CHAPTER 1

Foundational Research

Natural History and Epidemiology
Etiology and Pathogenesis

Natural History and Epidemiology

AREA OF EMPHASIS

Natural History and Epidemiology

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A

Characterize the risk factors and mechanisms of HIV transmission in domestic and international populations to guide prevention and treatment strategies.

(The scientific objectives of A, B, and C are of equal weight.)

STRATEGIES

- Utilize existing cohorts, including incidence cohorts, to further assess HIV transmission and acquisition.
- Model how results from existing cohorts might be altered in socioeconomically and demographically different populations (specifically based upon race, ethnicity, gender, age, and resource-rich and -poor settings).
- Conduct studies on the molecular epidemiology and the effects on HIV transmission of infection with different HIV subtypes, routes and modes of transmission, antiretroviral (ARV)-resistant viruses, multiple subtypes, and recombinant viruses.
- Conduct epidemiological and modeling research to improve estimates of per-contact risk of HIV transmission over the course of the disease process, from acute infection to onset of advanced HIV disease.
- Evaluate sexual and blood-borne HIV transmission and acquisition in relation to the following:
  - Viral factors such as viral quantity (measures of viral RNA and other quantification methods) in various body compartments (e.g., blood, saliva, and mucosal compartments), viral diversity (intrapatient diversity), and HIV genotype, including subtypes, recombinants, resistance mutants, and dual virus infections;
  - Host factors such as age, sex, hormonal status, strength and breadth of immune response, mental health, patterns of alcohol and drug use, and host genetic factors;
  - Modifiable host factors such as diet and nutritional status; drug, alcohol, and tobacco use; use of exogenous hormones; use of traditional medicines, herbal medicines, and supplements; other infections, including oral infections; other causes of mucosal pathology, including sexually transmitted diseases (STDs); and circadian rhythm;

  - Biological, behavioral, cultural, and environmental determinants of susceptibility to HIV acquisition and progression among women and girls;
  - Persistent exposure to HIV (i.e., in HIV-discordant couples);
  - Use of microbicides and barrier devices;
  - Social, cultural, behavioral, and ecologic factors, including such demographic characteristics as socioeconomic status, race, ethnicity, gender, culture, religion, community, and geographic location (e.g., rural, urban, suburban);
  - Sexual activity, abstinence, partner selection, partner concurrency, sexual networks, duration of partnership, marital fidelity, control of STDs, hygienic practices, contraception choices, and cultural practices such as use of traditional vaginal preparations, female genital mutilation, and male circumcision; and
  - Extent to which environmental and other macro-level factors such as war, migration, refugee status, homelessness, drug trafficking patterns, political will, and disasters influence vulnerability, risk behaviors, acquisition, and access to care in developed and developing countries.

- Conduct studies (including community-based studies) to understand and quantify the effect on HIV transmission and HIV incidence of widespread use of antiretroviral therapy (ART) by eligible individuals.
- Study the impact of widespread ART availability and resulting viral load suppression on patterns of risk behavior.
- Develop and evaluate effective interventions aimed at HIV-infected persons and their partners to promote behaviors that prevent acquisition and transmission of HIV.
- Conduct community-based participatory studies that assess the impact of community mobilization on prevention and treatment success.
- Study and quantify the impact on HIV transmission of adherence to ART and related factors such as therapy and regimen characteristics, drug characteristics, and symptom management.
- Conduct epidemiological studies on the role of coinfection and comorbidity with other microbial agents in modifying the acquisition and course of HIV infection and in predicting the evolution of particular HIV/AIDS epidemics. Research should focus on hepatitis GB virus C (GBV-C), *M. tuberculosis* (TB), *Plasmodium sp.* (malaria), human papillomavirus (HPV), Epstein-Barr virus (HHV-4/EBV), hepatitis C (HCV), herpes simplex virus (HSV-1 and HSV-2), herpesvirus type 8 (HHV-8/KSHV), or other sexually or nonsexually transmitted conditions within existing programs and settings (e.g., mother-to-child transmission [MTCT]).

