CHAPTER 3

Therapeutics

AREA OF EMPHASIS

Therapeutics

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A

Identify and validate viral and cellular functions required for HIV replication that can be targeted for viral inhibition, clearance, 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. Encourage collaborations between academia, industry, and the NIH.

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

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 agents (including natural products) and treatment strategies that target, inhibit, and clear HIV in cellular, anatomical, and organ reservoirs and sanctuaries.
  - Characterize potential agents, including their preclinical, immunologic, pharmacokinetic, pharmacodynamic, toxicity, and teratogenicity profiles.
  - Develop new compounds and chemical formulations, including microbicides and other methods, suitable for the genitourinary and gastrointestinal tracts.
  - Employ whole animal and *ex vivo* organ or tissue models of lentivirus infections to study the biologic and pharmacologic characteristics of therapeutic agents.
- Acquire structural information on HIV and cell constituents involved in HIV infection for the design of potent therapeutic agents and therapeutic vaccine candidates with activity against drug-resistant strains. Post lead structures on publicly accessible databases in real time.
  - Integrate genomics and informatics paradigms, concepts, and methodologies (microchip-based screens and analyzers) into mainstream drug discovery and development of therapeutic entities and strategies.

- Develop enabling technologies to accelerate and optimize the discovery and development of therapeutic entities and strategies; establish 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 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.

- Study the mechanisms and implications of drug resistance and viral fitness; evaluate early markers and genotypic mutations that lead to resistance and cross-resistance.

- Advance basic and applied gene-based strategies to treat HIV infection. Foster new approaches and technologies to optimize gene delivery that results in regulated and persistent gene expression. Optimize *ex vivo* gene delivery and advance new concepts, strategies, and vectors for direct *in vivo* delivery.

- 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.

OBJECTIVE–B

Conduct clinical trials (including the development of new methodologies) in domestic and international settings, especially in resource-developing nations, to: (1) evaluate the short- and long-term efficacy and effectiveness of therapeutic agents and strategies against HIV infection and transmission in treatment-naive and treatment-experienced HIV-infected individuals; and (2) 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.

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

STRATEGIES

Clinical Trials of Therapeutic Agents

- Conduct clinical trials of potential therapeutic agents and combinations of agents in adults, adolescents, and children to determine pharmacokinetics, tissue bioavailability, antiviral activity, effects on the immune system, safety, and clinical efficacy.
  - Evaluate optimal combinations of agents selected for antiviral synergy, complementary mechanism of action, minimal toxicity and cross-resistance, simplicity of administration, and tolerability.
  - Evaluate optimal therapies and 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; and
    - optimal treatment for heavily ARV-experienced individuals with treatment failure.
  - Evaluate novel therapeutic modalities (e.g., cell-based, gene-based, and therapeutic vaccine approaches) with state-of-the-art antiretroviral therapies.
  - Evaluate coformulated ARVs.
  - Evaluate the benefits or risks of commonly used complementary agents (herbal, homeopathic, and/or naturopathic) when used concomitantly with ART.

Clinical Trials Enrollment

- Strengthen efforts and implement new approaches to ensure the enrollment and retention of specific populations, including women, children, adolescents, minorities, substance abusers, and older adults in clinical trials to reflect the incidence of the epidemic.
- Strengthen efforts to evaluate new and existing drug treatment regimens in clinical trials that reflect the demographics of the epidemic, including traditionally underrepresented populations. 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 evaluate the viral and host factors, including human genomics, associated with ART failure including malabsorption, drug interactions, drug resistance, drug toxicities, pharmacogenetics, and suboptimal adherence.

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.
- Identify and test strategies to improve the recruitment and retention of individuals in clinical trials.
- Develop, incorporate, and validate appropriate quality-of-life parameters in clinical trials of ARV agents.
- Develop methodology to facilitate cross-protocol analysis and meta-analyses.
- Conduct research on how and why subjects decide to participate in clinical trials in order to increase enrollment and maintain adherence to study protocols.
- Develop methodology for research on the ethical conduct of clinical trials.

Pharmacology

- Determine the relationship between drug exposure (pharmacokinetics) and outcomes (antiviral effect, immune function, and safety) to facilitate dosing strategies within clinical trials, as well as for individual patient management.
- Investigate drug interactions among commonly used treatments for HIV-related disease and its complications, as well as other substances that may be used by HIV-infected individuals.
- Investigate the effect of drug-sparing regimens on efficacy, resistance, and transmission.

Viral Reservoirs

- Evaluate the presence and persistence of HIV in different tissue compartments during ART; investigate the role of anatomic and cellular sanctuaries in the development of HIV drug resistance, transmission, and establishment of long-term reservoirs.
- Evaluate the penetration of ARVs into different tissue compartments (e.g., genital secretions/semen, CNS, breast milk, etc.).

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.

