PRIORITY:

Expanding Basic Discovery Research

Etiology and Pathogenesis

AREA OF EMPHASIS

Etiology and Pathogenesis

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A: Biology of HIV Transmission

Delineate the viral, host genetic, and immune mechanisms involved in the transmission, establishment, and spread of HIV infection in diverse populations across the spectrum of age, gender, and transmission mechanism in national and international settings.

STRATEGIES

- Determine the role of phenotype/genotype/fitness/generation of variants and dose on transmission of cell-free and cell-associated HIV, in various bodily fluids at different portals of entry.
  - Define the role of cell-free and cell-associated HIV in various modes of transmission.
  - Determine the mechanisms by which virus-encoded genes and viral gene products regulate HIV infection and replication, and influence transmission, establishment, and spread of HIV infection.
  - Delineate the mechanisms by which host-encoded genes and gene products regulate HIV infection and replication, and influence the transmission, establishment, and spread of HIV infection.
  - Determine the role of the host microbiome (bacterial, fungal, and viral) in transmission, establishment, and spread of HIV infection.
  - Elucidate the genetic complexity and the biological characteristics and genetic features of viruses that are transmitted during sexually acquired acute and early HIV infection.
  - Determine the structures of and interactions between viral and host proteins that are important for the transmission, establishment, and spread of HIV infection.
  - Determine the cell subsets and tissue types that serve as portals of entry and dissemination of HIV and that support replication during different stages of infection.
- Delineate the mechanisms by which intrinsic cellular restriction factors, innate immunity, adaptive immunity, and mucosal immunity, and the effects of genetic or environmental factors on innate, adaptive, and mucosal immunity, influence HIV replication and modulate transmission, establishment, and spread of HIV infection.
- Investigate the role of inflammation and its mediators in tissue on HIV transmission and dissemination.
- Delineate the mechanisms by which sexually transmitted infections (STIs) and coinfections influence HIV transmission, replication, establishment, and spread.
- Evaluate the influence of prevention and treatment on the early events in HIV transmission, establishment, and spread.
- Evaluate the role and mechanisms of preventing or enhancing HIV transmission, establishment, and spread by soluble factors contained within bodily fluids.
- Determine the factors that lead to early evolution in founder viruses of acute HIV infection and their implications for HIV transmission, establishment, and spread.

To facilitate the research strategies listed above:

- Facilitate the translation of new insights from structural biology, computational biology, epigenetics, and systems biology (multiscale modeling and commonly used approaches to validate hypotheses such as genomics, proteomics, metabolomics, and cellular biology) to understand the etiology and pathogenesis of HIV infection.

- Further develop, validate, and utilize experimental human, nonhuman, *ex vivo*, and theoretical/mathematical models to study the transmission and establishment of HIV/SIV (simian immunodeficiency virus) infections with emphasis on models of direct relevance to human HIV infection and models that address important issues not readily approachable in human subjects.

- Define phenotypic markers, functional assays, and high throughput assays that will enhance our understanding of and ability to study innate and adaptive immune function in human mucosal tissues. This would include humoral immunity and cell-mediated immunity at mucosal surfaces.

- Promote augmented access to and sharing of key patient samples, animal model resources, laboratory reagents, new technologies and equipment, information databases, and quantitative as well as functional virologic and immunologic assays.

- Support and expand innovative research on the transmission, establishment, and spread of HIV infection.

- Develop and utilize natural and innovative technologies to procure, maintain, and expand the availability of *in vivo* nonhuman models of infection and facilitate collaborative research using these models.

OBJECTIVE–B: HIV Virology and Viral Pathogenesis

Delineate the viral and host mechanisms associated with HIV viral replication and dissemination, and those that influence viral setpoint, viral persistence, and disease progression in diverse populations across the spectrum of age and gender in national and international settings.

