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NIH Appendices typed by Jenny

Agency: National Institutes of Health

Goal: (Natural History and Epidemiology)

Objective 1: Develop and assess intervention strategies to reduce or prevent HIV transmission in both domestic and international settings.

Action Steps: Develop and maintain the infrastructures to define populations in the United States and throughout the world with incidence and prevalence suitable for vaccine and other intervention trials (e.g. microbicides, barriers, treatment, behavioral) for preventing HIV transmission.

Support development and evaluation of improved, acceptable, effective physical and chemical barrier methods and conduct research on existing barrier methods to prevent sexual transmission of HIV and STDs.

Develop strategies and conduct studies to evaluate vaccines, drugs, and other interventions such as caesarian sections, vaginal cleansing, breast-feeding practices, nutritional interventions, and other approaches that prevent perinatal transmission.

Develop and assess the efficacy of strategies that may decrease transmission of HIV among drug users.

Develop and evaluate biological and behavioral interventions to control STDs as cofactors in HIV transmission.

Develop strategies that enhance safe sex behaviors and provide information on safe and effective contraceptive choices for at-risk women.

Develop methods to prevent infection in hard-to-reach gay male populations such as young, substance-using, and minority gay and bisexual men.

Develop methods of accessing hard-to-reach populations to identify factors that contribute to recruitment (and retention) into prevention and intervention activities.

Evaluate access to, acceptability of, and compliance with interventions such as AZT for perinatal transmission, condoms, and virucides.

Evaluate improved procedures for screening, monitoring, and inactivating HIV and other retroviruses in the blood supply; and develop and evaluate alternatives to blood transfusion.

Assess the impact of drug and alcohol abuse and mental health impairment on efficacy of behavior modification interventions

directed at sexual transmission.

Develop effective drug treatment strategies for addiction, particularly focused on heroin and cocaine use.

Description: The development of biologically based interventions to interrupt transmission is an essential component of a comprehensive HIV prevention strategy that also includes behavioral intervention strategies as well as efforts to develop a vaccine(s). International studies should be supported with the goal of developing prevention strategies that can be used to reduce HIV transmission in the United States. Research is ongoing in these areas.

Epidemiologic studies, including vaccine preparedness research, provide opportunities for intervention research in defined cohorts of well-characterized populations. Strategies that employ therapies, devices, and other approaches, such as needle/syringe exchange programs using HIV seroconversion end points, are useful approaches for providing epidemiologic causation and evaluating effectiveness in preventing or reducing HIV transmission.

In addition, despite the fact that the blood supply in the United States is safer than it has ever been, it is important to develop even better methods for maintaining and improving its safety.

Objective 2: Characterize the risk factors and mechanisms of HIV transmission in both domestic and international populations, with the goal of preventing transmission.

Action Steps: Evaluate HIV transmission in relationship to: viral factors such as virus load in the blood and at mucosal sites, characteristics of HIV (genotype and phenotype), and pre-existing infection with other agents; host factors such as contraceptives, pregnancy, menstrual cycle, substance abuse, and nutritional, immunologic and genetic determinants; local factors including intercurrent STDs, exogenous irritants, oral and anogenital inflammation, mucosal immunity, circumcision and cervical ecotopy.

Further define the timing and mechanisms and risk factors in perinatal transmission, including breast-feeding.

Study mechanisms of resistance to HIV infection in persons who remain uninfected despite perinatal, sexual or parental exposure.

Define the determinants of high-risk behavior for transmission through drug use and sexual practices.

Characterize the dynamics of HIV transmission in epidemiologic studies of at-risk groups, including evaluation of sexual and drug-using networks, social and geographic mixing patterns, and turnover races of at-risk populations.

Characterize the transmission and host immune responses of related retroviruses.

Description: Understanding the role of risk factors and mechanisms of HIV transmission is critical to the development of biologically and behaviorally based strategies to interrupt transmission of HIV. Epidemiologic studies provide important biological and behavioral information including the role of cofactors that may reduce or enhance transmissibility.

Objective 3: Elucidate the progression of HIV infection, from its earliest stages through long-term sequelae, with the goal of understanding, preventing, and treating those factors.

Action Steps: Use epidemiologic studies to identify pathogenic mechanisms and cofactors for disease progression and disease-specific outcomes in well-defined subsets of individuals, individuals, including those with different rates of progression.

Conduct epidemiologic studies to understand the initiation and progression of early HIV infection, according to route of exposure, viral dose, viral genotype and phenotype, and host response, and how these early events influence disease progression.

Use epidemiologic studies to investigate the influence of viral genotype and phenotype on transmission efficacy and disease progression.

Use epidemiologic studies to evaluate the extent of dissemination of drug-resistant strains of HIV and its impact on pathogenesis.

Study the natural history of related retroviruses to elucidate retroviral pathogenesis.

Elucidate the mechanisms of HIV-associated carcinogenesis to improve strategies for early diagnosis and intervention.

Study HIV-infected children to determine: (1)mechanisms that contribute to impaired growth and neurodevelopment;(2)impact on childhood infectious diseases and the safety and efficacy of immunization;(3)impact on childhood psychosocial development, and (4)childhood-specific complications.

Evaluate the interaction of hormonal factors (including pregnancy, contraceptives, and hormonal replacement therapy) and HIV disease progression.

Study the progression of HIV-related disease in adolescents who have acquired their diseases as a result of drug use and/or sexual activity.

Study the natural history of HIV infection in the nervous system,

including cognitive impairment, dementia, and neuropathy.

Describe the full spectrum of HIV-related diseases in HIV-infected populations.

Maintain and effectively utilize national specimen repositories for HIV-related studies.

Description: Epidemiologic studies provide a critical knowledge and resource base for more basic investigations of HIV pathogenesis. A better understanding of the diversity of HIV-related disease outcomes, cofactors for progression, and predictors of disease progression will be important in furthering attempts to develop HIV vaccines and more effective therapeutic interventions against HIV and its sequelae.

Objective 4: Undertake epidemiologic research to reduce or prevent the occurrence of opportunistic illness in HIV-infected persons.

Action Steps: Study the impact of HIV infection on the emergence of new human pathogens and the impact of HIV infection on the reemergence of infectious diseases domestically and internationally.

Identify risk factors for the acquisition of opportunistic pathogens.

Study the determinants of the continuing occurrence of preventable opportunistic illnesses.

Study the role of transmissible and other preventable exposures in the etiology of AIDS-associated cancers and other outcomes.

Description: Most morbidity and mortality in HIV-infected persons result from the occurrence of opportunistic illnesses, including both infections and malignancies. Strategies to prevent these illnesses include prevention of exposure to the etiologic agents, prevention of disease in those who are exposed, and prevention of disease recurrence. Additional epidemiologic data are needed to design more effective strategies to prevent the occurrence of these opportunistic illnesses.

Objective 5: Develop and evaluate new laboratory assays, behavioral methods, and statistical techniques for epidemiologic studies.

Action Steps: Promote development and evaluation of virologic and immunologic assays to elucidate mechanisms of HIV transmission and disease.

Develop new survey and interview techniques to better measure HIV risk behaviors.

Develop new biostatistical techniques, including mathematical models, to better characterize transmission dynamics and disease progression.

Develop innovative approaches for record linkages to study HIV-associated diseases and mortality.

Characterize the epidemiologic features of emerging HIV variants, including drug-resistant strains, diverse genotypes, and newly recognized geographic distribution.

