate strategies for reducing MTCT when maternal antepartum and intrapartum ART is not given or available (e.g., postpartum prophylaxis of the infant only).
- Support international collaborative efforts to conduct clinical trials of interventions to prevent MTCT.
- Study the effects of ARV regimens used for maternal health indications on preventing MTCT (including postnatal or oropharyngeal transmission through breast milk and drug resistance in infants who become HIV-infected despite prophylaxis).
- Support research and development of new clinical trial designs, statistical methodologies, and investigation of biologic markers, surrogates, and/or other outcomes to evaluate the activity, clinical efficacy, or reasons for failure of new agents and approaches in the prevention of MTCT.

- Use and/or develop suitable animal models to evaluate novel strategies to prevent transplacental and postpartum breastfeeding transmission of HIV, and to evaluate transplacental passage of ARV agents and their effects on placental function and on fetal development and viability.

Issues Related to ARV Drug Resistance

- Evaluate the effects of pre-existing viral drug resistance in pregnant women on the effectiveness of ARV regimens to prevent MTCT.
- Evaluate the risk for the development of HIV variants with detectable ARV drug resistance in pregnant women who receive different types of ARV prophylactic regimens and the kinetics and durability of such resistance in cell-free and cell-associated virus in plasma, breast milk, and genital secretions.
- Evaluate the risk for development of HIV variants with detectable ARV drug resistance in infants who become infected despite maternal receipt of ARV prophylaxis regimens and the kinetics and durability of such resistance in cell-free and cell-associated virus.
- Evaluate the effects of developing drug resistance following ARV prophylaxis on the health and response to future ART in women and infants who become infected with HIV despite prophylaxis.
- Evaluate the effects of drug resistance following ARV prophylaxis in an initial pregnancy on the efficacy of the prophylactic regimen in reducing transmission in subsequent pregnancies.
- Evaluate effective, safe, simple, and short alternative ARV regimens that have lower risk of development of resistance in women or infants despite prophylaxis than those currently used for prevention of MTCT in resource-limited settings.
- Evaluate the public health impact of ARV resistance that develops in pregnant HIV-infected women secondary to use of ARVs solely for prevention of MTCT.

Issues Related to Short- and Long-Term Effects of ARV Prophylaxis for Reducing MTCT

- Evaluate the short-term toxicities, pharmacokinetics (including transplacental drug transfer to the fetus/infant), and ARV activity of new agents, existing agents, and combinations of agents in pregnant HIV-infected women and their neonates.
- Evaluate whether pregnancy increases the risk of potential ARV toxicities, the pathogenesis of such toxicities in pregnancy, and clinical findings or laboratory assays that might be predictive of such effects.
- Study the effects of ARV regimens used during pregnancy for treatment of maternal HIV disease on maternal health and pregnancy outcome.
- Evaluate the optimal regimen(s) for preventing MTCT in women who are receiving ART for the sole purpose of preventing perinatal transmission, and short- and long-term clinical, immunologic, and virologic effects of receiving ART during pregnancy in such women who choose to discontinue ART after delivery.
- Evaluate the short- and long-term clinical, immunologic, and virologic effects in women who receive ART during lactation solely to prevent breast milk transmission, but who discontinue treatment following weaning.
- Evaluate the potential mechanisms for possible carcinogenic or mutagenic effects of *in utero* ARV exposure.
- Evaluate the pathogenesis of potential ARV toxicities (e.g., mitochondrial toxicity and bone toxicity) in uninfected, HIV-exposed infants with perinatal ARV exposure, and develop animal models or laboratory assays that might be predictive of such effects with exposure to an individual ARV agent alone or in combination with other ARVs.
- Develop better clinical algorithms and laboratory assays to diagnose/assess mitochondrial toxicity associated with ARV exposure in infants and children.

- Develop and implement feasible studies that assess the long-term effects of *in utero* and/or postpartum exposure to ARVs on both HIV-infected and -uninfected children, both domestically and internationally.

Implementation Issues

- Develop and evaluate strategies for implementation of effective perinatal transmission prevention interventions in developed and developing countries, including ways to increase the availability and acceptability of prenatal HIV testing and of prophylaxis to prevent MTCT.

- Improve the sensitivity and specificity of diagnostic procedures that are accessible, cost-effective, and have utility in developed and developing settings to permit the earliest possible determination of HIV infection in infants, and whether ARV and/or immunopreventive therapies affect the timing and sensitivity of these assays for diagnosis.

- Evaluate innovative methods, including rapid HIV antibody testing, to identify HIV infection in pregnant women with unknown HIV serostatus who present in labor, and to assess the acceptability of such testing and acceptability and efficacy of ARV prophylaxis to reduce MTCT, when administered to the woman intrapartum and her infant, or to her infant alone.

- Evaluate the public health impact of programs to prevent MTCT.

OBJECTIVE–B: Therapeutic Approaches to Prevent Horizontal Transmission

Evaluate the impact of ARV and immunotherapeutic strategies and their roles in the prevention of horizontal HIV transmission (e.g., sexual, noninjection drug use, or injection drug use transmission) in appropriate domestic and international settings.

STRATEGIES

Mechanisms of Transmission

- Evaluate the influence of drug resistance on the efficacy of ARV regimens to prevent sexual transmission.
- Evaluate changes in the microbiome, mycobiome, and viriome in HIV-infected individuals, including potential effects on HIV transmission and the effects of antiviral therapy on the microbiome, mycobiome, and viriome.
- Develop and/or use suitable animal models and clinical studies to evaluate genital, anal, and oral passage of cell-free and cell-associated virus and ARVs.
- Evaluate the influence of systemic HIV treatment on viral shedding in the anogenital tract.
- Evaluate the impact of anti-sexually transmitted infection treatment on transmission of HIV and HIV shedding in the oropharyngeal or anogenital tracts.
- Develop novel tools and approaches to understand HIV and/or prevention agent interaction with genital, gastrointestinal, or orpharyngeal tract cells and tissues and the mechanisms of HIV transmission in these tissues.

Interventions to Reduce Transmission

- Support domestic and international collaborative efforts to conduct trials of ARV, immunotherapeutic, and other treatment interventions with an endpoint of horizontal transmission in acute and chronic infection, including studies in adolescents/young adults.
- Develop and evaluate strategies for reducing the risk of sexual transmission of HIV without compromising treatment of the HIV-infected individual; such strategies may include ARVs, therapeutic vaccines, anti-HIV immunoglobulin, monoclonal antibodies, and immunotherapeutic agents, alone or in combination.
- Develop delivery systems for non-topical agents to prevent HIV transmission, including postexposure prophylaxis, pre-exposure prophylaxis (PrEP), and other ARV methods of prevention.

Issues Related to ARV Interventions

- Evaluate the risk for developing ARV drug resistance (in cell-free and cell-associated virus, and in sequestered genital or anorectal sites) when using ARVs in interventions to reduce horizontal transmission, including the development of ARV drug resistance in individuals who become HIV-infected while receiving such therapy or in HIV-infected individuals being administered such therapy solely to reduce horizontal transmission.
- Evaluate the public health impact of ARVs on reducing horizontal transmission.
- Develop the methodology and metrics to assess the outcomes of “test and treat” regimens.
- Develop novel approaches to evaluate data on PrEP and exposure in occupational settings.