

NATIONAL INSTITUTES OF HEALTH  
FISCAL YEAR 2005  
PLAN FOR HIV-RELATED RESEARCH

II: ETIOLOGY AND  
PATHOGENESIS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES  
NATIONAL INSTITUTES OF HEALTH  
OFFICE OF AIDS RESEARCH

**AREA OF EMPHASIS:**

## Etiology and Pathogenesis

### **SCIENTIFIC ISSUES**

In the quest for vaccines and microbicides to prevent HIV infection and for more effective drugs and immune-based therapies to contain the infection and treat the opportunistic infections (OIs), tumors, and other manifestations of a dysfunctional immune system, a better understanding is needed of two areas: how HIV infection is established and maintained, and what causes the profound immune deficiency and terrible clinical complications that accompany this infection. What role do specific HIV proteins play in the viral life cycle in individual cells and within the bodies of infected individuals? What are the primary modes of HIV transmission between cells and between individuals? What contribution does the immune system make to controlling the infection and to the disease process? What mechanisms are involved in cell injury and death in the immune, nervous, and other organ systems afflicted by HIV? What host factors and co-factors influence primary infection and the course and outcome of HIV infection? What is the relationship of HIV infection to the associated malignancies, OIs and co-infections, neurological impairments, and metabolic disturbances that characterize AIDS? These outstanding questions define the central contemporary issues encompassed within the area of etiology and pathogenesis research.

## HIV BIOLOGY

### PRIORITY FOR FUTURE RESEARCH:

- **Facilitate the translation of new insights into HIV biology to develop novel interventions for the prevention and treatment of HIV infection. Identify and validate cofactors for viral genes as new targets capitalizing on novel technologies including viral interference and genomic screening.**

Since the initial isolation of HIV in 1983 and its identification as the causative agent of AIDS shortly thereafter, tremendous progress has been made in understanding the genetic structure and variability of the viral genome, the critical aspects of the virus life cycle, and the function of viral gene products and their interaction with the host. The knowledge that has emerged from basic research in these areas has provided and continues to provide the foundation for all efforts to develop current therapies to treat HIV infection. The elucidation of the structure and function of critical viral enzymes—reverse transcriptase, protease, and integrase—has represented a critical step in the development of effective anti-HIV drugs. Similar insights from basic research into the mechanisms of viral entry and the mechanisms by which the infection becomes established and spreads also are crucial for vaccine and microbicides development efforts.

The challenges remain to develop new drugs for the treatment of HIV infection that are less expensive, easier to take, more potent, and with fewer adverse effects than those currently in use, along with microbicides to prevent sexual transmission of HIV infection; and to identify immunogens able to elicit strong cellular and neutralizing responses for the development of an effective vaccine.

Scientific advances in AIDS research, such as the resolution of the crystal structure of gp41 and gp120 bound to CD4 and a neutralizing antibody, the delineation of many of the molecular interactions between virally encoded regulatory proteins and host cell factors, recent insights into critical requirements for viral attachment and replication, and the identification of conserved structural intermediates of gp41 that might be able to elicit a strong and cross-reactive neutralizing response are affording us the opportunity to identify new viral and cellular targets for therapeutic and preventive interventions. New technologies like genomic screening and transcriptional gene silencing by interfering small RNAs will be instrumental in validating new targets and prioritizing drug discovery candidates.

Emphasis should be placed on the elucidation of structures and a better understanding of the biochemistry, interaction, and biologic function of relevant virus and host cell constituents. These studies should focus on defining the roles of specific host cell and viral gene products in HIV replication, persistence, and pathogenesis. The NIH should play an instrumental role in facilitating collaborative research aimed at developing and implementing biologically relevant validated assays for drug screening.

**TRANSMISSION,  
ESTABLISHMENT,  
AND SPREAD OF  
HIV INFECTION**

**PRIORITY FOR FUTURE RESEARCH:**

- **Elucidate the biologic determinants of HIV transmission between individuals, and define the mechanisms by which host factors, viral factors, and cofactors may influence the process of virus transmission and dissemination.**

The early interaction of HIV with target cells at the portal of entry is critical for the subsequent establishment and spread of infection. However, in spite of the tremendous scientific advances in AIDS research, the factors that determine the transmissibility of HIV and the variables that may influence a person's susceptibility to HIV infection following exposure have yet to be clearly understood. The observed resistance to HIV-1 infection of multiply exposed subjects bearing a homozygous deletion in one of the genes encoding a chemokine coreceptor for primary HIV-1 isolates highlighted the importance of coreceptors in HIV-1 transmission.

Prospective studies in discordant couples have provided evidence that peripheral blood viral load is the most important predictor of the risk of heterosexual transmission of HIV. These findings have important implications for the development of prevention strategies, since they suggest that reducing viral load in HIV-infected persons will result in their decreased infectiousness. In the same studies, circumcision also appeared to protect against acquisition of HIV, highlighting the role of biologic factors as well as behavior in HIV transmission.

NIH-funded research is giving special emphasis to studies aimed at defining the role of components of the mucosal compartment, cellular and molecular aspects of mucosal innate and adaptive immunity, viral heterogeneity, disease stage, viral genotype/phenotype/clade, hormones, cofactors such as other infectious agents, sexually transmitted infections (STIs), and systemic and local inflammatory processes on the ability of infected individuals to transmit HIV. The factors affecting susceptibility or resistance to HIV acquisition including coreceptor expression, innate and adaptive immune responses, hormones, vaginal flora, STIs, and inflammatory processes are also studied by NIH-funded investigators. Systemic and genital tract

inflammation has a major effect on HIV acquisition since it results in an increased expression of viral receptors on target cells, recruitment of target immune cells from the circulation, and increased permeability of the epithelium. The ability to support active local replication and subsequent establishment and spread of infection might also depend on the local inflammatory milieu.

This basic knowledge is crucial for our efforts to develop effective vaccines and microbicides. In the developing world, where infection rates have climbed to more than 20 percent in some countries and few people can afford antiretroviral drugs, the main issue continues to be how to stop transmission of the virus by effective preventive interventions.

