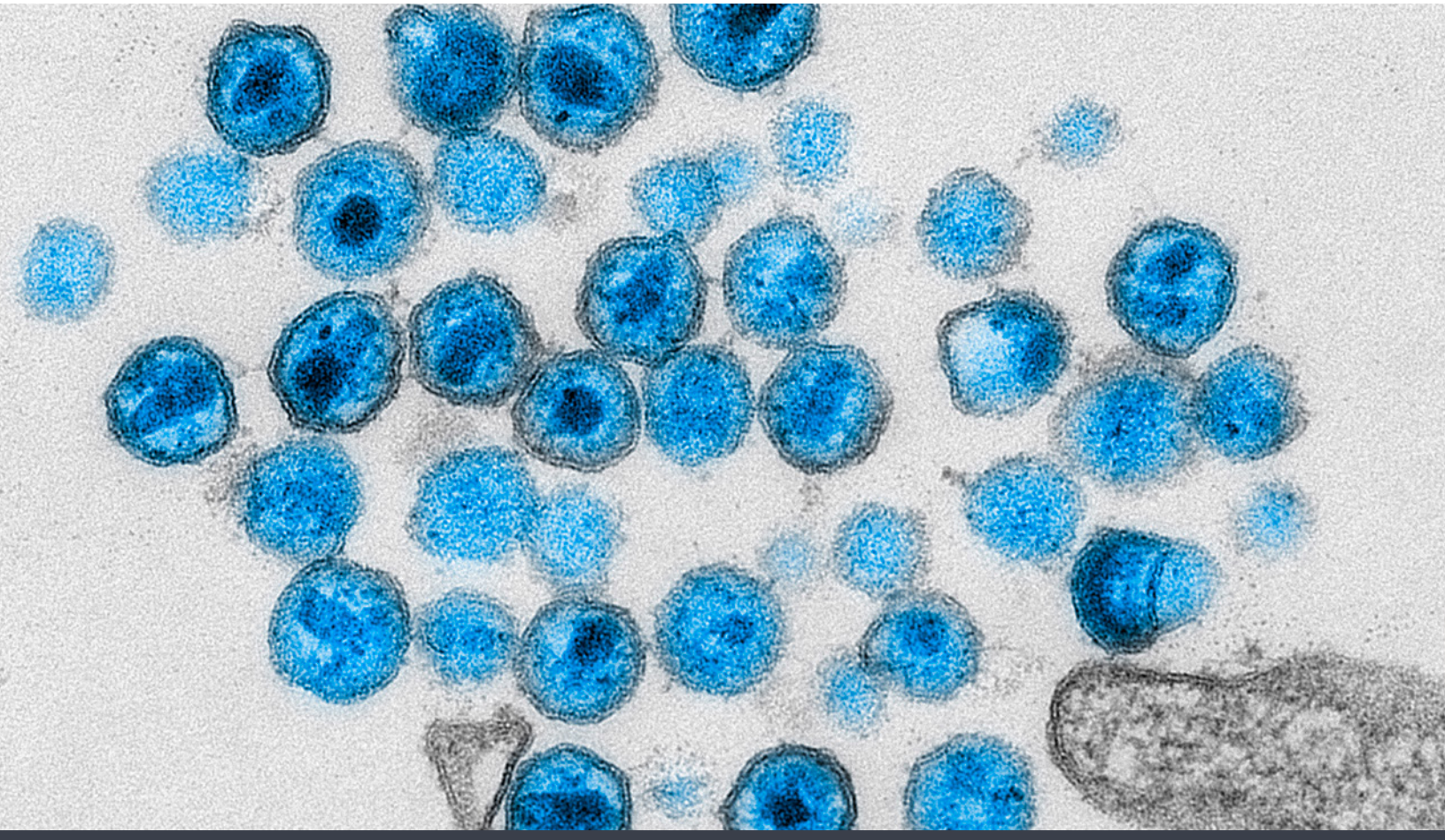
FY 2015

National Institutes of Health

TRANS-NIH PLAN FOR HIV-RELATED RESEARCH



Prepared by the Office of AIDS Research
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Dedicated to the Memory of

SPENCER COX

1968–2012

An AIDS pioneer, treatment activist, research advocate, and friend.

Spencer brought a unique energy and commitment to help us build an AIDS research program that is responsive to the epidemic, based on the most promising science, and inclusive of the voices of the community.

He advocated for the highest possible scientific standards for clinical trials to provide clear and useful information for the trial participants and for HIV-infected individuals who may benefit from the research in the future.

His voice will be missed.

FY 2015 Trans-NIH Plan for HIV-Related Research

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FY 2015 Trans-NIH Plan for HIV-Related Research

Legislative Mandate

Section 2353 of the Public Health Service Act requires that the Director of OAR shall: (1) establish a comprehensive plan for the conduct and support of all AIDS activities of the agencies of the NIH; (2) ensure that the Plan establishes priorities among the AIDS activities that such agencies are authorized to carry out; (3) ensure that the Plan establishes objectives regarding such activities; (4) ensure that all amounts appropriate for such activities are expended in accordance with the Plan; (5) review the Plan not less than annually, and revise the Plan as appropriate; and (6) ensure that the Plan serves as a broad, binding statement of policies regarding AIDS activities of the agencies, but does not remove the responsibility of the heads of the agencies for the approval of specific programs or projects, or for other details of the daily administration of such activities, in accordance with the Plan. The law also specifically requires that the Plan provide for basic research, applied research, research conducted by the NIH, research supported by the NIH, proposals developed pursuant to solicitations by the NIH and investigator-initiated proposals, and behavioral and social sciences research. In accordance with the law, the NIH Office of AIDS Research, a component of the NIH Office of the Director, has developed this document.

Introduction

Overview

In the three decades since AIDS was first reported, the National Institutes of Health (NIH) has been the global leader in research to understand, prevent, diagnose, and treat HIV and its many related conditions. Recent scientific advances resulting from NIH-funded research represent a turning point for AIDS research. New avenues for discovery have been identified, providing possibilities for the development of new strategies to prevent, treat, and potentially cure HIV. The NIH is leading global research efforts to capitalize on those advances, move science forward, and begin to turn the tide against this pandemic.

NIH research has resulted in landmark advances that have led to:

- *Co-discovery of HIV*, the virus that causes AIDS;
- *Development of the first blood test for the disease,* which has allowed diagnosis of infection as well as ensured the safety of the blood supply;
- *The critical discovery of key targets to develop antiretroviral therapy (ART) and multidrug regimens* that have resulted in improved life expectancy for those with access to and who can tolerate these drugs; and the development of treatments for many HIV-associated coinfections, comorbidities, malignancies, and clinical manifestations, with benefits for patients also suffering from those other diseases;
- *Groundbreaking strategies for the prevention of mother-to-child transmission,* which have resulted in dramatic decreases in perinatal HIV in the United States and in low-income countries;
- Demonstration that the *use of medical male circumcision can reduce the risk of HIV acquisition;*
- The first step in *proving the concept that a vaccine to prevent HIV infection is feasible*; and discovery of two potent human antibodies that can stop more than 90 percent of known global HIV strains from infecting human cells in the laboratory;
- Demonstration of the *first proof of concept for the feasibility of a microbicide gel capable of preventing HIV transmission*;
- Demonstration that the *use of therapy by infected individuals can dramatically reduce transmission* to an uninfected partner;
- Demonstration of the *potential feasibility of pre-exposure prophylaxis (PrEP)*, that long-term use of ART regimens by some groups of high-risk uninfected individuals can reduce risk of HIV acquisition;
- Discovery *that genetic variants may play a role in protecting some individuals*, known as "elite controllers," who have been exposed to HIV over an extended period, from developing symptoms and enabling them to control the infection without therapy;
- Critical *basic science discoveries* that continue to provide the foundation for novel research; and
- *Progress in both basic and treatment research efforts aimed at eliminating viral reservoirs in the body*, which is, for the first time, leading scientists to design and conduct research aimed at a cure.

NIH intramural and extramural researchers have produced two new exciting advances. NIH researchers published the results of studies utilizing potent human neutralizing antibodies that successfully suppressed a form of HIV in primates. This important research could potentially result in a new form of treatment for HIV that could be used as an adjunct to ART and could lead to opportunities for novel research to treat and potentially cure HIV. NIH-sponsored researchers also have made tremendous strides in producing and analyzing proteins that may provide an important new pathway in AIDS vaccine design.

The NIH is leading global research efforts to capitalize on all of these advances, move science forward, and begin to turn the tide against this pandemic.

HIV/AIDS Pandemic

Despite this progress, the HIV/AIDS pandemic will remain the most serious global public health crisis of our time. The Joint United Nations Programme on HIV/AIDS (UNAIDS) reports that in 2013:

- More than 35 million people were estimated to be living with HIV/AIDS.
- About 2.1 million people became HIV-infected (about half of them women), or about 6,000 infected per day.
- 1.5 million people died of AIDS-related illnesses.

In the United States, HIV/AIDS continues to be an unrelenting public health crisis, disproportionately affecting racial and ethnic populations, women of color, young adults, and men who have sex with men. The Centers for Disease Control and Prevention (CDC) estimates that:

- Approximately 1.1 million people are HIV-infected.
- Approximately 50,000 new infections occur each year.
- One in four people living with HIV infection in the United States is female.

NIH AIDS Research Program

To address this pandemic, the NIH conducts and supports a comprehensive program of basic, clinical, translational, and behavioral research on HIV infection and its associated coinfections, opportunistic infections, malignancies, and other complications. AIDS research is carried out by all of the NIH Institutes and Centers (ICs) in accordance with their mission, in both intramural and extramural programs.

Key NIH Institutes and Centers Conducting AIDS Research

NATIONAL CANCER INSTITUTE: The National Cancer Institute (NCI) supports and conducts a broad range of research on HIV/AIDS, with a focus on AIDS-associated and non-AIDS-defining malignancies. NCI scientists co-discovered HIV and proved that the virus caused AIDS; developed the first blood test for HIV, which permits diagnosis of the disease and ensures the safety of the blood supply; conducted clinical trials of the first AIDS drugs; and developed the technology for the first vaccine for human papillomavirus (HPV), which can protect against cervical cancer (an AIDS-defining cancer) and other cancers. While the development of anti-HIV therapy has lowered the incidence of AIDS-defining cancers substantially, the number of non-HIV-defining cancers has been increasing as people infected with HIV live longer and the HIV-infected population overall increases in age. Cancer is now one of the leading causes, if not the leading cause, of death for people infected with HIV. NCI supports a wide range of basic, translational, and clinical research on malignancies associated with HIV infection, including research initiatives to address the increasing number of AIDS-defining malignancies in the developing world.

NIH AIDS RESEARCH PROGRAM

- Largest public investment in AIDS research in the world
- Encompasses all NIH Institutes and Centers
- Transcends every area of clinical medicine and basic scientific investigation
- Comprehensive program of basic, clinical, behavioral, and translational research on HIV infection, its associated coinfections, opportunistic infections, malignancies, and other complications
- Research or training projects in more than 100 countries
- Unprecedented trans-NIH scientific coordination and management of research funds

NATIONAL EYE INSTITUTE: The National Eye Institute (NEI) supports research on HIV-associated ophthalmic disorders, such as retinitis caused by cytomegalovirus (CMV) infection, and potential therapies for these disorders. Blindness is one of the many complications of HIV infection and AIDS. NEI also supports studies on the possible development of ocular toxic effects related to the treatment of HIV infection, as well as research on ocular comorbidities associated with HIV, such as herpes simplex virus.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE: As the HIV population ages, there has been a rise in the prevalence of chronic HIV-related cardiovascular, lung, and blood diseases. The mission of the National Heart, Lung, and Blood Institute (NHLBI) AIDS program is to support and facilitate research and training to address the emerging medical challenges facing the evolving HIV population. NHLBI is particularly interested in

encouraging collaboration between HIV specialists and heart, lung, and blood specialists to further expand knowledge about HIV-associated coronary artery disease, heart failure, hypertension, sudden cardiac death, smoking cessation, chronic obstructive lung disease, and pulmonary hypertension.

NATIONAL INSTITUTE ON AGING: The National Institute on Aging (NIA) works to improve the care of older adults with HIV/AIDS. The increasing prevalence of HIV in older Americans is due in large part to the improved survival of individuals receiving therapy and to ongoing new infections in older adults. Older adults with HIV are at risk of developing a variety of comorbid conditions, including cardiovascular disease, dyslipidemia, insulin resistance, and diabetes. NIA research addresses aging-related factors that contribute to the pathogenesis, disease progression, treatment, quality of life, and access to care among older HIV-infected individuals.

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM: The National Institute on Alcohol Abuse and Alcoholism (NIAAA) supports epidemiologic, behavioral, and biomedical research exploring the complex and intertwined issues of alcohol abuse and HIV/AIDS. NIAAA supports research to understand the ecology and clinical epidemiology of alcohol use, abuse, and dependence in HIV-infected populations; understand the role of alcohol in disease progression and premature mortality related to co-occurring disease processes such as organ and tissue inflammation and immune response; develop and test interventions to decrease risky sexual and substance use behaviors and disseminate interventions in a wide range of settings; and improve medication adherence in alcohol-using and -abusing HIV-infected persons.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES: The National Institute of Allergy and Infectious Diseases (NIAID) is the largest Federal institute for HIV/AIDS research. NIAID conducts and supports an extensive range of basic and clinical domestic and international research to better understand HIV and how it causes disease; find new tools to prevent HIV infection, including a preventive vaccine, a microbicide, and treatment as prevention strategies; develop new and more effective treatments for people infected with HIV and related coinfections and comorbidities; and conduct research that can one day lead to a cure for HIV infection.

A key component of the NIH intramural program is the Dale and Betty Bumpers Vaccine Research Center (VRC). The primary focus of research is the development of vaccines for AIDS, but the VRC also is working on vaccines for other diseases, including Ebola virus, Marburg virus, and influenza. The VRC conducts a comprehensive program of research on the NIH intramural campus and works with scientists in academic, clinical, and industrial laboratories through a program of national and international collaborations. The potential scientific advances, methodologies, and resources also will provide the basis for research on vaccines for other diseases.

NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES: The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports research on skin immunity and integrity and chronic diseases of muscle and bone related to HIV-associated comorbidities and inflammatory conditions. Advances in degenerative muscle and bone conditions are particularly relevant to an aging HIV-AIDS patient population. NIAMS-sponsored HIV-related research includes studies on barrier and immune function in skin, which may provide important insights into the ability of HIV to enter the body through mucosal tissues and establish infection; the molecular mechanisms of muscle degeneration in HIV-infected and aging populations, and how it may be reversed; and the effects of HIV infection, ART, and aging on bones.

EUNICE KENNEDY SHRIVER NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT: The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) supports and conducts research related to the unique features of HIV infection and AIDS in women, pregnant women, infants, children, adolescents, young adults, and families. Areas of focus for NICHD research include investigation of the biologic mechanisms of sexual transmission of HIV in the female genital tract; HIV interaction with endogenous and exogenous hormones; demographic and population-based studies related to sexual behavior; the interrelationship between HIV, pregnancy, and contraception; and research on HIV orphans and vulnerable children.

NATIONAL INSTITUTE OF DENTAL AND CRANIOFACIAL RESEARCH: The National Institute of Dental and Craniofacial Research (NIDCR) supports studies on the oral manifestations and oral malignancies of HIV/AIDS. HIV-related oral opportunistic infections, coinfections, and malignancies represent early diagnostic indicators of HIV infection, disease progression, immunosuppression, optimal or suboptimal therapies, drug resistance, and treatment compliance. The NIDCR AIDS and Immunosuppression Program supports global, basic, translational, and clinical research.

NATIONAL INSTITUTE ON DRUG ABUSE: The National Institute on Drug Abuse (NIDA) supports a broad range of research to reduce the spread of HIV among drug abusers and their partners and to minimize the associated health and social consequences of the disease both domestically and internationally. Drug and alcohol intoxication is linked with increased HIV risk behavior, and injection and noninjection drug use continues to contribute significantly to the spread of HIV.

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES: The National Institute of General Medical Sciences (NIGMS) supports research to answer critical scientific questions in cell biology, biophysics, genetics, developmental biology, pharmacology, physiology, biological chemistry, biomedical technology, bioinformatics, and computational biology, along with selected aspects of the behavioral sciences. NIGMS supports the structural characterization of HIV enzymes and viral proteins, which has been instrumental in the development of antiretroviral (ARV) drug therapies, such as protease inhibitors. NIGMS continues to support the characterization of viral proteins and is expanding its program to include cellular and viral complexes.

NATIONAL INSTITUTE OF MENTAL HEALTH: The National Institute of Mental Health (NIMH) supports a broad range of AIDS-related research. NIMH sponsors studies on the basic neuroscience of HIV infection, including research to elucidate the mechanisms underlying HIV-induced neuropath genesis; understand HIV-related motor and cognitive impairments; develop novel treatments to prevent or mitigate the neurobehavioral complications of HIV infection; and minimize the neurotoxicities induced by long-term use of ART. Eradication of the virus from HIV-infected individuals to achieve a cure or a functional cure is a high research priority. NIMH behavioral science research targets prevention of HIV transmission and acquisition, adherence to interventions to reduce the burden of disease, and studies that address the behavioral consequences of HIV/AIDS.

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE: The National Institute of Neurological Disorders and Stroke (NINDS) supports basic, translational, and clinical research on the effects of chronic HIV infection and comorbidities on the central nervous system. NINDS-supported research includes studies of HIV-associated peripheral neuropathy; progressive multifocal leukoencephalopathy; cryptococcal meningitis;

cytomegalovirus infection; herpes virus infections; neuropathy; neurosyphilis; HIV-related psychological and neuropsychiatric disorders; and the effects of ART on the nervous system. Studies to define and elucidate novel mechanisms of pathogenesis that are driving neurocognitive decline at the intersection of HIV-associated neurodegenerative processes, aging-associated central nervous system disease, chronic highly active antiretroviral therapy (HAART) treatment effects, and host susceptibility factors also are priorities.

NATIONAL INSTITUTE OF NURSING RESEARCH: The National Institute of Nursing Research (NINR) sponsors domestic and international HIV/AIDS research focused on health promotion, disease prevention, and symptom management, including approaches to reduce HIV risk, develop and implement culturally appropriate HIV prevention education for adolescents, and overcome barriers to prevention in the United States and developing countries. NINR is focused on research to promote health and quality of life and prevention strategies across the course of HIV/AIDS disease, particularly in areas of symptom mechanism(s), biobehavioral interventions, prevalence disparity, age-related decisionmaking, and palliative and end-of-life care.

NATIONAL LIBRARY OF MEDICINE: The National Library of Medicine (NLM) works to translate biomedical research into practice. NLM's electronic information services deliver trillions of bytes of data to millions of users, including scientists, health professionals, and the public in the United States and around the globe every day. NLM's information resources include AIDSinfo—a service of the U.S. Department of Health and Human Services, managed by NLM with support from OAR and NIAID—that offers access to the latest, federally approved HIV/AIDS medical practice guidelines, HIV treatment and prevention clinical trials, and other research information for health care providers, researchers, people affected by HIV/AIDS, and the general public. In addition, NLM supports MEDLINE®/PubMed®, PubMed Central®, MedlinePlus®, and Medline Plus en español. MedlinePlus includes a series of HIV/AIDS-specific pages in English and Spanish. ClinicalTrials.gov provides the public with comprehensive information about all types of clinical research studies.

CENTER FOR SCIENTIFIC REVIEW: The Center for Scientific Review (CSR) ensures that NIH grant applications receive fair, independent, expert, and timely reviews. CSR organizes peer review groups composed of experienced and respected researchers from across the country and abroad that evaluate the majority of NIH grant applications for their scientific merit. These reviews allow NIH to fund the most scientifically promising research. All AIDS-related grant applications are reviewed by a study section or special emphasis panel within the AIDS and Related Research (AARR) Integrated Review Group on an expedited cycle mandated by Congress. AARR reviews grant applications in the areas of basic, translational, clinical, and behavioral aspects of HIV/AIDS research.

FOGARTY INTERNATIONAL CENTER: The Fogarty International Center (FIC) is the NIH focal point for international cooperation in biomedical research, facilitating the global exchange of ideas and collaborative research. FIC builds partnerships between health research institutions in the United States and in low- and middle-income countries to support and facilitate basic, clinical, and applied research and research training for investigators interested in addressing the global HIV pandemic. With co-funding from other NIH Institutes, Centers, and Offices, FIC provides support to HIV-related research and to the development of multidisciplinary biomedical and behavioral and social science research capacity for the prevention, care, and treatment of HIV/AIDS and HIV-related conditions for adults and children in low- and middle-income countries. The Fogarty HIV Research Training Program strengthens the capacity of researchers and institutions in low- and middle-income countries to conduct HIV-related research in their countries and to compete independently for research funding.

OFFICE OF RESEARCH INFRASTRUCTURE PROGRAMS: The Office of Research Infrastructure Programs (ORIP), a component of the Division of Program Coordination, Planning, and Strategic Initiatives in the NIH Office of the Director, supports the NIH's research infrastructure and research-related resources programs and coordinates the NIH's science education efforts. ORIP's infrastructure programs are designed to ensure that NIH effectively addresses and coordinates important areas of emerging scientific opportunities. The eight National Primate Research Centers and other ORIP-funded primate resources provide comprehensive support for investigators engaged in HIV/AIDS research using nonhuman primates, including studies of mechanisms of pathogenesis and development of vaccines and microbicides. ORIP also funds cooperative agreements that support a consortium of specific pathogen-free macaque breeding colonies that provide animals to investigators studying many aspects of HIV/AIDS.

NIH Office of AIDS Research

The Office of AIDS Research (OAR) *(http://www.oar.nih.gov/),* established in 1988, has unique legislative authorities unlike any other NIH entity to plan, coordinate, evaluate, and budget the entire NIH AIDS research program, which represents approximately 10 percent of the total NIH budget—the largest and most significant public investment in AIDS research in the world. OAR serves as the principal liaison with the U.S. Department of Health and Human Services, other Federal agencies, and domestic and international governmental and nongovernmental organizations on behalf of NIH AIDS-related research.

OAR serves as a model of trans-NIH planning and management, operating as an "Institute without walls," vested with primary responsibility for overseeing all NIH AIDS-related research, and thus allowing the NIH to pursue a united research front against the global AIDS epidemic.

AIDS research thoroughly transcends every area of clinical medicine and basic scientific investigation, crossing the boundaries of every Institute and Center (IC). This diverse research portfolio demands an unprecedented level of trans-NIH scientific coordination and management of research funds. OAR coordinates the scientific, budgetary, legislative, and policy elements of the NIH AIDS research portfolio and sets the trans-NIH scientific priorities for this large and diverse program. Utilizing its legislative authorities, OAR has established comprehensive trans-NIH planning, budgeting, and portfolio analysis processes to identify the highest priority areas of scientific opportunity, enhance collaboration, minimize duplication, and ensure that precious research dollars are invested effectively and efficiently.

OFFICE OF AIDS RESEARCH MISSION

Establish a unified NIH research agenda to address the AIDS pandemic through:

- Annual trans-NIH strategic planning process to identify highest scientific priorities and opportunities to address changing epidemic
- Annual trans-NIH budget based on Strategic Plan
- Trans-NIH coordination, management, and evaluation
- Facilitation and implementation of domestic and international collaborative AIDS research agreements

OAR identifies emerging scientific opportunities and public health challenges that require focused attention; manages and facilitates multi-Institute and trans-Institute activities to address those needs; fosters research by designating funds and supplements to jump-start or pilot program areas; sponsors reviews or evaluations of research program areas; and facilitates international AIDS research and training. OAR's unique budget authorities also allow it to transfer funds across ICs and across scientific areas.

OAR supports a number of initiatives to enhance dissemination of research findings to researchers, physicians, institutions, communities, constituency groups, and patients. OAR also has placed high priority on research and community outreach initiatives to address the disproportionate impact of the epidemic on racial and ethnic minority communities in the United States.

Trans-NIH Strategic Plan

Each year, OAR develops the Trans-NIH Plan for HIV-Related Research *(http://www.oar.nih.gov/strategicplan)*. The Plan is developed in collaboration with scientists from the NIH Institutes and Centers (ICs), other Government agencies, and nongovernmental organizations, as well as community representatives. During the planning process, the state of the science is reviewed, newly emerged and critical public health needs are assessed, and scientific opportunities are identified. The annual process culminates with the identification of the highest strategic priorities and critical research needs in each of the following scientific areas: Natural History and Epidemiology; Etiology and Pathogenesis; Microbicides; Vaccines; Behavioral and Social Science; Therapeutics; Treatment as Prevention; Training, Infrastructure, and Capacity Building; and Information Dissemination. Research Toward a Cure was added several years ago as a new scientific area of emphasis. The Plan also addresses research in special populations, including Women and Girls, Racial and Ethnic Populations, and Research in International Settings.

To facilitate tracking and analysis, OAR requires ICs to report all AIDS-related expenditures, including extramural, intramural, and research management and support, on a quarterly basis, to the OAR trans-NIH AIDS Research Information System (ARIS) database. Expenditures are coded by the ICs to the objective(s) of the Plan. This database also serves as the primary resource for AIDS research information in the Research Conditions and Diseases Categorization (RCDC) system.

THE STRATEGIC PLAN IS A UNIQUE AND CRITICAL DOCUMENT THAT SERVES AS THE FRAMEWORK FOR:

- Developing the annual AIDS research budget for each IC
- Determining the use of AIDS-designated dollars
- Developing the annual Presidential by-pass budget
- Tracking and monitoring all NIH AIDS research expenditures

OAR PLANNING PROCESS PARTICIPANTS

- Trans-NIH Coordinating Committees
- NIH ICs
- Other Government entities with research responsibilities (CDC, FDA, USAID, VA, DoD, HRSA, IHS)*
- Nongovernment experts from academia and foundations
- Community representatives
- Office of AIDS Research Advisory Council

* These Federal Government agencies are the Centers for Disease Control and Prevention, the Food and Drug Administration, the U.S. Agency for International Development, the Department of Veterans Affairs, and the Department of Defense, respectively.

OAR Budget Development Process

OAR is mandated to develop the annual trans-NIH AIDS research budget in partnership with the Institute and Centers (ICs) and explicitly tied to the objectives of the Strategic Plan. The law provides that OAR "shall receive directly from the President and Director of the OMB all funds available for AIDS activities of the NIH" for allocation to the ICs in accordance with the Plan.

Subsequently, however, an agreement with Congress established the tradition that rather than receiving a separate single appropriation, OAR would determine each IC's AIDS research allocation to be included within the IC total appropriation. It also was agreed that AIDS and non-AIDS research would grow at approximately the same rate, that is, as an "Institute without walls"; AIDS research, as determined by OAR, would grow at the same rate as the other Institutes. Thus, AIDS research has historically represented approximately 10 percent of the total NIH budget.

For all appropriated funds, the OAR Director and the NIH Director determine the total amount to be allocated for AIDS-related research within the overall NIH budget. Within that total, OAR develops each IC's allocation. The ICs submit their AIDS-related research budget requests to OAR, presenting proposed new, expanded, or recompeting program initiatives, coded to specific Plan objective(s). OAR reviews the IC initiatives in relation to the Plan, its priorities, and to other IC submissions to eliminate redundancy and/or to ensure cross-Institute collaboration. The unique budget authorities allow OAR to build each IC budget from the commitment base, rather than from the previous year's appropriation.

OAR BUDGET DEVELOPMENT PROCESS

1. ICs develop new or expanded program initiatives with budget requests for each scientific area.
2. OAR reviews IC initiatives in relation to the Plan and OAR priorities.
3. Consultations occur between the ICs and OAR throughout the process.
4. The budget is developed in consultation between the OAR Director and the NIH Director.
5. OAR allocates budget levels to each IC.

The careful determination of the balance of the research budget—among Institutes, across areas of science, between intramural and extramural research programs, between basic and clinical research, and between investigator-initiated and targeted research—requires a comprehensive knowledge of the science and of the ICs' portfolios. Dollars are allocated to the ICs based on the priorities of the Plan, scientific opportunities, and the ICs' capacity to absorb and expend resources for the most meritorious science—not on a formula. This process reduces redundancy, promotes harmonization, and ensures cross-Institute collaboration. At the time of the appropriation, OAR informs each IC of its AIDS-related budget allocation, specifying amounts for each approved initiative. OAR also has a 3 percent transfer authority to move dollars across ICs during the fiscal year.

Extraordinary Opportunities for FY 2015

This strategic Plan establishes the critical priorities for trans-NIH AIDS research. The advances made by NIH intramural scientists and extramural investigators have opened doors for new and exciting research opportunities to answer key scientific questions that remain in the search for strategies to prevent and treat HIV infection both in the United States and around the world. These advances also represent the building blocks for the development of the trans-NIH AIDS research budget.

The key scientific priorities for NIH AIDS research address the goals of the President's National HIV/AIDS Strategy as well as the HIV Care Continuum Initiative established by Presidential Executive Order. The priorities also are aligned with the NIH Director's themes.

In FY 2015, OAR will place highest priority on the following key areas:

- Basic research on HIV that will underpin further development of critically needed prevention methodologies, including vaccines.
- Innovative multidisciplinary research and international collaborations to develop novel approaches and strategies to eliminate viral reservoirs that could lead toward a cure or lifelong remission of HIV infection, including studies on viral persistence, latency, reactivation, and eradication.
- Research to develop better, less toxic treatments and to investigate how genetic determinants, sex, gender, race, age, nutritional status, treatment during pregnancy, and other factors—including adherence and stigma—interact to affect treatment success or failure and/or disease progression.
- Studies to address the increased incidence of comorbidities, including AIDS-associated malignancies; cardiovascular, neurological and metabolic complications; and premature aging associated with long-term HIV disease and antiretroviral therapy (ART).

Specific programmatic areas include:

ETIOLOGY AND PATHOGENESIS

The NIH supports a comprehensive portfolio of research focused on the transmission, acquisition, establishment, and maintenance of HIV infection and the causes of its associated profound immune deficiency and severe clinical complications. Research on basic HIV biology and AIDS pathogenesis has revolutionized the design of drugs, methodologies for diagnosis of HIV infection, and tools for monitoring disease progression and the safety and effectiveness of antiviral therapies. Groundbreaking strides have been made toward understanding the fundamental steps in the life cycle of HIV, the host–virus interactions, and the clinical manifestations associated with HIV infection and AIDS. Additional research is needed to further the understanding of the virus and how it causes disease, including studies to delineate how sex, gender, age, ethnicity, race, pregnancy, nutritional status, and other factors interact to influence vulnerability to infection and disease progression; determine the role of immune dysfunction and chronic inflammation in HIV pathogenesis; and further the understanding of

the development of HIV-associated comorbidities, such as cardiovascular, neurological, and other clinical complications, malignancies, and coinfections (including tuberculosis and hepatitis C).

Research examining the genetic determinants associated with HIV susceptibility, disease progression, and treatment response also is needed. These studies may lead to the development of customized therapeutic and preventive regimens formulated for an individual patient based on his or her genetic sequence. The NIH also prioritizes research examining the mechanisms by which HIV establishes and reactivates latent reservoirs of infection and studies that further the understanding of factors that are associated with the ability of the host to restrict HIV infection and/or mitigate HIV disease progression. A better understanding of these processes could help identify key targets for the development of new therapeutic and vaccine strategies to prevent or control HIV infection and possibly lead to a cure for HIV disease.

RESEARCH TOWARD A CURE

Research related to the potential for a cure or lifelong remission of HIV infection is a key NIH research priority, which currently involves research across a number of areas. The NIH plans to increase this area of research over the next 3 fiscal years focused on:

- **Pathogenesis studies:** Basic research on viral reservoirs, viral latency, and viral persistence, including studies on genetic factors associated with reactivation of the virus and other barriers to HIV eradication.
- **Animal models:** Identification and testing of various animal and cellular models to mimic the establishment and maintenance of viral reservoirs. These studies are critical for testing novel or unique strategies for HIV reactivation and eradication.
- **Drug development and preclinical testing:** Programs to develop and preclinically test new and better antiretroviral (ARV) compounds capable of entering viral reservoirs, including the central nervous system and brain.
- **Clinical trials:** Studies to evaluate lead compounds, drug regimens, and immune-based strategies capable of a sustained response to HIV, including clinical studies of drugs and novel approaches capable of eradicating HIV-infected cells and tissues.
- **Therapeutic vaccines:** Design and testing of vaccines that would be capable of suppressing viral replication and preventing disease progression.
- **Adherence/compliance:** Development and testing of strategies to maintain adherence/compliance to treatment, in order to improve treatment outcomes and reduce the risk of developing HIV drug resistance.

MICROBICIDES

A safe and effective microbicide will be an important asset to the HIV prevention toolkit. Microbicides are products, including ARV drugs and other agents, that could be applied topically or injected to prevent acquisition of HIV and other sexually transmitted infections (STIs). Microbicides could be used alone or in combination with other strategies. The NIH supports a comprehensive and innovative microbicide research program that includes the screening, discovery, development, preclinical testing, and clinical evaluation of microbicide candidates. The NIH supports basic science research aimed at

understanding how HIV crosses mucosal membranes and infects cells. In addition, the NIH supports behavioral and social science research on adherence to, and the acceptability and use of, microbicides among different populations. These projects include the safety of microbicide use during pregnancy and menopause; studies in adolescents and in men who have sex with men; and implementation research to better understand how to integrate a potential product into community prevention practices. Basic science and clinical studies have shown promise for the use of ARV-based microbicides as HIV prevention strategies. Followup studies are underway or being developed to test different ARV- and non-ARV-based products, microbicides combined with a contraceptive for multipurpose prevention, and microbicides combined with antimicrobial agents to prevent HIV and other STIs. Microbicide formulations and new technologies that enhance adherence, such as injectable products, nanofibers, films, suppositories, and intravaginal rings, also are being developed and studied.

VACCINES

The best long-term hope for controlling the AIDS pandemic is the development of safe, effective, and affordable AIDS vaccines that may be used in combination with other prevention strategies. The NIH supports a broad AIDS vaccine research portfolio encompassing basic, preclinical, and clinical research, including studies to identify and better understand potentially protective immune responses in HIV-infected individuals and studies of improved animal models for the preclinical evaluation of vaccine candidates. Information gained from these studies is being used to inform the design and development of novel vaccine strategies. Since the modest success of the RV144 trial in Thailand using a pox virus vector and HIV envelope protein boosts, the NIH has supported unprecedented international collaborative investigations to identify how specific immune responses may protect against HIV acquisition. Samples from the HVTN 505 trial in the United States with DNA and adenovirus vectors are being subjected to similar analyses to understand why that vaccine strategy failed to protect against HIV acquisition. To build on the knowledge gained from these studies, clinical trials in other populations and in other parts of the world with new and potentially improved products and alternative vectors have been designed and are currently underway. Recent data from several Phase I and Phase II vaccine clinical studies present new scientific opportunities for the development of improved HIV vaccine candidates.

