PRIORITY:

Improving Disease Outcomes for HIV-Infected Individuals

Drug Discovery, Development, and Treatment

AREA OF EMPHASIS

Drug Discovery, Development, and Treatment

FY 2012 RESEARCH PRIORITIES

- Advance and share the discovery and validation of therapeutics strategies, including new and existing viral and cellular targets, to provide safe, tolerable, maximally long-term suppressive viral activity against existing viral strains, as well as emerging multi-drug-resistant viral strains.

- Advance the discovery and validation of therapeutics strategies to combat progression of HIV and its associated comorbidities, coinfections, and other clinical complications in HIV-infected individuals across the lifespan, including in older adults.

- Support research on the nature of HIV persistence and develop strategies to decrease or eliminate the viral reservoirs remaining despite optimal treatment.

OBJECTIVE–A: Discover and Develop Anti-HIV Treatments

Identify and validate viral and host cellular functions required for HIV replication that can be targeted for viral inhibition, eradication of persistent virus, and prevention of transmission. Discover and develop novel agents and therapeutic strategies directed against viral and host factors involved in HIV transmission, infection, replication, and persistence, and that are effective to prevent and treat drug-resistant virus. Encourage collaborations between academia, industry, private and public organizations, the community, and the NIH.

STRATEGIES

- Identify, characterize, and validate new and understudied viral and host targets for anti-HIV therapy (e.g., factors involved in viral fusion, entry, integration, transcription, replication, assembly, budding, infectivity, virulence, and pathogenicity). Develop predictive test models, including appropriate lentivirus animal models, to aid in identifying agents and strategies active against these targets.
  - Develop new agents and treatment strategies that target, inhibit, and clear HIV in cellular, anatomical, and organ reservoirs and sanctuaries, including agents that can suppress HIV in non-T-cell reservoirs.
  - Identify the cellular reservoirs of latent HIV *in vivo* and develop physiologically relevant *in vitro* and *ex vivo* organ or tissue models that can be used to discover agents/approaches that target and eliminate reservoirs.
  - Characterize potential agents, including their preclinical, immunologic, pharmacokinetic, pharmacodynamic, toxicity, and teratogenicity profiles.
  - Develop new compounds and chemical formulations and novel routes of administration.
  - Employ whole animal and *ex vivo* organ or tissue models of lentivirus infections to study the biologic and pharmacologic characteristics of therapeutic agents.
  - Evaluate the potential to inhibit HIV replication and spread by modifying chemokine receptor expression and/or chemokine levels. Develop agents to block the attachment of HIV to receptors and coreceptors and thus inhibit entry into target cells.
- Acquire structural information on HIV and cell constituents involved in HIV infection for the design of potent and selective therapeutic agents and therapeutic vaccine candidates. Post lead structures on publicly available databases.
  - Support genome-wide association studies and integrate systems biology approaches, including genomics and informatics paradigms, concepts, and methodologies (e.g., microchip-based screens [including siRNA] and analyzers), into mainstream drug discovery and the development of therapeutic entities and strategies.
  - Develop enabling, rapid, and high-throughput technologies to accelerate and optimize the discovery and development of therapeutic entities and strategies; expand the infrastructure to provide services and reagents needed by the scientific community.
  - Evaluate the intracellular pharmacokinetics and activity of antiretroviral (ARV) agents in different cell types, different stages of the cell cycle, and in all age groups. Correlate intracellular pharmacokinetic parameters with drug efficacy/toxicity.
  - Develop novel tools (including nanotechnology) for drug discovery and the investigation of drug efficacy.
  - Develop novel tools and systems biology approaches to better understand viral pathogenesis and drug pharmacokinetics in various intracellular and extracellular compartments.

- Develop novel bioimaging applications (including nanotechnology) to evaluate viral transmission and reservoirs, immune induction and modulation, and drug transport and metabolism.
- Develop novel delivery systems that target specific tissues, cells, organelles, proteins, and/or nucleic acids.
- Develop agents with desirable biopharmaceutical characteristics (e.g., improved bioavailability and tissue penetration to the central nervous system [CNS] and other sanctuaries); develop drug delivery devices or systems that improve the pharmacokinetic profile of therapeutic agents, target specific organs or tissues, reduce toxicities and adverse effects, and result in improved adherence to therapeutic regimens.