Emphasis should be placed on studies focused on cohorts that are most representative of the expanding HIV epidemic. This can be facilitated by studies whose designs reflect the collaborative interaction of basic scientists and population-based researchers. Efforts should also be directed at understanding the relative efficiency of transmission of cell-free and cell-associated virus in various bodily fluids at different portals of entry (particularly mucosal), mechanisms and timing of initial entry, the cells that represent the first target of infection, mechanisms of virus compartmentalization in genital secretions, the relationship between biologic findings and the anatomical organization of mucosal tissue, and the role of viral genotypes/phenotypes and dose on HIV entry and establishment of infection. Emerging technologies in genetics, computational biology, *in vivo* imaging, functional genomics and proteomics, and the assessment of host immune responses should also be brought to bear on studying the biology of HIV transmission.

**PATHOGENIC  
MECHANISMS OF  
HIV INFECTION**

**PRIORITY FOR FUTURE RESEARCH:**

- **Understand the dynamic of virus-host interaction through the course of HIV infection.**

Many factors regulate the dynamics of virus replication and host responses. Characterizing these factors *in vivo* and determining how they change over the course of infection; how they are influenced by age, ethnicity, sex, gender, and health status; and how they differ in international setting with different viral, host, and environmental influences has great implications for a better understanding of the effects and nature of the host response to HIV, the processes leading to the loss of control of HIV replication, and the pathogenesis of AIDS.

Interaction of HIV with its host is a dynamic process that varies through the course of infection; from the very early to the late stages. CD4+ T helper cell activity diminishes rapidly after primary HIV infection and is not restored by effective antiviral therapies administered at a later time. Different CD8 epitopes are targeted by cytotoxic T lymphocyte (CTL) in acute versus chronic infection, and both CD4 and CD8 responses change before and after the establishment of the viral set point. In addition, HIV-1-specific CD8+ T-cell responses differ in their ability to drive viral escape by sequence variation.

NIH-funded research conducted at the molecular, cellular, tissue, and organ system levels is elucidating the pathogenic mechanisms associated with HIV infection. Investigators are focusing on studies of the mechanisms by which HIV infects various cell types, the interaction between the viral regulatory elements and host cell factors that maintain a persistent infection, and the viral- and host-mediated mechanisms that influence the level of viral expression seen in progressive stages of HIV disease. Since HIV so profoundly affects the immune system, ongoing research is also aimed at elucidating the viral- and immune-mediated pathogenic processes that result in the severe loss of immune function, inappropriate immune activation, and disruption of immunomodulatory cytokine production and regulation observed in HIV infection and disease. Recent data have shown that HIV preferentially infects HIV-specific CD4 T cells during the process of immune recognition and response, thereby providing a potential mechanism to explain the predominant loss of HIV-specific CD4 T-cell responses and consequently the loss of immunologic control of HIV replication.

NIH-supported investigators have demonstrated that significant levels of virus are present in plasma during all stages of HIV infection, including the clinically asymptomatic phase, and that active virus replication is linked directly to the depletion of T-cell populations and is correlated with progression to disease. This model of AIDS pathogenesis would imply that HIV induces disease by replicating at high levels in CD4+ T cells, eventually weakening the immune system and causing it to fail. However, simian immunodeficiency virus (SIV) replicates at high levels in the infected natural hosts of African green monkeys and sooty mangabeys without causing significant symptoms or disease, clearly indicating that high levels of viremia do not necessarily lead to disease. Therefore, host factors or the particular nature of the host response play a critical role in determining whether and when disease arises following infection.

The emphasis on the dynamic and quantitative aspects of HIV replication is also paralleled by efforts to quantify T-cell population dynamics *in vivo* during different stages of HIV infection and disease. These efforts have great implications for understanding the mechanism behind the most central and unresolved issues in HIV-mediated immunopathogenesis: the depletion of CD4+ T cells and the failure of the regenerative capacity of the immune system to compensate for virus-induced damage. Several mechanisms, either direct or indirect, have been suggested; however, the critical mechanisms remain to be elucidated. New technological developments that permit the measurement of lymphocyte population dynamics and numbers of cells recently emigrated from the thymus during HIV infection, disease, and therapy are providing valuable insights into this pathogenic process. Innovative techniques for *in vivo* imaging also will provide crucial information on tissue reservoirs and compartments of HIV infection. Elucidation of these mechanisms will be critical for generating new therapeutic principles and approaches that will take into account both viral and cellular kinetic parameters.

In the last several years, NIH-funded research has identified multiple host genetic determinants that influence both the level of viral replication and host immune responses, and have a great impact on disease progression. New discoveries regarding the host machinery used by the virus for replication open the possibility of additional host polymorphisms that may exist, as well as providing novel therapeutic targets. Viral phenotypes that have a powerful impact on the course of disease have been identified, but a true understanding of viral determinants of replication *in vivo* and viral fitness requires further clarification. Finally, the role of copathogens in regulating the virus-host dynamic is a critical area of further study. Importantly, these factors will also vary in nature and relative importance at different stages of disease, and will also differ in international settings based on distinct host genetic, viral genetic, and environmental influences.

Gender, health status, race, and age affect the biology of HIV infection and the responses to therapies and vaccines. The basic science underlying HIV etiology and pathogenesis research is considered to be gender neutral. Basic mechanisms of viral replication and viral-induced pathogenesis are not expected to differ in women and men. However, there are differences in the way HIV infection is transmitted and how the disease is manifested in women and men. In addition, it is well recognized that induced autoimmune phenomena are more prevalent in the general population of women. Moreover, recent studies have highlighted differences in viral dynamics in women compared with men, and further studies are warranted to elucidate the biological underpinnings for these findings. Some of the

studies that examine gender differences compare factors other than sex in patients. HIV-infected women are more likely to be poor, to belong to racial minorities, to be of poor health status, and to use injection drugs. These are all factors that might have important effects on health outcomes for both men and women infected with HIV. Age also is emerging as another important factor to consider, due to the increased survival of HIV-infected persons and the increased number of newly HIV-infected individuals at different life stages.

