FY 2011

National Institutes of Health

TRANS-NIH AIDS RESEARCH BY-PASS BUDGET ESTIMATE

and

TRANS-NIH PLAN FOR HIV-RELATED RESEARCH

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National Institutes of Health

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Dedicated to the memory of two heroes, icons, and friends
whose passing we have mourned during this past year.

SENATOR EDWARD M. KENNEDY

and

RUTH L. KIRSCHSTEIN, M.D.

Their contributions were enormous, their loss is overwhelming,
but their passion, commitment, and vision will always inspire us.

FY 2011 Trans-NIH AIDS Research By-Pass Budget Estimate

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FY 2011 Trans-NIH AIDS Research By-Pass Budget Estimate

Legislative Mandate

Authorizing Legislation:

Section 2353 of the Public Health Service Act requires that "the Director of the Office of AIDS Research establish a comprehensive plan for the conduct and support of all AIDS activities of the agencies of the National Institutes of Health." It also requires that the Director "shall prepare and submit directly to the President, for review and transmittal to the Congress, a budget estimate for carrying out the Plan for the fiscal year...." That budget "shall estimate the amounts necessary for the agencies of the National Institutes of Health to carry out all AIDS activities determined by the Director of the Office to be appropriate, without regard to the probability that such amounts will be appropriated."

Appropriations Language:

The FY 2010 House Appropriations Committee report stated, "The Committee believes that NIH continues to be the world's leader in research to respond to the critical needs of the AIDS pandemic, both in the U.S. and around the world. The Committee commends NIH for supporting the NIH AIDS and non-AIDS funding allocation at the current relative rate and endorses the continuation of this policy. The Committee continues to endorse the importance of OAR, including its critical trans-NIH budget authority and its status as a unique 'institute without walls.' The Committee commends the Office for its leadership in setting trans-NIH AIDS research priorities, including important new basic science initiatives in the area of genomics, and its ongoing support for innovative research and community outreach to address the complex issues of AIDS in racial and ethnic minority populations in the U.S."

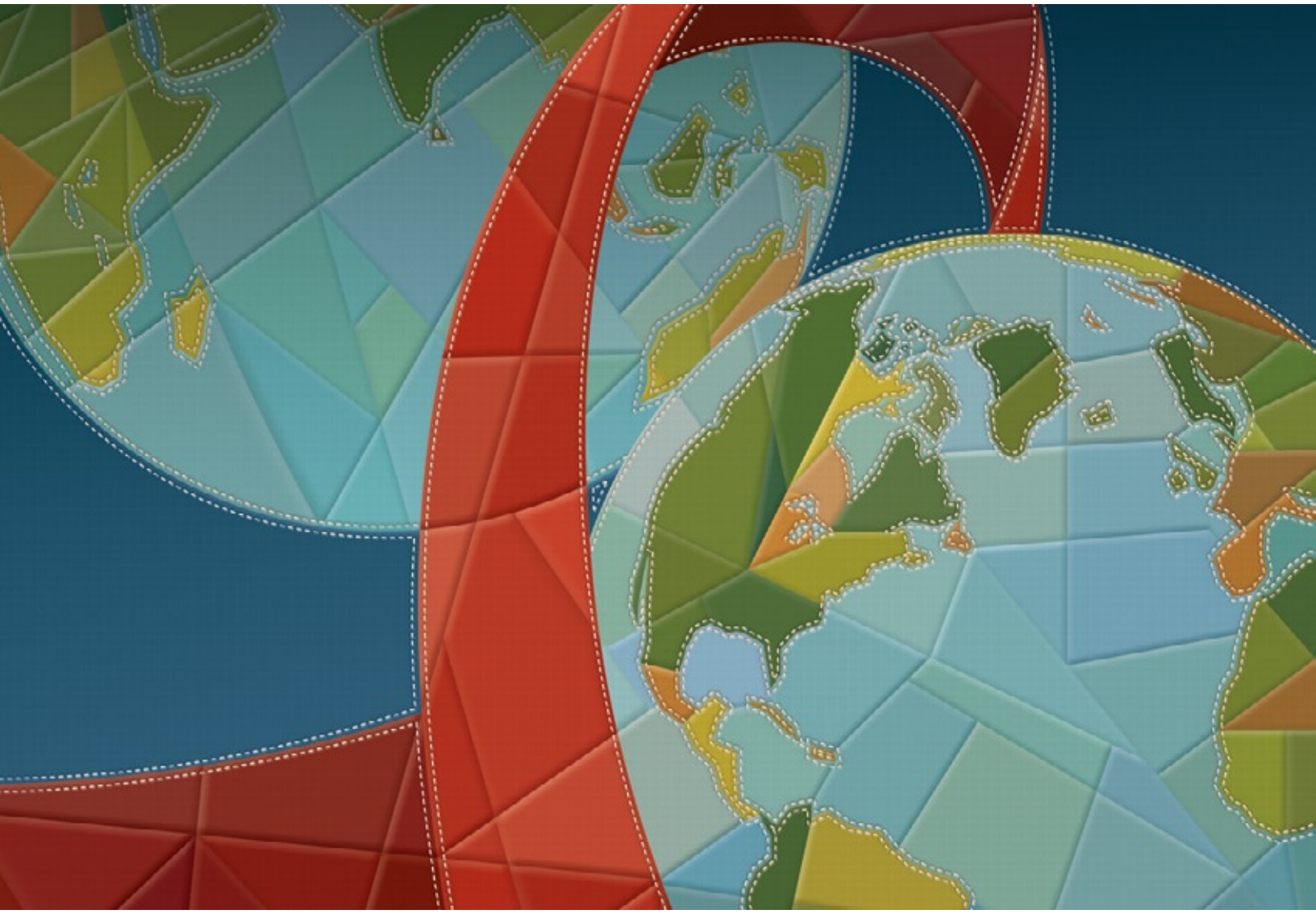
Introduction

The National Institutes of Health (NIH) Office of AIDS Research (OAR), a component of the Office of the Director, is the only NIH office that is legislatively mandated to develop an annual Presidential by-pass budget estimate. Only the National Cancer Institute has a similar authority. In accordance with the law, OAR has developed this *Fiscal Year (FY) 2011 Trans-NIH AIDS Research By-Pass (Professional Judgment) Budget Estimate* to carry out the scientific priorities established in the *FY 2011 Trans-NIH Plan for HIV-Related Research*. The by-pass budget estimate is based solely on the current scientific opportunities, and the commitment and urgent need to support the highest quality research.

This by-pass budget estimate:

- Addresses critical scientific needs
- Addresses gaps in our understanding through a renewed emphasis on basic science
- Capitalizes on emerging scientific opportunities by providing additional funds for new, exciting areas of investigation
- Addresses critical needs in prevention research, including research focused on the domestic AIDS epidemic, particularly in racial and ethnic populations
- Begins to restore vital resources that have been drained by the dual effects of inflation and a flat budget
- Establishes the biomedical and behavioral research foundation necessary to implement the major goals of the President's National HIV/AIDS Strategy.

The FY 2011 by-pass budget request for NIH AIDS research is $3.5 billion, which represents a 15 percent increase over the FY 2010 budget request level. This increase represents an investment—a down payment—that must be maintained and enhanced to take advantage of critical emerging scientific advances, to address the impact of the erosion of buying power on critical research programs, and to restore lost opportunity. This amount includes the total trans-NIH support for intramural and extramural research; research management support; research centers; training; and basic and clinical biomedical and behavioral research on HIV/AIDS and the wide spectrum of AIDS-associated malignancies, opportunistic infections, coinfections, and clinical complications.



HIV/AIDS Pandemic

More than 25 years since the recognition of AIDS and the identification of HIV as its causative agent, the HIV/AIDS pandemic remains a global scourge that affects people in nearly every country. UNAIDS reports that in 2007, more than 33 million people were estimated to be living with HIV/AIDS, 2.7 million people were newly infected, and 2 million died of AIDS-related illnesses.[1]

1 UNAIDS. *2008 Report on the Global AIDS Epidemic.* Available at *http://www.unaids.org/en/KnowledgeCentre/HIVData/GlobalReport/2008/.*

The majority of people infected with HIV live in developing countries. Africa has been disproportionately affected, and sub-Saharan Africa remains the most affected region globally. In 2007, more than 65 percent of all people living with HIV resided in sub-Saharan Africa. The epidemic has expanded in other parts of the world as well. UNAIDS reports that between 2001 and 2007, the number of people living with HIV in Eastern Europe and Central Asia more than doubled.[2]

In the United States, more than 1.1 million people are estimated to be HIV-infected. HIV/AIDS remains an unrelenting public health crisis, disproportionately affecting racial and ethnic populations, women of color, young adults, and men who have sex with men (MSM). Centers for Disease Control and Prevention (CDC) statistics show that the number of annual new infections was actually higher than previously estimated (approximately 56,300 new infections per year), and the incidence of new infections has not declined for more than a decade. Since the beginning of the AIDS epidemic, there have been more than 583,000 cumulative AIDS deaths.[3] Someone is infected with HIV in the United States every 9½ minutes.

According to CDC statistics, gay and bisexual men of all races and ethnicities and African American men and women are the most affected groups in the United States. Fifty-three percent of all new infections in 2006 occurred in gay and bisexual men. In 2006, blacks accounted for 45 percent of all new infections, even though they comprise only 12 percent of the total U.S. population.[4] Moreover, the overall prevalence of HIV/AIDS was more than 7 times higher for blacks than for Caucasians.

Further, the populations affected by AIDS continue to shift. HIV/AIDS began its deadly course in the United States mostly as a disease of young men, but today the epidemic touches people of all ages, including adults aged 50 and older. With the advent of potent, multidrug therapy against HIV in the mid-1990s, many HIV-infected Americans are living into their fifties and well beyond. Although the majority of new HIV infections are in younger Americans, individuals 50 years of age and older accounted for approximately 10 percent of all new HIV infections in the United States in 2006. As a consequence of these trends, approximately one-quarter of HIV-infected adults in the United States in 2006 were at least 50 years old.[5] Older adults with long-term or new HIV infection experience complex interactions with HIV, antiretroviral therapy (ART), age-related changes to the body, and, often, treatment for illnesses associated with aging. The research agenda must address the medical implications of aging with HIV and continue developing more sophisticated treatment strategies, so these older adults can live longer, healthier lives.

In addition, HIV disease itself appears to cause premature aging. The NIH-sponsored Multicenter AIDS Cohort Study has shown that HIV disease accelerates the development of frailty.

The maturing U.S. epidemic has the potential to generate concentric mini-epidemics of liver disease, tuberculosis, cardiovascular disease, and other HIV-associated morbidities, foreshadowing an epidemic of greater complexity in the coming years. The HIV/AIDS pandemic will remain the most serious public health crisis of our time until better, more effective, and affordable prevention and treatment regimens are developed and made universally available.

2 Ibid.

3 Centers for Disease Control and Prevention. *Cases of HIV Infection and AIDS in the United States and Dependent Areas, 2007.* Available at *http://www.cdc.gov/hiv/topics/surveillance/resources/reports/2007report/default.htm.*

4 Ibid.

5 Centers for Disease Control and Prevention. 2008. HIV prevalence estimate—United States, 2006. *MMWR* 57(39):1073–1076.

NIH AIDS Research Program

To address this pandemic, the NIH supports and conducts 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 the NIH Institutes and Centers (ICs) in accordance with their mission, in both intramural and extramural programs.

NIH-funded research has led to: the critical discovery of antiretroviral therapies and regimens that have resulted in improved quality of life and life expectancy for those with access to these drugs; the development of treatments for some HIV-associated coinfections and comorbidities, including malignancies, neurological complications, tuberculosis, and other clinical manifestations; and a number of significant advances in HIV prevention, including groundbreaking strategies for the prevention of mother-to-child transmission. NIH clinical trials also have demonstrated that medically supervised circumcision of adult men can reduce risk of heterosexual HIV acquisition.

Despite these important advances, the epidemic continues to expand, and improved prevention strategies and therapeutic regimens are critically necessary. The AIDS pandemic will continue to wreak devastating consequences in the United States and around the world for decades to come. The pandemic affects the future of families, communities, military preparedness, national security, political stability, national economic growth, agriculture, business, health care, child development, and education in countries around the globe.

NIH AIDS RESEARCH PROGRAM

Represents the 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

Comprises a comprehensive program of basic, clinical, translational, and behavioral research on HIV infection, its associated coinfections, opportunistic infections, malignancies, and other complications

Includes research or training projects in more than 100 countries

Requires unprecedented trans-NIH scientific coordination and management of research funds

NIH Office of AIDS Research

OAR *(http://www.oar.nih.gov/)*, established in 1988, has unique legislative authorities unlike those of any other NIH entity to plan, coordinate, evaluate, and budget the entire $3 billion 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" that is vested with primary responsibility for overseeing all NIH AIDS-related research, thus allowing NIH to pursue a united research front against the global AIDS epidemic.

Perhaps no other disease so thoroughly transcends every area of clinical medicine and basic scientific investigation, crossing the boundaries of every 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, to enhance collaboration, to minimize duplication, and to ensure that precious research dollars are invested effectively and efficiently.

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.

OFFICE OF AIDS RESEARCH MISSION

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

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

Trans-NIH Strategic Plan

Each year, OAR develops the *Trans-NIH Plan for HIV-Related Research (http://www.oar.nih.gov/strategicplan/)*. This Strategic Plan (see second tab in this document) is developed in collaboration with scientists from the NIH 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: Etiology and Pathogenesis; Vaccines; Microbicides; Behavioral and Social Science; Treatment as Prevention; Drug Discovery, Development, and Treatment; Training, Infrastructure, and Capacity Building; Natural History and Epidemiology; and Information Dissemination. The Plan also addresses research in special populations, including: Women and Girls, Racial and Ethnic Populations, and Research in International Settings.

OAR requires ICs to report all AIDS-related expenditures, including those for extramural, intramural, and research management and support, on a quarterly basis, to the OAR trans-NIH AIDS Research Information System database. All expenditures must be coded to the appropriate objective(s) of the Plan. This database also serves as the primary resource for AIDS research information in the new Research, Condition, and Disease Categorization process, which permits OAR to review, monitor, and analyze the total intramural and extramural AIDS research program.

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 estimate
- Tracking and monitoring all NIH AIDS research expenditures.

OAR Budget Development Process

OAR is mandated to develop the annual trans-NIH AIDS research budget *(http://www.oar.nih.gov/budget/)* in partnership with the 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 appropriations would grow at approximately the same rate; that is, as an "institute without walls," AIDS research, as determined by OAR, would receive the same increase as the other ICs. Thus, AIDS research has historically represented approximately 10 percent of the total NIH budget.

For all appropriated funds, the OAR Director and NIH Director determine the total amount to be allocated for AIDS-related research within the overall NIH budget. Within that total, OAR develops each ICs 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's initiatives in relation to the Plan, to its priorities, and to other IC submissions, to eliminate redundancy and/or to assure cross-IC collaboration. The unique budget authorities allow OAR to build each IC budget from the commitment base, rather than from the previous year's appropriation.

The careful determination of the balance of the research budget—among ICs, 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, and not according to a formula. This process reduces redundancy, promotes harmonization, and assures cross-IC 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.

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.

President's National HIV/AIDS Strategy

The critical priorities of this by-pass budget estimate are aligned and in concert with the major goals of the President's National HIV/AIDS Strategy. The goals of the Strategy are:

Reducing HIV incidence

Increasing access to care and optimizing health outcomes

Reducing HIV-related health disparities

The role of NIH is to conduct research that will provide the science base and the necessary tools to facilitate the implementation of the President's National HIV/AIDS Strategy.

FY 2011 Trans-NIH AIDS Research Priorities

The overarching research priorities of the *FY 2011 Trans-NIH Plan for HIV-Related Research* and this Presidential by-pass budget estimate are to conduct and support biomedical and behavioral research that will establish the scientific foundation to address the goals of the President's National HIV/AIDS Strategy. These priorities are:

- Expanding basic discovery research
- Reducing new HIV infections
- Improving disease outcomes for HIV-infected individuals
- Reducing HIV-related disparities
- Translating research from bench to bedside to community

PRIORITY:

Expanding Basic Discovery Research

The NIH will continue its strong commitment to basic science, which is fundamental to the mission of the NIH and essential to enable innovation, to address critical gaps, and to capitalize on emerging scientific opportunities. Progress in basic science provides the building blocks to progress across all other scientific areas to ultimately achieve the goals of the President's National HIV/AIDS Strategy.

ETIOLOGY AND PATHOGENESIS: 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. However, additional research is needed to further the understanding of the virus and how it causes disease, including studies to delineate how gender, age, ethnicity, and race influence vulnerability to infection and HIV disease progression.

The NIH will increase support for genomics studies and breakthroughs in sequencing the human genome, and will provide new opportunities to apply these valuable tools to the search for new HIV prevention and therapeutics strategies. OAR devoted a meeting of its Advisory Council to this area of research and, in collaboration with the National Human Genome Research Institute, the National Institute of Allergy and Infectious Diseases (NIAID), and other NIH ICs, convened a scientific workshop of international scientific experts for recommendations on research priorities. As a result of those consultations, this by-pass budget estimate includes increased funding for new, exciting areas of investigation, including studies on the application of genetics, genomics, epigenetics, proteomics, systems biology, and other related technologies, to better understand HIV/AIDS and the host immune response.

Research is needed to monitor epidemic trends, develop and evaluate prevention modalities, follow the changing clinical manifestations of HIV disease in different populations, and measure the effects of treatment regimens. The NIH supports research in domestic and international settings to examine HIV transmission, HIV/AIDS disease progression (including the occurrence of coinfections and opportunistic infections, malignancies, metabolic complications, and neurological and behavioral dysfunctions), the development of other HIV/AIDS-related conditions, and improved methodologies to support this research. Epidemiologic research is instrumental in identifying and describing AIDS-related comorbidities, and in disentangling effects related to treatment from those related to HIV disease itself.

This by-pass budget estimate also provides funding for basic research to:

- Examine the fundamental viral and host mechanisms associated with the acquisition and inhibition of HIV infection and disease progression;
- Examine the fundamental mechanisms by which HIV establishes and reactivates latent reservoirs of infection, and identify ways to eradicate them;
- Investigate the biological-behavioral interactions and social dynamics related to changes in transmission risks over the course of HIV infection and disease, such as those differentially associated with acute infection, recent diagnosis, chronic infection accompanied by antiretroviral treatment, and later-stage disease;
- Identify determinants and patterns of HIV-related stigma and discrimination, and their impact on HIV testing, treatment, disclosure, and prevention;
- Develop and validate improved animal models for basic research studies, as well as preclinical testing of biomedical prevention interventions and therapeutics;

- Develop improved nonhuman primate animal models that can be used in studies of HIV etiology and pathogenesis, and in the development and preclinical testing of vaccines, microbicides, therapeutics, and other biomedical interventions;
- Investigate the interrelatedness of HIV disease and nutrition;
- Develop and test research models, methods, and measures to accurately assess risk and protective behaviors in diverse populations; and
- Develop and test innovative methods and measures to assess more accurately the individual-, interpersonal-, organizational-, cultural-, and societal-level determinants of risk in racial and ethnic populations, with special emphasis on communities that are small in number and/or underrepresented in current clinical studies.

HIV/AIDS IS REAL
PROTECT YOURSELF

PRIORITY:

Reducing New Infections

Prevention of new HIV infections remains a top priority for NIH research. A vaccine that prevents the acquisition of HIV is our best hope for ending the HIV pandemic, but we also must work with and improve the many HIV prevention tools currently available, and add new ones to the toolbox. A varied set of available HIV prevention tools is imperative, because reducing HIV incidence inevitably will require a combination of various biomedical, behavioral, and structural interventions, and not just a single "silver bullet." For example, an HIV vaccine, a microbicide, and/or preexposure prophylaxis with antiretroviral drugs—even if only partially effective—used in combination with behavioral interventions—could prove highly effective in preventing new infections. Biomedical and behavioral interventions are urgently needed to reach individuals at risk, particularly in racial and ethnic populations in the United States, in international settings, among women, and among MSM.

NIH investment in prevention research has paid great dividends. Some of the prevention strategies demonstrated to be effective are: HIV testing, because knowing one's status has been shown to result in substantial reductions in risk behaviors; prevention programs for people at risk of HIV infection and for people living with HIV; ART to prevent mother-to-child transmission of HIV; substance abuse treatment; and access to condoms and sterile syringes. NIH researchers in two clinical trials demonstrated that heterosexual HIV acquisition was reduced by 50 percent in adult males who had been medically circumcised. Although some gains have been made, the NIH must continue to support research aimed at reducing HIV incidence and ultimately halting the pandemic.

It is well established that the risk of transmitting HIV changes over the course of HIV infection and disease. This by-pass budget estimate addresses the need for a better understanding of the biological, behavioral, and social dynamics related to these changes, such as those associated with acute infection, recent diagnosis, chronic infection, and late-stage disease. A better understanding of these changes may lead to better strategies for preventing HIV acquisition and transmission.

This by-pass budget estimate provides critical support for NIH prevention research in the following scientific areas of emphasis:

VACCINES: AIDS vaccine research remains a high priority to ensure that new and innovative concepts continue to advance through the pipeline. The recent release of data from a Phase III vaccine clinical trial conducted in Thailand, cosponsored by the NIH, represents progress in the area of vaccine research. These trial results present new scientific opportunities for investigation that will require additional investment and realignment of resources. OAR is exploring possible mechanisms to utilize its budget authorities in FY 2010 to ensure that NIAID has additional funds to begin pursuing these new avenues, including:

- Additional basic research studies on the virus and host immune responses that can inform the development of new and innovative vaccine concepts
- Studies on correlates of immunity
- Animal model studies

- Production of vaccine and evaluation of clinical samples from study participants, which will contribute to our understanding of why the vaccine had no effect on viral load in trial volunteers who became infected.

This FY 2011 by-pass budget request includes critical funding to further build on the results from the Thai trial for:

- Developing and preclinically testing new constructs against other HIV clades that are prevalent in other parts of the world
- Further refining new vaccine candidates
- Initiating clinical studies of these new candidates.

MICROBICIDES: Microbicides—antimicrobial products that can be applied topically for the prevention of HIV and other sexually transmitted infections—may offer one of the most promising primary preventive interventions. The NIH supports a comprehensive microbicide research program that includes the screening, discovery, development, preclinical testing, and clinical evaluation of microbicide candidates, as well as fundamental research aimed at understanding how HIV transverses mucosal membranes and infects cells. The NIH supports behavioral and social science research on the acceptability and use of microbicides among different populations.

BEHAVIORAL AND SOCIAL SCIENCE: The NIH supports research to further our understanding of how to change the behaviors that lead to HIV acquisition, transmission, and disease progression—including preventing their initiation—and how to maintain protective behaviors once they are adopted. In addition, the NIH supports research aimed at better understanding the social and cultural factors associated with HIV risk or protection, particularly in communities at high risk of HIV acquisition. This research will contribute to the implementation of a broader range of preventive and/or therapeutic strategies. Behavioral issues associated with adherence to therapies are another area of priority investigation. Lack of complete adherence to drug regimens may result in the development of drug-resistant strains of HIV, which could have devastating public health implications. In addition, HIV-infected individuals taking antiretroviral therapies who experience improved health and a decline in detectable virus may believe that they are less infectious and may lapse into unsafe sexual and drug-using behaviors. This could have the effect of increasing HIV transmission among at-risk populations, if the virus is still viable at undetectable levels.

HIV transmission and acquisition also must be considered at the community level and within specific populations (e.g., MSM, racial and ethnic populations, women). There is a continuing need to better understand how HIV is transmitted in the course of human relationships occuring in social contexts that vary by location and culture. Interventions to reach and change the behaviors of large numbers of at-risk individuals are urgently needed. These include interventions that reduce the stigma and discrimination associated with HIV, because they can deter the use of proven behavioral interventions (e.g., condoms, needle exchange), and reduce an individual's willingness to be tested for HIV and/or adhere to therapeutic regimens. In the United States, there is an urgent need for interventions that target racial and ethnic populations and MSM of all races and ethnicities.

TREATMENT AS PREVENTION: A critical new area of prevention research is the study of treatment strategies as a method to prevent new infections. This new approach builds on NIH-sponsored research that successfully demonstrated that treatment of HIV-infected pregnant women could significantly reduce transmission of HIV from mother to child. Strategies currently being investigated include: postexposure prophylaxis, the use of treatment to prevent HIV infection after accidental exposure, including those in a health care environment; preexposure prophylaxis, the long-term use of treatment regimens for high-risk uninfected populations to prevent HIV acquisition; and a potential prevention strategy known as "test and treat," to determine

whether a communitywide testing program with immediate treatment can decrease the overall rate of new HIV infections in that community.

This by-pass budget request includes funding for a number of critical new and expanded initiatives in prevention research to reduce HIV incidence, including:

- **Mechanisms and Prevention of Sexual Transmission HIV and Simian Immunodeficiency Virus (SIV):** New initiative to characterize the mechanisms involved in acquisition and cell-to-cell transmission of HIV and SIV, with the goal of identifying novel approaches for preventing HIV infection. Benefits from this program may result in the development of improved vaccine, microbicide, and preexposure prophylaxis drug candidates.

- **Next Generation Preexposure Prophylaxis:** New initiative targeting the discovery, development, and preclinical testing of potential drug candidates that are safe and effective for long-term use to prevent HIV acquisition in high-risk populations. The goal of this initiative is to develop a pipeline of new lead drug candidates to prevent the further spread of HIV infection among groups involved in high-risk sexual behaviors.

- **Applying Systems Biology to HIV Vaccine Discovery:** New initiative to utilize multidisciplinary approaches involving genomics, proteomics, virology, immunology, bioinformatics, and mathematics to better understand the immune responses to HIV and SIV. The goal is to use these applied systems approaches to advance the development of better AIDS vaccine candidates to prevent or control HIV infection.

- **Behavioral and Social Science Aspects of Biomedical Strategies to Avert Incident HIV Infections:** New initiative designed to integrate behavioral and biomedical strategies in order to scale up innovative interventions to prevent HIV infections.

- **Universal Voluntary Testing and Treatment for Prevention of HIV Transmission:** New initiative designed to evaluate prevention interventions specifically targeted to young MSM and adolescents in racial and ethnic populations. The goal is to identify innovative "test and treat" strategies that can better decrease the further spread of HIV infections in these populations.

- **Seek, Test, and Treat:** Expansion of an ongoing program examining approaches to engage drug users in frequent HIV counseling and testing programs, ART treatment, and care, as well as studies to evaluate drug users' responses and adherence to ART. The overall goal is to identify prevention interventions that can effectively decrease HIV transmission among drug-using populations.

- **Acute/Early HIV Infection:** Expansion of an ongoing program studying acute/early-stage HIV infection in injection drug users with the goals of identifying acutely infected injection drug users in regions with high incidence, evaluating the effects of drugs of abuse on early stages of HIV infection, and developing new strategies to prevent HIV infection in this population and their sexual and injection-sharing partners.

- **Consortia for AIDS Vaccine Research in Nonhuman Primates:** New initiative designed to evaluate potential SIV vaccine candidates that will provide critical information for the design and development of HIV vaccine candidates and the protective immune responses they elicit in humans.