- Evaluate the impact on HIV transmission and disease progression of hormonal contraceptives and replacement therapies, composition of such therapies, pharmacokinetics, and duration of action of repository-form contraceptives.
- Examine the effects of vaccine trials on HIV transmission characteristics, including the effects on the alteration of transmission by vaccine-induced immunity. Examine the clinical course and markers of infectiousness among vaccine trial participants with breakthrough HIV infection to determine the vaccine's effect on viral load, rates of progression, and on population HIV incidence.
- Examine the effects of oral chemoprophylaxis (PrEP) and microbicides trials on HIV transmission characteristics, including viral load setpoints and viral drug resistance.
- Conduct studies on medication-assisted substance abuse treatment modalities and access to service (e.g., methadone maintenance, buprenorphine/naloxone, naltrexone, antabuse, acamprosate, and stimulant abuse therapy), alone or in combination with mental health and/or behavioral interventions, as HIV prevention interventions, and examine their effects on HIV disease progression, adherence to ART, and acceptance of care and treatment.
- Identify effective individual, network, and community-level interventions and determine the coverage needed to decrease HIV incidence in developing and developed countries.
- Further define the timing, mechanisms, and risk factors in perinatal and postnatal transmission, including treatment of the mother, infant feeding modalities, physiology of lactation, long-term effects of perinatal interventions, maternal and infant genetic variation, and kinetics of viral resistance.
  - Define how the physiology of lactation affects HIV transmission.
  - Assess the impact of maternal ARV regimens of different potency and duration on MTCT of HIV and on the short- and long-term health of women and their children who are eligible for ART.
  - Study the safety and effectiveness of low-cost, sustainable approaches to prevention of MTCT of HIV, including exclusive breastfeeding in the first months of life with rapid weaning, and determine the effects of such approaches on infant morbidity and mortality.
  - Assess the impact of environmental factors, mental health, comorbidities, and coinfections on the risk for postnatal infection.
  - Assess the impact of perinatal treatment and prophylaxis regimens on emergence of ARV drug resistance in the mother and in those infants who become infected despite prophylaxis.
  - Assess the impact of maternal ART on HIV transmission during pregnancy and lactation.
  - Assess the impact of maternal and infant adherence to ARV regimens on the effectiveness of MTCT, the risk of subsequent ARV resistance, and the effectiveness of ART in mothers and their children.

- Assess the impact of perinatal treatment and prophylaxis regimens on communitywide HIV resistance to ARVs.
- Determine the impact of ARV resistance on perinatal transmission and pediatric infection.
- Assess the impact of MTCT programs on public health measures, including maternal, paternal, and infant morbidity/mortality rates; overall life expectancy; disability-adjusted life years; and child developmental milestones.
- Assess the impact of maternal ARV use for MTCT on morbidity in HIV-uninfected infants and children.

OBJECTIVE–B

Use epidemiological research in domestic and international settings to identify the influence of therapeutics and other biological (e.g., age, host genetics, coinfections, HIV subtypes) and behavioral (e.g., access to and use of health care system, adherence) factors on HIV progression and response to therapy, as shown by virologic, immunologic, and clinical outcomes.

(The scientific objectives of A, B, and C are of equal weight.)

STRATEGIES

Strategies Related to Disease Progression and Response to ART

- Investigate the contribution of innate host characteristics to viral measures, immune function, disease progression, and mechanisms for these effects (including host genetic factors and their modulators, sex, race, and age).
- Examine how chronic inflammatory processes (and such mediators as inflammatory cytokines) that result from HIV and other concurrent infections, stress, depression, or behaviors (e.g., smoking) modify immune function, disease outcomes and survival, and response to ART.
- Assess the effect of treatment for HIV on the incidence and pathogenesis of cancer. Leverage international cohorts to characterize the impact of host genetics, environmental factors, standard-of-care treatment, and HIV subtypes on the full spectrum of cancers observed in HIV-positive individuals.
- Characterize the changing spectrum of clinical outcomes (morbidity and mortality), including causes of death associated with evolving therapeutic strategies, domestically and internationally.
- Elucidate the pathogenic mechanisms that influence residual HIV replication in ART recipients.
- Investigate the effect on disease progression of viral factors, including viral clade/subtype, fitness, viral tropism, and innate and acquired genotypic and phenotypic resistance to ARVs.
- Determine the global patterns of viral resistance (innate and acquired) to ART and how these patterns could influence the long-term effectiveness of these therapies.
- Define the prevalence and incidence of HIV-associated nephropathy, its predictors, and its influence on mortality and response to ART, domestically and in developing countries.
- Define the prevalence and incidence of HIV-associated neurologic, behavioral, and psychiatric manifestations and their relation to disease progression and response to ART, both nationally and internationally.
- Identify, characterize, and determine the frequency, changing manifestations, and effects of HIV-related respiratory disease on morbidity, mortality, and HIV disease progression (e.g., immune reconstitution syndromes affecting the lungs [including sarcoidosis], HIV-related pulmonary hyper-