Description: Epidemiologically defined populations contain well-characterized cohorts that can provide insights into HIV transmission, including resistance and susceptibility to infection and infectiousness, and into progression of HIV-related disease, from early infection through long-term sequelae, including cancer and neurocognitive impairment. The application of innovative biomedical research and behavioral strategies to such populations will greatly increase understanding at the biological level and will help to identify strategies for prevention of transmission and for clinical management of patients.

Agency: National Institutes of Health

Goal: (Etiology and Pathogenesis)

Objective 1: Delineate the cellular and molecular mechanisms associated with the viral immunopathogenesis of HIV-related immune dysfunction.

Action Steps: Delineate the direct and indirect mechanisms underlying HIV-induced depletion and dysfunction of target cells/tissues.

Define the virologic (load, phenotype, and genotype), immunologic (specific and nonspecific), pharmacologic, and environmental factors that contribute to disease progression and non progression.

Delineate the mechanisms of virally triggered immunopathogenesis, including immune activation, induction of nonresponsiveness, and production of host factors, including cytokines, in pathogenesis.

Delineate the molecular mechanisms by which virus-encoded genes, gene products, and cellular factors regulate HIV replication and influence pathogenesis, with special emphasis on the use of primary virus isolates and cells.

Delineate the mechanisms of host genetic factors that mediate resistance or sensitivity to infection and influence disease progression.

Delineate the physiology and HIV-related pathophysiology of primary and secondary lymphoid organs, including hematopoietic precursor cells and their microenvironment.

Study the mechanisms of HIV infection that uniquely influence the developing immune system.

Further develop and utilize experimental models to examine the pathogenesis of lentiviral infections.

Establish and expand programs to facilitate access to and sharing of key patient samples, animal model resources, laboratory reagents, information databases, and quantitative virologic and immunologic assays.

Description: Basic scientific information regarding the cellular and molecular mechanisms that underlie HIV-related immune dysfunction and viral pathogenesis is critical to all areas of AIDS research.

Objective 2: Delineate the molecular and cellular mechanisms of transmission and establishment of infection and their impact on disease progression.

Action Steps: Define the cellular and immune mechanisms that inhibit/enhance the early events in establishing HIV infection.

Determine the impact of early events in the establishment of HIV infection on the clinical course of the disease.

Determine the roles of specific and nonspecific mucosal and systemic immunity and other host factors that inhibit/enhance HIV transmission.

Determine the cell or tissue type that serves as the portal of entry of HIV and the impact of STDs and other pathogenic processes that influence HIV transmission.

Determine the role of viral phenotype/genotype and load on transmission of cell-free and cell-associated virus.

Elucidate unique aspects of HIV transmission and disease progression in under-researched populations.

Determine the mechanisms of vertical HIV transmission.

Description: The mechanisms of HIV transmission and the early events in the establishment of infection, and their relationship to disease progression, need to be better understood.

Objective 3: Elucidate the etiologic factors and cofactors in the pathogenesis of AIDS-associated disease states. Enhance a bidirectional flow between basic and clinical observations and intervention programs ion HIV-related complications and foster interdisciplinary collaborations.

Description: Knowledge of AIDS-associated disease pathogenesis is urgently needed.

Sub-Objective 3a: Elucidate the etiologic factors, cofactors, and mechanisms in the pathogenesis of HIV-related malignancies.

Description: Knowledge about the origins and pathogenesis of HIV-related cancers is urgently needed.

Action Steps: Elucidate the role of HIV infection, immune dysfunction, and interactions with potential cofactors in the development of HIV-associated malignancies.

Identify the characteristics of the host that predispose to development of malignant disease, including genetic, hormonal, and growth factors and immunologic characteristics.

Identify the pathogenic contributions of oncogenes, suppressor genes, carcinogens, and non-HIV viral and other microbial genes and proteins to HIV-associated malignancies; correlate these molecular factors with epidemiologic studies.

Establish and expand programs to facilitate development and sharing of *in vivo* animal models and patient specimens for HIV-associated malignancies.

Sub-objective 3b: Elucidate the pathogenic mechanisms involved in HIV-associated neurological disease and neurobehavioral dysfunction.

Description: The damage that leads to both central and peripheral nervous system dysfunction must be better understood through studies of HIV-associated neuropathogenesis.

Action Steps: Investigate the characteristics of lentiviruses that invade the nervous system and the mechanisms by which these viruses cause nervous system impairment.

Study the effects of neurotrophins and immunoregulatory and proinflammatory cytokines on both host and viral gene expression.

Employ animal models of CNS-lentivirus infection that are crucial to understanding neuropathophysiology.

Delineate the role of OIs and drug treatment in neurologic complications of AIDS, including CNS dysfunction and peripheral neuropathies.

Investigate biological and enviormental factors that may affect nervous system function in the context of HIV-1 infection, emphasizing the role of psychoactive drug use.

Study mechanisms of HIV infection that uniquely influence the developing nervous system.

Develop technologies for correlative structural-functional analysis of progressive HIV-associated neurological and behavioral disorders and the progression of CNS disease.

Sub-objective: Elucidate the pathogenic mechanisms of HIV-related opportunistic infections.

Description: It is critical to understand the pathogenic mechanisms responsible for the development of HIV-associated OIs.

Actions Steps: Elucidate the mechanisms of immune function that mediate protection against OIs.

Study the effects of OIs on immune dysfunction and HIV disease progression.

Conduct studies of the basic biology and pathogenic mechanisms of opportunistic pathogens and their interactions with the host.

Develop *in vitro* techniques and animal models to propagate the opportunistic pathogens associated with HIV disease.

Develop and validate diagnostic assays for the reliable and raid identification of HIV-associated OIs.

Identify biologic markers that are correlative for susceptibility and disease progression for HIV-associated OIs.

Identify and elucidate the genetic and environmental risk factors associated with susceptibility to and development and progression of OIs.

Sub-objective 3c: Elucidate the etiology and pathogenesis of HIV-related disorders: gastrointestinal, renal, endocrine, cardiovascular, cutaneous, hematologic, oral, pulmonary, and other diseases.

Description: It is critical to understand various other organ/tissue-specific complications of HIV infection.

Action Steps: Investigate the etiologic and pathogenic mechanisms of HIV-associated gastrointestinal disease.

Identify the etiologic and pathogenic mechanisms of HIV-associated nephropathy.

Elucidate the etiology and pathogenesis of endocrine dysfunction and the role of alteration in the endocrine/immune axis in progression of HIV disease.

Elucidate the etiology and pathogenesis of HIV-related autoimmune disorders and cardiovascular, cutaneous, hematologic, oral, pulmonary, and other organ/tissue-specific disorders.

Agency: National Institutes of Health

Goal: (Therapeutics)

Objective 1: Improve understanding of the structure and function of molecular targets in order to develop improved assays for such targets; conduct screening, discovery, and preclinical development of novel anti-HIV agents and strategies (such as gene transfer technology and interruption of transmission) directed to the virus and/or host cell; and foster activity by and in collaboration with industry.

Description: Identify and develop novel anti-HIV therapies, particularly those therapies that impact at different stages of the life cycle of the virus.

Action Steps: Identify and characterize promising targets for anti-HIV therapy and extend knowledge of their mechanisms of action, develop relevant assays for identifying drugs active against those targets, and develop new compounds active at those targets, with emphasis placed on identifying agents active at novel targets other than reverse transcriptase inhibitors; emphasize agents that can effectively cross the blood-brain barrier.