- Advance basic and applied gene-based strategies to treat HIV infection. Foster new approaches and technologies to optimize gene delivery that result in regulated and persistent gene expression. Optimize *ex vivo* gene delivery and advance new concepts, strategies, and vectors for direct *in vivo* delivery.
- Develop therapeutic strategies, including approaches to identify patients in the early stage of HIV infection, with emphasis on the early T-cell depletion in the gastrointestinal tract.
- Study the mechanisms and implications of drug resistance and viral fitness; evaluate early markers and genotypic mutations that lead to resistance and cross-resistance.
- Study the effects of recombination within and between HIV clades on the evolution of drug resistance.
- Develop and evaluate interventions aimed at HIV-related immune activation.
- Develop mathematical and computer models of HIV infection and therapeutic interventions that stimulate and predict *in vivo* efficacy, toxicity, and other outcomes of drug regimens and clinical trials. Investigate the use of pharmacogenetics in identifying optimum therapies.
- Investigate the host cell effects of ARV drugs.
- Develop and perform the preclinical evaluation of fixed-dose combination formulations of approved ARV drugs, including doses appropriate for children.
- Develop and evaluate pediatric drug formulations of available and new ARV drugs, with emphasis on low-dose dividable solid formulations appropriate for use in resource-limited settings, as well as liquid formulations.
- Develop therapeutic agents for the treatment of HIV/AIDS that do not interact with psychotropic medications, drugs of abuse, or medications to treat drug abuse.

OBJECTIVE–B: Conduct Clinical Trials of Anti-HIV Treatments

Assess the short- and long-term efficacy and effectiveness of therapeutic agents and strategies against acute, established or latent, HIV infection, viral reservoirs, and transmission in treatment-naive and treatment-experienced HIV-infected individuals, across the lifespan, including in older individuals, through the conduct of clinical trials and cohort-based studies in domestic and international settings, especially in resource-developing nations; develop new clinical trial methodologies; and develop strategies to mitigate factors that adversely affect the success of therapeutic strategies against HIV infection. Develop domestic and international partnerships to design and conduct clinical studies where the epidemic is prevalent.

STRATEGIES

Clinical Trials of Therapeutic Agents

- Conduct clinical trials of potential therapeutic agents and combinations of agents in adults, including older populations, adolescents, and children, to determine pharmacokinetics, tissue bioavailability, antiviral activity, effects on the immune system, safety, and clinical efficacy.
  - Evaluate novel combinations of agents selected for maximizing antiviral synergy, complementary mechanism of action, minimal toxicity and cross-resistance, simplicity of administration, and tolerability.
  - Evaluate optimal therapies and novel strategies for individuals who have acute or recent infection (including neonates/young infants with perinatal infection), chronic infection but no prior antiretroviral therapy (ART), and those with prior ART, including individuals with multiple-drug-resistant virus.
  - Support clinical trials to study:
    - long-term effectiveness (including toxicities) of therapeutic strategies;
    - timing, selection, and strategic sequencing of ARV agents to optimize clinical outcome;
    - optimal treatment for heavily ARV-experienced individuals with treatment failure;
    - the effect of ART on HIV-related comorbidities;
    - gender-based and genetic differences in special populations; and
    - evaluation of interventions to minimize ART-related comorbidities.
  - Support small clinical studies to validate potential new targets and/or explore novel therapeutics (e.g., cell-based and gene-based).
  - Evaluate coformulated ARVs in all age groups.
  - Investigate the effects of drug-sparing regimens on efficacy, resistance, and transmission.
  - Evaluate treatment as prevention, including studies on factors (e.g., genital tract viral load, variations in genital tract microbiome, and genital coinfections) that may increase transmission from an HIV-infected individual to an uninfected individual.
  - Evaluate novel approaches and treatment regimens to prevent and eradicate viral reservoirs that may lead to a cure for HIV disease.

Clinical Trials Enrollment

- Strengthen efforts and implement new approaches and in novel locations to ensure the enrollment and retention of specific populations, including women, children, adolescents, minorities, substance abusers, men who have sex with men, older adults, and marginalized high-risk populations in clinical trials and cohort-based studies to reflect the incidence of the epidemic.