**PRIORITY FOR FUTURE RESEARCH:**

• **Investigate the mechanisms of persistence of HIV infection.**

The dramatic success of effective antiretroviral therapy (ART) in reducing plasma viremia to undetectable levels had raised the intriguing possibility that prolonged therapy might lead to virus eradication. However, HIV rebounds very quickly upon discontinuation of therapy, and recent data indicate that the virus can persist in HIV-infected patients for almost a lifetime. HIV can persist through continued low-level replication, even in the presence of ART that is able to drive viremia below the limits of detection, and in a latent reservoir of resting memory CD4 T cells that is established very early after infection. Persistent ongoing viral replication might explain the apparent long half-life of the latently infected reservoir, since this replication could be reseeded continuously from activated CD4 T cells and monocytes/macrophages newly infected with HIV. Monocytes and macrophages, as well as natural killer (NK) cells, the brain, the rectal mucosa, and the renal epithelial cells appear to represent reservoirs for viral persistence in patients on ART. We still do not know how many different cells and tissue types may represent potentially important reservoirs of HIV or their relative contribution to viral replication rebound following treatment failure or discontinuation. Residual viral replication is a complex phenomenon and probably involves more than one mechanism. A better understanding of the different mechanisms of viral persistence is needed to discern the reasons for drug failure, to design rational approaches for virus control or eradication, and to better assess the impact of virus persistence on HIV transmission and its implications for HIV prevention.

Research efforts should focus on the explication of cells, tissue reservoirs, and compartments of HIV latency and/or residual replication during suppressive ART, their rates of turnover, the mechanisms of viral latency and reactivation, the impact of low-level viral replication on virus transmissibility, and the ability of natural and induced immunity to control and eliminate persistent infections. Studies directed toward identifying the origin of virus rebound in patients who have stopped therapy, the

contribution of virus from latently infected cells and/or residual replicating virus to virus rebound, the best cellular and molecular techniques to measure HIV-1 reservoirs and ongoing replication *in vivo*, and approaches to purge these reservoirs and compartments of virus are also of particular importance. Development of *in vitro* models of HIV pro-viral latency and *in vivo* models of HIV residual disease will be beneficial in answering remaining questions in this field.

**PRIORITY FOR FUTURE RESEARCH:**

- **Develop innovative technologies in human and nonhuman primate immunology to guide vaccine development and immune reconstitution efforts.**

Elucidation of the normal development and functioning of the human immune system is crucial to our ability to understand the effects of HIV on the immune system and the pathogenesis of AIDS. This understanding also holds the key to the design of rational immune reconstitution approaches in persons undergoing antiretroviral treatment and to identifying the characteristics of the immune response that are needed for a protective vaccine. It is important to acquire this knowledge for all the populations affected by HIV: men and women throughout their life spans and for all racial and ethnic backgrounds.

Emphasis should be placed on obtaining a better understanding of the immunologic components and responses present in mucosal surfaces. Special attention should be paid to understanding the elicitation of mucosal immune responses and the trafficking of cells between peripheral immunological sites and mucosal sites, as well as the trafficking between distal mucosal compartments and innate immunity. The importance of the early events (first days or weeks) following HIV infection have stimulated interest in understanding the innate immune responses and the interface between innate and adaptive immunity. These areas have been largely unexplained in HIV/AIDS research and could have major implications for vaccines and microbicides development.

Emphasis should also be placed on a better understanding of the elicitation and maintenance of immunologic memory and on the definition and validation of markers and assays that will enhance our understanding of and ability to study immune function in humans, especially those approaches that permit the study of *in vivo* regulation and function of the immune system. Recent technological breakthroughs are affording us the opportunity to assess more accurately the quantity and function of T cells in HIV infection, the impact of these T-cell responses on viral sequence evolution, and the ability of the

virus to escape from T-cell-mediated immune pressure by sequence variation within targeted epitopes. The use of these innovative techniques is providing investigators with critical insights into the effects of HIV infection, viral sequence evolution, ART, and potential preventive or therapeutic vaccines on the immune system. Our attempts to preserve or reconstitute the immune function in HIV-infected persons will benefit also from focused efforts directed at elucidating the homeostatic and regenerative mechanisms of various lymphocyte populations, the markers for true thymic-derived cells, the factors that may influence T-cell proliferative capacity or survival in the normal state and in HIV disease, the immunological impact of long-term therapies, and potential interventions to improve thymic function and the generation of naive T cells. Potential compensatory mechanisms to replenish T cells lost during infection include peripheral expansion of residual memory cells and increased production of naive cells by the thymus. Current effective ART leads to a rapid increase in circulating memory CD4 and CD8 T cells, probably due to redistribution from lymphoid organs, a decrease in cell death, and peripheral expansion. However, reconstitution of the T-cell repertoire is generally delayed for many months and may ultimately require production of new T cells from the thymus.

Focused efforts directed at characterizing the functional diversity of CD8 effector cells, at analyzing humoral and cellular immunity in microenvironments (especially at mucosal sites), and at an enhanced understanding of mechanisms leading to maintenance of immunological memory will greatly benefit research aimed at the development of effective HIV vaccines.

Continued support of *in vivo* research is a high priority at the NIH to further an understanding of the interactions between the virus and host immune system response. NIH-sponsored longitudinal cohort studies constitute a major resource for pathogenesis research. Specific cohorts, such as long-term nonprogressors, HIV-exposed but uninfected individuals, and rapid progressors, will provide clues for treatment and vaccine research by helping to characterize immune response profiles and by providing information on correlates of immunity. *In vivo* research into mechanisms of virus-mediated immunopathogenesis also utilizes animal models. All the available animal models, but in particular the nonhuman primate models, have contributed and continue to contribute to our understanding of disease mechanisms.

## **DISEASE MANIFESTATIONS**

HIV infection affects the functioning of virtually all the organ systems within the body. Current NIH-supported basic and clinical studies are focused on the characterization of HIV/AIDS-associated diseases and on the assessment of their relative contribution to the overall disease progression in AIDS. The NIH is striving to enhance the bidirectional

flow between basic and clinical observations and intervention programs on HIV-related complications.

**PRIORITY FOR FUTURE RESEARCH:**

- **Advance the understanding of the mechanisms responsible for the toxicities and long-term complications of ART and the factors that underlie changes in the causes of morbidity and mortality in an era of increasingly effective therapies.**

The availability of new and more effective antiviral drugs and treatment modalities is having a beneficial effect on the course of HIV infection and has altered the incidence and nature of some of its manifestations. The influence of ART, which is able to lower viral load to undetectable levels, on the natural history of AIDS is providing an unprecedented opportunity to gain insights into the pathogenic mechanisms underlying the disease manifestations associated with HIV infection and AIDS. Unfortunately, use of these therapies also is associated with a series of side effects and complications that we are just starting to appreciate and study. Although most metabolic complications were initially blamed on ART, it is now clear that other factors, mainly HIV disease, may contribute to their development. Assessing the time line, absolute risk, and severity of outcome for these complications is essential for an effective clinical management of HIV-infected patients.