Adherence

- 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.

International

- Enhance the development of international collaborations that will assist in addressing relevant therapeutic research in populations of HIV-infected adults, adolescents, and children.
- Assist developing nations, as appropriate, in technology transfer through training, infrastructure, and capacity building to facilitate the evaluation of ARV agents and other therapies in local settings.
- Assess the barriers to delivery of effective HIV/AIDS health care including treatment and the capability of conducting international therapeutic clinical trials through the establishment or expansion of multidisciplinary clinical centers.
- Develop and evaluate simpler, reliable, user-friendly, and inexpensive surrogate markers and assay technologies 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 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

Develop strategies to evaluate, prevent, predict, and treat complications and toxicities of antiretroviral treatment in domestic and international settings.

STRATEGIES

- Evaluate potential delayed or late effects of ART following short-term administration of prophylaxis regimens, as well as during chronic treatment.
- 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 suppression of HIV replication may affect metabolic processes.
- Integrate metabolic, endocrine, cardiovascular, neurologic, renal, and bone studies into ongoing and planned treatment trials which may provide an opportunity to answer important questions related to potential complications of ART.
- Develop approaches to monitor and evaluate the effects of gender, race, age, pregnancy 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, drugs to prevent and treat coinfections (particularly tuberculosis), and medications used in the treatment of drug addiction and mental disorders; develop strategies to avoid or minimize the clinical impact of these interactions.

OBJECTIVE–D

Develop and evaluate new agents and strategies for preventing and treating hepatitis B virus (HBV), hepatitis C virus (HCV), tuberculosis (TB), Epstein-Barr virus (EBV), human papillomavirus (HPV), malaria, and the most significant coinfections in the context of HIV disease in domestic and international settings.

(The scientific objectives of D and E are of equal weight.)

STRATEGIES

Preclinical Discovery and Development

- Support preclinical drug design and development programs to develop therapies against associated pathogens, especially HBV, HCV, Kaposi's sarcoma herpesvirus/human herpesvirus (KSHV/HHV-8), HPV, EBV, cytomegalovirus (CMV), malaria, and *Mycobacterium tuberculosis*, 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 requiring Federal Government support; 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.

- Continue to support studies and develop vaccines and interventions for coinfections (e.g., TB, HPV, Rotavirus) in HIV-infected children, adolescents, and adults.

Clinical Trials of Therapeutic Regimens

- Assess the impact of new ARV regimens on the risks for and manifestations of infections associated with HIV/AIDS in adults, adolescents, and children.

- Improve our understanding of the interplay between HIV-associated immune deficiencies and the onset and types of infectious complications.

Clinical Trial Methodology

- 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; develop improved strategies to minimize toxicities and the development of drug-resistant microorganisms.
- 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 for treatment.
- Develop clinically useful assays and methodologies for early and rapid diagnosis of OIs and coinfections, quantitative assessment of microbiological responses, and drug sensitivity testing.

Coinfections

- Support research on the interactions between ART and coinfections.
- Study the interaction between HIV infection and infectious complications upon pathogenesis, presentation, and disease outcomes in adults, adolescents, and children.
- Support clinical trials, domestic and international, of adults and children coinfected with HIV and TB (both active and latent infection). Evaluate safety and efficacy of treatment regimens in coinfected individuals. Determine 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 infection) and effects on HIV disease progression.

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 multiple drug-resistant TB.

Adherence

- 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.

International

- Conduct clinical trials in adults 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

Develop, evaluate, and implement strategies for interrupting mother-to-child transmission (MTCT), applicable to resource-limited and -rich countries, with emphasis on strategies to interrupt transmission through breastfeeding, the short- and long-term effects of interventions for interrupting MTCT on the health of women and infants, and development of drug resistance after antiretroviral MTCT prophylaxis and its effect on subsequent antiviral therapy and efficacy in future pregnancies.

(The scientific objectives of D and E are of equal weight.)

STRATEGIES

Mechanisms of Transmission

- Investigate the mechanisms and timing of MTCT to facilitate and develop targeted drugs/strategies to further decrease MTCT or provide alternatives to currently identified effective strategies.
- Investigate risk factors (e.g., immune, viral, and host-related) associated with breast milk HIV transmission.
- Develop reproducible, sensitive, and specific assays to detect and quantitate the amount of cell-free and cell-associated virus in breast milk.

Interventions and Trials to Evaluate Interventions to Reduce Transmission

- Use and/or develop suitable animal models to evaluate novel strategies to prevent transplacental and postpartum breastfeeding transmission of HIV, and to evaluate transplacental passage of ARV agents and their effects on placental function and on fetal development and viability.
- Develop safe and conveniently administered strategies to interrupt MTCT using interventions that are affordable in resource-limited nations, including specific strategies to prevent postnatal transmission of HIV through breast milk by providing prophylaxis to the infant, mother, or both during the lactational period.
- Evaluate the pharmacokinetics and safety of ARV drugs in pregnant women and their fetuses/infants, and the penetration of ARV drugs into breast milk and genital fluids.
- Evaluate strategies for reducing MTCT when maternal antepartum and intrapartum ART is not given or available (e.g., postpartum prophylaxis of the infant only).
- Support international collaborative efforts to conduct clinical trials of interventions to interrupt MTCT.