- Strengthen efforts to evaluate new and existing drug treatment regimens in clinical trials and cohort-based studies that reflect the demographics of the epidemic. When appropriate, evaluate potential gender, race, ethnicity, age-specific, pregnancy-related, and nutrition-related differences in drug efficacy and safety, including pharmacokinetics, metabolism, tissue absorption, and drug elimination.
- Identify and test strategies to improve the recruitment and retention of individuals in clinical trials.
- Strengthen efforts to enroll HIV-infected children in clinical trials to test pediatric formulations of ARVs.

Clinical Trial Methodology

- Develop and evaluate standardized virologic, immunologic, and clinical markers to assess drug activity; determine and validate surrogate markers in response to various therapeutic interventions, including those most applicable to resource-limited settings.
- Develop novel inexpensive and rapid platforms, as well as point-of-care assay systems, for detection, diagnosis for recent HIV infection, biomarker evaluation, and genetic testing for both *in vitro* and *in vivo* evaluations.
- Develop, incorporate, and validate appropriate quality-of-life parameters in clinical trials of ARV agents.
- Develop a methodology to facilitate creative statistical analyses that will facilitate the understanding of clinical trial outcomes.
- Conduct research on how and why subjects decide to participate in clinical trials in order to increase enrollment and maintain adherence to study protocols.
- Conduct studies on behavioral factors and prevention approaches that are critical to optimizing ART.
- Improve research methodologies for the ethical conduct of clinical trials.

Pharmacology

- Determine the relationship between drug exposure (pharmacokinetics), pharmacogenomics, and outcomes (antiviral effect, immune function, and safety) to facilitate dosing strategies within clinical trials, as well as for individual patient management, including the utility of therapeutic drug monitoring and potential application of pharmacogenetics.
- Investigate drug interactions, including pharmacokinetic and pharmacodynamic impacts, among commonly used treatments for HIV-related disease and its complications, including medications taken by older individuals for pre-existing conditions, as well as other substances that may be used by HIV-infected individuals.
- Evaluate the effects of nutritional deficiency on the pharmacokinetics and activity of ARV drugs.

Viral Reservoirs

- Quantitate persistent HIV in different tissue compartments during effective ART, and evaluate strategies to reduce or eradicate such reservoirs.
- Evaluate the penetration of ARVs into different body fluids and tissue compartments.

Viral Resistance and Fitness

- Explore the utility of real-time ARV phenotypic and genotypic assays in managing ART across a broad spectrum of individuals.
- Evaluate the impact of transmission of drug-resistant strains of HIV on disease progression or therapy.

Mechanisms of Viral Failure

- Identify and evaluate the viral and host factors, including human genomics, associated with ART failure, including drug interactions, drug resistance, drug toxicities, pharmacogenetics, malabsorption, and suboptimal adherence.

Adherence and Self-Management

- Support research on the effectiveness of pharmacological approaches, behavioral interventions, and other approaches to facilitate better adherence to ARV regimens.
- Develop better methods to assess adherence to treatment regimens across a variety of affected populations; compare and validate adherence measures in the context of HIV treatment.
- Investigate strategies for managing symptoms that are attributed to therapy, and investigate the relationship between symptom management and improved adherence to ARV regimens. This may include self-management or other combined biobehavioral approaches.

International

- Expand the development of international collaborations that will assist in addressing relevant therapeutic research in populations of HIV-infected adults, adolescents, and children, including studies on factors resulting in early deaths occurring within the first 3 months of treatment/care.
- Assist and encourage resource-limited nations, as appropriate, in technology transfer through training in the United States and onsite in-country, infrastructure, and capacity building to facilitate the evaluation of ARV agents and other therapies in local settings.
- Assess the barriers to delivery of effective health care for HIV disease, including treatment and the capability of conducting international therapeutic clinical trials through the establishment or expansion of multidisciplinary clinical centers.
- Develop and evaluate simpler, sensitive, reliable, user-friendly, and inexpensive surrogate markers, assay technologies, and rapid point-of-care diagnostics for monitoring immunologic and virologic status and ARV drug responses that can be used in resource-limited settings.
- Develop standardized clinical indicators to determine how and when to initiate ART, to monitor responses to therapy, and to determine when to change therapy.
- Determine acceptable laboratory monitoring methods for drug toxicity in resource-limited settings.
- Evaluate whether nutritional status (particularly chronic malnutrition) affects the efficacy of therapy and whether it affects the risk or severity of adverse events associated with ART.

