

FY 2012

National Institutes of Health  
TRANS-NIH AIDS  
RESEARCH BY-PASS  
BUDGET ESTIMATE  
and  
TRANS-NIH PLAN FOR  
HIV-RELATED RESEARCH



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Dr. Michael Gottlieb, Dame Elizabeth Taylor, and Dr. Jack Whitescarver in the NIH Clinical Center on the occasion of her visit to the NIH AIDS research program in 1988.

Dedicated to the memory and legacy of

**DAME ELIZABETH TAYLOR**

A true AIDS pioneer

She used her formidable fame,  
influence, and compassion to make  
the world better for all of us whose lives  
have been touched by AIDS.

# FY 2012 Trans-NIH AIDS Research By-Pass Budget Estimate

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# FY 2012 Trans-NIH AIDS Research By-Pass Budget Estimate

## Legislative Mandate

### **AUTHORIZING LEGISLATION**

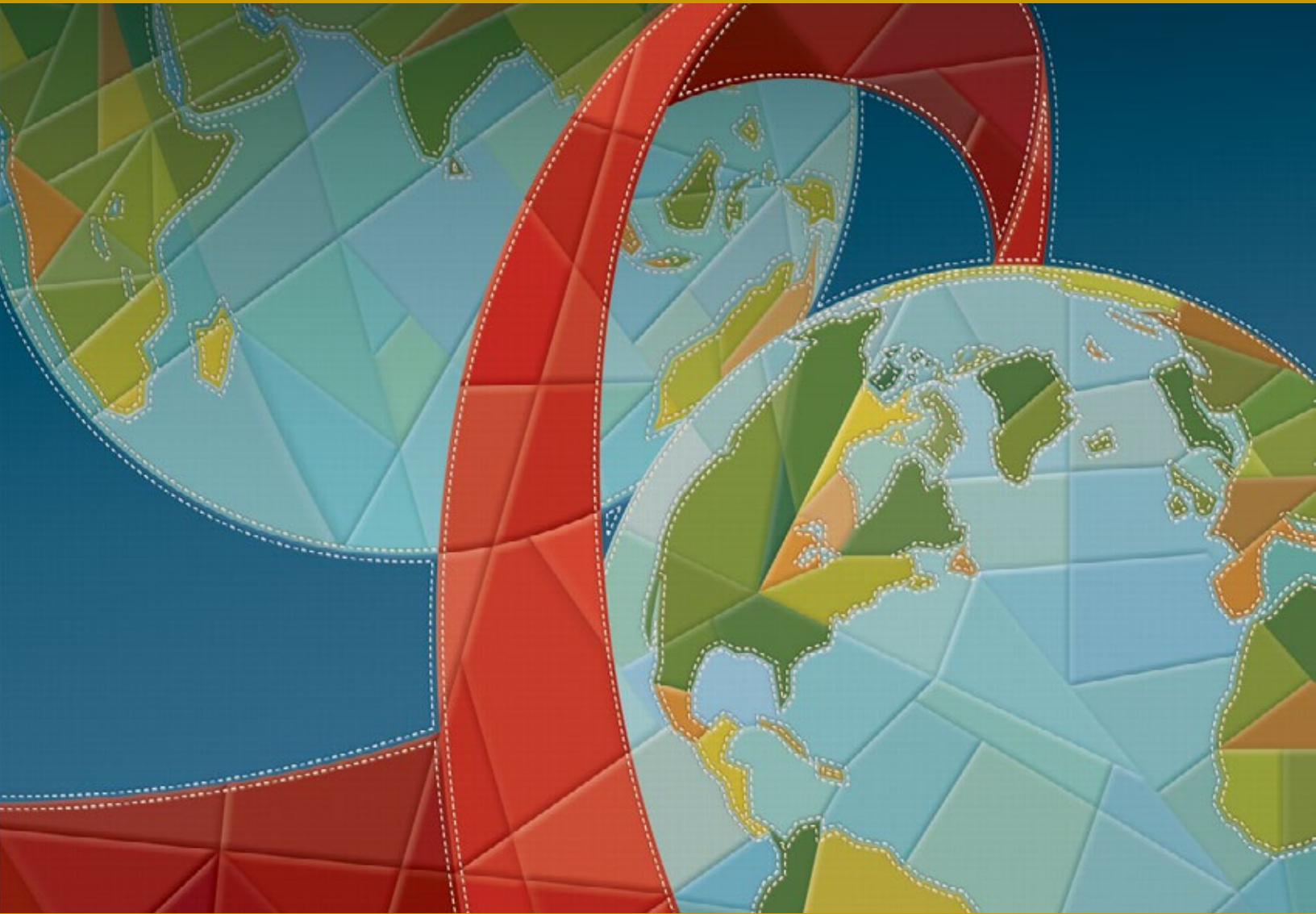
Section 2353 of the Public Health Service Act requires that “the Director of the Office of AIDS Research establish a comprehensive plan for the conduct and support of all AIDS activities of the agencies of the National Institutes of Health.” It also requires that the Director “shall prepare and submit 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

In accordance with the law, the National Institutes of Health (NIH) Office of AIDS Research (OAR) has developed this *Fiscal Year (FY) 2012 Trans-NIH AIDS Research By-Pass (Professional Judgment) Budget Estimate* to carry out the scientific priorities established in the *FY 2012 Trans-NIH Plan for HIV-Related 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.

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
- Restores 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
- Addresses the key themes of the NIH Director.

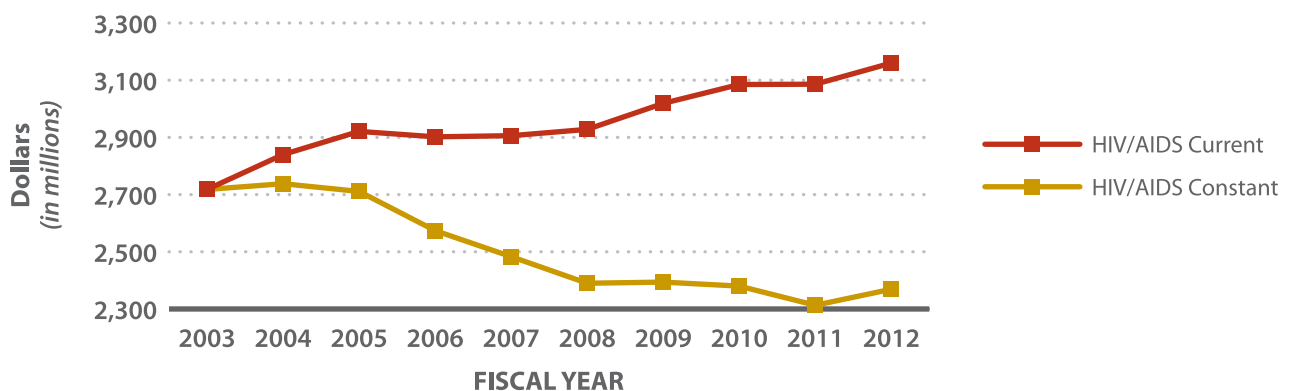
This by-pass budget request establishes the critical priorities for trans-NIH AIDS research. These include:

- Prevention research, including biomedical and behavioral research focused on the domestic AIDS epidemic, particularly in racial and ethnic populations of the United States

- Research to build on important advances in prevention research gained in the past year in the areas of microbicides, vaccines, and treatment as prevention
- Research to prevent and treat HIV-associated comorbidities, malignancies, and clinical complications
- Research to address the issues around AIDS and aging
- Research to better understand the issues of adolescents and AIDS
- Basic and therapeutic research focused on elimination of viral reservoirs, leading to a cure
- Genetic studies to delineate the genetic basis for immune responses to HIV and to sequence HIV-associated tumors
- Research on the feasibility, effectiveness, and sustainability required for the scale-up and implementation of interventions in communities at risk.

The FY 2012 by-pass budget request for NIH AIDS research is \$3.546 billion, which represents a 15 percent increase over the FY 2011 estimate. At the time of this writing, the final FY 2011 appropriation had not been determined, and the estimate represents the level of the Continuing Resolution.

### Impact of Inflation on NIH HIV/AIDS Research Dollars (Current and Constant)



This level includes the total trans-NIH support for intramural and extramural research; research management support; research centers; training; and basic, clinical, behavioral, social science, and translational research on HIV/AIDS and the wide spectrum of AIDS-associated malignancies, opportunistic infections, coinfections, and clinical complications.

This increase represents an investment—a down payment—that must be maintained and enhanced to take advantage of critical emerging scientific advances, and to restore lost opportunity. This amount also is essential to address the impact of the erosion of buying power on critical research programs. The total AIDS research budget at the FY 2011 estimate level was approximately equivalent in constant dollars to the FY 2001 appropriation. Further, there was a 25 percent loss in buying power for NIH AIDS research between FY 2003 and FY 2011.





# HIV/AIDS Pandemic

Nearly 30 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 worldwide. UNAIDS reports that in 2009, more than 33 million people were estimated to be living with HIV/AIDS, 2.6 million were newly infected, and 1.8 million people died of AIDS-related illnesses.<sup>1</sup>

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<sup>1</sup> UNAIDS. *Report on the Global AIDS Epidemic 2010*. Available at [http://www.unaids.org/globalreport/Global\\_report.htm](http://www.unaids.org/globalreport/Global_report.htm).



In the United States, more than 1.1 million people are estimated to be HIV-infected, and someone is infected with HIV every 9 ½ minutes. 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). The Centers for Disease Control and Prevention (CDC) estimates 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 617,000 cumulative AIDS deaths.<sup>2</sup>

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

2 Centers for Disease Control and Prevention. *HIV Surveillance Report: Diagnoses of HIV Infection and AIDS in the United States and Dependent Areas, 2009*. Available at <http://www.cdc.gov/hiv/surveillance/resources/reports/2009report/>.

## GLOBAL EPIDEMIC

*More than 7,000 new HIV infections a day in 2009:*

About 97 percent are in low- and middle-income countries

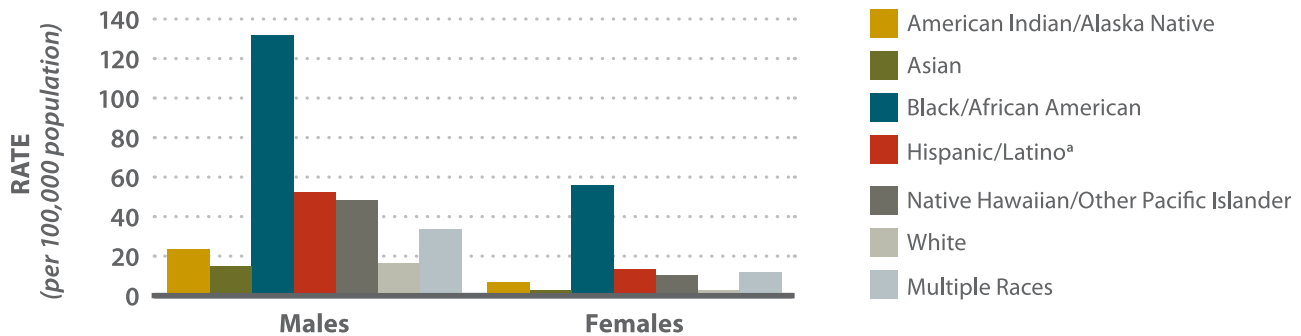
About 1,000 are in children under 15 years of age

About 6,000 are in adults aged 15 years and older, of whom:

- ▶ almost 51 percent are among women
- ▶ about 41 percent are among young people (aged 15–24)

SOURCE: UNAIDS. *Core Slides: Report on the Global AIDS Epidemic 2010*. Available at [http://www.unaids.org/global-report/Epi\\_slides.htm](http://www.unaids.org/global-report/Epi_slides.htm).

### Rates of Diagnoses of HIV Infection Among Adults and Adolescents, by Sex and Race/Ethnicity, 2008—37 States

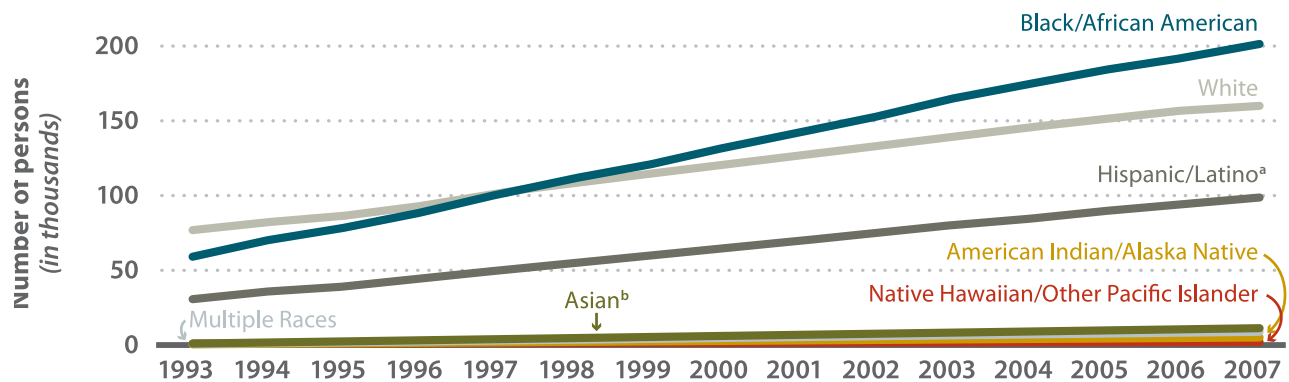


NOTES. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. Data from 37 states with confidential name-based HIV infection reporting since at least January 2005. All displayed data have been estimated. Estimated numbers resulted from statistical adjustment that accounted for reporting delays, but not for incomplete reporting.

<sup>a</sup> Hispanics/Latinos can be of any race.

SOURCE: Centers for Disease Control and Prevention. *HIV Surveillance Report, 2008*; vol. 20. Published June 2010.

## Persons Living with an AIDS Diagnosis, by Race/Ethnicity, 1993–2007—United States and Dependent Areas



NOTES. All displayed data have been estimated. Estimated numbers resulted from statistical adjustment that accounted for reporting delays, but not for incomplete reporting.

<sup>a</sup> Hispanics/Latinos can be of any race.

<sup>b</sup> Includes Asian/Pacific Islander legacy cases.

SOURCE: Centers for Disease Control and Prevention. *HIV Surveillance Report, 2008*; vol. 20. Published June 2010.

12.6 percent of the total U.S. population.<sup>3</sup> Moreover, the overall prevalence of HIV/AIDS was more than 7 times higher for blacks than for whites.

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, multi-drug 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, the number of persons aged 50 years and older living with HIV/AIDS has been increasing. In 2005, an estimated 29 percent of HIV-infected adults in the United States were at least 50 years old, and individuals aged 50 and older accounted for approximately 15 percent of all new HIV/AIDS diagnoses.<sup>4</sup> As a consequence of these trends, it has been estimated that by 2015, 50 percent of HIV-infected individuals in the United States may be 50 or older.

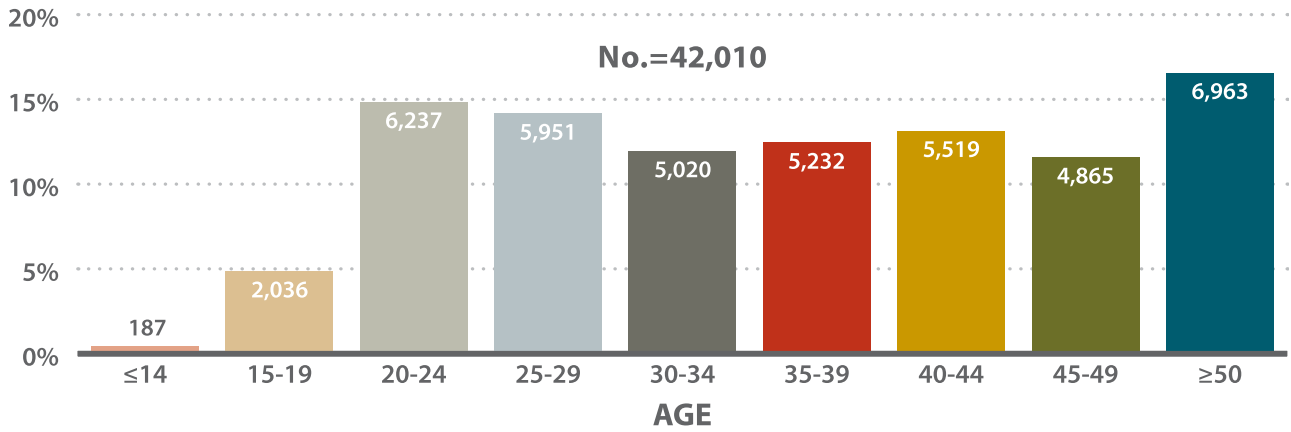
3 U.S. Census Bureau. 2010 Census. Available at <http://2010.census.gov/2010census/data>.