**Metabolic and Body Composition Changes**

The study of HIV-associated manifestations is rapidly changing as a result of the introduction of effective ART and the concomitant decline in the incidence of OIs. The incidence of wasting has declined, and hyperglycemia, insulin resistance, diabetes, hypercholesterolemia, hypertriglyceridemia, and fat redistribution (either depletion or accumulation) have been described in HIV-infected individuals taking ART. These manifestations are a real cause for concern with broad public health implications. Patients are experiencing problems in adhering to regimens when these symptoms occur: some stop taking medications, and others are not initiating therapies due to the possible occurrence of disfiguring physical changes and the long-term risk of cardiovascular complications. These changes were initially considered a single syndrome commonly referred to as lipodystrophy. Recent data are instead suggestive of multiple syndromes with different etiologies. Protease inhibitors were first associated with these metabolic and body composition changes, but recent data have indicated that HIV patients treated with only nucleoside reverse transcriptase inhibitors (NRTIs) also develop these symptoms. In addition to the direct effects of

these drugs, age, duration of therapy, HIV disease, and return to health following suppression of viral replication also may play a role in the development of these abnormalities. With the longer duration of therapy, many other complications have been reported in association with current anti-HIV treatment including bone disease, lactic acidosis, pancreatitis, and liver toxicities. Mitochondrial damage and depletion resulting from the inhibitory activity against gamma DNA polymerase of some of these drugs could potentially be involved in the etiology of some of these complications. Several complications might be due to the host response to HIV infection, as it occurs as a result of other chronic infections. Studies of the immune response to HIV in untreated and antiretroviral-treated subjects should incorporate assessment of metabolic parameters.

Elucidation of the factors contributing to metabolic and body composition changes, toxicities, and long-term consequences of ART will allow effective therapies to be tailored to the specific mechanism by which they occur, with the potential for enhancing quality of life in HIV-infected persons.

Although the incidence of wasting has declined, it remains one of the most devastating aspects and one of the major causes of morbidity and mortality in HIV-infected individuals who do not respond or lack access to potent ART, an issue in the developing countries. Weight loss in AIDS results in a significant reduction in survival, independent of other influencing factors, including CD4 cell count and history of infection or malignancy.

The introduction of effective ART has changed the natural history of HIV infection and has led to a dramatic decline in morbidity and mortality in HIV-infected persons in developed countries. However, anti-HIV therapy is not a cure and does not successfully benefit every infected individual. End-stage liver disease and liver failure are becoming an increasing cause of mortality in HIV-infected patients. However, since multiple concurrent causes of liver damage are associated with HIV infection, including hepatitis viruses co-infection, antiretroviral hepatotoxicities, OIs, and cancers, the impact of each cause of liver injury on a patient's survival in an era of effective therapies is unclear.

Epidemiological studies in large cohorts will be instrumental in identifying changes in the causes of morbidity and mortality as a result of the availability of effective therapies in HIV-infected communities and in providing us with useful insights into their etiologies.

### **AIDS-Related Malignancies**

AIDS is associated with a broad spectrum of neoplasms, including Kaposi's sarcoma (KS); lymphomas; human papillomavirus (HPV)-related, oral, cervical, and anogenital carcinomas; Castleman's disease; leiomyomas; leiomyosarcomas; and hepatitis B-related hepatocellular carcinomas. Because HIV causes immunosuppression and because most AIDS-associated malignancies are strongly associated with viruses, HIV infection provides a unique model to study the interplay of viruses, a dysfunctional immune system, and the development of cancers. NIH-supported investigators are trying to clarify the mechanistic role of chronic stimulation mediated by viral and cellular proteins, high levels of growth-promoting cytokines present in HIV-infected subjects, and human DNA and RNA viruses and their direct or indirect interaction with HIV in the development of AIDS-associated malignancies. Studies of AIDS-related KS have highlighted the potential causative role of a newly discovered human herpesvirus (HHV-8), angiogenic growth factors, and HIV proteins released in the extracellular milieu in the etiology of this neoplasm. Elucidation of the interactive factors involved in the pathogenesis of AIDS-associated malignancies will possibly translate to the identification of new targets for prevention and treatment.

Following the introduction of effective ART, preliminary studies have shown a dramatic decline in the incidence of KS, but no decrease in non-Hodgkin's lymphoma (NHL) or other AIDS-related malignancies has been reported. More extensive followup is needed to clearly discern the impact of effective therapy and prolonged survival of HIV-infected persons on their risk of developing cancer.

### **Neuropathogenesis**

Neurological disease and neurobehavioral dysfunction associated with HIV infection cause considerable morbidity and mortality in afflicted children and adults. These manifestations include diseases associated with opportunistic infection of the brain resulting from the underlying immunodeficiency and the AIDS dementia complex, a disorder that is unique to HIV infection. HIV enters the central nervous system (CNS) very early during infection, although manifestation of neurologic impairment occurs in late-stage HIV infection. Intense research efforts have focused on elucidating the role of HIV persistence in the brain parenchyma in the development of CNS disease. The cells expressing HIV or SIV in patients or monkeys with AIDS have been found to be primarily perivascular macrophages, that is, cells derived from monocytes trafficking to the brain

that have a very rapid turnover. These findings raise the intriguing possibility that the viral reservoir in the CNS is not composed of persistently or latently infected cells but of cells undergoing continual turnover. NIH-supported research is directed at understanding how HIV infection contributes to nervous system damage through direct interaction of HIV with neuronal and non-neuronal cells and indirect mechanisms, such as those mediated by cytokine, chemokine, and neurotoxins released in response to the infection or the local inflammatory response to the infection. Important areas of ongoing research include the determination of how HIV enters and establishes infection in the different compartments of the CNS and the correlation between the extent of HIV replication *in vivo* and the incidence and severity of neurologic complications. The possible role of the CNS as a reservoir of HIV infection in the setting of ART with limited CNS bioavailability also is under investigation. Special emphasis in all these studies is given to *in vivo* models of neuropathogenesis and to the integration of basic research studies on the neurologic complications of AIDS with natural history studies and ongoing clinical trials.