OBJECTIVE–C: Approaches to Manage Consequences of HIV Infection and Its Treatment

Develop strategies to predict, evaluate, treat, and prevent complications of long-term HIV disease and toxicities of antiretroviral treatment, and the interaction of comorbidities in HIV infection in domestic and international settings.

STRATEGIES

- Develop and evaluate therapeutic strategies for preventing and treating complications of HIV infection.
- Evaluate potential delayed or late effects of ART following short-term administration of prophylactic regimens (e.g., for prevention of mother-to-child transmission), as well as during chronic treatment.
- Develop standards and definitions to allow better comparisons of late complications across clinical trials (i.e., meta-analysis between and studies and efficacy of interventions in clinical trials versus effectiveness in public health practice).
- Support research on the pathogenesis and mechanisms of toxicity of drugs used to treat HIV disease.
- Develop and test approaches to prevent or reverse potential metabolic abnormalities (e.g., changes in body composition, development of atherogenicity and endocrine disorders, and changes in bone and muscle structure) based on an understanding of the mechanisms by which ART and/or HIV disease may affect metabolic processes.
- Develop and validate early markers of renal, liver, CNS, bone, and other complications of ART and/or long-term survival with HIV infection.
- Integrate metabolic, endocrine, cardiovascular, neurologic, renal, liver, and bone studies into ongoing and planned clinical studies, which may provide an opportunity to answer important questions related to potential complications of ART.
- Study the effects of gender, race, age, pregnancy and lactation status, and type of exposure on complications of ART.
- Evaluate the impact of nutritional deficiencies, impaired access to safe drinking water, regionally significant coinfections, and other population- and area-specific factors on complications of ART in developing countries.
- Evaluate the impact of nutrition and nutritional interventions in undernourished populations or lactating mothers provided concurrently with ART on improved clinical outcomes.
- Evaluate drug interactions with potential clinical significance for HIV-infected individuals, particularly the pharmacokinetics and pharmacodynamics between ARVs and drugs used to treat HIV-related comorbidities or medications used in the treatment of drug addiction and mental disorders; develop strategies to avoid or minimize the clinical impact of these interactions.
- Study the effects of treatment and long-term HIV disease on the natural aging process and vice versa, including development of comorbidities across the lifespan of the HIV-infected individual.
- Evaluate approaches to prevent and treat immune activation associated with HIV disease and treatment.
- Develop novel delivery systems to increase safety, tolerability, and ease of use of therapeutic agents.
- Develop novel tools (including nanotechnology, proteomics, and immunotechnology) for rapid DNA sequence identification to facilitate toxicogenomic research and applications.
- Evaluate the safety of current and proposed novel platforms and strategies for use in HIV-related applications.

OBJECTIVE–D: Prevent and Treat Coinfections

Develop and evaluate new agents and strategies for diagnosis, prevention, and treatment of the most significant coinfections in the context of HIV disease in domestic and international settings and across the lifespan of HIV-infected individuals, including but not limited to tuberculosis (TB), malaria, hepatitis C virus (HCV), hepatitis B virus (HBV), and Kaposi's sarcoma herpesvirus (KSHV). Develop and evaluate new therapeutic agents and strategies to prevent and treat drug-resistant coinfections, particularly TB.