PRIORITY:

Improving Disease Outcomes for HIV-Infected Individuals

NIH-supported research has led to the development of combination antiretroviral therapies for the treatment of HIV disease that have resulted in improved immune function in patients who are able to adhere to the treatment regimens and tolerate the toxicities associated with antiretroviral drugs. These drug regimens have delayed the progression of HIV disease, extending the time between initial infection and the development of AIDS. Until these therapeutic regimens were introduced in the mid-1990s, many HIV-infected individuals rapidly progressed to AIDS and died. However, a growing proportion of patients receiving long-term therapy are demonstrating treatment failure, experiencing serious drug toxicities and side effects, and developing drug resistance. Recent epidemiologic studies and clinical reports of HIV-infected individuals have shown an increased incidence of malignancies, as well as cardiovascular and metabolic complications, associated with long-term HIV disease and ART.

DRUG DISCOVERY, DEVELOPMENT, AND TREATMENT: Epidemiologic research examining the incidence and prevalence of comorbidities associated with long-term HIV disease and ART in different populations and across the lifespan is a priority area in the NIH AIDS research portfolio. There also is a need to investigate how sex, gender, race, age, pregnancy status, nutritional status, and other factors interact to affect treatment success or failure and/or the development of HIV-associated comorbidities and coinfections.

A better understanding of the etiology and pathogenesis of HIV disease and the mechanisms of toxicity of antiretroviral drugs that contribute to the development of HIV-associated comorbidities and mortality may provide the foundation upon which improved prevention interventions and therapeutic regimens can be developed. In addition, research examining the mechanisms by which HIV establishes and reactivates latent reservoirs of infection is a high priority for the NIH. A better understanding of these processes could lead to the development of therapies that eradicate, or functionally eradicate, persistent virus reservoirs. Some have speculated that the eradication of persistent virus reservoirs might cure HIV disease.

Another priority for NIH AIDS therapeutics research is the development of improved antiviral drugs and strategies that maintain long-term undetectable viral load in HIV-infected individuals. Research on the identification and characterization of viral and cellular drug targets, as well as the development of drug resistance and treatment failure, could lead to improved disease outcomes for HIV-infected individuals. In addition, studies of the genetic determinants associated with HIV-disease progression and treatment response may lead to the development of customized therapeutic regimens formulated for an individual patient based on his or her genetic sequence. A gene sequence associated with allergic reactions to the drug abacavir already has been identified. This finding led the Food and Drug Administration to recommend that doctors conduct genetic screening before prescribing abacavir to patients.

Optimal HIV-disease outcomes are most likely to be achieved when HIV-infected individuals adhere to prescribed therapeutic regimens. Failure to do so can lead to the development of drug-resistant viruses and treatment failure. Although it has been demonstrated that simplified and better-tolerated regimens do improve adherence, additional biomedical,

behavioral, and structural interventions are needed to improve adherence to therapeutic regimens, hence improving HIV-disease outcomes.

The development of optimal strategies for the prevention and treatment of HIV coinfections (including tuberculosis, hepatitis C virus [HCV], and malaria) requires additional basic and clinical research on the effects of these coinfections on HIV transmission, pathogenesis, and disease progression. Similarly, further studies are needed to determine the effects of HIV disease across the spectrum of its clinical course on the pathogenesis and progression of these coinfections. Additional pharmacokinetic and pharmacodynamic studies are critical to the evaluation of drug-drug interactions between antiretroviral drugs and agents used to prevent and treat coinfections associated with HIV.

This by-pass budget request includes funding for a number of critical new and expanded initiatives to improve disease outcomes in HIV-infected individuals, including:

- **Understanding HIV Persistence:** New initiative to develop and test new drug candidates targeting viral reservoirs, building on basic research that identifies and characterizes HIV reservoirs that persist despite ART. The goal is to develop safe and effective treatment regimens that eradicate HIV throughout the body and result in a cure for HIV disease.

- **Research on Malignancies in the Context of HIV/AIDS:** Expansion of an ongoing program designed to support basic, preclinical, and clinical research on AIDS-defining and non-AIDS-defining malignancies in HIV-infected individuals. The goal is to translate basic research findings into potential effective treatments for these cancers in HIV-infected individuals. A crossover benefit of this research is that these potential treatment strategies may be applicable to cancers in individuals who are not HIV-infected.

- **Pathogenesis of Hepatitis C Infection and/or Coinfection With HIV Infection:** Expansion of the basic research portfolio on the pathogenesis of HCV infection that provides the foundation for the development of new and better strategies to prevent and treat liver disease in HIV-infected individuals. A crossover benefit of these studies is the development of safe and effective treatment interventions for individuals with HCV infection who are not HIV-infected.

- **Research on Cardiovascular Complications of HIV Disease and Treatment:** Expansion of an ongoing program studying the prevention of and treatment for cardiovascular complications associated with HIV disease and ART.

- **Innovative Strategies for NeuroAIDS Biomarker Discovery and Therapeutics:** Expansion of an ongoing program to identify unique clinical diagnostic and prognostic biomarkers of neurocognitive and neurobehavioral complications of HIV disease and ART. A component of this initiative also will focus on development of innovative drug delivery systems for eradicating HIV reservoirs in the central nervous systems and brains of HIV-infected individuals.

PRIORITY:

Reducing HIV-Related Disparities

The NIH Strategic Plan and budget address significant health disparities that are critical factors in the epidemic. These include racial and ethnic disparities in the United States, disparities between developed and resource-constrained nations, disparities between men and women, disparities between youth and older individuals, and health disparities based on sexual identity. The NIH will continue to place high priority on understanding the causes of HIV-related health disparities, both in the United States and around the world. The Plan addresses the need to better understand the causes of HIV-related health disparities, their role in disease transmission and acquisition, and their impact on treatment access and effectiveness.

TRAINING, INFRASTRUCTURE, AND CAPACITY BUILDING: The NIH supports the training of domestic and international biomedical and behavioral AIDS researchers, as well as the equipment for the conduct of AIDS-related research and clinical studies. The expansion of NIH-funded HIV research globally has necessitated the development of research infrastructure in many locations, including resource-limited settings in Africa, the Caribbean, India, and Asia. Numerous NIH-funded programs have increased the number of training positions for AIDS-related research, including programs specifically designed to recruit individuals from underrepresented populations into research careers and to build research infrastructure at minority-serving institutions in the United States. This by-pass budget requests additional funds to support training programs for U.S. and international researchers to build the critical capacity to conduct AIDS research in both racial and ethnic communities in the United States and developing countries. The NIH is working to improve international research and training to better address the challenges of the AIDS pandemic in resource-constrained nations.

SPECIAL POPULATIONS: OAR supports a multifaceted initiative to address the U.S. epidemic, particularly in racial and ethnic populations. OAR's efforts include activities addressing African Americans, Native populations, and populations in the Caribbean. OAR is launching several critical new activities to address the serious and complex AIDS epidemic in U.S. Latino/Hispanic populations through community outreach, information dissemination, regional workshops, leadership development, and research collaborations. OAR also has provided key support and leadership to a new trans-NIH initiative for the District of Columbia that involves intramural and extramural NIH program staff and staff from CDC, Health Resources and Services Administration, District of Columbia government, and George Washington University. Funds in this by-pass budget request are critical to continuing support for this important initiative for prevention and treatment of HIV disease in the Nation's capital, where rates of new HIV infections rival those of some sub-Saharan countries.

This by-pass budget request includes funding for a number of critical new and expanded initiatives to reduce HIV-related disparities, including:

- **Addressing HIV/AIDS at the Community/Neighborhood Level:** Expansion of an ongoing program to develop and test innovative, multifaceted HIV prevention interventions tailored to the specific needs of neighborhoods, drug-using populations, and distinct communities disproportionately affected by the epidemic. The goal is to identify improved strategies to engage racial and ethnic populations, immigrant communities, and drug-using groups into HIV prevention, treatment, and care programs.

- **Structural Interventions to Prevent HIV/AIDS:** Expansion of an ongoing program designed to develop and evaluate novel prevention interventions that use social structures within communities and social networks (e.g., churches, community centers) to reach racial and ethnic populations at high risk for HIV infection.

- **Addressing the HIV Epidemic Among MSM:** Expansion of an ongoing program designed to test new, innovative HIV prevention approaches targeting racial and ethnic MSM, including young MSM. The latter group represents the population with the highest incidence of new HIV infections.

- **Community-Based Participatory Research:** Expansion of an ongoing program to reduce HIV and other sexually transmitted infections in African American rural youth, as well as to reduce HIV health disparities among Latino/Hispanic men.

- **Centers for Translational and Community Research in Minority and Immigrant Populations:** Expansion of an ongoing program designed to develop and test prevention interventions to reduce alcohol-related HIV risk behaviors in racial and ethnic populations, immigrant communities, and migrant worker groups.

- **Use of Incentives and Other Strategies to Improve HIV Testing, Adherence to Medications, and Retention in AIDS Treatment:** Expansion of an ongoing program designed to evaluate incentives for bringing drug users in racial and ethnic populations into prevention programs, and to test approaches for improving adherence to ART regimens and long-term participation in treatment programs.

- **Research on HIV/AIDS-Related Cancers Among Racial/Ethnic Minority and Underserved Persons in the United States:** Expansion of an ongoing program designed to support research on the prevention, early detection, and treatment of AIDS-defining and non-AIDS-defining cancers in racial and ethnic populations that have the highest incidence of new HIV infections and AIDS cases in this country. The initiative also includes an important training component to develop the next generation of basic and clinical researchers involved in studies on cancers in HIV-infected racial and ethnic minority populations. The program's overall goal is to reduce the incidence of HIV-associated comorbidities among these populations.

- **Medical Management of Older Patients With HIV/AIDS:** Expansion of an ongoing program addressing clinical and translational medical research on the diagnosis and medical management of HIV disease and its complications in older individuals who have underlying age-associated conditions and comorbidities.

- **Adolescent Medicine Trials Network:** Recompetition of this successful clinical trials network will permit increased evaluation of prevention interventions and treatment regimens in adolescents. A special initiative will target the development and evaluation of prevention strategies for Latino/Hispanic adolescents at high risk.

PRIORITY:

Translating Research From Bench to Bedside to Community

The NIH supports a broad range of activities categorized under the rubric of translational or implementation science—moving research advances from basic science, to preclinical studies to clinical studies, and finally into practice in the community. These research activities focus on analyses of the feasibility, effectiveness, and sustainability required for the scale-up and implementation of interventions from a structured behavioral or clinical study to a broader "real-world" setting.

NATURAL HISTORY AND EPIDEMIOLOGY: For example, the NIH supports research aimed at better understanding how to influence the behaviors that lead to HIV transmission, including research on how to prevent initiation of such behaviors, and how to maintain protective behaviors once they have been adopted. A large number of behavioral interventions already have been shown to reduce the risk of HIV infection in clinical studies. However, the challenge has been scaling up the interventions and getting them adopted outside of a clinical study.

This by-pass budget includes funding for critical epidemiologic and natural history studies to evaluate various operational strategies that can be employed to scale up and evaluate ART programs and successful prevention interventions in communities at risk. There is an urgent need for additional translational research that will foster the scale-up and optimization of interventions demonstrated to be effective in small groups or populations. OAR convened an agenda-setting workshop in July 2009 of U.S. and international experts to recommend emerging scientific opportunities and priorities in this area.

This by-pass budget estimate reflects the recommendations of those experts and includes funding for a number of key areas of NIH implementation science research, including:

- **Intervention and Outcome Studies:** Studies of care and treatment-monitoring strategies, efficacy, and effectiveness of interventions.
- **Human Resources, Infrastructure, and Health Services Strengthening:** Studies of strategies and models of access to and provision of treatment services, integrating prevention into treatment, and training of health care workers.
- **Economic Evaluations and Financing:** Cost-benefit and cost-effectiveness studies, and studies on the impact of payor status at the patient level.
- **Impact and Integration of Programs:** Studies of efficiency of and equity in access to treatment and prevention programs.
- **Adoption of Interventions:** Studies of organizational changes required for the adoption of an evidence-based intervention.

INFORMATION DISSEMINATION: Effective information dissemination approaches are integral to HIV prevention and treatment efforts, and are critical in light of the continuing advent of new and complex antiretroviral treatment 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 HIV infections in specific population groups, such as racial and ethnic populations and women, highlight the need to disseminate HIV research findings and other related information to communities at risk. The flow of information among researchers, health care providers, and the affected communities represents new opportunities to rapidly translate research results into practice and to shape future research directions.

This budget requests additional funding to support initiatives to: enhance dissemination of research findings; develop and distribute state-of-the-art treatment guidelines; and enhance recruitment and retention of participants in clinical studies, including women and racial and ethnic populations. Funding in this budget also will continue support for *AIDSinfo* (*www.aidsinfo.nih.gov*), a comprehensive resource for state-of-the-science Federal treatment and prevention guidelines for perinatal, pediatric, adolescent, and adult populations.

Crossover Benefits

It is essential to note that NIH research investment is reaping even greater dividends as AIDS research is unraveling the mysteries surrounding many other infectious, malignant, neurologic, autoimmune, and metabolic diseases. AIDS research has provided an entirely new paradigm for drug design, development, and clinical trials to treat viral infections. For example, the drug known as 3TC, developed to treat HIV/AIDS, is now the most effective therapy for chronic hepatitis B infection. Drugs developed to prevent and treat AIDS-associated opportunistic infections also benefit patients undergoing cancer chemotherapy or receiving anti-transplant rejection therapy. AIDS research also is providing a new understanding of the relationship between viruses and cancer. Thus the research advances resulting from funds in this by-pass budget request will have far broader benefit.

Conclusion

The AIDS pandemic will continue to wreak devastating consequences around the world for decades to come for virtually every sector of society. OAR has shifted AIDS research program priorities and resources to meet the changing epidemic and scientific opportunities. This investment in AIDS research has produced groundbreaking scientific advances. However, serious challenges lie ahead. This by-pass budget request represents the collective professional judgment of scientific experts from around the country and the world on the highest priority areas of scientific opportunity and investment of our precious research dollars to move us forward, to find new tools in the fight against AIDS—the deadliest epidemic of our generation.

Budget Tables

TABLE 1: NIH AIDS Research Funding by Scientific Area of Emphasis (Dollars in Millions)

AREA OF EMPHASIS	FY 2009 Actual Budget Authority	FY 2010 Estimate	FY 2011 By-Pass Estimate	Percent Change FY 2010 to FY 2011
Etiology and Pathogenesis	$730	$738	$829	12.3%
Vaccines	561	557	702	26.0
Microbicides	129	124	148	19.4
Behavioral and Social Science	434	442	511	15.6
Treatment as Prevention	*85*	*88*	*95*	*8.0*
Drug Discovery, Development, and Treatment	*585*	*606*	*651*	*7.4*
Total Therapeutics	670	694	746	7.5
Training, Infrastructure, and Capacity Building	198	203	240	18.2
Natural History and Epidemiology	248	262	295	12.6
Information Dissemination	49	43	52	20.9
TOTAL	**$3,019**	**$3,063**	**$3,523**	**15.0%**

TABLE 2: NIH AIDS Research Funding by Mechanism (Dollars in Millions)

	FY 2009 Actual Budget Authority		FY 2010 Estimate		FY 2011 By-Pass Estimate		Percent Change FY 2010 to FY 2011
	NO.	AMT.	NO.	AMT.	NO.	AMT.	
RESEARCH PROJECTS							
Noncompeting	1,790	1,369	1,804	1,289	1,823	1,353	5.0
Administrative supplements	(134)	24	(144)	30	(166)	35	16.7
Competing	542	268	736	353	1,067	538	52.4
Subtotal, RPGs	2,332	1,661	2,540	1,672	2,890	1,926	15.2
SBIR/STTR	90	37	82	33	90	38	15.2
Total, RPGs	2,422	1,698	2,622	1,705	2,980	1,964	15.2
RESEARCH CENTERS							
Specialized/comprehensive	69	145	66	135	73	155	14.8
Clinical research	8	56	10	60	11	69	15.0
Biotechnology	2	4	3	4	3	5	25.0
Comparative medicine	21	61	17	61	18	70	14.8
Research centers in minority institutions	5	12	4	11	4	13	18.2
Subtotal, Centers	105	278	100	272	109	312	14.7
OTHER RESEARCH							
Research careers	264	40	279	41	307	47	14.6
Cancer education	—	—	—	—	—	—	—
Cooperative clinical research	16	26	12	23	13	26	13.0
Biomedical research support	1	1	—	1	—	2	100.0
Minority biomedical research support	—	—	—	—	—	—	—
Other	148	55	150	58	163	66	13.8
Subtotal, Other Research	429	121	441	123	483	141	14.6
Total, Research Grants	2,956	2,097	3,163	2,099	3,572	2,417	15.2
TRAINING	**FTTPS**		**FTTPs**		**FTTPs**		
Individual	74	3	75	3	82	4	33.3
Institutional	658	31	709	32	775	37	15.6
Total, Training	732	34	784	35	857	41	17.1
Research and development contracts	138	411	204	441	235	529	20.0
(SBIR/STTR)	—	—	—	—	—	—	—
Intramural research	—	306	—	314	—	346	10.2
Research management and support	—	107	—	110	—	121	10.0
Construction	—	—	—	—	—	—	—
Office of the Director	—	64	—	64	—	69	7.8
Buildings and Facilities	—	—	—	—	—	—	—
TOTAL, Budget Authority	**—**	**$3,019**	**—**	**$3,063**	**—**	**$3,523**	**15.0%**

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FY 2011 Trans-NIH Plan for HIV-Related Research

Legislative Mandate

Section 2353(c)(1) of the Public Health Service Act provides that the Director of the Office of AIDS Research (OAR) "shall plan, coordinate and evaluate research and other activities conducted or supported" by the NIH. The Director of OAR "shall act as the primary Federal official with responsibility for overseeing all AIDS research conducted or supported by the National Institutes of Health" and "shall establish a comprehensive plan for the conduct and support of all AIDS activities of the agencies of the National Institutes of Health…; ensure that the Plan establishes priorities among the AIDS activities that such agencies are authorized to carry out; ensure that the Plan establishes objectives regarding such activities…; and 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 further provides that "the Director of the OAR shall ensure that the Plan provides for basic research; provides for applied research; provides for research that is supported and conducted by the agencies; provides for proposals developed pursuant to solicitations by the agencies and for proposals developed independently of such solicitations; and provides for behavioral research and social science research."

PRIORITY:

Expanding Basic Discovery Research

Etiology and Pathogenesis

AREA OF EMPHASIS

Etiology and Pathogenesis

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A: Biology of HIV Transmission

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

STRATEGIES

- Determine the role of phenotype/genotype/fitness/generation of variants and dose on transmission of cell-free and cell-associated HIV, in various bodily fluids at different portals of entry.
  - Define the role of cell-free and cell-associated HIV in various modes of transmission.
  - Determine the mechanisms by which virus-encoded genes and viral gene products regulate HIV infection and replication, and influence transmission, establishment, and spread of HIV infection.
  - Delineate the mechanisms by which host-encoded genes and gene products regulate HIV infection and replication, and influence the transmission, establishment, and spread of HIV infection.
  - Determine the role of the host microbiome (bacterial, fungal, and viral) in transmission, establishment, and spread of HIV infection.
  - Elucidate the genetic complexity and the biological characteristics and genetic features of viruses that are transmitted during sexually acquired acute and early HIV infection.
  - Determine the structures of and interactions between viral and host proteins that are important for the transmission, establishment, and spread of HIV infection.
  - Determine the cell subsets and tissue types that serve as portals of entry and dissemination of HIV and that support replication during different stages of infection.
- Delineate the mechanisms by which intrinsic cellular restriction factors, innate immunity, adaptive immunity, and mucosal immunity, and the effects of genetic or environmental factors on innate, adaptive, and mucosal immunity, influence HIV replication and modulate transmission, establishment, and spread of HIV infection.
- Investigate the role of inflammation and its mediators in tissue on HIV transmission and dissemination.
- Delineate the mechanisms by which sexually transmitted infections (STIs) and coinfections influence HIV transmission, replication, establishment, and spread.
- Evaluate the influence of prevention and treatment on the early events in HIV transmission, establishment, and spread.
- Evaluate the role and mechanisms of preventing or enhancing HIV transmission, establishment, and spread by soluble factors contained within bodily fluids.
- Determine the factors that lead to early evolution in founder viruses of acute HIV infection and their implications for HIV transmission, establishment, and spread.

To facilitate the research strategies listed above:

- Facilitate the translation of new insights from structural biology, computational biology, epigenetics, and systems biology (multiscale modeling and commonly used approaches to validate hypotheses such as genomics, proteomics, metabolomics, and cellular biology) to understand the etiology and pathogenesis of HIV infection.

- Further develop, validate, and utilize experimental human, nonhuman, *ex vivo*, and theoretical/mathematical models to study the transmission and establishment of HIV/SIV (simian 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.

- Define phenotypic markers, functional assays, and high throughput assays that will enhance our understanding of and ability to study innate and adaptive immune function in human mucosal tissues. This would include humoral immunity and cell-mediated immunity at mucosal surfaces.

- Promote augmented access to and sharing of key patient samples, animal model resources, laboratory reagents, new technologies and equipment, information databases, and quantitative as well as functional virologic and immunologic assays.

- Support and expand innovative research on the transmission, establishment, and spread of HIV infection.

- Develop and utilize natural and innovative technologies to procure, maintain, and expand the availability of *in vivo* nonhuman models of infection and facilitate collaborative research using these models.

OBJECTIVE–B: HIV Virology and Viral Pathogenesis

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

STRATEGIES

- Define the viral, host, and environmental factors and mechanisms that regulate initial HIV replication, control virus during primary infection, and establish viral setpoint and disease progression.
- Determine how early events that regulate the establishment and systemic spread of HIV infection define the later clinical course of the disease in HIV-infected populations.
- Define the viral, host, pharmacologic, copathogenic, and environmental factors that contribute to disease progression and nonprogression.
- Define the virologic and host factors that enable HIV to establish and maintain a persistent infection *in vivo* in the setting of both treatment-naïve individuals and patients on highly active antiretroviral therapy (HAART).
- Delineate the molecular mechanisms by which virus-encoded genes, viral gene products, host cellular factors, and intracellular compartments regulate HIV replication and influence pathogenesis.
- Determine the factors that influence the susceptibility of target cells to HIV infection and their ability to support HIV replication.
- Determine the structures of complexes between viral proteins and host factors involved in the processes that underlie HIV disease progression.
- Elucidate host/pathogen interactions occurring during acute/early infection that contribute to the establishment of the disease process.
- Determine the consequences of long-term physiological and/or immunological damage caused by HIV disease and/or HIV therapy.
- Evaluate whether and to what extent viral-induced damage to the systemic and mucosal immune systems can be reversed following suppression of HIV replication by therapeutic interventions.
- Define the reservoirs of virus in both acute and chronic infection that permit HIV persistence throughout the course of HIV infection, including in the setting of therapies and in the presence of ongoing immune responses.
- Determine the viral and host factors associated with clinical response and lack of response to therapeutic interventions in HIV-infected subjects.
- Determine the role of the host microbiome (bacterial, fungal, and viral) in the pathogenesis of HIV infection and disease progression as well as its role on antiretroviral therapy (ART) effectiveness.

To facilitate the research strategies listed above:

- Further develop and utilize experimental human, nonhuman, *ex vivo*, and theoretical/mathematical models to study the pathogenesis of lentiviral infections with emphasis on models of direct relevance to human HIV infection and models that address important issues not readily approachable in human subjects.
- Further develop mathematical models or other approaches to integrate environmental, host, and viral factors that influence HIV-AIDS pathogenesis.
- Develop relevant *in vitro* and *ex vivo* assay systems and relevant animal model systems to model cellular reservoirs of latent and/or persistent HIV infection in the context of effective ART.

- Promote augmented access to and sharing of key patient samples, animal model resources, laboratory reagents, new technologies and equipment, information databases, and quantitative virologic and immunologic assays.

- Facilitate the translation of new insights from structural biology, computational biology, and systems biology (multiscale modeling and commonly used approaches to validate hypotheses such as genomics, proteomics, and cellular biology) to understand the immunopathogenesis of HIV infection.

- Develop and exploit *in vitro* systems that accurately recapitulate different stages of the HIV life cycle (e.g., viral entry, uncoating, nuclear targeting, chromatin integration, assembly, trafficking, budding, maturation, and latency).

- Enable the translation of basic and preclinical research findings into clinical studies in humans to advance the understanding, treatment, and prevention of HIV infection.

- Promote the characterization of the host microbiome (bacterial, fungal, and viral) in different body cavities and skin of HIV-infected individuals through the use and development of novel technologies, equipment, shared resources, and databases.

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.

STRATEGIES

- Delineate the mechanisms by which innate and adaptive immunity, and the effects of genetic or environmental factors on innate and adaptive immunity, influence HIV replication.
- Delineate the mechanisms by which innate immunity modulates the quality of HIV-specific adaptive immunity, with particular emphasis on the earliest immunologic event occurring during primary infection.
- Investigate how the effectiveness of immune control may vary through the course of infection, depending on the identity and location of infected host cells and the influence of therapeutic interventions.
- Delineate the direct and indirect mechanisms underlying HIV-induced depletion and dysfunction of immune cells and tissues in humans and nonhuman models, focusing on:
  - the loss of specific CD4+ T lymphocyte subpopulations and clones;
  - the impact of HIV infection on T-cell population numbers, specificities, and functions in blood and in primary and secondary lymphoid tissues, including mucosal tissues;
  - HIV-triggered immunopathogenesis, including immune activation, cell death, induction of nonresponsiveness, dysregulation in the number and function of innate and adaptive immune effector cells, and production of host factors, including cytokines and other mediators;
  - the structural and functional compromise of primary and secondary lymphoid organs, including mucosal tissues (e.g., gastrointestinal, reproductive, and oral mucosa) and hematopoietic precursor cells and their microenvironment;
  - influences on the developing and aging immune system; and
  - disruption of host compensatory mechanisms that govern the generation, regeneration, and homeostasis of immune cell populations.
- Determine the contribution of immune activation/inflammation to HIV disease progression, and elucidate the mechanisms driving this activation.
- Determine the role of chronic HIV-1 infection and/or therapy on innate or adaptive immune senescence.
- Define the fundamental mechanisms responsible for differences between pathogenic infection and nonpathogenic natural host infection.
- Evaluate whether and to what extent viral-induced damage to the systemic and mucosal immune systems can be reversed following suppression of HIV replication by therapeutic interventions.
- Determine the lifespan, developmental, and regenerative pathways of cells of the innate and adaptive immune system in humans and nonhuman primate (NHP) models; elucidate the mechanisms that regulate the size and composition of these cell populations and how they may change with antiviral treatment and with age.
- Define viral and host markers and functional assays that will enhance our understanding of and ability to study innate and adaptive immune function in humans, especially those approaches that permit study of the *in vivo* activity of the immune system.
- Determine the impact of host immunity on viral evolution and viral fitness, and the influence of viral factors on host immunity.

To facilitate the research strategies listed above:

- Define markers and functional assays that will enhance our understanding of and ability to study innate and adaptive immune function in humans, including humoral immunity and cell-mediated immunity at mucosal surfaces.

- Facilitate the translation of new insights and concepts from basic immunology research, structural biology, computational biology, and systems biology to understand the immunopathogenesis of HIV infection.

- Promote augmented access to and sharing of key patient samples, animal model resources, laboratory reagents, new technologies and equipment, information databases, and quantitative immunologic assays.

- Further develop and utilize experimental human, nonhuman, *ex vivo*, and theoretical/mathematical models to study the pathogenesis of lentiviral infections with emphasis on models of direct relevance to human HIV infection and models that address important issues not readily approachable in human subjects.