### **Opportunistic Infections and Co-Infections**

HIV infection results in progressive damage of the immune systems of infected individuals and makes them susceptible to a diverse collection of bacteria, viruses, fungi, and protozoa that represent the major causes of suffering and death for HIV-1-infected individuals. OIs can affect virtually every tissue and organ system in the body, resulting in severe functional compromise. The NIH currently supports a comprehensive portfolio of basic research on the pathogenesis of AIDS-associated OIs. Currently supported research is directed toward developing methods to culture and grow these pathogens *in vitro*, developing animal models to study disease pathogenesis, sequencing these infectious microorganisms' genomes, identifying new targets for therapeutic interventions, and facilitating discovery and development of prophylactic and therapeutic agents. Special emphasis is given to the interactions between the pathogen and the host and its immune system. This research will permit a better understanding of the establishment of infection, mechanisms of immune control by the host, evasion by the pathogen, and the contribution of the host immune response to disease.

The use of potent ART has resulted in a dramatic decline in the incidence of OIs in HIV-infected persons, suggesting that the increase in the number of immune cells that follows effective ART is accompanied by the recovery of functional responsiveness to antigens of several important opportunistic pathogens. However, development of OIs during the first 2 months of

effective ART has also been described, suggesting that the restoration of immune function may be partial or delayed. As a result of reconstitution of their immune responses, new manifestations also have been reported in HIV-infected persons taking anti-HIV drugs.

OIs remain one of the most important complications of HIV infection and the principal cause of death in AIDS patients. Understanding the fundamental biology and pathogenesis of these organisms, their interaction with the host immune system, and the effect of therapy-associated immune reconstitution on the clinical course and manifestations of OIs will translate into new or more rational approaches to the prevention and treatment of OIs in patients on ART, as well as in patients who lack access to or who are not responding to ART.

As the classic OIs that were the hallmark of HIV/AIDS have increasingly become less frequent as a result of the introduction of effective ART and the use of OI prophylaxis, co-infections have emerged as important complications in HIV infection. Hepatitis B and C virus (HBV and HCV) co-infections are becoming increasingly prevalent in HIV-infected patients in developed countries, and epidemiologic studies have indicated that chronic liver disease now represents a major cause of morbidity and mortality in this population. Worldwide, tuberculosis (TB) is a key co-infection suffered by the HIV-infected, and the numbers of TB cases in the world are rising, driven in large part by the HIV epidemic. Furthermore, the impact of endemic parasitic infections in the developing world, which are known to influence the immune response, is not clear with respect to HIV transmission or disease progression. On the other hand, there are intriguing preliminary data to suggest that certain co-infections (e.g., scrub typhus, GB virus C, and HHV-6) may interfere with HIV replication. There is a clear need to conduct research directed at assessing the impact of co-infections on immune dysfunction and HIV progression and likewise the impact of HIV infection on the natural history and pathogenesis of co-infecting pathogens.

### **Organ System-Specific Complications of HIV Infection**

Organ system-specific manifestations also attend HIV infection and disease. Gastrointestinal dysfunction and malabsorption are commonly observed in HIV-infected subjects. The gastrointestinal tract is one of the most important routes of transmission of HIV and appears to be a major site of viral replication and the major site of CD4+ T-cell depletion in early stages of infection in the SIV model. NIH-supported researchers are investigating the contribution of OIs, of micronutrient deficiencies, of acquired deficiencies in intestinal enzymes, of malignancies, and of potential HIV

infection of cells in the gastrointestinal tract to the gastrointestinal complications observed in HIV-infected individuals. HIV infection is also associated with multiple endocrine alterations, probably reflecting critical interaction between the endocrine and the immune systems. HIV-associated hematologic, pulmonary, cardiac and vascular, renal, mucocutaneous, and liver complications also represent causes of morbidity in infected subjects. Some of these complications are disproportionately affecting racial groups. For instance, HIV-associated nephropathy, the most common cause of chronic renal failure in HIV-infected individuals, occurs almost exclusively in African Americans and represents the third most common cause of end-stage renal disease in this population. The pathogenic mechanisms involved in all these AIDS manifestations are not well understood and are under investigation. Their definition will permit a more rational approach to both preventive and therapeutic interventions.



## SCIENTIFIC OBJECTIVES AND STRATEGIES

### OBJECTIVE - A:

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

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

### STRATEGIES:

- Determine the role of viral phenotype/genotype and dose on transmission of cell-free and cell-associated virus, in various bodily fluids at different portals of entry.
- Determine mechanisms by which virus-encoded genes and viral gene products regulate HIV replication and influence transmission, establishment, and spread of HIV infection.
- Determine the structures and interactions of viral and host proteins that are important for the transmission, establishment, and spread of HIV infection.
- Delineate the mechanisms by which host-encoded genes and gene products regulate HIV replication and influence transmission, establishment, and spread of HIV infection.
- Determine the cell molecules and tissue types that serve as portals of entry and support subsequent spread of HIV.
- Delineate the mechanisms by which innate and adaptive immunity influence HIV replication and modulate transmission, establishment, and spread of HIV infection.
- Delineate the mechanisms by which co-infections influence HIV replication, transmission, establishment, and spread of HIV infection.
- Evaluate the influence of prevention and treatment on the early events in HIV transmission, establishment, and spread.

To facilitate the research goals listed above:

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

- Further develop and utilize experimental human, nonhuman, *ex vivo*, and theoretical/mathematical models to study the transmission and establishment of lentiviral infections with emphasis on models of direct relevance to human HIV infection and models that address important issues not readily approachable in human subjects.
- Promote augmented access to and sharing of key patient samples, animal model resources, laboratory reagents, new technologies and equipment, information databases, and quantitative virologic and immunologic assays.
- Support and expand innovative research on the transmission, establishment, and spread of HIV infection.
- Develop and utilize natural and innovative technologies to procure, maintain, and expand the macaque model of AIDS.