Complete preclinical development, in cooperation with industry when appropriate, of promising new compounds and combinations of compounds and novel natural products, including assessment of toxicity, immunologic effects, pharmacokinetics, teratogenicity, and fertility in animal models and development of analytical method and chemical formulations.

Continue and accelerate domestic and international collection screening of large numbers of natural and synthesized compounds for anti-HIV activity in the AIDS Drug Screen, with a particular emphasis on the detection of agents that act at unique steps of the HIV life cycle with the intent of identifying lead compounds that can be modified for increased potency and other attributes (such as bioavailability and central nervous system penetration); develop and screen combinatorial libraries.

Emphasize basic and applied research to advance cross-NIH development of gene therapy; support development of preclinical laboratories to advance gene therapies; advance gene therapies, including new strategies for streamlining or eliminating ex vivo manipulation of cells; develop more efficient and safe viral and nonviral gene delivery vectors; target tissue cells and subcellular compartments; develop effective antiviral genes; standardize evaluation of different gene therapies singly and in combination; and develop suitable lentivirus animal models for in vivo efficacy and safety studies.

Determine the high-resolution molecular structures for several of

the HIV proteins and apply these structures to the rational design of drugs as part of the targeted drug development program; determine generalizable and effective approached for the use of macromolecular structure in designing drugs to combat HIV infection and AIDS; make resolved structures available in publicly accessible data bases.

Increase understanding of the mechanisms and limitations of drug resistance; study the effect of various agents on HIV replication and viral variation; evaluate early markers of resistance; evaluate the activity of anti-HIV drugs in various cell types (including macrophages) and in various stages of the cell cycle.

Develop new compounds capable of inhibiting the sexual transmission of HIV, such as topical microbocides (which may inhibit HIV and STDs associated with enhanced HIV transmission), HIV-specific viricides, and systemic agents.

Develop formulations that would be suitable for infants and children for both existing and experimental agents.

Evaluate transplacental passage of antiretroviral and other agents as well as the effects of these drugs on placental function and on the embryo/fetus in animal models.

Objective 2: Conduct clinical trials and develop new trial methodologies for the treatment of HIV infection. Trials should be designed in order to rapidly develop new therapeutic strategies, optimize clinical efficacy and proper use of available modalities, define factors that affect the success of therapeutic strategies (including the role of resistance), and advance our understanding of disease pathogenesis and progression.

Description: Trials to evaluate new antiretroviral therapies alone and in combination will provide important information regarding resistance and synergistic effects of drugs that may eventually prolong the disease-free state and survival in HIV-infected individuals.

Action Steps: Support and improve clinical trials of potential therapeutic agents and combinations of agents in studies to determine pharmacokinetics and bioavailability and evaluate anti-HIV combinations that are non-cross-resistant, synergistic, and toxicity-sparing and that may delay development of drug-resistant HIV strains; enhance collaboration between and within ICDs to facilitate opportunities for clinical trials.

Implement the development and evaluation of virologic, immunologic, and clinical markers to assess drug activity and determine the prognostic value of surrogate markers in response to therapeutic interventions.

Support research and development of clinical trials methodology and study design so that appropriate pathways are taken rapidly to evaluate the activity, clinical efficacy, and ultimate acceptability of new agents and approaches that translate into clinical use.

Increase the understanding of the pathogenesis of HIV disease based on the evaluation of antiretroviral agents in clinical trials; establish effective mechanisms to evaluate therapeutic interventions and elucidate the pathogenesis of acute/early HIV infection.

Foster collaboration and better interactions with industry in drug development and evaluation efforts.

Evaluate safety, toxicity, and pharmacokinetics of retroviral agents provided to pregnant women, including transplacental passage of the agent, safety to the fetus/infant, and pharmacokinetics of drug elimination in the newborn. (Also noteworthy, assess the potential efficacy and feasibility of obstetric interventions to prevent vertical transmissions, such as cesarean deliveries and other aspects of intrapartum care.)

Enhance utilization of GCRCs for the conduct of single and multi-institutional clinical trials.

Develop and validate quality-of-life parameters included in patient assessments of clinical trials.

Support research on the effectiveness of pharmacologic (including compliance with therapies and STD prevention) and non-pharmacologic including psychosocial) interventions (including nutritional factors and adherence improvement).

Investigate possible interactions between therapies for HIV-related disease and other substances that HIV-infected individuals might use, such as drug-abuse treatment medications, oral contraceptives or other prescription drugs, nonprescription drugs, alternative or complementary therapies, or drugs of abuse.

Coordinate studies to encourage co-enrollment of patients on all trials where appropriate (co-enrollment would not only allow for better utilization of limited resources but also enable assessment of concomitant medications and their interactions, improving the efficiency of the primary study).

Develop a coordinated plan to evaluate long-term therapeutic strategies, e.g., develop plans for long-term followup, enroll patients in sequential randomized trials once they have reached an end point in their initial trial.

Support clinical trials to evaluate the safety and pharmacokinetics of existing and experimental agents for use in treating HIV-infected infants and children; evaluate the effects

of puberty on the pharmacokinetics of antiretroviral agents and other drugs for the treatment/prophylaxis of HIV infection and the pharmacokinetics of drugs in adolescents.

Evaluate potential late toxic effects of antiretroviral therapy given to infants and children.

Objective 3: Develop and evaluate strategies that will enhance, restor, and/or maintain the immune systems of HIV-infected individuals and extend our understanding of immunopathogenesis.

Description: Essential to HIV research efforts are studies directed toward finding therapies that can restore, enhance, or maintain the integrity of the immune system.

Action Steps: Evaluate therapeutic approaches that test specific hypotheses of HIV immunopathogenesis,

Develop and validate new methods for evaluating immune function in the context of clinical trials.

Continue and accelerate the testing of cytokines, modulators of cytokines, and other immunomodulating agents either singly or in combination with antiretroviral agents for the purpose of reconstituting the deficient immune systems of HIV-infected individuals.

Develop and evaluate various approaches of active and passive immunotherapy for both HIV infection and its sequelae.

Develop a program of reconstituting the immune systems of HIV-infected individuals by administration of cellular elements in an autologous, syngeneic, or allogeneic fashion, including use of expanded peripheral blood T cells, bone marrow transplantation, thymic transplantation, cord blood, stem cells, and/or xenogeneic transplantation.

Develop new therapeutic strategies based on gene therapy approaches to protect hematopoietic stem cells and thereby reconstitute the immune system with HIV-resistant lymphoid, monocytic and other cellular compartments.

Use structural biologic techniques to determine the structures of various cytokines and cytokine receptors as potential targets for HIV therapies.

Increase collaboration of ICDs by joint funding of projects to facilitate the conduct of immune-based therapeutic trials and to enhance pathogenesis-related research in HIV-infected individuals.

Foster collaboration and better interactions with industry in developing and evaluating immunorestorative/immune-enhancing agents.

Define the mechanisms of immunomodulating agents and proceed with preclinical studies of the most promising agents.

Objective 4: Discover, develop, and evaluate potential agents for prevention and treatment of HIV-associated OIS and other infections modified by HIV infection.