OBJECTIVE–D: Pathogenesis of Opportunistic Infections and Coinfections

Elucidate the pathogenic mechanisms and consequences of opportunistic infections (OIs) and significant coinfections in HIV-infected individuals in diverse populations across the spectrum of age and gender in national and international settings and the factors that regulate susceptibility to infection or disease that might 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 of the basic biology of opportunistic and coinfecting pathogens and their interaction with the HIV-infected host.
- Define the relationships in which HIV enhances coinfections and by which coinfections enhance HIV disease progression, including those that are a major cause of morbidity or disease progression (e.g., tuberculosis [TB] and hepatitis C virus [HCV]) or that contribute to HIV transmission and acquisition (e.g., STIs).
- Identify and elucidate the genetic and environmental risk factors associated with the susceptibility to, the development of, and the progression of OIs and coinfections in HIV-infected individuals.
- Study the effects of OIs and coinfections on immune dysfunction, nutritional status, and HIV disease progression.
- Define immunologic responses to OI/coinfection pathogens at mucosal surfaces and determine how they may be altered by HIV infection and/or ART.
- Study how HIV infection changes the pathogenesis of the coinfecting pathogens.
- Elucidate the mechanisms of innate and adaptive immune function that mediate protection against OIs.
- Study the effects of HIV therapy on the clinical course and manifestation of OIs and coinfections, including pathogenesis of immune reconstitution inflammatory syndrome.
- Probe the pathogenic mechanisms of HIV-associated OIs, and evaluate how the causes, agents, and manifestations of these HIV-associated infections are altered by ARTs and the extension of life afforded by those therapies.
- Define the molecular and phylogenetic characteristics of major AIDS OIs and pathogens; standardize and improve techniques of phylogenetic analysis; and integrate strain-specific characterization of data into studies of the pathogenesis, mechanisms of transmission, and epidemiology of OIs.
- Determine the influence of the human microbiome on protection or susceptibility to OIs, coinfections, and HIV disease progression.
- Determine biomarkers and factors associated with clinical response and lack of response to therapeutic interventions against OIs and coinfections in HIV-infected subjects.
- Identify basic mechanisms that will facilitate the development of vaccines and new treatments for OIs that will be effective in HIV-infected individuals.

To facilitate the research strategies listed above:

- Facilitate the translation of new insights from structural biology, computational biology, and systems biology (multiscale modeling and commonly used approaches to validate hypotheses such as genomics, proteomics, metabolomics, and cellular biology) to understand the etiology and pathogenesis of HIV coinfections and HIV-related OIs.

- Develop *in vitro* techniques and novel animal models to propagate and define the life cycles of the opportunistic pathogens and coinfections associated with HIV disease.
- Develop and validate diagnostic assays for the reliable and rapid identification of HIV-associated OIs, including stable, inexpensive, easy-to-perform assays appropriate for use in developing countries.
- Facilitate collaborative and interdisciplinary studies to elucidate the etiology and pathogenesis of significant HIV OIs and coinfections (e.g., TB and HCV).

OBJECTIVE–E: Pathogenesis of Metabolic and Body Composition Change

Define the etiology, pathophysiology, and consequences of HIV infection and treatment-related metabolic disorders, body composition changes, nutritional status, endocrine dysfunction, oral health status, and cardiovascular disease in diverse populations across the spectrum of age and gender 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 manifestations, and skin disease to determine:
  - the effects of antiviral therapies and suppression of virus replication;
  - the influence of disease stages, including the degree of initial immunosuppression and immune reconstitution;
  - the contributions of individual virologic and host factors, including genetic loci;
  - the contributions of OIs, hormonal dysregulation, and other consequences of HIV infection;
  - the role of nutritional status on malabsorption, malnutrition, immune status and exacerbation of metabolic disorders, comorbidities, and HIV pathogenesis; and
  - the influence of hormones on HIV pathogenesis.
- Study the impact of HIV on an aging population, including the implications of HIV infection for cardiovascular, metabolic, bone, skeletal muscle, 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, diabetes, and bone, skeletal muscle, skin, renal, oral, and atherosclerotic cardiovascular disease.
- Determine factors associated with clinical response or lack of response to therapeutic interventions against AIDS-associated metabolic and body composition changes, impaired growth and development, diabetes, and bone, skeletal muscle, skin, renal, and atherosclerotic cardiovascular disease.

To facilitate the research strategies listed above:

- Transfer expertise from the endocrine, metabolic, cardiovascular, obesity, renal, bone, skeletal muscle, reproductive biology, oral health, and skin research fields to the HIV field and promote linkage between HIV researchers and established individuals and centers of excellence in these areas of research. Encourage and facilitate collaborative and interdisciplinary research in these areas.
- Promote programs to facilitate access to and sharing of patient samples, animal model resources, reagents, biomarkers, new technologies, equipment, information databases, and modeling/calculation tools used in metabolic, nutrition, cardiovascular, bone, skeletal muscle, oral health, and skin research.
- Facilitate the translation of new insights from structural biology, computational biology, and systems biology (multiscale modeling and commonly used approaches to validate hypotheses such as genomics, proteomics, metabolomics, and cellular biology) to understand the metabolic, endocrine, cardiovascular, renal, bone, skeletal

muscle, reproductive, oral, and skin disease complications associated with HIV infection and treatment.

- Support the development of new and improved research techniques to address the emerging metabolic, endocrine, cardiovascular, renal, bone, skeletal muscle, reproductive, and skin complications in HIV-infected populations.
- Integrate metabolic, nutritional, endocrine, cardiovascular, renal, bone, skeletal muscle, reproductive immunology, oral health, and skin studies into ongoing and planned treatment trials and observational studies.
- Link advances in understanding the immune response to HIV with changes in lipid, glucose, bone metabolism, nutritional status, muscle wasting, skin disease, endocrine parameters, oral health status, reproductive aging, and cardiovascular disease.

OBJECTIVE–F: Pathogenesis of Malignancies

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

STRATEGIES

- Elucidate the fundamental immune defects in HIV infection that predispose to the development of AIDS-defining and other malignancies that are associated with HIV infection.
- Elucidate the mechanisms by which HIV infection and its treatment enhance the development of various AIDS-defining malignancies, non-AIDS-defining malignancies, preneoplastic lesions, and other hyperproliferative conditions.
- Identify the mechanisms by which immune dysfunction, oncogenes, suppressor genes, carcinogens, and non-HIV viral 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 herpesvirus [KSHV]) and investigate their interaction with the host and the mechanisms by which they cause malignancy 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) that may emerge in the aging HIV-infected population.
- Identify the host factors that increase the risk of AIDS-defining and other HIV-associated malignant disease in HIV-infected individuals.
- Investigate the contribution of HIV-associated or opportunistic-pathogen-associated inflammatory pathways and immune dysregulation to cancers whose incidence is increased in HIV-infected individuals.
- Determine the impact of AIDS-defining and other HIV-associated malignancies on the immune response to HIV.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms of HIV-related malignancies, and evaluate how the development and the manifestations of HIV-associated malignancies are altered by such therapies.
- 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 treatment.
- Determine factors associated with clinical response and lack of response to antineoplastic therapeutic intervention in HIV-infected subjects.

To facilitate the research strategies listed above:

- Promote programs to facilitate the development of and augmented access to *in vivo* animal models, patient specimens for AIDS-defining and other HIV-associated malignancies, sharing of key patient samples, laboratory reagents, new technologies and equipment, information databases, and quantitative virologic and immunologic assays.
- Foster collaborative research between HIV and cancer researchers.

- Promote the collection of cancer specimens that occur in HIV-infected individuals, in different geographic locations in domestic and international settings.
- Facilitate the translation of new insights from structural biology, computational biology, and systems biology (multiscale modeling and commonly used approaches to validate hypotheses such as genomics, proteomics, metabolomics, and cellular biology) to understand the etiology and pathogenesis of AIDS-related malignancies.

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 in national and international settings.

STRATEGIES

- Determine the cellular and molecular mechanisms involved in HIV-associated neurobehavioral and neurological dysfunction, and peripheral neuropathies, including:
  - identifying how HIV enters, establishes infection in specific cells and regions, spreads, and persists in the central nervous system (CNS);
  - investigating the connection between blood-brain barrier dysfunction, immune cell trafficking, and neuronal injury in the context of HIV infection;
  - determining the relationship of virologic (including distinct subtypes of HIV and acute infection), host (including the genetics of the virus/host interactions, blood-brain barrier dysfunction, and neuronal injury), pharmacologic, substance abuse, and environmental factors to susceptibility of neurological disease and HIV-associated neuropathogenesis;
  - investigating mechanisms of neuropathogenesis in the acute and early phases of infection, including reversible and irreversible changes in neuronal function and neuronal-glial communication that lead to CNS manifestations of disease;
  - determining the consequences of the biological activity of cytokines, other mediators, and their receptors on the neurologic tissue in the context of HIV infection; and
  - developing methods to monitor the levels of HIV replication and consequences of HIV infection within the CNS of living subjects.
- Determine factors associated with clinical response and lack of response to therapeutic interventions for neurologic and neurobehavioral complications of HIV disease, including the role of CNS drug penetration.
- Determine the host and viral factors influencing independent evolution of drug-resistant HIV strains in the CNS compartment as well as its functional consequences.
- Determine the impact of HIV infection of CNS on systemic disease progression.
- Determine the role of the CNS as a reservoir of, and sanctuary for, persistent HIV infection.
- Define mechanisms of innate and adaptive immunologic control of HIV, OIs, and coinfections in the CNS.
- Investigate aspects of HIV infection that uniquely influence the developing nervous system or the processes of neurocognitive decline with aging.
- Define mechanisms of immune reconstitution syndrome in the CNS in the setting of OIs and coinfections.
- Delineate the role of OIs, coinfections, other disease complications, and drug treatment in neurologic and neurobehavioral complications of AIDS, including CNS dysfunction and peripheral neuropathies.
- Employ therapies that effectively suppress HIV replication 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 symptomatology of HIV-associated nervous system disease in the current era of ART.

- Define the roles and interactions among HIV peripheral neuropathy and neuropathogenesis associated with drugs (including TB and antiretroviral therapeutics) and other environmental factors (alcohol, nutrition).
- Define the role of antiretroviral drug toxicity in CNS disease in patients on ART.
- Define the relationship between HIV-associated neurological disease and CNS changes associated with normal aging or aging-related diseases.

To facilitate the research strategies listed above:

- Develop and employ appropriate animal models (e.g., NHP models) of CNS HIV/SIV infection that best reflect specific aspects of the human HIV infection of CNS disease course on treatment that are crucial to understanding neurobehavioral and neurologic disorders.
- Develop methods to investigate, diagnose, and monitor HIV-associated neurological and neurobehavioral disorders in a range of populations, including those of the developing world.
- Ensure that information, materials, and specimens needed for neuro-AIDS research are appropriately collected, catalogued, classified, stored, and distributed, and promote access to and sharing of new technologies and equipment.
- Encourage new multidisciplinary approaches to investigate HIV-associated neurological disease and neurobehavioral dysfunction, and facilitate interactions between HIV and neuroscience and neurobehavioral researchers.
- Improve existing and develop new technologies for biochemical markers and the imaging of neurologic dysfunction.
- Facilitate the translation of new insights from structural biology, computational biology, epigenetics, and systems biology (multiscale modeling and commonly used approaches to validate hypotheses such as genomics, proteomics, metabolomics, and cellular biology) to understand HIV-related neurologic disease.
- Integrate neurologic studies into the design and conduct of observational studies and treatment trials.

OBJECTIVE–H: Pathogenesis of Organ/Tissue Disorders

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

STRATEGIES

- Investigate the etiologic and pathogenic mechanisms and consequences of HIV-related:
  - oropharyngeal cavity and gastrointestinal tract, including intestinal, liver, and biliary, diseases,
  - nephropathy,
  - hematologic disorders,
  - pulmonary disorders,
  - autoimmune disorders,
  - cutaneous disease,
  - bone disease,
  - adipose dysfunction,
  - muscle wasting,
  - oral disease, and
  - other organ/tissue-specific disorders.
- Determine the consequences of aging on the pathogenesis of the above disorders.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms of HIV-related organ/tissue-specific complications, and evaluate how the manifestations of HIV-related organ/tissue-specific complications are altered by such therapies.
- Determine factors associated with clinical response and lack of response to therapeutic interventions against HIV-related disorders.
- Employ animal models to investigate the etiology and pathogenesis of HIV/SIV-associated disorders in the above systems.
- Define the host genetic, viral, and environmental factors that contribute to organ-specific dysfunction relevant to populations differentially affected by organ-specific disease.

To facilitate the research strategies listed above:

- Facilitate the translation of new insights from structural biology, computational biology, and systems biology (multiscale modeling and commonly used approaches to validate hypotheses such as genomics, proteomics, metabolomics, and cellular biology) to understand the etiology and pathogenesis of HIV-related disorders.
- Integrate studies of HIV-related disorders in the design and conduct of treatment trials and observational studies.

PRIORITY:

Reducing New Infections

Vaccines

Microbicides

Behavioral and Social Science

Treatment as Prevention

AREA OF EMPHASIS

Vaccines

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A: 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 infections; 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 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 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/SIV (simian immunodeficiency virus)

antigen presentation to induce different cytokine or chemokine responses, innate immunity, and host factors; carry out comparative translational research in nonhuman primate (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 (chimeric simian/human immunodeficiency virus), 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, 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 nonprogressors) 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 might be manipulated or 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 NHP.

- 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 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 a genetic sequencing, particularly of selected regions of the macaque genome.

  - 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 trials.

  - Study the function of HIV/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 or improve sensitive quantitative measures of HIV (and SIV) in body fluids and low-level tissue reservoirs, including genital secretions 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/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/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 collaboration 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. Where necessary, the NIH will provide products produced under clinical grade Good Manufacturing Practices (cGMP) and ensure that products meet these 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 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/SIV antigens;
  - Agents that stimulate or modulate mucosal immune responses to HIV or other host defenses, including cytokines or chemokines;
  - HIV/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/SIV vaccine and other immune prevention strategies in NHP animal models of HIV and closely related lentiviruses by:
  - Testing HIV/SIV vaccine 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/SIV vaccines;
  - Determining the effect of HIV/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/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, autoimmune diseases), and biologic characteristics of breakthrough virus, including transmissibility;
  - Determining the impact of genetic factors, age, and concurrent prophylactic antiretroviral therapy or topical microbicides on HIV/SIV vaccine responses and on protection against virus at various challenge sites; and
  - Studying the efficacy of the HIV/SIV immune response in the face of viral variation.
- Investigate HIV/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 might compromise 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/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 potency of candidate HIV vaccines;
  - Standardizing and validating assays to be used as Phase III study endpoints; and
  - Abiding by Good Laboratory Practice (GLP) regulations to perform endpoint assays in support of 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 regulations stated in 21 CFR Part 58 and Part 11.
- Foster research on the safety and regulatory considerations of candidate HIV/AIDS vaccines in development:
  - That are produced utilizing human-derived tumor cell and other continuous cell lines;
  - That utilize vectors that have the potential to integrate into the host chromosome or have the potential for chronic expression;
  - That might have the ability to be generated as either replicating or nonreplicating vectors;
  - That have the potential to cause autoimmunity or suppression of immunity, or to generate highly immunogenic antivector responses;
  - That might have the ability to increase the risk of HIV infection through vector-specific activation of T cells or other vaccine-induced enhancement of infection; or
  - That express 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 need to 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/SHIV that can:
    - Determine preclinical safety and immunogenicity of various HIV vaccines and adjuvants, particularly in pregnant and newborn primates;
    - Determine 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 infant cellular and humoral immunity to HIV in the context of breastfeeding from an HIV-infected mother, and determine immune correlates of protection for potential exploitation in vaccine strategies;
    - Evaluate 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 and behavioral prevention strategies.
  - Determine virologic and nonimmunologic/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 might control HIV replication in either the mother and/or the infant and prevent transmission of HIV or establishment of infection in infants.
- Define immune approaches that will provide specific and sustained protection against HIV/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/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 might 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 both HIV-infected pregnant women and newborns exposed *in utero* and intrapartum to HIV (born to HIV-infected women) as well as breastfeeding infants.

- 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 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.
  - 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 and HIV vaccines given while on effective ART, on the maintenance or regeneration of naïve T cells and antiviral immune responses in HIV-infected infants.

OBJECTIVE–D: Conduct Phase I, II, and III Vaccine 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, II, and III HIV 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 the efficacy of different preventive vaccine candidates. This includes the following:
  - Develop and implement strategies to coordinate studies in NHP 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 concepts, 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. Trials also should include an appropriate representation of the general populations (gender, age, ethnic and racial minority), 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 vaccinees 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, the immune correlates of protection, long-term safety, behavioral factors that might 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 that will be involved in trials.
  - Characterize the clinical course, detailed immune responses, and other characteristics of vaccinees (e.g., behavioral risk of infection) 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 efficiency of HIV vaccine efficacy studies (e.g., determine the impact of HIV vaccines on subsequent transmission from vaccinated individuals who become infected after administration of the trial vaccine or utilizing initially concordant HIV-uninfected couples at high risk or discordant couples). 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 early ART on HIV infections in complex 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, II, and 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 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 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 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 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 vaccinees and infected individuals.
  - Analyze MHC genetic differences and other relevant genetic or medical factors of populations at potential trial sites that might affect the qualitative or quantitative levels of immune responses to candidate HIV vaccines, susceptibility to infection, control of virus peak and set point, and disease progression.
  - Acquire and analyze HIV isolates from mucosal sites, as well as blood from recently infected people 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+ and HIV- 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 nurture linkages with communities and community organizations where vaccine trials might be conducted to optimize education, recruitment, and followup activities; consider and address community concerns and social issues, and ensure ethical conduct of HIV/AIDS vaccine efficacy trials. This includes the following:
  - For all HIV vaccine trials, enlist participation of local representatives or community advisory boards (CABs) in the development of appropriate 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; work to establish trust in the community through open discussions of scientific rationale, expectations, and concerns.

- For international 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 (WHO), the Joint United Nations Programme on HIV/AIDS (UNAIDS), 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-HSV treatment, HPV vaccine, breastfeeding strategies) that might have a substantial impact on either the design or the conduct of an HIV vaccine trial. This includes the following research:

  - Evaluate other biomedical and behavioral interventions that could prove of benefit 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 (e.g., vaccines, microbicides, rapid testing), 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 (DHHS) agencies and community-based organizations to develop education programs to facilitate the conduct of Phase III HIV vaccine trials in hard-to-reach populations in domestic sites; collaborate with the U.S. Military HIV Research Program (USMHRP), the Centers for Disease Control and Prevention (CDC), the U.S. Agency for International Development (USAID), and other organizations to develop vaccine trial sites in international settings.

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

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

- Determine optimal methods of achieving informed consent for HIV vaccine efficacy trials.
- Design comparative effectiveness research to compare effective vaccine candidates with 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

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A: Basic Mechanisms of Mucosal Transmission

Elucidate basic mechanisms of HIV transmission (virus and host factors) at mucosal/epithelial surfaces that are important for the development of topical and oral microbicide prevention strategies in diverse populations.

STRATEGIES

Basic Biological and Physiological Research Related to Topical and Oral Microbicides

- Identify, investigate, and characterize new and understudied viral and host targets and kinetic sequencing of infection important for the transmission and early dissemination of HIV in the upper and lower female and male genital tracts and the anus/rectum.
- Develop exploratory techniques such as genomics and proteomics to better characterize the functions and secretomes of female and male genital and anus/rectum immune and mucosal/epithelial cells.
- Investigate the importance of innate and adaptive host defenses that protect against HIV transmission and acquisition, and explore strategies to harness these defenses to protect against HIV acquisition in the upper and lower female and male genital tracts and in the anus/rectum.
- Determine the impact of microbicides on innate and adaptive mucosal/epithelial defense mechanisms and integrity in the female and male genital tracts and in the anus/rectum.
- Study the interactions between microbicides and genital tract physiology, microbiology, viral population dynamics, and mucosal/epithelial secretions and surfaces.
- Study the impact of normal and abnormal microflora on innate and adaptive mucosal/epithelial defenses in the upper and lower female and male genital tracts, in the anus/rectum, and on HIV susceptibility, transmission, and acquisition.
- Study the physiology, immunology, microbiology, and physical changes that occur during intercourse and discern how they impact HIV transmission, acquisition, and susceptibility and the safety, efficacy, and acceptability of, and adherence to, microbicides.
- Study the effect of semen on the immunology, physiology, microbiology, and structural integrity of the female and male upper and lower genital tracts and anus/rectum in the presence or absence of candidate microbicides, and the impact of semen on HIV transmission and acquisition.
- Determine the cells, secretions, and/or tissue types that serve as portals of entry and/or facilitate transport processes that support the subsequent spread and dissemination of HIV/SIV (simian immunodeficiency virus) to the lymphoid and other reservoir tissue in small animal and primate models of infection.
- Determine the role of viral phenotype, genotype, clade, and resistance patterns in microbicide activity, and delineate their relative impact on the efficiency of transmission of cell-free and

cell-associated virus in secretions and tissues in the upper and lower female and male genital tracts and in the anus/rectum.

- Determine the mechanisms by which genital tract and anus/rectum inflammation, adaptive and maladaptive immune responses, and infections (including sexually transmitted infections [STIs]) influence HIV transmission and early propagation and dissemination of virus to lymphoid and other tissue reservoirs.
- Investigate the effect of variations in male and female endogenous hormonal status, including puberty, pregnancy, and menopause and exogenous hormonal exposure, throughout the life cycle on HIV susceptibility, transmission, and acquisition in the female and male upper and lower genital tracts and anus/rectum.

OBJECTIVE–B: Discovery, Development, and Preclinical Testing

Support the discovery, development, and preclinical evaluation of topical and oral microbicide candidates alone and/or in combination.

STRATEGIES

Topical and Oral Microbicide Development and Preclinical Studies

- Support the development, validation, and standardization of specific, sensitive, reproducible methods and algorithms to assess the antimicrobial and contraceptive activity of microbicide candidates.
- Support the development, validation, and standardization of specific, sensitive, and reproducible methods and biomarkers for assessing and quantifying innate, adaptive, and maladaptive responses in mucosal/epithelial tissues, semen, and other secretions before and after the use of microbicides.
- Promote the development and validation of biomarkers and other methods to assess the safety and efficacy of microbicide candidates, determine adherence to product usage, and document the sexual activity of female and male participants in clinical studies.
- Support the development, validation, and standardization of upper and lower genital tract, anus/rectum, and foreskin explant and cell culture models of human and nonhuman primate tissue that might provide a useful approach to investigate the very early events in HIV or SIV/SHIV (chimeric simian/human immunodeficiency virus) transmission.
- Support the development, validation, and standardization of *ex vivo* upper and lower genital tract, anus/rectum, and foreskin explant and cell culture models of human or nonhuman primate tissue that facilitates the evaluation of the activity and toxicity of microbicide candidates and the determination of safety profiles, including the impact on susceptibility to HIV and STI infection.
- Develop, validate, and standardize new and existing nonhuman primate and small animal microbicide safety and efficacy models.
- Support the development, validation, and standardization of new cellular and animal models, including primate and small animal transgenic and humanized models, for HIV susceptibility that closely reflects the dynamics of sexual transmission of HIV, and the potential safety and impact of microbicide use in humans.
- Support the development of animal models of HIV transmission in the presence of other STIs that may affect the safety and efficacy of microbicide products.
- Support and promote the development of novel models and assays to discover, develop, and evaluate microbicide candidates.
- Evaluate the efficacy of microbicides against a variety of HIV viral resistance types, subtypes, and clades.
- Develop exploratory techniques such as genomics and proteomics to identify novel candidate agents or targets for microbicide strategies.
- Facilitate the study of potential microbicide candidates for their effect(s) on innate, adaptive, and maladaptive immunologic, microbiologic, and inflammatory parameters associated with HIV susceptibility, acquisition, transmission, and replication.
- Study the effect of microbicides used before, during, and after intercourse on the structural integrity of the upper and lower genital tract and anus/rectum, and the impact on the risk for HIV susceptibility, transmission, and acquisition.
- Support the study of preclinical, pharmacokinetic, pharmacodynamic, and acute, chronic, and extended exposure toxicity testing of microbicide

candidates. This should include, but not be limited to, genotoxicity, reproductive toxicology, and carcinogenicity studies. This may include the development of new methodologies and technologies to measure product concentration and activity *in vivo*.

- Investigate the potential interactions between microbicides and the use of complementary medical therapies.

- Investigate the effect of variations in female and male endogenous hormonal status, including puberty, menopause, and pregnancy and exogenous hormonal states, across the life cycle on the innate and adaptive and maladaptive immunity of the female and male genital tracts and the anus/rectum, and on microbicide safety and efficacy.

- Foster the development of methods to solve manufacturing and synthesis hurdles that may prevent the advancement of microbicides through the preclinical pathway, by providing support for early Good Manufacturing Practice (GMP) manufacturing design and scale-up.

- Collaborate with the Food and Drug Administration (FDA) to accelerate the pace of development of combination topical and oral microbicide strategies.

OBJECTIVE–C: Formulations and Modes of Delivery

Develop and evaluate safe and acceptable topical and oral microbicide formulations and modes of delivery, bridging knowledge and applications from the chemical, pharmaceutical, physical, bioengineering, biologic, social, and behavioral sciences.

STRATEGIES

Topical and Oral Microbicide Formulations and Modes of Delivery

- Develop microbicide formulations, and dosage and delivery systems suitable for the upper and lower female and male genital tracts and the anus/rectum, that reduce or eliminate tissue toxicity and trauma while maintaining product acceptability.
- Develop placebo formulations with rheological, physical, and chemical properties that are identical to their microbicide-containing counterparts.
- Identify and validate methods that improve the understanding of rheological and physical properties that provide optimal bioadhesion, biodispersion, retention, distribution, and tissue concentration of microbicide formulations before, during, and after intercourse in the female and male upper and lower genital tracts and anal/rectal compartments.
- Develop, standardize, and validate methods to measure local tissue, target cell, and systemic absorption following topical microbicide use, and relate this to microbicide safety, efficacy, and potency.
- Develop and incorporate culturally sensitive measures and mechanisms to assess the acceptability of microbicides and their mode of delivery in females and males, including adolescents and young adults, that can be used in exploratory clinical studies and phased clinical trials domestically and internationally.
- Conduct research on and develop and study methods to better understand the biological mechanisms and physiologic and biological changes that contribute to the safety, efficacy, adherence, and acceptability of microbicide formulations. This includes, but is not limited to, the interaction between the rheological and biophysical properties of the formulation and hormonal status, age, menstrual cycle, nature of sexual activity, concomitant use of sexual enhancement products and other vaginal practices, pregnancy, frequency of use, sexual arousal, and concomitant STIs.
- Develop, validate, and standardize methodologies to analyze the physical, biological, rheological, and chemical properties of microbicides, formulated as individual and combination products.
- Develop methodologies and supportive studies to evaluate product characteristics of microbicides (such as taste, smell, color, lubricity, texture, and other factors) that can affect acceptability and use of, and adherence to, microbicides in females and males across the life cycle, in varied communities and cultures, and for different types of sexual acts.
- Support the discovery and development of reference formulations with known safety and acceptability profiles that can be used as a starting point for optimization and production of microbicide delivery systems suitable for the upper and lower female and male genital tracts, the anus/rectum, and the oral cavity.
- Support the development of novel, alternative formulation strategies for microbicide delivery systems such as sustained release, absorbable, and other delivery systems that will facilitate coital-independent and extended delivery (days to weeks to months) dosing.
- Evaluate the interaction of vaginal practices such as douching and the use of vaginal drying agents on the rheologic and physical properties and safety of candidate microbicides.