STRATEGIES

- Define the viral, host, and environmental factors and mechanisms that regulate initial HIV replication, control virus during primary infection, and establish viral setpoint and disease progression.
- Determine how early events that regulate the establishment and systemic spread of HIV infection define the later clinical course of the disease in HIV-infected populations.
- Define the viral, host, pharmacologic, copathogenic, and environmental factors that contribute to disease progression and nonprogression.
- Define the virologic and host factors that enable HIV to establish and maintain a persistent infection *in vivo* in the setting of both treatment-naïve individuals and patients on highly active antiretroviral therapy (HAART).
- Delineate the molecular mechanisms by which virus-encoded genes, viral gene products, host cellular factors, and intracellular compartments regulate HIV replication and influence pathogenesis.
- Determine the factors that influence the susceptibility of target cells to HIV infection and their ability to support HIV replication.
- Determine the structures of complexes between viral proteins and host factors involved in the processes that underlie HIV disease progression.
- Elucidate host/pathogen interactions occurring during acute/early infection that contribute to the establishment of the disease process.
- Determine the consequences of long-term physiological and/or immunological damage caused by HIV disease and/or HIV therapy.
- Evaluate whether and to what extent viral-induced damage to the systemic and mucosal immune systems can be reversed following suppression of HIV replication by therapeutic interventions.
- Define the reservoirs of virus in both acute and chronic infection that permit HIV persistence throughout the course of HIV infection, including in the setting of therapies and in the presence of ongoing immune responses.
- Determine the viral and host factors associated with clinical response and lack of response to therapeutic interventions in HIV-infected subjects.
- Determine the role of the host microbiome (bacterial, fungal, and viral) in the pathogenesis of HIV infection and disease progression as well as its role on antiretroviral therapy (ART) effectiveness.

To facilitate the research strategies listed above:

- Further develop and utilize experimental human, nonhuman, *ex vivo*, and theoretical/mathematical models to study the pathogenesis of lentiviral infections with emphasis on models of direct relevance to human HIV infection and models that address important issues not readily approachable in human subjects.
- Further develop mathematical models or other approaches to integrate environmental, host, and viral factors that influence HIV-AIDS pathogenesis.
- Develop relevant *in vitro* and *ex vivo* assay systems and relevant animal model systems to model cellular reservoirs of latent and/or persistent HIV infection in the context of effective ART.

- Promote augmented access to and sharing of key patient samples, animal model resources, laboratory reagents, new technologies and equipment, information databases, and quantitative virologic and immunologic assays.
- Facilitate the translation of new insights from structural biology, computational biology, and systems biology (multiscale modeling and commonly used approaches to validate hypotheses such as genomics, proteomics, and cellular biology) to understand the immunopathogenesis of HIV infection.
- Develop and exploit *in vitro* systems that accurately recapitulate different stages of the HIV life cycle (e.g., viral entry, uncoating, nuclear targeting, chromatin integration, assembly, trafficking, budding, maturation, and latency).
- Enable the translation of basic and preclinical research findings into clinical studies in humans to advance the understanding, treatment, and prevention of HIV infection.
- Promote the characterization of the host microbiome (bacterial, fungal, and viral) in different body cavities and skin of HIV-infected individuals through the use and development of novel technologies, equipment, shared resources, and databases.

OBJECTIVE–C: HIV Immunopathogenesis

Delineate immunological mechanisms of HIV control, and elucidate the viral and host mechanisms associated with HIV-induced immunopathogenesis, including immune dysfunction, aberrant immune activation, and inflammation.

STRATEGIES

- Delineate the mechanisms by which innate and adaptive immunity, and the effects of genetic or environmental factors on innate and adaptive immunity, influence HIV replication.
- Delineate the mechanisms by which innate immunity modulates the quality of HIV-specific adaptive immunity, with particular emphasis on the earliest immunologic event occurring during primary infection.
- Investigate how the effectiveness of immune control may vary through the course of infection, depending on the identity and location of infected host cells and the influence of therapeutic interventions.
- Delineate the direct and indirect mechanisms underlying HIV-induced depletion and dysfunction of immune cells and tissues in humans and nonhuman models, focusing on:
  - the loss of specific CD4+ T lymphocyte subpopulations and clones;
  - the impact of HIV infection on T-cell population numbers, specificities, and functions in blood and in primary and secondary lymphoid tissues, including mucosal tissues;
  - HIV-triggered immunopathogenesis, including immune activation, cell death, induction of nonresponsiveness, dysregulation in the number and function of innate and adaptive immune effector cells, and production of host factors, including cytokines and other mediators;
  - the structural and functional compromise of primary and secondary lymphoid organs, including mucosal tissues (e.g., gastrointestinal, reproductive, and oral mucosa) and hematopoietic precursor cells and their microenvironment;
  - influences on the developing and aging immune system; and
  - disruption of host compensatory mechanisms that govern the generation, regeneration, and homeostasis of immune cell populations.
- Determine the contribution of immune activation/inflammation to HIV disease progression, and elucidate the mechanisms driving this activation.
- Determine the role of chronic HIV-1 infection and/or therapy on innate or adaptive immune senescence.
- Define the fundamental mechanisms responsible for differences between pathogenic infection and nonpathogenic natural host infection.
- Evaluate whether and to what extent viral-induced damage to the systemic and mucosal immune systems can be reversed following suppression of HIV replication by therapeutic interventions.
- Determine the lifespan, developmental, and regenerative pathways of cells of the innate and adaptive immune system in humans and nonhuman primate (NHP) models; elucidate the mechanisms that regulate the size and composition of these cell populations and how they may change with antiviral treatment and with age.
- Define viral and host markers and functional assays that will enhance our understanding of and ability to study innate and adaptive immune function in humans, especially those approaches that permit study of the *in vivo* activity of the immune system.
- Determine the impact of host immunity on viral evolution and viral fitness, and the influence of viral factors on host immunity.