BEHAVIORAL AND SOCIAL SCIENCE

As studies continue to define a role for the use of ARV medications for HIV prevention, the NIH is supporting research to understand how these drugs can best be used for prevention in specific populations and social contexts. The NIH will continue to study ways to change those behaviors and social contexts and to facilitate engagement and retention in HIV testing, prevention, and treatment services. The NIH is supporting research to address factors associated with the HIV Care Continuum, and specifically on HIV care outcomes. Investigations are focused not only on individual-level variables, but also on social and structural issues, such as the role of stigma, housing, employment, health care access, and interpersonal networks. Studies have suggested that modifying these variables can promote early access to medical care, reduce costs, extend life expectancy, and improve quality of life. The NIH will continue to develop new research methods that can be applied to behavioral and social science studies, as well as the integration of biomedical and behavioral strategies in clinical investigations. These include approaches to increase recruitment into clinical trials; enhance statistical analyses of behaviors, such as alcohol use, that can affect medication studies; and identify behavioral issues relevant to genetic or genomic studies.

DRUG DISCOVERY, DEVELOPMENT, AND TREATMENT

ART has resulted in improved immune function in patients who are able to adhere to the treatment regimens and tolerate the toxicities and side effects associated with ARV drugs. ART also has delayed the progression of HIV disease to the development of AIDS. Unfortunately, the treatment is beginning to fail in an increasing number of patients who have been on ART. These patients are experiencing serious drug toxicities and developing drug resistance. Recent epidemiologic studies have shown that the incidence of coinfections, comorbidities, AIDS-defining and non-AIDS-defining malignancies, and complications associated with long-term HIV disease and ART are increasing. These include tuberculosis, hepatitis C, metabolic disorders, cardiovascular disease, conditions associated with aging, and neurologic and neurocognitive disorders. The NIH supports a comprehensive therapeutics research program to design, develop, and test drugs and drug regimens. Under development are new combinations of drugs and sustained release formulations and delivery systems to maintain undetectable viral load, to overcome drug resistance and treatment failure, and to prevent and treat HIV-associated coinfections, comorbidities, and other complications. The program supports cure research with a focus on developing drugs and cell- and gene-based strategies that can target and eradicate persistent viral reservoirs in various cells, tissues, and organ systems, including the central nervous system and brain. This program also is supporting preclinical trials of innovative strategies to eliminate viral reservoirs, including testing therapeutic anti-HIV monoclonal antibodies with and without ARV drugs.

TREATMENT AS PREVENTION

A critical new area of prevention research is the study of treatment strategies as a method to prevent new HIV infections. This approach builds on NIH-sponsored landmark clinical trials that demonstrated that treatment of HIV-infected pregnant women could significantly reduce transmission of HIV from mother to child. Recent groundbreaking studies have demonstrated the successful use of ARVs to prevent transmission of HIV in specific populations. Clinical results from a large NIH-sponsored international clinical trial (HIV Prevention Trials Network [HPTN] 052) showed that early initiation of ART for HIV-infected heterosexual individuals resulted in a 96 percent reduction in sexual transmission of HIV to their uninfected partner. Another major NIH-sponsored clinical trial, the Chemoprophylaxis for HIV Prevention in Men study, also known as iPrEx, demonstrated that daily use of an ARV drug by some high-risk uninfected men could reduce their risk of acquiring HIV. The findings from this study showed proof of concept and the effectiveness of a novel HIV prevention strategy known as pre-exposure prophylaxis (PrEP). Recent studies have shown PrEP to be effective in preventing HIV acquisition among two at-risk populations: women in heterosexual discordant couples and injection drug users. The NIH supports ongoing basic, translational, clinical, and implementation research to develop combinations of ARV drugs and compounds that can be used in sustained release formulations for potential new PrEP strategies; test PrEP in high-risk uninfected populations, including adolescents; evaluate postexposure prophylaxis, the use of ART to prevent infection after HIV exposure, including in a health care setting; develop improved regimens to prevent mother-to-child transmission; and evaluate a potential innovative prevention strategy known as "test and treat" to determine the impact of increased testing with immediate referral to treatment at the community level.

NATURAL HISTORY AND EPIDEMIOLOGY

Natural history and epidemiologic research on HIV/AIDS is critical to the monitoring of epidemic trends, evaluation of prevention modalities, characterization of the clinical manifestations of HIV disease, and measurement of the effects of treatment regimens at the population level. Novel methodologies in the area of biostatistics, mathematical modeling, and laboratory technology have provided the basis for new epidemiological approaches in addressing HIV/AIDS. Multi-site epidemiologic studies in the United States are identifying new HIV-related comorbidities and helping to differentiate effects related to ART from those related to HIV disease. As the AIDS epidemic continues to evolve, there is a crucial need for epidemiologic studies in domestic and international settings. The NIH supports a comprehensive research portfolio in both settings to study the epidemiologic characteristics of populations in which HIV is transmitted and the changing spectrum of HIV-related disease (including the occurrence of coinfections, malignancies, metabolic, cardiovascular, neurological, skeletal, and other complications). These studies have delineated the significant health disparities that are critical factors in the epidemic (e.g., racial and ethnic disparities in the United States; between industrialized and resource-constrained nations; between men and women; and health disparities based on sexual identity). Ongoing observational studies are adding focus on at-risk individuals from the rural South in the United States as well as on individuals over the age of 50. Research on HIV-related health disparities and their impact on treatment access and effectiveness, as well as HIV prevention, will continue to be an NIH AIDS research priority.

TRAINING, INFRASTRUCTURE, AND CAPACITY BUILDING

The NIH supports the training of domestic and international biomedical and behavioral HIV researchers. The NIH also provides infrastructure and capacity building support as integral aspects of its commitment to carrying out scientifically and ethically sound and highly productive HIV-related research. The expansion of NIH-funded HIV research globally has necessitated the development of research training and infrastructure and capacity-building efforts in many resource-limited settings throughout the world. NIH-funded programs have increased the number of training positions for HIV-related researchers, including domestic and international programs specifically designed to recruit individuals from populations underrepresented in research into research careers and to build research capacity at minority-serving institutions in the United States. Equipment, shared instrumentation, and tissue and specimen repositories are examples of the research infrastructure and capacity-building support that the NIH provides to strengthen the conduct of AIDS-related research, both domestically and internationally.

INFORMATION DISSEMINATION

The NIH supports initiatives to enhance dissemination of research findings; develop and distribute state-of-the-art treatment and prevention guidelines; and enhance recruitment and retention of participants in clinical studies. Effective information dissemination approaches are an integral component of HIV prevention and treatment efforts. These efforts are crucial in light of the advent of new and complex ART regimens, issues related to adherence to prescribed treatments, and the need to translate behavioral and social prevention approaches into practice. The changing pandemic and the increasing number of new infections in specific population groups in the United States underscore the need to disseminate HIV research findings and other related information to communities at risk, such as racial

and ethnic populations, women, older individuals, and men who have sex with men. The flow of information among researchers, health care providers, and the affected communities represents additional opportunities to use new and emerging technologies to speed the translation of research results into practice and to shape future research directions.

Global Impact of NIH AIDS Research: Research to address the global pandemic is essential. AIDS research represents the largest component of the total NIH global research investment. Since the early days of the epidemic, the NIH has maintained a strong international AIDS research portfolio that has grown to include projects in approximately 100 countries around the world. NIH AIDS research studies are designed so that the results are relevant for both the host nation and the United States. These research programs also enhance research infrastructure and training of in-country scientists and health care providers. New collaborations have been designed to improve both medical and nursing education as a mechanism to build a cadre of global health leaders. Most of these grants and contracts are awarded to U.S.-based investigators to conduct research in collaboration with in-country scientists; some are awarded directly to investigators in international scientific, academic, or medical institutions.

Benefits of AIDS Research to Other Areas: It is essential to point out that AIDS research also pays extensive dividends in many other areas of biomedical research, including in the prevention, diagnosis, and treatment of many other diseases. AIDS research:

- Has deepened our understanding of immunology, virology, microbiology, molecular biology, and genetics.
- Is helping to unravel the mysteries surrounding so many other diseases because of the pace of discovery and the unique nature of HIV (i.e., the way the virus enters a cell; causes infection; affects every organ system; and unleashes a myriad of opportunistic infections, comorbidities, cancers, and other complications).
- Continues to make discoveries that can be applied to other infectious, malignant, neurologic, autoimmune, and metabolic diseases, as well as to the complex issues of aging and dementia.
- Has led to more effective drugs for multiple bacterial, mycobacterial, and fungal diseases and fostered significant improvements in drug design technologies.
- Has led to the development of new models to test treatments for other diseases in faster, more efficient, and more inclusive clinical trials.
- Continues to benefit patients undergoing cancer chemotherapy and patients receiving anti-transplant rejection therapy as a result of drugs developed to prevent and treat AIDS-associated opportunistic infections.
- Has advanced understanding of the relationship between viruses and cancer.

Most recently, the development of protease inhibitors to treat HIV has led to development of a new drug combination that can cure hepatitis C, which affects about 150 million people globally. That advance in hepatitis C research may, in turn, provide important knowledge toward an HIV cure. New investments in AIDS research will continue to fuel biomedical advances and breakthroughs that will have profound benefits far beyond the AIDS pandemic.

Conclusion

The recent scientific advances resulting from NIH-funded research represent a turning point for AIDS research. New avenues for discovery have been identified, providing possibilities for the development of new strategies to prevent, treat, and potentially cure HIV. Despite these advances, however, AIDS is not over, and it is far too soon to declare victory. Serious challenges lie ahead. There is little doubt that, despite our progress to date, the AIDS pandemic will continue to affect virtually every sector of society in nearly every nation in the world for decades to come. In light of this reality, the U.S. national commitment to AIDS research remains strong.

This strategic Plan represents the collective professional judgment of scientific experts from around the country and throughout the world on the highest priority areas of scientific opportunity to move us forward from this important moment in science. This Plan is designed to identify critical research to find new tools to begin to turn the tide in the fight against AIDS—so that we can all once again live in a world without AIDS.

PRIORITY:

Expanding Basic Discovery Research

Etiology and Pathogenesis

AREA OF EMPHASIS

Etiology and Pathogenesis

FY 2015 RESEARCH PRIORITIES

- Further the understanding of fundamental viral and host mechanisms associated with the transmission, acquisition, replication, control, and persistence of HIV at the cellular, tissue, and organism level.
- Elucidate the determinants of disease progression versus non-progression, including intrinsic cellular restrictions, and the mechanisms and role of immune activation and inflammation in pathogenesis.
- Identify the sites, mechanisms of persistence, and strategies for immune containment and eradication of HIV reservoirs.
- Develop novel strategies to treat and prevent HIV using knowledge gained from studies on HIV reservoirs, host mechanisms involved in acquisition and inhibition of HIV infection, and immune activation and inflammation.
- Study the interaction of aging with HIV infection and the mechanisms responsible for the pathogenesis of comorbid conditions, including research on the relative contribution of the immune system and immune response to infection on these comorbidities.
- Study the impact of sex and race/ethnicity on the transmission and acquisition of HIV, as well as the disease progression and pathogenic consequences of HIV infection.
- Elucidate the pathogenesis of HIV-related coinfections and HIV-associated malignancies, and the mechanisms by which HIV infection and other factors in HIV-infected individuals contribute to the development and progression of these conditions.

OBJECTIVE–A: Biology of HIV Transmission

Delineate the viral, host genetic, and immune mechanisms involved in the transmission, establishment, and dissemination of HIV in diverse populations across the spectrum of age, gender, race and/or ethnicity, and transmission mechanism in national and international settings.

STRATEGIES

- Determine the role of cell-free and cell-associated HIV in different routes of transmission.
- Determine the role of phenotype/genotype/fitness of HIV variants and dose in various bodily fluids on different routes of transmission.
- Elucidate the genetic complexity, molecular features, and biological characteristics of HIV variants that are transmitted to the uninfected host, and mechanisms that affect the transmitted virus.
- Determine the mechanisms by which virus-encoded genes or viral gene products regulate and influence transmission, establishment, dissemination, and persistence of HIV infection.
- Determine the cell types/subsets and tissues at portals of entry responsible for HIV transmigration, acquisition, replication, and dissemination of HIV during the initial stages of infection.
- Delineate the mechanisms and impact of genetic, metagenomic, viral and host epigenetic, and environmental factors on innate, adaptive, and mucosal immune responses that influence HIV replication, transmission, establishment, and dissemination.
- Delineate the mechanisms by which other sexually transmitted infections (STIs), other coinfections, and the microbiome (bacterial, fungal, and viral) influence HIV transmission, replication, establishment, and dissemination, and contribute to HIV pathogenesis.
- Evaluate the role and mechanisms of preventing or enhancing HIV transmission, establishment, and spread by soluble factors contained within bodily fluids.
- Investigate the role of immune activation, inflammation, and their mediators in various cell types, tissues, and organs on the establishment of HIV infection, transmission, dissemination, and persistence.
- Use new technologies, including computational biology, bioimaging, and high-throughput "omics" to advance the understanding of the earliest events in HIV transmission, establishment of foci of infection, and dissemination.
- Develop and optimize animal models of HIV and simian immunodeficiency virus (SIV) infection to facilitate study of HIV transmission and establishment of initial foci of infection.

OBJECTIVE–B: HIV Virology, Viral Pathogenesis, and Viral Persistence

Delineate the viral and host mechanisms associated with HIV replication, dissemination, and latency, and those that influence viral setpoint, disease progression, and viral persistence in diverse populations across the spectrum of age, gender, race, and/or ethnicity in national and international settings.

STRATEGIES

- Define the molecular mechanisms and pathogen–host interactions underlying infection replication and latency/persistence at the cellular and molecular level, including viral gene products and their interactions with cellular cofactors and host restriction factors.
- Determine the mechanisms of dissemination (within the host) during acute infection; the viral, host, and environmental factors that regulate the establishment of viral setpoint following acute infection; and how viral, host, and environmental factors influence subsequent disease progression.
- Determine the mechanisms by which infection causes chronic bystander immune cell activation and establishes immune activation setpoint, and how generalized immune activation combined with viral replication affects disease progression.
- Define the sites of infection and replication in the untreated host at the cellular and cell subset level, both anatomically and functionally; how these sites of productive infection are established; and how cell subset targeting determines disease progression or non-progression.
- Define sites and mechanisms of latent/persistent infection in patients before and after suppressive therapy, the mechanisms by which reservoirs are established and maintained, and the host and viral factors that regulate reservoir establishment.
- Define the viral and host polymorphisms and exogenous/environmental factors that regulate virus replication and the development of disease.
- Define co-pathogens that interact with virus to affect disease pathogenesis and viral persistence.
- Characterize the role of the microbiota at different sites within the body on HIV pathogenesis, and determine the interactions between HIV and the host microbiome that lead to changes in HIV disease progression over time.
- Further develop and facilitate the use of models and systems biology approaches to study key features of infection, pathogenesis, and persistence not amenable to study in the human host, such as nonhuman primate (NHP) models of infection and pathogenesis, comparative studies of nonpathogenic natural hosts, novel nonprimate animal models, and *ex vivo*, *in vitro,* and theoretical/mathematical models.

OBJECTIVE–C: HIV Immunopathogenesis

Delineate immunological mechanisms of HIV control, and elucidate the viral and host mechanisms associated with HIV-induced immunopathogenesis, including immune dysfunction, aberrant immune activation, and inflammation across the spectrum of age, gender, race and/or ethnicity, and geographical location.

STRATEGIES

- Delineate the mechanisms by which innate and adaptive immunity, and the effects of genetic, epigenetic, or environmental factors on innate and adaptive immunity, influence HIV or SIV replication throughout acute and chronic infection.
- Elucidate mechanisms by which epigenomic modifications of HIV interact with and enable host immune responses to control viral replication, setpoint, spread, immune dysfunction, and disease progression.
- Delineate mechanisms responsible for the differences between pathogenic and nonpathogenic infection in humans and NHPs.
- Explore the role of HIV and other common coinfections in the development of premature immune senescence in HIV-infected individuals.
- Explore mechanisms of host response to HIV or SIV infection that involve the interface between innate and adaptive immunity.
- Delineate innate and adaptive immune responses to HIV at mucosal surfaces, including the gastrointestinal, genitourinary, and respiratory tracts.
- Investigate the role of the microbiome (including bacteria, viruses, and fungi) in HIV immunopathogenesis.
- Elucidate the mechanisms of CD4+ T-cell depletion and dysfunction in the infected host.
- Delineate the pathogenic consequences of HIV infection on leukocyte homeostasis and on the structure and function of primary and secondary lymphoid tissues.
- Examine the role of immune activation, inflammation, and dysfunction/dysregulation in HIV or SIV pathogenesis, and delineate the mechanisms leading to pathological immune activation, immunosenescence, and autoimmunity in HIV or SIV infection.
- Determine the impact of host immunity on viral evolution and fitness, and the influence of viral factors on host immunity.
- Evaluate the extent to which HIV or SIV-related immunopathogenesis can be prevented or reversed by therapeutic interventions.

OBJECTIVE–D: Pathogenesis of Opportunistic Infections and Coinfections

Elucidate the pathogenic mechanisms and consequences of opportunistic infections (OIs) and significant coinfections in the context of HIV infection in diverse populations across the spectrum of age, gender, and race and/or ethnicity in national and international settings and the factors that regulate susceptibility to infection or disease that may be targeted for prevention. Priority should be given to OIs and coinfections that (a) are a major cause of morbidity and/or HIV disease progression in HIV-infected individuals and/or (b) contribute significantly to HIV transmission or acquisition.

STRATEGIES

- Conduct studies on the pathogenic consequences of opportunistic and non-opportunistic co-pathogens and their interactions with the HIV-infected host.
- Define the relationships in which HIV enhances coinfections and by which coinfections enhance the risk of HIV acquisition or those that are a major cause of morbidity or disease progression.
- Identify and elucidate the genetic, metagenomic, viral and host epigenetic, and environmental risk factors, as well as mechanisms of immune dysfunction, associated with the susceptibility to, the development of, and the progression of OIs, emerging non-opportunistic infections, and coinfections in the context of HIV infection.
- Elucidate the mechanisms of innate and adaptive immune function that mediate protection against OIs and the effects of these mechanisms on HIV infection.
- Study the effects of HIV therapy on the clinical course and manifestation of OIs and coinfections, including pathogenesis of immune reconstitution inflammatory syndrome (IRIS), and the effect of OI therapy on the clinical course of HIV disease progression.
- Probe the pathogenic mechanisms of HIV-associated OIs and emerging non-opportunistic infections, and evaluate how the causes, agents, and manifestations of these infections persist or are altered by antiretroviral therapy (ART).
- Define the molecular and phylogenetic characteristics of the major HIV-associated OIs and pathogens, and integrate strain-specific characterization of data into studies of the pathogenesis, mechanisms of transmission, and epidemiology of OIs.
- Determine biomarkers and factors associated with clinical response to therapeutic interventions and vaccines against OIs and coinfections, and identify basic mechanisms that will provide new targets for the development of vaccines and new treatments for OIs and coinfections that will be effective in HIV-infected individuals.

OBJECTIVE–E: Pathogenesis of Metabolic and Body Composition Change and Organ System Dysfunction

Define the etiology, pathophysiology, and consequences of HIV infection and treatment-related disorders; body composition changes; nutritional status; endocrine dysfunction; oral health; gastrointestinal disorders; skin, muscle, and bone disorders; pulmonary disorders; nephropathy; hematologic disorders; and cardiovascular disease in diverse populations across the spectrum of age, gender, race, and/or ethnicity in national and international settings.

STRATEGIES

- Define the mechanisms underlying alterations in metabolism, body composition, nutritional status, endocrine function, growth and development, and the risks of atherosclerotic cardiovascular, vascular, renal, bone, skeletal muscle, oral, gastrointestinal, pulmonary, hematologic, and skin diseases or manifestations to determine:
  - The effects of antiviral therapies and suppression of virus replication, viral setpoint, episodic viremia, and sites of viral reservoirs;
  - The influence of disease stages, including the degree of initial immunosuppression and immune reconstitution, residual immune dysfunction, disruption of lymphoid architecture, and cytokine response;
  - The contributions of individual virologic and host factors, including host genetic variation;
  - The role of diet, OIs, non-opportunistic infections, and nutritional status on malabsorption, malnutrition, immune status and exacerbation of metabolic disorders, steatosis, comorbidities, and HIV pathogenesis;
  - The influence of (endogenous and exogenous) hormones and hormonal imbalances on HIV pathogenesis; and
  - The impact of pharmacokinetics, pharmacogenomics, and drug–drug interactions.
- Study the impact of HIV infection on an aging individual, including physical function; cardiovascular, pulmonary, hematologic, metabolic, bone, skeletal muscle, and neurocognitive function; and skin, oral, and renal diseases.
- Define the relationship between natural aging and HIV-induced pathological changes in multiple organ systems both without and on treatment.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms underlying alterations in metabolism, body composition, nutritional status, growth and development, and bone and organ system disorders.
- Determine factors associated with clinical response or lack of response to therapeutic interventions against AIDS-associated metabolic and body composition changes, physical function, impaired growth and development, diabetes, and bone, skeletal muscle, skin, renal, pulmonary, and atherosclerotic cardiovascular disease.
- Study the influence of the microbiome in conjunction with metabolic abnormalities and body composition changes associated with HIV infection.
- Integrate studies of these disorders and diseases into ongoing and planned treatment trials and observational studies.

OBJECTIVE–F: Pathogenesis of Malignancies

Elucidate the etiologic factors, cofactors, pathogenesis, and consequences of AIDS-defining and other HIV-associated malignancies in diverse populations across the spectrum of age, gender, race, and/or ethnicity in national and international settings.

STRATEGIES

- Explore the mechanisms involved in the shifts in the spectrum on both AIDS-defining and emerging non-AIDS-defining malignancies that are occurring in HIV-infected individuals whose lives are extended by ART. Conduct studies on how the interplay of HIV infection, host factors, and aging (including natural aging and premature aging that may be caused by HIV) affect the development of these cancers.
- Elucidate the mechanisms by which HIV infection and its treatment enhance the development of various AIDS-defining malignancies, non-AIDS-defining malignancies, pre-neoplastic lesions, and other hyper-proliferative conditions.
- Identify the mechanisms by which immune dysfunction (including inflammatory changes), oncogenes, suppressor genes, carcinogens, environmental factors, epigenomic changes, non-HIV oncogenic and non-oncogenic viruses, and other microbial organisms, genes, and proteins contribute to the development of cancer and preneoplastic lesions and hyperproliferative conditions in the context of HIV infection and HIV-associated malignancies; correlate these molecular factors with epidemiologic studies.
- Conduct studies on the biology of opportunistic pathogens that are the principal etiologic agents for HIV-associated malignancies (e.g., Kaposi's sarcoma-associated herpes virus [KSHV] and human papillomavirus [HPV]-associated cancers), and investigate their interaction with the host and the mechanisms by which they cause malignancies in HIV-infected populations.
- Address the impact of HIV infection and prior therapy on the pathogenesis and treatment of common non-AIDS-related cancers (e.g., breast, colon, lung, prostate, liver, and skin) that may emerge in the aging HIV-infected population.
- Elucidate the pathogenic mechanisms of AIDS-defining and other HIV-related tumors that arise in HIV-infected patients, including genetic changes, by comparing these tumors to similar tumors that arise in HIV-uninfected patients.
- Identify basic mechanisms that will facilitate the development of effective therapies, diagnostic measures, and preventive measures (including vaccines) for AIDS-defining and other HIV-associated tumors.
- Determine factors associated with clinical response and lack of response to antineoplastic therapeutic intervention in HIV-infected patients.

OBJECTIVE–G: Pathogenesis of Neurological Disease

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

STRATEGIES

- Define the neurobiological, immunological, and molecular basis of HIV-associated neurological and neurobehavioral dysfunction, including neurocognitive impairment, peripheral neuropathies, chronic pain, sleep disorders, and those associated with long-term, effectively treated HIV infection.
- Determine factors associated with clinical response and lack of response to therapeutic interventions for neurologic and neurobehavioral complications of HIV disease, including the role of central nervous system (CNS) drug penetration.
- Explore the relationship of virologic, host, pharmacogenetic, and environmental factors (including substance abuse) to susceptibility of HIV-associated neurological and neurobehavioral dysfunction or neuropathogenesis.
- Explore the role of viral and host genetic factors in HIV neuropathogenesis.
- Investigate the mechanisms and determinants of HIV neuroinvasion (e.g., via blood–brain barrier), spread, persistence, and latency within the CNS.
- Determine the host and viral factors influencing independent evolution of drug-resistant HIV strains in the CNS compartment as well as its functional consequences.
- Define the roles of innate and adaptive immunity in the control of HIV, OIs, and coinfections in the CNS.
- Investigate the pathophysiology of HIV-associated CNS disease in the asymptomatic, acute, and early stages of infection.
- Identify aspects of HIV infection that uniquely influence or interact with the developing nervous system or the processes of neurocognitive decline with aging or aging-related diseases.
- Employ therapies that effectively suppress HIV replication and/or stimulate neuroprotection to probe pathogenic mechanisms of HIV-associated neurologic diseases and neurobehavioral dysfunction; evaluate how the manifestations of HIV-associated neuropathogenesis are altered by such therapies.
- Determine the mechanisms regulating the changing/fluctuating symptoms of HIV-associated nervous system disease in the current era of ART.
- Define the impact of treatment drugs (including antiviral therapeutics for HIV as well as infectious and noninfectious comorbidities) and other environmental factors (alcohol, smoking, substance abuse, and nutrition) on HIV-associated neuropathogenesis and peripheral neuropathy.
- Examine the role of substance use and its potential relation to increasing neurological symptoms and/or cognitive decline in HIV-infected individuals.

PRIORITY:

Reducing New Infections

Vaccines

Microbicides

Behavioral and Social Science

Treatment as Prevention

AREA OF EMPHASIS

Vaccines

FY 2014 RESEARCH PRIORITIES

- Test a range of new concepts for inducing and maintaining effective immune responses both to prevent HIV transmission and to control HIV replication. Utilize combination approaches to engage relevant B-cell populations for long-term protective antibody production against the HIV envelope and to optimize appropriate cellular immune responses to HIV antigens that are able to eliminate HIV-infected cells.

  In the past several years, new concepts have emerged for inducing broadly neutralizing antibodies to HIV. These new approaches need to be tested in the most appropriate preclinical models and moved forward to the clinic as rapidly as possible. To attain highly effective HIV vaccine-induced protection against infection and/or disease progression, continued support for the testing of truly novel alternative approaches to HIV vaccines is needed, in addition to building on concepts that have shown partial success. Comparative immune response studies using vectors incorporating various HIV antigen inserts with or without adjuvants will be aided by characterization of the complex cytokine and chemokine patterns induced by various vaccine constructs in nonhuman primates (NHPs) and human volunteers. Designs and strategies that trigger focused B-cell recognition of HIV envelope sites will be needed, as well as studies of immunogen designs that incorporate repetitive motifs, which may be required to induce potent and durable protective antibody responses. Studies of other host responses or factors in selected subsets of cells, especially in mucosal tissues, may enable improved assessment of vaccine-induced adaptive and innate protective responses.

- Develop and refine NHP models using simian/human immunodeficiency virus (SHIV) chimeras to evaluate immunity and breadth of protection induced by HIV envelope vaccine candidates. Dissect vaccine-induced responses in clinical trials and animal models in parallel, with an emphasis on protection from mucosal viral challenge.

  With the continued need to explore vaccine concepts that induce strong protective antibody responses to HIV envelope, animal models that directly evaluate HIV envelope immunogenicity and subsequent protection from SHIV chimeric virus challenges need to be further refined. Improved surrogate simian immunodeficiency virus (SIV) models and animal models that can directly test HIV immunity also should be explored. Considering the limited number of transmitted/founder variants of HIV that appear to successfully establish infection, it is important to develop models that will examine transmission at different mucosal sites. SHIV models that can enable testing of diverse HIV envelope clades also need to be developed to study the breadth of protection achieved by different HIV vaccine approaches. It is of utmost importance to bridge animal models and clinical HIV vaccine studies during all phases, from product testing and immune analyses to defining correlates of protection, especially when NHP and/or clinical studies are partially effective.

- Develop clinical products and initiate expanded clinical trials to test HIV candidate vaccines with potentially improved immunogenicity and efficacy as rapidly as possible. Design and conduct immune correlate analyses with novel tools to confirm and improve upon the suggested correlates of risk observed in the HIV vaccine clinical trial of pox-vectored HIV antigens plus HIV envelope proteins conducted in Thailand.

Ongoing Phase I and Phase II HIV vaccine clinical trials will enable the advanced study of several additional candidate HIV vaccine products and vaccination strategies starting in 2015 and beyond. Efficacy trials will become increasingly large and complex with the further implementation of other partially successful prevention strategies, such as circumcision, antiretroviral treatment, and microbicides. Continued monitoring and engagement of potential cohorts with different modes of HIV transmission will be essential for rapid enrollment and conduct of clinical trials. It is essential that different populations be included in testing HIV vaccines to determine the limits and ability of various vaccine concepts to effect protection. Due to the expense and complexity of product development for clinical trials, it is essential for the National Institutes of Health (NIH) to engage in partnerships at multiple levels to enable the study of products that will test different vaccine strategies or potential correlates of immune protection.

- Support mentorship of early career investigators that bridge preclinical and clinical evaluation of HIV vaccines.

  Since it will be necessary for continued HIV vaccine evaluation efforts through at least the next decade, it is essential that a new generation of scientists be trained and mentored by established senior investigators who can impart their knowledge of vaccine product development and testing. The purpose is to engage and retain the next generation of investigators who bring not only new ideas but also sustained commitment to vaccine development. To achieve these goals effectively, preclinical NHP investigators should be integrated into large clinical trial networks and programs that are already funded by the NIH. Only by supporting and mentoring these young scientists can the HIV vaccine field ensure their success.

OBJECTIVE–A: Adaptive and Innate Host Defense Mechanisms

Increase scientific knowledge through basic research on protective immune responses and host defenses against HIV to facilitate the development of vaccines and other biomedical intervention strategies to prevent and/or control HIV infection.

STRATEGIES

- Define the mechanisms underlying protective systemic and mucosal immunity to HIV and other closely related lentiviruses by pursuing research in models that will provide information directly relevant to HIV infection; this includes the following areas of interest:
  - Determine the mechanisms of immunologically mediated control of infection with HIV and other related lentiviruses, including the role of antigen-specific (adaptive) and antigen-nonspecific (innate) cellular and humoral immunity in inhibiting viral replication to provide a basis for optimal vaccine design.
  - Define the structure–function relationships and the antigenicity and immunogenicity of HIV envelope proteins, including transient or intermediate and conformational domains induced by virus interacting with CD4, chemokine, dendritic cell (DC) surface proteins and adhesion molecules, and other cellular receptors to improve vaccine designs to more effectively induce immune responses to block infection by active T-cell immunity and protective antibody.
  - Define and characterize viral B-cell and T-cell epitopes that induce protective immunity in HIV or AIDS-related disease; utilize structural analysis of the HIV envelope to determine whether and how their immunogenicity can be improved and exploited in vaccine development.
    - Determine the mechanism of how HIV and closely related lentiviruses evade or escape from humoral and cellular, innate and adaptive immune responses; design vaccine approaches to prevent this; and define conserved epitopes in which genetic substitutions cannot be tolerated by the virus.
    - Characterize pathways of antigen processing of HIV proteins, including envelope glycoproteins, for presentation by major histocompatibility complex (MHC) class I and class II molecules. Investigate the interaction of HIV proteins with antigen-processing mechanisms that enhance or inhibit specific epitope presentation to the immune system.
    - Study the role of DCs in the induction of immunological memory and long-term protective function of different subsets of human lymphocytes in HIV-related disease and in response to vaccination.
    - Define factors that favor establishment and maintenance of memory cells able to generate effective recall to vaccine antigens, particularly HIV and viral antigens of closely related lentiviruses, and development of long-term protective immunity, particularly in human subjects.
    - Study the mechanism of action of vaccine adjuvants for HIV immunogens that enhance HIV or SIV antigen presentation to induce different cytokine or chemokine responses, innate immunity, and host factors; conduct comparative translational research of NHP and human vaccines.
    - Determine how chronic infection with one strain of HIV or closely related lentivirus, including attenuated viruses, confers protection against subsequent infection or reduces viral replication of a second pathogenic virus strain. Define the properties of the virus and of the immune responses that are responsible for lack of disease induction by attenuated viruses and/or protection from challenge with related pathogenic virus, and determine the protective mechanism, duration, and extent of cross-protection.

- Define the heterogeneity of specific responses to vaccine immunogens, specifically those derived from HIV, SIV, and SHIV, within diverse tissue compartments, and identify factors that confer protection from infection by various routes, including vaginal, rectal, oral, and parenteral exposure.
- Determine which factors promote development of particular human anti-HIV effector cell types; promote production of antiviral substances, including chemokines; or enhance non-antigen-specific innate protective mechanisms.
- Define the basis for adaptive, antigen-specific immune reactivity (humoral, cellular, and other) across divergent HIV types (clades and biological phenotypes or immunotypes); study clinical samples from human volunteers participating in HIV vaccine trials to determine the extent of cross-reactive immune responses that can be achieved with different candidate vaccines.
- Determine whether HIV immune responses that can contribute to immune enhancement of viral replication *in vitro* can interfere with induction or propagation of vaccine-induced effector responses *in vivo*.