OBJECTIVE–D: Conduct Topical and Oral Microbicide Clinical Trials

Conduct clinical studies of candidate topical and oral microbicides to assess safety, efficacy, acceptability, and adherence in the reduction of sexual transmission of HIV in high-risk female and male populations, including adolescents, young adults, and pregnant women, in domestic and international settings.

STRATEGIES

Clinical Trials of Topical and Oral Microbicide Candidate Products

- Identify populations in domestic and international settings with sufficient size and HIV seroprevalence, taking into account the estimates of participant attrition and other dilution factors of observed efficacy, to meet the power threshold for the conduct of Phase I, II, III, IV, and accessory clinical studies.
- Assess and integrate the community-level cultural beliefs, behaviors, practices, and expectations in the design and conduct of microbicides clinical trials.
- Integrate and analyze the impact of behavioral and sociological HIV prevention interventions into microbicides trials.
- Ensure the validity and comparability of study outcomes by optimizing all phases of microbicide clinical study design and evaluation, including the use of standardized measures.
- Conduct pre-Phase I and accessory clinical research to address the issues of safety, efficacy, and acceptability in Phase I, II, III, and IV microbicide clinical studies.
- Conduct and evaluate novel culturally appropriate strategies to recruit and retain female and male participants across the life cycle in Phase I, II, III, and IV microbicide clinical studies in domestic and international settings.
- Design and implement Phase I, II, III, and IV clinical studies within HIV-infected populations and during pregnancy to evaluate the safety, efficacy, and acceptability of, and adherence to, microbicide products.
- Design, develop, and implement Phase I, II, III, and IV microbicide clinical studies that address and evaluate the influence of variations in endogenous (including menopause and pregnancy) and exogenous hormonal status on the safety, efficacy, and acceptability of, adherence to, and the usage of candidate microbicide products in females and males across the life cycle.
- Identify, develop, and validate behavioral markers to evaluate the safety, efficacy, acceptability of, adherence to, and use of microbicides.
- Design, develop, and evaluate tools that measure product use and acceptability within and outside the clinical study environment. These tools should be adapted for applicability to female and male and adolescent and young adult populations.
- Address ethical issues in the design and conduct of microbicide clinical studies, including methods to enhance communication with community stakeholders and to evaluate and improve the informed consent process for participants.
- Address the ethical-legal challenges inherent in adolescent participation in HIV prevention intervention research, including community and geographic policy variation, comprehension of partial efficacy, age of consent/assent, decision-making capacity, right to autonomy, and local legal definitions of statutory rape.
- Conduct research on the acceptability and efficacy of microbicide candidates, used alone and in combination with other behavioral and therapeutic HIV prevention methods. Compare these outcomes to non-microbicide-based approaches to HIV prevention.

- Implement novel translational research strategies to develop criteria for the movement of microbicide agents from preclinical animal studies to Phase I human trials.
- Identify and develop improved techniques to evaluate the safety and efficacy of microbicides applied to upper and lower female and male genital tract, anus/rectum, and other mucosal/epithelial surfaces.
- Conduct followup research with participants who have seroconverted during the course of microbicide clinical studies in order to assess the impact of long-term product use and the effect of the product on contraception, pregnancy, and the acquisition of STIs and other coinfections.
- Study microbicide candidates in HIV-infected participants to determine the impact of product use on the development of HIV progression, superinfections/reinfections, the progression of coinfections, and on drug resistance, drug interactions, and the potential for other adverse events.
- Design, implement, and evaluate Phase IV post-marketing surveillance studies on microbicides.
- Design, develop, and implement preclinical studies and Phase I and II clinical studies in pregnant women to assess the pharmacokinetics, safety, and acceptability of the agents likely to enter Phase IIB/III clinical trials.
- Study the contraceptive and noncontraceptive properties of microbicides *in vivo* and the impact of microbicides exposure on fertility, fetal development, maternal and infant pregnancy outcome, and childhood development.
- Investigate the development of resistance when antiretroviral (ARV) and non-ARV-based microbicides are used alone or in combination in HIV-infected individuals. Identify and study the correlates of increased risk for ARV resistance.
- Promote and support the rigorous use of comparative effectiveness research (CER) in evaluating various biomedical and behavioral interventions for HIV/AIDS.

OBJECTIVE–E: Conduct Topical and Oral Microbicide Behavioral and Social Science Research

Conduct basic and applied behavioral and social science research to inform and optimize topical and oral microbicide development, testing, acceptability, and use in domestic and international settings among female and male populations, including adolescents, young adults, and pregnant women.

STRATEGIES

Social and Behavioral Science Research Related to Topical and Oral Microbicides

- Support the development and study of epidemiological models of risk and protection within community and population, social, and cultural contexts, to inform research on and the implementation and evaluation of microbicide use.
- Conduct behavioral and social science research on individuals, their partners, and communities at the onset of microbicide use. Assess the influence of behavioral and social factors on the continuation or discontinuation of product usage.
- Conduct behavioral and social science research with individuals, their partners, and communities on methods to improve adherence to microbicide products with varied formulations and to research protocols during clinical studies.
- Develop and evaluate the efficacy of behavioral and social interventions to enhance correct and consistent use of microbicide products in diverse populations and in diverse settings.
- Develop and evaluate the efficacy of behavioral interventions aimed to reduce sexual risk behaviors among participants in microbicide studies.
- Support operations research on the implementation and costs of behavioral interventions designed to support microbicide usage, implementation, acceptance, sustainability, and dissemination.
- Develop and improve methods and tools for measurement and analysis in behavioral and social science microbicide research.
- Develop and improve methods and tools for behavioral and social science research on microbicides, to inform techniques for the enhanced recruitment and retention of participants in all phases of clinical studies and the prediction of sustained microbicide use in female and male at-risk populations across the life cycle.
- Conduct behavioral and social science research on counseling strategies for females, males, families, and communities that address the decisionmaking process that determines use or nonuse of sexual and HIV prevention methods in general and determines the optimal means for the prevention of HIV acquisition by sexual transmission while using a microbicide that is known to have partial efficacy.
- Use the tools and measures of behavioral and social science research to predict and evaluate potential trends in microbicide usage, adherence, sustainability, and pregnancy rates in at-risk populations of males and females, including, but not limited to, adolescents, young adults, pregnant women, and older age groups in clinical trials.
- Evaluate the effects of family and community pregnancy expectations on the use or nonuse of microbicides with contraceptive properties.
- Evaluate the effect of vaginal, rectal, and other sexual practices, including the use of products for hygiene, lubrication, sexual enhancement, and prevention of HIV transmission, on the use and efficacy of microbicides.

OBJECTIVE–F: Topical and Oral Microbicide Infrastructure

Establish and maintain the appropriate educational, physical, and human resource infrastructure needed to conduct basic, preclinical, clinical, behavioral, and social science topical and oral microbicide research domestically and internationally among HIV-negative and -positive females and males, including adolescents, young adults, and pregnant women.

STRATEGIES

Infrastructure

- Establish and strengthen training and infrastructure for the development of domestic and international institutional capacity for basic, translational, and preclinical microbicide research, including studies that facilitate the discovery and development of new microbicide candidates and assays for discovery, testing, and clinical evaluation and implementation.
- Establish clinical study sites and the infrastructure required for Phase I, II, III, and IV studies domestically and internationally; coordinate with other domestic and international organizations to optimize the availability of resources and encourage harmonization.
- Identify site-specific gaps in basic science, biomedical, behavioral, sociological, ethical, clinical, regulatory, and administrative training and support in national and international microbicide research sites, and design strategies that respond to those needs.
- Provide microbicide research training activities to foster and develop the skills of independent national and international investigators.
- Support and fund the dissemination of microbicide-related discovery and development strategies that will assist the research process, including assay standardization and validation, to domestic and international investigators.
- Strengthen training and infrastructure for the development of national and international institutional capacity for microbicide clinical research, including laboratory capability, appropriate study design, data management/analysis, operational support, physical and human resource infrastructure, and the development of high standards of conduct for clinical research.
- Ensure the collaborative involvement of national and international community representatives and leaders in the planning and implementation of microbicide research.
- Foster and support the development of pilot and large-scale GMP production systems for the manufacture of microbicide agents and their formulations.
- Develop and evaluate strategies to promote and sustain the involvement of local governments, researchers, communities, and advocacy groups in the identification of priorities for the design and conduct of basic, translational, clinical, behavioral, and social science research strategies, and in the maintenance of participants in research projects.
- Develop and evaluate strategies to encourage community participation in research and facilitate community acceptance of microbicides. Develop and evaluate appropriate communication strategies for affected communities in which candidate microbicides are being tested, and prepare for the eventual integration of microbicides into domestic and international comprehensive prevention and care programs.
- Foster public-private partnerships to integrate NIH microbicide activities with external organizations to facilitate the cost-effective use of available resources and accelerate microbicide development.
- Foster collaborative partnerships between established investigators and between established and young investigators for the conceptualization, design, and conduct of innovative microbicide research.

AREA OF EMPHASIS

Behavioral and Social Science

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A: Preventive Interventions

Develop, evaluate, and advance prevention interventions: Support research to develop, evaluate, and diffuse effective behavioral, social, environmental, and economic interventions to prevent HIV transmission and acquisition by reducing HIV-related risk behaviors and increasing protective behaviors, including implementation research and studies of "scaling up" effective interventions.

STRATEGIES

- Develop and evaluate the efficacy, effectiveness, and cost-effectiveness of demographically and culturally appropriate behavioral, social, and structural interventions in different domestic and international settings and populations to reduce high-risk HIV-related sexual and drug-use behaviors and HIV transmission.
- Translate and apply basic behavioral and social science research to optimize the development of innovative and effective intervention strategies.
- Support new research to identify or adapt the active ingredients of efficacious, theory-based interventions for broader adaptation and uptake.
- Modify, adapt, or refine existing efficacious HIV prevention interventions to increase their potency, and also to make them more easily administered and used in the community.

Populations and Contexts

- Develop and test interventions targeted at HIV-infected persons to reduce sexual and drug-use transmission risk behaviors.
- Support intervention research that addresses the impact of alcohol and/or drugs on sexual encounters that may contribute to HIV transmission and acquisition.
- Continue development of interventions targeting at-risk populations (e.g., injection drug users [IDUs], other drug users, partners of drug users, street children, and men who have sex with men [MSM]), with particular emphasis on drug-use and sex-related risks.
- Continue development of interventions for persons with multiple mental and physical disorders.
- Support domestic and international intervention research on the HIV prevention role of programs designed to enhance healthy sexual development and protective behaviors (including avoidance of too-early or nonconsensual sex, abstinence from unsafe sexual behavior, and access to and use of barrier methods) throughout one's lifetime.
- Support interventions for populations that are currently at low risk or that perceive themselves to be at low risk for HIV infection, but that may be susceptible to engaging in high-risk behaviors (e.g., non-sexually active, non-drug-using adolescents; subpopulations of heterosexual men and women; and certain middle-aged and older populations).

- Support intervention research that addresses important contextual risk factors for disproportionately affected groups that continue to demonstrate high-risk behaviors. This research also should identify which public health applications most effectively attend to cultural contexts.

- Develop, test, and evaluate interventions that target individuals both within prisons and returning to society from correctional settings; strategies include increasing access to education, information, therapeutic care, substance abuse treatment, prevention services, and clinical trials.

- Develop, test, and evaluate interventions that make use of existing systems of care that serve at-risk populations but do not routinely provide HIV prevention services (e.g., primary care or mental health settings) or address limited aspects of HIV prevention (e.g., sexually transmitted infection [STI] clinics that address sexual, but not drug-use, risks).

- Develop, test, and evaluate interventions that target individuals both within the military and returning to society from the military; strategies include increasing access to education, information, therapeutic care, substance abuse treatment, prevention services, and clinical trials.

- Support the capacity to develop rapidly domestic and international intervention studies in response to changes in the epidemic.

- Evaluate complementary and alternative practices targeting high-risk behaviors.

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.

- Support research to increase the effectiveness, as strategies of HIV prevention, of interventions already used in service delivery systems for high-risk populations, such as family planning interventions; drug and alcohol abuse prevention; and treatments for STIs, HIV (e.g., antiretroviral therapy [ART] for preexposure prophylaxis), drug and alcohol abuse, and mental disorders.

- Conduct studies to identify key components of efficacious interventions to facilitate transfer, adaptation, and application of them.

- Support research in the United States and abroad to improve the transfer of effective HIV interventions among communities, particularly research on the adoption and adaptation of efficacious HIV interventions by communities (including studies of diffusion processes and the exchange of knowledge between service providers and researchers); this research includes study of the maintenance of effective interventions and assessment of the generalizability of interventions with diverse populations.

- Evaluate novel interventions identified as high priority by HIV community planning groups and other service providers.

- Support 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 dosages of certain prevention components are assigned to different individuals, or within individuals, across time, with dosage varying in response to the intervention needs of the individuals.

- Support research on broadened testing programs and early (or immediate) use of ART for those with HIV infection to determine impacts on HIV transmission.

Systems

- Support research 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 planning, and other social services that reduce HIV risk behaviors and HIV transmission.
- Support research to understand and improve prevention services' linkages, coordination, and integration with primary medical and dental care; drug, alcohol, and mental health treatment; STI treatment; reproductive health and family planning services; services for orphans and vulnerable children; and other social services.
- Support 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.
- Support intervention research on strategies for improving the willingness and capacity of communities to adopt and sustain primary prevention interventions.

Methods

- Design and test behavioral interventions for relevant populations 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.
- Support behavioral intervention studies that include HIV seroincidence data and other biologic markers as outcome measures.
- Support development of new approaches for addressing "hidden" or "hard-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 behaviors and on the consequences of HIV disease: Support 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 therapeutic regimens on adherence to treatment for HIV and cooccurring infections, sexual risk behaviors, drug-related risk behaviors, and psychosocial adaptation (i.e., improved quality of life).
- Examine neurobiological mechanisms of motivation that underlie HIV risk behaviors.
- Define the applicability and limits of rational models of behavior versus models that address states such as sexual arousal or drug- or alcohol-altered cognitive processing that do not conform well to existing models.
- Develop new models of behavioral 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 individuals and understudied groups, both domestically and internationally.
- Support theory-building studies developed in the context of HIV prevention research, as well as study theories developed for other areas (e.g., drug and alcohol abuse prevention, family planning, sexual development, and interpersonal social skill development) to see how they inform HIV prevention research.
- Support research that can more closely monitor the HIV/AIDS epidemic and associated risk behaviors so that emerging needs for basic behavioral and intervention research can be identified.
- Elucidate genetic and epigenetic factors associated with risk behaviors and behavior change.

Consequences

- Support 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.

- Support 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.

- Support behavioral research to study end-of-life transition strategies for patients with AIDS and their caregivers.

- Support 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.

- Support 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.

Prevention

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

- Study how HIV risk changes over time as a function of developmental and life-course events, such as 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.

- Support 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, 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.

- Support 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, age, and gender) that influence HIV-related behavior.

- Support 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 by communities and public health entities in the United States and abroad.

- Support research that investigates the impact of laws and policies on behaviors associated with HIV transmission and acquisition.
- Conduct research that identifies the social and behavioral factors affecting recruitment, retention, and adherence to prevention and treatment interventions, including clinical trials of HIV-related vaccines and therapeutics.
- Support behavioral and social research on the acceptability, initiation, and use of biomedical and barrier HIV prevention methods (e.g., condoms, rapid tests, and vaccines), and determine their impact on adherence to risk-reduction guidelines.
- Support 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.
- Support basic and preintervention research on behavior modification and maintenance of new behavioral patterns for developing prevention and intervention strategies.
- Support 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.
- Support 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.

OBJECTIVE–C: Consequences of HIV

Conduct treatment, health, and social services research for people infected and affected by HIV: Support research into 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. Support 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, counseling, and treatment services for HIV-infected persons and persons at risk for HIV infection.
- Support 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.
- Promote research to identify and remove barriers to effective health care utilization among persons with or at risk of HIV infection, including barriers associated with fear and stigmatization that affect access, 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.
- Support health services research and evaluation research to determine the impact of changes in the health care delivery system on HIV/AIDS care.
- Support research to foster more effective participation in treatment planning, decisionmaking, and formulating advance directives by patients with HIV and their families.
- Support behavioral and social research on the acceptability, initiation, and use of methods for HIV screening, counseling, and testing directed toward seropositive persons, and determine their impact on adherence to risk-reduction guidelines and entry to and initiation of appropriate care and treatment.
- Support research on the special factors affecting adherence in older patients and medical decisionmaking in care of older patients.

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.
- Support 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: Support 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

- 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, the elderly, prisoners) and that reflect age-appropriate concerns.
- Develop and refine techniques for measuring social networks associated with HIV transmission.
- Develop and refine techniques for studying use of the Internet and its 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 disease.
- Develop improved methods for the reliable and valid collection of sensitive information regarding sexual and drug-use risk behaviors.
- Where appropriate, develop and/or adapt innovative substance abuse assessment approaches, such as biomarkers and passive alcohol sensors, ecological momentary assessment approaches, interactive voice response technology, personal data assistants (PDAs) to monitor substance use, wireless keypad surveys, Web-based surveys, cell phones, palmtop-assisted self-interviewing, and audio-enhanced PDAs.
- Assess new methodologies for testing efficacy of environmental-level (e.g., laws, policies) interventions for reducing HIV risk.
- Support 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.

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

Design and Statistical Analysis

- Develop improved methods for sampling subpopulations (e.g., children, homeless persons, drug users, the elderly, MSM of color) and spatial units (e.g., migration routes, drug or human trafficking routes, political jurisdictions of interest), with particular attention to "hidden" or "hard-to-reach" populations.
- Develop improved and innovative methods and techniques for conducting and analyzing longitudinal studies of HIV-vulnerable and HIV-infected populations, including improved participant retention strategies; statistical methods for dealing with participant attrition, missing data, and nonnormal 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 intervention strategies at the individual, group, and community levels.
- 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 multisite, intercultural, and international studies.
- Encourage secondary data analysis; develop approaches to protect and document confidentiality.

AREA OF EMPHASIS

Treatment as Prevention

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A: Approaches to Interrupt Vertical Transmission

Develop and assess strategies to prevent mother-to-child transmission (MTCT), applicable to resource-limited and -rich countries, with emphasis on strategies to prevent transmission through breastfeeding, the short- and long-term effects of interventions for preventing MTCT on the health of women and infants, and development of drug resistance after antiretroviral MTCT prophylaxis and its association with efficacy of subsequent ART in future pregnancies.

STRATEGIES

Mechanisms of Transmission

- Investigate the mechanisms and timing of MTCT to facilitate and develop targeted drugs/strategies to further decrease MTCT or provide alternatives to currently identified effective strategies, including genomic studies.
- Investigate risk factors (e.g., immune, viral, and host-related) associated with transmission of HIV 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.

Interventions and Trials to Evaluate Interventions to Prevent Transmission

- Develop and evaluate strategies for preventing transmission of HIV from pregnant women to their offspring, and evaluate the impact of those strategies on maternal health treatment options; such strategies may include antiviral agents, anti-HIV immunoglobulin, monoclonal antibodies, agents targeted to cellular targets (e.g., blocking cytokine receptors), cell- and gene-based strategies, HIV vaccines, and adjuvants, alone or in combination.
- Develop safe and conveniently administered strategies to prevent MTCT using interventions that are affordable in resource-limited nations, including specific strategies to prevent postnatal transmission of HIV through breast milk by providing prophylaxis to the infant, mother, or both during the lactational period.
- Evaluate the pharmacokinetics and safety of ARV drugs in pregnant women and their fetuses/infants, and the penetration of ARV drugs into breast milk and genital fluids.
- Encourage development of nanotechnology delivery methods to both enhance the efficacy and decrease the toxicity of existing and future drugs used for the prevention of MTCT, particularly agents with long half-lives in formulations able to be used in neonates and infants.
- Evaluate strategies for reducing MTCT when maternal antepartum and intrapartum ART is not given or available (e.g., postpartum prophylaxis of the infant only).
- Support international collaborative efforts to conduct clinical trials of interventions to prevent MTCT.

- Study the effects of ARV regimens used for maternal health indications on preventing MTCT (including postnatal transmission through breast milk).
- Support research and development of new clinical trial designs, statistical methodologies and investigation of biologic markers, surrogates, and/or other outcomes to evaluate the activity, clinical efficacy, or reasons for failure of new agents and approaches in the prevention of MTCT.
- 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 Antiretroviral Drug Resistance

- Evaluate the effects of preexisting viral drug resistance in pregnant women on the effectiveness of ARV regimens to prevent MTCT.
- Evaluate the risk for the development of HIV variants with detectable antiretroviral drug resistance in pregnant women who receive different types of ARV prophylactic regimens and the kinetics and durability of such resistance in cell-free and cell-associated virus in plasma, breast milk, and genital secretions.
- Evaluate the risk for development of HIV variants with detectable antiretroviral drug resistance in infants who become infected despite maternal receipt of ARV prophylaxis regimens and the kinetics and durability of such resistance in cell-free and cell-associated virus.
- Evaluate the effects of developing drug resistance following ARV prophylaxis on the health and response to future ART in women and infants who become infected with HIV despite prophylaxis.
- Evaluate the effects of drug resistance developing following ARV prophylaxis in an initial pregnancy on the efficacy of the prophylactic regimen in reducing transmission in subsequent pregnancies.
- Evaluate effective, safe, simple, and short alternative antiretroviral regimens that have lower risk of development of resistance in women or infants infected despite prophylaxis than those currently used for prevention of MTCT in resource-limited settings.
- Evaluate the public health impact of ARV resistance that develops in pregnant HIV-infected women secondary to use of ARVs solely for prevention of MTCT.

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

- Evaluate the short-term toxicities, pharmacokinetics (including transplacental drug transfer to fetus/infant), and ARV activity of new agents, existing agents, and combinations of agents in pregnant HIV-infected women and their neonates.
- Evaluate whether pregnancy increases the risk of potential ARV toxicities, the pathogenesis of such toxicities in pregnancy, and clinical findings or laboratory assays that might be predictive of such effects.
- Study the effects of ARV regimens used during pregnancy for treatment of maternal HIV disease on maternal health and pregnancy outcome.
- Evaluate the optimal regimen(s) for preventing MTCT in women who are receiving ART for the sole purpose of preventing perinatal transmission, and short- and long-term clinical, immunologic, and virologic effects of receiving ART during pregnancy in such women who choose to discontinue ART after delivery.

- Evaluate the short- and long-term clinical, immunologic, and virologic effects in women who receive ART during lactation solely to prevent breast milk transmission, but who discontinue treatment following weaning.

- Evaluate the potential mechanisms for possible carcinogenic or mutagenic effects of *in utero* ARV exposure.

- Evaluate the pathogenesis of potential ARV toxicities (e.g., mitochondrial toxicity, bone toxicity) in uninfected, HIV-exposed infants with perinatal ARV exposure, and develop animal models or laboratory assays that might be predictive of such effects with exposure to an individual ARV agent alone or in combination with other ARVs.

- Develop better clinical algorithms and laboratory assays to diagnose/assess mitochondrial toxicity associated with ARV exposure in infants and children.

- Develop and implement feasible studies that assess the long-term effects of *in utero* and/or postpartum exposure to ARVs on both HIV-infected and -uninfected children, both domestically and internationally.

Implementation Issues

- Develop and evaluate strategies for implementation of effective perinatal transmission prevention interventions in developed and developing countries, including ways to increase availability and acceptability of prenatal HIV testing and of prophylaxis to prevent MTCT.

- Improve the sensitivity and specificity of diagnostic procedures (including use of nanotechnology) that are accessible, cost-effective, and have utility in developed and developing settings to permit the earliest possible determination of HIV infection in infants, and whether ARV and/or immunopreventive therapies affect the timing and sensitivity of these assays for diagnosis.

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

- Evaluate the public health impact of programs to prevent MTCT.

OBJECTIVE–B: Therapeutic Approaches to Prevent Horizontal Transmission

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

STRATEGIES

Mechanisms of Transmission

- Evaluate the influence of drug resistance on the efficacy of ARV regimens to prevent sexual transmission.
- Use and/or develop suitable animal models and clinical studies to evaluate genital and anal passage of cell-free and cell-associated virus and ARVs.
- Evaluate the influence of systemic HIV treatment on viral shedding in the anogenital tract.
- Evaluate the impact of anti-STI (sexually transmitted infection) treatment on transmission of HIV and HIV shedding in the anogenital tract.
- Develop nanotechnology tools and approaches to understand HIV and/or prevention agent interaction with genital or gastrointestinal 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 with an endpoint of 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, anti-HIV immunoglobulin, monoclonal antibodies, and immunotherapeutic agents, alone or in combination.
- Develop delivery systems for non-topical agents to prevent HIV transmission, including postexposure prophylaxis (PEP), preexposure prophylaxis (PrEP), and other antiretroviral methods of prevention.

Issues Related to ARV Interventions

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

PRIORITY:

Improving Disease Outcomes for HIV-Infected Individuals

Drug Discovery, Development, and Treatment

AREA OF EMPHASIS

Drug Discovery, Development, and Treatment

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A: Discover and Develop Anti-HIV Treatments

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

STRATEGIES

- Identify, characterize, and validate new and understudied viral and host targets for anti-HIV therapy (e.g., factors involved in viral fusion, entry, integration, transcription, replication, assembly, budding, infectivity, virulence, and pathogenicity). Develop predictive test models, including appropriate lentivirus animal models, to aid in identifying agents and strategies active against these targets.
  - Develop new agents and treatment strategies that target, inhibit, and clear HIV in cellular, anatomical, and organ reservoirs and sanctuaries, including agents that can suppress HIV in non-T-cell reservoirs.
  - Identify the cellular reservoirs of latent HIV *in vivo* and develop physiologically relevant *in vitro* models that can be used to discover agents/approaches that target and eliminate reservoirs.
  - Characterize potential agents, including their preclinical, immunologic, pharmacokinetic, pharmacodynamic, toxicity, and teratogenicity profiles.
  - Develop new compounds and chemical formulations, and other methods, suitable for the gastrointestinal tract.
  - Employ whole animal and *ex vivo* organ or tissue models of lentivirus infections to study the biologic and pharmacologic characteristics of therapeutic agents.
  - Evaluate the potential to inhibit HIV replication and spread by modifying chemokine receptor expression and/or chemokine levels. Develop agents to block the attachment of HIV to receptors and coreceptors and thus inhibit entry into cells.
- Acquire structural information on HIV and cell constituents involved in HIV infection for the design of potent and selective therapeutic agents and therapeutic vaccine candidates with activity against drug-resistant strains and across different clades. Post lead structures on publicly available databases.
  - Support genome-wide association studies and integrate genomics and informatics paradigms, concepts, and methodologies (microchip-based screens [including siRNA] and analyzers) into mainstream drug discovery and the development of therapeutic entities and strategies.

- Develop enabling technologies to accelerate and optimize the discovery and development of therapeutic entities and strategies; expand the infrastructure to provide services and reagents needed by the scientific community.
- Evaluate the intracellular pharmacokinetics and activity of antiretroviral (ARV) agents in different cell types, different stages of the cell cycle, and in all age groups. Correlate intracellular pharmacokinetic parameters with drug efficacy/toxicity.
- Develop nanotechnology-based tools for drug discovery and the investigation of drug efficacy.
- Develop nanotechnology-based tools and approaches to better understand viral pathogenesis and drug pharmacokinetics in various intracellular and extracellular compartments.
- Develop nanotechnology-based bioimaging applications to evaluate viral transmission and reservoirs, immune induction and modulation, and drug transport and metabolism.
- Develop nanotechnology-based delivery systems that target specific tissues, cells, organelles, proteins, and/or nucleic acids.
- Develop agents with desirable biopharmaceutical characteristics (e.g., improved bioavailability and tissue penetration to the central nervous system [CNS] and other sanctuaries); develop drug delivery devices or systems that improve the pharmacokinetic profile of therapeutic agents, target specific organs or tissues, reduce toxicities and adverse effects, and result in improved adherence to therapeutic regimens.