STRATEGIES

Preclinical Discovery and Development

- Support preclinical drug design and development programs to develop therapies against HIV-associated pathogens and their disease manifestations, especially *Mycobacterium tuberculosis* (TB) (including multi-drug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB)), malaria, HCV, HBV, human papillomavirus (HPV), KSHV/human herpesvirus type 8 (KSHV/HHV-8), cryptococcal infection, Epstein-Barr virus (EBV), and cytomegalovirus, with emphasis on innovative approaches and agents with favorable bioavailability and pharmacokinetics, as well as development of formulations appropriate for use in children.
- Support and encourage mechanism-based screening of novel synthetic compounds and natural products to identify candidate agents for treating the most significant coinfections; provide support for medicinal chemistry, structural databases, resynthesis, and toxicity testing.
- Cooperate with the private sector to increase involvement and investment in anti-opportunistic infection (OI) and anti-coinfection drug discovery and development research, especially in areas where public health needs are substantial; assume full responsibility, when necessary, for the development of potential therapies with high public health relevance and need.
- Support studies and develop vaccines and interventions for coinfections (e.g., TB, HPV, rotavirus) in HIV-exposed and HIV-infected children, adolescents, and adults.
- Support and encourage development of novel platforms for fast, accurate, and cost- effective detection and diagnosis of pathogenic organisms and related biomarkers.
- Encourage development of novel delivery methods to both enhance the efficacy and decrease the toxicity of currently existing and future therapeutic agents.
- Support development of nano-targeting modalities to selectively infiltrate and treat infected compartments/tissues/cells.

Clinical Trials of Preventive and Therapeutic Regimens

- Assess the impact of new ARV regimens on the risks for and manifestations of infections associated with HIV disease in adults, adolescents, and children.
- Improve understanding of the interplay between HIV-associated immune deficiencies and the onset and types of infectious complications.
- Improve strategies for prevention of multiple infections in the context of ART; determine the optimal timing for initiating/discontinuing prophylaxis for different OIs and coinfections; and develop improved strategies to minimize toxicities and the development of drug-resistant microorganisms.
- Support clinical trials in HIV-infected individuals, including children, of preventive and therapeutic regimens for HIV-related coinfections.

Detection of HIV Coinfections

- Develop clinically useful assays and methodologies for early and rapid diagnosis of OIs and coinfections (particularly TB), quantitative assessment of microbiological responses, and drug sensitivity testing, including assays appropriate for use in children with coinfections.
- Develop tools to identify HIV-infected individuals at high risk for development of specific OIs and coinfections, to improve the efficiency of clinical trial design and the risk-benefit ratio of the currently utilized drugs for prophylaxis and treatment.

Coinfections

- Support research on the interactions between ART and treatments for coinfections.
- Study the interaction between HIV infection and infectious complications upon pathogenesis, presentation, and disease outcomes in adults, adolescents, and children.
- Develop models for studying biological interactions between HIV and coinfections that may lead to the development of new and better treatments.
- Support clinical trials, domestic and international, of adults and children coinfected with HIV and TB (both active and latent infection). Evaluate the safety and efficacy of treatment regimens in coinfected individuals. Determine the optimal length of treatment. Evaluate regimens in the context of degree of immunosuppression.
- Investigate surrogate markers of TB disease that could distinguish between latent, active, and eradicated infection in coinfected individuals; determine how each infection influences or alters the other disease in respect to progression and response to therapy.
- Support clinical trials investigating the efficacy and risks of treatment of HCV in individuals who are coinfected with HIV; determine how each infection influences or alters the other disease in respect to progression and response to therapy.
- Study the interaction of coinfections with HIV transmission (e.g., placental malaria and perinatal infections) and effects on HIV disease progression.
- Investigate the role of HIV-associated coinfections in stillbirths, perinatal delivery, and pregnancy/neonatal outcomes.

Pharmacology and Toxicology

- Conduct preclinical studies of anti-OI and anti-coinfection drugs (alone or in partnership with industry) to assess their immunologic, pharmacokinetic, pharmacodynamic, toxic, reproductive, and teratogenic effects, as well as transplacental carcinogenicity; develop pediatric formulations of anti-OI drugs, including lower dose solid as well as liquid preparations.
- Support clinical studies to evaluate the safety and pharmacokinetics of existing and experimental agents intended to treat or prevent OIs and coinfections in HIV-infected infants, children, and pregnant women.
- Evaluate drug interactions between anti-TB agents and HIV medications. Support the investigation of new anti-TB agents with fewer side effects, drug interactions, and/or action against MDR- and XDR-TB.

Adherence and Self-Management

- Support research on the effectiveness of pharmacologic and other approaches in promoting adherence to anti-coinfection regimens.
- Develop formulations, routes of administration, and delivery systems for existing and experimental anti-OI and anti-coinfection drugs appropriate for use in infants, children, and other populations.
- Develop and evaluate interventions to facilitate better adherence to therapies among populations with HIV infection and substance abuse and/or mental illness.
- Investigate strategies for managing symptoms that are attributed to HIV infection, coinfection, and/or therapy, and investigate the relationship between symptom management and improved adherence to ARV regimens. This may include self-management or combined biobehavioral approaches.