- Seek new clues for correlates of immune protection and vaccine design by studying HIV-infected or highly exposed but seronegative individuals across the lifespan, and SIV or SHIV NHP lentivirus models by conducting the following research:
  - Study acutely HIV-infected individuals and exposed/seronegative or possibly transiently infected humans (including uninfected children born to or breastfed by HIV-infected mothers, individuals with controlled therapy interruptions, HIV-infected individuals vaccinated with therapeutic vaccines while on antiviral therapy, and non-progressors) to define immune responses to HIV-1 and HIV-2, potential vaccine-inducible host immune responses, and viral factors (or viral attenuations) or host factors that enhance or reduce the amounts of circulating virus and influence disease course.
  - Elucidate the functional mechanisms for protective immunity against HIV, SIV, and SHIV, including identification of specific responses by passive transfer of antibody or immune cells and deletion of selected immune subsets in NHP models.
  - Investigate the sequence of events required for mucosal transmission/infection of HIV, SIV, or SHIV at different portals of entry to define how and where specific immune effector mechanisms can impede viral entry and/or prevent establishment of infection.
  - Study mucosal immunity to HIV and SIV antigens and other infectious pathogens being used as HIV vaccine vectors in relevant animal models and humans to develop optimal vaccine strategies for HIV antigen delivery and effective immune-based prevention of HIV transmission.
  - Acquire clinical specimens from populations relevant to HIV vaccine trials for laboratory studies; explore the molecular epidemiology, humoral, and cell-mediated immune responses to HIV-1 and their relationship to class I and class II MHC alleles; and define constraints on HIV evolution under immune selection pressure so as to guide vaccine development. Acquire appropriate, linked, epidemiological information to optimize interpretation of these analyses.
  - Explore genome-wide association studies, in addition to targeted genetic analyses, to reveal novel viral protection/control mechanisms, particularly those that may be manipulated or may inform HIV vaccine studies.
  - Monitor the effects on immune activation with intercurrent sexually transmitted diseases (STDs), malaria, tuberculosis (TB), hepatitis B and C, human papillomavirus (HPV), and other infectious diseases, and with administration of drugs of abuse or effects of antiretroviral therapy (ART) on HIV shedding in vaccinated subjects. Model these confounding elements in NHPs.

- Develop *in vitro* experimental approaches for analysis of HIV vaccine responses that will combine sensitivity, specificity, high throughput, and the ability to use small sample volumes; develop *in vitro* and *in vivo* tools to study systemic and mucosal immune mechanisms of control of virus for analysis of vaccinated individuals (across the lifespan) and animals protected against SIV or SHIV by undertaking the following research activities:
  - Develop and improve NHP animal models of lentivirus infection that are practical and representative of the spectrum of HIV infections and development of AIDS, including use of appropriate HIV cellular receptors and different modes of transmission; develop genetically defined and histocompatible NHP models to facilitate immune cell transfer studies; in general, make models amenable to use in evaluating protection by vaccines and other biomedical interventions. This may be approached, in part, by genetic sequencing of selected regions of NHP genomes.
  - Establish cryo-repositories of cells isolated from NHP tissues (including blood, primary lymphoid organs, and mucosal specimens) from immune-naive, HIV- or SIV-vaccinated, or SHIV- or SIV-infected animals to provide a resource for assay development in parallel with human studies.
  - Develop improved methodologies and assays to measure HIV neutralization; explore the mechanisms of virus neutralization and the reason(s) for the relative difficulty to neutralize primary HIV isolates.
  - Develop and standardize immunological reagents for HIV vaccine trials; standardize cell, fluid, and tissue processing to ensure viability and maintenance of functional capacity of cells and stability of factors in serum, plasma, and culture supernatants; and develop quality control procedures for collecting, processing, freezing, storage, recovery, viability, shipping, and tracking of samples that will be essential in large-scale HIV vaccine clinical trials.
  - Study the function of HIV or SIV-specific CD4 T cells, CD8 T cells, and viral suppressive immune responses; develop and adapt high-throughput assays with specificity for primary HIV isolates; and make available those reagents required for HIV vaccine-related studies. Develop and utilize system biology approaches, including functional genomics to characterize vaccine-induced protective immune responses.
  - Develop or improve sensitive quantitative measures of HIV or SIV in body fluids and low-level tissue reservoirs, including genital secretions, oral fluids, and breast milk, to assess the effectiveness of vaccines designed to lower viral load and interrupt transmission or prevent disease progression.

OBJECTIVE–B: Vaccine Design, Development, and Animal Testing

Design HIV antigens, adjuvants, immunomodulators, and vaccine delivery methods that elicit long-lasting protective immune responses against a broad range of HIV isolates by applying findings from basic, epidemiologic, and clinical research; facilitate development and preclinical evaluation of vaccine strategies in laboratory studies and animal models; and foster early and continued collaboration between academicians, other Government agencies, nongovernmental organizations (NGOs), and industry in the research and development of candidate vaccines to test a broad array of vaccine concepts and combinations of different approaches for development of potential HIV vaccine products, including vaccines for particular populations such as breastfeeding infants, adolescents, and women.

STRATEGIES

- Multiple parallel approaches to development and testing of candidate HIV and AIDS vaccines will be investigated to provide complementary and comparative preclinical data on safety and immunogenicity questions about HIV vaccines. Such studies should achieve the following:
  - Support the design, development, production, and testing of novel active and passive HIV and AIDS vaccine candidates for safety and for their ability to elicit appropriate antiviral immune responses. This may include, but is not limited to:
    - Virus-like particles containing one or more virus proteins, peptides, or antigens;
    - Whole-inactivated HIV rendered noninfectious by chemical and/or genetically engineered deletions of pathogenic viral elements;
    - Naturally occurring and genetically engineered, live-attenuated strains of HIV;
    - DNA or RNA coding for viral proteins;
    - Live, recombinant viral and bacterial vectors engineered to express one or more HIV proteins, with attention to vectors that might provide dual benefit for HIV and some other pathogen or to vaccine vectors that target mucosal immune responses;
    - Viral replicons or other immunogen strategies designed to target DCs;
    - Recombinant HIV envelope protein subunits produced by a variety of methods, with an emphasis on retention or exposure (e.g., through deglycosylation) of critical nonlinear or conformational structural epitopes for induction of effective antibody responses;
    - Structurally constrained HIV envelope fragments, peptides, mimetopes, or complex peptides capable of inducing and boosting cellular or humoral immunity to HIV;
    - Antibodies or other virus-neutralizing molecules, delivered by passive transfer or by a recombinant vector; and
    - Cell surface components carried on the viral surface.
- Foster collaborations between academic investigators, industry sponsors, the NIH, the Food and Drug Administration (FDA), other Government agencies, and NGOs on research and development of novel vaccine design concepts. These collaborations should:
  - Enable production of pilot lots of HIV vaccine candidates for testing in NHPs and human subjects. When necessary, the NIH will provide clinical-grade products produced under Good Manufacturing Practice and ensure that products meet these regulatory standards;

- Develop programs to design and conduct comparative testing of vaccine approaches with industry and academic partners that will permit long-term followup to assess disease progression in animal models; and
- Develop infrastructure; address scientific, legal, ethical, and regulatory issues to foster and encourage participation by, and collaboration among, academic investigators, industry, affected communities and populations, and other agencies involved in the research, development, production, and clinical testing of candidate vaccines.

- Foster the development of HIV vaccines to optimize characteristics appropriate for broad international use, including designs exhibiting low cost with ease of production, stability, and ease of administration. This may include:
  - Combined use of two or more vaccine strategies with mixed modalities to boost the same component and/or to engage different arms of the immune response; and
  - Multivalent vaccine candidates incorporating different genetic clades and/or antigenic types to increase the breadth of immune responses.
- Support HIV vaccine design and development, incorporating methods to improve or modulate vaccine-elicited immune responses (qualitatively or quantitatively), including:
  - Novel adjuvants and delivery methods that might enhance effective DC presentation of HIV or SIV antigens;
  - Agents that stimulate or modulate innate and mucosal immune responses to HIV or other host defenses, including cytokines or chemokines;
  - HIV or SIV vaccines formulated with cytokines or incorporating cytokine genes or other biologically active molecules in vectors to improve the avidity of T cells and/or the functional activity of antigen-specific T cells; and
  - Other novel strategies, including nutritional supplementation and treatment of underlying infections and/or diseases that might have an impact on HIV vaccine responses.
- Evaluate the efficacy of HIV or SIV vaccine candidates and other immune prevention strategies in NHP animal models of HIV and closely related lentiviruses by:
  - Testing HIV or SIV vaccine candidates and other biomedical prevention strategies in animal models that most closely mimic HIV infection in humans;
  - Determining *in vitro* correlates of an *in vivo* protective immune response generated by HIV or SIV vaccines;
  - Determining the effect of HIV or SIV vaccine formulation, site of delivery, and regimen, as well as the nature, timing, phenotype, and route of infectious SIV or SHIV challenge, on the effectiveness of the vaccine-induced immunity;
  - Defining the impact of different HIV or SIV vaccine approaches on the kinetics of immune responses; kinetics and localization of viral replication, including long-term followup of disease progression in the presence of low-level chronic infection and concomitant diseases (e.g., TB, hepatitis, or autoimmune diseases); and biologic characteristics of breakthrough virus, including transmissibility;
  - Determining the impact of genetic factors, age, and concurrent prophylactic ART or topical microbicides on HIV or SIV vaccine responses and on protection against virus at various challenge sites; and
  - Studying the efficacy of the HIV or SIV immune response in view of viral variation.
- Investigate HIV or SIV vaccines and other biomedical prevention strategies with attention to potential factors such as integrity of the mucosal surface, changes in vaginal/cervical epithelium during puberty, hormonal changes during pregnancy, use of contraceptives or hormone replacement therapy, and presence of STDs; wherever possible, study potential concomitant effects on the genital tract immune responses and how inflammatory activity may compromise the integrity of the mucosal surface or the inductive ability of HIV vaccines.

- Support development of reagents and standardized methods to assess specific HIV or SIV vaccine-induced immune responses in NHP animal models and humans, including infants, for both humoral and cellular aspects of systemic and mucosal immunity. This includes:
  - Developing and refining assays to distinguish between serological and cellular responses due to immunization versus those due to HIV, SIV, or SHIV infection;
  - Characterizing and evaluating potential negative side effects of candidate HIV or SIV vaccine designs, including the potential to increase the susceptibility to infection or the rate of disease progression in NHP animal models;
  - Standardizing and validating assays to assess the potency of candidate HIV vaccines;
  - Standardizing and validating assays to be used as Phase III study endpoints; and
  - Developing novel endpoint assays under conditions of Good Laboratory Practice to support eventual product licensure and instituting quality assurance programs to assure sponsors and vaccine manufacturers that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with FDA regulations.
- Foster research on the attributes of candidate HIV and AIDS vaccines in development that may raise safety and regulatory concerns such as:
  - Immunogens produced utilizing human-derived tumor cell and other continuous cell lines;
  - Vectors that have the potential to integrate into the host chromosome or have the potential for chronic expression;
  - The ability to be generated as either replicating or non-replicating vectors;
  - The potential to cause autoimmunity or suppression of immunity, or to generate highly immunogenic antivector responses;
  - The ability to increase the risk of HIV infection through vector-specific activation of T cells or other vaccine-induced enhancement of infection; or
  - Expression of potentially harmful vector proteins.

OBJECTIVE–C: Active and Passive Pediatric Vaccines

Identify mechanisms of protective immunity to HIV in newborns and infants, and support the development of distinct study designs for safe and effective vaccine strategies and passive immune interventions, alone or in combination with other interventions, for preventing or controlling HIV infection in this population worldwide.

STRATEGIES

- Investigate the unique immune status and develop immune interventions in both pregnant women and infants to interrupt HIV transmission. Active and passive HIV vaccine strategies should be modeled and evaluated, particularly in infants, in parallel to studies in uninfected adults. To accomplish this goal, it is important to develop research that will achieve the following:
  - Develop relevant NHP animal models of maternal–fetal and maternal–infant perinatal transmission of HIV, SIV, or SHIV that can:
    - Determine the preclinical safety and immunogenicity of various HIV vaccines and adjuvants, particularly in pregnant and newborn primates;
    - Determine the safety of various monoclonal and polyclonal antibody preparations against HIV;
    - Determine the best immunization routes or protocols to induce antibodies to HIV in milk and other secretions;
    - Evaluate NHP infant cellular and humoral immunity to HIV or SIV in the context of breastfeeding from a SHIV- or SIV-infected mother, and determine immune correlates of protection for potential exploitation in vaccine strategies;
    - Evaluate the efficacy of vaccines and passive immunotherapy for prevention of perinatal or breastfeeding HIV transmission; determine whether there is attenuation of disease progression among neonatal animals that become infected despite immune intervention; determine correlates of protective immunity; and
    - Evaluate the effect of ART in combination with immune prevention strategies.
  - Determine virologic and non-immunologic/genetic host factors that influence transmission of HIV-1 from mother to infant that would have an impact on selection of viral antigens for the design of an HIV vaccine or for identifying the target of immune-based intervention to prevent perinatal transmission. This includes:
    - Determining the importance of viral load and viral phenotypes and genotypes in perinatal or early infant HIV transmission and what additional viral factors are associated with differences in perinatal transmissibility;
    - Developing standardized methods to collect specimens and to detect, characterize, and quantify HIV in cervicovaginal secretions and in breast milk to determine their potential relevance in mother-to-child transmission (MTCT); and
    - Determining if HIV in maternal genital secretions or breast milk is distinguishable from virus found in blood and which type is transmitted from mother to fetus and mother to infant.
  - Identify maternal and infant immune responses that may control HIV replication in either the mother and/or the infant and prevent transmission of HIV or establishment of infection in infants, particularly in breastfeeding infants.

- Define immune approaches that will provide specific and sustained protection against HIV or SIV transmission; develop the products necessary to achieve these goals; and develop the capacity to evaluate their safety in human subjects. This research includes the following activities:
  - Determine specific immune strategies for perinatal intervention that blocks interaction of HIV or SIV with its receptors and coreceptors and/or that targets infected cells.
  - Characterize the transmitted viral strains and monitor changes that may occur in proposed HIV vaccine trial sites; evaluate the impact that genetic polymorphism in different racial or ethnic backgrounds may have on receptor usage or immune responsiveness.
  - Evaluate, in Phase I and Phase II studies, the safety and immunogenicity of various HIV vaccines, adjuvants, vaccine administration regimens, and the pharmacokinetics of passive antibody preparations among HIV-infected pregnant women and newborns exposed to HIV *in utero* and/or intrapartum, as well as breastfeeding infants exposed to maternal HIV.
- Test the safety and efficacy of active and passive HIV vaccine interventions alone or in combination with other modes of intervention, particularly in international settings with high seroprevalence. This testing includes the following activities:
  - Identify and characterize the important issues to consider in the feasibility and development of criteria for advancement of candidate HIV vaccines, adjuvants, and passive antibody preparations from Phase I and Phase II to Phase III clinical trials in pregnant HIV-infected women and/or HIV-exposed children. These criteria may include evidence of therapeutic effectiveness in mothers in addition to prevention of infection in HIV-exposed children or adults.
  - Develop the capacity in domestic and foreign trial sites necessary to enroll mothers and infants in trials of both preventive and therapeutic HIV vaccines, passive immunity, and other perinatal interventions with prospective long-term followup. For vaccines, this should include the assessment both of duration and breadth of detectable humoral immune responses and of memory or recall responses in the cellular immunity compartment(s).
  - Conduct Phase III clinical trials for evaluation of efficacy of the most promising candidate HIV vaccines and/or passive antibody preparations that meet established criteria in pregnant HIV-infected women and/or children exposed to HIV.
  - Develop criteria to define infant HIV infection status as a perinatal intervention trial endpoint in countries where breastfeeding is recommended despite maternal infection status, including type of diagnostic tests, timing of the tests, length of followup, and adherence to followup visits.
  - Study HIV isolates and the immune response in infants who become infected despite administration of active and/or passive immunization to evaluate the effects of immune intervention on the characteristics of transmitted (escape) virus and on the quality, quantity, and timing of the infected infant's antiviral responses.
  - Study the impact of early ART interventions on HIV vaccines, or passive antibodies administered while on effective ART, on the maintenance or regeneration of naive T cells and antiviral immune responses in HIV-infected infants.
  - Characterize transmitted viruses obtained from infants and children receiving vaccines or passive antibodies for prevention of MTCT to establish the timing of transmission or establishment of productive infection.

OBJECTIVE–D: Conduct Phase I, Phase II, and Phase III Vaccine Clinical Trials

Conduct Phase I, Phase II, and Phase III trials for safety, immunogenicity, and efficacy with suitable candidate HIV vaccines or concepts in domestic and international settings.

STRATEGIES

- Support the conduct of Phase I, Phase II, and Phase III HIV vaccine clinical trials that will determine short- and long-term safety; immunologic responses measured by a broad range of humoral, cell-mediated, innate, and mucosal immune parameters; and the efficacy of different preventive vaccine candidates. This includes the following:
  - Develop and implement strategies to coordinate studies in NHPs with clinical trials so that data from NHP studies inform decisions about clinical trials and data from clinical trials can be used to improve NHP animal models.
  - Design and conduct Phase I and Phase II trials using promising HIV vaccine candidates. Trials should determine safety, test immunogenicity of vaccine candidates, and address questions about optimal vaccine strain/gene insert selection (i.e., the properties of a strain [immunologic, genotypic, or phenotypic]) that make it optimal for use in a selected population. The feasibility of trials to test concepts of immune prevention and control by antibodies may be explored via passive administration of antibodies. Vaccine trials should include an appropriate representation of the general population (gender, age, and ethnic and racial minorities), particularly including understudied populations affected by HIV, such as women and adolescents, and should be of an appropriate size to provide data on the frequency, magnitude, and breadth of immune responses to facilitate decisions regarding initiation and evaluation of larger test-of-concept (TOC) or efficacy trials.
- Develop a comprehensive plan for conducting HIV vaccine trials with rapid accrual, high retention, and adequate long-term followup of vaccines to reach predefined endpoints, as follows:
  - Conduct research into methods to effectively recruit and retain diverse populations into HIV vaccine trials.
  - Prepare for adequate long-term followup of volunteers in HIV vaccine clinical trials to determine the durability of immune responses and protection, immune correlates of protection, long-term safety, behavioral factors that may influence adherence of followup visits, the impact of participation on risk-taking behavior, and vaccine-related reduction (or enhancement) of disease progression and HIV transmission.
  - Conduct collaborative, large-scale efficacy trials of preventive HIV vaccine candidates that have proven promising, safe, and immunogenic in Phase II trials and that meet appropriate criteria by:
    - Evaluating HIV vaccine candidate efficacy against HIV infection, disease progression, and/or transmission;
    - Evaluating additional virologic, immunologic, and behavioral outcomes, particularly potential correlates of protective immunity against HIV;
    - Ensuring that HIV vaccine trials are conducted with the highest regard for social, legal, and ethical standards and in populations that reflect the racial and ethnic burden of HIV disease, also including women and adolescents;
    - Ensuring access to achievable, sustainable, and culturally appropriate best practices to prevent HIV exposure; and
    - Developing, adapting/modifying, and coordinating educational and information programs about HIV and HIV vaccines suitable for the individual participants and communities of different ethnic, racial, age (adolescents), and cultural backgrounds who will be involved in trials.

- Characterize the clinical course, detailed immune responses, and other characteristics of vaccines (e.g., behavioral risk of infection) in those who become HIV-infected; isolate and characterize viral isolates from participants in vaccine trials with intercurrent HIV infections to explore the possible effects of vaccination on the characteristics of escape (transmitted) viruses.

- Explore innovative trial designs to improve the efficiency of HIV vaccine efficacy studies (e.g., determine the impact of HIV vaccines by studying initially concordant HIV-uninfected couples at high risk or discordant couples or by studying subsequent transmission from vaccinated individuals who become infected after administration of the trial vaccine to new partners identified through partner tracing). This includes the following areas of trial design research:

  - Consider the use of secondary endpoints, particularly immune correlates of protection, surrogates of disease progression, clinical outcomes, and the benefit of long-term followup.

  - Encourage linkage between vaccine preparedness studies in high-risk populations and other research activities, including research on TB and STDs.

  - Utilize information from trials of other biomedical and behavioral interventions to consider novel trial designs (including, but not limited to, factorial designs and cluster-randomized designs) and the timing and impact of data from other trials on HIV vaccine trial design and conduct.

  - Consider the impact of prophylactic or early ART on HIV infections in complex vaccine trial designs.

  - Continue to use existing strategies to avert social harm and develop additional strategies to complement existing mechanisms at the local and national levels to reduce the risk of social and economic harm to volunteers in Phase I, Phase II, and Phase III HIV vaccine trials, particularly to vulnerable populations of women and adolescents, and assist in providing solutions.

  - Conduct behavioral risk assessment research in all appropriate subgroups during HIV vaccine trials, particularly with Phase II, TOC, and Phase III trial participants, to identify and evaluate any changes in risk behavior as a result of participation in an HIV vaccine trial; develop, test, and ensure access to interventions to prevent high-risk behaviors; conduct behavioral research with specific emphasis on individuals who become infected during trials to identify interventions that may prevent high-risk behaviors in future trials or application of HIV vaccines.

  - Closely coordinate the evaluation of research findings on prophylactic AIDS vaccines with preclinical vaccine research and HIV immunotherapeutic interventions to facilitate and expedite translation of basic research to clinical practice.

OBJECTIVE–E: Research and Preparation for HIV Vaccine Clinical Trials

Develop strategies, infrastructure, and collaborations with researchers, communities, other U.S. Government agencies, other governments, international and domestic NGOs, and industry that are necessary to ensure adequate performance of HIV vaccine trials, while balancing the prevention needs of the at-risk populations, including women and adolescents; identify domestic and foreign populations; and perform necessary research to define seroincidence and viral subtypes and to determine and optimize the feasibility of vaccine studies in appropriate cohorts or populations.

STRATEGIES

- Identify and develop potential domestic and foreign sites with a high HIV seroincidence and improve access to populations at high risk for acquiring HIV infection, where vaccine or other prevention research activities may be feasible. This includes the following activities:

- Track the course of the epidemic by applying newer epidemiologic tools for estimating the HIV incidence in various populations with documented high-risk behaviors in the United States and worldwide; improve methods to identify and evaluate emerging risk groups and those groups most likely to be informed, willing, and able participants in HIV vaccine clinical trials.

- Identify and address barriers to participation in clinical trials among all at-risk groups, so that all relevant populations, especially women and adolescents, are included in HIV vaccine clinical trials.

- Develop and apply new laboratory diagnostic tools, including rapid, point-of-care tools, that can be adapted for high throughput to detect, characterize, and amplify virus in blood and mucosal fluids from individuals with new HIV infections and allow distinction between vaccines and infected individuals.

- Analyze MHC genetic differences and other relevant genetic or medical factors of populations at potential trial sites that may affect the qualitative or quantitative levels of immune responses to candidate HIV vaccines, susceptibility to infection, control of virus peak and setpoint, and disease progression.

- Acquire and analyze HIV isolates from mucosal sites, as well as blood from recently infected individuals' representative of potential efficacy trial populations, so that genetic and antigenic information about viruses being transmitted in the population can be obtained.

- Develop and maintain the necessary immunology and virology laboratory infrastructure for conducting domestic and international HIV vaccine efficacy trials. This includes education and training of personnel from international sites hosting vaccine trials; development of laboratory infrastructure; standardization of assays and development of panels of geographic-specific reagents composed of local, indigenous HIV-positive and HIV-negative samples, as well as peptide reagents to serve as controls when validating and standardizing assays that will be used in support of clinical trials in that region; and participation of trained personnel in studies related to the trial.

- Establish, build, and maintain linkages with communities and community organizations where vaccine clinical trials may be conducted to optimize education, recruitment, and followup activities; consider and address community concerns and social issues, and ensure ethical conduct of HIV and AIDS vaccine efficacy trials. This includes the following:

  - For all HIV vaccine clinical trials, enlist participation of local representatives or community advisory boards (CABs) in the development of appropriate clinical trial protocols as well as responsive mechanisms to inform and educate the participating individuals; establish networks within the community that will effectively, and on a continuing basis, address the social and medical

concerns of the participants; establish mechanisms to provide ongoing information and open discussions concerning the scientific rationale and public health need for the study.

- Develop mechanisms (including CABs) to engage in collaboration and to provide education and the means to inform communities about HIV vaccines on a continuing basis so that social as well as medical concerns are addressed; establish trust in the community through open discussions of scientific rationale, expectations, and concerns.

- For international vaccine trials, in addition, work closely with national (host) governmental and regulatory authorities, collaborating institutions or agencies, local community representatives, vaccine manufacturer(s), the World Health Organization, the Joint United Nations Programme on HIV/AIDS, and the Global HIV Vaccine Enterprise to prepare for, plan, and conduct HIV vaccine trials adhering to the highest ethical and scientific standards.

- Support the education of local CABs and local institutional review boards on issues concerning the conduct of HIV vaccine clinical trials in their communities.

- In collaboration with Government agencies, institutions, NGOs, and communities being identified as potential collaborators, explore behavioral and social issues and prevention activities (e.g., circumcision, microbicides, pre- or postexposure prophylaxis, anti-herpes simplex virus treatment, HPV vaccine, and breastfeeding strategies) that may have a substantial impact on either the design or the conduct of an HIV vaccine clinical trial. This includes the following research that will:

  - Evaluate other biomedical and behavioral interventions that could prove beneficial in decreasing the incidence of HIV infection in one or more populations identified for future vaccine efficacy trials; address their potential impact on the evaluation of HIV 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, unblinding, and retention strategies pertinent to the design and execution of a successful vaccine efficacy trial, especially for populations that have been historically underrepresented in clinical trials and where the HIV epidemic is expanding disproportionately.

  - Identify and develop strategies to involve the populations with highest risk for HIV transmission in different communities; particular attention should be given to high-incidence populations of adolescents and young persons.

  - Develop research that anticipates and addresses effectively the potential adverse or unintentional effects of biomedical advances in HIV prevention (vaccines, microbicides, rapid testing, etc.), including behavioral disinhibition or increases in risk behavior such as failure to use condoms in sexual encounters, which may offset gains in prevention.

  - Collaborate with other U.S. Department of Health and Human Services agencies and community-based organizations to develop education programs to facilitate the conduct of Phase III HIV vaccine clinical trials in hard-to-reach populations in domestic sites; collaborate with the U.S. Military HIV Research Program, Centers for Disease Control and Prevention, U.S. Agency for International Development, and other organizations to develop vaccine clinical trial sites in international settings.

  - Evaluate the impact of community-based participatory research in the acceptability of HIV vaccine clinical trials.

  - Develop appropriate communication strategies involving affected communities in the process of testing HIV vaccines and prepare for the eventual integration of preventive vaccines into comprehensive prevention and care programs in the United States and in countries where HIV vaccine clinical trials are conducted.

  - Assess possible adverse social, economic, behavioral, or legal consequences of participation in vaccine clinical trials; develop broadly applicable strategies for mitigating potential harm.

- Optimize methods of achieving informed consent for HIV vaccine efficacy trials in different populations.
- Design comparative effectiveness research to evaluate vaccine candidates independently or in the context of other various biomedical and behavioral interventions.

- Develop tools to enhance recruitment, training, and retention of new investigators and staff involved in conducting HIV vaccine research globally.

AREA OF EMPHASIS

Microbicides

FY 2015 RESEARCH PRIORITIES

- Develop, maintain, and advance a sustainable and diverse pipeline of antiretroviral (ARV) and non-ARV-based microbicide candidates and multipurpose prevention technologies (MPTs) that prevent HIV, HIV and other sexually transmitted infections (STIs), and HIV and pregnancy.
- Develop standard pharmacokinetics (PK) and pharmacodynamics (PD) correlates of effectiveness and safety for microbicides and MPT studies.
- Develop and incorporate new technologies to bridge animal and tissue models and human studies in HIV research.
- Develop, standardize, and validate biomarkers and other tools for the assessment of sexual activity and the assessment and enhancement of adherence in microbicides and MPT studies.
- Determine the changes that occur in the genital tract, anal/rectal mucosa, and mucosal microenvironment that affect HIV acquisition and transmission in men and women across the lifespan and the factors including exogenous and endogenous hormones that affect those changes.
- Develop and implement community participatory approaches to microbicide and MPT research.

OBJECTIVE–A: Basic Mechanisms of Mucosal Transmission

Elucidate basic mechanisms of HIV transmission and protection for virus and host factors at mucosal surfaces important for the development of microbicides and MPTs.

STRATEGIES

Basic Biological and Physiological Research Related to Microbicides, Including MPTs

- Identify, investigate, and characterize viral and host targets important for the early transmission and dissemination of HIV in the genital tract and the anus/rectum.
- Apply systems biology approaches to better characterize the physiologic and immune function of genital and anal/rectal immune and mucosal epithelial cells.
- Study the interactions between candidate microbicide candidates and the innate and adaptive genital and anal/rectal microenvironment, HIV viral population dynamics, and mucosal secretions and epithelial surfaces that enhance susceptibility to or protect against HIV transmission and acquisition.
- Study the genital tract and anal/rectal changes that occur during intercourse and discern how they affect HIV transmission, acquisition, and susceptibility, as well as the safety, effectiveness, acceptability of, and adherence to microbicides.
- Study the factors involved in HIV entry, transport, and dissemination in humans, *ex vivo* tissue, and nonhuman primate models of infection.
- Determine the role of viral phenotype, genotype, clade, and resistance patterns on the transmission efficiency of cell-free and cell-associated HIV in secretions and tissues in the genital tract and anus/rectum.
- Investigate the effect of variations in male and female endogenous and exogenous hormonal status on HIV susceptibility, transmission, acquisition, and prevention and the possible impact on ARV and non-ARV product metabolism across the lifespan.
- Investigate sex, gender, geographical location, and other underlying differences that may affect the mucosal microbiome and HIV susceptibility, transmission, and acquisition.
- Study the impact of pregnancy physiology on the genital and anal/rectal mucosal microbiome, innate and adaptive immunity, immune activation, and on HIV susceptibility, transmission, acquisition, and prevention.
- Establish *in vitro* and *in vivo* models to study the impact of other STIs on the biology of HIV transmission and on microbicide efficacy.
- Study the effect of remote and current sexual violence on HIV susceptibility, transmission, and acquisition.

OBJECTIVE–B: Discovery, Development, and Preclinical Testing

Support the discovery, development, and preclinical evaluation of ARV and non-ARV-based microbicide and MPT candidates.

STRATEGIES

Microbicide, Including MPT, Development and Preclinical Studies

- Discover, develop, and advance antimicrobial and contraceptive microbicide candidates to maintain a diverse and sustainable pipeline of products.
- Develop, standardize, and validate methods and algorithms to assess the antimicrobial and contraceptive activity of microbicide candidates.
- Develop, standardize, and validate new technological approaches and biomarkers to document microbicide safety, efficacy, and adherence.
- Determine the response of the microbiome to microbicide candidates; sexual activity, including violence; HIV; and other sexually transmitted diseases.
- Conduct preclinical pharmacologic and virologic evaluations of microbicide candidates alone and under diverse biologic conditions, including STIs, physical trauma, and endogenous and exogenous hormone exposure.
- Identify the efficacy and toxicity relationships between preclinical model systems and allometric dose scaling requirements for topical agents.
- Facilitate the advancement of microbicides through the preclinical pathway by supporting studies that meet the Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) requirements for strategy design and scale-up.
- Determine the optimal safety assays for screening microbicide candidates.

OBJECTIVE–C: Formulations and Modes of Delivery To Optimize HIV Prevention

Develop and evaluate safe, acceptable, and effective formulations and modes of delivery for ARV- and non-ARV-based microbicides and MPTs.

STRATEGIES

Formulations and Drug Delivery Strategies (DDS) Supporting the Targeted and Sustained Delivery of Microbicides, Including MPTs

- Develop and optimize microbicide formulations and delivery systems to be used in concurrence with or independent of coital activity that minimize toxicity and maximize product acceptability, adherence, and effectiveness.
- Identify and validate methods that improve the understanding of rheological and physical properties of microbicide candidate formulations and their impact on product acceptability and adherence before, during, and after intercourse.
- Evaluate the interaction of cultural and coital practices among men, women, and transgender individuals on the physiology, rheology, and safety of microbicide candidates.
- Discover, develop, and validate methodologies to evaluate DDS and the formulation of individual and combination microbicide products.
- Identify GMP requirements and tests needed to ensure candidate microbicide product stability, longevity, and shelf life.

OBJECTIVE–D: Conduct Microbicide and MPT Clinical Trials

Conduct clinical safety and efficacy studies on candidate microbicides and MPTs that include assessments of acceptability and adherence.

STRATEGIES

Clinical Trials of Candidate Microbicide and MPT Products

- Identify communities in which to conduct microbicide and MPT clinical trials with adequate HIV and other STI incidence in domestic and international settings,
- Develop, implement, and evaluate novel HIV and other STI testing assays and incidence assessments to support clinical studies.
- Study the systemic and local PK and PD of microbicides in multiple formulations and delivery systems and the effect of intercourse and other physical and biologic alterations on PK and PD.
- Identify biological, behavioral, and sociocultural factors that influence effectiveness, adherence, and outcomes in microbicide clinical trials.
- Assess and integrate community-level cultural beliefs, practices, and expectations in the design, development, and implementation of microbicide clinical trials.
- Develop and optimize systems to more rapidly and accurately measure and enhance adherence in microbicide clinical trials.
- Optimize strategies to recruit and retain participants in clinical studies who are representative of HIV-affected and at-risk populations. Investigate the differences between trial participants and the general population in a clinical trial community that may affect Phase IV clinical effectiveness.
- Develop and implement the use of standardized biological and behavioral measures to facilitate the combination and comparison of data from different microbicide studies.
- Conduct clinical bridging studies in HIV-infected and uninfected populations, including adolescents; lesbian, gay, bisexual, and transgender (LGBT) individuals; and women who are pregnant, breastfeeding, peri- or postmenopausal, or over the age of 50; to evaluate the PK, safety, and acceptability of and adherence to microbicide candidates.
- Conduct Phase IIB and Phase III studies designed to test the effectiveness of candidate microbicides and combined prevention approaches.
- Define and develop plans to address the ethical, legal, and regulatory challenges inherent in the inclusion of younger adolescents, LGBT individuals, and pregnant or lactating women as participants in microbicide research.
- Conduct followup research with participants who seroconvert while participating in microbicide clinical trials to assess the impact of product use on HIV pathogenesis, ARV resistance, and other adverse events.
- Conduct followup research on infants born to women who conceive while participating in microbicide clinical trials to evaluate long-term effects of exposures.

OBJECTIVE–E: Conduct Microbicide Behavioral and Social Science Research

Conduct basic and applied behavioral and social science research to inform and optimize the effectiveness of candidate microbicides and MPTs.