Description: Opportunistic infections (PIs) are the most common cause of morbidity and mortality in HIV-infected individuals. Continuing to develop and evaluate therapies for preventing and treating OIs is essential for decreasing morbidity and improving survival.

Action Steps: Support basic research on OIs in order to increase fundamental knowledge and to identify new therapeutic targets and strategies and understand how pathogens contribute to morbidity. Determine the high resolution molecular structures for OI proteins and apply these structures to the rational design of drugs as part of the targeted drug development program and determine generalizable and effective approaches for the use of macromolecular structure in designing drugs to combat OIs associated with AIDS.

Support discovery and preclinical programs to develop therapies especially targeting cryptosporidia, microsporidia, JC virus, HPV, and azole-resistant fungal organisms, with emphasis on bioavailable agents with favorable pharmacokinetics. Develop *in vitro* culture systems for OIs such as *Pneumocystis carinii* (PCP).

Further conduct clinical trials for the prophylaxis and treatment of HIV-associated OIs in HIV-infected individuals. Important OIs include *Mycobacterium tuberculosis* infection (TB), *Mycobacterium avium* complex, cytomegalovirus infection, cryptosporidiosis, microsporidiosis, cryptococcal disease, azole-resistant fungal infection, toxoplasmosis, PCP, acyclovir-resistant herpes infections, progressive multifocal leukoencephalopathy (PML), bacterial infections, and other infections whose course is affected by HIV. Evaluate immune-based therapies as adjuncts for treating OIs.

Determine the optimal strategies and combinations of agents to prevent and treat multiple OIs (by simultaneous prophylaxis of multiple opportunistic pathogens) and determine their effects in combination with antiretroviral agents. Strategies need to focus on the subgroups at increased risk, time of initiation, compliance, pharmacologic interactions, toxicities and adverse reactions (e.g. trimethoprim sulfamethoxazole reactions), and minimizing development of resistance; studies should include quality-of-life assessments and cost-benefit analyses.

Develop and utilize animal models for preclinical efficacy, pharmacokinetics, and safety testing of potential agents for OIs, including mutagenicity and teratogenicity.

Develop clinically useful assays for the rapid diagnosis of disease, treatment response, and sensitivity testing of OIs, especially TB, MAI, enterics, and infections produced by CMV, fungi, Toxoplasma, and JC virus, including use of specimens in existing repositories.

Determine the role and capability of preexisting immunity (both induced and natural) to control OIs and the ability of HIV-infected individuals to respond to vaccination throughout the course of infection and disease; assess possible interaction of vaccination and HIV replication.

Explore the bidirectional interactions between OIs and HIV infection including possible impact of opportunistic pathogens on the clinical expression and acceleration of HIV disease and vice versa.

Support clinical trials to evaluate the safety and pharmacokinetics of existing and experimental agents for use in preventing and treating OIs in HIV-infected infants, children, and pregnant women.

Objective 5: Develop, evaluate, and implement strategies for interrupting vertical transmission of HIV from mother to child and extend out understanding of perinatal transmission and the pathogenesis of early infection (treatment of children will be addressed in other objectives).

Description: Vertical transmission of HIV from mother to child is the predominant mode of transmission for pediatric HIV infection. The identification, development, and testing of interventions should be based on the pathogenesis of transmission.

Action Steps: Support the rapid translation of basic research observations to strategies for the interruption of vertical transmission; apply the results of clinical trials to the investigation of pathogenesis and to clinical practice.

Support national and international collaborative studies to retrospectively and prospectively evaluate potential obstetric factors associated with vertical transmission including non-protocol use of antiretroviral agents.

Develop and evaluate strategies for interrupting the vertical transmission of HIV from pregnant women to their offspring that are simpler and less costly than the current AZT regimen and derive information on pathogenesis of transmission from the study of these strategies. Such strategies include antiviral agents, anti-HIV immunoglobulin, monclonal antibodies, vitamin supplementation (e.g. vitamin A), HIV vaccines, adjuvants, virucides, and other intrapartum interventions alone and in combination.

Evaluate the safety, toxicity, pharmacokinetics, and

antiretroviral activity of anti-HIV agents in pregnant women and newborns; explore the use of highly active agents that may develop resistance rapidly and could be used in this setting.

Assess the potential efficacy and feasibility of obstetric interventions to prevent vertical transmissions, such as cesarean deliveries and other aspects of intrapartum care.

Develop and improve sensitive and specific diagnostic parameters that are accessible and cost-effective to permit early differentiation of HIV infection status in children born to HIV-infected mothers.

Investigate the role of the placenta in transmission of anti-HIV drugs from mother to fetus.

Expand the obstetrical and pediatric infrastructure for the conduct of perinatal trials through collaborative efforts, particularly in the international setting.

Support the long-term followup of women and children who participate in perinatal trials to evaluate potential distant effects of antiretroviral agents and/or biologicals.

Evaluate the risk of vertical transmission of drug-resistant virus.

Evaluate incorporation of ACTG 076 AZT regimen into clinical practice in the United States.

Evaluate therapeutic strategies for treating infants during acquisition of HIV to determine whether disease progression can be significantly altered.

Objective 6: Discover, develop, and evaluate improved strategies for the treatment and prevention of HIV-associated malignancies and extend our understanding of the risk factors for and pathogenesis of such malignancies.

Description: HIV-associated malignancies have a significant impact on morbidity and mortality, and some are expected to become increasingly common as survival with sever immune dysfunction is prolonged and as the demographics of HIV infection change. The development of methods to identify persons at high risk for subsequent malignancy, and the identification, development, and clinical testing of new therapeutic strategies for these malignancies are essential.

Action Steps: Support basic research on HIV-associated malignancies to increase fundamental knowledge of the etiology, pathogenesis, and biology of these neoplasms; develop preclinical models for testing potential therapeutic strategies.

Identify novel mechanisms and targets (e.g. cytokines,

angiogenesis, viral or hormonal cofactors) for treatment and prevention of HIV-associated tumors, including Kaposi's sarcoma (KS), non-Hodgkin's lymphoma, HPV-associated malignancies, and others, and develop new therapeutic strategies on the basis of these findings.

Use structural biologic and biochemical information to rationally design drugs to inhibit specific pathogenic factors of HIV-associated malignancies.

Develop *in vivo* models (SCID/nude mouse) for pathogenesis and drug sensitivity testing.

Develop *in vitro* models of KS as well as assays for angiogenesis inhibitors.

Encourage the develop and coordinate the conduct of clinical trials that concurrently evaluate antiretroviral and anti-OI therapeutic strategies directed against the malignancy in order to assess the effects of such treatment on the malignancy as well as on the underlying HIV infection, immune function, and clinical course.

Continue and expand screening, discovery and development of novel therapeutic agents with activity against HIV-associated malignancies (e.g. agents with better CNS penetration, agents with better safety profiles).

Develop trials to optimize existing therapies for malignancies in HIV-infected patients, including therapeutic adjuncts such as hematopoietic colony-stimulating factors and supportive care; develop and validate quality-of-life assessments.

Encourage collaborative studies to develop mechanisms for early identification of patients at high risk for malignancy and to develop and assess interventional strategies to reduce or prevent the development of malignancies.

Improve diagnostic methods for early diagnosis of malignancies and for early detection of recurrent cancer.

Improve collaboration between various adult and pediatric cooperative groups conducting clinical trials of HIV-associated malignancies and ICDs and industry to accelerate trials completion and approval of active agents.