International

- Conduct clinical trials in adults (including pregnant women) and children to evaluate agents for the prophylaxis and treatment of HIV-associated OIs and coinfections; target infections shown to cause significant morbidity by epidemiologic studies, and made worse by HIV-induced immunosuppression.

- Develop and evaluate strategies for treatment and prevention of prevalent opportunistic and endemic infections in the context of HIV infection.

- Evaluate the role of nutrition, malnutrition, and severe malnutrition on treatment and prophylaxis regimens for OIs and coinfections.

OBJECTIVE–E: Treatment of AIDS-Related Neurologic Disease

Develop strategies for assessing, preventing, and treating HIV nervous system infection and central and peripheral nervous system manifestations of HIV disease in domestic and international settings.

STRATEGIES

Preclinical Development

- Develop therapeutic agents to block HIV entry into the CNS and treat HIV infection in the CNS; develop and evaluate novel strategies such as neuroprotective agents that are active against putative pathways of HIV-induced CNS dysfunction in adults, adolescents, and children.
- Develop, optimize, and utilize *in vitro* and animal models of CNS lentivirus infections and CNS injury to identify therapeutic agents (tailored for needs during neurodevelopmental and mature brain periods) for the nervous system complications of HIV infection.
- Assess the pathogenic role of viral sequestration in the CNS, including its potential role as a reservoir of viral persistence and as a site of independent selection of antiviral drug-resistant strains and other mutants.
- Assess the interactions between chronic HIV infection, HIV-associated neurocognitive disorders, and aging-related neurodegenerative disease.
- Develop objective quantitative assessments (e.g., surrogate markers in cerebrospinal fluid [CSF] and neuroimaging) of HIV disease progression and treatment effects as they relate to the nervous system.
- Characterize the CNS pharmacokinetics and pharmacodynamics of ARVs; determine the importance of CNS drug penetration, particularly penetration of the blood-brain barrier, in reducing CNS infection in neurologically symptomatic and asymptomatic subjects.
- Develop novel bioimaging applications and bioassays to facilitate assessment of compartmental pharmacokinetics/pharmacodynamics.
- Develop strategies for manipulating drug transporters at the blood-brain barrier to facilitate entry of ARVs into the CNS compartment.
- Develop novel tools (e.g., nanotechnology) to facilitate and modulate delivery of ARVs into the CNS compartments.
- Develop better strategies, including complementary and alternative medicine approaches, to prevent, diagnose, and treat peripheral neuropathies and other CNS complications in HIV-infected individuals.
- Develop optimal therapies for pain management in HIV-infected individuals.
- Monitor CSF for HIV viral load and immune activation markers in individuals enrolled in studies of ART.
- Further elucidate the correlation among CSF HIV viral load, chemokine levels, proinflammatory cytokines, and markers of immune activation with CNS disease.
- Support research on the effectiveness of pharmacologic and other approaches to facilitate better adherence to therapeutic regimens in neurologically impaired individuals.
- Evaluate the effectiveness of reducing HIV-associated CNS disease burden by therapeutic agents currently used to treat other neurologic diseases (e.g., Parkinson's and Alzheimer's disease) that may share pathophysiologic features with HIV-associated neurologic disease.
- Assess the incidence and prevalence of HIV-1- and HIV-2-induced neurological and neurobehavioral complications, and assess the impact of other viral, bacterial, fungal, or parasitic infections on HIV disease in the CNS.

- Assess the impact of HIV clade diversity, the generation of HIV variants, and changes in virus tropism on neuropathogenesis and response to therapy.
- Determine anatomical, structural, and genetic contributors (e.g., haplotypes and epigenetics) to neurological vulnerability to HIV infection and related inflammatory processes.
- Conduct studies to determine drug interactions between commonly used treatments for HIV disease and their complications, with treatments for drug abuse and co-occurring mental health disorders; develop treatments and regimens that are optimized for HIV-infected individuals with comorbid depression and other psychiatric disorders.
- Develop adjunctive therapeutic agents that have not only immunomodulatory functions but also neuroprotective functions to reduce comorbid psychiatric conditions (markedly depression and anxiety disorders) in HIV-infected individuals.
- Develop novel or adapt existing rehabilitative strategies to ameliorate HIV-associated CNS disease manifestations that affect social–emotional, motor, sensory, cognitive, and daily functioning.