**OBJECTIVE - B:**

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

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

**STRATEGIES:**

- Determine the impact of early events in the establishment and systemic spread of HIV infection on the clinical course of the disease.
- Define the virologic, host, pharmacologic, copathogens, and environmental factors that contribute to disease progression and nonprogression.
- Define the virologic and host factors that enable HIV to establish and maintain a persistent infection *in vivo* in the setting of both drug-naive and drug-treated individuals.
- Delineate the mechanisms of host immune control of HIV replication and investigate how the effectiveness of immune control may vary through the course of infection, depending on the identity and location of infected host cells and the influence of therapeutic interventions.
- Delineate the molecular mechanisms by which virus-encoded genes, viral gene products, and host cellular factors regulate HIV replication and influence pathogenesis.
- Determine the factors that influence the susceptibility of target cells to HIV infection and their ability to support HIV replication.
- Determine the structures of viral and host proteins involved in the processes that underlie disease progression.
- Delineate the direct and indirect mechanisms underlying HIV-induced depletion and dysfunction of immune cells and tissues, focusing on:
  - ▶ the loss of specific CD4+ T lymphocyte subpopulations and clones;
  - ▶ the impact of HIV infection on T-cell population numbers, specificities, and functions;
  - ▶ virally triggered immunopathogenesis, including immune activation, cell death, induction of nonresponsiveness, dysregulation in the number and function of immune effector cells

other than T lymphocytes, and production of host factors, including cytokines and other mediators;

- ▶ the structural and functional compromise of primary and secondary lymphoid organs including hematopoietic precursor cells and their microenvironment;
  - ▶ influences on the developing immune system; and
  - ▶ disruption of host compensatory mechanisms that govern the generation, regeneration, and homeostasis of T-cell populations.
- Evaluate whether and to what extent viral-induced damage to the immune system can be reversed following suppression of HIV replication by therapeutic interventions.
  - Determine the life span and developmental and regenerative pathways of T lymphocytes; elucidate the mechanisms that regulate the size and composition of T-cell populations and how these may change with age.
  - Define markers and functional assays that will enhance our understanding of and ability to study innate and adaptive immune function in humans, especially those approaches that permit study of the *in vivo* activity of the immune system.
  - Define the reservoirs of virus infection that permit HIV persistence throughout the course of HIV infection, including in the setting of therapies and in the presence of ongoing immune responses.
  - Determine the viral and host factors associated with clinical response and lack of response to therapeutic interventions in HIV-infected subjects.

To facilitate the research goals listed above:

- Further develop and utilize experimental human, nonhuman, *ex vivo*, and theoretical/mathematical models to study the pathogenesis of lentiviral infections with emphasis on models of direct relevance to human HIV infection and models that address important issues not readily approachable in human subjects.
- Promote augmented access to and sharing of key patient samples, animal model resources, laboratory reagents, new technologies and equipment, information databases, and quantitative virologic and immunologic assays.

- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand the immunopathogenesis of HIV infection.
- Enable the translation of basic and preclinical research findings into clinical studies in humans to advance the understanding, treatment, and prevention of HIV infection.

**OBJECTIVE - C:**

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

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

**STRATEGIES:**

- Define the mechanisms underlying alterations in metabolism, body composition, endocrine function, growth and development, and the risks of atherosclerotic, cardiovascular, vascular, and bone disease:
  - ▶ to determine the effects of antiviral therapies and suppression of virus replication;
  - ▶ to determine the influence of disease stages;
  - ▶ to determine the contributions of individual virologic and host factors; and
  - ▶ to determine the contributions of OIs, hormonal dysregulation, and other consequences of HIV infection.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms underlying alterations in metabolism, body composition, growth and development, and the long-term risks of diabetes, bone disease, and atherosclerotic cardiovascular disease.
- Determine factors associated with clinical response or lack of response to therapeutic interventions against AIDS-associated metabolic and body composition changes, impaired growth and development, and the long-term risks of diabetes, bone, and atherosclerotic cardiovascular disease.

To facilitate the research goals listed above:

- Transfer expertise from the endocrine, metabolic, cardiovascular, and bone research fields to the HIV field and promote linkage between HIV researchers and established individuals and centers of excellence in these areas of research.
- Promote programs to facilitate access to and sharing of patient samples, animal model resources, reagents, new technologies, equipment, information databases, and modeling/calculation tools used in metabolic, cardiovascular, and bone research.

- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand the metabolic, endocrine, vascular, and bone disease complications associated with HIV infection and treatment.
- Support the development of new and improved research techniques to address the emerging metabolic, endocrine, cardiovascular, and bone complications.
- Integrate metabolic, endocrine, cardiovascular, and bone studies into ongoing and planned treatment trials.

**OBJECTIVE - D:**

**Elucidate the etiologic factors, cofactors, pathogenesis, and consequences of HIV-related malignancies in diverse populations across the spectrum of age and gender in national and international settings. (The scientific objectives C through G are of equal weight.)**

**STRATEGIES:**

- Elucidate the role of HIV infection and its associated immune dysfunction in the development of HIV-associated malignancies.
- Elucidate the role of infectious agents other than HIV, including novel pathogens, in the development of HIV-associated malignancies and develop new methodologies for novel pathogen identification.
- Define the biologic processes underlying transmission and pathogenesis of infectious pathogens associated with AIDS-related malignancies.
- Identify the mechanisms by which immune dysfunction, oncogenes, suppressor genes, carcinogens, and non-HIV viral and other microbial genes and proteins contribute to the development of HIV-associated malignancies; correlate these molecular factors with epidemiologic studies.
- Identify the characteristics of the host that modulate the risk of HIV-associated malignant disease.
- Determine the impact of AIDS-associated malignancies on the immune response to HIV.
- Determine the role played by immunologic control of infectious etiologic agents in the susceptibility to AIDS-associated malignancies.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms of HIV-related malignancies, and evaluate how the manifestations of HIV-associated malignancies are altered by such therapies.
- Determine factors associated with clinical response and lack of response to antineoplastic therapeutic intervention in HIV-infected subjects.

To facilitate the research goals listed above:

- Promote programs to facilitate the development of and augmented access to *in vivo* animal models, patient specimens for HIV-associated malignancies, sharing of key patient samples, laboratory reagents, new technologies and equipment, information databases, and quantitative virologic and immunologic assays.
- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand the etiology and pathogenesis of AIDS-related malignancies.

**OBJECTIVE - E:**

**Elucidate the mechanisms and consequences of HIV-associated neurological disease and neurobehavioral dysfunction in diverse populations across the spectrum of age and gender in national and international settings.**

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

**STRATEGIES:**

- Determine the cellular and molecular mechanisms involved in HIV-associated neurobehavioral and neurological dysfunction including:
  - ▶ identifying how HIV enters, establishes infection, spreads, and persists in the CNS;
  - ▶ examining the effects of HIV infection on specific cell populations and regions of the nervous system;
  - ▶ investigating the connection between blood-brain barrier dysfunction and neuronal injury;
  - ▶ determining the relationship of virologic, host (including the genetics of the virus/host interactions), pharmacologic, substance abuse, and environmental factors to HIV-associated neurologic dysfunction (including peripheral neuropathies);
  - ▶ determining the consequences of the biological activity of cytokines, other mediators, and their receptors on the neurologic tissue in the context of HIV infection; and
  - ▶ developing methods to monitor the levels of HIV replication and consequences of HIV infection within the CNS of living subjects.
- Determine factors associated with clinical response and lack of response to therapeutic interventions for neurologic and neurobehavioral complications of HIV disease.
- Determine the host and viral factors influencing independent evolution of drug-resistant HIV strains in the CNS compartment.
- Determine the impact of HIV/CNS infection on systemic disease progression.
- Determine the role of the CNS as a reservoir of, and sanctuary for, persistent HIV infection.
- Define mechanisms of immunologic control of HIV and OIs in the CNS.