To facilitate the research strategies listed above:

- Define markers and functional assays that will enhance our understanding of and ability to study innate and adaptive immune function in humans, including humoral immunity and cell-mediated immunity at mucosal surfaces.
- Facilitate the translation of new insights and concepts from basic immunology research, structural biology, computational biology, and systems biology to understand the immunopathogenesis of HIV infection.
- Promote augmented access to and sharing of key patient samples, animal model resources, laboratory reagents, new technologies and equipment, information databases, and quantitative immunologic assays.
- Further develop and utilize experimental human, nonhuman, *ex vivo*, and theoretical/mathematical models to study the pathogenesis of lentiviral infections with emphasis on models of direct relevance to human HIV infection and models that address important issues not readily approachable in human subjects.

OBJECTIVE–D: Pathogenesis of Opportunistic Infections and Coinfections

Elucidate the pathogenic mechanisms and consequences of opportunistic infections (OIs) and significant coinfections in HIV-infected individuals in diverse populations across the spectrum of age and gender in national and international settings and the factors that regulate susceptibility to infection or disease that might be targeted for prevention. Priority should be given to OIs and coinfections that (a) are a major cause of morbidity and/or HIV disease progression in HIV-infected individuals, and/or (b) contribute significantly to HIV transmission or acquisition.

STRATEGIES

- Conduct studies of the basic biology of opportunistic and coinfecting pathogens and their interaction with the HIV-infected host.
- Define the relationships in which HIV enhances coinfections and by which coinfections enhance HIV disease progression, including those that are a major cause of morbidity or disease progression (e.g., tuberculosis [TB] and hepatitis C virus [HCV]) or that contribute to HIV transmission and acquisition (e.g., STIs).
- Identify and elucidate the genetic and environmental risk factors associated with the susceptibility to, the development of, and the progression of OIs and coinfections in HIV-infected individuals.
- Study the effects of OIs and coinfections on immune dysfunction, nutritional status, and HIV disease progression.
- Define immunologic responses to OI/coinfection pathogens at mucosal surfaces and determine how they may be altered by HIV infection and/or ART.
- Study how HIV infection changes the pathogenesis of the coinfecting pathogens.
- Elucidate the mechanisms of innate and adaptive immune function that mediate protection against OIs.
- Study the effects of HIV therapy on the clinical course and manifestation of OIs and coinfections, including pathogenesis of immune reconstitution inflammatory syndrome.
- Probe the pathogenic mechanisms of HIV-associated OIs, and evaluate how the causes, agents, and manifestations of these HIV-associated infections are altered by ARTs and the extension of life afforded by those therapies.
- Define the molecular and phylogenetic characteristics of major AIDS OIs and pathogens; standardize and improve techniques of phylogenetic analysis; and integrate strain-specific characterization of data into studies of the pathogenesis, mechanisms of transmission, and epidemiology of OIs.
- Determine the influence of the human microbiome on protection or susceptibility to OIs, coinfections, and HIV disease progression.
- Determine biomarkers and factors associated with clinical response and lack of response to therapeutic interventions against OIs and coinfections in HIV-infected subjects.
- Identify basic mechanisms that will facilitate the development of vaccines and new treatments for OIs that will be effective in HIV-infected individuals.