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

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

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

STRATEGIES

Clinical Trials of Therapeutic Agents

- Conduct clinical trials of potential therapeutic agents and combinations of agents in adults, including older populations, adolescents, and children to determine pharmacokinetics, tissue bioavailability, antiviral activity, effects on the immune system, safety, and clinical efficacy.
  - Evaluate optimal combinations of agents selected for antiviral synergy, complementary mechanism of action, minimal toxicity and cross-resistance, simplicity of administration, and tolerability.
  - Evaluate optimal therapies and strategies for individuals who have acute or recent infection (including neonates/young infants with perinatal infection), chronic infection but no prior antiretroviral therapy (ART), and those with prior ART, including individuals with multiple drug-resistant virus.
  - Support clinical trials to study:
    - long-term effectiveness (including toxicities) of therapeutic strategies;
    - timing, selection, and strategic sequencing of ARV agents to optimize clinical outcome;
    - optimal treatment for heavily ARV-experienced individuals with treatment failure;
    - the effect of ART on HIV-related comorbidities; and
    - gender-based and genetic differences in special populations.
  - Support small clinical studies to validate potential new targets and/or explore novel therapeutics (cell-based, gene-based).
  - Evaluate coformulated ARVs in all age groups.
  - Investigate the effects of drug-sparing regimens on efficacy, resistance, and transmission.

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

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 nanotechnology-based inexpensive and rapid platforms, as well as point-of-care assay systems, for detection, diagnosis, biomarker evaluation, and genetic testing for both *in vitro* and *in vivo* evaluations.
- Develop, incorporate, and validate appropriate quality-of-life parameters in clinical trials of ARV agents.
- Develop methodology to facilitate cross-protocol analysis and meta-analyses.
- Conduct research on how and why subjects decide to participate in clinical trials, in order to increase enrollment and maintain adherence to study protocols.
- Improve research methodologies for the ethical conduct of clinical trials.

Pharmacology

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

Viral Reservoirs

- Quantitate persistent HIV in different tissue compartments during effective ART and evaluate strategies to reduce or eradicate such reservoirs.
- Evaluate the penetration of ARVs into different tissue compartments (e.g., genital secretions/semen, CNS, breast milk, gastrointestinal tract).

Viral Resistance and Fitness

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

Mechanisms of Viral Failure

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

Adherence and Self-Management

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

International

- Expand the development of international collaborations that will assist in addressing relevant therapeutic research in populations of HIV-infected adults, adolescents, and children, including studies on factors resulting in early deaths occurring within the first 3 months of treatment/care.

- Assist and encourage resource-limited nations, as appropriate, in technology transfer through training, infrastructure, and capacity building to facilitate the evaluation of ARV agents and other therapies in local settings.

- Assess the barriers to delivery of effective health care for HIV disease, including treatment and the capability of conducting international therapeutic clinical trials through the establishment or expansion of multidisciplinary clinical centers.

- Develop and evaluate simpler, reliable, user-friendly, and inexpensive surrogate markers, assay technologies, and rapid point-of-care diagnostics for monitoring immunologic and virologic status and ARV drug responses that can be used in resource-limited settings.

- Develop standardized clinical indicators to determine how and when to initiate ART, to monitor responses to therapy, and to determine when to change therapy.

- Determine acceptable laboratory monitoring for drug toxicity in resource-limited settings.

- Evaluate whether nutritional status (particularly chronic malnutrition) affects the efficacy of therapy and whether it affects the risk or severity of adverse events associated with ART.

OBJECTIVE–C: Approaches to Manage Treatment-Related Complications

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

STRATEGIES

- Develop and evaluate therapeutic strategies for preventing and treating complications of HIV infection.
- Evaluate potential delayed or late effects of ART following short-term administration of prophylaxis regimens (e.g., for prevention of mother-to-child transmission [MTCT]), as well as during chronic treatment.
- Develop standards and definitions to allow better comparisons of late complications across clinical trials (i.e., meta-analysis between 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 or reverse potential metabolic abnormalities (e.g., changes in body composition, development of atherogenicity and endocrine disorders, and changes in bone and muscle structure) based on an understanding of the mechanisms by which ART and/or HIV disease may affect metabolic processes.
- Integrate metabolic, endocrine, cardiovascular, neurologic, renal, and bone studies into ongoing and planned clinical studies that may provide an opportunity to answer important questions related to potential complications of ART.
- Study the effects of gender, race, age, pregnancy status, and type of exposure on complications of ART.
- Evaluate the impact of nutritional deficiencies, impaired access to safe drinking water, regionally significant coinfections, and other population- and area-specific factors on complications of ART in developing countries.
- Evaluate the impact of nutrition and nutritional interventions in undernourished populations or lactating mothers provided concurrently with ART on improved clinical outcomes.
- Evaluate drug interactions with potential clinical significance for HIV-infected individuals, particularly the pharmacokinetics and pharmacodynamics between ARVs 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.
- Evaluate factors associated with and ways to prevent immune reconstitution syndrome.
- 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.
- Develop nanotechnology-based delivery systems to increase safety, tolerability, and ease of use of therapeutic agents.
- Develop nanotechnology-based tools for rapid DNA sequence identification to facilitate toxicogenomic research and applications.
- Evaluate the safety of current and proposed nanotechnology platforms and strategies for use in HIV-related applications.

OBJECTIVE–D: Prevent and Treat Coinfections

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

STRATEGIES

Preclinical Discovery and Development

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

Clinical Trials of Preventive and Therapeutic Regimens

- Assess the impact of new ARV regimens on the risks for and manifestations of infections associated with HIV disease in adults, adolescents, and children.
- Improve our understanding of the interplay between HIV-associated immune deficiencies and the onset and types of infectious complications.
- Improve strategies for prevention of multiple infections in the context of ART; determine the optimal timing for initiating/discontinuing prophylaxis for different OIs and coinfections; develop improved strategies to minimize toxicities and the development of drug-resistant microorganisms.
- Develop tools to identify HIV-infected individuals at high risk for development of specific OIs and coinfections, to improve the efficiency of clinical trial design and the risk-benefit ratio of the currently utilized drugs for prophylaxis and for treatment.

- Develop clinically useful assays and methodologies for early and rapid diagnosis of OIs and coinfections (particularly TB), quantitative assessment of microbiological responses, and drug sensitivity testing, including assays appropriate for use in children with coinfections.
- Support clinical trials in HIV-infected individuals, including children, of preventive and therapeutic regimens for HIV-related coinfections.

Coinfections

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

Pharmacology and Toxicology

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

Adherence and Self-Management

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

International

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

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

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

OBJECTIVE–E: Treatment of AIDS-Related Neurologic Disease

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

STRATEGIES

Preclinical Development

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

- Determine anatomical, structural, and genetic contributors (haplotypes, epigenetics) to neurological vulnerability to HIV infection and related inflammatory processes.

- Conduct studies to determine drug interactions between commonly used treatments for HIV disease and its complications, with treatments for drug abuse and cooccurring mental health disorders; develop treatments and regimens that are optimized for HIV-infected individuals with comorbid depression and other psychiatric disorders.

- Develop adjunctive therapeutic agents that have not only immunomodulatory functions but also neuroprotective functions to reduce comorbid psychiatric conditions (markedly depression and anxiety disorders) in HIV-infected individuals.

- Develop novel or adapt existing rehabilitative strategies to ameliorate HIV-associated CNS disease manifestations that affect social-emotional, motor, sensory, cognitive, and daily functioning.

Clinical Neuroassessment, Methodologies, and Trials

- Design and support clinical trial studies addressing nervous system complications of HIV infection and treatments in adults, adolescents, and children.

- Improve existing and develop novel, sensitive, reliable, and valid measures of neuropsychological performance and neuropsychiatric status having cross-cultural and international applicability and sensitivity to HIV-associated neurological complications and ARV treatment, including appropriate and standardized measures of neurodevelopment in children applicable to resource-limited settings.

- Determine the incidence and prevalence of HIV-associated neurologic disorders, primarily HIV-associated dementia (HAD), minor cognitive and motor disorders (MCMD), and peripheral neuropathy, in the context of long-term ART.

- Determine the effects of ART on neurodevelopmental function in HIV-infected children.

- Support the research and development of new statistical methodologies, clinical trial designs, and selection and investigation of biologic markers, to evaluate the safety and clinical efficacy of new agents and approaches in the treatment of neurologic and cognitive complications of HIV disease.

- Develop, incorporate, and validate functional neurologic and quality-of-life scales in clinical trials that are aimed at measuring the impact of nervous system complications of HIV infection.

OBJECTIVE–F: Treatment of AIDS-Related Cancers

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

STRATEGIES

Preclinical Development

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

Diagnostic Methods

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

Clinical Evaluation of Therapeutic and Prevention Strategies

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

malignancies. Develop and assess interventional strategies to reduce the risk or prevent the development of AIDS-related malignancies.

- Study the role of immunomodulating agents in the treatment and prevention of AIDS-related tumors.
- Support clinical studies of HIV-infected individuals with non-AIDS-defining malignancies in order to define the best treatment of these malignancies in HIV-infected individuals. Evaluate the impact of cancer therapy on virologic, immunologic, and tumor parameters including viral reservoirs; assess the toxicity of anticancer modalities in HIV-infected patients; and evaluate the pharmacokinetics of anticancer agents in HIV-infected patients, including a study of drug-drug interactions.
- Explore strategies for attenuating or preventing toxicities associated with anticancer therapy in HIV-infected patients, and study the effects of such strategies on virologic and immunologic parameters in HIV-infected individuals.
- Study the role of *in utero* and long-term exposure to ARVs on the risk of later development of tumors.
- Study populations in resource-limited settings at increased risk of AIDS-defining and other HIV-related malignancies due to endemic infectious agents (e.g., KSHV/HHV-8), EBV, and HPV-associated cervical cancer.

OBJECTIVE–G: Immune Reconstitution Approaches

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

STRATEGIES

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

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

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

STRATEGIES

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

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: Environmental and Social Determinants of Health

Encourage high-risk, high-impact research that explores unique environmental and societal factors that affect: (1) HIV-risk behavior; (2) HIV acquisition, transmission, and disease progression (including development of resistance); and (3) access to, as well as adoption of, preventive and therapeutic interventions for those at highest risk for HIV infection within racial and ethnic minority communities.

STRATEGIES

- Explore the effects of poverty, residential segregation, educational opportunities, incarceration, and health literacy upon HIV transmission among racial and ethnic populations across the lifespan.
- Identify the synergistic effects of the provision of stable housing, treatment, and prevention interventions upon HIV-risk behavior, disease outcome, and treatment adherence in marginalized and high-risk racial and ethnic populations.
- Quantify the impact of insurance payor status on HIV care-seeking behavior, treatment, and treatment adherence, as well as on cost of care and years of life lost, among racial and ethnic populations.
- Investigate the effect of population migrations (e.g., migrant workers) upon HIV-risk behavior, comorbid sexually transmitted infections, and disease burden within racial and ethnic populations.
- Identify effective, efficient, and sustainable HIV prevention interventions for rural communities with significant numbers of undocumented immigrants and limited access to health care and health care information.
- Evaluate interventions that incorporate traditional and indigenous medicines and medical practices for prevention of high-risk behaviors.
- Determine the effect of stigma, racism, and racial/cultural stereotyping on access to HIV prevention, care, and treatment.
- Examine the influence of bias, racial and cultural prejudice, and homophobia upon health care providers, health care systems, and HIV-testing behaviors among the racial and ethnic populations they serve.
- Identify venues that can effectively deliver acceptable, efficient, and dependable HIV testing for racial and ethnic populations.
- Study the intersection between community and health organizations required for effective prevention message delivery, including the role of key informants, key community organizations, and the linkages necessary for community acceptance.
- Test, evaluate, and adapt private sector social marketing and health communication strategies to develop new effective HIV prevention interventions in racial and ethnic minority populations.
- Adapt, test, and evaluate private sector social marketing and health communication strategies to promote effective HIV prevention interventions.
- Develop, test, and evaluate new HIV prevention interventions in racial and ethnic minority populations modeled upon widely disseminated and effective social marketing campaigns.

OBJECTIVE–B: Family and Community Level

Conduct basic behavioral and intervention research that focuses on the familial, cultural, and community-level factors that enhance or decrease HIV risk in racial and ethnic populations.

STRATEGIES

- Identify practical and cost-effective HIV prevention interventions for racial and ethnic communities, including for those in a sexual minority within these communities.
- Examine the influence of race, ethnicity, language fluency, and gender, independently and collectively, upon the social and cultural contexts of HIV acquisition, transmission, and risk.
- Incorporate implementation science in the development of HIV prevention interventions for racial and ethnic populations to facilitate prompt scale-up and delivery of effective interventions.
- Conduct community-based and community-driven participatory studies of HIV interventions that incorporate community observations and experiences to: (1) create practical and community-appropriate interventions, and (2) facilitate bidirectional transfer of knowledge and observations of interest to both the community and the investigator(s).
- Explore processes of engagement of community leaders and organizations that make for effective community mobilization and receptivity to evidence-based prevention interventions.
- Identify the factors that reliably predict the level of community readiness to engage with HIV prevention or other research interventions.
- Explore the impact of the intersection of residential segregation, poverty, and community isolation upon HIV acquisition and transmission in racial and ethnic populations.
- Examine the impact of intergenerational trauma upon HIV-risk behavior and HIV resiliency in indigenous domestic populations, including Native Americans, Alaska Natives, Native Hawaiians, and Pacific Islanders.
- Assess the impact of acculturative stress and historical trauma upon HIV-risk behavior and HIV-health-seeking behavior among individuals in communities disproportionately affected by the HIV epidemic, including racial and ethnic populations.
- Develop, pilot, and test new models of HIV behavioral interventions that incorporate common stressors and experiences in racial and ethnic communities, including acculturation, racism, and stigma.
- Study the linkages between age of sexual partner, social networks, and race upon the HIV risk of racial and ethnic youth and those within their sexual networks.
- Study the impact of social and sexual networks upon HIV resiliency and risk in racial and ethnic populations.
- Conduct basic behavioral research on the determinants of HIV risk, including substance abuse and underlying health disparities, in racial and ethnic minority transgendered individuals and their social networks.
- Investigate the impact of adolescent and youth culture on HIV-risk behaviors and risk of HIV acquisition in adolescents, especially among racial and ethnic adolescents, and their social peer networks.
- Develop, pilot, and test models of HIV behavioral interventions that incorporate common resilience factors for racial and ethnic populations, such as cultural identity, spirituality, family ties and collectivism.

OBJECTIVE–C: Individual-Level Risk

Develop and conduct population-specific primary research that focuses on individual-level determinants of risk, including resiliency and cultural and social norms, in populations at highest risk for HIV acquisition.

STRATEGIES

- Develop, pilot, and test synergistic prevention interventions for high-risk HIV-uninfected individuals within health care systems.
- Study the biological (including genetic), physiological, and environmental factors that affect HIV acquisition, transmission, and disease progression among racial and ethnic individuals.
- Identify factors that increase HIV risk among racial and ethnic minority transgendered individuals, and develop, pilot, and test models of HIV prevention that reduce or eliminate those factors.
- Identify factors that affect an individual's perception of risk within racial and ethnic populations, and determine the effect of those factors upon HIV testing and testing frequency.
- Identify what constitutes sexual behavior "norms" in racial and ethnic populations.
- Identify the behavioral, biological, cultural, and social factors that affect HIV risk, acquisition, and transmission in racial and ethnic older women.
- Determine the impact of gender-based violence, intimate partner violence, and a history of childhood trauma, such as sexual abuse and violence, upon adoption of HIV prevention strategies in individuals within racial and ethnic populations, with particular emphasis on adolescents in sexual minority and transgenders.
- Explore the effects of hormonal replacement and its biological impact upon racial and ethnic minority transgendered individuals and risk of HIV acquisition and transmission.
- Develop, pilot, and test effective models for increasing the awareness of the benefits of HIV testing in racial and ethnic minority individuals.
- Determine the impact of increased education levels on health literacy, HIV awareness, and risk behavior in racial and ethnic minorities.
- Explore the relationship between employment type (e.g., day labor versus part-time) and HIV-risk behavior in communities heavily affected by HIV, including racial and ethnic communities.

OBJECTIVE–D: Methods

Develop and test innovative methods and measures to accurately assess the individual, interpersonal, organizational, cultural, and societal-level determinants of risk in racial and ethnic populations, with special emphasis on communities that are small in number and/or underrepresented in current clinical studies.

STRATEGIES

- Develop novel sampling methods to enhance the proportion of underrepresented populations that are disproportionately affected by HIV infection in clinical and prevention research (e.g., those in sexual minority, such as lesbian, gay, bisexual, transgender, and queer [LGBTQ] adolescents; homeless individuals; and those living with mental and/or physical disabilities).
- Develop and standardize assessment tools that are designed for the community in which they are to be used, including rural populations, populations with foreign-born individuals, and racial and ethnic populations at risk for HIV acquisition.
- Develop measures to assess the impact of evidence-based quality-of-care and best practices upon HIV disease outcome in racial and ethnic individuals.
- Develop models to incorporate community-initiated HIV prevention interventions and evaluation in community-academic partnerships, especially in communities disproportionately affected by HIV.
- Recruit and retain racial and ethnic minorities using existing and novel sampling methods to ensure numbers sufficient to provide adequate statistical power to detect racial and gender differences in NIH-sponsored studies, especially Phase III clinical trials.
- Utilize operational research to identify what determines what HIV prevention interventions are ready or necessary for efficient and rapid translation into the field.
- Develop, pilot, test, and evaluate new measures of HIV-risk behavior that are culturally and contextually appropriate for racial, ethnic, and sexual minority populations.
- Identify the components of effective outreach to racial and ethnic populations; develop models of successful outreach with quantification of that success.
- Evaluate interventions that incorporate traditional and indigenous medicines and/or medical practices that encourage adherence to prevention and/or treatment protocols.

OBJECTIVE–E: Treatment and Mental Health Comorbidities

Develop and conduct primary and intervention research to examine the individual and societal-level factors that influence adoption of HIV treatment and treatment adherence among racial and ethnic populations.

STRATEGIES

- Advance the study of the biology of HIV infection among racial and ethnic populations by:
  - Evaluating the effect of race/ethnicity and gender upon immune dysfunction and the development of opportunistic infection;
  - Determining the effect of race/ethnicity and gender upon p-glycoproteins and their role in the individual response to HIV therapy and the development of HIV drug resistance; and
  - Exploring the role of preexisting health conditions disproportionately found in racial and ethnic minorities, such as cardiovascular disease, diabetes, and hepatitis, upon HIV disease course and progression.
- Determine the impact of treatment interventions upon progression of HIV disease and HIV-associated coinfections and comorbidities, including hepatitis B and C infection, tuberculosis, and HIV-associated malignancies, in racial and ethnic individuals.
- Examine the impact of alcohol, drug use, and chronic medical and neuropsychiatric comorbidities on the success or failure of HIV clinical interventions and HIV disease progression in racial and ethnic minorities.
- Develop novel clinical research methodologies for prospective studies of the effect of racial, ethnic, gender, and sexual orientation differences on HIV transmission, disease pathophysiology, and treatment outcomes.
- Determine the impact of race-related factors on HIV risk in understudied indigenous populations, including Native Americans, Alaska Natives, Pacific Islanders, and Native Hawaiians.
- Identify successful interventions to increase access to and quality of care in racial and ethnic communities, and assess the impact of increased care upon HIV transmission in these communities.
- Evaluate models for HIV prevention, care, and treatment that utilize comprehensive, culturally and contextually appropriate interventions for HIV-infected individuals in disproportionately affected communities.

AREA OF EMPHASIS

Women and Girls

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A: Determinants of HIV Transmission

Elucidate the biologic determinants of HIV transmission; and define the mechanisms by which innate and adaptive viral and host immune factors influence HIV transmission, acquisition, and resistance to infection in nonpregnant and pregnant women and girls across the life cycle.

STRATEGIES

- Evaluate the role of viral and host immune function on HIV transmission, acquisition, and resistance to infection.
- Study mucosal immune activity and response in the upper and lower genital tract, anus/rectum, and oral cavity.
- Identify and study cellular mechanisms responsible for HIV acquisition and propagation at mucosal surfaces in the upper and lower genital tract, anus/rectum, and oral cavity.
- Investigate the relationship of age and endogenous and exogenous hormone status on HIV transmission, acquisition, and resistance to infection.
- Evaluate the role of oral, anal/rectum, and genital tract physiology, microbiology, and concomitant infections on HIV transmission and acquisition.
- Study host and viral genetic factors that influence HIV transmission, acquisition, and resistance to infection.
- Elucidate mechanisms of innate and adaptive immunity and other cellular factors that affect HIV transmission, acquisition, and resistance to infection.
- Determine the impact of host factors, including anatomic/physiologic changes, nonhormonal contraception use, and vaginal practices, on HIV transmission, acquisition, and resistance to infection.
- Study the impact of other sexually transmitted infections (STIs) and syndromic or disease-specific STI treatment on HIV susceptibility, transmission, acquisition, and resistance to infection.
- Study the impact of antiretroviral therapies (ARTs) on genital tract and anal/rectum viral dynamics and vertical and sexual HIV transmission, acquisition, and resistance to infection.
- Identify and study appropriate animal models to explain host-viral-immune interactions.
- Develop standardized assays to investigate host, viral, and immune factors that impact HIV acquisition, transmission, and resistance to infection.
- Develop techniques for sampling upper and lower genital tract, anus/rectum, and oral mucosa that are minimally invasive or noninvasive and do not promote HIV acquisition.

OBJECTIVE–B: Biomedical and Behavioral Prevention Interventions

Conduct and support basic, translational, preclinical, and clinical biomedical and behavioral intervention research to prevent HIV and other STI transmission, acquisition, and resistance to treatment in pregnant and nonpregnant, HIV-infected and -uninfected women and girls across the life cycle.

STRATEGIES

Joint Biomedical and Behavioral Strategies

- Support an integrated approach to HIV and STI prevention research that includes linked behavioral and biomedical studies that consider the social context of the population in which the interventions will be applied.
- Support research to understand how the organization, financing, management, access, delivery, cost-effectiveness, and cost-utility of health care, reproductive health, family planning, and social services affect HIV-risk behaviors, HIV transmission, acquisition, and resistance to infection.
- Analyze the impact of community-level sociologic and behavioral norms on the acceptability and efficacy of and adherence to biomedical and behavioral HIV/STI prevention interventions.
- Analyze the impact of prevention interventions conducted in males on HIV and STI acquisition and transmission in females.
- Develop and evaluate methods to access, recruit, and retain women and girls who are demographically representative of the populations at risk for HIV infection into separate and integrated biomedical and behavioral prevention intervention studies.
- Develop and assess the effectiveness of utilizing multiple prevention approaches, including biological, behavioral, and community-level strategies both individually and in combination, as a potential means for preventing HIV and other STI transmission and acquisition.
- Support research to identify effective methods to improve the translation, dissemination, and increased adoption of effective HIV prevention technologies by communities, health care providers, and prevention services providers who serve women and girls.
- Support research to understand the impact of policy and policy change on HIV-risk behavior and transmission.
- Develop and evaluate innovative ways to obtain culturally and age-appropriate fully informed consent for participation in HIV prevention trials, and document the critical components of informed consent.
- Support research to identify and develop methods to overcome barriers to enrolling girls under the age of 18; racial and ethnic populations; and hard-to-reach populations including girls living outside of family care, involved in the juvenile justice system, and substance users into HIV biomedical and behavioral prevention intervention trials.
- Support research to evaluate the differences between trial participants and their in-trial behaviors compared with the general population in which HIV prevention interventions will be used.
- Develop and evaluate biomedical and behavioral interventions that target HIV-serodiscordant couples to prevent transmission.
- Investigate the interaction of HIV-risk perception and sexual behaviors and sexual activity, age of sexual debut, and the impact of the interactions on the use of HIV prevention methods.
- Develop, implement, and evaluate biomedical and behavioral HIV/STI prevention interventions that identify and decrease the role of relationship and sexual violence, relationship power discordance, intimate partner drug and alcohol use, and economic survival sex on HIV/STI risk.

- Support research to improve the translation and dissemination and increase the adoption of effective HIV prevention technologies and interventions, including treatment and care by communities and health care and prevention service providers who serve women and girls.
- Support the discovery, development, and preclinical and clinical evaluation of new and current biomedical and behavioral prevention interventions to reduce the transmission and acquisition of HIV and STIs during pregnancy.
- Support research to understand the impact of fertility intentions on the use of HIV prevention technologies and behaviors.
- Develop, implement, and evaluate culturally focused HIV behavioral prevention, treatment, and care interventions targeting populations at risk due to vulnerable and/or isolating circumstances such as being orphaned, incarcerated, a refugee, a runaway, a gang member, or a victim of sexual exploitation, trauma, violence, war, homelessness, and drug and alcohol abuse.

Biomedical Strategies

- Support the discovery, development, and preclinical and clinical evaluation of new and current biomedical prevention interventions to reduce the transmission and acquisition of HIV superinfection and other STIs among HIV-positive women and girls.
- Evaluate the impact of biomedical prevention interventions on upper and lower genital tract and anal/rectal physiology, microbiology, mucosal integrity, and the risk for the transmission or acquisition of HIV and other STIs.
- Evaluate the impact of endogenous and exogenous hormones on upper and lower genital tract and anal/rectal physiology, microbiology, mucosal integrity, and the risk for the transmission or acquisition of HIV and other STIs.
- Evaluate the impact of hormonal and nonhormonal intrauterine contraception and other nonhormonal contraception on upper and lower genital tract physiology, microbiology, mucosal integrity, and subsequent risk for the transmission or acquisition of HIV and other STIs.
- Support the development of contraceptive and noncontraceptive biomedical interventions to prevent HIV and other STIs.
- Support the evaluation of the contraceptive efficacy of current and future biomedical prevention interventions.
- Support the discovery and development of HIV/STI biomedical prevention interventions with varied rheologic properties, modes of delivery, and contraceptive and noncontraceptive properties designed to improve acceptability and adherence.
- Support studies that determine how mode of delivery, rheologic properties, and contraceptive efficacy of biomedical HIV/STI prevention interventions affect acceptability and adherence.
- Analyze the interaction between HIV and other STIs and how the presence of STIs and syndromic management or specific treatment of STIs impact upper and lower genital tract and anal/rectal physiology, microbiology, mucosal integrity, and risk for HIV acquisition and transmission.
- Study the impact of biomedical interventions to prevent mother-to-child transmission, including antiretrovirals (ARVs), cesarean section, and breastfeeding interventions, on maternal morbidity and mortality.
- Evaluate the impact of ARV treatment on HIV transmission.
- Develop treatment and technological interventions to prevent mother-to-child HIV transmission.
- Develop HIV prevention interventions for HIV-serodiscordant couples that do not prevent pregnancy.