Foster prompt referral of patients (co-registration) from antiretroviral trials to trials for AIDS-related malignancies.

Objective 7: Develop strategies for assessing,preventing, and treating central and peripheral nervous system dysfunction in the course of HIV infection.

Description: Nervous system impairment, including AIDS-related cognitive/motor dysfunction (formerly AIDS dementia complex), and peripheral nerve/spinal cord dysfunction are serious sequelae of HIV disease.

Action Steps: Develop novel strategies and agents that are active against putative pathways of HIV-induced CNS dysfunction, e.g inhibitors of quinolinic acid, excitatory neurotransmitters, gp160/120, and other potential neurotoxins.

Implement studies related to the delineation of mechanisms responsible for impaired neurocognitive development in children born to HIV-infected mothers, and develop strategies directed at the prevention and treatment of this complication of HIV infection; utilize insights from the impaired state to better understand the course of normal neurocognitive development.

Implement clinical trials addressing nervous system complications of HIV infection and incorporate neurologic and neuropsychological assessments into other HIV-related clinical trials.

Develop therapeutic agents and/or delivery systems that are capable of crossing the blood-brain barrier and develop carriers that capitalize on different mechanisms to deliver drug to the CNS and are active against HIV infection; assess the safety of these different preparations; develop an understanding of physical and physiological mechanisms involved in penetration of the blood-brain barrier, and possibly develop agents that could conceivably block HIV entry into the CNS.

Better delineate etiologies of peripheral neuropathy in HIV infection, and develop strategies to prevent and treat this complication.

Develop and utilize *in vitro* and animal models of CNS impairment and AIDS-related cognitive/motor dysfunction to further identify agents that can reverse HIV neuropathogenesis.

Implement assessments and approaches for the diagnosis of HIV-related dementia in clinical studies; improve implementation of standardized adult, adolescent, and pediatric neuropsychologic and neurologic assessment batteries in clinical studies and evaluate treatment-induced changes in neurocognitive impairment in a linguistically and culturally sensitive context.

Develop alternative methods for detecting and assessing response to treatment of central and peripheral nervous system dysfunction including brain structural, spectroscopic, and functional imaging (for dementia); develop quantitative summary testing and examination of cutaneous nerve fibers in neuropathy.

Objective 8: Develop and evaluate therapies for the treatment and prevention of serious HIV-associated complications, especially

wasting syndrome and growth failure, as well as other disorders including hematologic, dermatologic, renal, metabolic, pulmonary, and oral manifestations.

Description: Important clinical sequelae of HIV infection include wasting syndrome, growth failure, metabolic disorders, dermatologic disorders, ITP, nephropathy, oral diseases, and other symptoms and serious complications. Drugs and strategies that can treat these sequelae are needed to ameliorate these conditions.

Action Steps: Develop and evaluate therapeutic strategies for preventing and ameliorating the various sequelae of HIV infection (listed above in the Description) and increasing understanding of their pathogenesis.

Develop and validate quality-of-life parameters for adults and children for the various sequelae of HIV infection (listed above in the Description).

Develop and evaluate therapeutic strategies for alleviating the various symptoms of unclear etiology in HIV-infected persons (listed above in the Description) and improving the quality of life.

Agency: National Institutes of Health

Goal: (Vaccines)

Objective 1: Increase scientific knowledge of host defense mechanisms leading to protection against HIV infection and disease.

Description: More basic knowledge is needed to define protective immune responses to HIV in order to facilitate the development of vaccines and other immunologic strategies to prevent and control HIV infection.

Action Steps: Develop animal models that are practical and as much as possible are representative of the spectrum of HIV infections and AIDS; models should be amenable to use in evaluating protection by vaccines and, where this can be demonstrated, determining the correlates of protective immunity.

Determine the mechanisms of immunologically mediated control of infection with HIV and other related retroviruses, including the role of specific and nonspecific immunity in inhibiting viral replication.

Additional basic knowledge is needed to determine:

- factors, including persistence of antigens, that favor establishment of memory and development of long-term protective immunity;
- the heterogeneity of specific responses to an immunogen within distinct compartments of the immune system;
- factors that promote development of particular effector cell types;
- mechanisms resulting from exposure to HIV that interfere with induction or propagation of vaccine-induced effector responses;
- mechanisms of virus neutralization.

Study acutely infected individuals, exposed/uninfected humans (and other primates), and rapid/nonprogressors to determine viral and host factors that impact amounts of circulating virus and disease course; ensure that plasma, PBMC, biopsy, autopsy, and other key patient and animal samples, including CNS samples, are accessible to qualified laboratories.

Define and characterize viral B cell and T cell epitopes that induce protective immunity; understand their structure and antigenicity and determine whether and how their immunogenicity can be exploited in vaccine development; and define epitopes in

which substitutions cannot be tolerated by the virus.

Determine whether infection with one strain of HIV or related retroviruses confers protection against subsequent infection with a second strain; determine the protective mechanism and timing.

Understand how and why HIV and related lentiviruses evade or escape from humoral and cellular arms of the immune response.

Explore strategies to elucidate the obligate mechanisms for protective immunity against HIV, including amplification of selected responses by passive transfer of Ab or immune cells and subtraction by deletion of selected components of the immune system.

Study chronic infection with attenuated viruses, such as SIV variants shown to induce strong protection against virulent SIV strains in macaques, to understand what properties of the virus and the immune system are responsible for lack of disease induction and protection from challenge with wild-type virus.

Explore the molecular epidemiology and serology of HIV-1 populations relevant to vaccine trials and collect clinical material from these populations for scientific analysis. Acquire epidemiological information to assist in interpretation of these analyses.

Develop quantitative measures of HIV concentration in bodily fluids to determine whether there is a relationship between HIV concentration and transmission and to determine the effect of concurrent STDs on HIV shedding.

Objective 2: Apply findings from basic, epidemiologic, and clinical research to the design and evaluation of vaccine strategies in laboratory studies and animal models, and foster collaboration with industry in the research and development of candidate vaccines.

Description: The identification of viral antigens and vaccine delivery methods that elicit long-lasting protective immune responses against a broad range of HIV isolates will facilitate development of effective vaccines.

Action Steps: Support the design and development of potential vaccines, including vaccines composed of:

- whole-killed HIV and genetically engineered, noninfectious HIV mutants that lack the viral RNA genome or have a defect in a critical gene necessary for replication but contain an array of HIV genes for expression of antigenic proteins;

- live, recombinant viral and bacterial vectors engineered to express one or more HIV proteins;

- naturally occurring and genetically engineered, live-attenuated strains of HIV;
- synthetic peptide candidates capable of inducing and boosting both cellular and humoral immunity;
- DNA coding for viral proteins;
- agents that stimulate mucosal immune responses;
- a combination of the above agents and preparations;
- other novel agents and preparations.

Evaluate the efficacy of vaccine strategies in animal models of HIV and related lentiviruses. To accomplish this:

- test vaccine strategies in animal models that most closely mimic the HIV infection in humans;
- determine the effect of vaccine formulation and regimen as well as the nature, timing, and route of vaccine challenge on the characteristics and effectiveness of the vaccine-induced immune response;
- define the impact of different vaccine approaches on kinetics of immune responses, kinetics and localization of viral replication, disease progression, and biologic characteristics of breakthrough virus including transmissibility;
- conduct long-term followup of vaccinated animals that become chronically infected to determine the impact of vaccination on disease progression;
- develop assays to distinguish between infection and serological responses due to immunization.