4 Centers for Disease Control and Prevention. HIV/AIDS Statistics and Surveillance. *HIV/AIDS among Persons Aged 50 and Older*. Available at <http://www.cdc.gov/hiv/topics/over50/resources/factsheets/over50.htm>.

Older adults with long-term or new HIV infection experience complex interactions with HIV, antiretroviral therapy, age-related changes to the body, and, often, treatment for illnesses associated with aging. The research agenda addresses the medical implications of aging with HIV and continues 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 chronic diseases.

The maturing U.S. epidemic has the potential to generate concentric mini-epidemics of liver disease, tuberculosis (TB), cardiovascular disease, and other HIV-associated comorbidities, 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.

## Estimated Number of Diagnoses of HIV Infection,\* By Age—2009



\* in the 40 states with confidential name-based HIV infection reporting.

SOURCE: Centers for Disease Control and Prevention. *HIV Surveillance Report: Diagnoses of HIV Infection and AIDS in the United States and Dependent Areas, 2009*. Available at <http://www.cdc.gov/hiv/topics/surveillance/basic.htm>.



# 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 of the NIH Institutes and Centers (ICs) in accordance with their mission, in both intramural and extramural programs.

NIH-funded research has led to:

- Critical discovery of antiretroviral therapies and regimens that have resulted in improved life expectancy for those with access to and who can tolerate these drugs
- Development of treatments for many HIV-associated coinfections, comorbidities, malignancies, neurologic complications, TB, and other clinical manifestations
- Advances in HIV prevention, including groundbreaking strategies for the prevention of mother-to-child transmission, safety of the blood supply, and effectiveness of medically supervised circumcision of adult men in reducing the risk of heterosexual HIV acquisition
- Critical basic science discoveries that continue to provide the foundation for novel research. Research on basic HIV biology and AIDS pathogenesis also has revolutionized the design of drugs, methodologies for diagnosis, and monitoring of the safety and effectiveness of antiviral therapies.

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

## 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

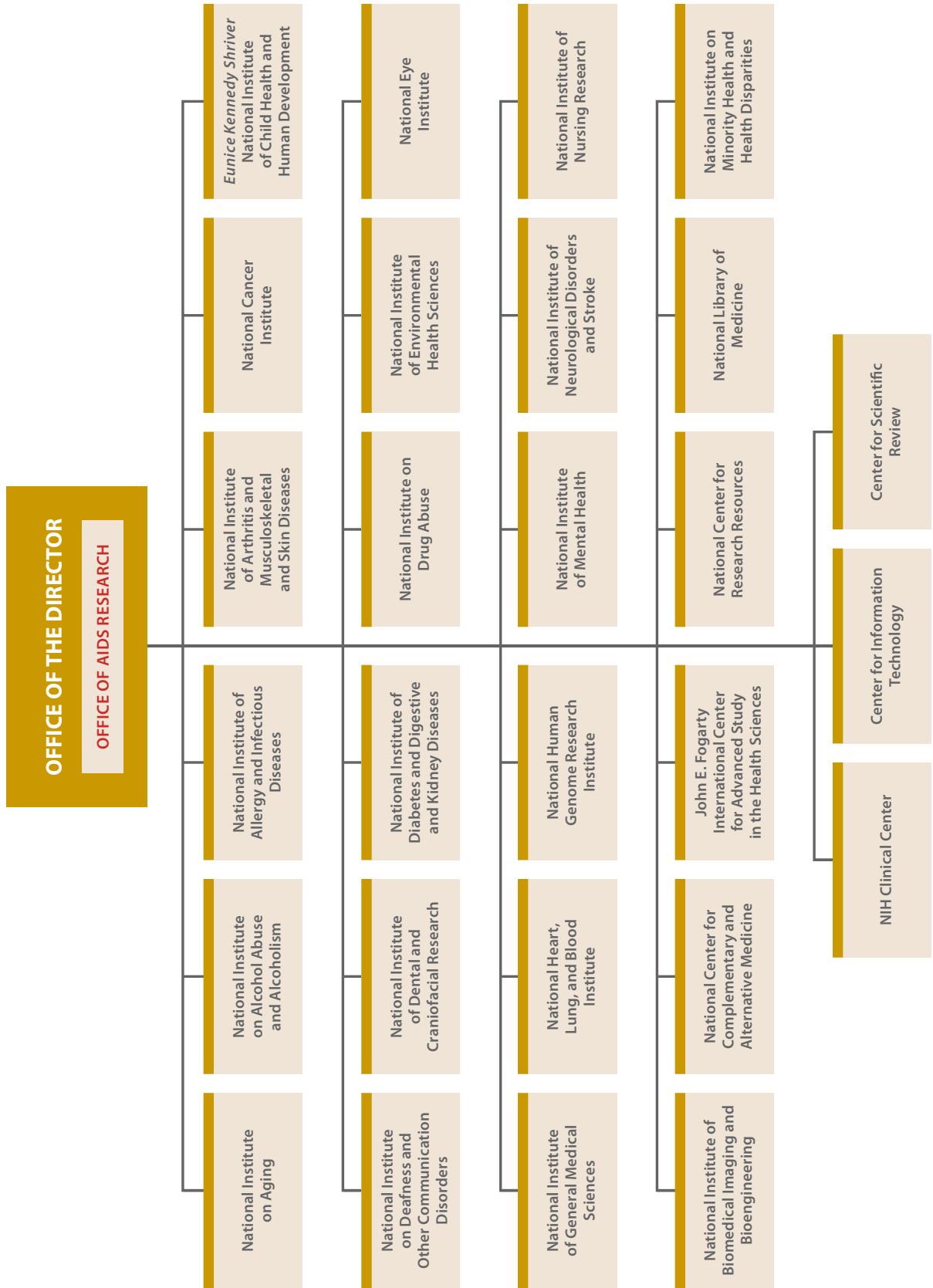
Comprises a comprehensive program of basic, clinical, translational, and behavioral research on HIV infection, its associated coinfections, opportunistic infections, malignancies, and other complications

Includes research or training projects in more than 100 countries

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

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.

# NATIONAL INSTITUTES OF HEALTH



# NIH Office of AIDS Research

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

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.

## 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

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

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

# Trans-NIH Strategic Plan

Each year, OAR develops the *Trans-NIH Plan for HIV-Related Research* (<http://www.oar.nih.gov/strategicplan/>). 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: Racial and Ethnic Populations; Women and Girls; and Research in International Settings.

OAR requires ICs to report all AIDS-related expenditures, including extramural, intramural, and research management and support, on a quarterly basis, to the OAR trans-NIH AIDS Research Information System 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 Conditions and Diseases 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 Planning Process Participants

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

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

# OAR Budget Development Process

OAR is mandated to develop the annual trans-NIH AIDS research 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 IC’s allocation. The ICs submit their AIDS-related research budget requests to OAR, presenting proposed new, expanded, or recompeting program initiatives, coded to specific Plan objective(s). OAR reviews the IC initiatives in relation to the Plan, to its priorities, and to other IC submissions to eliminate redundancy and/or to ensure cross-Institute collaboration. The unique budget authorities allow OAR to build each IC budget from the commitment base, rather than from the previous year’s appropriation.

## OAR BUDGET DEVELOPMENT PROCESS

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

The careful determination of the balance of the research budget—among Institutes, across areas of science, between intramural and extramural research programs, between basic and clinical research, and between investigator-initiated and targeted research—requires a comprehensive knowledge of the science and of the ICs’ portfolios. Dollars are allocated to the ICs based on the priorities of the Plan, scientific opportunities, and the ICs’ capacity to absorb and expend resources for the most meritorious science, and not according to a formula. This process reduces redundancy, promotes harmonization, and ensures 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 authority also requires the development of this by-pass budget, based solely on scientific opportunity.

# National and International Impact and Need

The role of the 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.

## **GLOBAL IMPACT OF NIH AIDS RESEARCH:**

In addition to addressing the U.S. epidemic, NIH research to address the global pandemic is essential. Since the early days of the epidemic, the NIH has supported research efforts in countries affected by AIDS. Beginning in 1983 with a research project in Haiti, the NIH has maintained a strong international AIDS research portfolio that now includes projects in approximately 100 countries around the world. AIDS research represents the largest component of the total NIH global research investment. NIH AIDS research studies are designed so that the results are relevant for both the host nation and the United States. Implementation studies are critical to translating clinical trial research results into community-based interventions that can be operational in international settings. The development of research infrastructure, including training of scientists and health care providers, is an essential component of these research programs. Most of these grants and contracts are awarded to U.S.-based investigators to conduct research in collaboration with in-country scientists; some are awarded directly to investigators in international scientific or medical institutions.

## **THE 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



## New Scientific Advances and Opportunities

The past year has been a significant one for AIDS research. The NIH investment in the priority areas of HIV prevention research and in basic science over the past several years has reaped rewards resulting in important progress in critical areas of the NIH AIDS research program. Recent research advances by NIH intramural and extramural investigators have opened doors for new and exciting research opportunities in the search for strategies to prevent, treat, and ultimately cure HIV infection.



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All of these important advances, while preliminary and incremental, provide the groundwork for further scientific investigation and the building blocks for the development of this by-pass budget request.

#### **ANTIBODY DISCOVERIES PROPEL HIV VACCINE**

**RESEARCH:** A team of scientists led by researchers at the National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Center discovered two potent human antibodies that can stop more than 90 percent of known global HIV strains from infecting human cells in the laboratory and determined the structural analysis of how they work. The novel techniques used in this research may accelerate HIV vaccine research, as well as the development of vaccines for other infectious diseases.

**PROOF-OF-CONCEPT OF MICROBICIDES:** For the first time in nearly 15 years of research, scientists discovered a vaginal microbicide gel that gives women a level of protection against HIV infection. Conducted by the Centre for the AIDS Programme of Research in South Africa (CAPRISA), and sponsored by USAID, the CAPRISA 004 study showed that the use of a microbicide gel containing a 1 percent concentration of the antiretroviral drug tenofovir resulted in 39 percent fewer HIV infections compared with a placebo gel. The NIH provided substantial support and resources to establish the infrastructure and training for CAPRISA. Ongoing and future clinical trials will build on these study results with the goal of bringing a safe and effective microbicide to the general public.



#### **Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women\***

*QA Karim, SS Karim et al.*

- Double-blind, randomized controlled trial ( $n=889$ ) in sexually active, HIV-uninfected 18- to 40-year-old women in South Africa
- 1% tenofovir vaginal gel reduced HIV incidence by 54% with high adherence (>80 percent)
- No serious adverse events

\* From *Science* Vol. 329, No. 5996, 3 September 2010. Reprinted with permission from AAAS. Published online 19 July 2010. <http://www.sciencemag.org/content/329/5996/1168.abstract>. [DOI:10.1126/science.1193748].

#### **EFFECTIVENESS OF PRE-EXPOSURE PROPHYLAXIS (PrEP):**

A large international NIH clinical trial provided strong evidence that the use of pre-exposure prophylaxis—that is, the use of antiretroviral treatment before exposure to prevent infection—can reduce risk of HIV acquisition in MSM. Additional and continued research is needed to determine whether PrEP will be similarly effective at preventing HIV infection in other at-risk populations.

**RESEARCH TOWARD A CURE:** Progress in both basic science and treatment research aimed at eliminating viral reservoirs has resulted in the establishment of an international alliance to plan and conduct research that could lead to a cure.

**ADVANCES IN HIV GENETICS:** NIH-sponsored researchers made an important discovery related to the genetics of an individual's immune system. These genes appear to be involved in the control of disease progression among a group of individuals considered “elite controllers,” who have been exposed to HIV over an extended period, but whose immune systems have controlled the infection without therapy and without symptoms.



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**FURTHER ADVANCES IN PREVENTION OF MOTHER-TO-CHILD TRANSMISSION:** Two recent studies have demonstrated the effectiveness of new multi-drug antiretroviral regimens for the prevention of mother-to-child-transmission of HIV during pregnancy and breastfeeding.

**Preliminary Results of RV144 Announced**

**“For First Time,  
AIDS Vaccine Shows  
Some Success”**

*The New York Times*, September 24, 2009\*

\* Available at <http://www.nytimes.com/2009/09/25/health/research/25aids.html>.

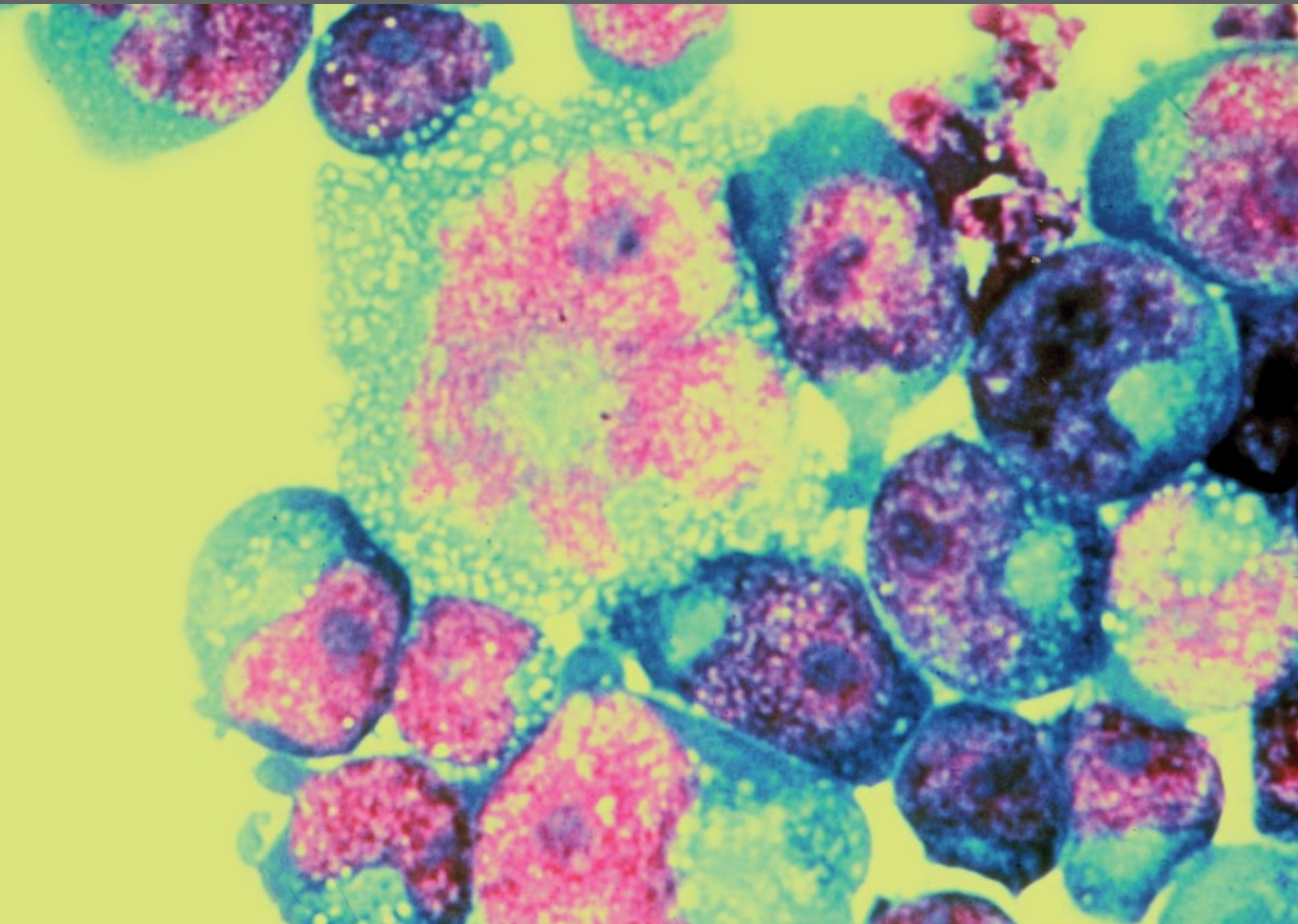
**HIV VACCINE PROOF-OF-CONCEPT:** An HIV vaccine clinical trial conducted in Thailand by the NIH and the Department of Defense demonstrated the first indication of a modest but positive effect in preventing HIV infection. The trial marked the first step in proving the concept that a vaccine to prevent HIV infection is feasible.

**NEW HOPE FOR PEOPLE COINFECTED WITH HIV AND TB:** A Cambodia-based study co-funded by NIAID and the French National Agency for Research on AIDS and Viral Hepatitis demonstrated that the survival of untreated, HIV-infected adults with very weak immune systems and newly diagnosed TB can be prolonged by starting antiretroviral therapy 2 weeks after beginning TB treatment, rather than waiting 8 weeks, as had been standard.