tension, accelerated emphysema, and coinfections) in domestic and international populations, including both untreated patients and those receiving ART.

- Develop new cohorts and maintain long-term followup of existing cohorts, including observational cohorts and intervention populations, to determine the changing spectrum of HIV disease and evaluate interventions, especially in minority populations and developing countries.
- Characterize the epidemiology of those recently HIV infected, including host and viral genetic characteristics, and continue to characterize the epidemiology of HIV/AIDS among those who have minimal exposure to ART, those who have virologic and/or immunologic responses to these therapies, and those who have experienced failure of these therapies.
- Conduct studies on the pharmacogenomic determinants of the distribution and fate of ARV drug distribution throughout body compartments and of the treatment response in racially and ethnically diverse populations, as well as populations with body mass indices in the underweight, overweight, and obese ranges.

Strategies Related to Complications of Therapy

- Identify the effects of ARV therapies, treatment strategies, and pharmacogenetics on disease outcomes, including (1) other HIV-associated diseases, such as central and peripheral nervous system conditions; (2) other infectious diseases; and (3) noninfectious comorbid conditions and diseases, including lipoatrophy, hyperlipidemia, diabetes mellitus, hypertension, osteopenia/osteoporosis, and steatosis, and long-term disease outcomes, including liver failure, renal failure, bone marrow suppression, malignancies, and atherosclerosis and related cardiovascular diseases.
- Identify the ART-associated toxicities (over and above metabolic syndrome) in special populations, including coinfected populations (e.g., TB), pregnant women, pediatrics, populations receiving traditional medicines, and according to nutritional status.
- Investigate the role of coinfections, particularly HCV, on metabolic disorders commonly associated with ART.
- Investigate the role of chronic inflammation as a result of multiple chronic infections, such as HIV and HCV, or other chronic conditions, such as autoimmune disease, on metabolic disorders commonly associated with ART.
- Assess the effect of other non-ART interventions (e.g., statin use, cancer treatment) that are often used to treat the complications of ART on disease outcomes and survival.

Strategies Related to Comorbidities

- Intensify research on the spectrum of HIV-associated malignant diseases that may develop in HIV-infected patients who have responded to ART and are expected to live longer with subclinical immune deficiency.
- Establish normative data for lymphocyte subsets, total white blood cell count, and total lymphocyte count, and determine the influence of common comorbidities, especially malaria, TB, and helminth infection, on the "normal" values in patients from different regions of the developing world particularly affected by the HIV epidemic, such as Africa and Asia.
- Investigate TB–HIV interactions, including the effects of dual infection on the infectiousness and progression of both TB and HIV and the effect of various treatment strategies on disease control.
- Evaluate the impact of treatment of alcohol abuse, drug abuse, and mental health disorders on the effectiveness of ART, including in the context of specific forms of drug use.
- Assess the effect of HIV on other infections (e.g., hepatitis B [HBV], HCV, GBV-C, other blood-borne infections, cytomegalovirus [CMV], JC virus, HPV, EBV, KSHV, TB, HSV, and malaria and other parasitic diseases) and the effect of these infections and their treatment on HIV outcomes.
- Study the emergence and reemergence of infectious diseases and the development of antimicrobial-resistant infections (e.g., multidrug-resistant TB, sulfa-resistant malaria, antibiotic-resistant pneumococcus, cotrimoxazole-resistant *Pneumocystis carinii* pneumonia [PCP], methicillin-resistant *Staphylococcus aureus* [MRSA], and lamivudine-resistant HBV) in HIV-infected populations.
- Encourage epidemiological studies of dual infection with HIV and HCV, and incorporate research on HCV infection within existing programs of research on HIV/AIDS.
- Evaluate the effectiveness of HPV vaccines among HIV-positive individuals from geographically diverse regions.
- Assess the effect of other non-ART interventions (e.g., statin use, cancer treatment) on disease outcomes and survival.