- Develop methods to investigate, diagnose, and monitor HIV-associated neurological and neurobehavioral disorders.
- Investigate aspects of HIV infection that uniquely influence the developing nervous system.
- Delineate the role of OIs, other disease complications, and drug treatment in neurologic and neurobehavioral complications of AIDS including CNS dysfunction and peripheral neuropathies.
- Employ therapies that effectively suppress HIV replication to probe pathogenic mechanisms of HIV-associated neurologic diseases and neurobehavioral dysfunction; evaluate how the manifestations of HIV-associated neuropathogenesis are altered by such therapies.

To facilitate the research goals listed above:

- Develop and employ appropriate animal models (e.g., nonhuman primate models) of CNS-lentivirus infection that best reflect specific aspects of the human HIV/CNS disease course on treatment that are crucial to understanding neurobehavioral and neurologic disorders.
- Ensure that information, materials, and specimens needed for neuro-AIDS research are appropriately collected, catalogued, classified, stored, and distributed, and promote access to and sharing of new technologies and equipment.
- Encourage new multidisciplinary approaches to investigate HIV-associated neurological disease and neurobehavioral dysfunction.
- Improve existing and develop new technologies for biochemical markers and the imaging of neurologic dysfunction.
- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand HIV-related neurologic disease.
- Integrate neurologic studies into the design and conduct of treatment trials.

**OBJECTIVE - F:**

**Elucidate the pathogenic mechanisms and consequences of OIs and co-infections (especially HBV, HCV, TB, HPV, and GB virus C) in HIV-infected individuals in diverse populations across the spectrum of age and gender in national and international settings.  
(The scientific objectives C through G are of equal weight.)**

**STRATEGIES:**

- Conduct studies of the basic biology and pathogenic mechanisms of opportunistic pathogens and their interactions with the host, including definition of:
  - ▶ normal flora;
  - ▶ portals of entry of opportunistic pathogens into the human host;
  - ▶ processes that underlie the establishment and spread of infection; and
  - ▶ mechanisms of tissue and organ system damage.
- Identify and elucidate the genetic and environmental risk factors associated with the susceptibility to, the development of, and the progression of OIs.
- Study the effects of OIs and co-infections on immune dysfunction and HIV disease progression.
- Define immunologic responses to pathogens at mucosal surfaces and determine how they may be altered by HIV infection.
- Study how HIV infection changes the natural history and pathogenesis of the co-infecting pathogens.
- Elucidate the mechanisms of immune function that mediate protection against OIs.
- Study the effects of HIV therapy-associated immune reconstitution on the clinical course and manifestation of OIs and co-infections.
- Characterize the molecular and phylogenetic relationships of major AIDS OIs and pathogens; standardize and improve techniques of phylogenetic analysis; and integrate strain-specific characterization of data into studies of the pathogenesis, mechanisms of transmission, and epidemiology of OIs.

- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms of HIV-associated OIs, and evaluate how the causes, agents, and manifestations of these HIV-associated infections are altered by such therapies.
- Determine factors associated with clinical response and lack of response to therapeutic interventions against OIs and co-infections in HIV-infected subjects.
- Study clinical syndromes seen in HIV-infected persons that are not associated with known opportunistic pathogens in order to identify novel pathogens and characterize their biology and pathogenic mechanisms.

To facilitate the research goals listed above:

- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand the etiology and pathogenesis of HIV co-infections and HIV-related OIs.
- Develop and validate assays of opportunistic pathogen-specific immune responses.
- Develop *in vitro* techniques and animal models to propagate and define the life cycles of the opportunistic pathogens associated with HIV disease.
- Develop and validate diagnostic assays for the reliable and rapid identification of HIV-associated OIs.

**OBJECTIVE - G:**

**Elucidate the etiology, pathogenesis, and consequences of HIV-related organ-specific disorders in diverse populations across the spectrum of age and gender in national and international settings.**

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

**STRATEGIES:**

- Investigate the etiologic and pathogenic mechanisms and consequences of HIV-associated:
  - ▶ gastrointestinal, including liver and biliary, diseases,
  - ▶ nephropathy,
  - ▶ endocrine dysfunction,
  - ▶ hematologic disorders,
  - ▶ pulmonary disorders,
  - ▶ autoimmune disorders,
  - ▶ cardiac and vascular disease,
  - ▶ cutaneous disease,
  - ▶ oral disease, and
  - ▶ other organ/tissue-specific disorders.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms of HIV-related organ/tissue-specific complications, and evaluate how the manifestations of HIV-related organ/tissue-specific complications are altered by such therapies.
- Determine factors associated with clinical response and lack of response to therapeutic interventions against HIV-related disorders.
- Employ animal models to investigate the etiology and pathogenesis of lentivirus-associated disorders in the above systems.