**IMPROVED THERAPY FOR AIDS-RELATED LYMPHOMA:** The development of new lymphoma regimens and the tailoring of these regimens to specific tumor types have markedly improved the therapeutic outcome and survival of patients with AIDS-related lymphoma. In a recent study, 95 percent of patients with germinal center B-cell lymphoma were progression-free at 5 years.

**PREVENTION OF CANCER IN HIV-INFECTED INDIVIDUALS:** The human papillomavirus (HPV) vaccine, which was developed in the National Cancer Institute and licensed to Merck & Co. and to GlaxoSmithKline, has been shown to prevent anal intraepithelial neoplasm or anal cancer by preventing infection with oncogenic strains of HPV. In addition, this vaccine has been demonstrated to be safe and immunogenic in HIV-infected individuals. The incidence of anal cancer is rising very rapidly in the HIV-infected population.





## FY 2012 Trans-NIH AIDS Research Priorities

To capitalize and build on these important scientific advances, the research priorities of the *FY 2012 Trans-NIH Plan for HIV-Related Research* and this trans-NIH AIDS research by-pass budget request represent the most critical and promising areas of research to address the continuing pandemic.

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# 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. Research is needed to better understand 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. OAR will increase support for genetic studies and breakthroughs in sequencing the human genome, and for new opportunities to apply these valuable tools to the search for new HIV prevention and therapeutics strategies. OAR also will increase research on eliminating viral reservoirs toward identifying a cure.

## ETIOLOGY AND PATHOGENESIS

The NIH supports a comprehensive portfolio of research focused on gaining a better understanding of how HIV infection is established and maintained and what causes the associated profound immune deficiency and severe clinical complications. Research on basic HIV biology and AIDS pathogenesis has revolutionized the design of drugs, methodologies for diagnosis, and monitoring of the safety and effectiveness of antiviral therapies. Groundbreaking strides have been made toward understanding the fundamental steps in the life cycle of HIV, the host-virus interactions, and the clinical manifestations associated with HIV infection and AIDS.

Additional research is needed to further the understanding of the virus and how it causes disease, including studies to delineate how sex, gender, age, ethnicity, race, pregnancy, nutritional status, and other factors interact to affect treatment success or failure and influence vulnerability to infection and HIV-disease progression, including the development of HIV-associated comorbidities, malignancies, and coinfections. Additional studies of the genetic determinants associated with HIV susceptibility, disease progression, and treatment response may lead to the development of customized therapeutic and preventive regimens formulated for an individual

patient based on his or her genetic sequence. A gene sequence associated with adverse 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.

### Research Toward a Cure

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 persistent viral reservoirs. Some have speculated that the eradication of these reservoirs might provide a cure for HIV disease. This represents an important priority for AIDS research and this by-pass budget request.

The FY 2012 by-pass budget request for this area is \$862 million, which is an increase of 16 percent over the FY 2011 estimate. This 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

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and the host immune response. 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. The results from recent microbicide and vaccine clinical studies have revealed gaps in knowledge and understanding of HIV etiology and pathogenesis, particularly with regard to host immune responses, how HIV interacts with and transverse mucosal surfaces, and the establishment and maintenance of latent viral reservoirs. The amount requested includes funding for research on the biology of HIV transmission and pathogenesis, including studies on coinfections, malignancies, premature aging, and other complications.

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# 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 pre-exposure 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.

## VACCINES

The best long-term hope for controlling the AIDS pandemic is the development of safe, effective, and affordable AIDS vaccines that may be used in combination with other prevention strategies. AIDS vaccine research remains a high priority to ensure that new and innovative concepts continue to be tested. The NIH supports a broad AIDS vaccine research portfolio encompassing basic, preclinical, and clinical research, including studies to identify and better understand potentially protective immune responses in HIV-infected individuals and studies of improved animal models for the preclinical evaluation of vaccine candidates. Information gained from these studies is being used to inform the design and development of novel vaccine strategies. The recent release of data from several vaccine clinical studies presents new scientific opportunities for investigation that will require realignment of resources.

The FY 2012 by-pass budget request for this activity is \$625 million, an increase of 17 percent over the FY 2011 estimate. Basic research studies, particularly those using samples from the clinical trials, are critically needed on the virus and host immune responses that can inform the development of new and innovative vaccine concepts, as well as on the development of improved animal models to conduct preclinical evaluations of vaccine candidates.

### Advances in Basic and Clinical Vaccine Research Provide New Scientific Opportunities

In FY 2012, the NIH will capitalize on the important incremental findings from the NIH-supported vaccine clinical trial conducted in Thailand that demonstrated for the first time that a vaccine candidate could have a protective effect. With by-pass funding, the NIH will support:

- Additional basic research on HIV and host immune responses
- Design and development of new vaccine concepts
- Preclinical development and testing, including research involving nonhuman primates
- Evaluation of vaccine candidates in the pipeline
- New initiatives to integrate systems biology with HIV vaccine discovery.



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## MICROBICIDES

Microbicides are antimicrobial and other products that can be applied topically or orally as pre-exposure prophylaxis (oral PrEP), alone or in combination with other strategies, for the potential prevention of HIV and other sexually transmitted infections. These products may represent promising primary prevention interventions. The NIH supports a comprehensive and innovative microbicide research program that includes the screening, discovery, development, preclinical testing, and clinical evaluation of microbicide candidates; basic science aimed at understanding how HIV transverses mucosal membranes and infects cells; behavioral and social science research on adherence to and acceptability and use of microbicides among different populations; studies of the safety of microbicide use during pregnancy; and implementation research to better understand how to integrate a potential product into community prevention practices.

The FY 2012 by-pass budget request for this area is \$169 million, which represents an increase of 18 percent over the FY 2011 estimate for this high-priority area of research. In FY 2012, the NIH will continue to support the discovery, design, development, and evaluation of microbicide candidates.

## BEHAVIORAL AND SOCIAL SCIENCE

The NIH supports research to better understand how to change the risk behaviors that lead to HIV infection and disease progression, as well as how to maintain protective behaviors once they are adopted. This research includes studies to develop and evaluate interventions that directly target the substance abuse and sexual behaviors associated with HIV transmission. Other research aims toward better understanding the environmental, social, and cultural factors associated with HIV infection and

### Research to Build on Important Microbicide Advances

Microbicide research is a high priority in this by-pass budget estimate to continue the momentum of science in this area. Key activities include:

- Support for the microbicide clinical trials network and the necessary infrastructure to conduct microbicide trials and oral PrEP trials—especially to build on recent research advances of a clinical trial, known as CAPRISA 004, conducted in South Africa and supported primarily by USAID
- Development of innovative, novel, high-risk, high-reward approaches for the development and testing of microbicide candidates
- Development of criteria for selecting potential products to be evaluated in clinical trials and for advancing them through the different phases of preclinical and clinical studies
- Research to define and analyze normal and abnormal male and female genital tract and anal/rectal immune function and their impact on HIV risk and acquisition
- Research on ethical, adherence, and other behavioral and social science research issues that can affect these clinical trials.

disease outcomes, including stigma. Determining effective strategies to test HIV-infected persons, to link them to care, and to promote adherence to antiretroviral therapy is another important area of research. Comprehensive approaches that integrate biomedical and behavioral science perspectives are necessary to develop the needed range of preventive and therapeutic strategies. The NIH also supports research to improve behavioral methodologies, including ways to improve recruitment into clinical

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trials, to enhance statistical analysis of behaviors such as alcohol use that can affect medication studies, or to characterize behavioral traits relevant to genetic or genomic studies.

The FY 2012 by-pass budget request for this area is \$494 million, which is an increase of 15 percent over the FY 2011 estimate. The NIH will continue to fund research to develop and evaluate effective interventions to prevent HIV transmission and acquisition by reducing HIV-related risk behaviors and increasing protective behaviors.

## TREATMENT AS PREVENTION

A critical new area of prevention research is the study of treatment strategies as a method to prevent new HIV infections. This approach builds on NIH-sponsored landmark clinical trials that successfully demonstrated that treatment of HIV-infected pregnant women could significantly reduce transmission of HIV from mother to child. During the past year, NIH-supported researchers reported a landmark finding that the use of antiretroviral treatment in high-risk, uninfected MSM can reduce risk of infection.

### Development of Combination Strategies

The long-term goal of prevention research is the development of combination strategies. No one prevention strategy alone will be sufficient. This by-pass budget request includes critical resources that will be directed toward several new prevention initiatives, including studies integrating behavioral and social science methods with biomedical prevention strategies, community-based approaches to engaging and retaining persons in care, and the impact of improved care on reducing HIV transmission. Strategies are particularly needed to address specific high-risk populations, including MSM, older individuals, and adolescents, particularly among racial and ethnic populations.

### Expanding Basic, Clinical, and Applied Knowledge About Treatment as Prevention

At the by-pass budget level, the NIH will increase and expand research in this new and emerging area to further advance knowledge about the uses of potential strategies, including:

- PrEP, the long-term use of treatment regimens for high-risk uninfected populations to prevent HIV acquisition
- Postexposure prophylaxis, the use of treatment to prevent HIV infection after accidental exposure, including in a health care environment
- Improved prevention of mother-to-child transmission, including prevention of transmission through breast milk
- A potential innovative prevention strategy known as “test and treat” to determine whether a community-wide HIV testing and counseling program with immediate treatment for HIV-infected individuals can decrease the overall rate of new HIV infections in that community.



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# PRIORITY: Improving Disease Outcomes for HIV-Infected Individuals

Antiretroviral therapy (ART) has resulted in improved immune function in patients who are able to adhere to the treatment regimens and tolerate the toxicities and side effects associated with antiretroviral drugs; consequently, ART has delayed the progression of HIV disease to the development of AIDS. However, a growing proportion of patients receiving long-term ART are demonstrating treatment failure, experiencing serious drug toxicities and side effects, and developing drug resistance. Recent epidemiologic studies continue to show an increasing incidence of coinfections, comorbidities, AIDS-defining and non-AIDS-defining malignancies, and complications associated with long-term HIV disease and ART, including TB, hepatitis C, metabolic disorders, cardiovascular disease, conditions associated with aging, and neurologic and neurocognitive disorders. There is a need to develop better, less toxic treatments and to investigate how genetic determinants, sex, gender, race, age, nutritional status, treatment during pregnancy, and other factors interact to affect treatment success or failure and/or disease progression.

## DRUG DISCOVERY, DEVELOPMENT, AND TREATMENT

The NIH supports a comprehensive therapeutics research program to design, develop, and test drugs and drug regimens to maintain long-term undetectable viral load, overcome drug resistance and treatment failure, prevent and treat HIV-associated comorbidities and complications, and eradicate persistent viral reservoirs that may lead to a potential or functional cure for HIV disease.

The FY 2012 by-pass budget request for this area is \$692 million, which represents an increase of 12 percent over the FY 2011 estimate. Improved therapeutic regimens for the treatment of HIV and its associated coinfections and comorbidities are urgently needed, especially regimens that can be implemented in resource-limited settings. Over the past several years, the highest priority has been placed on prevention research within constrained budgets. However, expanding research in this area is critical to address new findings regarding complications and side effects of long-term disease and treatment.

### Improved Therapies for Long-Term Survival

This by-pass budget provides critical support for:

- New and/or expanded initiatives for developing innovative therapies to control and eradicate HIV infection that may lead to a cure
- Identification of new drug targets based on the structure of HIV/host complexes
- Delineation of the interaction of aging and AIDS—including neurological, cardiovascular, and metabolic complications, and issues of frailty
- Discovery and development of improved therapies for AIDS-defining and non-AIDS-defining malignancies
- Discovery of the next generation of drugs that may be used in potential “treatment as prevention” strategies.

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# PRIORITY: Reducing HIV-Related Disparities

Research is needed 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. These include disparities among racial and ethnic populations in the United States, between developed and resource-constrained nations, between men and women, between youth and older individuals, and disparities based on sexual identity. The NIH will support research training for new investigators from racial and ethnic communities, development of research infrastructure, community outreach, information dissemination, and research collaborations to help reduce these disparities.

## **TRAINING, INFRASTRUCTURE, AND CAPACITY BUILDING**

The NIH supports the training of domestic and international biomedical and behavioral AIDS researchers, and provides support for the equipment necessary 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 researchers, 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.

The FY 2012 by-pass budget request for this area is \$251 million, which represents an increase of 16 percent above the FY 2011 estimate. The NIH will continue to support ongoing efforts to increase the supply of nonhuman primates, particularly rhesus macaques, for AIDS research and other areas of biomedical research in both the United States and abroad. The NIH also will 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 in developing countries. Support also will be provided for the NIH AIDS Research Loan Repayment Program and the Intramural AIDS Research Fellowship program that will help ensure an adequate number of trained AIDS researchers at the NIH.

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# PRIORITY: Translating Research From Bench to Bedside to Community

Research will 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. These research activities include critical epidemiologic and natural history studies, collaborative networks, and specimen repositories to evaluate various operational strategies that can be employed to scale up and evaluate treatment programs and successful prevention interventions in communities at risk.

## NATURAL HISTORY AND EPIDEMIOLOGY

Natural history and epidemiologic research is essential for monitoring epidemic trends, developing and evaluating prevention modalities, following the changing clinical manifestations of HIV disease in different populations, and measuring the effects of treatment regimens. The NIH supports research in domestic and international settings to examine HIV transmission, HIV disease progression (including the occurrence of coinfections and opportunistic infections; malignancies; and metabolic, cardiovascular, neurological, and other complications), development of other HIV-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.

The FY 2012 by-pass budget request for this area is \$308 million, which represents an increase of 12 percent above the FY 2011 estimate. As the AIDS epidemic continues to evolve, there is a crucial need to continue to conduct epidemiologic studies in both domestic and international settings. These studies have delineated the significant health disparities that are critical factors in the epidemic. The NIH will continue to place high priority on understanding the causes of HIV-related health disparities, in both

the United States and around the world, their role in disease transmission and acquisition, and their impact on treatment access and effectiveness.

### Addressing Critical Populations

The by-pass budget level will allow the NIH to provide adequate support for high-priority epidemiology studies of groups and populations affected by HIV and at high risk for infection in the United States and around the world, including individuals aged 50 and older, MSM, substance users, women, and adolescents, especially African American and Hispanic adolescents. The NIH also will increase support for studies on:

- Mechanisms of disease progression
- Role of race and gender
- Effects of increased HIV testing and linkage to care
- Implementation/operational science, including the evaluation of strategies to scale up efficacious and cost-effective interventions to the community level.

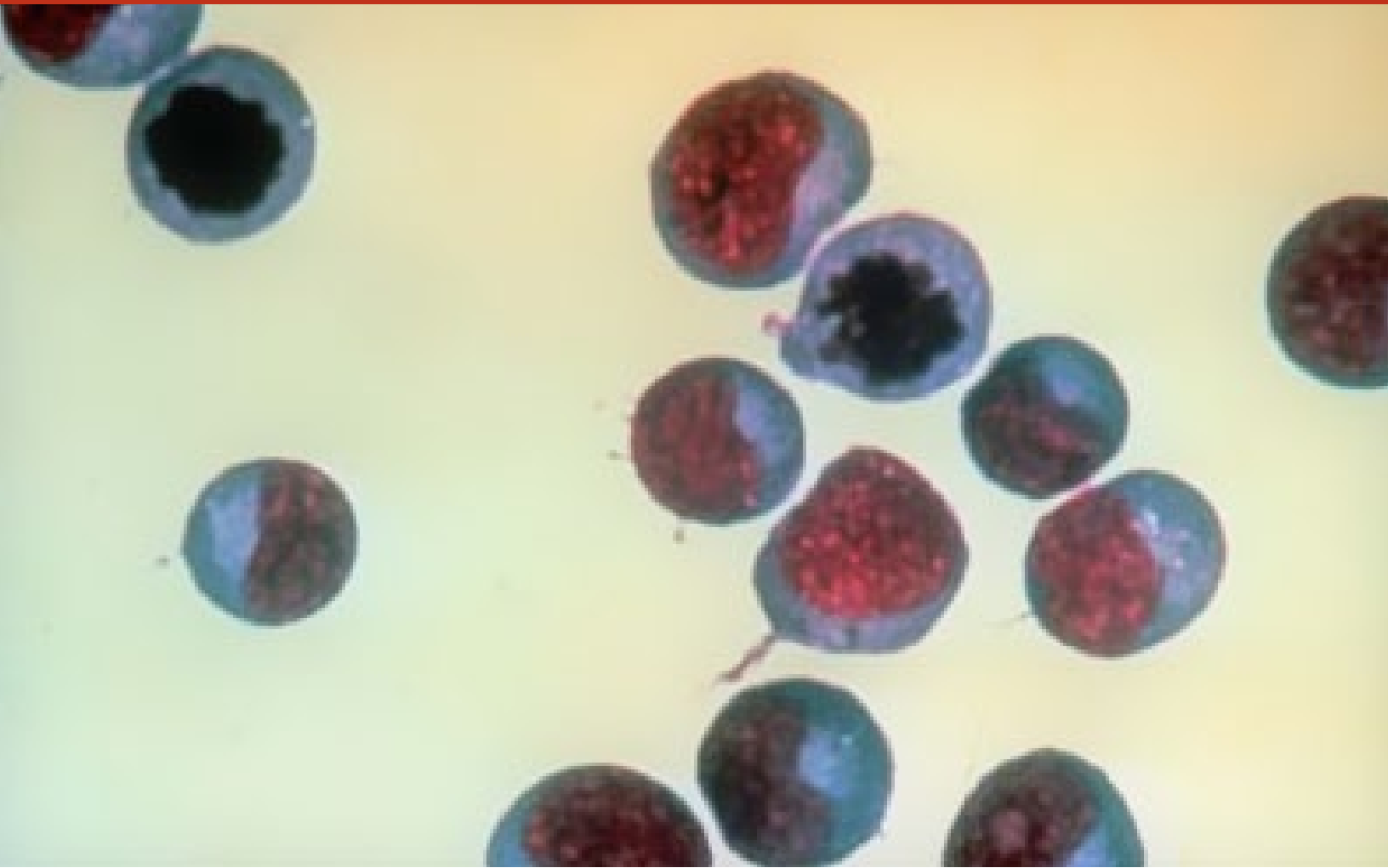
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## INFORMATION DISSEMINATION

Effective information dissemination approaches are integral to HIV prevention and treatment efforts and 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 incidence of HIV infection in specific population groups in the United States, such as racial and ethnic populations, MSM, and women, underscore 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. The NIH supports 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, adolescents, and racial and ethnic populations.