To facilitate the research strategies listed above:

- Facilitate the translation of new insights from structural biology, computational biology, and systems biology (multiscale modeling and commonly used approaches to validate hypotheses such as genomics, proteomics, metabolomics, and cellular biology) to understand the etiology and pathogenesis of HIV coinfections and HIV-related OIs.

- Develop *in vitro* techniques and novel animal models to propagate and define the life cycles of the opportunistic pathogens and coinfections associated with HIV disease.
- Develop and validate diagnostic assays for the reliable and rapid identification of HIV-associated OIs, including stable, inexpensive, easy-to-perform assays appropriate for use in developing countries.
- Facilitate collaborative and interdisciplinary studies to elucidate the etiology and pathogenesis of significant HIV OIs and coinfections (e.g., TB and HCV).

OBJECTIVE–E: Pathogenesis of Metabolic and Body Composition Change

Define the etiology, pathophysiology, and consequences of HIV infection and treatment-related metabolic disorders, body composition changes, nutritional status, endocrine dysfunction, oral health status, and cardiovascular disease in diverse populations across the spectrum of age and gender in national and international settings.

STRATEGIES

- Define the mechanisms underlying alterations in metabolism, body composition, nutritional status, endocrine function, growth and development, and the risks of atherosclerotic cardiovascular, vascular, renal, bone, skeletal muscle, oral manifestations, and skin disease to determine:
  - the effects of antiviral therapies and suppression of virus replication;
  - the influence of disease stages, including the degree of initial immunosuppression and immune reconstitution;
  - the contributions of individual virologic and host factors, including genetic loci;
  - the contributions of OIs, hormonal dysregulation, and other consequences of HIV infection;
  - the role of nutritional status on malabsorption, malnutrition, immune status and exacerbation of metabolic disorders, comorbidities, and HIV pathogenesis; and
  - the influence of hormones on HIV pathogenesis.
- Study the impact of HIV on an aging population, including the implications of HIV infection for cardiovascular, metabolic, bone, skeletal muscle, skin, oral, and renal diseases.
- Define the relationship between natural aging and HIV-induced pathological changes in multiple organ systems both without and on treatment.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms underlying alterations in metabolism, body composition, nutritional status, growth and development, diabetes, and bone, skeletal muscle, skin, renal, oral, and atherosclerotic cardiovascular disease.
- Determine factors associated with clinical response or lack of response to therapeutic interventions against AIDS-associated metabolic and body composition changes, impaired growth and development, diabetes, and bone, skeletal muscle, skin, renal, and atherosclerotic cardiovascular disease.

To facilitate the research strategies listed above:

- Transfer expertise from the endocrine, metabolic, cardiovascular, obesity, renal, bone, skeletal muscle, reproductive biology, oral health, and skin research fields to the HIV field and promote linkage between HIV researchers and established individuals and centers of excellence in these areas of research. Encourage and facilitate collaborative and interdisciplinary research in these areas.
- Promote programs to facilitate access to and sharing of patient samples, animal model resources, reagents, biomarkers, new technologies, equipment, information databases, and modeling/calculation tools used in metabolic, nutrition, cardiovascular, bone, skeletal muscle, oral health, and skin research.
- Facilitate the translation of new insights from structural biology, computational biology, and systems biology (multiscale modeling and commonly used approaches to validate hypotheses such as genomics, proteomics, metabolomics, and cellular biology) to understand the metabolic, endocrine, cardiovascular, renal, bone, skeletal

muscle, reproductive, oral, and skin disease complications associated with HIV infection and treatment.

- Support the development of new and improved research techniques to address the emerging metabolic, endocrine, cardiovascular, renal, bone, skeletal muscle, reproductive, and skin complications in HIV-infected populations.
- Integrate metabolic, nutritional, endocrine, cardiovascular, renal, bone, skeletal muscle, reproductive immunology, oral health, and skin studies into ongoing and planned treatment trials and observational studies.
- Link advances in understanding the immune response to HIV with changes in lipid, glucose, bone metabolism, nutritional status, muscle wasting, skin disease, endocrine parameters, oral health status, reproductive aging, and cardiovascular disease.

OBJECTIVE–F: Pathogenesis of Malignancies

Elucidate the etiologic factors, cofactors, pathogenesis, and consequences of AIDS-defining and other HIV-related malignancies in diverse populations across the spectrum of age and gender in national and international settings.