To facilitate the research goals listed above:

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

**APPENDIX A:**

**NIH Institutes and Centers**



## NIH INSTITUTES AND CENTERS

<b>NCI</b>	National Cancer Institute
<b>NEI</b>	National Eye Institute
<b>NHLBI</b>	National Heart, Lung, and Blood Institute
<b>NHGRI</b>	National Human Genome Research Institute
<b>NIA</b>	National Institute on Aging
<b>NIAAA</b>	National Institute on Alcohol Abuse and Alcoholism
<b>NIAMD</b>	National Institute of Allergy and Infectious Diseases
<b>NIAMS</b>	National Institute of Arthritis and Musculoskeletal and Skin Diseases
<b>NIBIB</b>	National Institute of Biomedical Imaging and Bioengineering
<b>NICHD</b>	National Institute of Child Health and Human Development
<b>NIDCD</b>	National Institute on Deafness and Other Communication Disorders
<b>NIDCR</b>	National Institute of Dental and Craniofacial Research
<b>NIDDK</b>	National Institute of Diabetes and Digestive and Kidney Diseases
<b>NINDS</b>	National Institute of Neurological Disorders and Stroke
<b>NIDA</b>	National Institute on Drug Abuse
<b>NIEHS</b>	National Institute of Environmental Health Sciences
<b>NIGMS</b>	National Institute of General Medical Sciences
<b>NIMH</b>	National Institute of Mental Health
<b>NINR</b>	National Institute of Nursing Research
<b>NLM</b>	National Library of Medicine
<b>CC</b>	Warren Grant Magnuson Clinical Center
<b>CIT</b>	Center for Information Technology
<b>NCCAM</b>	National Center for Complementary and Alternative Medicine
<b>NCRR</b>	National Center for Research Resources
<b>FIC</b>	John E. Fogarty International Center
<b>CSR</b>	Center for Scientific Review
<b>NCMHD</b>	National Center on Minority Health and Health Disparities



**APPENDIX B:**

FY 2005 OAR

Planning Group for  
Etiology and Pathogenesis



## FY 2005 ETIOLOGY AND PATHOGENESIS PLANNING GROUP

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**APPENDIX C:**

List of Acronyms



## LIST OF ACRONYMS

<b>ACSR</b>	AIDS and Cancer Specimen Resource, NCI
<b>ACTIS</b>	AIDS Clinical Trials Information Service
<b>AIDS</b>	acquired immunodeficiency syndrome
<b>AITRP</b>	AIDS International Training and Research Program, FIC
<b>ART</b>	antiretroviral therapy
<b>ARV</b>	antiretroviral
<b>ATI</b>	analytic treatment interruption
<b>ATIS</b>	AIDS Treatment Information Service
<b>AVEG</b>	AIDS Vaccine Evaluation Group
<b>BSL</b>	biosafety level
<b>B/START</b>	Behavioral Science Track Award for Rapid Transition
<b>CAB</b>	community advisory board
<b>CAPS</b>	Center for AIDS Prevention Studies (University of California, San Francisco)
<b>CBO</b>	community-based organization
<b>CDC</b>	Centers for Disease Control and Prevention
<b>CIPRA</b>	Comprehensive International Programs for Research on AIDS
<b>CMV</b>	cytomegalovirus
<b>CNS</b>	central nervous system
<b>CSF</b>	cerebrospinal fluid
<b>CTL</b>	cytotoxic T lymphocyte
<b>DC</b>	dendritic cell
<b>DHHS</b>	Department of Health and Human Services
<b>EBV</b>	Epstein-Barr virus
<b>FDA</b>	Food and Drug Administration
<b>GBV-C</b>	GB virus (hepatitis G)
<b>GCP</b>	Good Clinical Practices
<b>GCRC</b>	General Clinical Research Center
<b>GFATM</b>	Global Fund for AIDS, Tuberculosis, and Malaria

<b>GI</b>	gastrointestinal
<b>GLP/GMP</b>	good laboratory practice/good manufacturing practice
<b>GRIP</b>	Global Health Research Initiative Program, FIC
<b>HAART</b>	highly active antiretroviral therapy
<b>HBCU</b>	Historically Black Colleges and Universities
<b>HBV</b>	hepatitis B virus
<b>HCV</b>	hepatitis C virus
<b>HHV</b>	human herpesvirus
<b>HIV</b>	human immunodeficiency virus
<b>HPV</b>	human papillomavirus
<b>HSV</b>	herpes simplex virus
<b>HVTN</b>	HIV Vaccine Trials Network
<b>IC</b>	Institute and Center
<b>ICC</b>	invasive cervical cancer
<b>IDU</b>	injecting drug user
<b>IND</b>	investigational new drug
<b>IRB</b>	institutional review board
<b>IUD</b>	intrauterine device
<b>JCV</b>	JC virus
<b>KS</b>	Kaposi's sarcoma
<b>KSHV</b>	Kaposi's sarcoma herpesvirus
<b>LRP</b>	Loan Repayment Program, NIH
<b>MAb</b>	monoclonal antibody
<b>MAC</b>	<i>Mycobacterium avium</i> complex
<b>MDR-TB</b>	multidrug-resistant tuberculosis
<b>MHC</b>	major histocompatibility complex
<b>MSM</b>	men who have sex with men
<b>MTCT</b>	mother-to-child transmission
<b>NAFEO</b>	National Association for Equal Opportunity in Higher Education
<b>NGO</b>	nongovernment organization

<b>NHL</b>	non-Hodgkin's lymphoma
<b>NHP</b>	nonhuman primate
<b>NIH</b>	National Institutes of Health
<b>NK</b>	natural killer (cell)
<b>NMAC</b>	National Minority AIDS Council
<b>NNTC</b>	National NeuroAIDS Tissue Consortium, NIMH/NIDA/NINDS
<b>NRTIs</b>	nucleoside reverse transcriptase inhibitors
<b>OAR</b>	Office of AIDS Research, NIH
<b>OARAC</b>	Office of AIDS Research Advisory Council
<b>OD</b>	Office of the Director, NIH
<b>OI</b>	opportunistic infection
<b>PACTG</b>	Pediatric AIDS Clinical Trials Group
<b>PCP</b>	<i>Pneumocystis carinii</i> pneumonia
<b>PML</b>	progressive multifocal leukoencephalopathy
<b>RCT</b>	randomized clinical trial, randomized controlled trial
<b>RNA</b>	ribonucleic acid
<b>RPRC</b>	Regional Primate Research Center
<b>SCID</b>	severe combined immunodeficiency
<b>SHIV</b>	chimeric simian/human immunodeficiency virus
<b>SIT</b>	scheduled intermittent therapy
<b>SIV</b>	simian immunodeficiency virus
<b>SPF</b>	specific pathogen-free
<b>STD</b>	sexually transmitted disease
<b>STI</b>	structured treatment interruption; sexually transmitted infection
<b>TB</b>	tuberculosis
<b>UNAIDS</b>	Joint United Nations Programme on HIV/AIDS
<b>USAID</b>	U.S. Agency for International Development
<b>VRC</b>	Vaccine Research Center
<b>WHO</b>	World Health Organization
<b>WIHS</b>	Women's Interagency HIV Study
<b>WRAIR</b>	Walter Reed Army Institute of Research



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