The FY 2012 by-pass budget request for this area is \$64 million, which represents an increase of 12 percent above the FY 2011 estimate. As the number and complexity of clinical studies increase, resources must be invested in clinical-trials-related information dissemination to ensure recruitment of an adequate number of participants, particularly from populations at risk, including women and racial and ethnic populations in the United States. In addition, funding will be provided to ensure that critical Federal guidelines on the use of antiretroviral therapy, as well as guidelines for the management of HIV complications for adults and children, will be updated regularly and disseminated to health care providers and patients through the AIDSinfo Web site ([www.aidsinfo.nih.gov](http://www.aidsinfo.nih.gov)).



## Benefits to Other Areas of Research

Because of the unique nature of HIV—the way the virus enters a cell, causes infection, affects every organ system, and unleashes a myriad of opportunistic infections, comorbidities, cancers, and other complications—and the pace at which the knowledge base has been expanded, AIDS research also is helping to unravel the mysteries surrounding many other infectious, malignant, neurologic, autoimmune, and metabolic diseases, as well as complex issues of aging and dementia. Basic knowledge of the biology of HIV infection and the processes by which it causes disease benefits other areas of basic research, including immunology, virology, microbiology, molecular biology, and genetics. AIDS research has provided an entirely new paradigm for drug design, drug development, and clinical trials to treat viral infections and to address the special recruitment requirements of women, minorities, and other underserved and at-risk populations. Drugs developed to prevent and treat AIDS-associated opportunistic infections also now benefit patients undergoing cancer chemotherapy or receiving anti-transplant-rejection therapy. Thus AIDS research is providing a new understanding of the relationship between viruses and cancer.



## Conclusion

The scientific advances of the past year represent a turning point for AIDS research, opening new avenues for discovery and demonstrating the possibility of new strategies to prevent, treat, and potentially cure HIV. This by-pass budget estimate provides the resources necessary to capitalize on those advances to move science forward. 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. The AIDS pandemic will continue to wreak devastating consequences around the world for decades to come for virtually every sector of society. 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 from this important moment in science, 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 2010 Actual Budget Authority	FY 2011 Estimate	FY 2012 By-Pass Estimate	Percent Change FY 2011 to FY 2012
Etiology and Pathogenesis	\$745	\$745	\$862	16.0%
Vaccines	535	535	625	17.0
Microbicides	143	143	169	18.0
Behavioral and Social Science	429	430	494	15.0
<i>Treatment as Prevention</i>	68	69	81	17.0
<i>Drug Discovery, Development, and Treatment</i>	617	616	692	12.0
Total Therapeutics	685	685	773	13.0
Training, Infrastructure, and Capacity Building	216	216	251	16.0
Natural History and Epidemiology	275	275	308	12.0
Information Dissemination	57	57	64	12.0
<b>TOTAL</b>	<b>\$3,085</b>	<b>\$3,086</b>	<b>\$3,546</b>	<b>15.0%</b>



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

	FY 2010 Actual Budget Authority		FY 2011 Estimate		FY 2012 By-Pass Estimate		Percent Change FY 2011 to FY 2012
	NO.	AMT.	NO.	AMT.	NO.	AMT.	
<b>RESEARCH PROJECTS</b>							
Noncompeting	1,751	1,345	1,729	1,275	1,800	1,448	14.0
Administrative supplements	(114)	18	(114)	15	(125)	25	67.0
Competing	583	295	687	361	750	433	20.0
Subtotal, RPGs	2,334	1,658	2,416	1,651	2,550	1,906	15.0
SBIR/STTR	67	29	79	36	100	45	25.0
Total, RPGs	2,401	1,687	2,495	1,687	2,650	1,951	16.0
<b>RESEARCH CENTERS</b>							
Specialized/comprehensive	66	143	69	133	69	145	9.0
Clinical research	—	55	1	55	—	67	22.0
Biotechnology	—	5	1	5	—	6	20.0
Comparative medicine	14	56	18	57	15	72	26.0
Research centers in minority institutions	1	14	2	14	1	14	0.0
Subtotal, Centers	81	273	91	264	85	304	15.0
<b>OTHER RESEARCH</b>							
Research careers	248	43	237	41	259	55	34.0
Cancer education	—	—	—	—	—	—	—
Cooperative clinical research	13	21	12	18	17	34	89.0
Biomedical research support	—	2	1	2	1	2	0.0
Minority biomedical research support	—	—	1	—	—	—	—
Other	142	60	122	61	170	73	20.0
Subtotal, Other Research	403	126	373	122	447	164	34.0
Total, Research Grants	2,885	2,086	2,959	2,073	3,182	2,419	17.0
<b>TRAINING</b>							
Individual	86	4	86	4	86	4	0.0
Institutional	649	31	649	31	701	40	29.0
Total, Training	735	35	735	35	787	44	26.0
Research and development contracts (SBIR/STTR)	145 (2)	461 (1)	145 (2)	474 (1)	155 (2)	520 (2)	10.0 100.0
Intramural research	—	313	—	314	—	355	13.0
Research management and support	—	126	—	126	—	140	11.1
Construction	—	—	—	—	—	—	—
Office of the Director	—	64	—	64	—	68	6.0
Buildings and facilities	—	—	—	—	—	—	—
<b>TOTAL, Budget Authority</b>	—	<b>\$3,085</b>	—	<b>\$3,086</b>	—	<b>\$3,546</b>	<b>15.0%</b>



# FY 2012 Trans-NIH Plan for HIV-Related Research

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# FY 2012 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

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## FY 2012 RESEARCH PRIORITIES

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- Study the impact of aging with HIV infection on the mechanisms responsible for the pathogenesis of comorbid conditions such as cardiovascular disease, frailty, and immune dysfunction, including research on the relative contribution of the immune system and immune response to infection on these comorbidities.
- Develop and evaluate new strategies and drug regimens to prevent and treat comorbidities and comorbidities (malignancies, cardiovascular disease, metabolic disorders, nutritional deficiencies, neuropathies, and other complications) associated with long-term HIV disease and antiretroviral treatment.
- Identify and eradicate persistent reservoirs of HIV infection.
- Identify the fundamental viral and host mechanisms associated with the acquisition and inhibition of HIV infection and progression of disease, including intrinsic cellular restriction, and the role of immune activation and inflammation.
- Study the genetic and biological mechanisms that govern the entry of HIV into target cells, particularly in relation to the interactions of HIV envelope, cell receptors, components of innate immunity within different body cavities and portals of virus entry, and mucosal surfaces.
- Identify biomarkers and bioassays of HIV-host interaction at various stages throughout the entire course of HIV disease that are predictive of the efficacy and safety of biomedical interventions, including vaccines, microbicides, and oral/topical formulations.
- Develop and evaluate new strategies to prevent and treat HIV coinfections, including tuberculosis, hepatitis C virus, and other high-priority pathogens.
- Identify genetic determinants of HIV acquisition, disease progression, and treatment response, and develop methods to optimize therapeutic regimens based on an individual's genomic sequence.
- Develop novel strategies to treat and prevent HIV using knowledge gained from studies on HIV latency, host mechanisms involved in acquisition and inhibition of HIV infection, and immune activation and inflammation.

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

## OBJECTIVE–B: HIV Virology and Viral Pathogenesis

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

## **OBJECTIVE–C: HIV Immunopathogenesis**

Delineate immunological mechanisms of HIV control, and elucidate the viral and host mechanisms associated with HIV-induced immunopathogenesis, including immune dysfunction, aberrant immune activation, and inflammation.

### **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/SIV replication throughout acute and chronic infection.
- Delineate mechanisms responsible for the differences between pathogenic and nonpathogenic infection in humans and nonhuman primates.
- Explore the role of HIV and other common viral coinfections in the development of premature immune senescence in HIV-infected individuals.
- Explore mechanisms of host response to HIV/SIV infection that involve the interface between innate and adaptive immunity.
- Delineate innate and adaptive immune responses to HIV at mucosal surfaces, including the gastrointestinal and genitourinary tracts.
- Elucidate the mechanisms of CD4+ T-cell depletion in the infected host.
- Delineate the pathogenic consequences of HIV infection on leukocyte homeostasis and on the structure and function of primary and secondary lymphoid tissues.
- Examine the role of immune activation, inflammation, and dysfunction/dysregulation in HIV/SIV pathogenesis, and delineate the mechanisms leading to pathological immune activation, immunosenescence, and autoimmunity in HIV/SIV infection.
- Determine the impact of host immunity on viral evolution and fitness, and the influence of viral factors on host immunity.
- Evaluate the extent to which HIV/SIV-related immunopathogenesis can be prevented or reversed by therapeutic interventions.

## OBJECTIVE–D: Pathogenesis of Opportunistic Infections and Coinfections

Elucidate the pathogenic mechanisms and consequences of opportunistic infections (OIs) and significant coinfections in the context of HIV infection in diverse populations across the spectrum of age 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 and the risk of HIV acquisition, including those that are a major cause of morbidity or disease progression (e.g., tuberculosis [TB] and hepatitis C [HCV]) or that contribute to HIV transmission and acquisition (e.g., STIs).
- Identify and elucidate the genetic and environmental risk factors, as well as mechanisms of immune dysfunction, associated with the susceptibility to, the development of, and the progression of OIs and coinfections.
- 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, and the effect of OI therapy on the clinical course of HIV disease progression.
- Probe the pathogenic mechanisms of HIV-associated OIs, and evaluate how the causes, agents, and manifestations of these infections are altered by antiretroviral therapies (ARTs).
- Define the molecular and phylogenetic characteristics of major AIDS OIs and pathogens, and integrate strain-specific characterization of data into studies of the pathogenesis, mechanisms of transmission, and epidemiology of OIs.
- Determine biomarkers and factors associated with clinical response and lack of response to therapeutic interventions and vaccines against OIs and coinfections, and identify basic mechanisms that will provide new targets for the development of vaccines and new treatments for OIs and coinfections that will be effective in HIV-infected individuals.

## OBJECTIVE–E: Pathogenesis of Metabolic and Body Composition Change

Define the etiology, pathophysiology, and consequences of HIV infection and treatment-related metabolic disorders; body composition changes; nutritional status; endocrine dysfunction; oral health; gastrointestinal disorders; skin, muscle, and bone disorders; pulmonary disorders; nephropathy; hematologic disorders; and cardiovascular disease in diverse populations across the spectrum of age 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, gastrointestinal, pulmonary, hematologic, and skin diseases or manifestations to determine:
  - ▶ the effects of antiviral therapies and suppression of virus replication, viral setpoint, episodic viremia, and sites of viral reservoirs;
  - ▶ the influence of disease stages, including the degree of initial immunosuppression and immune reconstitution, residual immune dysfunction, lymph nodes disarray, and inflammation;
  - ▶ the contributions of individual virologic and host factors, including host genetic variation;
  - ▶ the contributions of OIs, nonopportunistic infections, hormonal dysregulation, and other consequences of HIV infection;
  - ▶ the role of diet, nonopportunistic infections, and nutritional status on malabsorption, malnutrition, immune status and exacerbation of metabolic disorders, steatosis, comorbidities, and HIV pathogenesis;
  - ▶ the influence of hormones on HIV pathogenesis; and
  - ▶ the impact of pharmacokinetics, pharmacogenomics, and drug–drug interactions.
- Study the impact of HIV on an aging population, including the implications of HIV infection for physical function and 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, physical function, impaired growth and development, diabetes, and bone, skeletal muscle, skin, renal, and atherosclerotic cardiovascular disease.
- Study the influence of the gut microbiome and other microbiota in conjunction with metabolic abnormalities, body composition changes, and cardiovascular disease associated with HIV infection.
- Integrate studies of these disorders and disease into ongoing and planned treatment trials and observational studies.

## OBJECTIVE–F: Pathogenesis of Malignancies

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

### STRATEGIES

- 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 (including inflammatory changes), oncogenes, suppressor genes, carcinogens, environmental factors, 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), 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, and skin) that may emerge in the aging HIV-infected population.
- 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. Conduct studies on how the interplay of HIV infection, host factors, and aging (including natural aging and premature aging that may be caused by HIV) enhance the development of these cancers.
- Elucidate the pathogenic mechanisms of AIDS-defining and other HIV-related tumors that arise in HIV-infected patients, including genetic changes, by comparing these tumors to similar tumors that arise in HIV-uninfected patients.
- Identify basic mechanisms that will facilitate the development of effective therapies and preventive measures (including vaccines) for AIDS-defining and other HIV-associated tumors.
- Determine factors associated with clinical response and lack of response to antineoplastic therapeutic intervention in HIV-infected subjects.

## **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**

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







**PRIORITY:**

# Reducing New Infections

Vaccines

Microbicides

Behavioral and Social Science

Treatment as Prevention



## AREA OF EMPHASIS

# Vaccines

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### FY 2012 RESEARCH PRIORITIES

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Research interest in HIV vaccines was re-energized at the beginning of FY 2010 with the report of limited efficacy to prevent infection that was observed in the HIV vaccine trial (RV 144) in Thailand. Major research efforts are being engaged to search for immune correlates of protection in samples derived from the 16,000 participants in the Thai trial. Teams have been developing new concepts for human HIV vaccine trials that either build on the RV 144 trial (of a pox virus vector to induce HIV-specific responses and a boost with envelope proteins) or substitute one or both components with newly designed candidate vaccines that might be even more effective. In addition, new data from the previous STEP trial that did not contain an envelope component and that failed to protect individuals from infection suggest that the HIV that infected some of the individuals was genetically different from the vaccine strain. Alternatively, the incoming virus is being rapidly modified by the vaccine-induced immune response in the individuals who became infected. This information added to the knowledge that the circumcised men who did not have high titers of antibody to adenovirus 5 also appeared to have a reduced risk of HIV infection.

The key priorities that were identified were the following.

- **KEEP THE BALANCE** *There is a strong sense that there still is much to learn about basic adaptive and innate immune mechanisms that might be triggered by HIV vaccines. Basic research on vaccine responses in animals must be complemented by basic research in human immunology to delineate the differences and similarities. Concerns have been expressed that the pipeline for new vaccine concepts and the availability of new candidate HIV vaccines for testing in humans will “dry up” if innovative research is not fostered at the same time that research is conducted on samples from large trials or nonhuman primate (NHP) studies. To this end, investigators should be encouraged to adapt and employ all of the new tools that might be appropriate for investigating immune responses and host defense mechanisms that are triggered by HIV vaccines.*

In the past few years, several teams have defined new sites on the virus envelope that appear to render the virus susceptible to attack by antibodies that can block virus entry into cells or block virus replication. These have been defined by monoclonal antibodies, and it is postulated that antibodies that do not score as positive in virus-neutralizing assays may have been effective in the trial in Thailand. Studies to investigate passive transfer of different types of antibodies might reveal new mechanisms that have not been considered previously for protection.