STRATEGIES

- Elucidate the fundamental immune defects in HIV infection that predispose to the development of AIDS-defining and other malignancies that are associated with HIV infection.
- Elucidate the mechanisms by which HIV infection and its treatment enhance the development of various AIDS-defining malignancies, non-AIDS-defining malignancies, preneoplastic lesions, and other hyperproliferative conditions.
- Identify the mechanisms by which immune dysfunction, oncogenes, suppressor genes, carcinogens, and non-HIV viral and other microbial organisms, genes, and proteins contribute to the development of cancer and preneoplastic lesions and hyperproliferative conditions in the context of HIV infection and HIV-associated malignancies; correlate these molecular factors with epidemiologic studies.
- Conduct studies on the biology of opportunistic pathogens that are the principal etiologic agents for HIV-associated malignancies (e.g., Kaposi's sarcoma-associated herpesvirus [KSHV]) and investigate their interaction with the host and the mechanisms by which they cause malignancy in HIV-infected populations.
- Address the impact of HIV infection and prior therapy on the pathogenesis and treatment of common non-AIDS-related cancers (e.g., breast, colon, lung, prostate, liver) that may emerge in the aging HIV-infected population.
- Identify the host factors that increase the risk of AIDS-defining and other HIV-associated malignant disease in HIV-infected individuals.
- Investigate the contribution of HIV-associated or opportunistic-pathogen-associated inflammatory pathways and immune dysregulation to cancers whose incidence is increased in HIV-infected individuals.
- Determine the impact of AIDS-defining and other HIV-associated malignancies on the immune response to HIV.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms of HIV-related malignancies, and evaluate how the development and the manifestations of HIV-associated malignancies are altered by such therapies.
- Explore the mechanisms involved in the shifts in the spectrum on both AIDS-defining and emerging non-AIDS-defining malignancies that are occurring in HIV-infected individuals whose lives are extended by ART treatment.
- Determine factors associated with clinical response and lack of response to antineoplastic therapeutic intervention in HIV-infected subjects.

To facilitate the research strategies listed above:

- Promote programs to facilitate the development of and augmented access to *in vivo* animal models, patient specimens for AIDS-defining and other HIV-associated malignancies, sharing of key patient samples, laboratory reagents, new technologies and equipment, information databases, and quantitative virologic and immunologic assays.
- Foster collaborative research between HIV and cancer researchers.

- Promote the collection of cancer specimens that occur in HIV-infected individuals, in different geographic locations in domestic and international settings.
- Facilitate the translation of new insights from structural biology, computational biology, and systems biology (multiscale modeling and commonly used approaches to validate hypotheses such as genomics, proteomics, metabolomics, and cellular biology) to understand the etiology and pathogenesis of AIDS-related malignancies.

OBJECTIVE–G: Pathogenesis of Neurological Disease

Elucidate the mechanisms and consequences of HIV-associated neurological disease and neurobehavioral dysfunction in diverse populations across the spectrum of age and gender in national and international settings.

STRATEGIES

- Determine the cellular and molecular mechanisms involved in HIV-associated neurobehavioral and neurological dysfunction, and peripheral neuropathies, including:
  - identifying how HIV enters, establishes infection in specific cells and regions, spreads, and persists in the central nervous system (CNS);
  - investigating the connection between blood-brain barrier dysfunction, immune cell trafficking, and neuronal injury in the context of HIV infection;
  - determining the relationship of virologic (including distinct subtypes of HIV and acute infection), host (including the genetics of the virus/host interactions, blood-brain barrier dysfunction, and neuronal injury), pharmacologic, substance abuse, and environmental factors to susceptibility of neurological disease and HIV-associated neuropathogenesis;
  - investigating mechanisms of neuropathogenesis in the acute and early phases of infection, including reversible and irreversible changes in neuronal function and neuronal-glial communication that lead to CNS manifestations of disease;
  - determining the consequences of the biological activity of cytokines, other mediators, and their receptors on the neurologic tissue in the context of HIV infection; and
  - developing methods to monitor the levels of HIV replication and consequences of HIV infection within the CNS of living subjects.
- Determine factors associated with clinical response and lack of response to therapeutic interventions for neurologic and neurobehavioral complications of HIV disease, including the role of CNS drug penetration.
- Determine the host and viral factors influencing independent evolution of drug-resistant HIV strains in the CNS compartment as well as its functional consequences.
- Determine the impact of HIV infection of CNS on systemic disease progression.
- Determine the role of the CNS as a reservoir of, and sanctuary for, persistent HIV infection.
- Define mechanisms of innate and adaptive immunologic control of HIV, OIs, and coinfections in the CNS.
- Investigate aspects of HIV infection that uniquely influence the developing nervous system or the processes of neurocognitive decline with aging.
- Define mechanisms of immune reconstitution syndrome in the CNS in the setting of OIs and coinfections.
- Delineate the role of OIs, coinfections, other disease complications, and drug treatment in neurologic and neurobehavioral complications of AIDS, including CNS dysfunction and peripheral neuropathies.
- Employ therapies that effectively suppress HIV replication and/or stimulate neuroprotection to probe pathogenic mechanisms of HIV-associated neurologic diseases and neurobehavioral dysfunction; evaluate how the manifestations of HIV-associated neuropathogenesis are altered by such therapies.
- Determine the mechanisms regulating the changing/fluctuating symptomatology of HIV-associated nervous system disease in the current era of ART.