- Develop and evaluate strategies for reducing the risk of vertical transmission of HIV from pregnant women to their offspring, and evaluate the impact of that intervention on maternal health treatment options; such strategies may include antiviral agents, anti-HIV immunoglobulin, monoclonal antibodies, agents targeted to cellular targets (e.g., blocking cytokine receptors), cell- and gene-based strategies, vitamin supplementation, HIV vaccines, adjuvants, and virucides, alone or in combination.

- Study the effects of ARV regimens used for maternal health indications on the risk of vertical transmission (including postnatal transmission through breast milk).

- Support research and development of new clinical trial designs, statistical methodologies and investigation of biologic markers, surrogates, and/or other outcomes to evaluate the activity, clinical efficacy, or reasons for failure of new agents and approaches in the treatment of HIV-infected pregnant women and their offspring.

Issues Related to Antiretroviral Drug Resistance

- Evaluate the effects of preexisting viral drug resistance in pregnant women on the effectiveness of ARV regimens to prevent MTCT.

- Evaluate the risk for the development of HIV variants with detectable antiretroviral drug resistance in pregnant women who receive different types of ARV prophylactic regimens and the kinetics and durability of such resistance in cell-free and cell-associated virus in plasma, breast milk, and genital secretions.

- Evaluate the risk for development of HIV variants with detectable antiretroviral drug resistance in infants who become infected despite maternal receipt of ARV prophylaxis regimens and the kinetics and durability of such resistance in cell-free and cell-associated virus.

- Evaluate the effects of developing drug resistance following ARV prophylaxis on the health and response to future ART in women and infants who become infected with HIV despite prophylaxis.

- Evaluate the effect of drug resistance developing following ARV prophylaxis in an initial pregnancy on the efficacy of the prophylactic regimen in reducing transmission in subsequent pregnancies.

- Evaluate effective, safe, simple, and short alternative antiretroviral regimens that have lower risk of development of resistance in women or infants infected despite prophylaxis than those currently used for prevention of MTCT in resource-limited settings.

- Evaluate the public health impact of ARV resistance that develops in pregnant HIV-infected women secondary to use of ARVs solely for prevention of MTCT.

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

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

Implementation Issues

- Develop and evaluate strategies for implementation of effective perinatal transmission prevention interventions in developed and developing countries, including ways to increase availability and acceptability of prenatal HIV testing and of prophylaxis to prevent MTCT.
- Improve the sensitivity and specificity of diagnostic procedures that are accessible, cost-effective, and have utility in developed and developing settings to permit the earliest possible determination of HIV infection in infants, and whether ARV and/or immunopreventive therapies affect the timing and sensitivity of these assays for diagnosis.

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

OBJECTIVE–F

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

(The scientific objectives of F and G are of equal weight.)

STRATEGIES

Mechanisms of Transmission

- Evaluate the influence of drug resistance on the efficacy of ARV regimens to prevent sexual transmission.
- Use and/or develop suitable animal models and clinical studies to evaluate genital and anal passage of ARVs.
- Evaluate the influence of systemic HIV treatment on viral shedding in the anogenital tract.
- Evaluate the impact of anti-STI (sexually transmitted infection) treatment on transmission of HIV and HIV shedding in the anogenital tract.

Interventions to Reduce Transmission

- Support domestic and international collaborative efforts to conduct trials of ARV, immunotherapeutic, and other treatment interventions with an endpoint of horizontal transmission in acute and chronic infection.
- Develop and evaluate strategies for reducing the risk of sexual transmission of HIV without compromising treatment of the HIV-infected individual; such strategies may include antiviral agents, therapeutic vaccines, anti-HIV immunoglobulin, monoclonal antibodies, immunotherapeutic agents, and microbicides, alone or in combination.

Issues Related to ARV Interventions

- Evaluate the risk for developing antiretroviral drug resistance (in cell-free and cell-associated virus, and in sequestered genital or anorectal sites) when using ARVs in interventions to reduce horizontal transmission, including the development of antiretroviral drug resistance in individuals who become HIV-infected while receiving such therapy or in HIV-infected individuals being administered such therapy solely to reduce horizontal transmission.
- Evaluate the public health impact of regimens to reduce horizontal transmission.

OBJECTIVE–G

Develop and evaluate therapeutic approaches, including therapeutic vaccine candidates, that will restore and sustain a competent immune system in HIV-infected individuals in domestic and international settings.