STRATEGIES

- Study the sociocultural and behavioral factors (e.g., HIV risk perception, fertility expectation, etc.) associated with product use that may affect the acceptability, effectiveness, and adherence to microbicides.
- Conduct research on acceptability, adherence, and effectiveness of microbicide candidates used in combination with other biomedical, behavioral, and community-level HIV prevention interventions.
- Conduct behavioral and social science research to inform and optimize the development, testing, acceptability, and adherence to topical and systemic microbicides.
- Conduct operations and cost-effectiveness research on behavioral and social science interventions designed to support microbicide implementation.
- Conduct research to understand the behavioral, social, and cultural norms that can affect the scale-up and distribution of microbicide products.
- Conduct studies to provide insight into the motivators, facilitators, and barriers to participation in microbicide research and how they can influence acceptability of and adherence to these prevention products.

OBJECTIVE–F: Microbicides Infrastructure

Establish and maintain the infrastructure needed to conduct research on microbicides and MPTs.

STRATEGIES

- Establish and strengthen training and infrastructure for the development of domestic and international institutional capacity for the discovery, development, and clinical study of candidate microbicides.
- Provide research training and career development opportunities for new microbicide investigators involved in HIV and HIV-related research.
- Provide opportunities for collaboration between microbicide researchers, other HIV research scientists, and non-HIV researchers whose work can assist the development and evaluation of microbicides.
- Support the development of GLP, GMP, and Good Clinical Practice requirements for product research and advancement and to enhance clinical testing of candidate microbicides.
- Develop and evaluate strategies for the collaborative involvement of domestic and international community representatives and leaders, regulatory agencies, advocacy groups, and researchers in the planning and implementation of research and the assessment of outcomes from microbicide and MPT studies.
- Conduct research to inform community and countrywide implementation of microbicides.
- Develop and evaluate effective communication strategies for key stakeholders (e.g., communities, researchers, and regulatory agencies) to support all phases of microbicide and MPT research and development.
- Foster strategic and synergistic public and public–private partnerships to support microbicide research and development activities, accelerate product development, and facilitate efficient use of resources.

AREA OF EMPHASIS

Behavioral and Social Science

FY 2015 RESEARCH PRIORITIES

- Improve the understanding of complex biological–behavioral, developmental, and social/environmental interactions (including political, economic, and natural events, as well as more localized phenomena such as the specifics of local geography and neighborhoods) that affect HIV transmission risks over the course of exposure, acute infection, chronic infection, and treatment; promote the development and use of research methods needed to capture and analyze these complex interactions, using community-based participatory research where appropriate.

- Conduct translational research (i.e., dissemination, implementation, or operational research) to foster and optimize the use of existing efficacious biomedical, behavioral, and social interventions to prevent, diagnose, and treat HIV infections and to promote access, acceptability, adherence, and continuation along the cascade from prevention to treatment, particularly among those currently underrepresented in such research (e.g., noninjection substance users, men who have sex with men [MSM], and incarcerated individuals).

- Study the continued disparities in HIV infection rates, access to testing and care, and treatment adherence and outcomes that are manifest along racial, ethnic, and socioeconomic lines in the United States and in international settings to identify epidemiologic, sociocultural, geographical, psychosocial, and structural factors that could explain the disparities, and suggest opportunities for novel and targeted interventions to reduce them.

- Foster integration of biomedical and behavioral methods and perspectives to develop and test interventions at structural, environmental, and community levels to reduce transmission and acquisition of HIV, especially focusing on: early intervention methods addressing structural factors that have promise for large, long-term impact; the role of stigma in prevention strategies for specific communities, such as racial and ethnic populations, MSM, youth, women, transgender individuals, and young adults in high-prevalence or high-risk areas; and older adult populations engaging in risk behaviors.

- Evaluate the use of social media, mobile devices, and other rapidly changing platforms for communication, social networking, community building, and partnering as tools to reduce HIV acquisition and transmission through sexual behavior, drug use, and alcohol use, and to improve treatment adherence, recognizing the interdependencies among existing barriers and the need to address multiple levels of interventions.

- Promote the use of laboratory-based behavioral and social methods with human participants to more intensively examine risk behaviors and HIV-related outcomes, to elucidate antecedents and determinants of risk, to clarify behavioral topography, to rigorously examine the role of alcohol and other drugs in risk behaviors, and to understand social forces affecting risk; develop methods to improve the ecological validity of laboratory studies.

- Evaluate approaches to maintaining the highest ethical standards in the conduct of HIV prevention science in order to ensure meaningful informed consent processes, decrease misunderstandings of the implications of clinical trial participation, minimize the risk of inadvertent harm to participants, and promote justice in research through the inclusion of difficult-to-recruit but critical populations.

- Evaluate how providers and at-risk individuals and groups negotiate the increasingly complex HIV prevention and treatment environment, including use of biomedical measures, different testing modalities and treatment regimens, and risk-reduction strategies for which there is currently little documentation of efficacy (e.g., using home-based testing as partner screening and other partner selection algorithms).

OBJECTIVE–A: Preventive Intervention Research

Conduct research to develop, evaluate, and implement behavioral, social, structural, environmental, and economic interventions that prevent HIV transmission and acquisition by targeting at multiple levels factors known to drive the epidemic.

STRATEGIES

- Estimate the efficacy, effectiveness, and cost-effectiveness of tailored behavioral, social, and structural interventions to maximize their potential, when deployed singly or in combination, for preventing HIV infections. Apply basic behavioral and social science research to optimize intervention strategies.
- Conduct new research to identify the active components of efficacious, theory-based interventions for broader, sustainable implementation.
- Modify, adapt, or refine existing efficacious behavioral or social HIV prevention interventions to increase their impact and make them more easily administered to segments of the population most vulnerable to the epidemic.
- Study structural and systems-level interventions that seem likely to produce lasting impact over time by addressing the development of risk in youth.
- Develop and evaluate behavioral and social interventions to improve "seek, test, treat, and retain" programs and to enhance the use of HIV diagnosis and treatment for prevention purposes and to improve adherence along the "treatment cascade."

Populations and Contexts

- Develop and test interventions targeted at HIV-infected persons to reduce sexual and drug-use behaviors that confer the greatest risk for HIV transmission.
- Conduct intervention research that addresses the impact of alcohol and/or drugs on sexual encounters that may contribute to HIV transmission and acquisition.
- Conduct research that addresses victimization history to reduce HIV transmission and acquisition.
- Develop interventions addressing modifiable determinants placing members of population subgroups at greatest risk for HIV transmission and acquisition (e.g., MSM, transgender individuals, ethnic minority heterosexuals, injection drug users, and migrants).
- Continue development of interventions for persons with comorbid psychiatric and physical disorders.
- Conduct studies on medication-assisted substance abuse treatment modalities and access to care (e.g., methadone maintenance, buprenorphine/naloxone, modafinil, naltrexone, and antabuse) alone or in combination with mental health and behavioral interventions, as HIV interventions.
- Examine the impact of widespread antiretroviral therapy (ART) availability on willingness to be tested for HIV, willingness to provide HIV testing, and decreased stigma associated with HIV.
- Conduct research on populations in which epidemiological evidence suggests a need for more effective HIV prevention interventions.
- Conduct intervention research that addresses important determinants of risk among disproportionately affected groups that continue to demonstrate high-risk behaviors. Develop, test, and evaluate interventions that target individuals within prisons, jails, under justice system supervision, or returning to society from correctional settings.
- Develop, test, and evaluate interventions to improve linkage to existing systems of care that serve at-risk populations, including those that address single factors associated with incident HIV infections in isolation (e.g., sexually

transmitted infection [STI] clinics) and those that do not routinely provide HIV prevention services (e.g., primary care or mental health clinics).

- Foster the development of intervention strategies that adapt rapidly to changes in the epidemic.

Effectiveness

- Develop, test, and evaluate interventions that target a range or combination of levels of social organization (i.e., individual, dyad, family, network, community, institution, and society) and that examine how these levels interact to affect HIV risk and protective behavior and HIV transmission in different cultural contexts.
- Conduct studies to identify key components of efficacious interventions and processes that facilitate behavior change.
- Conduct research to improve the transfer and scale-up of effective HIV interventions, particularly research on the diffusion, adoption, adaptation, and maintenance of efficacious HIV interventions. Evaluate novel interventions identified as high priority by HIV community-planning groups and other service providers.
- Conduct research on the long-term impact of HIV prevention interventions on individuals and communities (i.e., 5 or more years postintervention).
- Develop and test the efficacy of adaptive preventive interventions, in which different levels of certain prevention components are assigned to different individuals, with levels varying in response to the intervention needs of the individuals.
- Study the impacts of multicomponent interventions that integrate behavioral and social approaches with other perspectives.
- Intensively investigate the outcomes of intervention studies, perhaps in select subjects, to fully understand the natural course of behavior change resulting from the intervention.

Systems

- Conduct studies to understand and improve the organization, financing, management, access, delivery, cost-effectiveness, and cost-utility of health care (including care for substance abuse and other psychiatric disorders), family reproductive health services, and other services that reduce HIV-risk behaviors and HIV transmission.
- Conduct research to understand and improve comprehensive care that reduces HIV transmission through reducing the fragmentation of HIV prevention, primary medical and dental care, drug and alcohol treatment, mental health treatment, STI treatment, reproductive health services, services for orphans and vulnerable children, and other care services. Conduct research on integrating HIV prevention interventions into addiction treatment settings, with emphasis on behavioral treatments, alone or in combination with pharmacotherapies, for both HIV-infected and -uninfected patients.
- Conduct intervention research on strategies for improving the willingness and capacity of communities to adopt and sustain primary prevention interventions.
- Conduct research to develop flexible, pluripotent prevention intervention strategies for health care delivery systems providing prevention or treatment in other domains, such as family reproductive health services, alcohol and substance use treatment, and psychiatric care.

Methods

- Design and test behavioral interventions for highly vulnerable segments of the population to increase recruitment, retention, and adherence to protocols for HIV prevention research, including trials studying prophylactic vaccines, access to and use of HIV testing, microbicides, and other biomedical prevention methods.
- Encourage, where appropriate, the use of quasi-experimental designs and the evaluation of natural experiments in domestic and international HIV intervention research.

- Integrate behavioral, social, and biological measures to improve sampling, measurement of risk factors, and evaluation of outcomes, including measures of substance use, recent HIV infection, population-based outcomes (e.g., seroepidemiology), recent sexual exposure, and STIs, with the overall goal of increasing the reliability and validity of measurement and sampling in prevention research.

- Conduct behavioral intervention studies that include HIV seroincidence data and other biologic markers as outcome measures.

- Foster development of new, rigorous approaches for sampling "hidden" or "difficult to reach" populations in intervention studies.

OBJECTIVE–B: Basic Behavioral and Social Science Research

Conduct basic social and behavioral research on factors influencing HIV risk and on the consequences of HIV disease: Conduct basic social and behavioral research to strengthen understanding of the determinants, processes, and cultural and contextual issues influencing HIV-related risk and protective behaviors and the consequences and impact of HIV disease, including treatment for and management of HIV infection. This includes domestic and international research that examines the societal, community, organizational, social network, dyadic, and individual barriers to and facilitators of the adoption and utilization of effective preventive and treatment interventions across the life course.

STRATEGIES

Continuing Critical Areas

- Conduct basic research to better understand the impact of HIV preventive and therapeutic regimens on treatment adherence for HIV and co-occurring infections, sexual risk behaviors, drug-related risk behaviors, and psychosocial adaptation (i.e., improved quality of life).
- Examine genetic, epigenetic, neurobiological, cognitive, motivational, and other mechanisms that underlie HIV-risk behaviors and health decisionmaking.
- Develop new models of behavior change that integrate biological, psychological, and social perspectives to explain and predict the adoption and maintenance of HIV-risk and HIV-protective behaviors among vulnerable populations.
- Conduct theory-building studies developed in the context of HIV prevention research, as well as evaluation of theories originally developed for other contexts (e.g., drug and alcohol abuse prevention, family reproductive health, and interpersonal social skill development) to see how they can inform HIV prevention research.
- Elucidate genetic and epigenetic factors associated with risk behaviors and behavior change.

Consequences of HIV Disease

- Conduct (nonintervention) research on the decisionmaking processes and behaviors of health care workers regarding the offering of HIV counseling, testing, and other prevention services, as well as the prescription of HIV disease treatments, to those in need of HIV services and care; investigate the relationships between the health care workers' decisions and those of patients, family members, and community members.
- Conduct research concerning the health and life course of children, including orphans, affected by HIV. This research should include early identification and assessment of affected children for physical, psychological, and social consequences.
- Identify the neurobiological, behavioral, cognitive, social, and economic consequences of HIV disease for HIV-seropositive individuals (including children), their support systems (e.g., partners, family members, and other caregivers), health care systems, and communities.
- Conduct research on the economic and social implications for retired and older individuals who provide support and care to younger family members or friends with HIV/AIDS and their dependents, including studies of the support systems that may be in place for such individuals.
- Conduct behavioral research to study end-of-life transition strategies for patients with AIDS and their caregivers.

- Conduct interdisciplinary research, involving behavioral and biomedical scientists, to determine the relationships among stress, mood disorders, immune system functioning, and HIV infection, and to examine the psychosocial and physiological factors affecting those relationships.

- Conduct studies on animal models of behavior and behavioral change relevant to HIV infection and prevention; in particular, conduct behavioral neuroscience and neuropsychological research to determine the brain/behavior changes associated with exposure to HIV, the effects of HIV exposure on social behaviors (e.g., mother–infant attachment and peer interactions), and behavioral changes in relation to comorbidities of HIV and substance use and addiction.

- Conduct research on the impact of HIV and its clinical course on aging and adult development, with attention to the consequences of accelerated physical aging that may accompany HIV disease and its clinical course.

Prevention

- Study the acquisition and maintenance of HIV-related risk and protective behaviors associated with HIV transmission or disease progression in specific social and cultural contexts, such as the sexual dyad, peer groups, social and substance-using networks, families, and communities. This may include studies of HIV risk, transmission, and progression as related to cultural norms that affect disempowerment of and violence toward women.

- Study HIV risk changes over time as a function of changes in the perceived severity of or susceptibility to HIV disease and developmental and life-course events (e.g., adolescence, childbearing, marriage or entry into other committed partnership, divorce and separation, and aging).

- Conduct research on decisionmaking processes that relate to sexual and drug-related risk-taking across the life course.

- Conduct multidisciplinary research that investigates the biobehavioral and sociobehavioral determinants of sexuality, including processes of sexual and gender identity formation, as they relate to HIV risk.

- Conduct research on partner selection and relationship dynamics, including how partner choice, partner formation, relationship development, concurrency, sero-sorting, and partner stability change over the life course and affect HIV risk and HIV-related behavior; studies should examine psychological, cultural, and social factors that influence these phenomena. Interactions of alcohol/drug use with partner selection and demographic trends in partnering, as related to HIV risk, also should be addressed.

- Conduct multidisciplinary research that investigates biobehavioral and sociobehavioral determinants of injection drug use and the transition from noninjection to injection drug use as they relate to HIV transmission; such research also may include studies that investigate the relationship between any drug use and sexual risk behaviors.

- Conduct research on individual social and cultural differences in human sexuality that have an impact on the sexual transmission of HIV; such research may include studies that examine how sexual behavior is affected by substance use and abuse, sexual abuse or coercion, developmental processes, and the formation and dissolution of intimate relationships.

- Study the social, structural, cultural, and demographic factors (e.g., socioeconomic status, marital status, ethnicity, sexual identification, gender identification, age, and gender) that influence HIV-related behavior.

- Conduct research to understand how and whether communities engage in HIV preventive interventions, including studies to determine how to better ensure the use of prevention research findings by communities and public health entities in the United States and abroad.

- Conduct research that investigates the impact of structural issues on HIV transmission and acquisition.

- Conduct research that identifies the social and behavioral factors affecting recruitment, retention, and adherence to prevention interventions, including clinical trials of HIV-related vaccines, microbicides, and therapeutics.
- Conduct behavioral and social research on the acceptability, initiation, and use of biomedical and barrier HIV prevention methods and determine their impact on adherence to risk-reduction guidelines.
- Conduct behavioral and social research on the acceptability, initiation, and use of methods for HIV screening, counseling, and testing, and determine their impact on adherence to risk-reduction guidelines.
- Conduct behavioral surveillance research that measures changes, especially as a function of the diffusion of information and Internet use, in norms, attitudes, and expectancies regarding behaviors associated with HIV transmission and acquisition.
- Conduct research to identify how alcohol use (e.g., binge drinking trends) affects HIV risk among selected age groups.
- Study factors that enhance or preclude partner notification and the impact of partner notification on HIV testing and risk reduction.
- Evaluate consequences of coercive sex, sexual violence, and interpersonal violence on concurrent and subsequent sexual and drug use risk behaviors, with consideration of how intervention can mitigate or prevent coercion, violence, and their consequences.
- Evaluate the impact of assortative and dissortative mixing on HIV transmission rates, and identify modifiable factors related to these patterns of mixing.
- Conduct clinical studies on the role of alcohol in risk for HIV, including studies that provide evidence on the ecological validity of various experimental designs.
- Utilize clinical studies to better define risk behaviors and to inform prevention studies regarding points of intervention or measurement of variables (e.g., cues) associated with risk behaviors.

OBJECTIVE–C: Consequences of HIV Infection

Conduct treatment, health, and social services research for people infected with and affected by HIV: Study the development, evaluation, diffusion, and adoption of strategies to increase early identification of HIV infection; to improve treatment adherence; and to prevent or minimize the negative physical, psychological, cognitive, and social consequences of HIV infection, including stigmatization of persons with or at risk for HIV infection. Foster research strategies for promoting effective health care utilization among all persons with HIV infection and for promoting modifications in the health care delivery system to develop more effective, socially appropriate, and culturally sensitive methods to better serve treatment needs of infected populations, both domestically and internationally.

STRATEGIES

Treatment and Care

- Develop and test interventions to modify the practice behaviors and decisionmaking processes of health care providers to improve the quality of screening, diagnostic, counseling, and treatment services for HIV-infected persons.
- Conduct research on adherence to treatment regimens, including studies on communication techniques to improve shared decisionmaking between health care providers and HIV-infected individuals; issues such as how and when to initiate, interrupt, or cease therapy; and behavioral strategies to manage symptoms secondary to treatment protocols.
- Study how providers, policymakers, and at-risk individuals and groups negotiate the complex HIV care environment, including use of research-based and non-research-based risk-reduction strategies.
- Promote research to identify and remove barriers to effective health care utilization among persons with HIV infection, including barriers associated with fear and stigmatization that affect access, linkage, engagement, followup, and adherence to health and social services across the care continuum (e.g., early identification of HIV infection, testing and counseling, health-care-seeking behavior, adherence, case management, and home/hospice care) and across the life course (i.e., from childhood to old age).
- Develop and test interventions to increase recruitment, adherence, and retention in HIV/AIDS clinical trials and care by HIV-infected persons from all vulnerable populations, with special attention to developmental and life-course issues.
- Conduct health services research and evaluation research to determine the impact of changes in the health care delivery system on HIV/AIDS care.
- Conduct research to foster more effective participation in treatment planning, decisionmaking, and formulating advance directives by patients with HIV and their families.
- Conduct research on the special factors affecting adherence in older seropositive persons and medical decisionmaking in the care of older seropositives.

Biopsychosocial Consequences

- Develop and evaluate interventions to prevent the adverse psychological and social consequences of HIV infection and to assist HIV-affected populations in coping with HIV infections, maintaining quality of life, and avoiding engagement in HIV-related risk behaviors.
- Test interventions to address the neuropsychological, neurodevelopmental, and psychiatric sequelae of HIV infection.

- Develop and evaluate interventions to minimize the impact of stigmatization on HIV-infected persons, including on their decisions regarding treatment and quality of life.

- Test interventions designed to support formal and informal caregivers and family members of HIV-infected persons in order to prevent, for example, depression and burnout.

- Conduct research to enhance the quality of life and minimize the impact of pain, fatigue, physical symptoms, and treatment side effects and to integrate effective palliative care throughout the course of treatment for all people living with HIV and AIDS.

OBJECTIVE–D: Research Methods

Improve the quality of behavioral and social science methodology in HIV research: Conduct research to advance innovative quantitative and qualitative methodologies to enhance behavioral and social science on HIV prevention and care, and to address pressing ethical issues in the conduct of such research.

STRATEGIES

Measurement

- Use state-of-the-art methodologies, such as item response theory and computer adaptive testing, to measure patient-reported outcomes.
- Develop improved methodologies for collection and analysis of quantitative and qualitative data—including methods for obtaining and validating self-report data, culturally appropriate standardization of measurement tools for surveys, and the measurement of change over time—based on an assessment of the current status of qualitative and quantitative methodologies for studying behavioral and social factors associated with HIV and AIDS.
- Develop and strengthen research instruments that are culturally and linguistically appropriate for subpopulations (e.g., HIV-infected children, sexual minorities, the elderly, and incarcerated populations) and that reflect age-appropriate concerns.
- Develop and refine techniques for measuring social networks associated with HIV transmission.
- Develop and refine techniques for studying the use of digital technology, social media, and other innovations and their association with HIV transmission.
- Integrate behavioral, social, and biological measures to improve sampling, measurement of risk factors, and evaluation of outcomes, including measures of substance use, recent HIV infection, recent sexual exposure, and sexually transmitted diseases.
- Develop improved methods for the reliable and valid collection of sensitive information regarding sexual and drug-use risk behaviors.
- Develop and/or adapt innovative substance abuse assessment approaches.
- Assess new methodologies for testing the efficacy of environmental-level (e.g., laws and policies) interventions for reducing HIV risk.
- Conduct research to determine under what circumstances each of the following outcome measures—alone or in combination—is appropriate to use: self-report measures, HIV infection, and other disease outcomes, such as other STIs and blood-borne diseases.
- Develop improved qualitative approaches to theory building and to measurement of HIV-related behaviors, behavioral change, and factors that influence behavior and behavioral change.
- Develop improved approaches to formulate, integrate, and analyze theories founded on qualitative and quantitative observations.
- Develop and refine outcome measures and indicators appropriate for the evaluation of social policy and the societal impact of HIV prevention and treatment interventions.
- Develop new or improve existing adherence measures to more accurately measure adherence to treatments or to prevention protocols.

Modeling

- Develop and refine mathematical models for linking behavioral change interventions with a reduction in HIV transmission at different levels of seroprevalence.

- Improve methods for forecasting and modeling AIDS caseloads, health care needs, and health care utilization under different treatment and survival scenarios and for forecasting and modeling prevention services needs. Greater consideration needs to be given to probabilistic relationships among risk factors and other contributing variables, as well as practical constraints in the implementation and uptake of interventions.

- Develop and refine models of potential efficacy of environmental-level (e.g., laws and policies) interventions for reducing HIV risk.

- Develop and refine models of potential efficacy of network and dyad-level interventions for reducing HIV risk.

Design and Statistical Analysis

- Develop improved methods for sampling subpopulations (e.g., children, homeless persons, drug users, the elderly, sexual minorities, adolescents, and MSM of color) and spatial units (e.g., migration routes, drug or human trafficking routes, and political jurisdictions of interest), with particular attention to "hidden" or "hard to reach" populations.

- Research strategies for recruiting difficult-to-reach but critical populations, such as MSM, racial and ethnic populations, transgenders, women, adolescents, and other underaddressed or insufficiently understood groups, to better understand how to involve them in relevant research projects.

- Develop or adapt from other fields improved and innovative methods and techniques for conducting and analyzing longitudinal studies of at-risk and HIV-infected populations, including improved participant retention strategies; statistical methods for dealing with participant attrition, missing data, and non-normal distributions; and methods for measuring and analyzing nonlinear patterns of behavior change.

- Foster the development and dissemination of design alternatives to the randomized controlled trial that permit cost-effective evaluation of combination intervention strategies that simultaneously target factors that increase risk for HIV transmission or acquisition.

- Foster the development, maintenance, and use of shared databases that will enhance the ability to identify and detect significant interactions between and within a variety of behavioral domains and also to identify the role of behavioral actions as mediators of biological outcomes of importance in HIV research.

Ethics and Other Issues

- Evaluate the effects of legal and ethical constraints on methods of HIV research and service delivery, particularly among vulnerable or special populations.

- Use behavioral and social research methods to investigate factors associated with particular ethical and legal principles in research design (e.g., competence to provide consent, prevalence of adverse events, and associated remedies).

- Develop and refine research techniques to advance new studies as required by epidemiologic findings on HIV transmission. Encourage secondary data analysis; develop approaches to protect and document confidentiality.

- Develop and test an ethical framework for the use of biomedical interventions (e.g., ART) for HIV prevention that encompasses issues such as misconceptions of the preventive efficacy of experimental products, ensuring informed consent over the course of longitudinal studies, and the provision of products for HIV prevention that may not be available to persons living with HIV.

- Foster research designs that will be able to uncover the mechanisms of action in successful interventions that may be transferred and applied elsewhere.

- Evaluate the ethical considerations related to control groups and various approaches for comparison groups in clinical trials, examining the content and constructs utilized.

AREA OF EMPHASIS

Treatment as Prevention

FY 2015 RESEARCH PRIORITIES

- Develop safe, effective, feasible, and conveniently administered strategies for the prevention of HIV transmission, including mother-to-child transmission (MTCT), with a focus on resource-limited settings and a special emphasis on breastfeeding transmission.

- Evaluate the mechanisms of treatment failure and develop novel strategies to maintain long-term undetectable viral load in HIV-infected individuals in domestic and international settings and to evaluate the impact of these strategies on the prevention of HIV transmission.

OBJECTIVE–A: Approaches To Interrupt Vertical Transmission and Preserve Maternal Health

Develop and assess strategies to prevent MTCT, with emphasis on strategies to prevent transmission through breastfeeding and short- and long-term effects of interventions for preventing MTCT on the health of women and infants.

STRATEGIES

Mechanisms of Transmission

- Investigate the mechanisms and timing of MTCT to facilitate and develop targeted drugs and strategies that further decrease MTCT or provide alternatives to currently identified effective strategies, including passive and active immunization strategies.
- Evaluate the effects of acute HIV infection during pregnancy and lactation on MTCT.
- Investigate risk factors (e.g., immune, viral, and host-related, including infant microbiome and premastication) associated with transmission of HIV *in utero* and peripartum through breast milk.
- Develop reproducible, sensitive, and specific assays to detect and quantitate the amount of cell-free and cell-associated virus in breast milk and in oral and genital fluids.

Interventions and Trials To Evaluate Interventions To Prevent Transmission

- Develop and evaluate novel strategies for preventing transmission of HIV from pregnant women to their offspring, and evaluate the impact of those strategies on maternal health and treatment options; such strategies may include long-acting antiviral agents, novel delivery methods, anti-HIV immunoglobulin, monoclonal antibodies, agents targeted to cellular targets (e.g., blocking cytokine receptors), cell- and gene-based strategies, HIV vaccines, and adjuvants.
- Develop safe, affordable, and conveniently administered strategies to prevent MTCT in resource-limited nations, including specific strategies to maintain HIV-free survival of breastfeeding infants.
- Evaluate the pharmacokinetics and safety of antiretroviral (ARV) drugs in pregnant women and their fetuses/infants, and the penetration of ARV drugs into breast milk and genital fluids.
- Evaluate strategies for reducing MTCT when maternal antepartum and intrapartum antiretroviral therapy (ART) is not given or available (e.g., postpartum prophylaxis of the infant only) and for preventing MTCT in the setting of acute maternal infection during pregnancy or breastfeeding.
- Evaluate and validate safe conception strategies for both serodiscordant and seroconcordant couples, including use of pre-exposure prophylaxis (PrEP), sperm-washing, in vitro fertilization, and other novel methods.
- Conduct research and development of new clinical trial designs, statistical methodologies, and investigation of biologic markers, surrogates, and/or other outcomes to evaluate the activity, clinical efficacy, or reasons for failure of new agents and approaches in prevention of mother-to-child transmission (PMTCT).
- Use and/or develop suitable animal models to evaluate novel strategies to prevent transplacental and postpartum breastfeeding transmission of HIV, and to evaluate transplacental passage of ARV agents and their effects on placental function and on fetal development and viability.

Issues Related to ARV Drug Resistance

- Evaluate the effects of pre-existing viral drug resistance in pregnant women on the effectiveness of ARV regimens to prevent MTCT.
- Determine optimal ways to assess adherence to ARV regimens in pregnant and postpartum women and association of adherence with development of viral drug resistance in the mother (and infant, if infected).
- Evaluate the risk for the development of HIV variants with detectable ARV drug resistance in pregnant women who receive different types of ARV prophylactic regimens and in their infants, and the kinetics and durability of such resistance in cell-free and cell-associated virus in plasma, breast milk, and genital secretions. Determine optimal ARV regimens that minimize the development of ARV drug resistance in the mother (and infant, if infected).
- Evaluate the effects of developing drug resistance following ARV prophylaxis on the health and response to future ART in women, including the impact on PMTCT for future pregnancies, and in infants who become infected with HIV despite prophylaxis.

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

- Evaluate whether pregnancy increases the risk of potential ARV toxicities, the pathogenesis of such toxicities in pregnancy, and clinical findings or laboratory assays that might be predictive of such effects.
- Study the effects of ARV regimens used during pregnancy for treatment of maternal HIV disease on maternal health and pregnancy outcome.
- Evaluate the short- and long-term clinical, immunologic, and virologic effects of receiving ART during pregnancy and breastfeeding and stopping after transmission risk has ceased if the woman does not require ART for her own health—as per adult guidelines for non-pregnant adults—versus initiation of life-long ART in pregnancy regardless of CD4 count or clinical stage.
- Evaluate the potential mechanisms for possible carcinogenic or mutagenic effects of *in utero* ARV exposure.
- Evaluate the pathogenesis of potential ARV toxicities (e.g., mitochondrial toxicity and bone toxicity) in uninfected, HIV-exposed infants with perinatal ARV exposure, and develop animal models or laboratory assays that might be predictive of such effects with exposure to an individual ARV agent alone or in combination with other ARVs.
- Develop better clinical algorithms and laboratory assays to diagnose/assess mitochondrial toxicity associated with ARV exposure in infants and children.
- Develop studies that assess the long-term effects of *in utero* and/or postpartum exposure to ARVs on both HIV-infected and -uninfected children, both domestically and internationally.

Implementation Issues

- Develop and evaluate strategies for implementation of effective perinatal transmission prevention interventions in resource-limited countries, including ways to increase availability and acceptability of prenatal HIV testing and of ARV prophylaxis to prevent MTCT.
- Develop and evaluate rapid and improved diagnostic procedures to allow the earliest possible determination of HIV infection in infants, especially in resource-limited settings, and assess whether ARV and/or immunopreventive therapies affect the timing and sensitivity of these assays for diagnosis.
- Develop innovative methodologies for resource-limited countries to evaluate the impact of maternal ART (particularly ART being received at the time of conception and throughout pregnancy) on pregnancy outcome and birth defects.
- Evaluate the cost- and population-effectiveness and public health impact of programs to prevent MTCT.

OBJECTIVE–B: Therapeutic Approaches To Prevent Horizontal Transmission

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

STRATEGIES

Mechanisms of Transmission

- Evaluate the influence of drug resistance on the efficacy of ARV regimens to prevent sexual transmission.
- Evaluate changes in the microbiome, mycobiome, and viriome in HIV-infected individuals, including potential effects on HIV transmission and the effects of treatment on the microbiome, mycobiome, and viriome.
- Develop and/or use suitable preclinical models and clinical studies to evaluate genital, anal, and oral passage of cell-free and cell-associated virus and ARVs.
- Evaluate the influence of systemic HIV treatment on viral shedding in the anogenital tract, as well as the biodistribution of ARVs in the genital tract based on age and sex.
- Evaluate the impact of anti-STI (sexually transmitted infection) treatment on transmission of HIV and HIV shedding in the oropharyngeal or anogenital tracts.
- Develop novel tools and approaches to understand HIV and/or prevention agent interaction with genital, gastrointestinal, or oropharyngeal tract cells and tissues and the mechanisms of HIV transmission in these tissues.

Interventions To Reduce Transmission

- Support domestic and international collaborative efforts to conduct trials of ARV, immunotherapeutic, and other treatment interventions to prevent horizontal transmission in acute and chronic infection, including studies in adolescents/young adults.
- Develop and evaluate strategies for reducing the risk of sexual transmission of HIV without compromising treatment of the HIV-infected individual; such strategies may include ARVs, therapeutic vaccines, monoclonal antibodies, and immunotherapeutic agents, alone or in combination.
- Develop delivery systems for non-topical agents to prevent HIV transmission, including postexposure prophylaxis (PEP), PrEP, and other ARV methods of prevention.

Issues Related to ARV Interventions

- Evaluate the complications of PrEP and PEP and the risk for developing ARV drug resistance (in cell-free and cell-associated virus, and in sequestered genital or anorectal sites) when using ARVs in interventions to reduce horizontal transmission.
- Evaluate the public health impact of ARVs on reducing horizontal transmission.
- Develop the methodology and metrics to assess the outcomes of “test and treat” regimens.
- Identify surrogate markers for PrEP safety and efficacy.
- Develop novel approaches to evaluate data on PrEP and exposure in occupational settings.
- Develop implementation strategies to assess the feasibility and sustainability of PrEP and treatment as prevention within specific high-risk target populations, including studies on cultural barriers and facilitators, factors affecting adherence, treatment effectiveness, and cost-effectiveness.

Adherence

- Support research on the effectiveness of pharmacological approaches, behavioral interventions, and other approaches to improve adherence to ARV regimens and retention in care.

- Develop improved methods and surrogate markers to assess and enhance adherence to treatment regimens across a variety of affected populations; compare and validate adherence measures in the context of HIV treatment.

PRIORITY:

Improving Disease Outcomes for HIV-Infected Individuals

Drug Discovery, Development, and Treatment

Research Toward a Cure

AREA OF EMPHASIS

Drug Discovery, Development, and Treatment

FY 2015 RESEARCH PRIORITIES

- Accelerate the discovery and validation of strategies, targeting new and existing viral and cellular targets that provide safe, tolerable, maximally long-term suppressive antiviral activity.
- Advance the discovery and validation of therapeutic strategies to prevent progression of HIV and its associated comorbidities, including inflammation, coinfections, and other clinical complications across the lifespan of HIV-infected individuals.
- Support research on the mechanisms of HIV persistence and develop strategies to prevent the establishment of, decrease, or eliminate viral reservoirs that persist despite optimal antiretroviral (ARV) treatment.
- Develop and evaluate methods, tools, and intervention strategies that improve entry into, and retention in, HIV care.
- Develop and test strategies to improve adherence to ARV drug regimens and regimens to prevent and treat HIV-associated comorbidities used for treatment and prevention in domestic and international settings.