Clinical Neuroassessment, Methodologies, and Trials

- Design and support clinical trials addressing nervous system complications of HIV infection and treatments in adults, adolescents, and children.
- Improve existing and develop novel sensitive, reliable, and valid measures of neuropsychological performance and neuropsychiatric status having cross-cultural and international applicability and sensitivity to HIV-associated neurological complications and ARV treatment, including appropriate and standardized measures of neurodevelopment in children applicable to resource-limited settings.
- Identify and validate biomarkers to compare HIV-associated neurological disorders with other cognitive disorders.
- Determine the incidence and prevalence of HIV-associated neurologic disorders, primarily HIV-associated dementia, minor cognitive and motor disorders, and peripheral neuropathy, in the context of long-term ART.
- Determine the effects of ART on neurodevelopmental function in HIV-infected children.
- Support the research and development of new statistical methodologies, clinical trial designs, and selection and investigation of biologic markers, to evaluate the safety and clinical efficacy of new agents and approaches in the treatment of neurologic and cognitive complications of HIV disease.
- Develop, incorporate, and validate functional neurologic and quality-of-life scales in clinical trials that are aimed at measuring the impact of nervous system complications of HIV infection.

OBJECTIVE–F: Treatment of AIDS-Related Cancers

Develop and evaluate improved strategies for the assessment, treatment, and prevention of cancer-specific manifestations of HIV disease and ART in domestic and international settings.

STRATEGIES

Preclinical Development

- Promote screening, discovery, and development of novel therapeutic agents with activity against AIDS-defining and HIV-associated malignancies, including pathogenesis-based strategies, agents with better CNS penetration, and agents with better safety profiles.
- Promote discovery of nano-based drug enhancement opportunities and targeting modalities for malignancy-specific delivery of therapeutic agents.
- Based upon structural, biologic, immunologic, and biochemical information, develop agents for the prevention and treatment of HIV-associated malignancies.
- Develop preclinical and *in vivo* models for testing potential therapeutic and preventive strategies against HIV-associated malignancies.
- Utilize emerging information, including vaccination strategies, on the pathogenesis of malignancy complications of HIV infection, including new viral agents, to develop new preventive, diagnostic, and therapeutic strategies for such tumors.

Diagnostic Methods

- Develop and improve methods for early diagnosis of malignancies and determinants in the context of HIV disease and for early detection of recurrent cancer or secondary malignancies in both domestic and international settings, and in adults and children.

Clinical Evaluation of Therapeutic and Prevention Strategies

- Develop therapeutic and prevention strategies (including vaccines) for AIDS-defining and other HIV-associated malignancies based on an improved understanding of the role of infectious agents (e.g., KSHV/HHV-8, EBV, HPV, HCV, Merkel cell virus, and HBV) in their pathogenesis.
- Continue to support studies on the efficacy of HPV vaccines to prevent and treat cervical and anal cancer in HIV-infected populations, including adolescents.
- Evaluate novel approaches for the treatment of AIDS-defining and other HIV-associated malignancies through clinical trials, and evaluate the interactions between treatment of malignancies and treatment of the underlying HIV infection.
- Support approaches using gene- and protein-based technologies, such as tissue array and microarray, in targeting treatment of AIDS-defining and other HIV-associated malignancies.
- Conduct research to assess the optimum therapy for cancers in HIV-infected individuals, including elderly patients.
- Develop, incorporate, and validate clinical trial methodologies to correlate tumor-specific responses in HIV-infected individuals with clinical benefit, including quality-of-life parameters; develop a staging system indicative of prognostic response and survival.
- Identify surrogate endpoints indicative of response to therapy and novel methods for evaluating tumor response in HIV-infected individuals, including imaging technology.

- Encourage and facilitate collaborative studies within clinical trials networks to develop mechanisms for early identification of individuals at high risk for AIDS-defining and other HIV-related malignancies. Develop and assess interventional strategies to reduce the risk or prevent the development of AIDS-related malignancies.