Strategies Related to MTCT and Pediatric Infection

- Study HIV-infected and -uninfected children and adolescents to determine factors related to impaired growth and neurodevelopment, cognitive development, impact of other childhood infectious diseases, and safety and efficacy of immunizations, and how these may be affected by medical and behavioral interventions.
- Evaluate the long-term complications of maternal and infant ART among exposed, HIV-uninfected children.

- Examine the effect of the health status of HIV-infected mothers and of ART during pregnancy and lactation on survival of their children, both HIV-infected and -uninfected.
- Investigate the long-term outcome of complications due to HIV and ART use in HIV-infected pediatric populations as these children reach adolescence and adulthood.

Strategies Related to Aging

- Investigate the relationship between HIV infection and other comorbidities (HIV-associated and non-HIV-associated) that increase with aging, such as cancer, obesity, diabetes, hypertension, anemia (unexplained and anemia of chronic inflammation), emphysema, renal insufficiency, and hyperlipidemia, on disease outcomes (e.g., liver disease, cardiovascular disease, and renal disease) and survival.
- Study the incidence and determinants of physical and cognitive decline in aging HIV-infected individuals, and the effect of frailty and functional impairment on HIV, ARV use, and self-care behaviors.
- Characterize the changing spectrum of clinical outcomes, including cancers, in the treated, chronically infected, aging, HIV-infected populations living with prolonged immune suppression.
- Evaluate immunologic and virologic HIV disease progression and mortality in older versus younger adults on ART to identify treatment guidelines for older HIV-infected patients.
- Study the effect of HIV and ART (e.g., response to treatment, adverse effects) in aging populations with coexisting morbidities and polypharmacy.

Strategies Related to Adherence, Access, and Quality of Life

- Study determinants of adherence to ART and adverse events of such therapies in all age groups in domestic and international settings.
- Study the impact of access to ART, microbicides, and vaccines on risk behaviors and HIV acquisition among at-risk populations.
- Investigate how different patterns of access, adherence, and exposure to ART in treatment-experienced and treatment-inexperienced populations contribute to ARV resistance and disease progression.
- Identify the individual and provider factors, and communication and joint decisionmaking among them, as well as infrastructure factors associated with initiating, continuing, adhering to, and discontinuing ART, and evaluate the impact of these factors on therapeutic outcomes.

- Evaluate the effects of modifiable host characteristics, specifically behavioral characteristics including adherence, mental health, substance use, sexual behavior, and cultural practices, on viral measures, immune function, disease progression, and mechanisms for these effects.
- Elucidate the effects of HIV infection on sleep disturbances, including prevalence, possible immunological and endocrine mechanisms, associations with HIV outcomes, possible changes with ART, and influence on quality of life and cardiovascular health.

OBJECTIVE–C

Develop and evaluate methods and resources for HIV/AIDS epidemiological and clinical studies that use culturally appropriate approaches; incorporate new laboratory, sampling, and statistical methods with information systems; and better integrate research findings into clinical practice and regional, national, and international policy.

(The scientific objectives of A, B, and C are of equal weight.)

STRATEGIES

- Evaluate and promote the use of study designs that incorporate appropriate ethical, cultural, and policy context for HIV/AIDS studies in diverse domestic and international populations.
- Capitalize on existing sources of data by supporting harmonization efforts in existing observational and clinic cohorts.
- Ensure that the population composition of domestic epidemiological studies reflects the shifts in the populations at risk for and affected by HIV/AIDS, including older Americans, adversely affected minorities, and those with other comorbidities.
- For studies in both domestic and international settings, improve approaches for recruitment and retention of underrepresented populations, including minorities, children, adolescents, women, drug and alcohol abusers, incarcerated populations, and persons living with mental illness.
- Support training and mentorship of medical and health professionals from communities disproportionately affected by the epidemic, both in developing countries and domestically, in the areas of research ethics, study design, informatics, data management and analysis, and linking research trials to clinical care and clinical care to health policy and implementation.

