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: *Transmission of HIV (Prevention, Risk Factors, and Mechanisms)*

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, serodiscordant couples, and novel methods (e.g., social network analysis, molecular epidemiology, and geographic information systems) to further assess HIV transmission and acquisition.
- Model how results from existing cohorts might be altered in populations with differing demographics and socioeconomic status, specifically based upon race, ethnicity, gender, age, sexual orientation, acquisition risk, and in-country resource capacities and availability.
- Conduct molecular epidemiology studies to characterize the impact of different HIV types (i.e., HIV-1 and HIV-2), HIV subtypes, recombinant forms, and associated risk factors on routes and modes of HIV transmission, superinfection, natural history, response to antiretroviral therapy (ART) and preexposure prophylaxis (PrEP), and emergence of antiretroviral (ARV)-resistant viruses. Conduct studies that will determine the significance of multiple circulating subtypes and generation of dual, multiple, and recombinant viruses on population epidemiologic dynamics and potential implications for intervention and therapy.
- Conduct epidemiological and modeling research to improve estimates of per-contact risk of HIV transmission, based on type of sexual exposure, characteristics of the infected and uninfected partners (e.g., plasma and/or anogenital tract viral load, host genetics, and coinfections), and cofactors such as drug use.

Strategies Related to Transmission

- Evaluate sexual and blood-borne HIV transmission and acquisition in relation to the following:
  - Viral factors such as viral quantity, diversity, coreceptor usage, genotype (including subtypes, recombinants, and resistance mutants), and dual virus infections in various body compart-

ments (e.g., blood, saliva, semen, and mucosal compartments, such as the female genital tract and the anorectal mucosa);

- Host genetics and other host factors such as age, sex, race, hormonal status, comorbid chronic diseases, strength and breadth of immune response, circumcision status, mental health, and coinfections;
- Modifiable host factors such as diet and nutritional status, or drug, alcohol, and tobacco use and/or treatment, including substitution and other substance use treatment modalities;
- Other infections and their treatment, including *M. tuberculosis* (TB) and drug-resistant strains, multi-drug-resistant (MDR) and extensively drug-resistant (XDR) TB, *Plasmodium* sp. (malaria), and viral hepatitis;
- Social, cultural, and structural determinants of susceptibility to HIV acquisition (i.e., among women and girls and other adversely affected populations); and
- Sexual activity, abstinence (including during the postoperative period after male circumcision), sexual networks, choice of partner, multiple concurrent partners, duration of partnership, partner fidelity, control of sexually transmitted infections (STIs), hygienic practices such as douching, contraception choices, and cultural practices such as the use of traditional vaginal preparations and male circumcision.

- Further refine 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. These studies include:
  - Assessing the impact of maternal and infant ARV regimens of different potency and duration on mother-to-child transmission (MTCT) of HIV and on the short- and long-term health of women and their infants, and the emergence of ARV drug resistance in the mother and in those infants who become infected despite prophylaxis;
  - Studying the safety and effectiveness of sustainable approaches to prevention of MTCT of HIV, including identifying successful breastfeeding weaning strategies, methods for improving the safety of formula feeding, and determining the effects of such approaches on infant morbidity and mortality;
  - Assessing the impact of maternal ART on HIV transmission during pregnancy and lactation;
  - Assessing the impact of maternal and infant adherence to ARV regimens on the risk of subsequent ARV resistance, clinical outcomes, and the effectiveness of ART in mothers and their children;

- Assessing the impact of perinatal treatment and prophylaxis regimens on communitywide HIV resistance to ARVs;
- Assessing the impact of MTCT programs on public health measures, including maternal, paternal, and infant morbidity/mortality rates; overall life expectancy; disability and/or quality-adjusted life years; and pediatric neurobehavioral development; and
- Assessing clinical outcomes, cost, and cost-effectiveness of different strategies for prevention of MTCT in the United States as well as in developing countries.