Behavioral/Sociological Prevention Strategies

- Conduct and support behavioral intervention research to address the female-specific, psychological, social, environmental, economic, and cultural dynamics that impact HIV risk, acquisition, and transmission.
- Identify and study the impact of population-level and community-level social, economic, educational, and behavioral interventions on HIV acquisition and prevention.
- Investigate changes in HIV-related risk and prevention behaviors as a function of developmental and life-course events, such as adolescence, childbearing, sexual partnership choice and change, HIV treatment, menopause, and the presence or absence of family, social, and economic support.
- Develop innovative prevention strategies targeting male partners whose behaviors confer risk for HIV transmission to female partners, particularly in populations/areas with elevated HIV prevalence.
- Develop, implement, and evaluate culturally focused behavioral prevention interventions for populations traditionally perceived to be at low risk for HIV infection, such as middle-aged and older women, college students, persons with physical and mental disabilities, women who have sex with women, residents of rural areas, Asian/Pacific Islanders, Native Americans, and Alaskan Natives.
- Study the impact of macro events and social unrest such as (but not limited to) natural disasters, trauma, war, and refugee status on HIV risk for women and girls globally.
- Conduct basic research to understand the dynamics of gender-specific stigma/discrimination associated with HIV/AIDS and to inform the development of structural interventions to reduce HIV/AIDS-associated stigma.
- Develop and evaluate interventions to reduce or prevent adverse psychological, social, and economic consequences for women and girls infected with or affected by HIV/AIDS.

OBJECTIVE–C: Biology of HIV Disease

Study the biology of HIV infection in pregnant and nonpregnant women and girls across the life cycle, including the viral life cycle, disease progression, clinical manifestations, coinfections, sexual dimorphism, and other conditions.

STRATEGIES

- Develop and evaluate innovative and rapid testing strategies in diverse settings to identify acute and chronic HIV infection in women and girls.
- Identify the mechanisms that mediate virus/host interactions and impact disease progression.
  - Determine HIV viral dynamics, tissue distribution, and replication in blood and in all viral reservoirs in varied racial and ethnic populations across the human life cycle.
  - Identify normative laboratory values and the impact of HIV infection on those normative values in varied racial and ethnic populations across the life cycle.
  - Investigate the role of cofactors and mediators of disease progression in both early- and late-stage disease, including:
    - Endogenous and exogenous hormones, pregnancy, autoimmune diseases, and other concomitant diseases;
    - Opportunistic infections (OIs), other coinfections, HIV superinfection, HIV treatment, intermittent highly active antiretroviral therapy (HAART) and monotherapy for perinatal transmission, and genetic factors; and
    - Nutrition, biological indicators of stress, substance use, HIV-related and unrelated medication use, and complementary and alternative treatments.
- Develop approaches for identifying, recruiting, enrolling, and retaining recently exposed and newly HIV-infected women and girls for studies on the biology of HIV infection and prevention.
- Elucidate the sex-specific etiologies and pathogenic mechanisms of HIV disease manifestations in women and girls.
  - Investigate HIV-specific and therapy-associated metabolic and body composition changes at varied stages of HIV infection and at varied ages.
  - Study HIV-specific alterations of puberty, the menstrual cycle, fertility, menopause, and sexual function.
  - Conduct studies on the gynecologic (Gyn) manifestations of HIV disease and the impact of HIV on the efficacy of Gyn disease treatment.
  - Investigate the pathogenesis of OIs, coinfections, and autoimmune diseases unique to HIV-infected women and girls.
  - Investigate the characteristics, pathogenesis, treatments, and outcomes of HIV-related preneoplastic and neoplastic conditions that occur in women and girls.
  - Identify environmental changes that impact HIV disease and associated cancers in women and girls.
  - Elucidate the characteristics of neurological and neuropsychological manifestations of HIV disease and underlying cofactors specific to women and girls that impact these manifestations.
  - Investigate the impact of menopause and perimenopause on HIV disease manifestations and progression.
  - Investigate clinical manifestations and morbidity related to HIV and HIV-related therapies in pregnant, peripartum, and postpartum women.

- Investigate the impact of HIV, coinfections, and related therapy on fetal, infant, and childhood development.
- Evaluate the impact of HIV and HIV-related therapies on breast milk quantity and quality, and on the development of breast-fed infants.

- Explore the role of pharmacogenetics on variations in the course of HIV disease.
- Study the impact of HIV infection and disease progression on women's and girls' sexual development, reproductive health, and reproductive decisionmaking.
- Examine the association between sex-specific physical and psychosocial consequences of HIV disease and the initiation and maintenance of HIV-related care.

OBJECTIVE–D: Treatment and Care of HIV Disease

Conduct basic, translational, preclinical, and clinical research to inform the diagnosis, care, and treatment of HIV-infected women and girls across the life cycle, including puberty, pregnancy, and menopause. Emphasis should be on the inclusion of vulnerable and marginalized populations like adolescents and racial and ethnic minorities.

STRATEGIES

- Assess novel case-finding approaches, including social- and risk-network-based strategies to identify undiagnosed HIV infection in women and girls at risk.
- Develop and evaluate innovative strategies in diverse settings to identify and link HIV-infected women and girls to care and treatment services.
- Study the impact of receiving HIV-positive test results on HIV-risk behaviors, seeking access to and participating in treatment and care, and reproductive decisionmaking.
- Study the effectiveness and reasons for the success and failure of new and existing therapeutics in treatment-naive and treatment-experienced women and girls.
- Evaluate the short- and long-term effects of anti-HIV therapy on morbidity and mortality among women and girls across the life cycle.
- Evaluate the impact of therapy and other strategies for reducing mother-to-child HIV transmission on women's health and on reproductive decisionmaking.
- Study interventions and other factors that impact adherence to HIV therapeutic regimens and to medical care.
- Evaluate the impact of HIV-unrelated therapies and comorbidities, including substance use and mental health disorders, on access to health care and the enrollment of women and girls in clinical trials.
- Develop and evaluate strategies to increase the participation of women and girls in clinical trials.
- Support multidisciplinary research to identify unmet needs and elucidate barriers for women and girls to achieving optimal HIV/AIDS care, support, treatment, and prevention services.
- Conduct research to optimize the diagnosis and treatment of opportunistic infections and other HIV- related comorbidities and coinfections in women and girls.
- Explore the role of pharmacokinetics, pharmacodynamics, antiretroviral activity, and the toxicity of therapeutic agents on general health and on HIV disease progression in women and girls across the life cycle.
- Investigate the medication interactions of ARTs, and of ARTs with other HIV-related and -unrelated therapies in women and girls.
- Measure the quantity, frequency, and impact of alcohol and other substance use in HIV-related therapeutics trials.
- Study the effects of ART on human papillomavirus (HPV)-associated disease.
- Study the effect of the HPV vaccine on HIV disease.
- Study the impact of HPV vaccines in females and males on the reduction of HPV-associated lesions in HIV-infected women and girls.
- Study viral-specific and HIV therapy-associated changes in the menstrual cycle, fertility, and sexual function.
- Study the role of pharmacogenetics, pharmacodynamics, and pharmacokinetics on HIV disease course in women and girls as compared with males across the life cycle.

- Study the effect of ARTs and other HIV-related therapies on HIV viral dynamics, tissue distribution, and replication in blood and in all other viral reservoirs in women of varied race and ethnicity across the life cycle.
- Study how treatment interventions in acute compared with chronic HIV infection, including treatment during pregnancy, affect HIV disease progression.
- Design and evaluate effective models for service delivery that improve access and adherence to care.
- Identify appropriate female-specific HIV quality-of-care indicators and study the impact of implementing community-level and country-level quality-of-care guidelines on the health status of women and girls.
- Study the impact of stigma on access to health services and HIV treatment.
- Study the impact of access to care for women on family health.
- Support research to understand how the organization, financing, management, access to, delivery, and cost-effectiveness of general and reproductive health, family planning, and social services affect access to HIV/AIDS care, support, and treatment services.
- Support research to understand the impact of policy and policy change on the delivery and utilization of HIV/AIDS-related services, HIV-risk behavior and transmission, and HIV/AIDS disease outcomes in women and girls.
- Develop and evaluate accessible assisted reproductive technologies designed to assist in meeting fertility desire without vertical or horizontal HIV transmission.
- Study the impact of maternal treatment during pregnancy on fetal and infant outcome.

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/AIDS-related research.

STRATEGIES

- Develop and evaluate methods to facilitate obtaining fully informed consent from potential trial participants.
- Conduct research to examine and determine the factors that influence when the consent process is fully voluntary and informed.
- Investigate the unintended social and community consequences of policies and practices (including research practices) that provide special benefits to HIV-infected individuals.
- Investigate unintended harmful and beneficial consequences for women and girls, their families, and their communities as a result of participation in research studies.
- Examine the ethical risks and benefits of studies that involve treatment versus observation of women and girls.
- Investigate the ethical impact within a community of studies in which clinical trials provide the only access to therapeutics for women and girls.
- Investigate the ethics of conducting HIV treatment and biomedical intervention research in communities that are unable to afford the treatment or prevention intervention.
- Assess the potential risks and benefits for women and girls living where community-level epidemiological research is being conducted.
- Study the ethical issues related to HIV-specific diagnostic and therapeutic strategies implemented during pregnancy and lactation.
- Study the ethical issues related to providing family planning services and breastfeeding alternatives in communities where these interventions may not be acceptable.
- Study the ethical issues related to the participation of women and girls in clinical trials.

AREA OF EMPHASIS

Research in International Settings

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A: Capacity Building

Develop a sustainable, collaborative research environment by utilizing and enhancing in-country capacity.

(The scientific objectives of A and B are of equal weight and serve as a prerequisite foundation for objectives C through I.)

STRATEGIES

Site Development

- Encourage the integration of research programs being conducted in resource-limited countries by U.S. researchers with established in-country programs, including collaboration with local investigators on strategic planning for research.
- Assess existing sites and, as needed, further develop sustainable, existing in-country sites, or establish new international research sites as rapidly as possible to address urgent and emerging scientific opportunities.
- Enhance capacity for the conduct of basic and applied prevention and treatment research, with emphasis on maintaining and developing both Good Laboratory Practice (GLP) and Good Clinical Practice (GCP) requirements for large-scale clinical trials, through:
  - strengthening laboratory capacity through the provision of required equipment and human resource development, with appropriate quality assurance and training;
  - developing clinical capabilities through research training and "hands-on" research experiences;
  - developing affordable alternatives to viral load and CD4+ cell counts and expensive laboratory monitoring for treatment efficacy and toxicity;
  - supporting the analysis of scientific and research-based international databases and developing common laboratory information management systems;
  - enhancing data management and analysis capabilities;
  - addressing barriers in maintaining, optimizing the use of, and ensuring human subject protections related to repositories of biological samples in resource-constrained countries;
  - developing community entry, engagement, and involvement strategies that support the development of testing various strategies for recruitment and retention of participants in prevention, treatment, and care studies;
  - optimizing epidemiological assessment of at-risk populations, including refining respondent-driven sampling, venue-time sampling, and Internet-based sampling, among other approaches to population-based recruitment of hard-to-reach populations;

- enhancing the ability to ensure protection for human subjects involved in research and the ethical conduct of research, including informed consent and issues specific to women, children, adolescents, and the elderly, as well as vulnerable populations, including injection drug users (IDUs), men who have sex with men (MSM), prisoners, and sex workers;
- enhancing mechanisms for information exchange among investigators, including enhanced electronic communication;
- conducting research on rapid and sustainable scale-up from pilot projects and/or early Phase I and II trials to large research studies, including Phase III trials, and on how to apply and implement research findings to the general population;
- strengthening community advisory boards to participate in the development and design of clinical trials and other research, as well as in the translation of research results into programs and policies;
- strengthening financial management, accounting, and business office practices;
- strengthening library services and access to scientific resources; and
- strengthening the capacity of institutional review boards (IRBs), including information-sharing between IRBs, updates on recent development, and building capacity for IRBs for review and monitoring of approved protocols.

- Build global capacity to conduct operational research, including outcome and cost-effectiveness studies and modeling, to rapidly address emerging priorities in prevention, treatment, and care.
- Conduct studies on incidence and feasibility, using appropriate incidence measures (e.g., population-specific assays), in order to identify sites suitable for the conduct of efficacy trials of HIV prevention, treatment, and care interventions.
- Develop and provide training at international sites conducting vaccine studies on the role and responsibilities of an institutional biosafety committee (IBC).
- Develop regional approaches to research (e.g., through regional meetings and training) to enhance communication and to address common issues and needs among countries in a region.

Collaboration and Coordination

- Ensure that foreign investigators are full and equal partners with U.S. scientists in the design, conduct, analyses, reporting, and publication of clinical studies.
- Enhance coordination of NIH international AIDS research, particularly when multiple projects are active in the same country and/or region.
- Encourage the continued development of research collaborations between international and U.S. investigators, ensuring project relevance to strategic planning at the local level, to maximize the research effort in resource-limited settings; and encourage U.S. researchers to participate at the developing country research site to better understand the challenges of conducting research and providing care and services in such settings.
- Provide assistance to foreign collaborators in addressing regulatory issues and special oversight mechanisms.
- Coordinate with other U.S. Government agencies, including the Centers for Disease Control and Prevention (CDC), the U.S. Agency for International Development (USAID), the Department of Defense (DoD), the Health Resources and Services Administration (HRSA), and the State Department (e.g., the Office of the U.S. Global AIDS Coordinator [OGAC] and the President's Emergency Plan for AIDS Relief [PEPFAR]).
- Work with foreign governments, international organizations (e.g., the World Health Organization [WHO]), the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), nongovernmental organizations (NGOs), private industry, foundations, and alliances (e.g., the Global HIV Vaccine Enterprise) to help identify priorities; increase funding of basic infrastructure for prevention, treatment, and care of HIV/AIDS in developing countries and thereby help support NIH-funded

clinical research in the growing economically challenged global environment; gain efficiencies; and reduce overlap in the development and testing of vaccines, microbicides, drugs, and other prevention, care, and treatment strategies, including behavioral interventions.

- Explore and assess the efficacy of collaborations with nonphysician health professionals and community members (e.g., nurses, pharmacists, health aides) to facilitate their involvement as partners in global AIDS research, prevention, treatment, and care, including the optimization of antiretroviral (ARV) rollout in settings with limited numbers of physicians.

- Explore and assess the efficacy of collaborations with reputable indigenous health providers to better understand their role in AIDS care, prevention, and research, and to identify practices that may add value in treating and preventing diseases in diverse geographical settings.

Ethical Issues

- Ensure that research projects are designed to benefit the communities in which the research is being conducted (e.g., addressing locally relevant scientific questions).

- Enhance the capability of institutions in resource-limited settings to conduct independent scientific and ethical reviews, while ensuring timeliness of the review process.

- Ensure education/cross-fertilization between resource-limited countries' ethical review committees and U.S. IRBs, and educate U.S. IRBs about cultural issues in developing countries.

- Ensure the participation of local researchers/scientists, communities, NGOs, governments, indigenous leadership of vulnerable populations, and other stakeholders in the development of research protocols.

- Ensure that ethical challenges in both research and the implementation of research results in resource-limited settings are clearly described and addressed in grant proposals.

- Ensure confidentiality of information about HIV-infected individuals, including information on individuals in treatment for substance abuse.

- 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, local languages, etc.).

- Conduct training for all stakeholders on ethical principles and their implementation in research, 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.

- Encourage in-country scientists and leaders to work closely with local journalists to foster understanding of science, the role of research, and relevant ethical issues.

- Conduct research designed to identify ways to improve the application of ethical principles in the conduct of research in varied cultural settings, including a focus on informed consent.

Technology Transfer and Translation of Research Results

- Ensure results are provided to and understood by participants and the community in which the study is conducted, as well as to the community's health professionals and relevant Ministry of Health personnel.

- Develop distance learning approaches to enhance communication of research results and translation into prevention, treatment, and care programs.

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

- Facilitate development of locally appropriate and acceptable HIV prevention and treatment guidelines, by including behavioral, basic, epidemiological, and clinical research findings.
- Transfer clinical, laboratory, and public health technologies that may be sustained and used for implementation of prevention, symptom management, clinical training, and patient care programs once research studies are completed.
- Support operational research based on implementation science and innovative research designs not limited to randomized clinical trials (RCTs).

OBJECTIVE–B: Mentoring and Training Investigators

Develop an in-country community of investigators committed to a culture of leadership in research through providing sustainable mentoring for junior investigators and career development opportunities for new, mid-career, and senior investigators.

(The scientific objectives of A and B are of equal weight and serve as a prerequisite foundation for objectives C through I.)

STRATEGIES

- Collaborate with in-country investigators and stakeholders in resource-limited settings to assist them in prioritizing their research needs by considering gaps in epidemic control strategies and the kinds of data and knowledge necessary to influence policy (i.e., research should be country-driven).
- Ensure the leadership role of in-country investigators and influential individuals in countries where studies take place by involving them in all stages of the research, including conceptualization of the research question, study design, development of protocols, study implementation and collection of data, data analysis, publication, and presentation of research results to government and other relevant stakeholders and audiences.
- Provide sustainable career development opportunities for new, junior, mid-career, and senior investigators (e.g., similar to long-term career awards and institutional grants offered domestically) in resource-limited international settings.
- Provide opportunities for new, junior, mid-career, and senior investigators from developed countries to spend significant amounts of time working with investigators in developing countries (i.e., create career milestones in the United States that recognize collaborations on par with first authorship or principal investigator [PI] status).
- Develop in-country training partnerships, and support "south-to-south" training to enable investigators to obtain training appropriate for the areas in which they will work by (1) developing a cadre of in-country scientific professionals, and (2) providing opportunities to enable trained investigators returning to their home countries to serve as training resources for others.
- Continue to support research training, both in-country and in the United States, of clinicians (physicians and nonphysician professionals, e.g., nurses, midwives, pharmacists), public health professionals and community health workers, and scientists from developing nations to enhance the conduct of research on HIV, AIDS, sexually transmitted infections (STIs), and other HIV-related coinfections, malignancies, and comorbidities, including research training related to: (1) biomedical, social, and behavioral prevention research, (2) prevention of mother-to-child transmission (MTCT), (3) treatment and care, (4) clinical trials of therapeutic strategies, (5) development and testing of vaccine candidates, (6) prevention and treatment of substance abuse/dependence in the context of HIV transmission, ARV treatment, and disease outcome, (7) reproductive health, including microbicides, and (8) disease progression.
- Provide training in data collection, management, and analysis for in-country research personnel.
- Provide training to enable in-country researchers to meet the requirements of GCP and GLP, including training and maintenance of medical records.
- Provide training in the ethical conduct of research, including informed consent, establishment of community advisory boards, and other topics related to the protection of human subjects.
- 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.

- Provide training to ensure that clinicians and other health care workers are knowledgeable about infection control principles and can implement proper procedures in resource-constrained countries.
- Enhance training in translational, operational, and health services research, including training in cost-effectiveness.

OBJECTIVE–C: Structural Interventions

Conduct studies to identify effective structural and policy interventions to address the AIDS epidemic.

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

STRATEGIES

- Determine barriers and facilitators to acceptance of voluntary counseling and testing (VCT), and develop more comprehensive and integrated health system-level approaches to the provision of VCT, including:
  - assess new VCT approaches for effectiveness and cost-effectiveness with regard to reducing risk from sexual behavior and substance use in settings with varying levels of HIV seroprevalence;
  - integrate VCT into other existing health services, including family planning, maternal and child health care, and child immunization services; and
  - change community norms for seeking VCT that encourage knowledge of one's status, help mitigate social harm, and reduce HIV stigma.
- Identify the most effective and sustainable ways for schools, leisure locations, and worksites to support behavior change interventions.
- Investigate the effectiveness of community-based and community-level HIV prevention programs, including prevention education and strategies to evaluate, replicate, and extend effective behavioral interventions.
- Investigate the processes through which various governments implement structural interventions and how these processes might be systematically facilitated.
- Investigate the structural and policy-related human rights limitations that affect HIV prevention and access to treatment and care for vulnerable populations (e.g., MSM, IDUs, and sex workers), including laws and policies related to discrimination against minorities and criminalization of same-sex behavior between consenting adults, and evaluate the effectiveness of rights-based interventions to improve HIV disease outcomes in these groups.
- Investigate the effectiveness of structural interventions for HIV, STI, and tuberculosis (TB) prevention, treatment, and care among incarcerated populations, including in prisons, jails, mandatory drug remand centers, juvenile detention centers, and therapeutic communities.
- Ensure that all research is conducted in culturally appropriate content, form, and format and in accordance with local IRBs.
- Ensure that all research is conducted in accordance with international standards of human rights principles and in accord with the dignity of persons.
- Evaluate the effectiveness of interventions targeted to drug users, including testing and counseling outreach, access to resources for treatment of identified HIV-positive drug users, drug dependence treatment programs, availability of sterile injection equipment and needle syringe exchange programs, and the policy-level changes necessary to implement such expanded interventions.
- Develop and test strategies for encouraging voluntary partner notification within the context of families and couples counseling.
- Evaluate the effectiveness of expanded access to male circumcision programs and the policy-level changes necessary to implement such expanded interventions.
- Assess and determine optimal methodologies for evaluation of various structural interventions and ensure that research funding mechanisms recognize the need for innovative study designs not limited to RCTs.

OBJECTIVE–D: Interventions to Alleviate Stigma and Discrimination

Support AIDS research to develop interventions that address the issues of sex/gender, age, power relationships, stigma, and discrimination.

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

STRATEGIES

- Conduct research on sex/gender and age differences and/or inequities in access to and use of resources, information, and prevention and care services, as well as adherence issues.
- Evaluate the relationship between new technologies and structural interventions (e.g., male circumcision) and gender and power relationships.
- Encourage analysis of sex/gender and age differences in all relevant HIV-related research.
- Study gender-related social and behavioral factors affecting acquisition of HIV infection, including intimate partner violence and the conflicting demands of childbearing and avoidance of disease.
- Study gender-related biological factors affecting susceptibility to HIV infection, including the use of contraception and the presence of sex-specific conditions, such as human papillomavirus (HPV) infection and cervical cancer.
- Study age-related social, behavioral, and biological factors (including the use of medications) affecting susceptibility to HIV infection and its transmission.
- Study how HIV infection psychologically affects women, including their role as heads of households and/or caregivers, their reproductive health requirements, and family support.
- Evaluate strategies to reduce stigma related to choice of infant-feeding modality by HIV-infected women.
- Develop interventions to mitigate the negative social consequences of HIV infection related to AIDS stigma and discrimination, with particular emphasis on children infected with or affected by HIV (e.g., AIDS orphans).
- Evaluate laws, legal policies, and health programs at the local, State, and national levels that operate to possibly increase, perpetuate, sustain, or alleviate stigma.
- Design and evaluate strategies to reduce stigma and discrimination and increase willingness of individuals to enter into voluntary counseling and testing; identify, accept, and implement alternative infant-feeding practices; receive and adhere to antiretroviral therapy (ART) and anti-tuberculosis drug regimens; and participate in HIV/AIDS trials.
- Develop epidemic control strategies for prevention as well as care and treatment that are mainstreamed into communities, so that participation does not signify risk for infection.
- Support training of community and public health leaders to become role models in the implementation of such strategies and interventions (i.e., to lead by example, such as public displays of getting tested or revealing infection status).

OBJECTIVE–E: Prevention of Risk Behaviors in Social Settings and Networks

Study the significance of interactions among individuals in groups engaging in various risk behaviors, and develop and evaluate interventions and strategies to prevent HIV-risk behaviors in social settings and high-risk networks.

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

STRATEGIES

- Develop sustainable interventions at multiple levels (e.g., individual, couple, group, and society) that address multiple risk factors and reflect regional aspects of the epidemic.
- Develop and test prevention strategies that integrate the multiple, diverse components of sexuality, substance use, mental health, and sexual transmission into HIV prevention programs.
- Define sexual and substance use behaviors and their predictors in HIV-infected populations, and design and test interventions to reduce the risk of HIV transmission.
- Develop and test prevention strategies that address relationships between substance use and sexual transmission.
- Develop interventions targeted to both HIV-infected and HIV-uninfected individuals that are designed to appeal to specific populations such as women, men, adolescents, and the military.
- Develop and test prevention interventions to be used in the family context to prevent risky behavior and HIV acquisition and transmission by its members.
- Study the role of migration in the spread of the HIV epidemic in diverse geographical regions.
- Support cross-border studies to evaluate HIV transmission, as well as the effect of various policies and structural interventions related to migration and immigration.
- Identify the most effective means to reach and prevent HIV transmission among mobile or most at-risk populations, including sex workers, discordant couples, migrants (e.g., fishermen), refugees, and internally displaced persons (IDPs) displaced by national conflict or natural disaster.
- Conduct studies to develop interventions at multiple levels (e.g., individual, couple, group, and society) that reflect and address regional aspects of the epidemic.
- Investigate the role of mental health conditions (e.g., depression) and use of psychoactive substances in promoting or facilitating high-risk sexual behaviors that reduce the efficacy of prevention strategies.
- Determine the factors involved in high-risk social networks, especially in high-income groups (e.g., injection and noninjection drug users and heavy drinkers and/or alcohol-dependent individuals), that influence the rates and patterns of HIV infection, and design prevention programs based on these results.
- Encourage molecular epidemiology studies of viral diversity in the context of social networks.
- Study how alcohol use, including systems of payment using alcohol, affects increases in HIV risk in seasonal and nonseasonal migrant populations.
- Conduct studies to identify sustainable interventions at the levels of the individual, social network, community, and society to prevent HIV and hepatitis C virus (HCV) transmission at the population level as a result of high-risk sexual activity and/or practices related to substance use.
- Investigate the processes through which some social network interventions become self-sustaining forces for risk reduction and the frequency of this occurrence.

- Devise strategies to prevent initiation of substance use and dependence, and transition to riskier drug practices, such as initiating drug injection and sharing of injection equipment.
- Conduct research to determine the optimal way to provide HIV prevention in antenatal care (ANC) clinics for pregnant women who are found to be uninfected in VCT.

OBJECTIVE–F: Biomedical Prevention Interventions

Develop and evaluate biomedical prevention interventions and strategies.

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

STRATEGIES

- Evaluate techniques for detection of acute HIV infection, and study the effects of early identification of potential HIV transmitters on HIV infection spread in different settings.
- Utilize population-based studies to examine basic scientific questions about HIV infection, mechanisms of transmission, and host responses, including viral evolution, viral diversity, human immunology, and mucosal factors in transmission.
- Study the risk of transmission of drug-resistant strains of HIV.
- Develop and evaluate methods for increasing access to, acceptability of, and adherence to biomedical interventions.
- Study and integrate the behavioral aspects of biomedical interventions and strategies.
- Conduct research on how best to deliver prevention education in the care and treatment setting, targeting interventions to both HIV-uninfected and -infected individuals.

Male Circumcision

- Determine the durability of effectiveness of circumcision in reducing HIV transmission risk in men.
- Study the effectiveness of male circumcision for reducing HIV transmission from men to women and from men to men.
- Develop and evaluate innovative strategies for the safe and effective delivery of male circumcision and other male-oriented prevention services to prevent or reduce HIV transmission.
- Determine the factors affecting male circumcision use and acceptance.
- Study the sociocultural aspects that may inhibit or encourage the use of male circumcision.
- Study the technical training and implementation requirements for widespread uptake of male circumcision interventions.
- Determine the cost-effectiveness of male circumcision in limiting transmission and curtailing the expansion of the epidemic.

Antiretroviral Use

- Determine the effectiveness of pre- and postexposure ARV prophylaxis in prevention of sexual and blood-borne HIV transmission.
- Determine the most effective ARV agents or combinations of agents to reduce transmission risk.
- If proven effective, determine the social, cultural, and practical factors affecting ARV use and/or providing barriers to implementation of exposure prophylaxis.