Strategies Related to Natural History/Pathogenesis

- Develop epidemiologic and laboratory-based methods in conjunction with prospective cohort studies, domestically and in developing countries, to monitor response to ART and the incidence of metabolic complications related to chronic use of antiretrovirals, including:
  - Encourage development of and evaluate accurate, reproducible, and inexpensive virologic, immunologic, bacteriologic, pharmacologic, and genetic assays suitable for large-scale epidemiological research and surveillance in developing nations. Emphasis should be on simple and reliable staging of disease progression for the initiation and monitoring of ART and opportunistic infection (OI) prophylaxis; HIV resistance testing; and noninvasive diagnostic assays for STDs, other OIs including TB, and AIDS-related malignancies.

- Develop new epidemiological designs and statistical methods, including development of informatics tools, to better characterize transmission dynamics and monitor long-term trends in disease progression and development of toxicities in the setting of potent ART.
- Develop, maintain, and effectively cultivate ongoing and newly developed cohort studies, domestic or international specimen repositories, and databases for interdisciplinary HIV-related studies. Nested studies that utilize these resources should be particularly encouraged and developed.
- Use observational data to better characterize the natural and treated history of AIDS-associated conditions in international settings and trends in the epidemiology of these conditions.
- Develop methods for assessing HIV-related symptomatology (e.g., pain, fatigue) and quality of life that are feasible and culturally appropriate.
- Develop uniform assessment tools to measure host and environmental characteristics, including substance abuse and mental health, which may impact immediate and long-term HIV-related health outcomes. Assessment tools should be culturally appropriate without the loss of scientific validity.

Strategies Related to Interventions

- Study the various operational strategies that can be employed to "bring to scale" ART programs, including the use of operations research and integrated observational databases to evaluate treatment effectiveness at the individual, community, and population levels.
- Assess the effectiveness and comparability of clinical versus laboratory monitoring for the initiation, monitoring, and switching of ART, particularly in resource-poor settings, including laboratory monitoring with new methods that are technologically and cost-appropriate to the various international settings.
- Develop appropriate clinical and laboratory definitions of short- and long-term ARV failure, and develop mechanisms for monitoring and assessing drug resistance evolution in HIV-1 variants and subtypes in domestic as well as international settings.
- Develop, evaluate, and promote new, improved, and cost-effective methods to prevent HIV transmission via blood transfusion, medical treatments, and other iatrogenic exposures in developing countries, including instrument sterilization.
- Assess the impact of different strategies for HIV testing and their linkage to care.
- Develop and refine simulation strategies (modeling) of the impact of interventions on HIV transmission, cofactors of HIV infection, and communitywide morbidity and mortality, including non-HIV-infected individuals (i.e., survival of uninfected infants).

Strategies Related to Policy

- Evaluate the long-term clinical and nonclinical impact, cost, and health care utilization impact of different strategies for care, including treatment of AIDS-associated conditions (e.g., OIs, anemia) and ART.
- Improve methods for disseminating research, make research results more accessible to all stakeholders, and provide the scientific basis for regional and national standards of care as well as formal HIV best practice guidelines.
- Develop formal methods to assess the applicability and transportability of guidelines for care of HIV-infected individuals across countries.
- Support HIV policy research, including economic studies, necessary for translating epidemiological and clinical studies into policy.
- Encourage development of best care guidelines and national policy papers for the treatment and management of cancers in HIV-infected individuals in low- and middle-resource settings.

Etiology and Pathogenesis

AREA OF EMPHASIS

Etiology and Pathogenesis

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A

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

(The scientific objectives A and B are of equal weight.)

STRATEGIES

- Determine the role of phenotype/genotype/fitness 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 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 innate and adaptive 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 of HIV infection.

- Evaluate the influence of prevention and treatment on the early events in HIV transmission, establishment, and spread.

To facilitate the research goals listed above:

- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand the etiology and pathogenesis of HIV infection.
- Further develop 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.
- 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 macaque model of AIDS and facilitate collaborative research using this model.

OBJECTIVE–B

Delineate the viral and host mechanisms associated with the pathogenesis of immune dysfunction and disease progression in diverse populations across the spectrum of age and gender in national and international settings.