Strategies Related to Treatment and Interventions

- Conduct epidemiologic modeling studies on the aggregate impact of ART on HIV transmission, particularly in high-prevalence settings.
- Study the impact of widespread ART availability, adherence, and patterns of ART resistance on HIV prevalence, incidence, patterns of risk behaviors, and acquisition of resistant HIV strains.
- Conduct further studies on male circumcision as a prevention tool, including:
  - Assessing the impact of adult male circumcision on an individual and community level, including assessment of HIV prevention and incidence in circumcised males and their partners, sexual behavior, and attitudes, in the domestic and international setting;
  - Evaluating male circumcision delivery models with respect to safety, cost-effectiveness, and long-term impact on HIV transmission;
  - Evaluating male circumcision and its impact on HIV transmission and acquisition among men who have sex with men (MSM); and
  - Evaluating prevention approaches in the context of adult male circumcision, particularly those based on combinations of known methods, including reproductive health, partner reduction, condom use, and STI control.
- Develop and evaluate safe and effective individual-, network-, and community-based interventions aimed at HIV-infected persons and their partners to promote sustained behaviors that prevent acquisition and transmission of HIV.
- Conduct studies on medication-assisted substance abuse treatment modalities and access to care (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.

OBJECTIVE–B: *Disease Progression (Including Opportunistic Infections)*

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 viral genetic variation) and behavioral (e.g., access to and use of the health care system, adherence, and alcohol and drug use) factors on HIV progression and response to therapy, as demonstrated 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 effect on disease progression of viral factors, including viral type/subtype, fitness, viral tropism, and innate and acquired genotypic and phenotypic resistance to ARVs.
- Determine the global patterns of innate and acquired viral resistance to ART and how these patterns could influence the long-term effectiveness of these therapies.
- Elucidate the pathogenic mechanisms that influence residual HIV replication or reservoir latency in ART recipients, including tissue and lymphoid reservoirs, and body secretions such as cervicovaginal fluids and semen.
- 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 mediators such as inflammatory cytokines modify immune function, disease outcomes and survival, and response to ART.
- Characterize the changing spectrum of clinical outcomes, causes of morbidity and mortality, and complications of therapy associated with evolving therapeutic strategies, domestically and internationally.
- Assess the effect of ART treatment on the incidence and pathogenesis of and risk factors for cancer in the domestic and international settings.
- Define the prevalence, incidence, predictors, potential treatments of, and consequences of renal and liver disease in HIV-infected individuals.
- Characterize the long-term effect of HIV infection on the central nervous system, including the effect of viral burden in the cerebrospinal fluid (CSF), its effect on white matter degeneration, and the role of ART in reducing the neurocognitive burden of disease and differentiating these changes from other neurocognitive diseases, such as dementia and Alzheimer's disease.

- Evaluate and characterize immune reconstitution, including modifiable and nonmodifiable predictors of immune recovery in diverse populations.
- Define the prevalence, incidence, and determinants of HIV-associated neurologic, behavioral, and psychiatric manifestations and their relation to disease progression and response to ART, domestically and internationally.
- Identify, characterize, and determine the frequency, changing manifestations, and effects of HIV-related respiratory disease on morbidity, mortality, and HIV disease progression, in both untreated patients and those receiving ART (e.g., recurrent bacterial pneumonia; drug-resistant, MDR-TB, and XDR-TB/HIV cases; immune reconstitution syndromes affecting the lungs, including sarcoidosis and other immune-mediated diseases; HIV-related pulmonary hypertension; accelerated emphysema; and coinfections).
- Develop new interval-based or standard-of-care cohorts and maintain long-term followup of existing cohorts, including observational cohorts and intervention populations, to determine the changing spectrum of HIV disease, identify highly exposed uninfected persons and long-term nonprogressors, and evaluate interventions, especially in aging and minority populations, in developing countries, and in emerging epidemic zones, including Central Asia, the former Soviet Union, and South and Southeast Asia.
- Characterize short- and long-term consequences of recent HIV infections including host and viral genetic characteristics and differences by route of exposure, and continue to characterize the natural history of HIV disease and AIDS among those early in infection, those with minimal exposure to ART, those with virologic and/or immunologic responses to ART, and those who have experienced ART failure.