Vaccine Development

- Continue the accelerated efforts toward development of vaccine candidates suitable for use around the world, and foster the development of vaccines to optimize characteristics appropriate for broad international use, including candidates exhibiting low cost with ease of production and administration, as well as 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 (incidence, viral subtypes, major histocompatibility complex [MHC] types, and natural history) to guide decisionmaking regarding the need for clinical trials in international sites and to conduct trials in these sites and communities according to the highest clinical and ethical standards.
- Identify suitable populations of adults 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 for safety, immunogenicity, and efficacy, with appropriate surrogate markers and measures of correlates of protection with suitable candidate vaccines in domestic and international settings.
- Enlist the participation of local community representatives in the development of appropriate 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 vaccine research and its acceptability in diverse populations.
- Conduct research on the potential social and economic effect of vaccines and their cost-effectiveness.

Microbicides and Barrier Methods

- Discover and develop candidate microbicides and other physical/chemical barrier methods to prevent sexual HIV transmission.
- Conduct Phase I, Phase II, and Phase III clinical trials for safety and efficacy with suitable candidate microbicides in domestic and international settings.
- Develop appropriate biological and surrogate markers of safety or protection.
- Determine the efficacy and use of prevention interventions, including microbicides and other physical/chemical barrier methods, and determine the factors affecting their use and acceptance.
- Study the sociocultural aspects that may inhibit or encourage microbicide use and barriers to adherence.
- 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.
- If found to be effective in preventing HIV transmission/acquisition, determine the cost-effectiveness of microbicides and other physical/chemical barrier methods in limiting transmission and curtailing the expansion of the epidemic.

STIs and Other Diseases

- Determine the efficacy and cost-effectiveness of syndromic management of STIs among HIV-infected individuals to prevent HIV transmission.
- Improve clinical management of viral STIs in HIV-infected individuals, emphasizing coinfections with herpes simplex virus (HSV)-2 and HPV.
- Identify gender-related biological factors affecting susceptibility to HIV infection, including the use of hormonal contraceptives and the presence of gender-specific conditions such as HPV infection, cervical cancer, and genital ulcer disease.

- Examine how coinfection with other endemic diseases affects HIV transmission and acquisition and HIV disease progression.
- Determine the role of sexual transmission of HCV in coinfection with HIV.

Substance Abuse

- Develop and evaluate innovative, culturally relevant, contextually appropriate alcohol and drug abuse treatment programs for their utility as HIV and HCV prevention approaches in different international settings.
- Develop and evaluate approaches for drug and alcohol abuse programs among HIV- and HCV-coinfected patients to improve adherence with drug/alcohol treatment strategies.
- Develop and evaluate approaches to integrate risk-reduction prevention strategies for drug and alcohol use into HIV treatment and primary care settings.
- Develop and evaluate innovative strategies for identifying "hidden populations" of young, older, and out-of-treatment drug users, and those in the "high income" strata (e.g., visitors of night clubs and rave parties).

MTCT: Considerations for the Mother, Child, and Family

- Develop and evaluate strategies:
  - for primary prevention, i.e., prevention of HIV acquisition by adolescent girls and women;
  - to improve reproductive health in serodiscordant couples, including HIV-risk reduction in *in vitro* fertilization; and
  - for prevention of unwanted pregnancy by HIV-infected adolescent girls and women, and study factors associated with unwanted pregnancy.
- Investigate the mechanisms of and risk factors for *in utero*, intrapartum, and postnatal MTCT of HIV.
- Further evaluate and adapt known efficacious interventions in infants, mothers, or both to prevent MTCT (antiretroviral prophylaxis, cesarean section before labor and before ruptured membranes, complete avoidance of breastfeeding, exclusive breastfeeding, antiretroviral prophylaxis to breastfeeding infants).
- Evaluate acquisition of HIV infection during pregnancy:
  - quantify more precisely risk of MTCT when maternal HIV infection is acquired during pregnancy; and
  - develop strategies for detecting or reducing maternal incident infection during pregnancy.
- Develop new effective, safe, and feasible strategies to further decrease MTCT, especially postnatal (breast milk) transmission of HIV, or provide alternatives to currently identified effective strategies.
- Investigate the unique immune status of pregnant women and their infants and develop passive and active immunization interventions to interrupt HIV transmission.
- Evaluate risk factors for 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; and
  - the association of maternal HIV disease stage and mortality of both HIV-infected and HIV-uninfected children.
- Investigate the effect of ARV regimens used for prevention of MTCT (including repeated interventions) on subsequent response to ARV used for treatment in mothers and infants, if infected despite prophylaxis.
- Evaluate and develop strategies to reduce morbidity associated with interventions to reduce the risk of MTCT of HIV, including the facts that:

- antiretroviral prophylaxis may involve risks related to short- and long-term toxicity and ARV resistance;
- mode of delivery will determine outcome, i.e., cesarean section for prevention of MTCT of HIV is related to increased postpartum morbidity in the mother, while iatrogenic preterm birth and associated respiratory morbidity are risks for the newborn; and
- replacement feeding issues need to be considered.

- Evaluate strategies for scaling up successful interventions for prevention of MTCT of HIV.
- Evaluate strategies to ensure linkage of sites (and information from sites) conducting prevention of MTCT with sites providing ART treatment for mothers and with infant/child health clinics (e.g., immunization clinics) for infants to ensure maternal HIV status is known so that infant receives cotrimoxazole (CTX) provision and HIV diagnosis.

OBJECTIVE–G: Treatment Research

Develop and evaluate the most effective, setting-specific strategies for care and treatment of HIV and HIV-related conditions and their sequelae among HIV-infected and HIV-affected children, adolescents, and adults at all stages of the life course.

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

STRATEGIES

- Characterize the clinical course of HIV infection in diverse geographic settings.
- Conduct research on biological, behavioral, and psychosocial effects related to the natural history and care of HIV disease among children and adolescents.
- Develop and evaluate suitable and sustainable approaches to the diagnosis of HIV infection, especially for children under the age of 18 months.
- Collaborate with clinicians from resource-limited countries to identify (by testing high-risk groups for HIV every 3 months), recruit, and retain acute and early HIV infection cases in treatment research programs.
- Identify affordable, safe, and effective ARV regimens, including timing of initiation and durability of initial treatment, and study cost-effectiveness of starting early treatment.
- Determine the role of pharmacogenetics/pharmacokinetics and identify appropriate ARVs that can be used in specific populations (e.g., children, adolescents, and adults at all life stages) in resource-constrained countries.
- Determine the efficacy of ARV regimens on various clades prevalent around the world.
- Conduct studies, including clinical trials and operational research, on the quality of treatment, its effectiveness, and its efficacy.
- Develop and evaluate suitable and sustainable approaches to monitoring the effectiveness and safety of HIV treatment, especially with regard to affordable technologies to measure CD4+ cell counts and viral load (for appropriate alternatives) and validate low-cost monitoring technology.
- Assess the cost-effectiveness of ARVs in resource-limited settings and determine the minimal level and methods of targeted drug resistance monitoring necessary in those failing therapy and pregnant women.
- Evaluate and monitor treatment effectiveness, adherence, drug-drug interactions, and toxicity of ARVs and prophylaxis medications against major coinfections in pediatric, adolescent, and adult populations (including over age 50 and pregnant women) in resource-constrained settings.
- Examine the effectiveness of a variety of approaches to the administration of therapy (e.g., directly observed therapy, directly delivered therapy, or directly administered antiretroviral therapy).
- Develop and test strategies, including promotion of treatment literacy for health care workers, people living with HIV/AIDS, and family and community members, to support adherence in adults, adolescents, and children to medication regimens to enhance therapeutic outcomes and limit the development of drug resistance.
- Conduct community-based studies that assess the effect of community mobilization on VCT and treatment success.
- Investigate the effect of substance abuse and other associated comorbid conditions (and their integrated treatment) on HIV disease progression, adherence to treatment regimes, and clinical outcomes.
- Investigate interactions of ARVs with alcohol, drugs of abuse, or medications used for the treatment of substance abuse.

- 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.
- Develop culturally appropriate mechanisms to identify persons for whom treatment is indicated and to overcome factors such as stigma and discrimination, which can forestall testing and limit the provision of treatment and care.
- Develop, evaluate, and implement programs to prevent discrimination in the provision of ARV treatment.
- Support the long-term followup of children exposed to ART *in utero* and/or postpartum to evaluate possible late effects of ARV exposure.
- Identify and study conditions that emerge as a consequence of ART and longer survival, such as malignancies, neurological and neuropsychological conditions, and metabolic and nutritional dysfunctions.
- Develop and evaluate strategies to initiate and provide care to targeted groups of individuals such as health care workers, security forces, and teachers.
- Develop and evaluate public health models, such as family and community models of care for infants to older adults that integrate HIV/AIDS care and other existing health services in a single setting to maximize outcomes and avoid duplication of effort.
- Enhance interdependent programs such as programs for TB control and management of other comorbid conditions, alcohol and other substance abuse/dependence treatment programs, maternal and child health services, and support services for the elderly.
- Develop and initiate strategies to link HIV treatment and care centers with programs for diagnosis, evaluation, and management of HIV-associated malignancies to allow a continuum of care.

OBJECTIVE–H: Endemic Diseases and HIV

Study the interactions between HIV infection, comorbidities, and endemic diseases, with a particular focus on endemic diseases that affect HIV care and are a part of the spectrum of HIV comorbidities, and develop strategies to optimize their integrated prevention, diagnosis, treatment, and care.

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

STRATEGIES

- Define the spectrum, incidence, and risk factors for HIV-related sequelae (e.g., coinfections such as TB, HCV, and HPV, malignancies, and organ system-specific manifestations such as renal, eye, and urologic diseases, and neurological and neuropsychiatric conditions) in adult, adolescent, and pediatric populations specific to individual regions in diverse geographic settings.
- Investigate sustainable strategies for preventing, treating, and monitoring response to treatment of endemic diseases in HIV-infected adults, adolescents, children, and infants in resource-constrained settings.
- Develop simple clinical algorithms for guiding initiation of prevention or treatment of HIV-related opportunistic infections (OIs) and comorbidities.
- Identify affordable strategies to target high-risk patients for initiation of prophylaxis for HIV-related OIs and comorbidities.
- Develop, study, and widely and uniformly deploy new, low-cost, and rapid diagnostic and drug susceptibility tests for comorbid and endemic diseases (including TB).
- Examine the role of coinfection and other endemic diseases and their treatment in modulating HIV infection or disease, including risk of acquiring and/or transmitting HIV infection, disease progression, and the use of ART.
- Determine the effect of ART on susceptibility to infection with endemic diseases, and on their natural history.
- Determine the effect of ART on the efficacy of treatment and prophylaxis for other endemic diseases.
- Investigate drug-drug interactions of ARVs and drugs used to prevent and treat endemic infections and/or other manifestations of such endemic infections.
- Assess the burden of TB and the relative importance of reactivation versus *de novo* infection in HIV-coinfected individuals in various settings.
- Develop and study strategies for primary and secondary TB prevention, including prophylactic regimens.
- Develop and study feasible and effective strategies for prevention of transmission of drug-susceptible and -resistant TB in community and health care settings.
- Determine optimal ways of integrating treatment for HIV disease with prevention of and treatment for OIs, endemic diseases, and comorbidities, especially TB, including clinical research to assess clinical outcome and operational research to determine cost-effectiveness.
- Determine the safest and most efficient treatment modalities for endemic diseases (e.g., TB, HCV, HIV-associated cancers, and malaria) in the adult, pediatric, and adolescent populations infected with HIV, including pregnant women.
- Assess the impact of available antibiotic treatment and prophylaxis regimens to optimize therapeutic approaches for TB and other endemic coinfections in the context of ART, including new therapies for TB and new approaches to administering drugs.

- Develop new agents and therapeutic strategies to treat drug-sensitive and drug-resistant TB (including multi-drug-resistant [MDR]-TB and extensively drug-resistant [XDR]-TB).
- Investigate behavioral and cultural factors related to endemic coinfections, within the context of HIV, and develop strategies to enhance and monitor adherence to therapy and prophylaxis for endemic coinfections in HIV-infected individuals.
- Develop methods to monitor development of anti-microbial resistance by HIV-related and endemic pathogens infecting both study participants and the general population.
- Determine the safety and effectiveness of available immunizations for endemic pathogens in diverse HIV-infected populations.
- Conduct studies to better understand the role and mechanism of reinfection and/or superinfection with HCV in coinfected individuals.
- Develop and test the feasibility of low-cost assays for early diagnosis of viral cancers, particularly cervical cancer, non-Hodgkin's lymphoma, and Kaposi's sarcoma, and utilize these in a loco-regional setting to develop adequate clinical approaches to the management of such cancers.

OBJECTIVE–I: Integrated Prevention and Treatment

Evaluate the impact of prevention and treatment programs on the HIV epidemic, including the integration of comprehensive prevention and clinical care in existing health service delivery programs related to HIV/AIDS.

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

STRATEGIES

- Assess the social, psychological, societal, and economic impact of ART on risk behaviors, HIV transmission, and prevalence, including associated behavior change, in individuals (including children), families, and various communities.
- Determine how availability of ART affects utilization of VCT in various communities.
- Determine how availability of ART affects the entry into care and treatment.
- Determine how availability of ARV prophylaxis for prevention of MTCT affects entry into ANC and utilization of VCT within ANC.
- Determine whether expanded ART care and treatment leads to a decrease in HIV-associated stigma and discrimination.
- Determine effective strategies for integrating the delivery of HIV care with drug treatment, alcohol treatment, TB treatment, maternal and child health services, and other medical and social services commonly needed by HIV-infected individuals.
- Evaluate how ART, alcohol, psychoactive drugs, or medications used for the treatment of substance abuse interact and potentially affect adherence to anti-addiction therapy and MTCT.
- Determine how ART affects breastfeeding behaviors.
- Identify morbidities in HIV-exposed, uninfected infants and young children, using appropriate control populations, in resource-constrained settings.
- Study the direct effects of ART on HIV transmission, e.g., by evaluating the effectiveness of specific ART strategies in curtailing HIV transmission in HIV-serodiscordant couples.
- Consider the implications of ART use for prevention in settings where ART is not available for all those infected individuals who meet WHO eligibility criteria.
- Determine the public health impact of ART, specifically the likelihood of transmission of drug-resistant virus and the natural history of disease in people infected with a drug-resistant HIV strain.
- Examine the potential use of HIV therapeutic vaccines.
- Determine the impact of ART on the development of drug-resistant strains of HIV in diverse geographical settings, and develop strategies to limit its development. Develop biomarkers that can serve as surrogates for measurement of HIV-risk behavior and can be used to predict and monitor rapid escalation of HIV subepidemics.
- Integrate operational and health services research with clinical research to facilitate the translation of research findings to clinical practice and public health programs and to provide information to inform the scale-up of HIV prevention, care, and treatment programs.
- Develop strategies to ensure that prevention efforts in resource-limited countries are simultaneously preserved and enhanced when treatment clinical trials and, later, ART treatment programs are established, and when prevention trials are completed.

- Develop demonstration programs that simultaneously address prevention, care, and treatment.
- Examine risk-reduction among community health care workers involved in aspects of care or adherence.
- Develop links with other agencies and organizations to integrate research with service programs and to develop multidisciplinary prevention research in multiple settings, including medical treatment and community support and care organizations.
- Develop strategies to control the HIV epidemic that address multiple health outcomes simultaneously without compromising existing public health infrastructure, while at the same time strengthening infrastructure to improve health outcomes.
- Evaluate the impact of scale-up of HIV prevention, care, and treatment programs on the health system as a whole and its ability to deliver other public health services, particularly in resource-limited settings, and consider strategies for general health care strengthening that also effectively address HIV/AIDS.

AREA OF EMPHASIS

Training, Infrastructure, and Capacity Building

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A: Research Training

Provide training domestically and internationally in biomedical, social, and behavioral research on HIV, with an emphasis on multidisciplinary research in racially and culturally diverse settings domestically, and with attention to the needs of marginalized communities domestically and in developing countries with high incidence and/or high prevalence of HIV infection.

STRATEGIES

- Increase opportunities for predoctoral, doctoral, postdoctoral, and advanced research training across a broad range of AIDS-related disciplines.
- Expand the NIH AIDS Loan Repayment Program to increase the number of U.S. scientists and physicians from disadvantaged backgrounds, including racial and ethnic minorities, to come to the NIH to boost the cadre of trained HIV/AIDS researchers.
- Develop and implement programs at domestic institutions, with attention to institutions serving women and individuals from disadvantaged backgrounds, including racial and ethnic minorities, to provide precollege training to attract students interested in behavioral and biomedical sciences related to HIV/AIDS research.
- Expand programs for HIV/AIDS research to develop culturally appropriate and relevant training and mentoring models to be applied to HIV-affected minority communities.
- Create procedures to improve the supply of trained mentors by establishing a national mentoring network for the development and retention of new investigators in HIV/AIDS research.
- Support research that develops an evidence-based approach to effective mentoring so that future mentoring programs can build on the knowledge base of educational and social science research.
- Enhance opportunities through all Institutes and Centers (ICs) and programs to improve mechanisms for recruiting, training, mentoring, and retaining of intramural and extramural HIV investigators, especially those from diverse backgrounds, including biomedical, behavioral, and social scientists in the conduct of interdisciplinary sex and gender analyses in HIV/AIDS research.
- Support programs to implement active recruiting and retention strategies for mentorship that target key transition periods along the career path in view of data that a large proportion of potential scientists from underrepresented racial/ethnic groups and other populations are lost at key transition points in their developmental trajectories.
- Support multidisciplinary training and mentoring programs to strengthen HIV/AIDS intervention research including behavioral interventions, vaccines, microbicides, therapeutics, coinfections such as tuberculosis (TB), sexually transmitted diseases, interventions to interrupt mother-to-child transmission (MTCT), nutritional interventions,

substance abuse prevention and treatment, and precancerous and cancer detection, all in the context of HIV infection.

- Expand the pool of domestic HIV/AIDS diversity supplement awards to ensure the research capacity of underrepresented minority investigators to make them more competitive for independent funding.
- Support programs to address the leaks in the pipeline and remediate attrition by understanding the multiple paths that people can follow to a research career, from one career stage to the next and the optimal time of entry to a research project.
- Support HIV/AIDS research planning and organizational grants targeting domestic minority institutions and minority-serving communities. Emphasis should be placed upon grants that develop academy-community partnerships.
- Provide new opportunities and programs to attract newly trained investigators and established researchers from other fields to pursue HIV/AIDS research.
- Develop funding mechanisms to foster better linkages across AIDS-related scientific disciplines, including basic, clinical, epidemiologic, statistical, social, and behavioral science.
- Expand opportunities for institutions serving specific diverse populations at risk for HIV/AIDS to develop equal and productive partnerships with U.S. majority institutions.
- Facilitate the establishment of research partnerships between minority institutions and the communities they serve by enhancing and expanding initiatives that support research in diverse communities.
- Expand training to strengthen local capacity to conduct multidisciplinary AIDS-related prevention, vaccine, and therapeutic research in resource-limited countries by scientists from these countries.
- Strengthen cultural competency training and ethical training for the conduct of HIV/AIDS prevention, vaccine, and therapeutic clinical trials in vulnerable populations, in both domestic and international settings.
- Support training programs for the diagnosis, prevention, and treatment of HIV infection and/or disease in resource-limited countries.
- Support training programs for the diagnosis, prevention, and treatment of nosocomial infections control, including TB, in resource-limited countries.
- Support training programs that increase the capacity for research in HIV-associated malignancies in resource-limited countries.
- Provide support for all HIV/AIDS training materials such as CD-ROM- and Web-based training and training sessions; all training materials must be adapted for local languages.
- Provide training in Good Laboratory Practices (GLP)/Good Clinical Practices (GCP) for translational processes and in product development in both domestic and international settings conducting HIV/AIDS clinical trials or research.
- Implement new funding mechanisms to provide research training to nonphysician professionals (e.g., physician assistants and nurse practitioners) in resource-limited settings and to increase the pool of HIV/AIDS minority researchers at domestic sites.
- Develop collaborative evaluation research efforts to assess the efficacy of strategies to shift HIV care tasks in resource-limited settings to nonphysician-professional trained individuals.
- Support the training of biomedical and behavioral scientists in both developed and developing countries in the use of advanced computer and information technologies for HIV-related research, including distance learning, and ensure access to appropriate tools and equipment at the end of training.
- Support veterinary residency training programs in primate medicine at National Primate Research Centers (NPRCs) or other primate facilities to help to increase the number of highly trained veterinarians who can manage the increasing needs for HIV/AIDS nonhuman primate (NHP)-dedicated colonies.

- Support the training of veterinarian scientists who contribute to the growing need for interdisciplinary-trained researchers who help to understand both the microbial/infectious disease aspects as well as the animal model side of HIV/AIDS research in NHPs.

- Develop new models of integrated training that focus on the protection of human and animal subjects enrolled in HIV/AIDS clinical trials and on ethical issues of clinical trial design and implementation of vaccine and other prevention modalities in at-risk populations, in both domestic and international settings.

- Support training programs for personnel in institutions in resource-limited settings to strengthen the administrative and financial management capacity needed to conduct HIV/AIDS-related research.

- Expand programs to increase opportunities for scientists from developing and resource-limited countries trained through the NIH to conduct AIDS research in their home countries (e.g., reentry grants).

- Develop new funding mechanisms and expand existing ones 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.

- Take advantage of existing AIDS clinical trial infrastructures to develop specific training programs in clinical trials methodology, including issues related to the design, recruitment, retention, target population dynamics, and analysis of data, domestically and internationally.

- Expand training programs on the effective use of HIV/AIDS antiretroviral drugs and prophylactic and therapeutic interventions for coinfections/opportunistic infections as well as adequate monitoring for patient safety.

- Develop training to prevent transmission of HIV and hepatitis C virus (HCV) in resource-limited health care facilities, including recruitment and retention of appropriate blood donors, predonation counseling of all blood donors, improvement of blood screening strategies and technologies, and appropriate use of transfusion.

- Support training opportunities for HIV prevention researchers interested in adding specific methodological skills to their research expertise (e.g., methods to conduct cost-effectiveness analyses, 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 analysis).

- Support the training of HIV/AIDS-affected communities, to strengthen their ability to be informed partners in biomedical and behavioral science research.

OBJECTIVE–B: Infrastructure Development

Establish and maintain the appropriate infrastructure needed to conduct HIV research domestically and internationally with emphasis on populations of high prevalence.

STRATEGIES

- Increase research infrastructure at U.S. minority-serving institutions to improve capacity to support HIV/AIDS research.
- Enhance, improve, and maintain research capacity and infrastructure in resource-limited settings with high HIV incidence, with particular emphasis on construction and operation of facilities for research on HIV prevention, including the development of vaccines and microbicides, as well as clinical trials for therapies and behavioral interventions.
- Enhance and improve the clinical trial research infrastructure for the conduct of prevention, vaccine, and therapeutics trials in domestic and foreign sites, including laboratory capacity, trained scientists and other personnel, appropriate participant cohorts, and mechanisms to address ethical issues such as the implementation of ethical committees and translated human rights documents.
- Enhance and improve research capacity and infrastructure to advance research on AIDS-associated coinfections (HCV, herpes simplex virus type 2, Kaposi's sarcoma-associated herpesvirus or human herpesvirus type 8, human papillomavirus, Epstein-Barr virus, TB, and malaria) and associated malignancies.
- Support an adequate infrastructure for producing HIV/AIDS vaccine candidates, for preventive and therapeutic vaccine trials, under Good Manufacturing Practices (GMP).
- Support and expand adequate facilities and resources, including BSL-2/3 (Bio Safety Level 2/3) facilities for studies in NHP, as well as appropriate ethical and procedural training to house, breed, and conduct HIV-related research in various NHP models.
- Expand the production of genetically defined specific pathogen-free (SPF) NHP, 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 also other NHPs.
- Maintain programs that enhance the current research infrastructure, particularly the trans-NIH infrastructure, such as the Centers for AIDS Research (CFARs), the Research Facilities Improvement Program, the NPRCs, and the Clinical and Translational Science Awards.
- Provide support for, and awareness of, the Biomedical Technology Resources Program for structural studies of HIV proteins and host proteins in the context of HIV infection.
- Provide for the long-term support of advanced in-country research in resource-limited settings participating in priority AIDS-related intervention research, such as methods to interrupt mother-to-child, sexual, or parenteral transmission, or trials of candidate HIV vaccines.
- Increase collaboration between community-based organizations (CBOs) and other Government-supported service providers (such as those funded through the Health Resources and Services Administration [HRSA], the U.S. Department of Veterans Affairs, and the Centers for Disease Control and Prevention [CDC]) and academic researchers, to improve the quality and capacity of HIV/AIDS research endeavors in service settings.
- Establish and support quality-controlled repositories for, and ensure access by, qualified scientists to human samples (e.g., serum, peripheral blood mononuclear cell, plasma, patient-derived cell lines, cerebrospinal fluid, semen, breast milk, lymphoid tissues, and other key patient samples) and HIV strains from clinical trials and natural history and epidemiological studies, especially in complex study settings (e.g., MTCT studies).

- Develop, maintain, and effectively utilize domestic and international cohorts, repositories, and nested studies among populations experiencing emerging and ongoing HIV epidemics to maintain updated existing databases, allowing a broader and efficient use by the scientific community, when appropriate.

- Maintain the present AIDS-related tumor registries, and ensure linkages between AIDS and cancer registries, for both domestic and international studies.

- Improve and adequately disseminate the process of requesting, prioritizing, and receiving HIV/AIDS laboratory samples, so that access is as timely and equitable as possible.

- Promote Internet connections, cell-phone-based communication for training, infrastructure, and treatment, and online social networks including those with virtual worlds. Ensure availability of pertinent information technology at health science centers, hospitals, outpatient clinics, 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 report generation and enhance standardization, when appropriate, in the context of HIV/AIDS research.

- Promote research in, and application of, medical informatics (e.g., high-performance computing) for HIV/AIDS research and clinical practice in resource-limited settings, both domestically and internationally.

- Enhance coordination and collaboration among NIH-supported investigators, other U.S. Government agencies, and other international agencies conducting HIV/AIDS research in the same developing countries.

- Develop efficient and effective systems for collecting and managing HIV/SIV (simian immunodeficiency virus)/SHIV (chimeric simian/human immunodeficiency virus) multiple-center and single-site clinical and animal model trial data; ensure timely and accurate dissemination of clinical and animal model trial information.

- Develop and improve conventional and electronic systems for longitudinal documentation of medical care/tracking of HIV/AIDS in low-resource settings to improve longitudinal clinical care and facilitate health systems, care quality, and epidemiologic research.

- Encourage the development of stable and sustainable locally generated "green" power supply (e.g., wind, solar) for clinical care and research sites in low-resource settings.

PRIORITY:

Translating Research From Bench to Bedside to Community

Natural History and Epidemiology

Information Dissemination

AREA OF EMPHASIS

Natural History and Epidemiology

SCIENTIFIC OBJECTIVES AND STRATEGIES

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

Characterize the risk factors and mechanisms of HIV transmission in domestic and international populations to guide prevention and treatment strategies.

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

STRATEGIES

- Utilize existing cohorts, develop new cohorts of novel subpopulations, and employ novel methods such as social network analysis, molecular epidemiology, and geographic information systems to further assess HIV transmission.

- Model how results from existing cohorts may be altered in populations with differing demographics and socioeconomic status, specifically by race, ethnicity, gender, age, sexual orientation, acquisition risk, and in-country resource capacities and availability.