Information from potential vaccine cohorts around the world has confirmed findings from a number of years ago that the HIV that is transmitted from one individual to another is often very limited in its diversity—indicating that only one or a few virus particles are able to establish an infection in most people. However, the initial founder/transmitted HIV can change rapidly (within weeks) and become more complex as it tries to evade the response that the individual makes to keep it under control. The fact that only a limited amount of

virus is establishing infection has led HIV vaccine researchers to redesign the animal models, which are being used to evaluate vaccines, to more closely reflect the type of exposure that humans are encountering. These models also will be useful for microbicides and other prevention strategies.

- **BUILD MORE INTEGRATED, MULTIDISCIPLINARY HIV VACCINE CONSORTIA** Researchers are concerned that small groups of investigators have limited resources and lack sufficient interaction with others to develop products to the point where it is feasible to do definitive studies either in NHP or in human trials. Further, these small groups do not have the expertise to overcome in a timely fashion the barriers to vaccine development for clinical studies. *Consortia that engage multiple partners to test specific concepts and model challenges by different routes of exposure to HIV, especially when focused on mucosal transmission, may be the most efficient way to approach some of these questions.*
- **CONTINUE TO CONDUCT CLINICAL TRIALS OF HIV VACCINES** The combination of different candidate vaccines has indicated that unpredictable outcomes both in immune responses and in protection outcomes in humans can be observed. *The need for vaccine concepts to be more extensively studied in animal models that more closely mimic the transmission observed in human clinical studies has become evident from the efficacy trials that have been conducted thus far. Clinical vaccine trials need to be coupled with intensive and integrated immunological research to understand how the vaccines are working to prevent infection at the mucosal surfaces where humans are routinely exposed in the worldwide epidemic. The need to do this much more efficiently while retaining the ability to see benefit in different risk groups is a very high priority.*

## 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 infection; this includes the following areas of interest:
  - ▶ Determine the mechanisms of immunologically mediated control of infection with HIV and other related lentiviruses, including the role of antigen-specific (adaptive) and antigen-nonspecific (innate) cellular and humoral immunity in inhibiting viral replication to provide a basis for optimal vaccine design.
  - ▶ Define the structure–function relationships and the antigenicity and immunogenicity of HIV envelope proteins, including transient or intermediate and conformational domains induced by virus interacting with CD4, chemokine, dendritic cell (DC) surface proteins and adhesion molecules, and other cellular receptors to improve vaccine designs to more effectively induce immune responses to block infection by active T-cell immunity and protective antibody.
  - ▶ Define and characterize viral B-cell and T-cell epitopes that induce protective immunity in HIV or AIDS-related disease; utilize structural analysis of the HIV envelope to determine whether and how their immunogenicity can be improved and exploited in vaccine development.
    - Determine the mechanism of how HIV and closely related lentiviruses evade or escape from humoral and cellular 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; conduct comparative translational research of 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 non-progressors) to define immune responses to HIV-1 and HIV-2, potential vaccine-inducible host immune responses, and viral factors (or viral attenuations) or host factors that enhance or reduce the amounts of circulating virus and influence disease course.
    - ▶ Elucidate the functional mechanisms for protective immunity against HIV, SIV, and SHIV, including identification of specific responses by passive transfer of antibody or immune cells and deletion of selected immune subsets in NHP models.
    - ▶ Investigate the sequence of events required for mucosal transmission/infection of HIV, SIV, or SHIV at different portals of entry to define how and where specific immune effector mechanisms can impede viral entry and/or prevent establishment of infection.
    - ▶ Study mucosal immunity to HIV and SIV antigens and other infectious pathogens being used as HIV vaccine vectors in relevant animal models and humans to develop optimal vaccine strategies for HIV antigen delivery and effective immune-based prevention of HIV transmission.
    - ▶ Acquire clinical specimens from populations relevant to HIV vaccine trials for laboratory studies; explore the molecular epidemiology, humoral, and cell-mediated immune responses to HIV-1 and their relationship to class I and class II MHC alleles; and define constraints on HIV evolution under immune selection pressure so as to guide vaccine development. Acquire appropriate, linked, epidemiological information to optimize interpretation of these analyses.
    - ▶ Explore genome-wide association studies, in addition to targeted genetic analyses, to reveal novel viral protection/control mechanisms, particularly those that 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 NHPs.



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- Develop *in vitro* experimental approaches for analysis of HIV vaccine responses that will combine sensitivity, specificity, high throughput, and the ability to use small sample volumes; develop *in vitro* and *in vivo* tools to study systemic and mucosal immune mechanisms of control of virus for analysis of vaccinated individuals (across the lifespan) and animals protected against SIV or SHIV by undertaking the following research activities:
    - ▶ Develop and improve NHP animal models of lentivirus infection that are practical and representative of the spectrum of HIV infections and development of AIDS, including use of appropriate HIV cellular receptors and different modes of transmission; develop genetically defined and histocompatible NHP models to facilitate immune cell transfer studies; in general, make models amenable to use in evaluating protection by vaccines and other biomedical interventions. This may be approached, in part, by genetic sequencing of selected regions of NHP genomes.
    - ▶ Create cryorepositories of cells isolated from NHP tissues (including blood, primary lymphoid organs, and mucosal specimens) from immune-naïve, HIV- or SIV-vaccinated, or SHIV- or SIV-infected animals to provide a resource for assay development in parallel with human studies.
    - ▶ Develop improved methodologies and assays to measure HIV neutralization; explore the mechanisms of virus neutralization and the reason(s) for the relative difficulty of neutralizing primary HIV isolates.
    - ▶ Develop and standardize immunological reagents for HIV vaccine trials; standardize cell, fluid, and tissue processing to ensure viability and maintenance of functional capacity of cells and stability of factors in serum, plasma, and culture supernatants; and develop quality control procedures for collecting, processing, freezing, storage, recovery, viability, shipping, and tracking of samples that will be essential in large-scale HIV vaccine clinical trials.
    - ▶ Study the function of HIV/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.
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## 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 and ensure that products meet these standards;

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- ▶ 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 candidates and other immune prevention strategies in NHP animal models of HIV and closely related lentiviruses by:
    - ▶ Testing HIV/SIV vaccine candidates and other biomedical prevention strategies in animal models that most closely mimic HIV infection in humans;
    - ▶ Determining *in vitro* correlates of an *in vivo* protective immune response generated by HIV/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, or 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 view 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 the integrity of the mucosal surface or the inductive ability of HIV vaccines.
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- 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 the potency of candidate HIV vaccines;
  - ▶ Standardizing and validating assays to be used as Phase III study endpoints; and
  - ▶ Developing novel endpoint assays under conditions of Good Laboratory Practice to support eventual product licensure and instituting quality assurance programs to assure sponsors and vaccine manufacturers that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with FDA regulations.
- Foster research on the 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 should be modeled and evaluated, particularly in infants, in parallel to studies in uninfected adults. To accomplish this goal, it is important to develop research that will achieve the following:
  - ▶ Develop relevant NHP animal models of maternal–fetal and maternal–infant perinatal transmission of HIV/SIV/SHIV that can:
    - Determine the preclinical safety and immunogenicity of various HIV vaccines and adjuvants, particularly in pregnant and newborn primates;
    - Determine the safety of various monoclonal and polyclonal antibody preparations against HIV;
    - Determine the best immunization routes or protocols to induce antibodies to HIV in milk and other secretions;
    - Evaluate NHP infant cellular and humoral immunity to HIV or SIV in the context of breastfeeding from a SHIV- or SIV-infected mother, and determine immune correlates of protection for potential exploitation in vaccine strategies;
    - Evaluate the efficacy of vaccines and passive immunotherapy for prevention of perinatal or breastfeeding HIV transmission; determine whether there is attenuation of disease progression among neonatal animals that become infected despite immune intervention; determine correlates of protective immunity; and
    - Evaluate the effect of ART in combination with immune 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; 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, particularly in breastfeeding 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 feasibility and development of criteria for advancement of candidate HIV vaccines, adjuvants, and passive antibody preparations from Phase I and Phase II to Phase III clinical trials in pregnant HIV-infected women and/or HIV-exposed children. These criteria may include evidence of therapeutic effectiveness in mothers in addition to prevention of infection in HIV-exposed children or adults.
  - ▶ Develop the capacity in domestic and foreign trial sites necessary to enroll mothers and infants in trials of both preventive and therapeutic HIV vaccines, passive immunity, and other perinatal interventions with prospective long-term followup. For vaccines, this should include the assessment both of duration and breadth of detectable humoral immune responses and of memory or recall responses in the cellular immunity compartment(s).
  - ▶ Conduct Phase III clinical trials for evaluation of efficacy of the most promising candidate HIV vaccines and/or passive antibody preparations that meet established criteria in pregnant HIV-infected women and/or children exposed to HIV.
- ▶ Develop criteria to define infant HIV infection status as a perinatal intervention trial endpoint in countries where breastfeeding is recommended despite maternal infection status, including type of diagnostic tests, timing of the tests, length of followup, and adherence to followup visits.
- ▶ Study HIV isolates and the immune response in infants who become infected despite administration of active and/or passive immunization to evaluate the effects of immune intervention on the characteristics of transmitted (escape) virus and on the quality, quantity, and timing of the infected infant's antiviral responses.
- ▶ Study the impact of early ART interventions and HIV vaccines or passive antibodies administered 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 candidates, and address questions about optimal vaccine strain/gene insert selection (i.e., the properties of a strain [immunologic, genotypic, or phenotypic]) that make it optimal for use in a selected population. The feasibility of trials to test concepts of immune prevention and control by antibodies may be explored via passive administration of antibodies. Vaccine trials should include an appropriate representation of the general population (gender, age, and ethnic and racial minorities), particularly including understudied populations affected by HIV such as women and adolescents, and should be of an appropriate size to provide data on the frequency, magnitude, and breadth of immune responses to facilitate decisions regarding initiation and evaluation of larger test-of-concept (TOC) or efficacy trials.
- Develop a comprehensive plan for conducting HIV vaccine trials with rapid accrual, high retention, and adequate long-term followup of 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 the 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 vaccine trial designs.
  - ▶ Continue to use existing strategies to avert social harm and develop additional strategies to complement existing mechanisms at the local and national levels to reduce the risk of social and economic harm to volunteers in Phase I, 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 clinical trials.
  - ▶ Identify and address barriers to participation in clinical trials among all at-risk groups, so that all relevant populations, especially women and adolescents, are included in HIV vaccine clinical trials.
  - ▶ Develop and apply new laboratory diagnostic tools, including rapid, point-of-care tools, that can be adapted for high throughput to detect, characterize, and amplify virus in blood and mucosal fluids from individuals with new HIV infections and allow distinction between 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 setpoint, 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-positive and HIV-negative samples, as well as peptide reagents, to serve as controls when validating and standardizing assays that will be used in support of clinical trials in that region; and participation of trained personnel in studies related to the trial.
- Establish, build, and nurture linkages with communities and community organizations where vaccine clinical 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 clinical trials, enlist participation of local representatives or community advisory boards (CABs) in the development of appropriate clinical trial protocols as well as responsive mechanisms to inform and educate the participating individuals;

establish networks within the community that will effectively, and on a continuing basis, address the social and medical concerns of the participants; establish mechanisms to provide ongoing information and open discussions concerning the scientific rationale and public health need for the study.

- ▶ Develop mechanisms (including CABs) to engage in collaboration and to provide education and the means to inform communities about HIV vaccines on a continuing basis so that social as well as medical concerns are addressed; 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, the Joint United Nations Programme on HIV/AIDS, and the Global HIV Vaccine Enterprise to prepare for, plan, and conduct HIV vaccine trials adhering to the highest ethical and scientific standards.
- ▶ Support the education of local CABs and local institutional review boards on issues concerning the conduct of HIV vaccine clinical trials in their communities.
- In collaboration with Government agencies, institutions, NGOs, and communities being identified as potential collaborators, explore behavioral and social issues and prevention activities (e.g., circumcision, microbicides, pre- or postexposure prophylaxis, anti-herpes simplex virus treatment, HPV vaccine, and breastfeeding strategies) that might have a substantial impact on either the design or the conduct of an HIV vaccine clinical 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, and 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 agencies and community-based organizations to develop education programs to facilitate the conduct of Phase III HIV vaccine clinical trials in hard-to-reach populations in domestic sites; collaborate with the U.S. Military HIV Research Program, the Centers for Disease Control and Prevention, the U.S. Agency for International Development, and other organizations to develop vaccine clinical trial sites in international settings.
  - ▶ Evaluate the impact of community-based participatory research in the acceptability of HIV vaccine clinical trials.
  - ▶ Develop appropriate communication strategies involving affected communities in the process of testing HIV vaccines and prepare for the eventual integration of preventive vaccines into comprehensive prevention and care programs in the United States and in countries where HIV vaccine clinical trials are conducted.

- ▶ Determine possible adverse social, economic, behavioral, or legal consequences of participation in vaccine 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

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### **FY 2012 RESEARCH PRIORITIES**

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- Develop and test animal models that are predictive of microbicide safety and efficacy.
- Design and conduct microbicide studies that integrate the biological, behavioral, and social sciences.
- Develop, test, and standardize assays to assess the safety of microbicide candidates.
- Develop a robust pipeline of microbicide candidates and a standardized method for efficiently advancing candidates through the pipeline.
- Define and analyze normal and abnormal male and female genital tract and anal/rectal immune function and their impact on HIV risk and acquisition.

## OBJECTIVE–A: Basic Mechanisms of Mucosal Transmission

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

### STRATEGIES

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#### Basic Biological and Physiological Research Related to Topical and Oral Microbicides

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- 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 and study exploratory techniques such as genomics and proteomics and other systems biology approaches 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, adaptive, and maladaptive host defenses that protect against HIV transmission and acquisition or enhance susceptibility. 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.
- Study the impact of oral and topical 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 oral and topical candidate 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 affect 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 oral and topical 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 to and dissemination of HIV in humans, simian immunodeficiency virus (SIV) in small animals, and SIV or chimeric simian/human immunodeficiency virus (SHIV) in the lymphoid and other reservoir tissue in nonhuman primate models of infection.
- Determine the role of viral phenotype, genotype, clade, and resistance patterns on oral and topical microbicide activity. Delineate the relative impact of these factors 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.

- Study the impact of male circumcision and female genital cutting on HIV mucosal transmission mechanisms in the presence and absence of oral and topical microbicides.
- Investigate the effect of aging on the innate and adaptive immunity of the male and female genital tract and anus/rectum.

## OBJECTIVE–B: Discovery, Development, and Preclinical Testing

Support the discovery, development, and preclinical evaluation of oral and topical microbicide candidates, including probiotics and recombinant live microbicides used as single or multi-drug combinations and used alone and as oral/topical combinations.

### 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.
- Develop and validate biomarkers and other methods to assess the safety, efficacy, and genital pharmacodynamics of oral and topical microbicide candidates, determine adherence to product usage, and document the sexual activity and viral exposure 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 to investigate the very early events in HIV or SIV/SHIV 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 facilitate 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.
- 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 reflect the dynamics of sexual transmission of HIV, and the potential safety and efficacy of oral and topical 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 oral and topical microbicide products.
- Support and promote the development of novel models, technologies, and assays to discover, develop, and evaluate oral and topical microbicide candidates.
- Evaluate the efficacy of oral and topical microbicides against a variety of HIV viral resistance types, subtypes, and clades.
- Develop exploratory techniques such as genomics and proteomics and other systems biology approaches 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, pharmacogenetic, pharmacodynamic, and acute, chronic, and extended exposure toxicity testing of oral and topical 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 alternative, complementary, and nutritional therapies.
- Investigate the effect of variations in female and male endogenous and exogenous hormonal status 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 oral and topical microbicide safety and efficacy.
- Develop methods to solve manufacturing and synthesis hurdles that may prevent the advancement of microbicides through the preclinical pathway, by providing support for early Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP), manufacturing design, and scale-up.
- Collaborate with the Food and Drug Administration to accelerate the pace of development of combination topical and oral microbicide strategies.
- Develop and test specific assays that will inform which candidate microbicides should be advanced through the pipeline.
- Devise and test safety and pharmacokinetic algorithms that can determine which candidate microbicides should advance through the pipeline.