OBJECTIVE–A: Discover and Develop Anti-HIV Treatments

Identify and validate viral and host cellular functions required for HIV replication that can be targeted for viral inhibition, eradication of persistent virus, and prevention of transmission. Discover and develop novel agents and therapeutic strategies that have enhanced half-life and tissue penetration, as well as therapeutic strategies that are effective against drug-resistant virus. Encourage collaborations among academia, industry, private and public organizations, the community, and the NIH.

STRATEGIES

- Identify, characterize, and validate viral and host targets for anti-HIV therapy. Develop predictive test models, including appropriate lentivirus animal models, to aid in identifying agents and strategies active against these targets.
  - Identify the cellular reservoirs of latent HIV *in vivo* and develop physiologically relevant *in vitro* and *ex vivo* organ or tissue models that can be used to discover agents or approaches that target and eliminate reservoirs.
  - Develop new agents and treatment strategies that target, inhibit, and clear HIV in cellular, anatomical, and organ reservoirs and sanctuaries, including agents that can suppress or eradicate HIV in non-T-cell reservoirs.
  - Characterize novel antiviral agents with respect to their preclinical, immunologic, pharmacokinetic (PK), pharmacodynamic (PD), toxicity, and teratogenicity profiles.
  - Develop new drugs, biologics, extended-release formulations, and routes of administration to increase safety, tolerability, durability, and ease of use of therapeutic agents.
  - Employ whole animal and *ex vivo* organ or tissue models of lentivirus infections to study the biologic and pharmacologic characteristics of therapeutic agents.
  - Acquire structural information on HIV, including the RNA genome, and cell constituents involved in HIV infection and replication for the design of therapeutic agents and therapeutic vaccine candidates with improved potency and selectivity. Post lead structures on publicly available databases.
  - Support genome-wide association studies and integrate systems biology approaches, including genomics and informatics paradigms, concepts, and methodologies, into mainstream drug discovery and development of therapeutic entities and strategies.
  - Develop enabling, rapid, and high-throughput technologies to accelerate and optimize the discovery and development of therapeutic entities and strategies; expand the infrastructure to provide services and reagents needed by the scientific community.
  - Evaluate the intracellular PK and activity of ARV agents in different cell types, different stages of the cell cycle, and in all age groups. Correlate intracellular PK parameters with drug efficacy and toxicity.
  - Develop novel and improved tools for drug discovery and the investigation of drug efficacy.
  - Develop novel and improved tools and systems biology approaches to better understand viral pathogenesis and drug PK in various intracellular and extracellular compartments.
  - Develop novel delivery systems that target specific tissues, cells, organelles, proteins, and nucleic acids.
  - Develop agents and strategies to improve biopharmaceutical characteristics (e.g., bioavailability, tissue penetration, and long-acting formulation).
  - Develop long-acting formulations to improve adherence and achieve drug concentration.

  - Develop enhanced ways to measure and monitor drug adherence and barriers to adherence to antiretroviral therapy (ART).
  - Develop drug delivery devices or systems that improve the PK profile of therapeutic agents, target specific organs or tissues, reduce toxicities and adverse effects, and result in improved adherence to therapeutic regimens.
  - Develop novel agents, taking into account that patients need to be on treatment for an extended time.

- Develop novel bioimaging applications to evaluate viral transmission and reservoirs, immune induction and modulation, and drug transport and metabolism.

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

- Develop therapeutic strategies, including approaches to identify patients in the early stage of HIV infection, with emphasis on prevention of early T-cell depletion in the gastrointestinal tract.

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

- Develop and evaluate interventions aimed at reducing HIV-related immune activation, while also identifying critical pathways by which chronic immune activation leads to end-organ disease.

- Develop mathematical and computer models of HIV infection and therapeutic interventions that simulate and predict *in vivo* cost-effectiveness, efficacy, toxicity, and other outcomes of drug regimens and clinical trials, including generic therapies. Investigate the use of pharmacogenetics in identifying optimal therapies.

- Study the molecular basis of ARV drug toxicities and approaches to reducing these toxicities without loss of antiviral effect.

- Develop and perform the PK evaluation of fixed-dose combination formulations of approved ARV drugs, including doses appropriate for children and geriatric populations.

- Develop and evaluate pediatric drug formulations of available and new ARV drugs, with emphasis on low-dose dividable solid formulations appropriate for use in resource-limited settings, as well as liquid formulations.

- Develop therapeutic agents for the treatment of HIV/AIDS that do not interact with psychotropic medications, drugs of abuse, medications to treat drug abuse, or other drugs.

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

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

STRATEGIES

Clinical Trials of Therapeutic Agents

- Conduct clinical trials of potential therapeutic agents and combinations of agents in adults, including pregnant women and older populations, adolescents, children, infants, and other high-risk populations to determine PK, tissue bioavailability, antiviral activity, effects on the immune system, safety, and clinical efficacy.
  - Evaluate novel combinations of agents selected for maximizing antiviral synergy, complementary mechanism of action, minimal toxicity and cross-resistance, simplicity of administration, and tolerability.
  - Evaluate optimal therapies and novel strategies for individuals who have acute or recent infection (including neonates/young infants with perinatal infection), chronic infection but no prior ART, and those with prior ART, including individuals with multidrug-resistant virus.
  - Conduct clinical trials to study:
    - Long-term effectiveness (including toxicities) of novel therapeutic strategies;
    - Timing, selection, and strategic sequencing of ARV agents to optimize clinical outcome in relevant populations;
    - Simplified and maintenance regimens;
    - Optimal treatment for heavily ARV-experienced individuals with treatment failure;
    - Interaction of the effects of ART on HIV-related comorbidities;
    - Gender-based and genetic differences in special populations;
    - Evaluation of interventions to minimize ART-related comorbidities; and
    - ARVs and regimens that effectively inhibit virus replication in the central nervous system (CNS) and other sites that may be difficult to penetrate.
  - Conduct small clinical studies to validate potential new targets and/or explore novel therapeutics (e.g., cell-based and gene-based).
  - Evaluate coformulated and long-acting ARVs in all age groups.
  - Investigate the effects of class-sparing regimens on efficacy, resistance, and transmission.
  - Evaluate novel approaches and treatment regimens to prevent and eradicate viral reservoirs that may lead to a cure for HIV disease, including perinatally acquired infection.

Clinical Trials Enrollment

- Strengthen efforts and implement new approaches and in novel locations to ensure the enrollment and retention of specific populations, including women, children, adolescents, minorities, substance abusers, men who have sex with men, older adults, and marginalized high-risk populations in clinical trials and cohort-based studies to reflect the incidence of the epidemic.
- Strengthen efforts to evaluate new and existing drug treatment regimens in clinical trials and cohort-based studies that reflect the demographics of the epidemic. When appropriate, evaluate potential gender, race, ethnicity, age-specific, pregnancy-related, and nutrition-related differences in drug efficacy and safety, including PK, metabolism, tissue absorption, and drug elimination.

Clinical Trial Methodology

- Develop and evaluate standardized virologic, immunologic, and clinical markers to assess drug activity; determine and validate surrogate markers in response to various therapeutic interventions, including those most applicable to resource-limited settings.
- Develop novel inexpensive and rapid platforms, as well as point-of-care assay systems, for detection and quantification of HIV, diagnosis of recent HIV infection, ARV resistance testing, CD4 cell count, and adherence to therapy, biomarker evaluation, and genetic testing for both *in vitro* and *in vivo* evaluations.
- Develop, incorporate, and validate appropriate quality-of-life parameters and patient-reported outcome instruments in clinical trials of ARV agents.
- Develop methodologies to facilitate creative statistical analyses that will enhance the understanding of clinical trial outcomes.
- Develop methods to enhance the quality of trial conduct, including improved rates of enrollment, adherence, retention, and currentness of followup.
- Conduct studies on behavioral factors and prevention approaches that are critical to optimizing ART.
- Develop and test novel approaches to evaluate salvage therapy.
- Develop a framework to conduct clinical trials through research on bioethics.
- Develop novel approaches to expedite the development and conduct of clinical trials of anti-HIV treatments.
- Implement an informed consent process that permits patients' samples to be used for future clinical studies.

Pharmacology

- Determine the relationship between drug exposure, PK, pharmacogenomics, and outcomes (antiviral effect, immune function, and safety) to facilitate dosing strategies within clinical trials, as well as for individual patient management, including the utility of therapeutic drug monitoring and potential application of pharmacogenetics and the optimization of clinical trial design through clinical trial simulation.
- Investigate drug interactions, including PK and PD impacts, among commonly used treatments for HIV-related disease and its comorbidities, including medications taken by older individuals for pre-existing conditions, as well as other substances that may be used by HIV-infected individuals.
- Evaluate the effects of other host factors, including dietary intake and nutritional status, on the PK and activity of ARVs.
- Evaluate and optimize tissue penetration and concentration of ARVs.

Viral Reservoirs

- Quantitate persistent HIV in different tissue compartments during effective ART, and evaluate strategies to reduce or eradicate such reservoirs.
- Evaluate the penetration of ARVs into different body fluids and tissue compartments.
- Establish methodologies for accurate measurement of viral reservoirs.
- Develop more sensitive and less complicated tests for resistance.

Viral Resistance and Fitness

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

Mechanisms of Treatment Success/Failure

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

Adherence

- Support research on the effectiveness of pharmacological approaches, behavioral interventions, and other approaches to improve adherence to ARV regimens and retention in care.
- Develop improved methods to assess and enhance adherence to treatment regimens across a variety of affected populations; compare and validate adherence measures in the context of HIV treatment.
- Investigate strategies for managing symptoms that are attributed to therapy, and investigate the relationship between symptom management and improved adherence to ARV regimens.

International

- Expand the development of international collaborations to assist in addressing relevant therapeutic research in populations of HIV-infected adults, adolescents, and children, including studies on factors resulting in early deaths occurring within the first 3 months of treatment/care.
- Assist and encourage resource-limited nations, as appropriate, in technology transfer through training in the United States and on-site in-country, infrastructure, and capacity building to facilitate the evaluation of ARV agents and other therapies in local settings.
- Assess the barriers to delivery of effective health care for HIV disease, including treatment and the capability of conducting international therapeutic clinical trials through the establishment or expansion of multidisciplinary clinical centers.
- Develop standardized clinical indicators to determine how and when to initiate ART, to monitor responses to therapy, and to determine when to change therapy.
- Determine acceptable and practical laboratory monitoring methods for drug toxicity in resource-limited settings.
- Evaluate whether nutritional status (particularly chronic malnutrition) affects the efficacy of therapy and whether it affects the risk or severity of adverse events associated with ART.
- Evaluate ARV safety in pregnancy and lactation for mothers and their infants in resource-limited settings (e.g., prematurity, congenital abnormalities, breast milk ARV penetration, and infant toxicity).

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

Develop strategies to predict, evaluate, treat, and prevent complications of long-term HIV disease and toxicities of ART, and to investigate the role inflammation plays in these complications and comorbidities in HIV infection in domestic and international settings.

STRATEGIES

- Develop and evaluate therapeutic strategies for preventing and treating complications of HIV infection or its treatment.
- Evaluate potential delayed or late effects of ART following short-term administration of prophylactic regimens (e.g., for prevention of mother-to-child transmission [PMTCT]) or chronic drug administration.
- Develop standards that allow better comparison of late complications across clinical trials (i.e., meta-analysis between studies, efficacy of interventions in clinical trials versus effectiveness in public health practice).
- Support research on the pathogenesis and mechanisms of toxicity of drugs used to treat HIV disease.
- Develop and test approaches to prevent, reverse, or reduce potential metabolic abnormalities (e.g., changes in body composition, development of atherogenicity and endocrine disorders, and changes in bone and muscle structure and growth) based on an understanding of the mechanisms by which ART and/or HIV disease may affect metabolic processes.
- Develop and validate early markers of renal, liver, CNS, bone, cardiovascular, and other complications of ART and/or long-term survival with HIV disease.
- Integrate metabolic, endocrine, cardiovascular, neurologic, renal, liver, and musculoskeletal studies, including symptoms and symptom clusters, into ongoing and planned clinical studies, which may provide an opportunity to answer important questions related to HIV disease and the potential complications of ART. Conduct integrative multidisciplinary research for the management of medical complications associated with multiple infections of HIV, coinfections, and comorbidities, including addiction and mental disorders.
- Study the effects of gender, race, age, pregnancy and lactation status, and type of exposure on complications of ART.
- Evaluate the impact of nutritional status, impaired access to safe drinking water, regionally significant coinfections, and other population- and area-specific factors on complications of ART.
- Evaluate whether nutrition and nutritional interventions, provided concurrently with ART, improve clinical outcomes in HIV-infected patients, including lactating mothers.
- Evaluate drug interactions with potential clinical significance for HIV-infected individuals, particularly the PK and PD between ARVs and drugs used to treat HIV-related comorbidities or medications used in the treatment of drug addiction and mental disorders. Develop strategies to avoid or minimize the clinical impact of these interactions across all populations.
- In the context of clinical trials, study the effects of treatment and long-term HIV disease on the natural aging process and vice versa, including development of comorbidities across the lifespan of the HIV-infected individual.
- Define the pathogenesis of chronic inflammation in patients fully suppressed with ART.
- Evaluate approaches to prevent and treat immune activation, inflammation, and/or immune senescence associated with HIV disease and treatment.
- Evaluate the pathogenesis, diagnosis, and treatment of immune reconstitution inflammatory syndrome associated with the unmasking or paradoxical worsening of opportunistic infections following initiation of ART.

- Develop novel tools (including nanotechnology, proteomics, metabolomics, and immunotechnology) for rapid DNA sequence identification to facilitate toxicogenomic research and applications.

- Conduct research to evaluate biomarkers that predict end-organ disease.

OBJECTIVE–D: Prevent and Treat Coinfections

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

STRATEGIES

Preclinical Discovery and Development

- Support appropriate drug development programs to develop therapies against HIV-associated pathogens and their disease manifestations, especially *Mycobacterium tuberculosis* (TB) (including multidrug-resistant TB [MDR-TB] and extensively drug-resistant TB [XDR-TB]), malaria, HCV, HBV, human papillomavirus (HPV), KSHV/human herpesvirus (KSHV/HHV-8), cryptococcal infection, Epstein-Barr virus (EBV), and cytomegalovirus, with emphasis on innovative approaches and agents with favorable bioavailability and PK, as well as development of formulations appropriate for use in children.
- Utilize mechanism-based screening of novel synthetic compounds and natural products to identify candidate agents for treating the most significant coinfections; provide support for medicinal chemistry, structural databases, and toxicity testing.
- Support studies and develop vaccines and interventions for coinfections (e.g., TB, HPV, rotavirus) in HIV-exposed and HIV-infected individuals and other high-risk populations.
- Develop novel platforms for fast, accurate, and cost-effective detection and diagnosis of pathogenic organisms and related biomarkers.
- Develop novel delivery methods to both enhance the efficacy and decrease the toxicity of current and future therapeutic agents.
- Develop nano- and chemical-biology targeting modalities to selectively infiltrate and treat infected compartments, tissues, and cells.

Clinical Trials of Preventive and Therapeutic Regimens

- Assess the impact of new ARV regimens on the risks for and manifestations of infections associated with HIV disease.
- Improve understanding of the interplay between HIV-associated immune deficiencies and the onset and types of infectious complications.
- Improve strategies to prevent multiple infections in the context of ART; determine the optimal timing for initiating or discontinuing prophylaxis for different coinfections, particularly in resource-limited countries; develop improved strategies to minimize toxicities and the development of drug-resistant microorganisms.
- Support clinical trials of preventive and therapeutic regimens for HIV-related coinfections.
- Investigate the effects of maternal immunization for coinfections on pregnant women and on their infants.

Detection of HIV Coinfections

- Develop clinically useful assays and methodologies for early and rapid diagnosis of coinfections (particularly TB) and febrile illnesses, quantitative assessment of microbiological responses, and drug sensitivity testing, including assays appropriate for use in children with coinfections.

- Develop tools to identify HIV-infected individuals at high risk for development of specific coinfections, to improve the efficiency of clinical trial design and the risk–benefit ratio of the currently utilized drugs for prophylaxis and treatment.

Coinfections

- Study the interaction between HIV infection and infectious complications on pathogenesis, presentation, and disease outcomes.
- Develop models for studying biological interactions between HIV and coinfections to accelerate development of improved treatments.
- Support clinical trials, domestic and international, of adults and children coinfected with HIV and TB (both active and latent infection). Evaluate the safety and efficacy of treatment regimens in monoinfected, as appropriate, and coinfected individuals. Determine optimal length of treatment. Evaluate regimens in the context of degree of immunosuppression.
- Investigate surrogate markers of TB disease capable of distinguishing between latent, active, and eradicated infection in coinfected individuals; determine how each infection influences or alters the other disease in respect to progression and response to therapy.
- Conduct clinical trials investigating the efficacy and risks of treatment of coinfections including HBV, HCV, malaria, HPV, and TB in individuals who are coinfected with HIV; determine how each infection influences the other disease in respect to progression and response to therapy.
- Study the interaction of coinfections with HIV transmission (e.g., placental malaria and perinatal infections) and effects on HIV disease progression.
- Investigate the role of HIV-associated coinfections with pregnancy outcomes.
- Develop and evaluate biomarkers for HIV coinfections.

Pharmacology and Toxicology

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

Adherence and Self-Management

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

International

- Conduct clinical trials in adults (including pregnant women) and children to evaluate agents for the prophylaxis and treatment of HIV-associated coinfections; target infections shown to cause significant morbidity by epidemiologic studies, and made worse by HIV-induced immunosuppression.
- Develop and evaluate strategies for treatment and prevention of prevalent opportunistic and endemic infections in the context of HIV infection.
- Evaluate the role of nutrition, malnutrition, and severe malnutrition on treatment and prophylaxis regimens for coinfections.

OBJECTIVE–E: Treatment of AIDS-Related Neurologic Disease

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

STRATEGIES

Preclinical Development

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

- Assess the impact of HIV clade diversity, the generation of HIV variants, and changes in virus tropism on neuropathogenesis and response to therapy.
- Determine anatomical, structural, and genetic contributors (e.g., haplotypes and epigenetics) to neurological vulnerability to HIV infection and related inflammatory processes.
- Conduct studies to determine drug interactions between commonly used treatments for HIV disease and its complications and treatments for drug abuse and co-occurring mental health disorders; develop treatments and regimens that are optimized for HIV-infected individuals with comorbid depression and other psychiatric disorders.
- Develop adjunctive therapeutic agents with both immunomodulatory and neuroprotective functions to reduce comorbid psychiatric conditions (markedly, depression and anxiety disorders) in HIV-infected individuals.
- Develop novel or adapt existing rehabilitative strategies to ameliorate HIV-associated CNS disease manifestations that affect social–emotional, motor, sensory, cognitive, and daily functioning.

Clinical Neuroassessment, Methodologies, and Trials

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

OBJECTIVE–F: Assessment, Prevention, and Treatment of HIV-Related Cancers

Develop and evaluate improved strategies for the assessment, treatment, and prevention of cancer as a comorbidity of HIV disease in domestic and international settings.

STRATEGIES

Preclinical Development

- Promote screening, discovery, and development of novel therapeutic agents with activity against AIDS-defining and/or HIV-associated malignancies, including pathogenesis-based strategies, agents with optimal CNS penetration, agents with optimal safety profiles, and agents that are optimal in resource-limited settings.
- Promote discovery of drug enhancement and targeting modalities for malignancy-specific delivery of therapeutic agents.
- Develop agents utilizing structural, biologic, immunologic, and biochemical information for the prevention and treatment of HIV-associated malignancies.
- Develop preclinical and *in vivo* models for testing potential therapeutic and preventive strategies against HIV-associated malignancies.
- Utilize emerging information on the pathogenesis of malignancy complications of HIV infection, including new viral agents and the role of inflammation, to develop new preventive, diagnostic, and therapeutic strategies for such tumors, including vaccination strategies.
- Evaluate the role of inflammation as an accelerator for the development of malignancies.

Diagnostic Methods

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

Clinical Evaluation of Therapeutic and Prevention Strategies

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

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

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

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

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

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

- Develop and assess preventive, diagnostic, and therapeutic strategies that are appropriate in resource-limited settings for AIDS-defining and other HIV-related malignancies, especially those due to endemic infectious agents (e.g., KSHV/HHV-8), EBV, and HPV).

OBJECTIVE–G: Immune Reconstitution Approaches

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

STRATEGIES

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

OBJECTIVE–H: Management of HIV Disease With Nonpharmacologic and Complementary and Alternative Modalities

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

STRATEGIES

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

AREA OF EMPHASIS

Research Toward a Cure

FY 2015 RESEARCH PRIORITIES

- Further the understanding of fundamental viral and host mechanisms associated with the control and persistence of HIV at the cellular, tissue, and viral level, and identify the sites, mechanisms of persistence, and strategies for host molecular and/or immune containment and eradication of HIV reservoirs.

- Design and test novel approaches to eliminate viral reservoirs and persistent virus, as well as strategies to control viral pathogenesis.

- Identify and validate novel assays to measure the replication-competent viral reservoir. Evaluate the contribution of persistent HIV replication in the presence of effective antiretroviral therapy (ART). Develop and test animal and *in vitro* models that are predictive of HIV eradication.

- Assess knowledge, beliefs, and attitudes toward cure research and the possible scale-up of relevant eradication strategies and approaches.

OBJECTIVE–A: Biology of HIV Infection

Delineate the viral and host mechanisms involved in HIV infection, persistence, and dissemination, and the establishment and maintenance of the viral reservoir. Identify factors involved in the control of HIV disease progression and host restriction in the presence of ART in diverse populations across the spectrum of age, gender, and race and/or ethnicity in national and international settings.

STRATEGIES

Basic Research on the Establishment of Persistent HIV Infection

- Identify and validate viral and host cellular contributions required for HIV persistence that can be targeted for eradication of latent and persistent virus.
- Determine structural information on HIV and cell constituents involved in HIV infection that will inform future design of potent and selective therapeutic agents and therapeutic vaccine candidates needed for eradication.
- Determine the mechanisms by which host and virus-encoded genes or viral gene products regulate and influence establishment of HIV latency infection within specific cell populations and/or tissue compartments.
- Determine cellular or viral factors associated with transition from latent state to active replication.
- Assess the impact of transmission of drug-resistant strains of HIV on reservoir establishment, disease progression, or response to therapy.
- Examine the effect of route and duration of infection and of ART regimens on establishment, persistence, perturbation, and eradication of reservoirs.

HIV Replication and Viral Dissemination

- Determine whether ongoing viral replication occurs in individuals on fully suppressive ART regimens and the mechanisms responsible for ongoing replication.
- Characterize new and understudied viral and host targets, sequence of infection, and mechanisms of viral transfer important for the early dissemination of HIV *in vivo*.
- Evaluate the role and mechanisms of preventing or enhancing HIV replication and dissemination by soluble factors contained within bodily fluids.
- Investigate the role of immune activation, inflammation, immunosenescense, and their mediators in various tissues on the establishment and dissemination of HIV infection.
- Identify immunological predictors of immune control of viral replication.
- Delineate the mechanisms and impact of genetic or environmental factors on immune responses that influence HIV replication and dissemination to lymphoid and other tissues and reservoirs.

Latent and Persistent HIV Reservoirs

- Explore the role of innate and adaptive immunity in governing the size of the latent viral reservoir.
- Identify the tissue and cellular reservoirs of latent or persistent HIV.
- Determine whether latent virus infects and is maintained in non-T-cell populations and the contribution of cells of the monocyte lineage to the HIV reservoir.
- Define the role of different CD4+ T-cell subsets (central, transitional, and effector memory) in the establishment and persistence of latent reservoirs.

- Determine whether HIV clade differences and viral tropism play a role in establishing latent reservoirs.
- Determine the role of host genetics in the establishment and maintenance of latent reservoirs.
- Define sites and mechanisms of latent/persistent HIV infection in patients on suppressive therapy, and the mechanisms by which reservoirs are established and maintained in the presence of ART.
- Develop tools to measure and quantify HIV in reservoirs such as novel imaging techniques.
- Define the molecular mechanisms that lead to the initial establishment, subsequent maintenance, and reactivation of latently infected cells.
- Develop and evaluate novel mechanisms to eliminate HIV reservoirs or prevent viral reactivation in latently infected cells.
- Identify host or environmental factors that may alter the establishment and/or maintenance of tissue and cellular reservoirs.

Disease Progression and Pathogenesis

- Delineate the viral and host mechanisms responsible for the differences between pathogenic and nonpathogenic HIV/simian immunodeficiency virus (SIV) infection.
- Determine the correlates of immune control by studying HIV-infected individuals across the lifespan, and SIV or chimeric simian/human immunodeficiency virus nonhuman primate models.
- Explore mechanisms of host response to HIV or SIV infection that involve the interface between innate, mucosal, and adaptive immunity.
- Elucidate the mechanisms of CD4+ T-cell depletion in the infected host.
- Examine the role of immune dysfunction/dysregulation in HIV or SIV pathogenesis, and delineate the mechanisms leading to pathological immune activation and autoimmunity in HIV or SIV infection.
- Define the sites of infection and replication in the untreated host at the cellular and cell subset levels, both anatomically and functionally; and how cell subset targeting determines disease progression or non-progression.
- Identify the host immune responses to HIV-1, as well as the viral or host factors that enhance or reduce the amounts of circulating virus and influence disease course in long-term non-progressors and elite controllers.
- Delineate the mechanisms by which sexually transmitted infections, other coinfections, comorbidities, environmental factors, and the microbiome (bacterial, fungal, and viral) influence HIV replication and dissemination and contribute to HIV persistence.

Neurological Factors and Reservoirs

- Develop novel strategies to inhibit HIV spread in the central nervous system (CNS) during periods of release from persistently infected cells.
- Assess the pathogenic role of viral sequestration in the CNS, including its potential role as a reservoir of viral persistence and as a site of independent selection of antiviral drug-resistant strains and other mutants.
- Develop therapeutic agents to block HIV entry into the CNS and design novel tools (e.g., nanotechnology) to facilitate and modulate delivery of antiretrovirals (ARVs) and novel eradication agents into the CNS compartments to treat HIV infection.
- Determine the pharmacokinetics/pharmacodynamics (PK/PD) of ARVs in the CNS; determine the importance of CNS drug penetration, particularly penetration of the blood–brain barrier, in reducing CNS infection/reservoirs in neurologically symptomatic and asymptomatic individuals.

Methodology and Animal Models

- Develop cell-based models of the blood–brain barrier to test transport efficiencies of ARVs and transport of HIV into the CNS.
- Develop physiologically relevant *in vitro* and *ex vivo* organ or tissue systems and animal models that can be used to discover agents or approaches that target and eliminate HIV that persists in the presence of ART.
- Develop novel models to study key features of infection, pathogenesis, and latency.
- Develop novel tools and systems biology approaches to better understand viral persistence, pathogenesis, and drug PK in various intracellular and extracellular compartments.
- Develop novel bioimaging applications (including nanotechnology) and bioassays to evaluate viral reservoirs, immune induction and modulation, drug transport, metabolism PK, and PD in tissues that serve as potential viral reservoirs.
- Employ new technology, including computational biology, bioimaging, systems biology, stem cell technologies, and high-throughput technology, to advance the understanding of the earliest events in the establishment of foci of infection, latency, viral reactivation, and dissemination.
- Develop new statistical methodologies, quantitative assessments, clinical trial designs, and selection and investigation of biologic markers to evaluate the safety and clinical efficacy of new agents and approaches in the treatment of neurologic and cognitive complications of HIV disease targeting residual HIV infection in the CNS reservoir.
- Develop or improve sensitive quantitative measures of HIV or SIV in body fluids, including oral and genital secretions and breast milk, and tissue reservoirs, such as lymphatic tissue and the CNS, to assess the effectiveness of interventions designed to control or eradicate HIV infection.
- Coordinate the development of reagents and standardized methods to assess specific HIV or SIV eradication strategies *in vivo*.
- Support collaborative studies using genetic methods applied to diverse populations to elucidate mechanisms of susceptibility to HIV infection, control of disease progression, and related complications.

OBJECTIVE–B: Discover and Develop Strategies Targeted Toward a Cure for HIV/AIDS

Identify and validate viral and host cellular factors and functions that can be targeted for eradication of persistent virus. Discover and develop novel agents and virological, immunological, and cellular therapeutic strategies that are effective in eradicating HIV across the spectrum of age, gender, and race and/or ethnicity in national and international settings.

STRATEGIES

- Develop new agents and treatment strategies that target, inhibit, and clear HIV in cellular, anatomical, and organ reservoirs and sanctuaries, including agents that can suppress and clear HIV in non-T-cell reservoirs.
- Evaluate the intracellular PK and activity of ARVs in different tissue and cell types, different stages of the cell cycle, and across the lifespan. Correlate intracellular PK parameters with drug efficacy and toxicity.
- Develop agents and delivery systems to eradicate HIV with desirable biopharmaceutical characteristics (e.g., improved bioavailability; tissue penetration targeted to specific tissues, cells, organelles, proteins, and/or nucleic acids; reduced toxicities and adverse effects; and long-acting formulation) to facilitate uptake, adherence, and adherence monitoring.
- Advance gene-based strategies to protect cells subject to the cytopathic or cytotoxic effects of HIV infection.
- Determine the mechanisms of action of immunomodulating agents, and develop the most promising approaches alone or in combination with biopharmaceutical agents.
- Design, develop, produce, and preclinically test novel active and passive HIV therapeutic vaccine candidates for safety and for their ability to control or eliminate viral reservoirs.
- Develop and optimize the SIV/macaque model for studies of virus eradication in which the animals are treated with ART and then additional interventions are performed.

OBJECTIVE–C: Conduct Clinical Studies of Strategies Capable of Eradicating HIV

Assess the short- and long-term efficacy and effectiveness of therapeutic agents and novel strategies against acute, persistent, or latent HIV infection and viral reservoirs in HIV-infected individuals across the lifespan, including in older individuals, through the conduct of clinical studies across the spectrum of gender and race and/or ethnicity in national and international settings, especially in resource-constrained nations.

STRATEGIES

- Expand and improve on existing domestic and international partnerships to design and conduct clinical studies.
- Perform pilot studies of evidence-based potential therapeutic agents and combinations to determine proof of concept, validation of assay(s) and method(s), and tissue bioavailability in eradicating HIV reservoirs.
- Conduct clinical studies of potential therapeutic agents and combinations of strategies to determine safety and efficacy in diminishing or eliminating latent virus.
- Conduct clinical studies of potential therapeutic agents and combinations of strategies to determine whether ongoing viral replication is occurring in individuals with nondetectable virus while on ART.
- Conduct clinical trials to study long-term effectiveness (including toxicities) of novel therapeutic strategies to eradicate HIV.
- Evaluate coformulated and long-acting ARVs across the lifespan of the HIV-infected individual.
- Quantitate persistent HIV in different tissue compartments during effective ART, and evaluate strategies to reduce or eradicate such reservoirs.
- Improve methods to measure the penetration of ARVs and other agents into various body fluids and tissue compartments, including the cerebrospinal fluid as a surrogate marker for the CNS.
- Develop and assess therapeutic approaches that will restore, sustain, and enhance the immune system in HIV-infected individuals.
- Advance clinical testing of cytokines, modulators of chemokines, combinations of broad-based neutralizing monoclonal antibodies, and immunoactive agents to prevent further immune deterioration, to reconstitute deficient immune systems, and to enhance the immunogenicity of therapeutic HIV vaccines.
- Develop and evaluate active and passive immunotherapeutic approaches (including therapeutic vaccine candidates) for HIV infection and its sequelae, including the testing of optimum immunogens; determine optimal patient disease status for response, most effective immunization dose and schedule, and most meaningful readout of clinical impact of the intervention.
- Evaluate the immune system after partial restoration by ART. Define qualitative and quantitative differences between the restored immune system and the naive immune system to determine if identified deficiencies can be diminished by immunoactive agents.
- Assess immune-based therapy as an adjunct to salvage therapy strategies and/or reservoir elimination.
- Evaluate the extent to which HIV or SIV-related immunopathogenesis can be prevented or reversed by therapeutic interventions.
- Investigate the impact of cancer therapy, immunosuppressive agents, and other immunomodulatory and myeloablative therapy on virologic, immunologic, and tumor parameters, including viral reservoirs; assess the toxicity of anticancer modalities in HIV-infected patients; and evaluate the PK of anticancer agents in HIV-infected patients, including a study of drug–drug interactions.

- Investigate the mechanism by which graft-versus-host reaction contributes to reducing/eliminating latently infected host cells in the setting of allogeneic stem cell transplantation.

- Study the impact of early ART interventions and HIV therapeutic vaccines or passive antibodies administered while on effective ART on the maintenance or regeneration of naive T cells and antiviral immune responses in HIV-infected infants.

- Conduct Phase I, Phase II, and Phase III HIV evidence-based therapeutic vaccine clinical trials that will determine short- and long-term safety; immunologic responses measured by a broad range of humoral, cell-mediated, and mucosal immune parameters; and effects on inflammatory markers and reservoir size.

OBJECTIVE–D: Behavioral and Social Science Research

Support behavioral, social, structural, and environmental research to inform the development, testing, and implementation of HIV eradication and cure approaches, and to develop and test interventions to strengthen the reach and impact of HIV eradication and cure strategies across the spectrum of age, gender, and race and/or ethnicity in national and international settings.

STRATEGIES

- Conduct studies on psychosocial and ethical issues that may influence the willingness of patients, providers, and communities to participate in clinical trials for HIV eradication, including the acceptable levels of risks and benefits associated with HIV eradication in the context of effective treatment.
- Conduct studies to determine effective communication strategies for working with communities to accurately understand the risks and benefits of HIV eradication and cure research efforts.
- Develop methods to assess and enhance adherence in HIV eradication and cure research and clinical practice; closely monitor adherence to HIV eradication and cure strategies during clinical trials and examine the association between adherence and trial outcomes.
- Develop necessary and appropriate assessment tools to measure social and behavioral factors (e.g., risk perception, behavior, and stigma) that may change during the course of participation in HIV eradication research.
- Conduct assessments of social and behavioral factors during clinical trials of strategies to eradicate HIV to identify and evaluate any changes in those factors as a result of participation in a clinical trial.
- Conduct behavioral research with individuals who become reinfected during clinical trials to identify interventions that may prevent high-risk behaviors and nonadherence in future clinical studies.
- Conduct social and policy research to investigate potential health disparities associated with cure/eradication research and its implementation.

OBJECTIVE–E: Implementation Science

Establish research collaborations to advance HIV/AIDS cure research as well as translational research to enhance the uptake of strategies to eradicate HIV/AIDS across the spectrum of age, gender, and race and/or ethnicity in national and international settings.