Strategies Related to Complications of Therapy

- Comprehensively determine the effects of cumulative and current antiretroviral therapy exposure to specific drugs, classes of drugs, drug combinations, and treatment strategies.
- Characterize and investigate the role of ART-associated toxicities (including disorders in glucose, lipid, and bone metabolism, renal dysfunction, and hepatotoxicity) in specific populations, including coinfected populations (e.g., TB, XDR-TB, hepatitis C [HCV], and hepatitis B [HBV]), pregnant women, children and adolescents, the aged, populations receiving traditional medicines, resource-limited populations, minority populations, and according to nutritional status, in comparison with non-HIV-infected populations.
- Investigate age and gender differences in ART-associated toxicities and comorbidities in comparison with non-HIV-infected populations. Gender differences should also explore differences in sex steroid levels (androgens and estrogens) and ovarian reserve in women and how they impact metabolic, cardiovascular, bone, renal, and liver disorders.

- Investigate the role of chronic inflammation in the development of malignancies and metabolic, cardiovascular, bone, renal, and liver disorders in HIV-infected individuals and appropriate controls and how cumulative and current ART use might mediate the effects of chronic inflammation.

Strategies Related to Comorbidities

- Intensify research on the spectrum of HIV-associated malignancies, particularly those that may develop in HIV-infected patients who have responded to ART and are expected to live longer with immune deficiency.
- Establish normative data for lymphocyte subsets, total white blood cell count, and total lymphocyte count, and determine the influence of common comorbidities, such as malaria, TB, and helminthic infections, on the "normal" values in patients from different regions of the developing world affected by the HIV epidemic, notably in 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 and TB drug-resistant strains.
  - Investigate the XDR-TB epidemic, evaluating risk factors for XDR-TB prevalence, incidence, and therapeutic options among HIV-infected patients.
  - Develop novel TB diagnostics for use with HIV-infected patients in order to rapidly identify MDR-TB and XDR-TB in HIV/TB-coinfected populations.
  - Assess outcomes related to methods of integrating TB and HIV care on survival, quality of care, and cost.
  - Investigate the impact of treating latent TB on the epidemiology of HIV/TB coinfection in endemic countries to determine whether it is feasible, effective, and cost-effective.
- Evaluate the impact of treatment of alcohol use and abuse, illicit drug use, and mental health disorders on the effectiveness and consequences of ART, HIV disease progression, morbidity, and mortality.
- Support research efforts to link existing databases on cancer, TB, transplant, etc., and death registries to enhance understanding of HIV/AIDS outcomes in standard-of-care cohorts.
- Assess the interaction of HIV infection and ART on other infections and their treatment.
- Study the emergence and reemergence of infectious diseases and the development of antimicrobial-resistant infections (e.g., MDR-TB, sulfa-resistant malaria, antibiotic-resistant pneumococcus, cotrimoxazole-resistant *Pneumocystis jiroveci* pneumonia, methicillin-resistant *Staphylococcus aureus* [MRSA], and lamivudine-resistant HBV) in HIV-infected populations.

- Estimate the prevalence of specific human papillomavirus (HPV) types associated with cervical cancer and high-grade dysplasia in HIV-infected women, and evaluate the effectiveness of HPV vaccines among HIV-infected individuals from geographically diverse regions.
- Assess the interaction of ARVs on HPV persistence and regression of cervical lesions to understand the dynamics of the two viruses with a goal of optimizing care for HIV-infected women, especially in resource-limited settings.
- Assess the effect of primary care screening and interventions (e.g., statin use, hypertension management, smoking cessation, depression treatment, and cancer screening and treatment) on HIV disease outcomes and survival. Use these assessments to guide recommendations for adaptation and prioritization of primary care guidelines for those with HIV infection.

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, behavioral, and psychomotor development; impact of other childhood infectious diseases and nutritional status; and safety and efficacy of immunizations, and how these may be affected by biomedical and behavioral interventions.
- Study the effect of the health status of HIV-infected mothers and of ART during pregnancy, lactation, and early childlife on survival and quality of life of their HIV-infected and -uninfected children.
- 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.
- Assess the implications and outcomes of different strategies of prevention of MTCT on transmission and costs of care in HIV-infected mothers and their infants.
- Evaluate the differences in treatment response and HIV outcomes between adolescents, adults, and perinatally infected children; in behaviorally acquired versus perinatally infected adolescents; and in adolescents treated in pediatric versus adult HIV treatment centers.