## 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

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#### Topical and Oral Microbicide Formulations and Modes of Delivery

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- 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.
  - Study the impact of long-term oral and topical microbicide exposure on genital and anal/rectal mucosal immunology and integrity.
  - Study the systemic- and tissue-level dose-response and bioavailability of oral and topical microbicides.
  - Identify and validate methods that improve the understanding of rheological and physical properties and provide optimal bioadhesion, biodispersion, retention, distribution, and tissue concentration of candidate microbicide formulations before, during, and after intercourse in the female and male upper and lower genital tracts and anal/rectum compartments.
  - Develop, standardize, and validate methods to measure local tissue, target cell, and systemic absorption and concentration following oral and topical microbicide use, and relate this to microbicide safety and efficacy.
  - Develop and incorporate age-appropriate and culturally sensitive measures and mechanisms to assess the acceptability of microbicides and their mode of delivery in females and males, including adolescents and young and older-age adults, that can be used in exploratory clinical studies and phased clinical trials domestically and internationally.
  - Develop and study methods to better understand the biological mechanisms and the 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 properties of the formulation and hormonal status, age, timing in the menstrual cycle, sexual practices, use of sexual enhancement products, vaginal and rectal practices, pregnancy, frequency of candidate microbicide product 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. Analyze the properties of candidate microbicide products that facilitate tissue safety, efficacy, and desirable biologic properties.
  - 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 sexual acts.
  - Develop and study reference formulations of candidate microbicides 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.
  - Develop novel, alternative formulations for microbicide delivery systems such as microbicide rings, films, gels, and suppositories as coitally dependent and independent formulations with short-term and extended-delivery dosing.
  - Evaluate the interaction of vaginal practices and rectal practices on the safety, efficacy, and rheologic properties of candidate microbicides.
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## 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 at-risk female and male populations, including adolescents, young adults, pregnant women, and adults over the age of 50 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 current HIV seroprevalence to meet the power threshold for the conduct of Phase I, II, III, IV, and accessory clinical studies.
- Design, implement, and evaluate novel testing assays and seroincidence assessments to provide current data that will identify appropriate communities for clinical trials implementation.
- Assess and integrate 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 on community-level and individual risk behavior on microbicides trials over the course of trial implementation.
- 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 microbicides 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 at-risk and 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 adolescence, pregnancy, menopause, and older age) and exogenous hormonal status in women and men on the pharmacokinetics, safety, efficacy, and acceptability of, adherence to, and 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 culturally appropriate 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 populations of varied ages.
- 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, with emphasis on consent for minors.
- 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, decisionmaking 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, and HIV resistance.
- 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 non-contraceptive 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 HIV resistance when antiretroviral (ARV) and non-ARV-based microbicides are used alone or in combination in HIV-infected individuals and those who seroconvert while using microbicide products. Identify and study the correlates of increased risk for ARV resistance.
- Promote and support the rigorous use of comparative effectiveness research 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 across the lifespan, including adolescents, young adults, pregnant women, and adults over the age of 50.

### 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 targeting adolescents and individuals over the age of 50. 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 and cost analysis research on the implementation and costs of behavioral interventions designed to support microbicide intervention, implementation, acceptance, use, 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 and males at varied ages, families, and communities that address the decisionmaking processes that determine use or nonuse of microbicides.
- Determine and study the optimal combination of biomedical and behavioral HIV prevention strategies that decrease risk for acquisition while using a microbicide that is known to have partial efficacy.
- Develop and test behavioral and social science research tools to predict and evaluate trends in microbicide use, 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 candidate microbicides in clinical studies.
- 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.
- Evaluate the impact of microbicide clinical trials on individual and community-level HIV-risk behavior.

## 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-uninfected and -infected 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 and career development opportunities to foster and develop the skills of new independent domestic 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 domestic and international institutional capacity for microbicides research, including laboratory capability, epidemiology and statistics expertise, data management/analysis, operational support, physical resources, human capacity, and the development of high standards of conduct for clinical research.
- Ensure the collaborative involvement of domestic and international community representatives and leaders in the planning and implementation of microbicide research.
- Foster and support the development of pilot and large-scale GLP and 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 domestic and international 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

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### FY 2012 RESEARCH PRIORITIES

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- Develop further understanding of biological–behavioral interactions and social/environmental 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 with or without antiretroviral treatment, and later-stage disease.
- Conduct translational research (i.e., dissemination, implementation, or operational research) to foster the scale-up and optimize the use of existing efficacious interventions to prevent and treat HIV infections. This research should address the processes of identifying, adapting, and disseminating interventions, as well as methods of providing technical assistance and ensuring quality control. Priority should also be given to developing methodologies needed for designing, analyzing, conducting, and interpreting such research, and to securing relevant participants’ input into design, analysis, conduct, and interpretation of such research.
- Study the continued disparities in HIV infection that manifest themselves among racial and ethnic communities in the United States and among similarly disproportionately affected populations in international settings (e.g., mobile subpopulations; migrant workers; refugees; and persons subjected to discrimination on racial, ethnic, or religious grounds) in order to identify epidemiologic, sociocultural, psychosocial, and structural aspects of epidemics that are unique to these communities and that would explain the disparities in acquisition, transmission, prevention services, health equity (to encompass not only access to care but also the root causes of health disparities), treatment provision, and/or progression of HIV infection within these communities.
- Develop and test methods of intervening at structural, environmental, and community levels to reduce transmission and acquisition of HIV, especially focusing on early intervention methods that address structural factors that have promise for large, long-term impact. Focus attention on prevention strategies that could be implemented in specific communities with high needs for prevention interventions, such as racial and ethnic communities, men who have sex with men, youth, women, transgender individuals, young adults in high-prevalence or high-risk areas, and older adult populations engaging in risk behaviors. Ensure the most effective utilization of funds by developing methods of integrating HIV prevention approaches within the context of existing infrastructure to deliver medical services and care. Assess means of reducing stigma associated with HIV and the impact of these reductions on transmission. Where necessary, conduct research to develop the methodological and statistical approaches needed to develop, implement, and assess these structural, environmental, and community-level interventions.
- Evaluate innovative methods of intervening to reduce HIV acquisition and transmission associated with sexual behavior and with drug and alcohol use, using methods that recognize the interdependencies and interactions of sexual behavior and substance use variables at multiple levels (such as at the individual, dyadic, group, community, societal, or policy level), as well as advances in development of community-based participatory research that fosters the ecological validity of such complex research.



- Advance research on adolescents' development of healthy sexual and relationship functioning to elucidate factors reducing risk of HIV infection through fostering healthy relationships for persons of all genders and sexual orientations; integrate knowledge of healthy sexual functioning, understanding of gender identity development and management of gender issues, and approaches to reducing disparities related to gender and/or gender identity into the design and evaluation of HIV prevention and care interventions.
- Ensure the use of state-of-the art methods and findings from behavioral and social sciences in the conduct of domestic and international research into viral, host, and environmental factors that affect morbidity, mortality, and response to antiretroviral therapy, as well as ensure the use of state-of-the art behavioral and social science in clinical trials in order to assess adherence, behaviors (e.g., drug and alcohol use) affecting trial outcomes (and eventual implementation of interventions), changes in sexual behaviors, mental health symptoms, and related issues such as stigma, access to care, and impact on HIV-affected family and community members.
- Examine the use of research and design methodologies from a variety of disciplines (e.g., economics and political science), to better evaluate the relationships among HIV risk and structural and environmental factors; incorporate methods of intensively examining the natural course of behavior change caused by and associated with interventions to inform development of better interventions.
- Foster the use of laboratory-based behavioral and social methods with human participants to more intensively examine risk behaviors and HIV-related outcomes to elucidate antecedents and determinants of risk, to clarify behavioral topography, to rigorously examine the role of alcohol and other drugs in risk behaviors, and to understand social forces affecting risk; develop methods to improve the ecological validity of laboratory studies where needed.
- Examine and evaluate approaches to maintaining the highest ethical standards in the conduct of HIV prevention science in order to ensure meaningful informed consent processes, decrease misunderstandings of the implications of trial participation, minimize risk of inadvertent harm to participants, and promote justice in research through the inclusion of difficult-to-recruit but critical populations.
- Foster research that explicitly differentiates among approaches to HIV/AIDS epidemics of varying types and stages to define priority targets for intervention according to the type and stage.



## OBJECTIVE–A: Preventive Intervention Research

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

### STRATEGIES

- Estimate the efficacy, effectiveness, and cost-effectiveness of tailored behavioral, social, and structural interventions in order to maximize their potential, when deployed singly or in combination, for stemming incident HIV infections. Apply basic behavioral and social science research to optimize intervention strategies.
- Support new research to identify the active components of efficacious, theory-based interventions for broader, sustainable implementation.
- Modify, adapt, or refine existing efficacious behavioral or social HIV prevention interventions to increase their impact and make them more easily administered to segments of the population most vulnerable to the epidemic.
- Study structural and systems-level interventions that seem likely to produce lasting impact over time by addressing the development of risk in youth and acquisition (e.g., men who have sex with men [MSM], transgender individuals, ethnic minority heterosexuals, injection drug users, and migrants).
- Continue development of interventions for persons with comorbid psychiatric and physical disorders.
- Conduct studies on medication-assisted substance abuse treatment modalities and access to care (e.g., methadone maintenance, buprenorphine/naloxone, modafinil, naltrexone, and antabuse) alone or in combination with mental health and behavioral interventions, as HIV prevention interventions.
- Examine the impact of widespread antiretroviral therapy (ART) availability on willingness to be tested for HIV, willingness to provide HIV testing, and decreased stigma associated with HIV.
- Support research on populations in which epidemiological evidence suggests a need for more effective HIV prevention interventions.

### Populations and Contexts

- Develop and test interventions targeted at HIV-infected persons to reduce sexual and drug-use behaviors that confer the greatest risk for HIV transmission.
- Support intervention research that addresses the impact of alcohol and/or drugs on sexual encounters that may contribute to HIV transmission and acquisition.
- Support research that addresses victimization history to reduce HIV transmission and acquisition.
- Develop interventions addressing modifiable determinants placing members of population subgroups at greatest risk for HIV transmission
- Support intervention research that addresses important determinants of risk among disproportionately affected groups that continue to demonstrate high-risk behaviors. Develop, test, and evaluate interventions that target individuals within prisons, jails, under justice system supervision, or returning to society from correctional settings.
- Develop, test, and evaluate interventions to improve linkage to existing systems of care that serve at-risk populations, including those that address single factors associated with incident HIV infections in isolation (e.g., sexually transmitted infection [STI] clinics) and those that do not routinely provide HIV prevention services (e.g., primary care or mental health clinics).
- Support the development of intervention strategies that adapt rapidly to changes in the epidemic.

## Effectiveness

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

## Systems

- 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 services that reduce HIV-risk behaviors and HIV transmission.

- Support research to understand and improve comprehensive care that reduces HIV transmission through reducing the fragmentation of HIV prevention, primary medical and dental care, drug and alcohol treatment, mental health treatment, STI treatment, reproductive health services, services for orphans and vulnerable children, and other care services. 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.
- Support research to develop flexible, pluripotent prevention intervention strategies for health care delivery systems providing prevention or treatment in other domains, such as family planning services, alcohol and substance use treatment, and psychiatric care.

## Methods

- Design and test behavioral interventions for highly vulnerable segments of the population to increase recruitment, retention, and adherence to protocols for HIV prevention research, including trials studying prophylactic vaccines, access to and use of HIV testing, microbicides, and other biomedical prevention methods.
- Encourage, where appropriate, the use of quasi-experimental designs and the evaluation of natural experiments in domestic and international HIV intervention research.
- Integrate behavioral, social, and biological measures to improve sampling, measurement of risk factors, and evaluation of outcomes, including measures of substance use, recent HIV infection, population-based outcomes (e.g., seroepidemiology), recent sexual exposure, and STIs, with the

overall goal of increasing the reliability and validity of measurement and sampling in prevention research.

- Support behavioral intervention studies that include HIV seroincidence data and other biologic markers as outcome measures.
- Support development of new, rigorous approaches for sampling “hidden” or “difficult to reach” populations in intervention studies.

## OBJECTIVE–B: Basic Behavioral and Social Science Research

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

### Consequences of HIV Disease

- Support (non-intervention) 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.
- Support research on the impact of HIV and its clinical course on aging and adult development, with attention to the consequences of accelerated physical aging that may accompany HIV disease and its clinical course.
- 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, concurrency, serosorting, 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, should also 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 may also include studies that investigate the relationship between any drug use and sexual risk behaviors.

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## Prevention

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- Study the acquisition and maintenance of HIV-related risk and protective behaviors associated with HIV transmission or disease progression in specific social and cultural contexts, such as the sexual dyad, peer groups, social and substance-using networks, families, and communities. This may include studies of HIV risk, transmission, and progression as related to cultural norms that affect disempowerment of and violence toward women.
  - Study HIV risk changes over time as a function of changes in the perceived severity of or susceptibility to HIV disease and developmental and life-course events (e.g., adolescence, childbearing, marriage or entry into other committed partnership, divorce and separation, and aging).
  - Conduct research on decisionmaking processes that relate to sexual and drug-related risk-taking across the life course.
  - Conduct research on individual social and cultural differences in human sexuality that have an impact on the sexual transmission of HIV; such research may include studies that examine how sexual behavior is affected by substance use and abuse, sexual abuse or coercion, developmental processes, and the formation and dissolution of intimate relationships.
  - Study the social, structural, cultural, and demographic factors (e.g., socioeconomic status, marital status, ethnicity, sexual identification, gender identification, age, and gender) that influence HIV-related behavior.
  - 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 findings 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.
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- 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, microbicides, and therapeutics.
- Support behavioral and social research on the acceptability, initiation, and use of biomedical and barrier HIV prevention methods and determine their impact on adherence to risk-reduction guidelines.
- 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 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.
- Evaluate consequences of coercive sex, sexual violence, and interpersonal violence on concurrent and subsequent sexual and drug use risk behaviors, with consideration of how intervention can mitigate or prevent coercion, violence, and their consequences.
- Evaluate the impact of assortative and disassortative mixing on HIV transmission rates, and identify modifiable factors related to these patterns of mixing.
- Support clinical studies on the role of alcohol in risk for HIV, including studies that provide evidence on the ecological validity of various experimental designs.
- Utilize clinical studies to better define risk behaviors and to inform prevention studies regarding points of intervention or measurement of variables (e.g., cues) associated with risk behaviors.

**OBJECTIVE–C: Consequences of HIV Infection**

Conduct treatment, health, and social services research for people infected 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.
- 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 HIV infection, including barriers associated with fear and stigmatization that affect access, linkage, engagement, followup, and adherence to health and social services across the care continuum (e.g., early identification of HIV infection, testing and counseling, health-care-seeking behavior, adherence, case management, and home/hospice care) and across the life course (i.e., from childhood to old age).
- Develop and test interventions to increase recruitment, adherence, and retention in HIV/AIDS clinical trials and care by HIV-infected persons from all vulnerable populations, with special attention to developmental and life-course issues.

- 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 research on the special factors affecting adherence in older seropositive persons and medical decisionmaking in care of older seropositives.

**Biopsychosocial Consequences**

- Develop and evaluate interventions to prevent the adverse psychological and social consequences of HIV infection and to assist HIV-affected populations in coping with HIV infections, maintaining quality of life, and avoiding engagement in HIV-related risk behaviors.
- Test interventions to address the neuropsychological, neurodevelopmental, and psychiatric sequelae of HIV infection.
- Develop and evaluate interventions to minimize the impact of stigmatization on HIV-infected persons, including on their decisions regarding treatment and quality of life.

- Test interventions designed to support formal and informal caregivers and family members of HIV-infected persons in order to prevent, for example, depression and burnout.
- 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, sexual minorities, the elderly, and incarcerated populations) and that reflect age-appropriate concerns.
- Develop and refine techniques for measuring social networks associated with HIV transmission.
- Develop and refine techniques for studying the use of digital technology, social media, and other innovations and their association with HIV transmission.
- Integrate behavioral, social, and biological measures to improve sampling, measurement of risk factors, and evaluation of outcomes, including measures of substance use, recent HIV infection, recent sexual exposure, and sexually transmitted diseases.
- Develop improved methods for the reliable and valid collection of sensitive information regarding sexual and drug-use risk behaviors.
- Develop and/or adapt innovative substance abuse assessment approaches.
- Assess new methodologies for testing the efficacy of environmental-level (e.g., laws and policies) interventions for reducing HIV risk.
- 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. Greater consideration needs to be given to probabilistic relationships among risk factors and other contributing variables, as well as practical constraints in the implementation and uptake of interventions.

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

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### Design and Statistical Analysis

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- Develop improved methods for sampling subpopulations (e.g., children, homeless persons, drug users, the elderly, sexual minorities, adolescents, and MSM of color) and spatial units (e.g., migration routes, drug or human trafficking routes, and political jurisdictions of interest), with particular attention to “hidden” or “hard to reach” populations.
- Research means of recruiting difficult-to-reach but critical populations, such as MSM, racial and ethnic populations, transgenders, women, adolescents, and other underaddressed or insufficiently understood groups in order to better understand how to involve these in relevant research projects.
- Develop improved and innovative methods and techniques for conducting and analyzing longitudinal studies of at-risk and HIV-infected populations, including improved participant retention strategies; statistical methods for dealing with participant attrition, missing data, and non-normal distributions; and methods for measuring and analyzing nonlinear patterns of behavior change.
- Foster the development and dissemination of design alternatives to the randomized controlled trial that permit cost-effective evaluation of combination intervention strategies that simultaneously target factors that increase risk for HIV transmission or acquisition.
- Foster the development, maintenance, and use of shared databases that will enhance the ability to identify and detect significant interactions between and within a variety of behavioral domains and also to identify the role of behavioral actions as mediators of biological outcomes of importance in HIV research.