STRATEGIES

- Develop, validate, and standardize simple, sensitive, reliable, user-friendly, and inexpensive surrogate markers, assay technologies, and rapid point-of-care diagnostics for monitoring HIV virologic status that can be used in resource-limited settings, including viral persistence and responses to therapeutic strategies, as well as HIV drug resistance and adherence to treatment.

- Develop, validate, and standardize new methods and/or instrumentation for evaluating immune function in clinical trials, including assays that may be used in resource-limited settings.

- Develop cost-effective approaches to foster the scale-up of safe and efficacious therapeutic regimens, therapeutic vaccines, and other strategies to eradicate HIV for broad domestic and international use.

- Participate in collaborative efforts with other U.S. and international partners (i.e., research organizations and philanthropic institutions) to expedite cure and eradication research and the dissemination and uptake of its findings.

PRIORITY:

Reducing HIV-Related Disparities

Special Populations:

- Racial and Ethnic Populations
- Women and Girls
- Research in International Settings

Training, Infrastructure, and Capacity Building

AREA OF EMPHASIS

Racial and Ethnic Populations

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A: System Determinants of Health

Conduct research that explores and identifies the impact of health care systems, public health infrastructure, and financing structures on the delivery of HIV-associated prevention, care, and treatment to racial, ethnic, and sexual minority populations.

STRATEGIES

- Enhance and optimize research to examine the effects of HIV-related stigma, gender bias, racism, homophobia, and transphobia on HIV testing, care, and management within health care systems.
- Conduct research to examine the effects of public health and health care financing infrastructures on the HIV-associated risk- and care-seeking behaviors of those at highest risk for HIV infection, especially gay and bisexual men and male and female transgender persons.
- Develop, pilot, and test interventions that target health care systems and the barriers to HIV prevention and care associated with these systems and structures.
- Develop, pilot, and test provider-initiated HIV testing and risk-reduction interventions for individuals who are living with, or at risk for, HIV infection across a range of diverse health care settings.

OBJECTIVE–B: Environmental and Social Determinants of Health

Conduct research that identifies specific social, contextual, and environmental factors—including, but not limited, to economic disadvantage, racism, sexism, transphobia, and homophobia—that are correlated with HIV acquisition, transmission, and disease progression.

STRATEGIES

- Explore the intersection and cumulative effects of housing status, poverty, residential segregation, and incarceration on HIV transmission across the lifespan to inform the development and evaluation of effective, evidence-based interventions.
- Explore the link between poverty, stigma and racism, and presenting late for HIV testing care and treatment.
- Explore the effect of age, stigma, sexually transmitted infection prevalence, and transphobia on HIV acquisition in transgender individuals and across their networks.
- Examine the links between and intersections of poverty, racism, substance abuse, and historical displacement on HIV-associated risk behaviors and HIV resiliency among Native communities.
- Develop and disseminate culturally, linguistically, and contextually appropriate HIV testing and prevention interventions specifically targeting alcohol, drug, social, and sexual networks.
- Expand HIV prevention research to identify and reduce the impact of immigration status, population migration, displacement, and geographic location on the HIV-associated risk behaviors of migrant communities.

OBJECTIVE–C: Community-Level Determinants of Health

Conduct research that explores the effects of community preparedness and engagement on the uptake and dissemination of evidence-based, community-level HIV interventions.

STRATEGIES

- Examine the community, cultural, and familial level factors that are correlated with community acceptance and uptake of HIV prevention interventions.
- Utilize key informants, organizations, and associations to determine the effect of community mobilization on community acceptance of HIV-focused evidence-based behavioral and biomedical interventions.
- Identify evidence-based, cost-effective, sustainable, and scalable community-level prevention interventions for racial, ethnic, and sexual minority communities to optimize the uptake of HIV prevention, care, and treatment.
- Conduct research to identify the types of community and health care organizations necessary to facilitate the delivery and dissemination of effective community-level HIV prevention interventions.
- Conduct research to examine the effects of social and sexual norms (existing and evolving) on community acceptance of and engagement in HIV-associated risk reduction interventions.
- Utilize multiple strategies and methods, such as implementation science, to identify the core elements of effective HIV prevention interventions and to facilitate the efficient and rapid translation of these interventions to those populations disproportionately affected by HIV.

OBJECTIVE–D: Individual-Level Determinants of Health

Conduct research that targets individual-level determinants of HIV associated risk, including biological, cultural, ecological, and social factors.

STRATEGIES

- Conduct basic research on the socioecological determinants of sexual health and HIV risk in racial, ethnic, and sexual minority populations and their social networks to inform the development of contextually appropriate HIV prevention interventions.
- Identify cultural, social, and structural factors that increase or decrease HIV acquisition and transmission risk among populations that are most disproportionately affected by HIV infection.
- Conduct research to determine the biological (including genetic) and physiological factors that affect individual HIV acquisition, transmission, and disease progression among racial, ethnic, and sexual minority individuals across the lifespan.
- Determine the impact of personal trauma and violence on the adoption and maintenance of HIV prevention strategies in racial, ethnic, and sexual minority populations, to develop and evaluate sustainable HIV risk reduction interventions.
- Develop and test interventions that reduce sexual transmission risk through enhanced antiretroviral therapy (ART) and treatment adherence across the lifespan.
- Conduct research to identify those determinants of resiliency that are correlated with decreased risk of HIV acquisition, transmission, and progression.

OBJECTIVE–E: Expanding Research Methods and Measures

Develop, test, and evaluate innovative methods and measures to accurately assess the system, social, community, and individual determinants of HIV risk in racial and ethnic populations, with special emphasis on undersampled populations.

STRATEGIES

- Recruit and retain racial and ethnic minorities in HIV research using innovative sampling, recruitment, and retention methods to ensure sufficient numbers to provide adequate statistical power to detect racial and gender differences.
- Develop, test, and evaluate novel research methodologies to explore the intersection of race/ethnicity, gender, gender identity, and sexual orientation with the social determinants of health differences to better inform the development of prevention and treatment interventions that address the specific needs of these populations.
- Conduct research to develop, adapt, and validate standardized assessment tools that identify the full spectrum of HIV acquisition risks among rural, foreign-born, and displaced populations at risk for HIV infection.
- Develop, test, and evaluate new measures of HIV risk behavior that are culturally and contextually appropriate for racial, ethnic, sexual, and gender minority populations.
- Encourage the development and evaluation of innovative research methods that leverage the potential of novel technologies to enhance community, HIV prevention, linkage to treatment, adherence, and retention in care, including, but not limited to, social network approaches, media, and computer applications.
- Utilize implementation science methodologies that can identify and evaluate the impact of innovative, evidence-based interventions that are ready for field testing and rapid translation.

OBJECTIVE–F: Treatment and Treatment Access Disparities

Conduct research to identify those critical junctures where effective evidence-based interventions can result in improved treatment outcomes in racial, ethnic, and sexual minority populations.

STRATEGIES

- Advance the study of the biology of HIV infection among racial, ethnic, and sexual minority populations:
  - Evaluate the effect of race, ethnicity, gender identity, and age upon treatment adherence and the response to combination ART.
  - Determine the intersection of race, ethnicity, gender, and aging upon inflammation and immune dysregulation.
- Increase the number of indigenous populations, including Native Americans, Alaska Natives, Pacific Islanders, and Native Hawaiians, in NIH-funded research to better characterize the impact of HIV infection manifestations in these communities.
- Conduct research to identify the best use and timing of effective evidence-based interventions that mitigate barriers to HIV testing, care, and treatment, including adherence to HIV treatment.
- Expand and optimize research collaborations with tribal entities, community-based organizations, and nontraditional community partners to enhance HIV treatment and treatment adherence research participation to decrease HIV care and treatment disparities.
- Identify and test effective evidence-based interventions to both decrease those presenting late for care and increase engagement and retention in HIV care across the lifespan.
- Develop, pilot, and test interventions that effectively link those who have dropped out of HIV care into consistent care and followup.
- Develop, pilot, and test interventions to identify evidence-based interventions to improve HIV treatment outcomes in individuals with associated mental health disorders.
- Identify barriers (e.g. reading level and language) and facilitators to HIV care linkage, retention, and engagement for mobile and displaced populations to develop effective interventions.

OBJECTIVE–G: Comorbidities—The Intersection of Multiple Health Disparities

Conduct research to examine the link between HIV infection and its associated comorbidities in racial, ethnic, and sexual minority populations to determine their impact upon HIV care linkage and treatment, care engagement, disease progression, morbidity, and mortality.

STRATEGIES

- Identify, develop, and test interventions that reduce the impact of associated comorbid conditions on HIV treatment, adherence, retention in care, and health outcomes.
- Define the impact of substance use, violence, and mental health comorbidities upon HIV care and treatment for both the provider and the patient.
- Examine the impact of explicit gender phenomena, including, but not limited to, gender identity, gender history, gender confirmation, transphobia, and homophobia upon the management of comorbid conditions, including atherosclerosis, malignancies, and renal disease.
- Develop effective evidence-based interventions to mitigate the impact of race, ethnicity, gender, and age upon the management of HIV-related comorbidities, including, but not limited to, cardiovascular, metabolic, neurologic, psychiatric disorders, and other chronic conditions.
- Identify the consequences of late-stage initiation of combination ART on the progression or resolution of comorbid conditions, especially in understudied groups.
- Examine the impact of criminal justice involvement on the diagnosis, treatment, and long-term retention in care among HIV-infected persons, and the effects of criminal justice involvement on associated comorbidities.

OBJECTIVE–H: Enhancing Capacity To Conduct NIH-Funded HIV Research

Enhance and expand the capacity for NIH-funded HIV research by and for individuals from groups disproportionately affected by HIV infection as well as underrepresented among NIH-funded investigators and institutions.

STRATEGIES

For the Investigator

- Promote and expand predoctoral opportunities for the recruitment, training, and retention of investigators from underrepresented racial and ethnic backgrounds.
- Utilize existing funding mechanisms to establish incentives to develop, recruit, and retain intramural and extramural investigators from underrepresented groups (including sexual and racial minorities).
- Support initiatives that facilitate and promote the transition from junior to senior scientist for investigators from disproportionately affected populations.
- Expand and optimize partnerships between junior investigators and senior investigators with extensive research experience and infrastructure to promote the development and training of a diverse workforce in HIV-associated health disparities.

For the Institution

- Utilize NIH-funded collaborations to enhance linkages between resource-limited and research-intensive institutions to establish an environment that promotes mentoring and diversity and facilitates HIV research.
- Expand activities designed to optimize existing programs to enhance the retention of scientists from disproportionately affected populations during the key transition periods from junior to midcareer and ultimately senior investigator.
- Leverage existing resources such as the databases of established senior mentors from the clinical trial and other networks to quickly identify resources for promising junior investigators from disproportionately affected populations.

For the Community

- Optimize participation of underrepresented groups, including tribes and tribal entities, in the development of scientific research projects from inception to completion.
- Expand and optimize community-based and community-driven participatory research to facilitate: (1) the bidirectional transfer of scientific results of interest to both the community and the investigator(s) and (2) the culturally and contextually appropriate translation of these findings into community programs.

AREA OF EMPHASIS

Women and Girls

FY 2015 RESEARCH PRIORITIES

- Design and conduct studies that integrate the biological, behavioral, and social sciences to explain factors that influence HIV risk, pathogenesis, and prevention in women and girls across the life cycle.
- Examine the immunology and microbiome, including other sexually transmitted infections (STIs) of the genital and anal/rectal tracts and their relationship to HIV risk, prevention, acquisition, transmission, and pathogenesis.
- Devise specific strategies to prevent the acquisition of HIV and opportunistic infections (OIs) in the female reproductive and the oral/anal/rectal tracts.
- Study interactions between HIV, antiretrovirals (ARVs), and endogenous and exogenous hormones and the impact on HIV risk, prevention, acquisition, and pathogenesis.
- Design and conduct studies that assess the impact of social and behavioral aspects of stigma, discrimination, and disenfranchisement on women's ability to prevent exposure, as well as their linkage to and engagement in HIV services and retention in care.
- Design and conduct studies that facilitate the translation of behavioral, biomedical, social, and technological HIV prevention interventions into clinical care.

OBJECTIVE–A: Determinants of HIV Transmission

Define the mechanisms by which biologic targets for intervention, host microbiota, and innate and adaptive immune factors influence HIV transmission, acquisition, pathogenesis, and resistance to infection in women and girls across the lifespan.

STRATEGIES

- Investigate the relationship of age and endogenous and exogenous hormone status on HIV acquisition, transmission, resistance to infection, and prevention interventions.
- Evaluate the role of viral characteristics and female-specific normal and abnormal genital tract and anal/rectal physiology, immunology, microbiome, and concomitant infections on cellular and other tissue mechanisms on HIV transmission, acquisition, and prevention across the lifespan.
- Study the role of genital tract metagenomics on HIV transmission, acquisition, and resistance to infection.
- Study all aspects of sexual activity, including semen exposure, partner's circumcision status, sexual intercourse, and sexual trauma on HIV susceptibility, acquisition, transmission, and resistance to infection.
- Identify and study animal models to explain female-specific, host–viral immune interactions and mechanisms of infection, and evaluate prevention technologies.
- Develop and standardize assays and techniques for sampling the genital tract and the anus/rectum to assess host and viral immune factors and physiology that affect HIV transmission, acquisition, and resistance to infection.
- Evaluate the effect of seminal fluid on HIV transmission and factors that may facilitate HIV acquisition in women.
- Develop rapid tests to detect HIV in genital (vaginal/anal) compartments after sexual assault.

OBJECTIVE–B: Integrated Biomedical, Behavioral, and Social Science Prevention Interventions

Conduct and support integrated biomedical, behavioral, and social science interventions research to prevent HIV acquisition and transmission, including mother-to-child transmission and ARV resistance.

STRATEGIES

- Support integrated multipurpose prevention technologies research that considers the social and cultural norms and vaginal practices of the population in which the interventions will be applied.
- Support integrated research to understand how access to health care services, including sexual and reproductive health, mental health, and social services, affect HIV risk, transmission, acquisition, and resistance to infection.
- Analyze the impact of community-level social and behavioral norms on the acceptability, efficacy, and adherence to HIV and STI prevention interventions.
- Analyze the impact of integrated prevention interventions targeting men on HIV and STI acquisition in females.
- Develop and evaluate novel methods for recruiting and retaining women and girls who are demographically representative of the populations at risk for HIV infection into prevention research and for supporting their adherence.
- Conduct research to identify effective methods to improve the translation, dissemination, implementation, and adoption of female-focused, effective HIV prevention technologies.
- Conduct research to identify and develop methods to overcome barriers to enrolling girls under the age of 18, pregnant and lactating women, and hard-to-reach populations into HIV prevention and intervention trials.
- Conduct integrated biomedical, behavioral, and social science HIV and STI intervention research to address the couple-specific dynamics that affect HIV-risk perception and HIV risk, acquisition, and transmission.
- Develop and evaluate integrated interventions for both HIV-concordant and HIV-serodiscordant couples that prevent HIV and STI transmission and prevent or allow pregnancy.
- Investigate the interaction between HIV-risk perception and sexual behaviors and sexual activity on adherence to and effectiveness of HIV prevention methods.
- Study the impact of macro-level events and altered social structure such as natural disasters, trauma, war, migration, and refugee status on HIV risk and acquisition and on access to HIV care for women and girls globally.
- Conduct research on the effects of sex and gender-specific stigma, discrimination, and violence on HIV and STI risk, prevention, acquisition, and disease progression.
- Develop, implement, and evaluate HIV and STI prevention and care interventions that decrease the impact of sex and gender-related violence and power discordance on HIV and other STI risk.
- Develop and evaluate interventions to reduce or prevent adverse psychological and social consequences for women and girls infected with or affected by HIV.
- Develop, study, and implement interventions to decrease breastfeeding-related HIV transmission.
- Evaluate prevention interventions for use by HIV-discordant couples to allow safer conception.
- Conduct implementation projects on the acceptability and uptake of pre-exposure prophylaxis in heterosexual women.

- Study the effect of methods to prevent HIV transmission employed during pregnancy-related procedures such as amniocentesis, chorionic villus sampling, and percutaneous umbilical sampling.
- Design and study HIV prevention interventions to be used with HIV-infected individuals.

OBJECTIVE–C: Biology of HIV Disease

Study the biology of HIV disease and related coinfections in women and girls across the life cycle.

STRATEGIES

- Develop and evaluate innovative and rapid testing strategies, including point-of-care testing in diverse settings, to identify acute and chronic HIV infection and related coinfections and STIs in women and girls.
- Identify the mechanisms specific to women and girls that mediate complex virus/host interactions and affect disease progression.
- Elucidate the sex-specific differences in risk, etiology, and pathogenesis of HIV disease—including acute HIV, STIs, and HIV-related coinfections—and comorbidities, including cancers.
- Investigate the impact of HIV and its related coinfections, comorbidities, and treatment on fetal, infant, childhood, and adolescent development.
- Evaluate the impact of cell-free and cell-associated HIV in breast milk on HIV risk in uninfected breastfed infants and pathogenesis in HIV-infected breastfed infants.
- Study the impact of HIV exposure and antiretroviral (ARV) exposure during pregnancy and breastfeeding on HIV-uninfected infants and children.
- Study the morbidity and mortality differences between perinatally and behaviorally infected women and girls.
- Study the short- and long-term effects of strategies for cure in newborns.
- Investigate the relationship of age and endogenous and exogenous hormone status, including pregnancy, lactation, menopause, and contraception, on HIV pathogenesis and immune activation.
- Investigate female-specific responses in research toward a cure.
- Investigate the impact of HIV and chronic immune activation on aging-related morbidity in women.
- Investigate the effect of vaginal trauma on HIV transmission and acquisition.

OBJECTIVE–D: Treatment and Care of HIV Disease

Conduct and support research to inform the diagnosis, care, and treatment of HIV-infected women and girls across the life cycle.

STRATEGIES

- Develop and evaluate innovative strategies to diagnose HIV-infected women and girls in diverse settings, and to link, engage, and retain them in comprehensive HIV care and services.
- Evaluate the best strategies for fertility management across the life span for HIV-infected women.
- Study the impact of a new HIV diagnosis in women and girls on HIV-risk behaviors, participation in treatment and care, and reproductive decision. Study how these factors affect family well-being.
- Study the sex-specific differences in pharmacokinetics (PK), pharmacodynamics (PD), drug toxicity, and the success and failure of therapeutics for HIV, OIs, and other comorbidities and coinfections.
- Evaluate the short- and long-term effects of HIV and antiretroviral therapy (ART) on health, fertility, pregnancy outcome, morbidity, and mortality.
- Study the impact of ARV drugs used for HIV prevention and treatment on genital and anal/rectal viral dynamics, microbiota, and innate and adaptive immune function and the effect on HIV susceptibility, acquisition, transmission, and pathogenesis in women and girls. Study these effects in the context of endogenous and exogenous hormones across the lifecycle.
- Study factors including hormonal interactions that influence PK and PD of ARVs and other drugs used for HIV treatment and prevention and the impact on HIV susceptibility, acquisition, transmission, and pathogenesis.
- Study the factors that affect adherence to HIV therapeutic regimens and care, and develop and evaluate interventions to improve adherence.
- Evaluate the impact of comorbidities and their treatment, including metabolic abnormalities and other non-AIDS events, substance abuse, and mental health disorders, on HIV-related morbidity, mortality, and access to and retention in health care.
- Conduct multidisciplinary research to identify unmet needs and barriers for women and girls across the life cycle to achieving optimal HIV and AIDS care, support, treatment, prevention services, and inclusion in HIV research initiatives.
- Study the effects of ART on sex-specific cancers, other comorbidities, and clinical outcomes.
- Study the effect of the human papillomavirus (HPV) vaccine on HPV-associated cancers and premalignant lesions in HIV-infected women and girls.
- Investigate the relationship between HIV and HPV risk and infection and identify the factors that influence progression of HPV disease in the genital tract and anus/rectum.
- Study the mechanisms of HPV persistence and latency in HIV-infected women.
- Identify female-specific HIV quality-of-care indicators and study the impact of implementing quality-of-care guidelines, including cancer screening guidelines, on the community and country-level health status of women and girls.
- Study how stigma, discrimination, violence, and comorbidities affect access and adherence to treatment and care for women and girls.
- Develop and evaluate accessible and low-cost reproductive technologies and interventions to meet fertility desire without vertical or horizontal HIV transmission.

- Investigate the interaction between HIV, its treatment, aging, and age-related conditions or comorbidities.
- Develop and evaluate interventions to prevent mother-to-child- pregnancy- and breastfeeding-related HIV transmission, including testing strategies to identify acute infection among mothers.
- Examine sex-specific physical and psychosocial consequences of HIV disease and the effects on the initiation of and retention in treatment and care.
- Study the factors that influence the successful transition of adolescents to and retention in adult HIV treatment and care.
- Study the impact of contraception on the PK/PD of ARV drugs used for HIV prevention and treatment.
- Study the effectiveness of alternative methods (other than Pap smears) used to screening for HPV disease in HIV-infected women.

OBJECTIVE–E: Ethical Issues

Conduct and support research, training, and education on ethical issues that affect the access to and participation of women and girls in HIV-related research.

STRATEGIES

- Develop and evaluate methods, including literacy assessment, to facilitate obtaining fully informed consent from potential clinical trial participants.
- Investigate the unintended consequences of policies that limit the participation of women and girls in research.
- Examine the ethical risks and benefits of various study designs that involve treatment versus observation of women and girls.
- Investigate the ethics of providing a different standard of care for clinical trial participants than is available for women and girls who do not participate in trials.
- Study the ethical and legal issues related to the conduct of HIV-related research during adolescence, pregnancy, and lactation.
- Study the ethical issues related to providing reproductive health services and breastfeeding alternatives in communities where these interventions may not be available to the general population.
- Study the ethical issues related to providing incentive-based strategies for recruitment and retention of women and girls in clinical trials.
- Study economic, legal, and ethical barriers to providing assisted reproductive technologies to serodiscordant couples.

AREA OF EMPHASIS

Research in International Settings

FY 2015 RESEARCH PRIORITIES

- **Capacity Building:** Continue to develop and support in-country leadership and sustainable capacity in HIV/AIDS research in low- and middle-income countries, in cross-disciplinary collaboration with other partners, through: (1) development of research infrastructure and building of laboratory and clinical research as well as biostatistical and administrative capacity, (2) provision of formal training in prevention and treatment science and hands-on practical research experience, and (3) development of new training and communication methodologies, such as Web-based and distance learning.

- **Combination Prevention:** Design, implement, and evaluate combination and multilevel prevention programs that integrate biomedical, sociobehavioral, and structural strategies targeted to specific settings and populations at risk to prevent HIV transmission and its consequences.

- **Testing, Linkage, and Maintenance of Treatment Adherence:** Identify effective and cost-effective HIV testing, linkage, and care and treatment strategies that ensure success at each step in the care cascade and long-term adherence to treatment regimens, employing the latest technologies and interventions to achieve and sustain viral load suppression, decrease morbidity and mortality, prevent ongoing HIV transmission, and achieve the demise of HIV disease and AIDS.

- **Implementation Science:** Evaluate methods to increase uptake of existing interventions for HIV-related care and prevention, including innovative ways to deliver services and increase demand.

OBJECTIVE–A: Expand Combination Prevention Approaches

Design and evaluate the most effective combination of sustainable biomedical, behavioral, and structural prevention approaches at multiple levels (i.e., individual, couple, group, and society) that address multiple risk factors of HIV acquisition and transmission, tailored to local settings, epidemic conditions, and populations at risk.

STRATEGIES

- Develop complex models for further study that incorporate theories based on biology, behavioral and social science, psychology, neuroscience, and genetics.
- Identify and test combination interventions that strategically exploit new information technologies with the potential to revolutionize access to data, prevention, and treatment programs tailored to individuals.
- Develop and test new methodologies and analytic techniques that facilitate mixed method studies and multi-factorial design, permitting analysis of combination prevention approaches at multiple levels over time.
- Support mechanisms to standardize terms for the reporting of qualitative and quantitative prevention and treatment research (e.g., CONSORT and others) to facilitate rapid meta-analysis of results.

Eliminating Mother-to-Child (Perinatal) Transmission of HIV: Considerations for the Mother, Child, Adolescent, and Family

- Develop and evaluate strategies for preventing HIV acquisition by adolescent girls and women, including:
  - Studying and addressing factors associated with unintended pregnancy, such as gender inequalities and power dynamics; and
  - Enhancing informed reproductive decisionmaking and improving reproductive health in serodiscordant couples, including HIV risk reduction during *in vitro* fertilization.
- Evaluate the effectiveness and impact of different models of service organization and service delivery for provision of antiretroviral therapy (ART) and prevention of mother-to-child transmission (PMTCT) in maternal–child health and primary care settings and of interventions to expand health care services to include male partner involvement, particularly in serodiscordant couples.
- Evaluate pregnancy outcomes and efficacy of interventions to prevent MTCT in adolescent girls with perinatal HIV infection who become pregnant.
- Evaluate risk factors and strategies to reduce the morbidity and mortality associated with HIV infection in pregnant and postpartum women and their HIV-exposed infants, including maternal and infant nutrition during the peripartum and postpartum periods.

Expanding Medical Male Circumcision (MMC)

- Evaluate the sustainability and durability of male circumcision in limiting HIV transmission risk from men to women and from men to men.
- Develop and evaluate innovative strategies and technical devices to ensure uptake and the safe and effective delivery of male circumcision and other male-oriented prevention services to prevent or reduce HIV transmission, in particular:
  - Examine best methods for scale-up, such as nonsurgical devices, mobile clinics, and task shifting; and
  - Study the technical training and implementation requirements for widespread uptake of male circumcision interventions.

- Determine if circumcision is associated with behavioral disinhibition.
- Study the sociocultural aspects and other factors that may inhibit or encourage the use of MMC and assess the impact of mental health factors on its acceptability.
- Evaluate the cost-effectiveness and impact of expanded access to MMC programs.
- Develop novel strategies for demand creation to increase uptake of MMC services and evaluate commercial marketing methods to model their demand.

Antiretrovirals (ARVs) for Prevention

- Determine the most effective ARV agents, formulations, or combinations of agents to reduce transmission risk.
- Determine the effectiveness of oral and topical ARV pre-exposure prophylaxis (PrEP), including new formulations and combinations of vaginal and rectal microbicides, in the prevention of sexual and bloodborne HIV transmission, while continuing to study and monitor drug resistance.
- Conduct research on ARV optimization in genital secretions; blood; blood relevant to injection-related transmission and safety in health care settings; and in the anorectal, oropharyngeal, and gut mucosa.
- Determine the social, cultural, and practical factors affecting the provision of ARV-based prophylaxis and/or understanding the barriers to implementation of PrEP, particularly in settings where ART is not fully available.
- Examine strategies to implement topical and oral ARV PrEP in high-risk populations, and evaluate their cost-effectiveness, sustainability, and long-term adherence.

Management of Sexually Transmitted Infections (STIs)

- Improve the efficacy and cost-effectiveness of clinical management of STIs in those with and at risk for HIV infection, emphasizing coinfections with herpes simplex virus type 2 (HSV-2), human papillomavirus (HPV), and other STIs (syphilis, gonorrhea, and chlamydia) to prevent HIV transmission.
- Assess the impact of effective HSV-2 and HPV prevention strategies on HIV transmission.
- Promote behavioral research on the prevention of STIs in adolescents and the acceptability of cervical cancer prevention strategies.
- Evaluate methods to integrate HIV, STI, and reproductive health services.

Substance Use Treatment and Harm Reduction Strategies

- Evaluate implementation of effective substance use prevention interventions for youth and during early phases of substance use.
- Evaluate implementation of effective harm reduction strategies and other interventions known to reduce HIV risk, such as effective pharmacotherapy and behavioral interventions for drug treatment.
- Devise and evaluate strategies to promote transitions from injection drug use to non-injection drug use.
- Develop and evaluate innovative, culturally relevant, and contextually appropriate alcohol and drug treatment programs and strategies for HIV and hepatitis C virus (HCV) prevention.

Preventing HIV-Risk Behaviors in Social Settings and High-Risk Networks

- Evaluate the synergistic role of multiple risk factors (sexual risk, substance use, substance use contextual [e.g., housing, poverty, and stigma]) in HIV acquisition and transmission, and develop innovative interventions to address those behaviors.
- Identify and test the most effective strategies to reach and prevent HIV transmission among difficult-to-reach, mobile (e.g., migrant workers, truckers), and other at-risk populations.
- Investigate the role of mental health conditions or disabilities (e.g., depression) and use of psychoactive substances in promoting or facilitating high-risk injecting and sexual behaviors that reduce the efficacy of prevention strategies.
- Investigate ways to use social and sexual networks to disseminate and promote interventions for prevention and care.
- Devise and evaluate strategies for supporting outreach workers for high-risk populations.

OBJECTIVE–B: Reduce HIV-Related Health Disparities

Identify factors associated with HIV-related health disparities (across age, ethnicity, gender/gender identity, sexual orientation, socioeconomic status, geographic distribution) along the spectrum of HIV diagnosis, prevention, and access to care and treatment; develop and test interventions to reduce or eliminate these disparities by integrating preventive combination interventions at multiple levels.

STRATEGIES

Vulnerable Populations

- Study social, behavioral, and biological factors that are associated with susceptibility to HIV infection and its acquisition or transmission in both men and women, including poverty, food insecurity, migratory or seasonal employment patterns, intimate partner violence, and the use of hormonal contraceptives.
- Study how HIV infection affects women's mental, reproductive, and general health, the performance of multiple roles in their households, and the social support that they receive from their family and caregivers.
- Evaluate the effect of gender-based violence toward HIV-infected pregnant women on the development of their neonates and children.
- Evaluate tools to improve adherence among illiterate patients receiving ART.

Identifying New HIV Infections Early, Linking to Integrated Systems of Care

- Develop new diagnostics to identify the earliest stages of HIV infection for "test and treat" approaches.
- Develop and evaluate novel strategies and incentives to increase uptake of routine HIV testing that encourage early detection and identification of HIV status, especially among hidden or hard-to-reach populations and pregnant women and in settings where rights of minorities or vulnerable populations are limited and where stigma persists.
- Develop innovative and culturally adapted "seek, test, treat, and retain" programs to identify newly HIV-infected individuals, minimize barriers to their linkage to care, and mobilize their partners, families, and communities to provide support, strengthen adherence, reduce viral load, and maximize long-term outcomes in at-risk populations.
- Investigate gaps in the cascade that lead to substantial proportions of HIV-infected individuals not receiving or being sustained in HIV care and treatment services; particular attention should be paid to strategies that:
  - Increase testing and knowing your serostatus and repeat testing among those who test negative;
  - Keep infected individuals in care before they begin treatment; and
  - Ensure long-term adherence, including development of cost-effective methods to measure adherence over time.
- Investigate the cascade of steps for PMTCT beginning at prenatal care and extending to adherence at delivery, examine ways to prevent loss to followup at any point, and evaluate strategies to ensure linkage of sites (and data from sites) conducting PMTCT with sites providing maternal ART with pediatric health clinics.
- Develop and evaluate public health models, such as family and community models of care, that simultaneously address multiple health outcomes and integrate HIV/AIDS prevention and clinical care with other existing health and social service delivery programs and services (e.g., primary care, tuberculosis [TB] care and treatment, alcohol/substance use treatment, maternal and child health, family reproductive health, elder health, and health in prisons).
- Examine innovative ways to measure HIV incidence at a community level using cross-sectional samples.

Alleviating Stigma

- Develop innovative research methods, including metrics and study designs, for identifying and targeting key populations that face disproportional rates of stigma and discrimination, and investigate the impact of stigma on HIV prevention, care, and treatment-seeking behavior, especially among ethnic minority and low-income groups.
- Conduct cross-national studies to help understand social determinants of stigmatization and identify potential interventions to reduce stigmatization.
- Evaluate attitudes of health care providers regarding HIV-infected individuals and the effect of these attitudes on provision of care and treatment.
- Develop, evaluate, and implement programs to prevent stigma and discrimination in the provision of ARV treatment by health care workers, and determine whether expanded ART care leads to a decrease in HIV-associated stigma.

Structural Interventions

- Evaluate the various approaches used by different countries for implementing structural interventions and investigate how these approaches may be systematically facilitated.
- Investigate the effectiveness of community-based and community-level HIV prevention programs that affect the health and behavior of individuals by delivering biomedical interventions (e.g., circumcision), changing social norms, and by delivering prevention education using policy, technology, and effective behavioral interventions:
  - Identify the most effective and sustainable strategies for schools, leisure locations, and worksites to support behavior change interventions; and
  - Develop and evaluate structural interventions for HIV, STI, and TB prevention, treatment, and care among incarcerated populations.
- Assess and determine optimal methodologies for evaluation of various structural interventions and their impact, encouraging the use of innovative study designs not limited to randomized clinical trials.

OBJECTIVE–C: Support Innovative Research To Reverse the HIV Epidemic

Develop and evaluate setting-specific combination approaches and strategies to effectively prevent, treat, and cure HIV infection with the long-term goal of reversing the epidemic.

STRATEGIES

Research Toward a Cure

- Conduct basic research for the development of new, better targeted drugs that could lead toward a functional or actual cure of HIV.
- Conduct basic research on latency and eradication of viral reservoirs.
- Develop new technologies, such as immunotherapies, that could eradicate viral reservoirs.

Optimizing Treatment Outcomes

- Accelerate research on viable and sustainable "test and treat" options, including approaches to ensure effective linkage from HIV counseling and testing programs to HIV care and treatment.
- Identify barriers preventing access to care among key (most at risk) populations (men who have sex with men, female sex workers, people who use injection drugs, etc.) and develop implementation strategies to achieve high ARV coverage among these groups.
- Develop and evaluate methods to reduce loss to followup at each step in the cascade from HIV testing, linkage to care, CD4+ cell count enumeration, ARV treatment initiation, and treatment adherence to maximize the proportion of eligible HIV-infected individuals on effective treatment and achieve viral load suppression.
- Investigate the potential of ART to reduce HIV transmission, in combination with other HIV prevention strategies, in different epidemic and community settings.
- Develop and test region-specific strategies to support adherence to medication regimens in adults, adolescents (including those who acquired HIV through perinatal transmission), children, and pregnant and postpartum women to enhance therapeutic outcomes and limit the development of drug resistance, in particular:
  - Evaluate the effectiveness of different approaches to task shifting for HIV care and treatment from physicians to non-physician staff;
  - Determine the role of pharmacogenetics/pharmacokinetics and identify appropriate ARVs that can be used in specific populations throughout their life cycle;
  - Develop appropriate pharmacovigilance systems to evaluate short- and long-term effects of treatments provided to HIV-infected individuals (including special populations such as pregnant women and their infants and alcohol or substance users); and
  - Evaluate innovative interventions and technologies to promote and measure ARV adherence (e.g., rapid diagnostic readers, smartphones, etc.).
- Conduct research on biological, behavioral, and psychosocial effects related to the diagnosis, treatment, and care of HIV disease among children and adolescents (both horizontally and perinatally infected), in particular:
  - Develop and evaluate suitable and sustainable approaches for the diagnosis of HIV infection, especially for children under the age of 18 months;
  - Support the long-term followup of children exposed to ART *in utero* and/or postpartum in resource-limited settings to evaluate possible late effects of ARV exposure; and
  - Develop and evaluate suitable approaches for long-term care of adolescents, both horizontally and perinatally affected, including ways of promoting adherence and retention in care.