Strategies Related to Aging

- Investigate the relationship between HIV infection and the spectrum of physical and mental health outcomes that increase with aging, such as cancer, obesity, diabetes, hypertension, arthritis, unexplained anemia, anemia of chronic inflammation, emphysema, renal insufficiency, and dyslipidemia, as they affect 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.

- Evaluate immunologic and virologic measures of HIV disease progression and mortality in older versus younger adults receiving ART to refine treatment guidelines for older HIV-infected patients, including the appropriate CD4 cell count for initiation of ART.
- Study the effects of HIV and ART, such as immunologic and virologic response to treatment, and adverse effects, in aging populations that have coexisting morbidities and who receive numerous medications.
- Develop guidelines to help prioritize treatment of comorbidities when managing HIV in older patients with multiple diseases.
- Study the impact of expanding routine, voluntary HIV testing in improving diagnosis, care, and outcomes in elderly patients.

Strategies Related to Adherence, Access to Care, and Quality of Life

- Develop and evaluate novel methods, such as behavioral reports and biological markers of use, for accurately measuring adherence to therapy and efficacy of preventive therapies in patients throughout the lifespan.
- Study determinants of adherence to ART and adverse events of ART in all age and risk groups, as well as in times of transition such as pregnancy and growth from child to adolescent to adult, to inform interventions to improve adherence.
- Study the impact of access to care, ART, microbicides, and vaccines on risk behaviors and HIV acquisition among at-risk populations, including minorities, MSM, and adolescents.
- Investigate how different patterns of access, adherence, and exposure to ART in treatment-experienced and -inexperienced populations contribute to ARV resistance and disease progression.
- Elucidate the effects of HIV infection on pain and sleep disturbances, including prevalence, possible immunological and endocrine mechanisms, associations with HIV outcomes, possible changes with ART, and influence on quality of life and physical and mental health.
- Develop studies on the impact of routine, voluntary HIV testing, and its role in different prevalence settings in improving HIV-related outcomes.
- Examine predictors of successful linkage to and retention of HIV-infected patients in care, from the time of HIV testing through the time of ART provision and patient followup.
- Assess the impact of different approaches for testing, linkage, and retention in care in improving overall outcomes of HIV disease.

OBJECTIVE–C: *Methodologies*

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 multiple study designs that incorporate appropriate ethical, cultural, and policy context for studies of HIV disease and AIDS in diverse domestic and international populations.
- Continue to support local, regional, and international collaborations to integrate and harmonize existing data for scientific investigations.
- 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, MSM, adversely affected racial and ethnic populations, and those with other comorbidities.
- Involve representatives of the community and study participants in all phases of research planning, design, management, approval, and reporting, when possible and appropriate, and promote and support academic/community-based research collaborations.
- Implement research training and career development opportunities for medical and health professionals from communities disproportionately affected by the epidemic, both in developing countries and domestically. Training should include research ethics, study design, informatics, biostatistics and modeling, data management and analysis, manuscript preparation and publication, grant writing, and translational research to promptly bring basic science results to clinical care and clinical results to health policy and implementation.
- Promote study designs that provide the highest degree of human subject protection and benefit possible.
- Promote study designs that include plans for dissemination of findings to community representatives, study participants, health care practitioners, and policymakers.

Strategies Related to Natural History/Pathogenesis

- Develop epidemiologic, laboratory-based, and simulation modeling methods in conjunction with prospective cohort studies, domestically and internationally, to monitor response to ART and the incidence of complications related to chronic use of ART, including:

- Develop and test methods to produce accurate, reproducible, and inexpensive virologic, immunologic, bacteriologic, pharmacologic, neurobehavioral, 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; hepatitis testing; HIV resistance testing; and noninvasive, rapid, and inexpensive diagnostic assays for sexually transmitted diseases (STDs), other coinfections including malaria, TB and XDR-TB, and malignancies.
- 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.
- Identify and/or develop uniform assessment tools to measure host and environmental characteristics, including substance abuse and mental health, which may affect immediate and longer-term HIV-related health outcomes. Assessment tools should be both culturally appropriate and scientifically valid.
- Develop assays to identify recent HIV infection, including measures appropriate for international populations.