(The scientific objectives of F and G are of equal weight.)

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.
- Evaluate immune-based therapies for the purpose of improving ART-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 for HIV infection and its sequelae, including the testing of optimum immunogens; determine best 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, 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.
- 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 cells.
- Study the mechanisms of action of immunomodulating agents, and proceed with applied studies and development of the most promising approaches.
- Evaluate immunologic markers that may identify individuals at risk for late complications of therapy.
- Develop standards and definitions to allow better comparisons of late complications across clinical trials.
- Evaluate immune-based therapy as an adjunct to salvage therapy strategies.
- Identify immunological predictors of *in vivo* immune control of viral replication.

OBJECTIVE–H

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.

(The scientific objectives of H, I, and J are of equal weight.)

STRATEGIES

- 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.
- Design and conduct clinical trials addressing nervous system complications of HIV infection and treatments in adults, adolescents, and children.
- Develop and utilize *in vitro* and animal models of CNS lentivirus infections and CNS injury to identify therapeutic agents 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.
- Determine the incidence and prevalence of HIV-associated neurologic disease after long-term ART.
- Develop objective quantitative assessments (e.g., surrogate markers in cerebrospinal fluid [CSF] and neuroimaging) of treatment effects.
- 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 strategies for manipulating drug transporters at the blood-brain barrier to facilitate entry of ARVs into the CNS compartment.
- Develop better strategies including complementary and alternative medicine approaches to prevent, diagnose, and treat peripheral neuropathies in HIV-infected individuals.
- Improve existing and develop novel sensitive, reliable, and valid measures of neuropsychological performance having cross-cultural and international applicability and sensitivity to HIV neurological insult and ARV treatment.

- Determine the prevalence, causes, and pathogenesis of pain in HIV-infected individuals and develop optimal therapies for pain management.
- 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 in clinical trials.
- 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.
- 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.
- Develop, incorporate, and validate functional neurologic and quality-of-life scales that are aimed at measuring the impact of nervous system complications of HIV infection in clinical trials.
- 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.
- Conduct viral genetic analyses of HIV derived from CNS sources (including studies of the role of HIV-1 non-B subtypes and HIV-2) in causing neurologic, cognitive, and neurobehavioral dysfunction.
- Determine anatomical, structural, and genetic contributors (haplotypes, 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 its complications, with treatments for drug abuse and cooccurring mental health disorders; develop treatments and regimens that are optimized for HIV-infected individuals with comorbid depression and other psychiatric disorders.

OBJECTIVE–I

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

(The scientific objectives of H, I, and J are of equal weight.)

STRATEGIES

Preclinical Drug Development

- Promote screening, discovery, and development of novel therapeutic agents with activity against HIV-associated malignancies, including pathogenesis-based strategies, agents with better CNS penetration, and agents with better safety profiles.
- Based upon structural biologic and biochemical information, develop therapeutic agents for the treatment of HIV-associated malignancies.
- Develop preclinical and *in vivo* models for testing potential therapeutic strategies against HIV-associated malignancies.

Diagnostic Methods

- Develop and improve methods for early diagnosis of malignancies in the context of HIV disease and for early detection of recurrent cancer or secondary malignancies.

Clinical Evaluation of Therapeutic and Prevention Strategies

- Develop therapeutic and prevention strategies for HIV-associated malignancies based on an improved understanding of the role of infectious agents (e.g., KSHV/HHV-8, EBV, HPV, and HBV) in their pathogenesis.
- Continue to support studies of the efficacy of HPV vaccines to prevent and treat cervical cancer in HIV-infected populations.
- Evaluate novel approaches for the treatment of 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 micro-array, in targeting treatment of HIV-associated malignancies.
- Develop, incorporate, and validate clinical trial methodologies to correlate tumor-specific responses 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, 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-related malignancies. Develop and assess interventional strategies to reduce the risk or prevent the development of malignancies.
- Study the role of immunomodulating agents in the treatment and prevention of AIDS-related tumors.
- Encourage clinical studies of HIV-infected individuals with non-AIDS-defining malignancies. Evaluate the impact of therapy on virologic, immunologic, and tumor parameters, and on drug-drug interactions.
- Explore strategies for attenuating or preventing toxicities associated with therapy, and study the effects of such strategies on virologic and immunologic parameters.
- 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-related malignancies due to endemic infectious agents (e.g., KSHV/HHV-8) and HPV-associated cervical cancer.

OBJECTIVE–J

Develop and evaluate strategies for the treatment and prevention of serious manifestations of HIV disease including those prevalent in or unique to international settings.

(The scientific objectives of H, I, and J are of equal weight.)

STRATEGIES

- Develop and evaluate therapeutic strategies for preventing and treating complications of HIV infection, particularly those complications unique to or prevalent in international settings.
- 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.