- Assess the cost-effectiveness of ARVs in resource-limited settings, in particular:
  - Identify affordable, safe, and effective ARV regimens, including timing of initiation and durability of initial treatment;
  - Develop and evaluate suitable and sustainable approaches to monitoring the effectiveness and safety of HIV treatment, especially with regard to affordable point-of-care technologies to measure CD4+ cell counts and viral load (or appropriate alternatives) and validate low-cost monitoring technology; and
  - Determine the minimal level and methods of targeted drug resistance monitoring necessary in those failing therapy and in pregnant women and infants infected despite maternal ARV use.
- Assess the biological, social, psychological, societal, and economic impacts of ART on risk behaviors, HIV transmission, and prevalence, including associated behavior change, in individuals across the lifespan, families, and various communities, in particular:
  - Study the durability of the effect of ART on HIV transmission by evaluating the effectiveness of specific ART strategies over time in curtailing HIV transmission in HIV-serodiscordant couples and in persons with multiple risk partners; and
  - Evaluate how ART affects breastfeeding behaviors, including exclusive breastfeeding and duration of breastfeeding.
- Characterize the clinical course of HIV infection in diverse geographic settings and determine the efficacy of ARV regimens on various clades prevalent around the world.
- Conduct research on the pathogenesis of HIV-related comorbidities affecting HIV risk and ART outcomes at individual and population levels (e.g., interactions among HIV, HPV, and host immunity in the cervix).
- Assess the effect of nutritional status and nutritional interventions on patient survival and the efficacy and tolerability of ART, including measuring the rate of immune system deterioration.

Accelerate HIV Vaccine Development

- Continue accelerated efforts toward the development of HIV vaccine candidates suitable for use around the world, and foster the development of vaccines to optimize characteristics appropriate for broad international use, including low cost, ease of production and administration, and stability.
- Define immune approaches that will provide specific and sustained protection against HIV transmission; develop the products necessary to achieve these goals; and develop the capacity to evaluate their safety in human subjects.
- Provide a scientific knowledge base (HIV incidence, viral subtypes, major histocompatibility types, and natural history) to guide decisionmaking regarding identification of potential international clinical trial sites and the conduct of vaccine clinical trials in these sites according to the highest clinical and ethical standards.
- Identify suitable populations of adults, adolescents, and children to enroll in clinical trials of candidate vaccines while ensuring equitable and appropriately representative gender balance in enrollment.
- Conduct Phase I, Phase II, and Phase III clinical trials of suitable HIV candidate vaccines in diverse international settings for safety, immunogenicity, and efficacy, with appropriate surrogate markers and measures of correlates of protection.
- Enlist the participation of local community representatives in the development of appropriate clinical trial protocols, as well as responsive mechanisms to inform and educate the participating individuals; establish networks within the community that will effectively address the social and medical concerns of the participants; and establish mechanisms to provide ongoing information and open discussions concerning the scientific rationale of the study.
- Examine relevant behavioral issues related to the conduct of HIV vaccine research and its acceptability in diverse populations.

- Conduct research on the potential social and economic effects, including cost-effectiveness, of the use of HIV vaccines.
- Examine the potential use of HIV therapeutic vaccines.

Innovative Prevention Technologies: Microbicides and Other Methods

- Discover and develop candidate topical microbicides, oral or injectable ARV agents, and other physical/chemical barrier methods—particularly female-controlled methods that require minimal adherence—to prevent sexual HIV transmission, and identify barriers to adherence.
- Conduct Phase I, Phase II, and Phase III clinical trials of suitable candidate oral, injectable, and topical agents in various international settings and in diverse populations, including pregnant women, for safety and efficacy.
- Develop appropriate biological and surrogate markers of safety or protection.
- Investigate reasons for differences in clinical trial outcomes of oral and topical ARV agents.
- Study the sociocultural and behavioral concerns related to partner involvement and acceptance of microbicide use, or covert use in the absence of partner willingness or acceptance.
- Determine the cost-effectiveness of microbicides and other physical/chemical barrier methods in limiting transmission and curtailing the expansion of the epidemic.
- Develop and test strategies specifically targeted to preventing transmission between serodiscordant couples.

Risk Behaviors in Social Settings and Networks

- Develop analytical tools and support innovative methodologies, including ethnographic research, to better understand and evaluate risk behaviors within social networks.
- Encourage molecular epidemiology studies of viral diversity in the context of social networks.
- Study the movement of the HIV epidemic across borders and regions, and evaluate the effects of various structural interventions related to migration and immigration on HIV transmission.
- Study risk behaviors and prevention of such behaviors among individuals with perinatally acquired HIV who are surviving into adolescence and young adulthood.
- Develop biomarkers that can serve as surrogates for measurement of HIV-risk behaviors and can be used to predict and monitor rapid escalation of HIV subepidemics (i.e., in local areas or in high-risk groups).
- Develop tools and metrics to identify subpopulations that are likely to benefit most from effective new HIV prevention technologies such as treatment for prevention, ARV PrEP, and microbicides.

OBJECTIVE–D: Address HIV-Related Comorbidities

Study the interactions among HIV-related comorbid conditions (e.g., TB, viral hepatitis, malaria, cancer, organ system disease, alcohol/substance use, and mental illness) that affect HIV-related morbidity and mortality, and develop and evaluate strategies for integrating prevention, diagnosis, and sustained care and treatment of these comorbidities and HIV.

STRATEGIES

Early Identification of Comorbid Conditions and Their Role in HIV Disease Progression

- Define the incidence, prevalence, risk factors, clinical features, and outcomes for HIV-related infectious and noninfectious comorbidities and those associated with alcohol/substance use and mental health, specific to geographic regions, diverse settings, and populations across the lifespan.
- Develop, implement, and evaluate effective and culturally appropriate screening and early identification strategies for HIV-related comorbid conditions.
- Examine the role of HIV-related comorbid conditions in modulating HIV infection or disease, including risk of acquisition, transmission, clinical characteristics, and disease progression, and their impact on both effective and safe use of ART and therapies for comorbidities.

Assessment of Comorbid Conditions and Their Impact on HIV Clinical Tools

- Develop clinical algorithms for guiding prevention, screening, and treatment of HIV-related coinfections, opportunistic infections (OIs), malignancies, and other comorbidities, and identify and monitor acceptable, feasible, and affordable strategies to target high-risk patients for initiation of prophylaxis.
- Develop and test new, low-cost, effective, and rapid point-of-care diagnostic tools for comorbid diseases and conditions, including TB, malaria, and early precancerous lesions.
- Develop surrogate markers for rapid and accurate determination of the effectiveness of therapy for comorbid conditions.

Impact of ART on Development and Characteristics of Comorbid Conditions and HIV

- Identify and study conditions that emerge because of improved treatment and long-term survival (e.g., malignancies, neurological and neuropsychological conditions, metabolic and nutritional dysfunctions, cardiovascular disease, hepatitis, and conditions associated with aging) across the lifespan.
- Determine the bidirectional consequences of ART and the concomitant management of comorbid conditions on the overall efficacy of prophylaxis and treatment, including adverse effects, additive toxicities, drug interactions, and immune reconstitution syndromes.

Integrating Care of HIV and Comorbidities

- Conduct clinical research to assess best sustainable strategies, safest and most effective treatment modalities, timing of treatment initiation, and outcomes that integrate HIV prevention, care, and treatment with those of comorbid conditions, and assess their cost-effectiveness and impact across the lifespan.
- Evaluate the pharmacologic and pharmacodynamic interactions between ARVs and alcohol, psychoactive drugs, traditional medicines, or medications used for the treatment of substance use; and
- Investigate the effects of these comorbid conditions (and their integrated treatment) on HIV disease progression, adherence to treatment regimens, and clinical outcomes.

Issues Specific to Major Causes of Morbidity and Mortality Among People Living With HIV/AIDS

- Tuberculosis
  - Develop, implement, and evaluate strategies to promote the integration of TB and HIV screening, diagnosis, clinical care, and treatment, designed to improve the early identification and outcomes of both diseases;
  - Develop and evaluate new drugs and regimens for more effective prevention and treatment for drug-susceptible and drug-resistant TB, and strategies to optimize benefits and reduce adverse consequences of dual therapies (i.e., immune reconstitution syndromes, additive toxicities, and drug interactions) across the lifespan;
  - Develop and study effective and accurate surrogate markers for severity of disease, prognosis, and rapid assessment of therapeutic effectiveness;
  - Develop and study feasible and effective strategies for prevention of transmission of drug-susceptible and drug-resistant TB in community and health care settings, including airborne infection control strategies individually and in combination; and
  - Develop and evaluate candidates for an effective, safe, and durable vaccine for TB across the lifespan.
- Viral Hepatitis
  - Develop, implement, and evaluate noninvasive strategies to determine optimal timing for initiation of HCV therapies in HIV-coinfected patients;
  - Develop and study new drugs and drug combinations to provide well-tolerated, effective, and safe treatment and cure of HCV in diverse populations with HIV/HCV coinfection;
  - Refine methods to assess and monitor the development of resistance to anti-HCV drugs in HIV-coinfected patients and develop effective strategies for prevention of transmission of HCV in community and health care settings; and
  - Continue efforts to develop a safe, effective, and widely available vaccine for hepatitis.
- Malaria
  - Develop and test new safe, effective, and durable malaria prophylactic and therapeutic agents and regimens, compatible with HIV therapies and across the lifespan; and
  - Study HIV and malarial immune responses to enable development of an effective and durable malaria vaccine in HIV and non-HIV infected populations.
- Malignancies
  - Develop and test the feasibility of resource-appropriate technologies for better screening and diagnosis of cancers, particularly oral, cervical, and anal cancer, non-Hodgkin's lymphoma, and Kaposi's sarcoma, and utilize these methods to develop appropriate clinical approaches to the management of cancers in HIV-infected individuals;
  - Develop and test optimal strategies to integrate ART programs with region- and/or country-specific cancer services for prevention, diagnosis, and comprehensive care to ensure a continuum of care and enhanced outcomes, while supporting the utilization of standard anatomic pathology methods for diagnosis, staging, prognosis, and followup;
  - Support operational studies of large-scale HPV vaccination programs of adolescent girls as part of national efforts to expand access to HPV vaccines; and
  - Study and determine the epidemiologic and biologic relationships between HIV and other malignant diseases, particularly in aging populations.
- Noninfectious, Chronic Diseases Associated With HIV Infection (Cardiovascular, Renal, Neurologic, etc.)
  - Determine the types, prevalence, and risk factors of noninfectious conditions associated with chronic HIV infection; and
  - Develop and monitor screening, diagnostic, and clinical algorithms for prevalent conditions in patient populations.

- Substance Use
  - Identify changes in substance use patterns (e.g., increasing use of methamphethamine or injection opiates) and the characteristics of substances (e.g., increasing potency of drugs or available alcohol products) that may affect HIV acquisition (i.e., injection) or sexual risk (e.g., substance use that affects judgment or sexual drive);
  - Develop and evaluate strategies to integrate substance use prevention, assessment, and treatment into HIV care settings;
  - Evaluate the implementation of effective HIV risk-reduction strategies related to substance use, such as harm reduction services, behavioral and biologic substance use treatment, and implementation of HIV testing and sexual risk reduction in substance use treatment settings; and
  - Develop and evaluate integrated approaches to manage adherence to drug/alcohol treatment strategies as well as HIV treatment among HIV/HCV-coinfected patients.
- Mental Health and Psychiatric Disorders
  - Identify psychiatric conditions that contribute to increased risk of acquisition of HIV and those that have an adverse impact on HIV treatment; and
  - Develop and evaluate approaches to integrate treatment for HIV with treatment for mental health disorders.

OBJECTIVE–E: Expand Implementation Science and Translational Research

Expand translational research to enhance development of new HIV diagnostic, prevention, and therapeutic technologies and strategies, and implementation science to determine effectiveness and impact of new and existing prevention and treatment strategies, and provide an evidence base to inform policies and practice.

STRATEGIES

- Conduct impact evaluation, including cost-effectiveness analyses, outcomes studies, and mathematical modeling, to facilitate evidence-based priority setting or decisionmaking between competing or combined interventions, and determine their impact; in particular:
  - Determine required coverage levels for different interventions in order to attain basic efficiencies and maximal effectiveness, while addressing the local epidemic and targeting specific populations; and
  - Evaluate the impact of the scale-up of programs at a population level.
- Investigate alternative methods of delivery (comparative effectiveness and cost-effectiveness) to ensure uptake and sustainability of proven interventions, with a particular focus on innovative delivery systems (e.g., pay for performance, public report cards) and novel methods to increase demand.
- Investigate approaches to integrate health services research with clinical research to facilitate the translation of research findings into policies, clinical practice, and public health programs, including:
  - Provide information to inform the scale-up of comprehensive HIV prevention, care, and treatment programs; and
  - Develop strategies to evaluate and measure the impact of integrating services for prevention, treatment, and management of HIV-associated comorbidities.

PMTCT

- Identify barriers to scale-up and delivery of successful interventions for PMTCT of HIV.
- Evaluate the implementation of World Health Organization (WHO) guidelines for PMTCT, including:
  - Safety of ART drug regimens for the mother and infant (for both *in utero* and breastfeeding exposure);
  - Cost-effectiveness of different approaches;
  - Long-term adherence and retention in care for mother and child;
  - Overall effect of PMTCT interventions on short- and long-term maternal and child survival; and
  - Development of drug resistance.

Technology Transfer and Translation of Research Results

- Develop innovative technologies to enhance communication, dissemination, and diffusion of research results and translation into programs related to prevention, treatment, and care.
- Ensure that research results are provided to, and understood by, participants and the community in which the studies are conducted, as well as to the community's health professionals and personnel in relevant ministries and agencies.

- Provide improved access to information concerning treatment and prevention guidelines and research results through enhanced information technology.

- Transfer clinical, laboratory, and public health technologies that may be sustained and used for implementation of prevention, symptoms management, clinical training, and patient care programs after research studies are completed.

Multidisciplinary Collaboration for Public Health Programming

- Explore approaches to integrate research with service programs and to develop multidisciplinary prevention and treatment research in different settings, including medical treatment and community support and care organizations.

- Continue to collaborate with non-physician health professionals (e.g., nurses, pharmacists, and health aides) and community members (including faith and religious communities, elders, indigenous/traditional healers, student leaders, peer educators, and at-risk populations) as partners in HIV/AIDS research, prevention, and care to optimize program acceptability and feasibility, rollout, and outcomes.

- Foster cross-disciplinary collaboration and input by professions to streamline, improve effectiveness, and maximize the impact of translation of research results.

OBJECTIVE–F: Strengthen Efforts To Build Research Capacity

Continue to strengthen sustainable and collaborative research environments and systems by building on existing and developing new scientific, clinical, administrative, and public health institutional infrastructure, while enhancing in-country leadership, research training, and professional development.

STRATEGIES

Site Development

- Monitor existing international study sites supported by the NIH, and, as needed, further develop sustainable sites, or establish new in-country sites, to address urgent or unmet needs and emerging scientific opportunities, in coordination with ongoing NIH-funded research and other U.S. Government-funded programs.
- Enhance capacity in resource-constrained settings for the conduct of biomedical, behavioral, clinical, and translational research that integrates prevention and treatment approaches through:
  - Strengthening laboratory capacity through the provision of required equipment and human resource development with appropriate quality assurance and training;
  - Maintaining and developing both Good Laboratory Practice (GLP) and Good Clinical Practice (GCP) requirements for clinical trials;
  - Developing diagnostic and clinical capabilities through research training and "hands-on" research experiences;
  - Developing affordable and reliable point-of-care diagnostics suitable for use in low-resource settings (e.g., viral load and CD4+ cell counts), as well as reliable approaches to monitoring clinically important outcomes, such as ARV resistance, treatment efficacy, and toxicity;
  - Developing alternative technologies and assays for the diagnosis and monitoring of HIV-related coinfections (e.g., TB) and OIs, with a goal to be more affordable, simpler (i.e., not requiring electricity, refrigeration, and/or computer), more environmentally durable (i.e., withstanding high ambient temperature, humidity, and dust) than current technologies, and requiring less operator training;
  - Enhancing existing pathology practices to permit use of updated disease classification, according to international standards, in the diagnosis, ascertainment, and registration of HIV-associated comorbidities, including malignancies, and strengthening management of local supply chains of reagents and materials, particularly in regions such as sub-Saharan Africa;
  - Supporting the analysis of scientific and research-based international databases and developing laboratory information management systems;
  - Addressing barriers in establishing, maintaining, and enhancing human subject protection in light of complex scientific protocols that may include long-term storage of biological specimens;
  - Developing and testing strategies that support the recruitment and retention of participants in integrated prevention, treatment, and care studies;
  - Optimizing epidemiological assessments of targeted at-risk populations, including refining approaches to population-based recruitment of hard-to-reach populations, such as respondent-driven sampling, venue-time sampling, and Internet-based sampling;
  - Developing oversight mechanisms in culturally sensitive and appropriate approaches to address relevant research issues;
  - Conducting research on the feasibility, success, and sustainability of rapid scale-up of pilot projects and/or early Phase I and Phase II clinical trials to large research studies (including Phase III trials) and on how to apply and implement research findings in intended populations;

  - Enabling communities to participate appropriately and meaningfully in the development and design of HIV-related research (including clinical trials), as well as in the translation of research results into community-relevant programs, standards of care, and practices;
  - Enhancing capabilities in medical records management, data analysis, and biostatistics, and the use of such data in decisionmaking and evidence-based practices for improvement of services;
  - Strengthening library services, access to scientific resources, and enhanced information exchange, including electronic communications; and
  - Strengthening capabilities of in-country staff in financial/grants management, administrative practices, regulatory issues, and scientific/peer review.
- Continue to strengthen the capacity to conduct implementation science and operational research, including outcome studies, cost-effectiveness analysis, and modeling, to rapidly address emerging priorities in prevention, treatment, and care, and to ensure that research results are translated to the local setting.
- Conduct studies on HIV incidence and feasibility, using appropriate incidence measures (e.g., population-specific assays), to identify sites suitable for the conduct of efficacy trials of HIV prevention, treatment, and care interventions.

Ethical Issues

- Enhance the capability of institutions in resource-limited settings to conduct independent scientific and ethical reviews, in accordance with international standards of human rights principles, respecting the dignity of persons and protecting vulnerable populations, while ensuring timeliness of the review process.
- Identify ways to improve the application of ethical principles in the conduct of research in varied cultural settings by encouraging countries to develop their own set of ethical guidelines and procedures, to include the principles of respect for persons, beneficence, and justice, and the application of informed consent, assessment of risks and benefits, and selection of subjects.
- Support programs to develop and strengthen in-country capacity for the ethical and responsible conduct of research, including application of informed consent, establishment of community advisory boards, and other topics related to the protection of human subjects.
- Ensure that ethical review mechanisms, such as informed consent forms, are relevant and appropriate to the country where the research is conducted and are placed in an appropriate cultural context (including low literacy and local languages).
- Maximize understanding of the informed consent process through new communication technologies in vulnerable populations.
- Ensure that research projects are designed to benefit and engage the communities in which the research is being conducted by addressing locally relevant scientific questions and capacity needs.
- Strengthen the capacity of institutional review boards (IRBs), including information-sharing between IRBs, updates on recent developments, and monitoring of approved protocols.
- Ensure collaboration between resource-limited countries' ethical review committees and U.S. IRBs, and inform U.S. IRBs about culturally relevant issues in developing countries.
- Develop and provide training at international sites conducting clinical trials on the role and responsibilities of an institutional biosafety committee.

Collaboration and Coordination

- Ensure the leadership role of in-country investigators, academic leadership, community-based and indigenous leaders, and other stakeholders by involving them in all stages of research, including conceptualization of the research question, study design, development of protocols, study implementation, data collection

and analysis, publication, and presentation of research results to government and other relevant stakeholders and audiences.

- Encourage the integration and coordination of research projects being conducted by NIH-funded researchers in resource-limited settings with established in-country programs, while collaborating with local investigators, to ensure project relevance and to optimize the research effort.
- Encourage the continued development of research collaborations between U.S. and low- and middle-income institutions and investigators into more equal partnerships, including strategic planning for research.
- Encourage in-country pathology services to coordinate activities of NIH-funded researchers and build core clinical/research capacity to avoid duplication of resources, enhance consistent quality of effort, and improve efficiency of workflow.
- Coordinate with other U.S. Government agencies, the U.S President's Emergency Plan for AIDS Relief (PEPFAR), foreign governments, universities, and international organizations to help identify and support priorities for research infrastructure and capacity building in developing countries.
- Foster regional approaches to research to enhance communication, achieve economies of scale, help establish new collaborations, and address common issues and needs (i.e., gap analysis) for HIV-related research among countries in a given region.

Mentoring, Training, and Career Development

- Continue to develop a cadre of in-country scientific professionals and a community of investigators committed to a culture of leadership in research through fostering long-term mentoring and providing sustainable opportunities for career development, with incentives for working in-country, for new, mid-career, and senior investigators in resource-limited international settings.
- Provide opportunities for new, junior, mid-career, and senior investigators from developed and developing countries to collaborate on research projects in resource-limited settings and spend significant time working together in developing countries.
- Develop in-country partnerships and support "South–South" training to enable investigators to obtain training appropriate for the areas in which they will work by providing opportunities to enable trained investigators returning to their home countries to serve as faculty and mentors for others.
- Continue to support research training, including degree training where appropriate, of clinicians and non-physician professionals (such as nurses, midwives, and pharmacists), social and behavioral scientists, clinical pathologists, biostatisticians, public health professionals, community health workers, and other researchers from developing nations to enhance the conduct of research on HIV/AIDS, other STIs, and HIV-related coinfections, malignancies, and comorbidities.
- Provide training and mentoring in data collection, biospecimen processing/storage, biostatistics, and analysis for in-country research personnel.
- Provide training in all aspects of grantsmanship, including preparation of grant proposals, registration for electronic submission, grants management, reporting requirements, research administration, and fiscal accounting.
- Support research efforts to develop and assess the impact of novel training technologies with applications in low-resource settings (eCapacity), such as Web-based and distance learning, video conferencing, handheld platforms, and other innovative training tools.
- Identify barriers that international investigators encounter in the NIH application submission process through www.grants.gov, and work with relevant agencies to address the barriers that prevent application submissions.

AREA OF EMPHASIS

Training, Infrastructure, and Capacity Building

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A: Research Training

Provide training in biomedical, social and behavioral, intervention, and implementation science research to address the challenges of HIV and its associated complications, coinfections, and comorbidities. This is to be carried out with an emphasis on multidisciplinary research in populations that are diverse with respect to age, gender, race, and culture, including marginalized populations domestically and internationally, particularly in countries with high HIV incidence and/or high prevalence of HIV infection.

STRATEGIES

- Strengthen opportunities for prebaccalaureate, undergraduate, predoctoral, doctoral, postdoctoral, and advanced research training across a broad range of AIDS-related scientific disciplines, and support research to better understand the barriers and incentives along the research career pathways for investigators.
- Enhance programs that improve recruiting, training, mentoring, and retaining investigators—especially those from diverse scientific backgrounds, including biomedical, behavioral, and social scientists—in AIDS research.
- Improve opportunities for highly trained specialists to develop skills in AIDS research, such as, but not limited to:
  - Opportunities in disciplines needing more specialists to be research-proficient in HIV prevention, diagnosis, manifestations, complications, and treatment. Examples include, but are not limited to, pediatricians, obstetricians, adolescent medicine specialists, nurse scientists, mental health and neurocognitive specialists, and geriatricians;
  - Opportunities for HIV prevention researchers interested in adding specific methodological skills to their research expertise;
  - Opportunities for related specialists such as pharmacologists, hematologists, and dental scientists to develop skills in AIDS research; and
  - Opportunities for animal research scientists using animal models, including nonhuman primates (NHPs).
- Implement new research training programs for non-physician professionals—such as physician assistants, nurse practitioners, laboratory staff, therapists, and social workers—in resource-limited settings and at domestic sites to increase the diversity of the pool of AIDS researchers.
- Expand and strengthen training programs for basic and clinical/applied researchers across disciplines:
  - Provide training and promote standardized certification in Good Laboratory Practice/Good Clinical Practice for staff in domestic and international settings where clinical research on AIDS is being conducted.

- Expand the capacity for basic and clinical/applied research on HIV and HIV-related complications, coinfections, and comorbidities (e.g., tuberculosis, hepatitis, cancers, and antiretroviral therapy-related complications such as cardiovascular and metabolic consequences) in the United States and in resource-limited countries.
- Provide training programs for personnel in institutions in resource-limited settings to strengthen the administrative and financial management capacity needed to conduct HIV-related research, as well as to integrate best practices and applicable research results into program planning and implementation.
- Strengthen programs that provide support for international AIDS researchers trained in NIH-sponsored programs to continue their research in their home countries.
- Expand programs that utilize the infrastructure at NIH-sponsored AIDS research studies, including clinical trial sites, for training programs in the design and conduct of AIDS-related clinical research.
- Expand training programs in nontraditional settings such as in the private nonprofit and biotechnology sectors.

- Build and sustain training opportunities for tested and emerging research methodologies relevant to HIV, such as methods to conduct cost-effectiveness analyses, implementation research, measurement of biologic outcomes in behavioral intervention studies, appropriate use of behavioral and social science measures in clinical trials, ethnographic and other qualitative methods, and network/systems analysis.
- Utilize the NIH AIDS Loan Repayment Program to encourage promising U.S. scientists and physicians to pursue HIV-related research careers, placing an emphasis on those whose demographic profiles represent that of the HIV epidemic.
- Strengthen cultural competency training and ethics training for the conduct of AIDS research in vulnerable populations, in domestic and international settings.
- Develop new models of integrated training and mentoring that focus on the protection of human and animal subjects in AIDS research.
- Support the development and sharing of novel techniques from relevant research fields to the HIV/AIDS field, including structural biology, computational biology, genomics, metabolomics, proteomics, and systems science, to understand HIV/AIDS-associated disorders. Encourage and facilitate collaborative and interdisciplinary research in these areas.
- Expand the development and analysis of distance-learning/e-learning tools and approaches that can be used to teach research and research-related topics as well as to further assess and better understand the acquisition of research skills and competency.
- Design and implement mentorship programs that:
  - Encourage the development and testing of new models of mentorship that support the mentored career development awards or various types of fellowship programs designed to enhance the success and productivity of both U.S.-based and international investigators.
  - Increase the retention of trainees/investigators at each of the succeeding training stages (e.g., postbaccalaureate to predoctoral and/or predoctoral to postdoctoral) by specifically addressing weaknesses that may be identified along the training pipeline, such as at key transition periods along the career path where trainees are known to slow in their progress and/or otherwise be lost to followup.
  - Leverage existing training opportunities and existing clinical research networks for more immediate outcomes that enhance the breadth of scientific career options.
  - Improve the implementation of rigorous monitoring, tracking, and evaluation systems to gauge the impact of each new training program on its target population.

  - Further diversify the research workforce and align researchers to be more adept within relevant sociocultural contexts and economic infrastructures they operate in and/or will encounter (e.g., community, school, and/or business systems and settings).

- Strengthen mentor training programs and develop alumni networks of established NIH-supported investigators that could serve as standing resources for current trainees and improve the supply of trained mentors for the development and retention of new investigators in all aspects of AIDS research.

- Support research that develops an evidence-based approach to effective mentoring so that future mentoring programs can build on best practices and the knowledge base of educational and social science research.

OBJECTIVE–B: Infrastructure and Capacity-Building Development

Establish and maintain the appropriate infrastructure and capacity needed to conduct AIDS research domestically and internationally, with emphasis on highly affected populations.

STRATEGIES

- Enhance and improve research capacity and infrastructure to advance research on HIV and HIV-associated infections, coinfections, comorbidities, and other complications.
- Enhance and improve the infrastructure to conduct clinical trials of prevention and therapeutic strategies in domestic and international sites, including laboratory capacity, trained scientists, and other personnel in appropriate numbers; appropriate participant cohorts; and establishment of local institutional review boards to address bioethical issues.
- Expand the infrastructure necessary for producing AIDS vaccine candidates under Good Manufacturing Practice for preventive and therapeutic vaccine clinical trials.
- Support programs emphasizing age-specific symptom management, palliative and end-of-life care, and quality of life in HIV disease.
- Develop, maintain, and effectively utilize domestic and international cohorts, repositories, and nested studies among populations experiencing emerging and ongoing AIDS epidemics, and maintain updated databases to allow for their broader and more efficient use by the scientific community, when appropriate.
- Establish and maintain quality-controlled repositories, biobanks, and well-characterized panels of reagents to ensure access by qualified scientists to human blood and tissue specimens from clinical trials and cohorts. Improve and disseminate the process of requesting, prioritizing, and receiving these specimens to allow timely and equitable access.
- Develop, validate, and utilize experimental animal, *ex vivo, in silico,* and theoretical/mathematical models to study the transmission and establishment of HIV/SIV/SHIV (human immunodeficiency virus/simian immunodeficiency virus/simian-human immunodeficiency virus) infections, with emphasis on models of direct relevance to human HIV infection and models that address important issues not readily approachable in human subjects.
- Promote Internet connections, cell-phone-based communication, and online social networks, including those with computer-based simulated environments (i.e., "virtual worlds") for training, infrastructure, and treatment, taking into consideration appropriate levels of confidentiality/security.
- Ensure the availability of pertinent and secure information technology at health science centers, hospitals, outpatient clinics, community-based organizations (CBOs), and other access points, both domestically and internationally, for HIV-related research and patient care.
- Develop statistical sampling methodologies, data collection protocols, and statistical analysis tools that are easy to use and adaptable to different settings; facilitate efficient statistical analysis and enhance report generation and standardization when appropriate in the context of AIDS research.
- Promote research in, and application of, medical informatics (e.g., high-performance computing) for AIDS research and clinical practice in resource-limited settings, both domestically and internationally.
- Develop efficient and effective systems for collecting and managing HIV/SIV/SHIV multiple-center and single-site clinical and animal model trial data, and ensure timely and accurate dissemination of clinical and animal model trial information.
- Increase collaborations between CBOs/nongovernmental organizations and Government-supported health care service providers and academic researchers to improve the quality and capacity of AIDS research in health care service settings.

DOMESTIC

- Support enhanced research infrastructure at U.S. minority-serving institutions to improve capacity to support AIDS research.
- Support AIDS research planning and organizational initiatives targeting domestic minority institutions and minority-serving communities, with emphasis on initiatives that develop academic–community partnerships.
- Improve opportunities for institutions serving specific diverse populations at risk for HIV to develop equal and productive partnerships with U.S. institutions serving primarily broad-based, majority populations.
- Develop programs to sustain human capacity and to link U.S. AIDS research scientists, industry partners, and relevant institutions with each other and with investigators and institutions in both developed and developing countries.
- Develop strategies to promote the infrastructure for bidirectional translational science by enhancing national capacity for clinical and translational AIDS research, supporting team-building and consortium collaborations, and facilitating the use of national data-sharing HIV networks.
- Support and expand adequate facilities and resources, including BSL-2/3 (Bio Safety Level 2/3) facilities for studies in NHPs, and provide appropriate ethical and procedural training to house, maintain, and breed NHPs for use in AIDS research.
- Expand the breeding of genetically defined specific pathogen-free NHPs, with emphasis on Indian-origin rhesus macaques.
- Develop and characterize appropriate reagents for use in HIV-related research conducted in different species of macaques and other NHPs.
- Support programs that enhance the current AIDS research infrastructure, such as the Centers for AIDS Research, Clinical and Translational Science Awards Consortium, Research Facilities Improvement Program, and National Primate Research Centers.
- Support the HIV Structural Centers Program for structural studies on HIV proteins and host proteins.

INTERNATIONAL

- Strengthen and improve research infrastructure and capacity in resource-limited settings with high HIV incidence, with particular emphasis on facilities for research on HIV prevention, therapeutics, and behavioral interventions.
- Improve coordination and collaboration among NIH-supported investigators, other U.S. Government agencies, and other international agencies conducting AIDS research in the same countries.
- Enhance opportunities to evaluate successful HIV prevention and therapeutic strategies in resource-limited countries that also could be used in the United States.
- Develop and improve conventional and electronic systems for documentation of medical care and tracking of HIV infection and AIDS in low-resource settings to improve epidemiologic research.
- Increase pathology capacity and population-based cancer registration in resource-limited countries to allow for a better understanding of cancer rates in HIV-infected persons in these locations.
- Develop and improve pharmacovigilance systems for detection of short- and long-term adverse effects (including patient impact and congenital anomalies and other effects of fetal drug exposure) of investigational and newly approved HIV treatment regimens.

PRIORITY:

Translating Research From Bench to Bedside to Community

Natural History and Epidemiology

Information Dissemination

AREA OF EMPHASIS

Natural History and Epidemiology

FY 2015 RESEARCH PRIORITIES

- Conduct epidemiologic studies of HIV/AIDS prevention, treatment, and care interventions at population levels through the use of individual, dyadic, health system, community, and population-based approaches.

  This priority includes the development and maintenance of HIV cohorts and appropriate controls, demographic-based approaches, multilevel observational studies, analysis of electronic medical or health records, and community randomized study designs.

- Conduct studies to improve the implementation of research findings into diverse health care practices for HIV/AIDS and related comorbidities.

  This priority includes advancing the methodologies of implementation science and conducting implementation science studies that maximize program effectiveness by addressing organizational and system-level barriers to the scale-up of prevention and treatment interventions. This priority also includes interventions studies in diverse settings and underrepresented populations, and studies evaluating the economic impact (cost-effectiveness) of interventions.

- Develop novel methods and perform the next generation of transdisciplinary HIV research.