Strategies Related to Research on Design and Analysis of Epidemiologic Data

- Develop new epidemiological designs and statistical methods, including development of informatics tools and simulation, to better characterize transmission dynamics and monitor long-term trends in disease progression and development of toxicities in the setting of potent ART.
- Continue to develop and improve upon quantitative methods for making effective and appropriate use of data from large observational, cross-sectional, and cohort studies, such as:
  - Assessing costs of care for HIV disease management and treatment of comorbidities, both domestically and internationally;
  - Methods for inferring causal effects of nonrandomized exposures (e.g., treatment and policy changes);
  - Methods for estimating HIV infection rates in cross-sectional samples;
  - Methods for sampling hidden populations (e.g., respondent-driven sampling);
  - Models and inferential methods for characterizing multiple disease processes and events;

  - Methods for linking cohort data to cost data for direct health policy questions;
  - Methods for innovative study designs that can simultaneously address more than one hypothesis or intervention, including factorial randomized trials and quasi-experimental designs; and
  - Methods for collecting and analyzing spatio-temporal data, especially as they relate to transmission and spread of HIV infection.

- Encourage research on innovative design and analysis through interdisciplinary collaboration between methodologists from different fields, such as biostatistics, econometrics, epidemiology, computer science, biomathematics, decision sciences, operations research, health services research, and demography.

Strategies Related to Interventions

- Study and evaluate the various operational strategies that can be employed to "bring to scale" and to evaluate countrywide ART programs and successful preventive or therapeutic interventions, such as male circumcision, including the use of operations research and integrated observational databases to evaluate treatment effectiveness and cost-effectiveness at the individual, community, and population levels.
- Study and evaluate prevention packages that combine multiple strategies into one intervention, especially those that combine behavioral, biological, and structural interventions.
- Determine the outcome of different approaches to routine, voluntary HIV testing in different settings and in different racial/ethnic populations.
- Assess the optimal algorithms for HIV diagnosis in patients, including strategies for identification of acute infection.
- Assess the effectiveness and outcomes of clinical and/or laboratory monitoring for the initiation, monitoring, and switching of ART, particularly in resource-limited settings, including laboratory monitoring with new methods that are technologically appropriate and affordable in various international settings.
- Develop appropriate clinical and laboratory definitions of short- and longer-term ARV failure, and develop mechanisms for monitoring and assessing drug resistance evolution in HIV types, subtypes, and variants in domestic as well as international settings.
- Develop, evaluate, and promote new, improved, and cost-effective methods to prevent HIV transmission via blood transfusion, as well as other medical interventions and iatrogenic exposures in developing countries, including instrument sterilization.

- Assess the impact and cost-effectiveness of different strategies for HIV testing and linkage to and maintenance in care of different populations, including adolescents, seniors, racial and ethnic populations, and populations in diverse international settings.
- Develop strategies to validate the use of surrogate markers for HIV acquisition and/or transmission risk, including use of behavioral measures and biomedical markers.
- Develop and refine simulation strategies, such as modeling, to assess the impact of interventions on HIV transmission, cofactors of HIV infection, and communitywide morbidity and mortality, including non-HIV-infected individuals.

Strategies Related to Policy

- Develop studies of operational research and implementation science, which is the evaluation, translation, optimization, and scale-up of prevention, treatment, and health care innovations into effective new public health programs.
- Develop research efforts that measure and evaluate the outcomes of large-scale HIV treatment programs, with attention to clinical as well as economic outcomes of care.
- Evaluate the long-term clinical and nonclinical impact, cost, and health care utilization ramifications of different strategies for care, including treatment of HIV-associated conditions, ART, complications of ART, and other comorbidities.
- Assess the impact and acceptability of routine, voluntary HIV testing programs, including issues such as stigma and confidentiality.
- Support HIV policy research, including studies of laws and economics, necessary for translating epidemiological and clinical studies into policy to improve health and to make cost-effective decisions.
- Assess the impact of strategies for managing HIV coinfections in international settings using modeling and other integrative methodologies.