- Study the role of immunomodulating agents in the treatment and prevention of AIDS-defining and other HIV-related tumors.

- Support clinical studies of HIV-infected individuals with non-AIDS-defining malignancies in order to define the best treatment of these malignancies in HIV-infected individuals. Evaluate the impact of cancer therapy on virologic, immunologic, and tumor parameters, including viral reservoirs; assess the toxicity of anticancer modalities in HIV-infected patients; and evaluate the pharmacokinetics of anticancer agents in HIV-infected patients, including a study of drug–drug interactions.

- Explore strategies for attenuating or preventing toxicities associated with anticancer therapy in HIV-infected patients, and study the effects of such strategies on virologic and immunologic parameters in HIV-infected individuals.

- Study the role of *in utero* and long-term exposure to ARVs on the risk of later development of tumors.

- Study populations in resource-limited settings at increased risk of AIDS-defining and other HIV-related malignancies due to endemic infectious agents (e.g., KSHV/HHV-8), EBV, and HPV-associated cervical cancer.

OBJECTIVE–G: Immune Reconstitution Approaches

Develop and assess therapeutic approaches that will restore, sustain, and enhance a competent immune system in HIV-infected individuals in domestic and international settings.

STRATEGIES

- Employ approaches to enhance immune restoration in clinical trials; test specific hypotheses of HIV immunopathogenesis.
- Evaluate the capacity of the immune system to maintain or repair itself after maximal effective viral suppression, considering the effects of gender, race/ethnicity, and age.
- Evaluate immune-based therapies for the purpose of improving ARV-sparing regimens, permitting delay in initiating or reinitiating ART.
- Develop, validate, and standardize new methods for evaluating immune function in clinical trials that enroll adults, adolescents, and children, including assays that may be used in resource-limited settings.
- Accelerate the preclinical and clinical testing of cytokines, modulators of cytokines, combinations of broad-based neutralizing monoclonal antibodies, and immunoactive agents to prevent further immune deterioration, to reconstitute deficient immune systems, and to enhance the immunogenicity of therapeutic HIV vaccines.
- Develop and evaluate active and passive immunotherapeutic approaches (including therapeutic vaccine candidates) for HIV infection and its sequelae, including the testing of optimum immunogens; determine optimal patient disease status for response, most effective immunization dose and schedule, and most meaningful readout of clinical impact of the intervention.
- Support research on approaches to facilitate better adherence to immunoactive regimens.
- Evaluate the safety and efficacy of administering cellular immune elements, including use of expanded and/or modified peripheral blood T cells, bone marrow, cord blood stem cell transplantation, stem cell therapy, and thymic transplantation.
- Evaluate the immune system after partial restoration by effective ART. Define qualitative and quantitative differences between the restored immune system and the naive immune system to determine if identified deficiencies can be diminished by immunoactive agents, including the use of vaccines for specific OIs and coinfections.
- Develop new therapeutic strategies based on gene delivery strategies to protect mature, hematopoietic stem cells, hematopoietic pluripotent cells, and stromal cell elements from destruction by HIV.
- Study the mechanisms of action of immunomodulating agents, and proceed with applied studies and development of the most promising approaches.
- Evaluate immune-based therapy as an adjunct to salvage therapy strategies and/or reservoir elimination.
- Identify immunological predictors of *in vivo* immune control of viral replication.

OBJECTIVE–H: Treatment of HIV-Associated Complications with Complementary and Alternative Modalities

Develop and assess novel interventions (e.g., complementary and alternative medicine) for the prevention and symptom management of HIV disease and its complications, including those prevalent in or unique to international settings.

STRATEGIES

- Develop and evaluate conventional and nonconventional chemopreventive approaches, including those containing quantifiable doses of micronutrients (such as vitamins and trace elements) and macronutrients to delay the development of wasting and other complications of HIV disease.
- Evaluate the safety and efficacy of nonpharmacologic and complementary and alternative medicine approaches, such as exercise, nutrition, and sleep cycles, in the management of HIV disease and its complications.
- Evaluate the benefits or risks of commonly used complementary agents (herbal, homeopathic, and/or naturopathic) when used concomitantly with ART.
- Determine the role of traditional healers and the impact of the use of traditional medicines, herbal medicines, and supplements on HIV treatment and care.