  This priority includes transdisciplinary methods to examine the prevention, testing, and treatment cascade by integration of data from electronic medical records, observational studies, clinical trials and simulation, mathematical modeling, and molecular epidemiology.

- Conduct studies that assess epidemiologic aspects of HIV infection across populations from infancy through older adulthood.

  This priority includes the study of the long-term effects of HIV disease, the drivers of HIV-related disparities, common coinfections, and noncommunicable disease (NCD) comorbidities in populations who are aging with HIV.

OBJECTIVE–A: Transmission of HIV (Prevention, Risk Factors, and Mechanisms)

Further characterize the relative importance of major risk factors, population-attributable risk, and mechanisms of HIV susceptibility and transmission in domestic and international settings to guide prevention and treatment strategies.

STRATEGIES

Strategies Related to HIV Transmission, Prevention, and Care

- Study the seek, test, treat, and retain approach, both alone and in combination with other prevention interventions, using epidemiologic, mathematical, and simulation models and cost-effectiveness analyses.
- Evaluate new strategies to increase the uptake of HIV testing in at-risk and affected populations, including use of social network strategies, provider-initiated testing and counseling ("opt-out" approach), home-based testing, home self-test kits, financial incentives, Web-based and mobile technologies, and other novel strategies.
- Use novel epidemiologic methods to quantify the impact of widespread antiretroviral therapy (ART) availability, adherence, pre-ART and ART retention in care, early versus late treatment initiation, HIV-related and aging-related comorbidities, and patterns of antiretroviral (ARV) resistance on HIV prevalence, incidence, community-level viral load, risk behaviors, long-term care retention, and the transmission of resistant HIV strains.
- Utilize existing cohorts, develop new cohorts of selected subpopulations, and employ novel methods (e.g., social/sexual network analysis, molecular epidemiology and epigenetics, temporal phylogenetic analyses, geographic information systems, and mobile technologies) to further assess the magnitude of HIV incidence and risk factors for HIV transmission.
- Develop molecular and other methods and conduct studies to estimate incidence, prevalence, and correlates of divergent viral genotypes and recombinants, drug resistance, and neutralization profiles and their temporal trends; characterize how different HIV types, subtypes, and recombinant forms may influence superinfection, response to ART and other biomedical interventions, and emergence of ARV-resistant viruses.
- Incorporate measures such as community viral load (CVL) into population-based samples such as demographic and health surveys and AIDS Indicator Surveys.
- Refine epidemiologic and mathematical models to improve estimates of per-exposure risk of HIV transmission and to develop estimates of population-attributable risk, based on type of sexual and/or other exposure, characteristics of the infected and uninfected partners, cofactors (such as substance use), and biomedical interventions.
- Investigate viral, host, and environmental characteristics that distinguish high-efficiency transmitters and non-transmitters of HIV, through studies of serodiscordant partners, sexual and/or molecular network-based studies, simulations, and other strategies.
- Conduct epidemiologic modeling studies on the aggregate impact of factors such as frequent testing, early ART, pre-exposure prophylaxis (PrEP), postexposure prophylaxis (PEP), topical microbicides, and male circumcision on HIV transmission in the presence or absence of other biomedical, behavioral, and structural interventions.
- Study the effect of endogenous and exogenous sex steroids on the risk of HIV transmission and the mechanism by which hormonal contraception may alter the risk of HIV transmission.
- Evaluate the risk of sexual and blood-borne HIV transmission in relation to the following:
  - Viral factors such as viral quantity, diversity, coreceptor usage, genotype, and dual virus infections in various body compartments and mucosal compartments such as the oral mucosa, the female genital tract, and the anorectal mucosa;

- Host factors such as age, sex, race, socioeconomic status, functional capacity, strength and breadth of immune response, comorbid diseases, coinfections, transfusion, and presence of other highly prevalent NCDs;
- Host genetics, including genome-wide association and genome sequencing studies;
- Modifiable factors such as food security, diet, and nutritional status; geographic location; age at sexual debut; drug, alcohol, and tobacco use and treatment; mental health; housing; circumcision status; societal acceptance/stigma, sexual risk, and behavioral interventions; and linkage to, retention in, and use of health care barriers to unveiling risk behaviors in the health care setting;
- Other infections, including *Mycobacterium tuberculosis* (TB) and drug-resistant strains, multidrug-resistant (MDR)- and extensively drug-resistant (XDR)-TB, *Plasmodium* sp. (malaria), sexually transmitted infections (STIs), viral hepatitides and antibiotic-resistant bacterial infections, and the broader microbiome;
- Psychological, behavioral, social, cultural, geographic, and structural determinants of susceptibility to HIV acquisition among hard-to-reach and vulnerable populations;
- Sexual activity, pregnancy, sexual networks, partner choice, partner concurrency, partner fidelity, sexual partner violence, duration of partnership, physical and virtual venues for meeting sexual partners, sex trade, and control of STIs; and
- Hygienic practices such as douching (vaginal and rectal), contraception practices, and cultural practices such as the use of traditional vaginal and rectal preparations.

- Further refine the timing, mechanisms, and risk factors in perinatal and postnatal mother-to-child-transmission (MTCT) of HIV. These studies include:
  - Assessing the clinical outcomes, cost, and cost-effectiveness of different strategies for prevention of MTCT (PMTCT), including the access and provision of timely maternal ART, immediate ART in very high-risk neonates, and safe breastfeeding and formula feeding;
  - Studying efficient practices and barriers to HIV testing of the mother during prenatal care, labor, and of the infant after birth;
  - Assessing the impact of maternal and infant ARV regimens of different potency and duration on (1) MTCT, (2) the overall health of women and their HIV-infected and uninfected children, (3) the emergence of ARV drug resistance in the mother and in those infants who become infected despite prophylaxis, and (4) programmatic uptake, adherence, retention, and costs;
  - Studying the safety, effectiveness, and efficiency of sustainable approaches to PMTCT, and determining the effects of such approaches on infant growth, cognitive/behavioral development, morbidity, and mortality;
  - Studying strategies for maternal ART and prophylaxis in settings where limited or no laboratory monitoring may be available;
  - Assessing the impact of subsequent pregnancies after HIV diagnosis and enrollment in HIV care on loss to care and risk of MTCT.
- Conduct studies to assess the individual and public health value of prevention programs that promote widespread, frequent HIV testing and linkage to care, including voluntary HIV couples counseling and testing and partner notification with immediate linkage to counseling, care, and ART; and self-testing and opt-out programs.
- Identify the multilevel determinants of low CD4 at enrollment into care and ART initiation, with a focus on modifiable factors at the clinic level, contextual level, and individual level.
- Assess the efficacy, effectiveness, efficiency, and long-term sustainability of individual and various combinations of prevention strategies (e.g., behavioral changes, partner/couple testing and notification, biomedical interventions such as PrEP and PEP, and treatment for coinfections and comorbidities) in different populations, regions, and risk groups.

OBJECTIVE–B: Disease Progression (Including Opportunistic Infections [OIs] and Malignancies)

Use epidemiological research, including research through the use of electronic medical records, in domestic and international settings, to identify the effectiveness, impact, and interactions of HIV-related therapeutics, biological factors, behaviors, and community/policy-level factors (e.g., HIV testing coverage, impact of the Affordable Care Act) in relation to HIV progression, response to ART, and development of non-AIDS-defining chronic conditions, as indicated by virologic, immunologic, and clinical outcomes.

STRATEGIES

Strategies Related to HIV Disease Progression and Response to ART

- Develop new cohorts and maintain ongoing enrollment and long-term followup of existing cohorts to determine the changing spectrum of HIV disease coinfections and comorbidities; identify highly exposed uninfected persons, long-term non-progressors, and elite suppressors. Develop accurate and uniform definitions that may be applied across cohorts for multicohort analyses.
- Characterize short- and long-term consequences of recent HIV infections on HIV disease progression, including the roles of host and viral genetic characteristics and different routes of exposure; continue to characterize the epidemiology of HIV/AIDS early in infection, and in individuals who have experienced ART failure.
- Determine, using different epidemiologic study designs, the effects on disease progression of cumulative and current ART exposure to specific drugs; classes of drugs; drug combinations, including drugs for coinfections; and treatment strategies and laboratory monitoring overall and by sex and age groups.
- Characterize global patterns of innate and acquired viral resistance to ART and how these patterns influence the long-term effectiveness and cost-effectiveness of monitoring strategies and therapies.
- Characterize the changing spectrum of clinical outcomes, causes of morbidity and mortality, complications of ART, and cost patterns associated with evolving therapeutic strategies, in relation to person, medication, and system-level factors.
- Characterize the scope of use and anticipated changes in the cost and cost-effectiveness of care as more ARV formulations move from patented to generic type; evaluate how differences in the generic regimens influence use, adherence, and efficacy.
- Use observational studies in resource-limited settings to estimate the HIV prevalence, incidence, and correlates of treatment failure in first-line, second-line, and subsequent treatment regimens.
- Assess the effect of ART on the incidence, pathogenesis, and presentation of cancers and other noncommunicable diseases, and use mathematical models to project the frequency, and outcomes of treatment for these cancers.
- Characterize the long-term effect of HIV infection on the central nervous system, including the effect of viral burden in the cerebrospinal fluid and its effect on white matter degeneration, and differentiate these changes from other neurocognitive diseases, such as dementia and Alzheimer's disease.
- Evaluate and characterize immune reconstitution inflammatory syndrome (IRIS), including modifiable (e.g., the oral and gut microbiota) and non-modifiable predictors of immune recovery, and determine best treatment practices for IRIS in diverse populations.

Strategies Related to HIV Disease Progression and Comorbidities

- Define the prevalence, incidence, predictors, potential treatments, and consequences of HIV comorbid disease, including each comorbidity's estimated loss of life years and quality of life. Use mathematical models to project the frequency, outcomes, and treatment costs of these comorbidities in HIV survivors.
- Expand research on the spectrum of AIDS-defining malignancies and on non-AIDS-defining malignancies that may develop in HIV-infected patients who have responded to ART and are living longer.
- Identify effective and cost-effective screening strategies for such malignancies in HIV-infected populations.
- Identify host genetic differences in susceptibility to HIV-related complications and comorbidities by including classical, genome-wide association and genome sequencing methods.
- Investigate the role of risk factors such as chronic inflammation in the development of malignancies and noninfectious comorbidities in HIV-infected individuals, and how cumulative and current ART use, smoking, alcohol, and frailty might mediate the effects of chronic inflammation.
- Determine the influence of locally endemic diseases on markers used to predict complications of HIV, including lymphocyte subsets, activation markers, and hematologic and clinical chemistries.
- Develop and evaluate affordable diagnostic and clinical indices for comorbidities for tailoring care to individual risk in resource-limited settings.
- Assess the ability of health care systems in resource-limited settings to screen, diagnose, and treat individuals with AIDS-defining and non-AIDS-defining malignancies. Conduct analyses to evaluate "packages" of screening and treatment interventions for noncommunicable, high-burden diseases.
- Investigate TB/HIV interactions, including the effects of dual infection on the progression of both TB and HIV.
  - Investigate new approaches to successful diagnosis, as well as linkage to and retention in care of patients who are coinfected with HIV and TB.
  - Investigate the MDR/XDR-TB epidemic among HIV-infected patients, evaluating risk factors for MDR/XDR-TB prevalence, incidence, therapeutic options, and clinical outcomes for prophylaxis and treatment strategies.
  - Investigate the prevalence of disseminated (miliary) TB disease, including cerebral TB, its impact on everyday function, disease progression, and therapeutic options among HIV-infected patients.
  - Assess methods of integrating TB and HIV diagnostics, prophylaxis, care, and adherence, as well as other prevalent HIV-associated comorbid conditions, and their effects on survival, quality of care, cost, and cost-effectiveness of care.
  - Investigate the feasibility, effectiveness, and cost-effectiveness of screening for and treatment of latent TB on the epidemiology of HIV and TB coinfection in endemic countries.
  - Conduct implementation science research to understand barriers to implementation of preventive therapy and treatment of active TB in HIV and TB-coinfected patients.
- Evaluate the clinical and economic impact of treatment of smoking; alcohol and drug use, abuse, and dependence; and mental health disorders on the effectiveness, cost-effectiveness, and consequences of ART, HIV disease progression, development of comorbidities, and mortality.
- Support research efforts to link existing medical record systems and clinical, observational, and surveillance databases to enhance the understanding of HIV/AIDS outcomes in populations and in standard-of-care cohorts.
- Study the frequency, changing manifestations, and effects of HIV-related respiratory disease on morbidity, mortality, and HIV disease progression, in both untreated patients and those receiving ART.

- Study the emergence and reemergence of infectious diseases and the clinical and epidemiological characteristics of antimicrobial-resistant infections in HIV-infected populations.
- Estimate the prevalence of specific human papillomavirus (HPV) types associated with cervical, anal, and oropharyngeal cancer and pre-cancer in HIV-infected individuals.
- Evaluate different cervical and anal dysplasia and cancer identification and treatment methods in HIV-infected individuals for sensitivity, specificity, cost-effectiveness, and appropriateness.
- Evaluate the effectiveness and cost-effectiveness of HPV vaccines and barriers to their uptake among HIV-infected individuals from geographically diverse regions.
- Assess the effect of various primary care screening and interventions on HIV disease outcomes, survival, and costs of care.
- Investigate hemostatic disturbances in HIV-infected individuals and the role of coagulation and fibrinolytic mechanisms in risk of vascular events and other complications.
- Examine the impact of cryptococcal disease on early mortality, and evaluate strategies (including novel point-of-care antigen testing) for prevention and early detection of cryptococcal disease in HIV-infected individuals.

Strategies Related to HIV Disease Progression and Pediatric Populations

- Evaluate the differences in adherence and HIV outcomes between adolescents, adults, and perinatally infected children; in behaviorally acquired versus perinatally infected adolescents; and in adolescents treated in pediatric versus adult HIV treatment centers.
- Investigate the long-term outcome of both HIV and ART in perinatally HIV-infected infants and children as these children reach adolescence and adulthood. Determine whether a premature aging phenotype exists in these individuals as they enter the third and fourth decades of life.
- Assess the long-term impact of perinatal HIV and ART exposure in HIV-uninfected infants, children, and adolescents born to HIV-infected mothers.
- Study the effect of the health status of HIV-infected mothers and of ART during pregnancy, lactation, and early child life on survival, quality of life, and care costs of their HIV-infected and -uninfected children and on maternal outcomes. This strategy includes studies of reproductive and pregnancy outcomes.
- Study HIV-infected and -uninfected children and adolescents to determine factors related to impaired growth and neurodevelopment; cognitive, behavioral, and psychomotor development; impact of other childhood infectious diseases and nutritional status; and safety and efficacy of immunizations.
- Develop appropriate epidemiologic and surveillance studies to assess the immunologic responses to routine vaccinations of childhood and adolescence and the need for altered vaccine schedules in HIV-infected youth.
- Assess the risk factors for acquisition and natural history of HPV infection, and the impact of HPV vaccines in HIV-infected children and adolescents.
- Optimize ART monitoring strategies for settings where the World Health Organization Option B+ PMTCT strategy will be deployed widely.

Strategies Related to HIV Disease Progression, Aging, and NCD Comorbidities

- Investigate the relationship between HIV infection and the spectrum of physical and mental health outcomes that increase with aging.
- Study the incidence and determinants of physical, neurologic, and cognitive changes by age group and by duration of HIV infection and treatment among HIV-infected individuals and the linkage between frailty and functional impairment and HIV, ART use, response, and self-care behaviors.

- Study the epidemiologic association between immunologic and virologic responses to treatment and adverse effects of HIV and ART in aging populations, including those with coexisting morbidities or who receive numerous medications for other conditions.

- Characterize the long-term effects of HIV and HIV-associated conditions on multimorbidity, polypharmacy, and frailty. Develop means of incorporating these phenomena in analyses focused on solid organ systems or specific functions, including cognition and immune function.

- Examine the impact of polypharmacy in older HIV-infected individuals, including its effects on toxicity and adherence to and prioritization of critical drug regimens.

- Evaluate immunologic and virologic measures of HIV disease progression, ART-related toxicities, development and progression of comorbid conditions, and mortality in older versus younger adults receiving ART. Develop and validate indices that integrate these measures to predict important clinical outcomes, including all causes of mortality.

- Conduct studies of HIV and NCD comorbidities in the ART era, in high as well as low- and middle-income countries.

OBJECTIVE–C: Methodologies

Develop and evaluate methods and resources for HIV/AIDS epidemiological and clinical studies that use culturally appropriate approaches; incorporate new laboratory and statistical methods; better utilize information systems by complementing existing data; and better integrate research findings into clinical practice and regional, national, and international policies and guidelines.

STRATEGIES

- Evaluate and promote the use of multiple study designs that incorporate appropriate ethical, cultural, and policy context for studies of HIV/AIDS prevention, diagnosis, and treatment in diverse domestic and international populations.
- Evaluate study designs, including adaptive trials that more efficiently assess the effectiveness of prevention and treatment interventions and studies conducted in typical service delivery settings.
- Continue to support local, regional, and international collaborations to integrate, harmonize, and utilize existing data.
- Capture and utilize data from large U.S. and international HIV screening programs, such as blood donor screening programs, to monitor HIV incidence and temporal trends, viral genotypes, drug resistance, and neutralization profiles.
- Ensure that the population composition of domestic epidemiological and intervention studies is representative of populations at risk for and affected by HIV/AIDS, such as women, older Americans, persons from geographical regions most affected by the epidemic, adolescents and young adults, men who have sex with men and other sexual minorities, racial and ethnic populations, drug and alcohol users, persons with mental illness, and persons affected by other comorbidities.
- Ensure that studies reflect the needs and priorities of the countries or regions in which they are conducted and produce results that are quantifiable and applicable to diverse circumstances and geographic areas.
- Explore expanded utilization of new diagnostics designed for use at the point of care, which have potential to address access, disparity, and confidentiality issues for people at risk for or infected with HIV, especially in underserved areas and in stigmatized populations.
- Promote the development and dissemination of point-of-care tools appropriate for both industrialized and resource-limited settings to standardize the diagnosis and monitoring of treatment-limiting or life-threatening complications of chronic HIV infection and ART.
- Investigate the use of Internet-based or other mobile technologies (such as smartphones) as methods of recruitment, risk assessment, research education, and preventive interventions for HIV.
- Characterize HIV transmission dynamics among minorities (e.g., young sexual minority status populations) by using network analysis and similar techniques that identify and quantify network factors and related drivers of racial, ethnic, and sexual disparities; target such network factors for HIV testing and prevention interventions.

Strategies Related to Natural History Diagnosis and Monitoring

- Further develop epidemiologic, laboratory-based, and simulation modeling methods in conjunction with prospective cohort studies, domestically and internationally, to monitor HIV incidence, response to ART, and the incidence of complications of HIV infection and of chronic use of ART, including:
  - Develop and test methods to produce accurate, reproducible, and inexpensive virologic, immunologic, bacteriologic, mycologic, pharmacologic, neurobehavioral, and genetic assays suitable for large-scale epidemiological research and surveillance in resource-limited

settings. Emphasis should be on simple and reliable staging of disease progression for the initiation and monitoring of ART and OI prophylaxis, viral hepatitis testing, HIV resistance testing, TB screening, and assays for STIs and other coinfections.

- Effectively utilize ongoing and newly developed cohort studies, domestic or international specimen repositories, and databases for interdisciplinary HIV-related studies to address short-, medium-, and long-term outcomes. Encourage collaborative studies between cohorts and nested studies that utilize these resources.

- Develop uniform assessment tools to measure host and environmental characteristics, including food insecurity, malnutrition, substance abuse, and mental health, which may affect immediate and longer-term HIV-related health outcomes. Assessment tools should be both culturally appropriate and scientifically valid and made available for other researchers to assess, validate, and use.

- Develop new and evaluate existing assays to accurately measure HIV incidence at a population level, using rapid, inexpensive, and reproducible measures, including methods appropriate for resource-limited settings.

Strategies Related to Research on Study Design and Analysis of Epidemiologic Data

- Develop new epidemiological designs and statistical methods, and informatics tools and simulation, to better characterize HIV, STI, and hepatitis C virus (HCV) and other blood-borne infections and other coinfections transmission dynamics, and monitor long-term trends in disease progression and development of toxicities in the setting of potent ART.

- Continue to develop and improve upon quantitative methods for making effective and appropriate use of data from local, State, national, and international HIV/AIDS,TB, STI, and HCV and other blood-borne infection surveillance systems and from large observational studies, such as:

  - Methods to assess costs of care for HIV disease management and treatment of comorbidities, both domestically and internationally;

  - Methods for inferring causal effects of nonrandomized exposures (e.g., treatment and policy changes);

  - Methods for estimating HIV, TB, STI, and HCV and other blood-borne pathogens, and other coinfections incidence rates in cross-sectional samples;

  - Methods for sampling hidden populations (e.g., venue-based, Internet-based, mobile-phone-based, snowball, mixed method, respondent-driven, and time-location sampling);

  - Methods for standardizing the reporting of results from studies with novel recruitment and access approaches (e.g., Internet- and mobile-technology-based) and/or using respondent-driven sampling;

  - Models and inferential methods for characterizing multiple/comorbid disease processes and events;

  - Methods for linking cohort data to health care utilization and cost data to address health policy questions;

  - Methods for compiling and linking blood donation data across blood centers, and estimating trends in incidence and transfusion-transmitted risks for HIV;

  - Methods for simultaneously addressing more than one hypothesis or intervention, including the use of factorial randomized trials and quasi-experimental designs;

  - Methods for collecting and analyzing spatio-temporal data (including geo-sentinel mapping), especially as they relate to transmission and spread of HIV infection;

  - Methods for multilevel analysis of population-based HIV/AIDS surveillance data;

  - Research that explores how to increase utilization of population-based HIV/AIDS surveillance data and expand access to these data sources; and

  - Development of robust data presentation tools that can incorporate data from multiple sources for exploration by non-epidemiologists/statisticians.

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

- Conduct studies that make innovative use of existing data for well-designed, rigorous analyses, hypothesis generation, and hypothesis testing.

- Promote collaborative studies using genetic epidemiology methods (e.g., genome-wide association studies, and epigenetic methylation studies) applied to large, diverse populations to elucidate mechanisms of HIV infection, disease progression, and complications.

Strategies Related to Interventions

- Study and evaluate prevention packages that combine multiple strategies into one intervention or packages of interventions, especially those that combine behavioral, biomedical, and structural interventions.

- Develop novel approaches to mathematical and simulation modeling to address the challenges posed by combination prevention packages, and promote methods for communicating such models.

- Develop studies to compare effectiveness, efficacy, and cost-effectiveness of various HIV prevention strategies within and between populations with generalized or concentrated epidemics.

- Assess algorithms for HIV diagnosis and linkage to care, including point-of-care algorithms; diagnosis of acute HIV infection, acute STI, HCV, and other blood-borne infections; and strategies for retention in and adherence to treatment and prevention programs.

- Assess the effectiveness and outcomes of clinical and laboratory monitoring for the initiation, monitoring, and switching of ART, particularly in resource-limited settings.

- Use appropriate clinical and laboratory definitions of short- and longer-term ART failure, and mechanisms for monitoring drug resistance evolution in HIV types, subtypes, and variants in domestic and international populations.

- Develop, evaluate, and promote new, improved, and cost-effective methods and strategies to prevent HIV transmission via blood transfusion, tissue and/or organ transplantation, and other medical interventions in resource-rich and resource-limited settings.

- Assess the impact and cost-effectiveness of different strategies for HIV testing and counseling and linkage to/maintenance of care for different populations, including adolescents, older adults, racial and ethnic populations, vulnerable and displaced populations, and populations in diverse domestic and international settings.

- Develop effective programs to promote routine HIV retesting of high-risk populations.

- Validate the use of surrogate markers for HIV acquisition and transmission risk, including use of behavioral measures and biomedical markers.

- Assess the effectiveness of strategies designed to reduce the impact of HIV comorbidities, including smoking cessation, medication-assisted treatment for substance abuse, mental health treatment, HCV treatment, vaccination against hepatitis B virus and HPV, and cytologic screening for cervical and anal cancers.

- Conduct studies on the impact of mobile-device-supported (mHealth) interventions on HIV outcomes in different domestic and international settings.

- Adapt interventions initially developed in older adults to HIV-infected individuals with multiple comorbidities, functional impairments, polypharmacy, cognitive decline, and/or who are at risk of adverse outcomes common in geriatric populations.

Strategies Related to Implementation

- Conduct implementation science studies and population-based research necessary for translating epidemiology findings into practical guidelines for health care practices.
- Evaluate various operational strategies for implementation of efficacious, preventive, or therapeutic interventions, and evaluate countrywide ART programs and the use of implementation science research and integrated observational databases to assess effectiveness at the community and population levels.
- Evaluate novel methods for rapid dissemination of successful and reproducible findings for implementation into the field. This includes improving the understanding of how to efficiently deliver effective interventions, develop standardized methodologies to transfer interventions from one setting to another, and make informed choices among different interventions.
- Design and implement evaluations of both targeted and large-scale HIV testing, prevention, treatment, and retention programs, with attention to clinical outcomes, HIV incidence rates, viral resistance, long-term dynamics of the HIV epidemic, and comparative costs for programs relative to current strategies.
- Utilize implementation science to improve the operations and efficiency of a proven strategy or treatment and to determine to what degree it is scalable and applicable across a broad range of target populations.
- Evaluate the long-term clinical and public health impact, cost, and health care utilization ramifications of different strategies for care, including treatment of HIV-associated conditions and comorbidities, ART, and complications of ART.
- Assess the use of CVL or other markers of success in viral suppression as a population-level marker of program effectiveness. Establish CVL sensitivity, specificity, and predictive value in tracking the epidemic, allocating resources, and evaluating the effectiveness of HIV prevention and treatment programs.
- Design and evaluate implementation of system-level approaches for management of complex HIV-associated comorbidities and other noncommunicable diseases in settings or populations with limited available care.
- Evaluate different models of developing a continuum of screening, prevention, treatment, and care and the impact of expanded intervention availability, access, and coverage in various settings and populations.

AREA OF EMPHASIS

Information Dissemination

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A: Disseminate Information to all Constituencies

Support the effective dissemination, communication, and utilization of information about HIV infection, AIDS, coinfections, opportunistic infections, malignancies, and clinical complications to all constituent communities of the NIH, domestically and internationally.

STRATEGIES

- Rapidly disseminate new basic, translational, and clinical research findings, including information on the potential implications for HIV prevention, care, and treatment, using existing and innovative methods.
- Promote study designs that include plans for dissemination of appropriate and relevant findings to study participants, health care practitioners, community representatives, policymakers, program administrators, and the public, while ensuring that confidentiality of efficacy and safety data is maintained during the conduct of clinical trials.
- Facilitate the update and dissemination of HIV prevention and treatment guidelines based on the latest clinical research findings.
- Utilize computer and other information dissemination technology (including the Internet) to disseminate up-to-date HIV and AIDS information; information about HIV therapeutic, vaccine, microbicide, and other prevention trials; and information about HIV training programs.
- Expand access to and education about state-of-the-art treatment and patient management guidelines, including information on clinical trials, using multiple technologies such as online access and voice access (*AIDSinfo*).
- Widely disseminate information concerning specimen repositories, including existing repositories, specimens available, and relevant information concerning cohorts, contact information, and the process for obtaining access to samples.
- Collect, archive, and promote the use of existing data from NIH-supported basic and applied research for secondary data analysis, including rapid development of public use datasets that can be used for secondary data analysis in NIH-supported studies, especially baseline survey and HIV/STD (sexually transmitted disease) incidence data.
- Widely disseminate experimental findings regarding AIDS-related studies using nonhuman primates, as well as information concerning the availability of animals for AIDS-related studies.
- Improve current techniques and develop and evaluate new techniques for the two-way communication of information to scientific and lay audiences, particularly to hard-to-reach populations, including information about the importance of clinical trials participation, ongoing clinical trials, and trial results.
- Improve outreach and support access to AIDS information resources (including computers) by community groups, health care providers, and community-based AIDS service organizations, including those serving racial and ethnic populations.

- Work with community-based organizations (CBOs), nongovernmental organizations (NGOs), and local agencies to develop and promote effective methods of information dissemination on treatment, prevention, and research in target populations to increase awareness and clinical trial participation and to reduce stigma.

- Support dissemination of research findings to community representatives, study participants, health care practitioners, payers, policymakers, AIDS community organizations, and the public, in culturally and linguistically appropriate ways.

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

- Develop and disseminate information resources about HIV prevention, microbicide, vaccine, and treatment clinical trials, including cancer trials, to increase awareness about research in these areas and the importance of supporting and participating in clinical studies.

- Evaluate the effectiveness of communication efforts by appropriate means, including obtaining feedback from target audience members through methods such as usability testing of paper and computer interfaces (see www.usability.gov) and information dissemination intermediaries, such as journalists and health educators.

- Promote wide dissemination of the annual *Trans-NIH Plan for HIV-Related Research* and other HIV-related reports as they become available.

- Promote and enhance the exchange of scientific information and communication between public and private research enterprises, such as enhancing communication with the pharmaceutical industry concerning research on the development of therapeutics, vaccines, and microbicides, and working with industrial scientists to make information concerning basic science and HIV protein structures available to the general scientific community.

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

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

- Support the cross-collaborations of HIV and AIDS information providers to develop more integrated and comprehensive information dissemination approaches.

- Provide support for online access to presentation materials and other information (e.g., slides, graphics, and plenary presentations) from scientific meetings.

- Develop HIV/AIDS training materials using a variety of current technologies most appropriate for specific audiences, as well as materials adapted for local languages.

OBJECTIVE–B: Develop New Communication Strategies

Support research to identify existing gaps in communication approaches, identify and evaluate existing strategies, 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 target audiences, domestically and internationally.

STRATEGIES

- Continue to assess the changing information needs and resources used by various audiences, including biomedical and behavioral research communities, health care providers, service providers, persons living with HIV and their advocates, at-risk populations, scientific and lay media, and the general public.
- Identify obstacles to information dissemination and develop, test, and evaluate possible ways to overcome these obstacles.
- Develop, test, and evaluate innovative strategies for effectively reaching specific audiences (e.g., racial and ethnic populations, adolescents, drug users, other hard-to-reach populations, and health care providers) 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 practices in specific audiences.
- Promote the use of new technologies and evaluate their effectiveness for disseminating basic and clinical research findings.
- Work to reduce communication gaps between academic researchers and treatment providers so that research results are more effectively disseminated to providers and that research agendas reflect the needs of practicing clinicians.
- Work to facilitate effective dissemination and understanding of relevant prevention research results to HIV prevention workers and to those in community-based and other settings.

OBJECTIVE–C: Coordination and Collaboration Efforts

Develop, implement, and evaluate methods of coordination and collaboration on HIV/AIDS communication activities across NIH Institutes and Centers (ICs), among other Federal and non-Federal groups, and with international partners.

STRATEGIES

- Promote and foster information dissemination regarding research and programmatic efforts across the ICs, among U.S. Government agencies, and with international partners.
- Promote collaboration among all ICs in providing information about their HIV/AIDS clinical trials to *AIDSinfo* and *ClinicalTrials.gov*.
- Build and enhance partnerships among CBOs/NGOs and basic, clinical, and behavioral researchers to encourage exchange of information and experience.
- Continue collaborations with the Joint United Nations Programme on HIV/AIDS, the Pan American Health Organization, the International AIDS Society, and other international AIDS agencies or societies on information/communication efforts, including information about international clinical trials and training opportunities.
- Collaborate with public and health sciences libraries, health care providers, AIDS Education and Training Centers, and community-based HIV/AIDS service organizations to facilitate access to needed information and disseminate NIH HIV-related reports.
- Expand collaboration to include academic, medical, and other communities, as appropriate, in the dissemination of NIH HIV-related reports.
- Expand the development and sharing of HIV/AIDS resources on the Internet to facilitate national and international research collaboration and data sharing.

Appendices

A. Planning Groups

B. NIH Institutes and Centers

C. List of Acronyms

APPENDIX A

Planning Groups

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APPENDIX B

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NCI	National Cancer Institute
NEI	National Eye Institute
NHLBI	National Heart, Lung, and Blood Institute
NHGRI	National Human Genome Research Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIDA	National Institute on Drug Abuse
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIMH	National Institute of Mental Health
NIMHD	National Institute on Minority Health and Health Disparities
NINDS	National Institute of Neurological Disorders and Stroke
NINR	National Institute of Nursing Research
NLM	National Library of Medicine
CIT	Center for Information Technology
CSR	Center for Scientific Review
FIC	Fogarty International Center
NCCAM	National Center for Complementary and Alternative Medicine
NCATS	National Center for Advancing Translational Sciences
CC	NIH Clinical Center

APPENDIX C

List of Acronyms

AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral
CAB	community advisory board
CBO	community-based organization
CNS	central nervous system
CSF	cerebrospinal fluid
CVL	community viral load
DC	dendritic cell
DDS	drug delivery strategies
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GWAS	genome-wide association studies
HBV	hepatitis B virus
HCT	HIV counseling and testing
HCV	hepatitis C virus
HHV	human herpesvirus
HIV	human immunodeficiency virus
HPV	human papillomavirus
HSV-2	herpes simplex virus type 2
ICs	Institutes and Centers
IRB	institutional review board
IRIS	immune reconstitution inflammatory syndrome
KSHV	Kaposi's sarcoma-associated herpesvirus
KSHV/HHV-8	Kaposi's sarcoma-associated herpesvirus/human herpesvirus-8

LGBT	lesbian, gay, bisexual, and transgender
MDR	multidrug-resistant
MDR-TB	multidrug-resistant TB
MHC	major histocompatibility complex
MMC	medical male circumcision
MPTs	multipurpose prevention technologies
MRSA	methicillin-resistant Staphylococcus aureus
MSM	men who have sex with men
MTCT	mother-to-child transmission
NCD	noncommunicable disease
NGO	nongovernmental organization
NHP	nonhuman primate
NIH	National Institutes of Health
OAR	Office of AIDS Research, NIH
OI	opportunistic infection
PD	pharmacodynamic(s)
PEP	postexposure prophylaxis
PEPFAR	U.S. President's Emergency Plan for AIDS Relief
PK	pharmacokinetic(s)
PMTCT	prevention of mother-to-child transmission
PrEP	pre-exposure prophylaxis
SHIV	chimeric simian/human immunodeficiency virus
SIV	simian immunodeficiency virus
STD	sexually transmitted disease
STI	sexually transmitted infection
TB	tuberculosis
TOC	test of concept
WHO	World Health Organization
XDR-TB	extensively drug-resistant TB

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