- Conduct molecular epidemiology studies to identify divergent viral genotypes, drug resistance, and neutralization profiles and their temporal trends; and characterize how different HIV types (i.e., HIV-1 and HIV-2), HIV subtypes, recombinant forms, and associated risk factors influence routes and modes of HIV transmission, superinfection, natural history, response to antiretroviral therapy (ART), preexposure prophylaxis (PrEP), and emergence of antiretroviral (ARV)-resistant viruses. Conduct studies on the significance of multiple circulating subtypes and the generation of dual, multiple, and recombinant viruses in population epidemiologic dynamics and their potential implications for intervention and therapy.

- Conduct epidemiological and modeling research to improve estimates of per-contact risk of HIV transmission and to develop estimates of population-attributable risk, based on type of sexual exposure; characteristics of the infected and uninfected partners (e.g., plasma and/or anogenital tract viral load, host genetics, and coinfections); and cofactors such as drug use, psychiatric comorbidities, and antiretroviral therapy.

Strategies Related to Transmission and Its Prevention

- Evaluate sexual and blood-borne HIV transmission in relation to the following:

  - Viral factors such as viral quantity, diversity, coreceptor usage, genotype (including subtypes, recombinants, and resistance mutants), and dual virus infections in various body compartments (e.g., blood, saliva, semen, and mucosal compartments such as the female genital tract and the anorectal mucosa);

  - Host genetics and other host factors such as age, sex, race, country of origin, hormonal status, strength and breadth of immune response, comorbid chronic diseases, and coinfections;

  - Modifiable host factors such as diet and nutritional status; geographic location (urban, rural); drug, alcohol, and tobacco use and/or treatment, including substitution and other substance

use treatment modalities; mental health; circumcision status; and access to and use of health care;

- Other infections and their treatment, including *M. tuberculosis* (TB) and drug-resistant strains, multi-drug-resistant (MDR) and extensively drug-resistant (XDR) TB, *Plasmodium sp.* (malaria), sexually transmitted infections (STIs), and viral hepatitis;
- Psychological, social, cultural, geographic, and structural determinants of susceptibility to HIV acquisition among transient and migrating populations; sex workers; ethnic, sexual, and urban minorities; and other hard-to-reach populations; and
- Sexual activity, abstinence (including during the postoperative period after male circumcision), sexual networks, partner choice (e.g., serosorting), partner concurrency, partner fidelity, duration of partnership, control of STIs, hygienic practices such as douching, contraception choices, and cultural practices such as the use of traditional vaginal preparations and male circumcision.

- Further refine the timing, mechanisms, and risk factors in perinatal and postnatal transmission, including treatment of the mother, infant feeding modalities, physiology of lactation, long-term effects of perinatal interventions, maternal and infant genetic variation, and kinetics of viral resistance. These studies include:
  - Assessing the impact of maternal and infant ARV regimens of different potency and duration on mother-to-child transmission (MTCT) of HIV and on the short- and long-term health of women and their infants, and on the emergence of ARV drug resistance in the mother and in those infants who become infected despite prophylaxis;
  - Studying the safety and effectiveness of sustainable approaches to prevention of MTCT of HIV, including the provision of maternal ART, identifying successful breastfeeding weaning strategies, methods for improving the safety of formula feeding, and determining the effects of such approaches on infant morbidity and mortality;
  - Assessing the impact of maternal and infant adherence to ARV regimens on the risk of subsequent ARV resistance, clinical outcomes, and the effectiveness of ART in mothers and their children;
  - Assessing the impact of perinatal treatment and prophylaxis regimens on communitywide HIV resistance to ARVs;
  - Assessing the impact of MTCT programs on public health measures, including maternal, paternal, and infant morbidity/mortality rates; overall life expectancy; disability and/or quality-adjusted life years; and pediatric neurobehavioral development;
  - Assessing clinical outcomes, cost, and cost-effectiveness of different strategies for prevention of MTCT in the United States as well as in developing countries; and
  - Assessing the impact of not breastfeeding in high- and low-resource environments on the physical and mental health, as well as the quality of life (including stigma), of the mothers and children.

Strategies Related to Prevention and Treatment

- Conduct epidemiologic modeling studies on the aggregate impact of ART on HIV transmission, particularly in settings with endemic, high-prevalence, and emerging epidemics.
- Study the impact of widespread ART availability, adherence, and patterns of ART resistance on HIV prevalence, incidence, risk behaviors, and the transmission of resistant HIV strains.
- Conduct studies of male circumcision as a prevention tool, including:
  - Assessing the impact of adult male circumcision on an individual and community level, including assessment of HIV prevention and incidence in circumcised males and their partners, sexual behavior, and attitudes, in the domestic and international setting;

- Evaluating male circumcision delivery models with respect to safety, acceptability, cost-effectiveness, and long-term impact on HIV transmission;
- Evaluating male circumcision and its impact on HIV transmission and acquisition among men who have sex with men (MSM);
- Evaluating prevention approaches in the context of adult male circumcision, particularly those based on combinations of known methods, including reproductive health, partner reduction, condom use, and STI control; and
- Assessing the effect of male circumcision on transmission to uninfected female and male partners, considering the timing of male circumcision.

- Develop and evaluate the effectiveness of individual-, couple-, network-, and community-based interventions for HIV-infected persons and their partners to sustain behavioral change and prevent acquisition and transmission of HIV.
- Conduct studies on medication-assisted substance abuse treatment modalities and access to care (e.g., methadone maintenance, buprenorphine/naloxone, modafinil, naltrexone, antabuse, acamprosate, and stimulant abuse therapy), alone or in combination with mental health and/or behavioral interventions, as HIV prevention interventions.

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

Use epidemiological research in domestic and international settings to identify influences and interactions among therapeutics, biological factors (e.g., age, host genetics, coinfections, comorbidities, HIV subtypes, and viral genetic variation), and behaviors (e.g., using the health care system, adherence, sexual activity, and alcohol and drug use) in relation to HIV progression and response to therapy, as indicated by virologic, immunologic, and clinical outcomes.

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

STRATEGIES

Strategies Related to Disease Progression and Response to ART

- Develop new interval-based or standard-of-care cohorts and maintain long-term followup of existing cohorts, including observational cohorts and clinical cohorts, to determine the changing spectrum of HIV disease; identify highly exposed uninfected persons, long-term nonprogressors, and elite suppressors; and evaluate interventions, especially in aging and minority populations, in developing countries, and in emerging epidemic zones including Eastern Europe and Asia.
- Characterize short- and long-term consequences of recent HIV infections, including host and viral genetic characteristics and differences by route of exposure, and continue to characterize the natural history of HIV disease and AIDS among those early in infection, those with minimal exposure to ART, those with virologic and/or immunologic responses to ART, and those who have experienced ART failure.
- Investigate the effect on disease progression of viral factors, including viral type/subtype, fitness, viral tropism, and innate and acquired genotypic and phenotypic resistance to ARVs.
- Characterize global patterns of innate and acquired viral resistance to ART and how these patterns are influencing the long-term effectiveness of these therapies.
- Investigate the contribution of innate host characteristics to viral measures, immune function, disease progression, and mechanisms for these effects, including host genetic factors and their modulators, sex, race, and age.
- Examine how chronic inflammatory processes and mediators such as inflammatory cytokines modify immune function, disease outcomes and survival, and response to ART, and if they differ by age group.
- Characterize the changing spectrum of clinical outcomes, causes of morbidity and mortality, and complications of ARV therapy associated with evolving therapeutic strategies, domestically and internationally.
- Assess the effect of ART treatment on the incidence, pathogenesis, and presentation of cancer in the domestic and international settings.
- Define the prevalence, incidence, predictors, potential treatments of, and consequences of cardiovascular, renal, and liver disease in HIV-infected individuals.
- Characterize the long-term effect of HIV infection on the central nervous system, including the effect of viral burden in the cerebrospinal fluid (CSF), its effect on white matter degeneration, and the role of ART in reducing the neurocognitive burden of disease and differentiating these changes from other neurocognitive diseases, such as dementia and Alzheimer's disease.

- Evaluate and characterize immune reconstitution inflammatory syndrome (IRIS), including modifiable and nonmodifiable predictors of immune recovery in diverse populations as well as best treatment practices for IRIS.

- Define the prevalence, incidence, and determinants of HIV-associated neurologic, behavioral, and psychiatric manifestations and their relation to HIV disease progression and response to ART, domestically and internationally.

- Identify, characterize, and determine 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. These would include recurrent bacterial pneumonia; drug-resistant, MDR-TB, and XDR-TB/HIV cases; immune reconstitution syndromes affecting the lungs, including sarcoidosis and other immune-mediated diseases; HIV-related pulmonary hypertension; accelerated emphysema; lung cancer; and coinfections.

- Investigate hemostatic disturbances in individuals with HIV infection and the role of coagulation and fibrinolytic mechanisms in risk of vascular events and other complications.

Strategies Related to Complications of Therapy

- Determine the effects of cumulative and current ART exposure to specific drugs, classes of drugs, drug combinations, and treatment strategies, overall and by age group.

- Investigate factors that are linked to the early mortality documented soon after initiation of ART in patients in developing countries.

- Characterize and investigate the role of ART-associated toxicities (including disorders in glucose, lipid, and bone metabolism, renal dysfunction, hepatotoxicity, and carcinogenesis) in specific populations, including coinfected populations (e.g., TB, MDR/XDR-TB, hepatitis C [HCV], and hepatitis B [HBV]), pregnant women, children and adolescents, the aged, populations receiving traditional medicines, resource-limited populations, minority populations, and according to nutritional status, in comparison with appropriately matched non-HIV-infected populations.

- Investigate age and gender differences in ART-associated toxicities and comorbidities in comparison with appropriately matched non-HIV-infected populations. Gender differences should also explore differences in sex steroid levels and ovarian reserve in women and how they impact metabolic, cardiovascular, bone, renal, and liver disorders.

- Investigate the role of chronic inflammation in the development of malignancies and metabolic, cardiovascular, bone, renal, and liver disorders in HIV-infected individuals and appropriate controls and how cumulative and current ART use might mediate or mitigate the effects of chronic inflammation.

- Investigate complications associated with the simultaneous use of complementary and alternative medicine interventions and ART.

Strategies Related to Comorbidities

- Intensify research on the spectrum of HIV-associated malignancies, particularly those that may develop in HIV-infected patients who have responded to ART and are expected to live longer with immune deficiency.

- Intensify research on the effects of ART and immune reconstitution on chronic infection with viruses (particularly Kaposi's sarcoma herpesvirus [KSHV/HHV-8], HCV, HBV, human papillomavirus [HPV], and Merkel cell carcinoma polyomavirus) that are associated with malignancies in HIV-infected persons.

- Establish standards in different regions of the developing world affected by the HIV epidemic for lymphocyte subsets, activation markers, and hematologic and clinical chemistries, and determine the influence of endemic diseases (such as malaria, TB, hepatic viruses, and helminthic infections) on such standard values.

- Investigate TB-HIV interactions, including the effects of dual infection on the infectiousness and progression of both TB and HIV, and the effect of various treatment strategies on disease control and TB drug-resistant strains.
  - Investigate new approaches to successful diagnosis and linkage to care of both HIV and TB in high-prevalence settings.
  - Investigate the MDR/XDR-TB epidemic, evaluating risk factors for MDR/XDR-TB prevalence, incidence, therapeutic options, and clinical outcomes among HIV-infected patients.
  - Investigate the prevalence of disseminated (miliary) disease, including cerebral TB, its impact on everyday function, disease progression, and therapeutic options among HIV-infected patients.
  - Develop novel TB diagnostics for use with HIV-infected patients in order to rapidly identify MDR/XDR-TB in HIV/TB-coinfected populations.
  - Assess outcomes related to methods of integrating TB and HIV care on survival, quality of care, cost, and cost-effectiveness of care.
  - Investigate the impact of treating latent TB on the epidemiology of HIV/TB coinfection in endemic countries to determine whether it is feasible, effective, and cost-effective.
- Evaluate the impact of treatment of alcohol use and abuse, illicit drug use, and mental health disorders on the effectiveness and consequences of ART, HIV disease progression, development of comorbidities, and mortality.
- Support research efforts to link existing databases on cancer, TB, transplant, etc., and death registries to enhance understanding of HIV/AIDS outcomes in standard-of-care cohorts.
- Assess the interaction of HIV infection and ART on other infections and their treatments.
- Investigate the most appropriate triage of multiple comorbidities and the order in which comorbid conditions should be treated in HIV-infected patients.
- Study the emergence and reemergence of infectious diseases and the clinical and epidemiological characteristics of antimicrobial-resistant infections in HIV-infected populations (e.g., MDR-TB, sulfa-resistant malaria, antibiotic-resistant pneumococcal pneumonia, cotrimoxazole-resistant *Pneumocystis jiroveci* pneumonia, methicillin-resistant *Staphylococcus aureus* [MRSA] infections, and lamivudine-resistant HBV infections).
- Estimate the prevalence of specific HPV types associated with cervical cancer and high-grade dysplasia in HIV-infected women, and evaluate the effectiveness of HPV vaccines among HIV-infected individuals from geographically diverse regions.
- Assess the interaction of ARVs on HPV persistence and regression of cervical lesions to understand the dynamics of the two viruses with a goal of optimizing care for HIV-infected women, especially in resource-limited settings.
- Assess the effect of primary care screening and interventions (e.g., statin use, hypertension management, smoking cessation, depression treatment, and cancer screening and treatment) on HIV disease outcomes and survival. Use these assessments to guide recommendations for adaption and prioritization of primary care guidelines for those with HIV infection.

Strategies Related to MTCT and Pediatric HIV Infection

- Assess the implications and outcomes, including uptake, of different strategies of prevention of MTCT on transmission and costs of care in HIV-infected mothers and their infants.
- Evaluate the differences in adherence, treatment response, 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 complications due to HIV and ART use in HIV-infected pediatric populations as these children reach adolescence and adulthood.

- Study the effect of the health status of HIV-infected mothers and of ART during pregnancy, lactation, and early child life on survival and quality of life of their HIV-infected and -uninfected children and on maternal 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, and how these may be affected by biomedical and behavioral interventions.

Strategies Related to Aging

- Investigate the relationship between HIV infection and the spectrum of physical and mental health outcomes that increase with aging (e.g., cancer, renal disease, cardio- and cerebrovascular disease, diabetes, hypertension, arthritis, anemia, and dyslipidemia), as they affect disease outcomes and survival.

- Study the incidence and determinants of physical and cognitive decline in aging HIV-infected individuals and the effect of frailty and functional impairment on HIV, ARV use, and self-care behaviors.

- Study the effects, such as immunologic and virologic response to treatment, and adverse effects of HIV and ART in aging populations that have coexisting morbidities and who receive numerous medications.

- Evaluate immunologic and virologic measures of HIV disease progression, ART-related toxicities, and mortality in older versus younger adults receiving ART to refine treatment guidelines for older HIV-infected patients.

- Develop guidelines for treating comorbid and chronic conditions in aging HIV-infected patients.

Strategies Related to Adherence, Access to Care, and Quality of Life

- Develop and evaluate novel methods, such as behavioral reports and biological markers of use, for accurately measuring adherence to therapy and efficacy of preventive therapies.

- Study determinants of adherence to ART and adverse events of ART in all age and risk groups, as well as in times of transition such as pregnancy and growth from child to adolescent to adult, to inform interventions to improve adherence.

- Study the impact of access to care, ART, microbicides, and vaccines on risk behaviors and HIV acquisition among at-risk populations, including minorities, MSM, adolescents, and young adults.

- Investigate how different patterns of access, adherence, and exposure to ART in treatment-experienced and -inexperienced populations contribute to ARV resistance and disease progression.

- Elucidate the effects of HIV infection on pain and sleep disturbances, including prevalence, possible immunological and endocrine mechanisms, associations with HIV outcomes, possible changes with ART, and influence on quality of life and physical and mental health.

- Develop studies on the impact of routine, voluntary HIV testing, point-of-care rapid testing, home-based testing, and Internet-based test notification, and their roles in different prevalence settings in increasing access to care and improving HIV-related outcomes.

- Examine predictors of successful retention of HIV-infected patients in care, from the time of HIV testing through the time of ART provision and patient followup.

OBJECTIVE–C: Methodologies

Develop and evaluate methods and resources for HIV/AIDS epidemiological and clinical studies that use culturally appropriate approaches; incorporate new laboratory, sampling, and statistical methods with information systems; and better integrate research findings into clinical practice and regional, national, and international policy.

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

STRATEGIES

- Evaluate and promote the use of multiple study designs that incorporate appropriate ethical, cultural, and policy context for studies of HIV disease and AIDS in diverse domestic and international populations.
- Continue to support local, regional, and international collaborations to integrate and harmonize existing data for scientific investigations.
- Capture data from large U.S. and international HIV screening programs, such as blood donor screening programs, to monitor incidence and temporal trends, viral genotypes, drug resistance, and neutralization profiles.
- Ensure that the population composition of domestic epidemiological studies accurately represents populations at risk for and affected by HIV/AIDS, such as older Americans, adolescents and young adults, MSM, racial and ethnic populations, and persons affected by other comorbidities.
- Encourage more HIV prevention research studies in marginalized and vulnerable populations in the United States (e.g., immigrants, migrant workers).
- Involve representatives of the community and study participants in all phases of research planning, design, management, approval, and reporting, when possible and appropriate, and promote and support academic/community-based research collaborations.
- Implement research training and career development opportunities for medical and health professionals from communities disproportionately affected by the epidemic, both in developing countries and domestically. Training should include research ethics, study design, informatics, biostatistics and modeling, data management and analysis, manuscript preparation and publication, grant writing, and translational research to promptly bring basic science results to clinical care and clinical results to health policy and implementation.
- Promote study designs that provide the highest degree of human subject protection and benefit possible, according to U.S. Government requirements.
- Promote study designs that include plans for dissemination of findings to community representatives, study participants, health care practitioners, payors, and policymakers.

Strategies Related to Natural History/Pathogenesis

- Develop epidemiologic, laboratory-based, and simulation modeling methods in conjunction with prospective cohort studies, domestically and internationally, to monitor response to ART and the incidence of complications related to chronic use of ART, including:
  - Develop and test methods to produce accurate, reproducible, and inexpensive virologic, immunologic, bacteriologic, pharmacologic, neurobehavioral, and genetic assays suitable for large-scale epidemiological research and surveillance in developing nations. Emphasis should be on simple and reliable staging of disease progression for the initiation and monitoring of ART and opportunistic infection (OI) prophylaxis; hepatitis testing; HIV resistance testing; and

noninvasive, rapid, and inexpensive diagnostic assays for sexually transmitted diseases (STDs), other coinfections including malaria, TB and XDR-TB, and malignancies.

- Develop, maintain, and effectively cultivate ongoing and newly developed cohort studies, domestic or international specimen repositories, and databases for interdisciplinary HIV-related studies. Collaborative studies between cohorts and nested studies that utilize these resources should be particularly encouraged.
- Identify and/or develop uniform assessment tools to measure host and environmental characteristics, including 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.
- Develop assays to identify recent HIV infection, especially methods appropriate for international populations and measures integrated into point-of-care testing.
- Develop assays to distinguish between serological changes induced by HIV vaccine candidates and those induced by HIV infection in countries where NAT (nucleic acid test) testing is not readily available.

Strategies Related to Research on Design and Analysis of Epidemiologic Data

- Develop new epidemiological designs and statistical methods, including development of informatics tools and simulation, to better characterize 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 large observational, cross-sectional, and cohort studies, such as:
  - Assessing 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 incidence rates in cross-sectional samples;
  - Methods for sampling hidden populations (e.g., venue-based, Internet-based, snowball, mixed method, respondent-driven, and time-location 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 simultaneously addressing more than one hypothesis or intervention, including the use of factorial randomized trials and quasi-experimental designs; and
  - Methods for collecting and analyzing spatio-temporal data, especially as they relate to transmission and spread of HIV infection.
- Encourage research on innovative design and analysis through interdisciplinary collaboration between methodologists from different fields, such as biostatistics, econometrics, epidemiology, computer science, biomathematics, decision sciences, operations research, health services research, and demography.
- Promote collaborative studies using genetic epidemiology methods (e.g., genome-wide association studies [GWAS]) applied to large, diverse populations to elucidate mechanisms of HIV infection, disease progression, and complications.

Strategies Related to Interventions

- Study and evaluate the various operational strategies that can be employed to "bring to scale" and to evaluate countrywide ART programs and successful preventive or therapeutic interventions, such as male circumcision, including the use of

operations research and integrated observational databases to evaluate treatment effectiveness and cost-effectiveness at the individual, community, and population levels.

- Study and evaluate prevention packages that combine multiple strategies into one intervention, especially those that combine behavioral, biological, and structural interventions.
- Develop studies to compare the effectiveness and efficacy of various HIV prevention strategies (e.g., opt-out testing, secondary prevention) between populations with generalized versus concentrated epidemics.
- Determine the outcome of different approaches to routine, voluntary, and rapid HIV testing in different settings, and among different racial/ethnic populations.
- Assess the optimal algorithms for HIV diagnosis in patients, including strategies for identification of acute infection.
- Assess the effectiveness and outcomes of clinical and/or laboratory monitoring for the initiation, monitoring, and switching of ART, particularly in resource-limited settings, including laboratory monitoring with new methods that are technologically appropriate and affordable in various international settings.
- Develop appropriate clinical and laboratory definitions of short- and longer-term ARV failure, and develop mechanisms for monitoring and assessing drug resistance evolution in HIV types, subtypes, and variants in domestic as well as international settings.
- Develop, evaluate, and promote new, improved, and cost-effective methods and strategies to prevent HIV transmission via blood transfusion, as well as other medical interventions and iatrogenic exposures in developing countries, including instrument sterilization.
- 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, seniors, racial and ethnic populations, and populations in diverse international settings.
- Develop strategies to validate the use of surrogate markers for HIV acquisition and/or transmission risk, including use of behavioral measures and biomedical markers.
- Develop and refine simulation and modeling strategies to assess the costs and impacts of a variety of interventions on HIV transmission, cofactors of HIV infection, and communitywide morbidity and mortality.

Strategies Related to Policy

- Design and implement evaluations of large-scale HIV testing and treatment programs, with attention to clinical outcomes, HIV incidence rates, long-term dynamics of the HIV epidemic, and comparative costs for the programs relative to present-day strategies.
- Evaluate the long-term clinical and nonclinical impact, cost, and health care utilization ramifications of different strategies for care, including treatment of HIV-associated conditions, ART, complications of ART, and other comorbidities.
- Assess the impact and acceptability of routine, voluntary HIV testing programs and new models for point-of-care testing and results notification, including issues such as stigma and confidentiality.
- Support HIV policy research, including studies of laws and economics, necessary for translating epidemiological and clinical studies into policy to improve health and to make cost-effective clinical and policy decisions.
- Assess the impact of strategies for managing HIV coinfections in international settings using modeling and other integrative methodologies.

AREA OF EMPHASIS

Information Dissemination

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A: Disseminate Information to All Constituencies

Support the effective dissemination, communication, and utilization of HIV and AIDS information to all constituent communities of the NIH, domestically and internationally.

STRATEGIES

- Rapidly disseminate new research findings, including information on the potential implications for prevention, care, and treatment of HIV-infected individuals, 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, and the public.
- Facilitate the development 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 current 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.
- Widely disseminate experimental findings regarding AIDS-related studies using nonhuman primates (NHPs) as well as the availability of animals for AIDS-related studies.
- Collect, archive, and promote use of existing data from NIH-supported basic and applied research for secondary data analysis, including rapid development of public use data sets that can be used for secondary data analysis in NIH-supported studies, especially baseline survey and HIV/STD (sexually transmitted disease) incidence data.
- 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 clinical trials.
- 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), nongovernment 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 reduce stigma.

- Support dissemination of information, including to constituent communities, 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 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 such methods 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 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 online access to presentation materials, including full text of abstracts and other information (e.g., slides, graphics, plenary presentations) from scientific meetings.

OBJECTIVE–B: Develop New Communications 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

- Assess the 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 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.

OBJECTIVE–C: Coordination and Collaboration Efforts

Develop, implement, and evaluate methods of coordination and collaboration on HIV/AIDS communications activities among NIH Institutes and Centers (ICs) and with other Federal and non-Federal groups, and 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*.
- Expand the development of HIV/AIDS resources on the Internet to facilitate national and international research collaboration and data sharing.
- 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, and other international AIDS agencies or societies on information/communications efforts, including information about international clinical trials.
- 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.

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APPENDIX A

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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
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	John E. Fogarty International Center
NCCAM	National Center for Complementary and Alternative Medicine
NCMHD	National Center on Minority Health and Health Disparities
NCRR	National Center for Research Resources
CC	NIH Clinical Center

APPENDIX B

List of Acronyms

AIDS	acquired immunodeficiency syndrome
ANC	antenatal care
ART	antiretroviral therapy
ARV	antiretroviral
CAB	community advisory board
CBO	community-based organization
CDC	Centers for Disease Control and Prevention
CER	comparative effectiveness research
CFARs	Centers for AIDS Research
cGMP	clinical grade Good Manufacturing Practice
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
CTX	cotrimoxazole
DC	dendritic cell
DoD	U.S. Department of Defense
DHHS	U.S. Department of Health and Human Services
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFATM	Global Fund to Fight AIDS, Tuberculosis, and Malaria
GI	gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GWAS	genome-wide association studies
Gyn	gynecologic
HAART	highly active antiretroviral therapy

HAD	HIV-associated dementia
HBV	hepatitis B virus
HCV	hepatitis C virus
HHV	human herpesvirus
HHV-4/EBV	Epstein-Barr virus
HHV-8/KSHV	herpesvirus type 8
HIV	human immunodeficiency virus
HPV	human papillomavirus
HRSA	Health Resources and Services Administration
HSV-2	herpes simplex virus type 2
IBC	institutional biosafety committee
ICs	Institutes and Centers
IDU	injection drug user
IRB	institutional review board
IRIS	immune reconstitution inflammatory syndrome
KS	Kaposi's sarcoma
KSHV/HHV-8	Kaposi's sarcoma herpesvirus
LGBTQ	lesbian, gay, bisexual, transgender, and queer
MCMD	minor cognitive and motor disorders
MDR-TB	multi-drug-resistant TB
MHC	major histocompatibility complex
MRSA	methicillin-resistant *Staphylococcus aureus*
MSM	men who have sex with men
MTCT	mother-to-child transmission
NAT	nucleic acid test
NGO	nongovernmental organization
NHP	nonhuman primate
NIH	National Institutes of Health
NPRC	National Primate Research Center
OAR	Office of AIDS Research, NIH
OARAC	Office of AIDS Research Advisory Council
OGAC	Office of the U.S. Global AIDS Coordinator

OI	opportunistic infection
pK	pharmacokinetics
pD	pharmacodynamics
PDA	personal data assistant
PEP	postexposure prophylaxis
PEPFAR	U.S. President's Emergency Plan for AIDS Relief
PrEP	preexposure oral chemoprophylaxis
PI	principal investigator
RCTs	randomized clinical trials
SHIV	chimeric simian/human immunodeficiency virus
SIV	simian immunodeficiency virus
SPF	specific pathogen-free
STD	sexually transmitted disease
STI	sexually transmitted infection
TB	tuberculosis
TOC	test of concept
UNAIDS	Joint United Nations Programme on HIV/AIDS
USAID	U.S. Agency for International Development
USMHRP	U.S. Military HIV Research Program
VCT	voluntary counseling and testing
WHO	World Health Organization
XDR-TB	extensively drug-resistant TB

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