Support design and development of methods to improve or modulate immune responses (qualitatively or quantitatively), including:

- novel adjuvants and presentation methods;
- vaccines incorporating cytokines or other biologically active molecules;
- establishment of physical or biological reservoirs for long-term antigen presentation;
- other novel strategies.

Encourage development of candidate vaccines of suitable antigenic types and possessing stability and route of administration

characteristics appropriate for international as well as domestic use.

Characterize and evaluate the potential negative side effects of candidate vaccines, including production antibodies enhancing neurotoxicity and oncogenicity.

Develop better *in vitro* methodologies to measure immune responses to primary viral isolates.

Develop infrastructure, and address scientific, legal, and regulatory issues to foster and encourage participation by, and collaboration with, industry and other agencies in the research, development, production, and clinical testing of candidate vaccines.

Objective 3: Select candidate vaccines or concepts suitable for Phase I and Phase II trials and conduct these trials.

Description: Suitable candidate vaccines need to be selected and evaluated in Phase I and Phase II trials to determine safety and immunogenicity.

Action Steps: Support the conduct of Phase I and Phase II coordinated clinical trial that will determine long-term and short-term safety and compare immunologic responses to preventive vaccine candidates; include a broad range of humoral, cell-mediated, and mucosal immune parameters;

Develop a mechanism to evaluate the suitability of vaccine candidates for entry into Phase I and Phase II trials; evaluation criteria should include originality and intrinsic value of the concept and animal model data.

Develop strategies at the local and national levels to reduce social and economic risk to volunteers in Phase I and Phase II trials to facilitate broad participation.

Design and conduct Phase II trials using promising HIV vaccines that are also genetically or immunologically related to HIV isolates circulating in the proposed trial population and of an appropriate size to facilitate decisions regarding efficacy trials. Analyze immune responses in vaccines and appropriate controls. Isolate and characterize virus and follow clinical course and immune responses of vaccines who become HIV-infected.

Study viral isolates from participants in HIV vaccine trials and selected controls to explore the possible effects of vaccination on the characteristics of transmitted viruses.

Conduct behavioral research on trial participants to establish whether their risk behavior has been influenced by participation in a vaccine trial, with emphasis on individuals who become infected while participating.

Closely coordinate the evaluation of research findings on prophylactic AIDS vaccines with preclinical research and immunotherapeutic interventions.

Objective 4: Identify mechanisms of protective immunity to HIV in newborns and infants and support the development of safe and effective immunologic strategies for preventing or controlling HIV infection in this population.

Description: Distinct approaches and infrastructure are needed to achieve protection of newborns and infants because of the unique nature of their immune responses and modes of exposure to HIV.

Action Steps: Determine what viral, immunologic, and nonimmunologic host factors influence transmission of HIV-1 from mother to infant;

- Compare virus isolates that are and are not transmitted from mother to infant;
- Seek maternal and infant immune responses that might prevent transmission to infants.

Develop and maintain domestic and international infrastructure necessary to enroll mothers and infants in prospective long-term followup vaccine trials and other interventions.

Determine the safety and immunogenicity of various HIV vaccines and adjuvants in relevant animal models of maternal-fetal and maternal-infant transmission to evaluate safety, immunogenicity, and efficacy of candidate vaccines.

Select and evaluate antibody and/or cellular preparations in passive or passive/active HIV prevention studies.

Establish criteria for advancement of candidates in Phase I, Phase II, and Phase III clinical trials in children.

Conduct Phase I, Phase II, and Phase III clinical trials in children for the most promising candidates that meet established criteria.

Objective 5: Identify appropriate domestic and international population and develop infrastructure and collaborations with government, communities, and industry necessary for ensuring adequate performance of Phase III efficacy trials.

Description: Preparation for HIV vaccine efficacy trials requires development of an infrastructure and a series of studies and planning activities to ensure their feasibility.

Action Steps: Develop domestic and international sites with access to populations at high risk for acquiring HIV infection, where vaccine or other prevention research activities may be

feasible.

Establish linkages with communities or community organizations where efficacy trials might be conducted to optimize education, recruitment, and followup activities and to help address community concerns related to AIDS vaccine efficacy trials.

For international trials, work closely with national (host) governmental and regulatory authorities, collaborating institutions, vaccine manufacturer(s), and the World Health Organization to plan and conduct vaccine efficacy trials adhering to the highest ethical and scientific standards.

Carry out appropriate epidemiologic studies that determine the risk profiles and infection rates of various populations in the United States and worldwide in order to identify those groups most likely to be the participants in vaccine trials.

Maintain the necessary laboratory infrastructure at designated sites for conducting domestic and international vaccine efficacy trials.

Acquire and analyze HIV isolates from recent seroconverters representative of potential efficacy trial populations so that genetic and antigenic information about virus circulating in the population can be obtained.

Evaluate other biomedical and behavioral interventions that could prove of benefit in decreasing the incidence of HIV infection in the populations identified for future vaccine efficacy trials and assess their potential impact on the evaluation of vaccine efficacy.

Conduct behavioral research in populations at high risk for HIV infection to determine, for example, appropriate risk-reduction interventions and to estimate risk behavior and recruitment, adherence, and retention strategies pertinent to the design and execution of a successful efficacy trial, especially for populations that have been historically underrepresented in clinical trials.

Determine possible adverse social, economic, or legal consequences of participation in clinical trials, and develop strategies for mitigating potential harm.

Determine optimal methods of achieving informed consent for vaccine efficacy trials.

Prepare for adequate long-term followup of individuals participating in vaccine clinical trials where it will be necessary to determine the longevity of immune response, the correlates of immune protection, long-term safety, the impact of participation on risk-taking behavior, and the possible positive or negative effects of vaccine immunization against disease

progression and HIV transmission.

Encourage linkage between vaccine preparedness studies in high-risk populations and other research activities including research on TB and STDs; and integrate research on vaccines against opportunistic infections as appropriate.

Objective 6: Select suitable vaccine candidates and support efficacy trials when appropriate criteria are met.

Description: Conduct HIV vaccine efficacy trials of the most promising candidate vaccines in well-characterized, high-risk populations to identify effective vaccines for the control of HIV infection.

Action Steps: Establish criteria with concurrence of an advisory group that has the requisite scientific, public health, government and community expertise.

Conduct large-scale efficacy trials of preventive vaccine candidates that have proven promising, safe, and immunogenic in Phase II trials and that meet appropriate criteria;

- Evaluate HIV vaccine candidate efficacy against infection and disease;
- Evaluate additional virologic, immunologic, and behavioral outcomes, particularly correlates of protective immunity.
- Ensure that trials are conducted with the highest regard for social and ethical standards.

Agency: National Institutes of Health

Goal: (Behavioral and Social Science Research)

Objective 1: Support research to develop and evaluate social and behavioral interventions at the societal, community, organizational, and individual levels to reduce HIV transmission by reducing HIV-related risk behaviors and increasing protective behaviors. Multi-site and cross-national studies are encouraged.

Description: Studies have demonstrated that HIV-related risk behaviors can be measured and modified. In response to the evolving epidemic, an expanded HIV prevention research agenda is called for on what works, for whom, where, for how long, and at what cost.