(The scientific objectives A and B are of equal weight.)

STRATEGIES

- Define the factors that regulate initial HIV replication, control virus during primary infection, and establish viral setpoint.
- 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, copathogens, 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 drug-naive and drug-treated individuals.
- Delineate the mechanisms of host immune control of HIV replication and 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 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.
- Delineate the direct and indirect mechanisms underlying HIV-induced depletion and dysfunction of immune cells and tissues in humans and nonhuman primate (NHP) 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;
  - HIV-triggered immunopathogenesis, including immune activation, cell death, induction of nonresponsiveness, dysregulation in the number and function of immune effector cells other than T lymphocytes, and production of host factors, including cytokines and other mediators;

  - the structural and functional compromise of primary and secondary lymphoid organs including hematopoietic precursor cells and their microenvironment;
  - influences on the developing immune system; and
  - disruption of host compensatory mechanisms that govern the generation, regeneration, and homeostasis of T-cell populations.

- 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 and developmental and regenerative pathways of T lymphocytes in humans and NHP models; elucidate the mechanisms that regulate the size and composition of T-cell populations and how these may change with age.
- Define 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.
- 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.

To facilitate the research goals 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.
- 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, genomics, and proteomics to understand the immunopathogenesis of HIV infection.
- Enable the translation of basic and preclinical research findings into clinical studies in humans to advance the understanding, treatment, and prevention of HIV infection.

OBJECTIVE–C

Define the etiology, pathophysiology, and consequences of HIV infection and treatment-related metabolic and body composition changes in diverse populations across the spectrum of age and gender in national and international settings.

(The scientific objectives C through G are of equal weight.)

STRATEGIES

- Define the mechanisms underlying alterations in metabolism, body composition, endocrine function, growth and development, and the risks of atherosclerotic cardiovascular, vascular, and bone disease to determine:
  - the effects of antiviral therapies and suppression of virus replication;
  - the influence of disease stages;
  - the contributions of individual virologic and host factors, including genetic loci; and
  - the contributions of opportunistic infections (OIs), hormonal dysregulation, and other consequences of HIV infection.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms underlying alterations in metabolism, body composition, growth and development, and the long-term risks of diabetes, bone disease, 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, and the long-term risks of diabetes, bone, and atherosclerotic cardiovascular disease.

To facilitate the research goals listed above:

- Transfer expertise from the endocrine, metabolic, cardiovascular, and bone research fields to the HIV field and promote linkage between HIV researchers and established individuals and centers of excellence in these areas of research.
- Promote programs to facilitate access to and sharing of patient samples, animal model resources, reagents, new technologies, equipment, information databases, and modeling/calculation tools used in metabolic, cardiovascular, and bone research.
- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand the metabolic, endocrine, cardiovascular, and bone disease complications associated with HIV infection and treatment.

- Support the development of new and improved research techniques to address the emerging metabolic, endocrine, cardiovascular, and bone complications.
- Integrate metabolic, endocrine, cardiovascular, and bone studies into ongoing and planned treatment trials.
- Link advances in understanding the immune response to HIV with changes in lipid, glucose, bone metabolism, endocrine parameters, and cardiovascular disease.

OBJECTIVE–D

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

(The scientific objectives C through G are of equal weight.)

STRATEGIES

- Elucidate the fundamental immune defects in HIV infection that predispose to the development of HIV-associated malignancies.
- Identify the mechanisms by which immune dysfunction, oncogenes, suppressor genes, carcinogens, and non-HIV viral and other microbial genes and proteins contribute to the development of cancer and preneoplastic lesions in the context of HIV infection and HIV-associated malignancies; correlate these molecular factors with epidemiologic studies.
- Elucidate whether the mechanisms by which HIV-associated cancers and the same cancers that develop in HIV-seronegative individuals are shared or different.
- Identify the host factors that increase the risk of HIV-associated malignant disease.
- Determine the impact of AIDS-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 manifestations of HIV-associated malignancies are altered by such therapies.
- Determine the impact of AIDS-associated malignancies on the immune response to HIV.
- Determine factors associated with clinical response and lack of response to antineoplastic therapeutic intervention in HIV-infected subjects.