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### Ethics and Other Issues

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- Evaluate the effects of legal and ethical constraints on methods of HIV research and service delivery, particularly among vulnerable or special populations.
- Use behavioral and social research methods to investigate factors associated with particular ethical and legal principles in research design (e.g., competence to provide consent, prevalence of adverse events, and associated remedies).
- Develop and refine research techniques to advance new studies as required by epidemiologic findings on HIV transmission. Encourage secondary data analysis; develop approaches to protect and document confidentiality.
- Develop and test an ethical framework for the use of biomedical interventions (e.g., ART) for HIV prevention that encompasses such issues as misconceptions of the preventive efficacy of experimental products, ensuring informed consent over the course of longitudinal studies, and the provision of products for HIV prevention that may not be available to persons living with HIV.
- Foster research designs that will be able to uncover the mechanisms of action in successful interventions that may be transferred and applied elsewhere.

AREA OF EMPHASIS

# Treatment as Prevention

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**FY 2012 RESEARCH PRIORITIES**

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- Develop safe, effective, feasible, and conveniently administered strategies for the prevention of mother-to-child transmission of HIV, with a focus on resource-limited settings and a special emphasis on breastfeeding transmission.
- Evaluate the mechanisms of treatment failure and develop strategies to maintain long-term undetectable viral load in HIV-infected individuals in domestic and international settings and to assess the impact of these strategies on the prevention of HIV transmission.

## 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 the development of drug resistance after antiretroviral (ARV) MTCT prophylaxis and its association with the efficacy of subsequent antiretroviral therapy (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.
- Evaluate the effects of acute HIV infection on MTCT.
- Investigate risk factors (e.g., immune, viral, and host-related, including infant microbiome) associated with transmission of HIV *in utero* and through breast milk.
- Develop reproducible, sensitive, and specific assays to detect and quantitate the amount of cell-free and cell-associated virus in breast milk and in genital fluids.

#### 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 approaches to maintain HIV-free survival of HIV-uninfected babies who are breastfed.
- 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 novel 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 or oropharyngeal transmission through breast milk and drug resistance in infants who become HIV-infected despite prophylaxis).
- 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 ARV Drug Resistance

- Evaluate the effects of pre-existing 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 ARV 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 ARV 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 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 ARV regimens that have lower risk of development of resistance in women or infants 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 the 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 and bone toxicity) in uninfected, HIV-exposed infants with perinatal ARV exposure, and develop animal models or laboratory assays that might be predictive of such effects with exposure to an individual ARV agent alone or in combination with other ARVs.
- Develop better clinical algorithms and laboratory assays to diagnose/assess mitochondrial toxicity associated with ARV exposure in infants and children.

- Develop 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.

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### Implementation Issues

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- Develop and evaluate strategies for implementation of effective perinatal transmission prevention interventions in developed and developing countries, including ways to increase the availability and acceptability of prenatal HIV testing and of prophylaxis to prevent MTCT.
- Improve the sensitivity and specificity of diagnostic procedures that are accessible, cost-effective, and have utility in developed and developing settings to permit the earliest possible determination of HIV infection in infants, and whether ARV and/or immunopreventive therapies affect the timing and sensitivity of these assays for diagnosis.
- Evaluate innovative methods, including rapid HIV antibody testing, to identify HIV infection in pregnant women with unknown HIV serostatus who present in labor, and to assess the acceptability of such testing and acceptability and efficacy of ARV prophylaxis to reduce MTCT, when administered to the woman intrapartum and her infant, or to her infant alone.
- Evaluate the public health impact of programs to prevent MTCT.

## OBJECTIVE–B: Therapeutic Approaches to Prevent Horizontal Transmission

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

### STRATEGIES

#### Mechanisms of Transmission

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

#### Interventions to Reduce Transmission

- Support domestic and international collaborative efforts to conduct trials of ARV, immunotherapeutic, and other treatment interventions 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, pre-exposure prophylaxis (PrEP), and other ARV methods of prevention.

#### Issues Related to ARV Interventions

- Evaluate the risk for developing ARV drug resistance (in cell-free and cell-associated virus, and in sequestered genital or anorectal sites) when using ARVs in interventions to reduce horizontal transmission, including the development of ARV 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.
- Develop the methodology and metrics to assess the outcomes of “test and treat” regimens.
- Develop novel approaches to evaluate data on PrEP and exposure in occupational settings.





**PRIORITY:**

Improving Disease  
Outcomes for  
HIV-Infected Individuals

Drug Discovery, Development, and Treatment



AREA OF EMPHASIS

# Drug Discovery, Development, and Treatment

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## FY 2012 RESEARCH PRIORITIES

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- Advance and share the discovery and validation of therapeutics strategies, including new and existing viral and cellular targets, to provide safe, tolerable, maximally long-term suppressive viral activity against existing viral strains, as well as emerging multi-drug-resistant viral strains.
- Advance the discovery and validation of therapeutics strategies to combat progression of HIV and its associated comorbidities, coinfections, and other clinical complications in HIV-infected individuals across the lifespan, including in older adults.
- Support research on the nature of HIV persistence and develop strategies to decrease or eliminate the viral reservoirs remaining despite optimal treatment.

## OBJECTIVE–A: Discover and Develop Anti-HIV Treatments

Identify and validate viral and host cellular functions required for HIV replication that can be targeted for viral inhibition, eradication of persistent virus, and prevention of transmission. Discover and develop novel agents and therapeutic strategies 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* and *ex vivo* organ or tissue 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 novel routes of administration.
  - ▶ 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 target 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. Post lead structures on publicly available databases.
  - ▶ Support genome-wide association studies and integrate systems biology approaches, including genomics and informatics paradigms, concepts, and methodologies (e.g., microchip-based screens [including siRNA] and analyzers), into mainstream drug discovery and the development of therapeutic entities and strategies.
  - ▶ Develop enabling, rapid, and high-throughput technologies to accelerate and optimize the discovery and development of therapeutic entities and strategies; expand the infrastructure to provide services and reagents needed by the scientific community.
  - ▶ Evaluate the intracellular 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 novel tools (including nanotechnology) for drug discovery and the investigation of drug efficacy.
  - ▶ Develop novel tools and systems biology approaches to better understand viral pathogenesis and drug pharmacokinetics in various intracellular and extracellular compartments.

- ▶ Develop novel bioimaging applications (including nanotechnology) to evaluate viral transmission and reservoirs, immune induction and modulation, and drug transport and metabolism.
- ▶ Develop novel 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 result 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 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-naïve and treatment-experienced HIV-infected individuals, across the lifespan, including in older individuals, 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 novel combinations of agents selected for maximizing antiviral synergy, complementary mechanism of action, minimal toxicity and cross-resistance, simplicity of administration, and tolerability.
  - ▶ Evaluate optimal therapies and novel strategies for individuals who have acute or recent infection (including neonates/young infants with perinatal infection), chronic infection but no prior 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;
- gender-based and genetic differences in special populations; and
- evaluation of interventions to minimize ART-related comorbidities.
- ▶ Support small clinical studies to validate potential new targets and/or explore novel therapeutics (e.g., cell-based and gene-based).
- ▶ Evaluate coformulated ARVs in all age groups.
- ▶ Investigate the effects of drug-sparing regimens on efficacy, resistance, and transmission.
- ▶ Evaluate treatment as prevention, including studies on factors (e.g., genital tract viral load, variations in genital tract microbiome, and genital coinfections) that may increase transmission from an HIV-infected individual to an uninfected individual.
- ▶ Evaluate novel approaches and treatment regimens to prevent and eradicate viral reservoirs that may lead to a cure for HIV disease.

#### Clinical Trials Enrollment

- Strengthen efforts and implement new approaches and in novel locations to ensure the enrollment and retention of specific populations, including women, children, adolescents, minorities, substance abusers, men who have sex with men, older adults, and marginalized high-risk populations in clinical trials and cohort-based studies to reflect the incidence of the epidemic.

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

### Clinical Trial Methodology

- Develop and evaluate standardized virologic, immunologic, and clinical markers to assess drug activity; determine and validate surrogate markers in response to various therapeutic interventions, including those most applicable to resource-limited settings.
- Develop novel inexpensive and rapid platforms, as well as point-of-care assay systems, for detection, diagnosis for recent HIV infection, 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 a methodology to facilitate creative statistical analyses that will facilitate the understanding of clinical trial outcomes.
- Conduct research on how and why subjects decide to participate in clinical trials in order to increase enrollment and maintain adherence to study protocols.
- Conduct studies on behavioral factors and prevention approaches that are critical to optimizing ART.
- 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, including medications taken by older individuals for pre-existing conditions, as well as other substances that may be used by HIV-infected individuals.
- Evaluate the effects of 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 body fluids and tissue compartments.

### 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.

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### Adherence and Self-Management

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- 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.
- 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 methods for drug toxicity in resource-limited settings.
- Evaluate whether nutritional status (particularly chronic malnutrition) affects the efficacy of therapy and whether it affects the risk or severity of adverse events associated with ART.

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### International

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- 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 in the United States and onsite in-country, infrastructure, and capacity building to facilitate the evaluation of ARV agents and other therapies in local settings.
- Assess the barriers to delivery of effective health care for HIV disease, including treatment and the capability of conducting international therapeutic clinical trials through the establishment or expansion of multidisciplinary clinical centers.
- Develop and evaluate simpler, sensitive, 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.



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

Develop strategies to predict, evaluate, treat, and prevent complications of long-term HIV disease and toxicities of 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 prophylactic regimens (e.g., for prevention of mother-to-child transmission), 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 and studies and 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.
- Develop and validate early markers of renal, liver, CNS, bone, and other complications of ART and/or long-term survival with HIV infection.
- Integrate metabolic, endocrine, cardiovascular, neurologic, renal, liver, and bone studies into ongoing and planned clinical studies, which may provide an opportunity to answer important questions related to potential complications of ART.
- Study the effects of gender, race, age, pregnancy and lactation 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.
- 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.
- Evaluate approaches to prevent and treat immune activation associated with HIV disease and treatment.
- Develop novel delivery systems to increase safety, tolerability, and ease of use of therapeutic agents.
- Develop novel tools (including nanotechnology, proteomics, and immunotechnology) for rapid DNA sequence identification to facilitate toxicogenomic research and applications.
- Evaluate the safety of current and proposed novel 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

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### Preclinical Discovery and Development

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- Support preclinical drug design and development programs to develop therapies against HIV-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 papillomavirus (HPV), KSHV/human herpesvirus type 8 (KSHV/HHV-8), cryptococcal infection, Epstein-Barr virus (EBV), and cytomegalovirus, 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 novel platforms for fast, accurate, and cost-effective detection and diagnosis of pathogenic organisms and related biomarkers.
- Encourage development of novel 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

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- 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 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; and develop improved strategies to minimize toxicities and the development of drug-resistant microorganisms.
- Support clinical trials in HIV-infected individuals, including children, of preventive and therapeutic regimens for HIV-related coinfections.

### Detection of HIV Coinfections

- 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.
- 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 treatment.

### 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.
- Develop models for studying biological interactions between HIV and coinfections that may lead to the development of new and better treatments.
- Support clinical trials, domestic and international, of adults and children coinfecting with HIV and TB (both active and latent infection). Evaluate the safety and efficacy of treatment regimens in coinfecting individuals. Determine the 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 coinfecting 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 coinfecting with HIV; determine how each infection influences or alters the other disease in respect to progression and response to therapy.

- Study the interaction of coinfections with HIV transmission (e.g., placental malaria and perinatal infections) and effects on HIV disease progression.
- Investigate the role of HIV-associated coinfections in stillbirths, perinatal delivery, and pregnancy/neonatal outcomes.

### 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.

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**International**

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- Conduct clinical trials in adults (including pregnant women) 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, optimize, 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.
- Assess the interactions between chronic HIV infection, HIV-associated neurocognitive disorders, and aging-related neurodegenerative disease.
- 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 and pharmacodynamics of ARVs; determine the importance of CNS drug penetration, particularly penetration of the blood-brain barrier, in reducing CNS infection in neurologically symptomatic and asymptomatic subjects.
- Develop novel bioimaging applications and bioassays to facilitate assessment of compartmental pharmacokinetics/pharmacodynamics.
- Develop strategies for manipulating drug transporters at the blood-brain barrier to facilitate entry of ARVs into the CNS compartment.
- Develop novel tools (e.g., nanotechnology) to facilitate and modulate delivery of ARVs 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 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, the generation of HIV variants, and changes in virus tropism on neuropathogenesis and response to therapy.
- Determine anatomical, structural, and genetic contributors (e.g., haplotypes and epigenetics) to neurological vulnerability to HIV infection and related inflammatory processes.
- Conduct studies to determine drug interactions between commonly used treatments for HIV disease and their complications, with treatments for drug abuse and co-occurring mental health disorders; develop treatments and regimens that are optimized for HIV-infected individuals with comorbid depression and other psychiatric disorders.
- Develop adjunctive therapeutic agents 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.
- Determine the incidence and prevalence of HIV-associated neurologic disorders, primarily HIV-associated dementia, minor cognitive and motor disorders, 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.

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### **Clinical Neuroassessment, Methodologies, and Trials**

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- Design and support clinical trials 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.
- Identify and validate biomarkers to compare HIV-associated neurological disorders with other cognitive disorders.

## 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 ART 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 nano-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 both domestic and international settings, and in adults and children.

#### Clinical Evaluation of Therapeutic and Prevention Strategies

- Develop therapeutic and prevention strategies (including vaccines) for AIDS-defining and other HIV-associated malignancies based on an improved understanding of the role of infectious agents (e.g., KSHV/HHV-8, EBV, HPV, HCV, Merkel cell virus, and HBV) in their pathogenesis.
- 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.
- Conduct research to assess the optimum therapy for cancers in HIV-infected individuals, including elderly patients.
- Develop, incorporate, and validate clinical trial methodologies to correlate tumor-specific responses in HIV-infected individuals with clinical benefit, including quality-of-life parameters; develop 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-defining and other HIV-related tumors.
- Support clinical studies of HIV-infected individuals with non-AIDS-defining malignancies in order to define the best treatment of these malignancies 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, stem cell therapy, 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

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### FY 2012 RESEARCH PRIORITIES

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- Encourage high-risk, high-impact research that explores specific environmental and societal factors, including economic disadvantage, racism, sexism, and homophobia that drive: (1) HIV-risk behavior; (2) HIV acquisition, transmission, and disease progression (including the development of viral resistance); and (3) access to, as well as adoption and retention of, preventive and therapeutic interventions for those at highest risk for HIV infection.
- Fund systems-focused research that examines the impact of policies; organization; financing; and delivery of HIV/AIDS-related prevention, care, treatment, and support services in disproportionately affected racial and ethnic populations, including those at highest risk for HIV infection. This includes operations and policy research with a focus on the impact systems have on the health outcomes of gay men and other men who have sex with men (MSM).
- Expand behavioral, intervention, and implementation research that focuses on HIV-related community capacity, preparedness, and/or response readiness (e.g., readiness to adopt specific prevention intervention measures). This research includes the familial, cultural, and community-level factors and their intersection that affect HIV infection, risk of infection, and related health outcomes in racial and ethnic populations.
- Identify practical and cost-effective HIV prevention interventions for racial and ethnic communities, including for those in a sexual minority within these communities.
- Develop and conduct population-specific primary research that focuses on individual-level determinants of HIV risk and infection, including biologic factors, resiliency, and cultural and social norms, in populations at highest risk for HIV acquisition and in communities disproportionately affected by HIV/AIDS. These communities include gay men and other MSM, sexually active women, transgender women, and drug users.
- Identify factors that increase HIV risk among racial and ethnic minority transgender individuals, and develop, pilot, and test models of HIV prevention that reduce or eliminate those factors.
- Fund basic behavioral, intervention, and implementation research that: (1) identifies the factors that promote treatment readiness and treatment adherence; (2) examines the biological and individual factors that affect treatment complications and outcomes; and (3) explores the intersection of individual, community, and systems-level factors that affect treatment outcomes in racial and ethnic populations, with a focus on disproportionately affected communities.
- Determine the impact of race and ethnicity on HIV progression and disease manifestations in racial and ethnic populations, including indigenous populations such as Native Americans, Alaska Natives, Pacific Islanders, and Native Hawaiians.
- Fund studies that examine the impact of incarceration on HIV stage at presentation for care, as well as stage of other comorbid diseases at presentation.