Action Steps: Develop and evaluate the effectiveness and cost-effectiveness of demographically and culturally appropriate behavioral and social interventions in different domestic and international settings and populations to reduce high-risk HIV-related behaviors and HIV transmission (e.g. through safer sexual practices, increased use of condoms and other barrier methods, use of sterile injection equipment, and reduction of high-risk drug-related behaviors).

Support research on a range of HIV prevention strategies in a variety of settings for both emerging populations and groups that continue to be at high risk for HIV.

Support research to increase the effectiveness and cost-effectiveness of drug abuse, mental health, and alcoholism treatment, including the development of new pharmacotherapies, to reduce HIV-related risk behavior in different settings and populations.

Support research (including multi-site and cross national studies) on comprehensive interventions that integrate various HIV and STD prevention and family planning approaches.

Support research to improve the access to, delivery of, evaluation, and cost-effectiveness of services that reduce HIV risk behaviors and transmission.

Design and test interventions to increase recruitment, retention, and adherence to protocols for HIV prevention research, including prophylactic vaccines.

Support research to improve the transfer of effective interventions to and from community planning processes.

Objective 2: Support basic research to strengthen the understanding of determinants and processes that influence HIV-

related risk behaviors and the consequences of HIV disease.

Description: Understanding the basic factors influencing behavior and behavior change at the societal, community, organizational, and individual levels is necessary for the development of interventions to prevent the transmission of HIV and to ameliorate its adverse consequences. Research is needed to define the behavioral, psychological, cognitive, and social consequences of HIV infection, disease progression, and treatment.

Action Steps: Develop models of behavior and behavior change that integrate biological, psychological , and social perspectives to explain and predict the acquisition, change, and maintenance of HIV-related behaviors among individuals and groups in various settings.

Study the social, structural, and cultural factors such as class, ethnicity, sexual identification, age, and gender that influence HIS-related behavior, affect access and delivery of care, and determine intervention strategies.

Study the development and maintenance of HIV-related risk and preventive behaviors in specific social contexts such as the sexual dyad, peer groups, social and drug-using networks, families, and communities.

Conduct research on decision-making processes, which may include disclosure of one's HIV-status, choice of treatment options, and adoption of protective behaviors.

Support research to understand the processes of how communities become involved in HIV intervention research.

Identify the behavioral, psychological, cognitive, and social consequences of HIV disease for HIV-seropositive individuals, their support systems (e.g. partners, family members, and other care givers), and their communities.

Support studies in animal models in behavior and behavior change relevant to HIV infection and prevention.

Conduct research that identifies the social and behavioral factors affecting recruitment, retention, and adherence in clinical trials.

Conduct research on the barriers to preventive actions based on lack of trust and misinterpretations of meaning of information related to HIV.

Objective 3: Support research for the discovery, development, and evaluation of strategies for preventing or minimizing the negative physical, psychological, cognitive, and social consequences of HIV, including stigmatization of persons with or

at-risk for HIV infection. Support research strategies for promoting effective health care utilization among persons with HIV infection.

Description: Enhancement of the quality of life of seropositive individuals and facilitation of HIV treatment require further research on interventions to affect the physical, behavioral, psychological, cognitive, and social consequences of HIV infection, disease progression, and treatment. Research is also needed to improve delivery of care to diverse population groups.

Action Steps: Develop and evaluate interventions for promoting quality of life and to delay or prevent physical, behavioral, psychological, cognitive, and social consequences.

Promote research to identify and remove barriers to effective health care utilization among persons with or at-risk of HIV infection, including access, engagement, followup, and adherence to health and social services across the care continuum (e.g. testing and counseling, health care-seeking behavior, adherence, case management, and home/hospice care). This strategy may entail developing and testing innovative models of treatment delivery for HIV disease at all illness stages.

Develop and evaluate interventions for promoting increased recruitment, adherence, and retention, especially in underrepresented populations, in HIV treatment and clinical trials.

Test models of care-giving for people living with HIV disease, their significant others, extended family members, and care providers.

Develop and evaluate interventions for preventing social stigmatization of persons with or at-risk of HIV infection and AIDS in different settings (e.g. workplaces, schools, health care facilities, and prisons).

Objective 4: Support research to advance innovative quantitative and qualitative methodologies to enhance HIV behavioral and social science research.

Description: Behavioral and social science methods have greatly advanced our understanding of HIV transmission and health maintenance. Further refinement of established methods and rapid development of emerging technologies are essential to continued improvement of our knowledge of HIV-related behaviors; our understanding of linkages between HIV-related risk behaviors, transmission, and disease progression; and the evaluation of interventions.

Action Steps: Develop improved qualitative and quantitative methodologies for studying behavioral and social factors associated with HIV, including improved methods for validating

self-report data, improved measurement tools for surveys, and the measurement of change over time.

Develop improved sampling strategies for subpopulations and culturally and linguistically sensitive and appropriate research instruments.

Develop improved methods and techniques for dealing with subject attrition and missing data.

Encourage secondary data analysis by developing techniques to protect confidentiality and by using of meta-analysis.

Develop and refine techniques for measuring social networks associated with HIV.

Develop and refine research techniques for measuring responses by organizations to HIV and for characterizing organizations working in the HIV field.

Encourage studies that will support multi-site studies and cross-national comparisons.

Develop and refine mathematical models for linking behavior change interventions with reduction in HIV transmission.

Agency: National Institutes of Health

Goal: Training and Infrastructure

Objective 1: Provide both domestic and international training in biomedical and behavioral research on HIV.

Description: Meeting the needs of research on HIV/AIDS requires recruiting and training basic, clinical, and behavioral scientists in the United States and abroad in the many disciplines necessary to carry out this diverse scientific agenda.

Action Steps: Increase predoctural and postdoctural training, as well as advanced research training, in a range of AIDS-related disciplines to a level comparable (about 3 percent of the budget) to that of other training programs within NIH.

Sponsor an annual AIDS Fellows Meeting to promote collaboration and information dissemination.

Increase training of scientists and clinical investigators in basic AIDS research to better link basic and clinical pathogenesis research.

Stimulate predoctural and postdoctural training in prevention, behavior change, and adherence and compliance to treatment.

Promote training of biomedical and behavioral scientists in the use of high-performance computing systems for HIV-related research.

Expand training and research capacity to deal with the epidemic of tuberculosis (TB), including multiple drug resistance associated with HIV infection.

Increase participation in the Fogarty International Center (FIC)-sponsored international training and research programs and expand these programs by recruiting trainees from additional countries in Asia and Latin America, with the long-term goal of providing AIDS-related training for leading health scientists from all developing countries.

Develop new grant mechanisms to link U.S. AIDS research scientists and institutions with leading AIDS research scientists and institutions in foreign countries.

Expand both predoctural and postdoctural training in structural biology.

Expand the NIH AIDS Loan Repayment Program to bring scientists and physicians to the NIH to expand the cadre of trained intramural researchers.

Expand both pre- and post-doctoral domestic and international AIDS-related training in epidemiology, biostatistics, and behavioral methodologies.

Establish and expand appropriate career training programs for laboratory investigators, clinical investigators, and translational scientists (i.e. making the transition from bench to patient).

Enhance training of investigators in applied immunobiology.

Support training of basic investigators, clinical investigators, and translational investigators for OI research.

Support training of basic investigators, clinical investigators, and translational scientists for research on malignancies in HIV-infected patients.