To facilitate the research goals listed above:

- Promote programs to facilitate the development of and augmented access to *in vivo* animal models, patient specimens for HIV-associated malignancies, sharing of key patient samples, 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, genomics, and proteomics to understand the etiology and pathogenesis of AIDS-related malignancies.

OBJECTIVE–E

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.

(The scientific objectives C through G are of equal weight.)

STRATEGIES

- Determine the cellular and molecular mechanisms involved in HIV-associated neurobehavioral and neurological dysfunction including:
  - identifying how HIV enters, establishes infection, spreads, and persists in the central nervous system (CNS);
  - examining the effects of HIV infection on specific cell populations and regions of the nervous system;
  - investigating the connection between blood-brain barrier dysfunction and neuronal injury in the context of HIV infection;
  - determining the relationship of virologic (including distinct subtypes of HIV), host (including the genetics of the virus/host interactions), pharmacologic, substance abuse, and environmental factors to susceptibility of neurological disease and HIV-associated neuropathogenesis (including peripheral neuropathies);
  - 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.
- Determine the host and viral factors influencing independent evolution of drug-resistant HIV strains in the CNS compartment.
- Determine the impact of HIV/CNS infection on systemic disease progression.
- Determine the role of the CNS as a reservoir of, and sanctuary for, persistent HIV infection.
- Define mechanisms of immunologic control of HIV, OIs, and coinfections in the CNS.

- Develop methods to investigate, diagnose, and monitor HIV-associated neurological and neurobehavioral disorders.
- Investigate aspects of HIV infection that uniquely influence the developing nervous system.
- 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 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.

To facilitate the research goals 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/CNS disease course on treatment that are crucial to understanding neurobehavioral and neurologic disorders.
- 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.
- 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, genomics, and proteomics to understand HIV-related neurologic disease.
- Integrate neurologic studies into the design and conduct of treatment trials.

OBJECTIVE–F

Elucidate the pathogenic mechanisms and consequences of OIs and coinfections in HIV-infected individuals in diverse populations across the spectrum of age and gender in national and international settings. 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 (e.g., tuberculosis [TB]) or (b) contribute significantly to HIV transmission or acquisition (e.g., herpes simplex virus [HSV-2]).

(The scientific objectives C through G are of equal weight.)

STRATEGIES

- Conduct studies of the basic biology of such opportunistic pathogens and their interaction with the host.
- Identify and elucidate the genetic and environmental risk factors associated with the susceptibility to, the development of, and the progression of OIs in HIV-infected individuals.
- Study the effects of OIs and coinfections on immune dysfunction and HIV disease progression.
- Define immunologic responses to OI/coinfection pathogens at mucosal surfaces and determine how they may be altered by HIV infection.
- Study how HIV infection changes the pathogenesis of the coinfecting pathogens.
- Elucidate the mechanisms of immune function that mediate protection against OIs.
- Study the effects of HIV therapy-associated immune reconstitution on the clinical course and manifestation of OIs and coinfections.
- Probe the pathogenic mechanisms of HIV-associated OIs, and evaluate how the causes, agents, and manifestations of these HIV-associated infections are altered by ART 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 factors associated with clinical response and lack of response to therapeutic interventions against OIs and coinfections in HIV-infected subjects.

To facilitate the research goals listed above:

- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand the etiology and pathogenesis of HIV coinfections and HIV-related OIs.

- Develop *in vitro* techniques and animal models to propagate and define the life cycles of the opportunistic pathogens 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.

OBJECTIVE–G

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.

(The scientific objectives C through G are of equal weight.)

STRATEGIES

- Investigate the etiologic and pathogenic mechanisms and consequences of HIV-related:
  - GI, including liver and biliary, diseases,
  - nephropathy,
  - endocrine dysfunction,
  - hematologic disorders,
  - pulmonary disorders,
  - autoimmune disorders,
  - cardiac and vascular disease,
  - cutaneous disease,
  - oral disease, and
  - other organ/tissue-specific 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.

To facilitate the research goals listed above:

- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand the etiology and pathogenesis of HIV-related disorders.
- Integrate studies of HIV-related disorders in the design and conduct of treatment trials.