- Define the roles and interactions among HIV peripheral neuropathy and neuropathogenesis associated with drugs (including TB and antiretroviral therapeutics) and other environmental factors (alcohol, nutrition).
- Define the role of antiretroviral drug toxicity in CNS disease in patients on ART.
- Define the relationship between HIV-associated neurological disease and CNS changes associated with normal aging or aging-related diseases.

To facilitate the research strategies listed above:

- Develop and employ appropriate animal models (e.g., NHP models) of CNS HIV/SIV infection that best reflect specific aspects of the human HIV infection of CNS disease course on treatment that are crucial to understanding neurobehavioral and neurologic disorders.
- Develop methods to investigate, diagnose, and monitor HIV-associated neurological and neurobehavioral disorders in a range of populations, including those of the developing world.
- Ensure that information, materials, and specimens needed for neuro-AIDS research are appropriately collected, catalogued, classified, stored, and distributed, and promote access to and sharing of new technologies and equipment.
- Encourage new multidisciplinary approaches to investigate HIV-associated neurological disease and neurobehavioral dysfunction, and facilitate interactions between HIV and neuroscience and neurobehavioral researchers.
- Improve existing and develop new technologies for biochemical markers and the imaging of neurologic dysfunction.
- Facilitate the translation of new insights from structural biology, computational biology, epigenetics, and systems biology (multiscale modeling and commonly used approaches to validate hypotheses such as genomics, proteomics, metabolomics, and cellular biology) to understand HIV-related neurologic disease.
- Integrate neurologic studies into the design and conduct of observational studies and treatment trials.

OBJECTIVE–H: Pathogenesis of Organ/Tissue Disorders

Elucidate the etiology, pathogenesis, and consequences of HIV-related organ-specific disorders in diverse populations across the spectrum of age and gender in national and international settings.

STRATEGIES

- Investigate the etiologic and pathogenic mechanisms and consequences of HIV-related:
  - oropharyngeal cavity and gastrointestinal tract, including intestinal, liver, and biliary, diseases,
  - nephropathy,
  - hematologic disorders,
  - pulmonary disorders,
  - autoimmune disorders,
  - cutaneous disease,
  - bone disease,
  - adipose dysfunction,
  - muscle wasting,
  - oral disease, and
  - other organ/tissue-specific disorders.
- Determine the consequences of aging on the pathogenesis of the above disorders.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms of HIV-related organ/tissue-specific complications, and evaluate how the manifestations of HIV-related organ/tissue-specific complications are altered by such therapies.
- Determine factors associated with clinical response and lack of response to therapeutic interventions against HIV-related disorders.
- Employ animal models to investigate the etiology and pathogenesis of HIV/SIV-associated disorders in the above systems.
- Define the host genetic, viral, and environmental factors that contribute to organ-specific dysfunction relevant to populations differentially affected by organ-specific disease.

To facilitate the research strategies listed above:

- Facilitate the translation of new insights from structural biology, computational biology, and systems biology (multiscale modeling and commonly used approaches to validate hypotheses such as genomics, proteomics, metabolomics, and cellular biology) to understand the etiology and pathogenesis of HIV-related disorders.
- Integrate studies of HIV-related disorders in the design and conduct of treatment trials and observational studies.