Collaborate with other PHS agencies in the development of training regarding HIV prevention, treatment, research, and education for health care providers, AIDS service providers, and health educators.

Objective 2: Establish appropriate infrastructure for the conduct of HIV research domestically and internationally.

Description: The conduct of HIV research in the United States and abroad requires establishment of infrastructure to carry out this research program, including facilities and instrumentation, computers, data communications, laboratories, and animal colonies.

Action Steps: Provide additional facilities to study animal models of pediatric AIDS.

Foster animal models to study HIV-related malignancies.

Continue the Research Facilities Infrastructure Program (RFI) and General Clinical Research Centers (GCRC) Program.

Expand the use of the National Research and Education Network (NREN) for national and international collaboration and data communications.

Provide for expansion of breeding facilities to ensure the adequate supply of species of emerging importance, e.g. *M. nemestrina*.

Provide NCRR animal model support tied to needs of basic research grants.

Provide for the long-term support of advanced in-country research and research infrastructure in those developing countries

participating in efficacy trials of candidate HIV vaccines and other priority intervention research.

Develop and support animal models predictive of human behavior, specifically, models of non-human primate behavior of impaired impulse control and risk-taking.

Provide additional laboratory and biocontainment facilities for primate research.

Increase support for the Internet connections program at health sciences centers and hospitals for research and patient care.

Establish and support repositories of samples obtained from individuals with HIV infection for current and future studies.

Increase support for screening the development of HIV macaque monkey models.

Develop and support Regional Primate Research Center (RPRC) expertise in molecular immunology, peptide biochemistry, and pharmacology.

Provide for the establishment of specific pathogen-free (SPF) non-human primate programs at all the RPRCs.

Provide further support for the development of SPF macaque colonies.

Agency: National Institutes of Health

Goal: Information Dissemination

Objective 1: Support the effective dissemination and utilization of HIV/AIDS information to all constituent communities of NIH.

Description: Effective Communication: Exchange of information about basic, clinical, and behavioral HIV/AIDS research finds is essential to progress in research and ultimately to improved care and treatment for HIV-infected people. The traditional methods of reporting ongoing studies and research results in peer-reviewed journals and at scientific meetings may be slow and may reach only limited audience. Health educators, health care providers, and patients, particularly those in underserved communities, need to know the results of clinical and prevention intervention studies, state-of-the-art recommendations, and the most up-to-date standards of health care. This information should be timely, include discussion of the potential implications of research findings for patient care, and should be in a form that audiences can use. The latest computer and information technologies should be exploited whenever appropriate. The findings resulting from communications research should be incorporated into the strategies to carry out this objective.

Objective 1:Rapidly disseminate new research findings with information on their potential implications on prevention, care, and treatment of HIV-infected individuals.

Expand access to current treatment and patient management guidelines including state-of-the-art care and information on clinical trials using multiple technologies such as, but not limited to, on-line access AIDSTRIALS and AIDSDRUGS data bases) and voice access (HIV/AIDS Treatment Information Service and the AIDS Clinical Trials Information Service).

Improve current and develop and evaluate new techniques for the two-way communication of information to scientific and lay audiences, particularly to hard-to-reach populations.

Support community groups to access HIV/AIDS information resources in their development of educational materials.

Develop and disseminate educational information. Enhance understanding of HIV and basic and clinical research processes by health care providers, community-based HIV/AIDS service organizations, and persons with HIV/AIDS.

Develop mechanisms for rapidly disseminating information on research in progress to the research community in order to increase collaboration, reduce duplication of effort, and enhance the discovery process.

Enhance communication with the pharmaceutical industry concerning research on the development of therapeutics and vaccines.

Communicate and exchange information internationally on topics such as prevention and treatment information, patient management guidelines, and research results that impact on the care of HIV-infected individuals, particularly in developing countries.

Support the exchange of basic, clinical, and behavioral research information at community, regional, national, and international conferences and workshops.

Provide on-line, in advance when possible, the full text of abstracts and other information from scientific meetings.

Collect, archive, and make available existing data from NIH-supported basic and applied research for secondary data analysis.

Disseminate widely information concerning specimen repositories, including existing repositories, specimens available and relevant information concerning cohorts, contact people, and the process for obtaining access to samples.

Evaluate the effectiveness of communication efforts by appropriate means, including obtaining feedback from target audience members and information dissemination intermediaries.

Objective 2: Support research to identify existing gaps in communications approaches, identify existing strategies that are effective, and develop and test new and innovative communication strategies that will improve access to and use of state-of-the-art HIV information by all relevant audiences.

Description: Research: Past assessments have identified important information needs and barriers for relevant target audiences such as health care providers, service providers, people with HIV and their advocates, at-risk populations, basic and applied researchers, and the general public, and although significant communications efforts have been initiated, some communities still may not be (1) receiving needed information, (2) receiving information in a context appropriate for the audience, (3) comprehending the information, or (4) translating the information into action. New approaches are needed to ensure that the communication of information resulting from research is optimally effective.

Action Steps: Develop, test and evaluate innovative strategies for effectively reaching scientific audiences with relevant HIV information.

Investigate how and under what circumstances different communication and dissemination strategies influence the adoption of scientifically based HIV behavior change interventions and clinical practice activities in various populations.

Identify obstacles to information dissemination and develop and test possible ways to overcome these obstacles.

Assess the information needs of, and sources of information used by, various audiences, including biomedical and behavioral research communities, health care providers, service providers, people with HIV and their advocates, at-risk populations, and the general public.

Investigate the adoption of new technologies for disseminating basic and applied research findings.

Develop, improve, and evaluate the interface between human factors and emerging technologies for information exchange in HIV/AIDS.

Objective 3: Develop, implement, and evaluate mechanisms that promote coordination and collaboration on all current HIV/AIDS communication activities among NIH ICDs and with other Federal and non-Federal groups.

Description: Coordination: The scientific and lay communities look to the NIH as a central source of information on HIV/AIDS. Since multiple NIH ICDs disseminate HIV/AIDS information to these communities, coordination of efforts is essential. In order to make more effective use of limited Federal dollars, increase efficiency, make better use of new technologies, and ensure credibility with the scientific and lay communities, there must be more collaboration and better coordination of communication activities within the NIH and between the NIH and other Federal Agencies, community groups, universities, and the private sector.

Action Steps: Build ongoing partnerships between community-based organizations and basic, clinical, and behavioral researchers through both the intramural and extramural research programs to encourage exchange of information and experience throughout the research process to enhance research, treatment, and prevention efforts. For example, this could be accomplished through requirements in appropriate funding proposals to establish appropriate communication and coordination.

Promote closer interagency collaboration within PHS on information dissemination programs.

Coordinate collaboration among all ICDs in the provision of information about their clinical trials for HIV/AIDS to the AIDS Clinical Trial Information Service.

Maintain an interface with the Cancer Information Service and PDQ to provide information on clinical trials for AIDS-related malignancies.

Expand the development and use of HIV/AIDS resource on the Internet to facilitate domestic (NIH and non-NIH) and

international research collaboration and data sharing.

Continue collaborations with the United Nations/World Health Organization (WHO) AIDS program, the Pan American Health Organization (PAHO), and international AIDS agencies or societies to obtain and disseminate information about international clinical trials.

Collaborate with public and health sciences libraries to facilitate community group access to needed information.

Work within HHS, including HCFA, and with the private sector in the development of medical standards of care for determining guidelines for reimbursement.