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 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 role of the host microbiome in transmission, establishment, and spread of HIV infection.
  - Elucidate the genetic complexity and the biological characteristics 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 innate and adaptive immunity, and the effects of genetic or environmental factors on 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.
- 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, epigenetics, and systems biology (multiscale modeling and commonly used approaches to validate hypotheses such as genomics, proteomics, 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 markers and functional 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 nonhuman primate (NHP) models of both pathogenic and nonpathogenic infection and facilitate collaborative research using these models.

OBJECTIVE–B: *HIV Virology and Pathogenesis*

Delineate the viral and host mechanisms associated with the pathogenesis of immune dysfunction, aberrant immune activation/inflammation, 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, 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 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 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 (e.g., gastrointestinal mucosa) 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.
- Determine the contribution of immune activation/inflammation to HIV disease progression, and elucidate the mechanisms driving this activation.
- 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.
- 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 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.
- 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/math-ematical 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, 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.

- 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: *Pathogenesis of Opportunistic Infections*

Elucidate the pathogenic mechanisms and consequences of opportunistic infections (OIs) and 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 OIs 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 (e.g., tuberculosis [TB] and hepatitis C [HCV]) or (b) contribute significantly to HIV transmission or acquisition (e.g., sexually transmitted infections [STIs]).

(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 (e.g., methicillin-resistant *Staphylococcus aureus* [MRSA]).
- 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 antiretroviral therapies (ARTs).
- 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 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, and systems biology (multiscale modeling and commonly used approaches to validate hypotheses such as genomics, proteomics and cellular biology) 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.
- Facilitate collaborative and interdisciplinary studies to elucidate the etiology and pathogenesis of HIV OIs and coinfections (e.g., TB and HCV).

OBJECTIVE–D: *Pathogenesis of Metabolic and Body Composition Change*

Define the etiology, pathophysiology, and consequences of HIV infection and treatment-related metabolic disorders, body composition changes, endocrine dysfunction, and cardiovascular disease 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, renal, bone, skeletal muscle, 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; and
  - the contributions of OIs, hormonal dysregulation, and other consequences of HIV infection.
- Study the impact of HIV on an aging population, including the implications of HIV infection for cardiovascular, metabolic, bone, skeletal muscle, skin, and renal diseases.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms underlying alterations in metabolism, body composition, growth and development, diabetes, and bone, skeletal muscle, skin, renal, 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 goals listed above:

- Transfer expertise from the endocrine, metabolic, cardiovascular, obesity, renal, bone, skeletal muscle, 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, cardiovascular, bone, skeletal muscle, 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, and cellular biology) to understand the metabolic, endocrine, cardiovascular, renal, bone, skeletal muscle, 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, and skin complications in HIV-infected populations.
- Integrate metabolic, endocrine, cardiovascular, renal, bone, skeletal muscle, 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, muscle wasting, skin disease, endocrine parameters, and cardiovascular disease.

OBJECTIVE–E: *Pathogenesis of Malignancies*

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 AIDS-defining and other malignancies that are associated with HIV infection.
- 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.
- 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, etc.) that may emerge in the aging HIV-infected population.
- Identify the host factors that increase the risk of 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-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 shift in the spectrum on both AIDS-defining and emerging non-AIDS-defining malignancies occurring in HIV-infected individuals treated with ART.
- 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.
- 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, and cellular biology) to understand the etiology and pathogenesis of AIDS-related malignancies.

OBJECTIVE–F: *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.

(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, 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.
- 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 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.

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 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 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.
- 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, and cellular biology) to understand HIV-related neurologic disease.
- Integrate neurologic studies into the design and conduct of observational studies and treatment trials.

OBJECTIVE–G: *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.

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

STRATEGIES

- Investigate the etiologic and pathogenic mechanisms and consequences of HIV-related:
  - gastrointestinal (GI), including intestinal, liver, and biliary, diseases,
  - nephropathy,
  - hematologic disorders,
  - pulmonary disorders,
  - autoimmune disorders,
  - cutaneous disease,
  - bone disease,
  - adipose dysfunction,
  - 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.

To facilitate the research goals 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, 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.