## OBJECTIVE–A: System Determinants of Health

Support systems-focused research that examines the impact of policies, organization, financing, and delivery of HIV/AIDS-related prevention, care, treatment, and support services in disproportionately affected racial and ethnic populations, including those at highest risk for HIV infection. This includes operations and policy research, with a focus on the impact systems have on the health outcomes of gay men and other men who have sex with men (MSM), sexually active women across the lifespan, transgendered women, and drug users.

## STRATEGIES

- 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.
- Develop, pilot, and test synergistic prevention interventions for high-risk HIV-uninfected individuals within health care systems.
- Adapt, test, and evaluate new systems-based HIV prevention interventions in disproportionately affected populations modeled upon widely disseminated, effective private-sector social marketing and health communication strategies.
- Utilize implementation science to identify the necessary components of HIV prevention interventions for efficient and rapid translation into racial and ethnic minority populations.
- Identify and modify system-level factors that create barriers to HIV prevention, care, and treatment for incarcerated racial and ethnic minorities when they are released back into their communities.
- Explore the systems of care available to seasonal workers and what factors facilitate, as well as prevent, engagement in HIV testing, care, and treatment.
- Identify and modify system-level factors that create barriers to HIV testing, care, and treatment for aboriginal individuals, including the role that traditional or indigenous medicine does or does not play.
- Identify venues that can effectively deliver acceptable, efficient, and dependable HIV testing for racial and ethnic populations.
- Examine the influence of bias, prejudice, and homophobia upon health care systems and HIV-testing behaviors among 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.
- Study the influence of educational systems, educational levels, and health literacy upon HIV awareness and risk behavior within racial and ethnic populations.



## OBJECTIVE–B: Environmental and Social Determinants of Health

Encourage high-risk, high-impact research that explores specific environmental and societal factors, including economic disadvantage, racism, sexism, and homophobia, that drive: (1) HIV-risk behavior; (2) HIV acquisition, transmission, and disease progression (including the development of viral resistance); and (3) access to, as well as adoption and retention of, preventive and therapeutic interventions for those at highest risk for HIV infection.

## STRATEGIES

- Explore the effects of poverty, residential segregation, inadequate educational opportunities, incarceration, and health literacy upon HIV transmission among racial and ethnic populations across the lifespan.
- 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 influence of race, ethnicity, language fluency, and gender, independently and collectively, upon the social and cultural contexts of HIV acquisition, transmission, and risk.
- Examine the impact of the intersection of poverty, racism, substance abuse, and historical displacement upon HIV-risk behavior and HIV resiliency in indigenous domestic populations, including Native Americans, Alaska Natives, Native Hawaiians, and Pacific Islanders.
- Develop, test, and evaluate new HIV prevention interventions in racial and ethnic minority populations modeled upon widely disseminated and effective social marketing campaigns.
- Study the impact of social, sexual, and drug networks upon the HIV risk of racial and ethnic youth, especially youth in sexual minority.
- Study the impact of social and sexual networks upon HIV resiliency and risk in racial and ethnic populations.
- Develop culturally and racially appropriate HIV testing and prevention interventions that utilize adolescent and youth culture for dissemination in their social and sexual networks.
- Explore the impact of seasonal 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.
- Determine the effect of stigma, racism, and racial/cultural stereotyping on access to HIV prevention, care, and treatment.
- Examine the influence of bias, prejudice, and homophobia upon health care providers and HIV-testing behaviors among racial and ethnic populations.

## OBJECTIVE–C: Family and Community-Level Determinants of Health

Expand behavioral, intervention, and implementation research that focuses on HIV-related community capacity, preparedness, and/or response readiness (e.g., readiness to adopt specific prevention intervention measures). This includes the familial, cultural, and community-level factors and their intersection that affect HIV infection, risk of infection, and related health outcomes 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.
- Develop, test, and pilot multidisciplinary HIV prevention and treatment interventions that target intersecting antecedents of HIV transmission (e.g., incarceration and drug use, poverty, and homelessness).
- Develop processes for, and measures of, community leader and community organization engagement that predict and/or facilitate effective community mobilization for evidence-based prevention interventions.
- Identify the factors that consistently predict the level of community readiness to engage with HIV prevention research.
- 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.
- Develop models to incorporate community-initiated HIV prevention intervention and evaluation in community–academic partnerships, especially in communities disproportionately affected by HIV.
- Develop culturally and racially appropriate health information tools and dissemination techniques to increase health information literacy and study its impact.
- 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.
- Evaluate interventions that incorporate traditional and indigenous medicines and medical practices for prevention of high-risk behaviors.
- Identify what constitutes sexual behavior “norms” in racial and ethnic populations, including sexual minorities.
- Explore the impact of prevalent community-derived interventions in response to HIV transmission (e.g., serosorting).
- Conduct community-based and community-driven participatory research on 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).

## OBJECTIVE–D: Individual-Level Determinants of Health

Develop and conduct population-specific primary research that focuses on individual-level determinants of HIV risk and infection, including biologic factors, resiliency, and cultural and social norms, in populations at highest risk for HIV acquisition and in communities disproportionately affected by HIV/AIDS. These communities include gay men and other MSM, sexually active women, transgendered women, and drug users.

### STRATEGIES

- Develop, pilot, and test synergistic prevention interventions for high-risk HIV-uninfected individuals within health care systems.
- Identify factors that increase HIV risk among racial and ethnic minority individuals in sexual minority, 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 decisions concerning HIV testing and testing frequency.
- Develop, pilot, and test effective models for increasing the awareness of the benefits of HIV testing in racial and ethnic minority individuals.
- 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 on older women in racial and ethnic populations.
- Conduct basic behavioral research on the determinants of sexual health, as well as HIV risk, in racial and ethnic minority individuals in sexual minority and their social networks.
- Develop, pilot, and test new ecological models of HIV behavioral interventions that incorporate common stressors and experiences for racial and ethnic minority individuals.
- Determine the impact of antecedent personal trauma (e.g., gender-based violence and childhood abuse) upon the adoption and maintenance of HIV prevention strategies in racial and ethnic minorities, with particular attention to adolescents and other individuals in sexual minority.
- Study the biological (including genetic), physiological, and environmental factors that affect HIV acquisition, transmission, and disease progression among racial and ethnic minority individuals.
- Explore the effects of hormone replacement and its biological impact upon racial, ethnic, and sexual minority individuals and the risk of HIV acquisition and transmission.
- Determine the impact of increased education levels on health literacy, HIV awareness, and risk behavior in racial and ethnic minorities.

## **OBJECTIVE–E: Expanding Research Methods and Measures**

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

### **STRATEGIES**

- 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.
- Develop novel sampling methods to enhance the proportion of underrepresented populations that are disproportionately affected by HIV infection in clinical and prevention research.
- 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, pilot, test, and evaluate new measures of HIV-risk behavior that are culturally and contextually appropriate for racial, ethnic, and sexual minority populations.
- Develop novel methods of delivering HIV care and treatment interventions in nontraditional venues for racial and ethnic populations, including those that utilize social networks and technology to enhance community penetration and effectiveness.
- Develop measures to assess the impact of evidence-based quality-of-care and best practices upon HIV disease outcome in racial and ethnic minority individuals.
- 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.
- Utilize implementation science to identify what determines which HIV prevention interventions are ready or necessary for efficient and rapid translation into the field.
- Evaluate interventions that incorporate traditional and indigenous medicines and/or medical practices that encourage adherence to prevention and/or treatment protocols.
- Develop, pilot, and test models of HIV behavioral interventions that incorporate common resiliency factors for racial and ethnic populations, such as cultural identity, spirituality, family ties, and collectivism.

## OBJECTIVE–F: Treatment and Treatment Access

Fund basic behavioral, intervention, and implementation research that: (1) identifies the factors that promote treatment readiness and treatment adherence; (2) examines the biological and individual factors that affect treatment complications and outcomes; and 3) explores the intersection of individual, community, and systems-level factors that affect treatment outcomes in racial and ethnic populations, with a focus on disproportionately affected communities.

## 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 the individual response to HIV therapy and the development of HIV drug resistance; and
  - ▶ Exploring the role of pre-existing health conditions disproportionately found in racial and ethnic minorities, such as cardiovascular disease, diabetes, and hepatitis, upon HIV treatment, disease course, and progression.
- Determine the impact of race and ethnicity on HIV progression and disease manifestations in understudied indigenous populations, including Native Americans, Alaska Natives, Pacific Islanders, and Native Hawaiians.
- Identify successful interventions to increase access to care and quality of care in racial and ethnic communities, and assess the impact of increased care upon HIV transmission in these communities.
- Examine the intersection of race, gender, and socioeconomic factors upon seeking, accessing, and remaining in HIV care and treatment.
- Develop and evaluate therapeutic strategies for preventing and treating complications of HIV infection, particularly those complications more prevalent among racial and ethnic populations.
- Develop novel multidisciplinary interventions that target the barriers to HIV care and treatment.
- Evaluate models for HIV prevention, care, and treatment that utilize comprehensive, culturally and contextually appropriate interventions for HIV-infected individuals in disproportionately affected communities.
- Identify community and environmental factors that can facilitate seeking and remaining in care.
- Strengthen—through enhanced research collaboration—nontraditional community partners for the conduct of treatment and treatment adherence research in racial and ethnic populations.

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

Expand the study of the interrelationship between HIV infection and comorbid conditions as they affect: (1) access to appropriate care and treatment, (2) adherence to treatment, (3) retention in care, and (4) health outcomes for racial and ethnic populations.

### **STRATEGIES**

- Examine the impact of alcohol, drug use, and chronic medical and neuropsychiatric comorbidities on care-seeking behavior.
- Examine the impact of substance abuse and chronic mental health comorbidities upon retention in care and HIV morbidity in racial and ethnic populations.
- Determine the impact of treatment interventions upon progression of HIV disease and HIV-associated coinfections and comorbidities, including hepatitis B infection and hepatitis C infection, tuberculosis (TB), and HIV-associated malignancies, in racial and ethnic individuals.
- Determine the roles of providers and patients, individually and collectively, in the success or failure of HIV treatment interventions, transmission of HIV resistance, and ultimate HIV disease progression in racial and ethnic minorities.
- Examine the impact of incarceration upon HIV stage at presentation for care, as well as stage of other comorbid diseases at presentation.
- Evaluate the impact of underlying cardiovascular, endocrine, metabolic, neurologic, psychiatric, and renal disorders upon treatment acceptance, treatment effectiveness, and HIV disease progression.
- Examine the resurgence of sexually transmitted infections within racial and ethnic communities and the impact of such resurgence upon treatment options and HIV morbidity and mortality.
- Explore the impact of late testing and combination antiretroviral therapy on the progression of opportunistic infections among racial and ethnic minorities, especially hepatitis B infection, hepatitis C infection, TB, and HIV-associated malignancies.
- Develop effective interventions to decrease the risk factors associated with the development of HIV-associated malignancies among racial and ethnic minority individuals living with HIV infection.

AREA OF EMPHASIS

# Women and Girls

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**FY 2012 RESEARCH PRIORITIES**

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- Design and conduct studies that integrate the biological, behavioral, and social sciences to explain factors that influence HIV risk, pathogenesis, and prevention in women, girls, and infants.
- Define and analyze normal and abnormal female genital tract and anal/rectal immune function and their impact on HIV risk and acquisition.
- Define and analyze the impact of aging on HIV risk, pathogenesis, and prevention in women compared with men.
- Develop and study interventions to prevent intrapartum and breastfeeding-related mother-to-child HIV transmission.
- Define and study interventions to affect maternal factors that contribute to mother-to-child HIV transmission.

## **OBJECTIVE–A: Determinants of HIV Transmission**

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

### **STRATEGIES**

- Evaluate the role of viral characteristics and host immune function on HIV transmission, acquisition, and resistance to infection.
- 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, innate and adaptive immunity, microbiology, and concomitant infections on cellular mechanisms on HIV transmission, acquisition, and prevention.
- Study genetic factors and the impact of host factors, including anatomic/physiologic changes, non-hormonal and hormonal contraception use, and vaginal and rectal 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 and exposure to semen 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 and mechanisms of infection.
- Develop standardized assays to investigate host, viral, and immune factors.
- Develop standardized 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 non-pregnant, HIV-infected and -uninfected women and girls across the life cycle.

### STRATEGIES

#### Joint Biomedical and Behavioral Strategies

- Support an integrated approach to HIV, STI, and pregnancy 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, cost-effectiveness, and cost-utility of health care, including reproductive health and social services, affect HIV risk, 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 HIV prevention interventions conducted in males on HIV and STI acquisition 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 women and girls and by their communities, health care providers, and prevention services providers.
- Support research to understand the impact of HIV-related policies and policy changes on HIV-risk behavior and transmission.
- Support research to identify and develop methods to overcome barriers to enrolling girls under the age of 18 and from racial and ethnic populations and other hard-to-reach populations into HIV biomedical and behavioral prevention intervention trials.
- Support research to evaluate the differences between trial participants and their in-trial behaviors and the general community in which HIV prevention interventions will be used.
- Develop and evaluate biomedical and behavioral interventions that target HIV-serodiscordant couples to prevent HIV and STI transmission and prevent or allow pregnancy.
- Investigate the interaction between HIV-risk perception, sexual behaviors and activity, and age of sexual debut 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 violence, power discordance, intimate partner substance use, and economic survival sex on HIV/STI risk.
- Discover, develop, and conduct 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 and breastfeeding.
- Conduct research to understand the impact of pregnancy intention and obligation for individuals, couples, and communities on the use of HIV prevention technologies and behaviors.

### Biomedical Strategies

- Investigate the interaction between HIV, its treatment, and aging and age-related comorbidities.
- Develop novel interventions that prevent or treat the comorbidities related to the long-term sequelae of HIV infection or its treatment.
- Discover, develop, and conduct 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-infected women and girls.
- Evaluate the impact of biomedical prevention interventions on upper and lower genital tract and anal/rectal physiology, microbiology, mucosal integrity, and innate and adaptive immunity on 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 innate and adaptive immunity on the risk for the transmission or acquisition of HIV and other STIs.
- Develop and study the efficacy of contraceptive and non-contraceptive biomedical interventions to prevent HIV and other STIs.
- Determine how mode of delivery, rheologic properties, and contraceptive efficacy of biomedical HIV/STI prevention interventions affect and improve acceptability and adherence.
- Analyze the interaction between HIV, STIs, trauma, sexual practices, contraception, and female genital mutilation, and how the presence of STIs and their specific or syndromic management affect upper and lower genital tract and anal/rectal physiology, microbiology, mucosal integrity, innate and adaptive immunity, 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 and on long-term morbidity and mortality.

- Develop treatment and technological interventions to prevent mother-to-child breastfeeding-related HIV transmission.

### Behavioral/Sociological Prevention Strategies

- Conduct and support behavioral intervention research to address the female- and couple-specific psychological, social, environmental, economic, and cultural dynamics that affect 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, aging, 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 behaviors and acquisition 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.

- Support behavioral and social science intervention research to reduce stigma and sex-related inequalities that may increase transmission to women.
- 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 non-pregnant 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 affect disease progression.
  - ▶ Determine the HIV viral dynamics, tissue distribution, and replication in blood and in all viral reservoirs specific to females in varied racial and ethnic populations across the human life cycle.
  - ▶ Investigate the role of cofactors and mediators of disease progression in both early- and late-stage disease, including:
    - Endogenous and exogenous hormones, puberty, pregnancy, aging, autoimmune diseases, and other concomitant diseases;
    - Opportunistic infections (OIs), other coinfections, HIV superinfection, HIV treatment, intermittent ART and monotherapy for the prevention of 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 risks for and novel characteristics and interactions, pathogenesis, screening treatments, and outcomes of HIV-related preneoplastic and neoplastic conditions, including human papillomavirus (HPV), specific to women and girls.
  - ▶ Study and outline the female-specific neurological and neuropsychological manifestations of HIV disease and underlying cofactors that affect these manifestations.
  - ▶ Investigate the impact of aging, 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 and related coinfections and 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 breastfed infants.

- Explore the role of pharmacogenetics on variations in the course of HIV disease and outcomes of ARV therapies in women and girls.
- 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, including cancer prevention and screening services.
- Study the impact of receiving an HIV-positive test result 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-naïve 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.
- Study interventions and other factors that affect adherence to HIV therapeutic regimens and to medical care.
- Evaluate the impact of comorbidities 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 HIV treatment 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 pharmacogenetics, pharmacokinetics, pharmacodynamics, ARV activity, and the toxicity of therapeutic agents on general health and on HIV disease progression in women and girls as compared with males across the life cycle.
- Investigate the medication interactions of ARVs, and of ARVs with other HIV-related and -unrelated therapies, specifically in women and girls.
- Evaluate the interaction and pharmacokinetics of ART and hormonal contraception when used simultaneously.
- Measure the quantity, frequency, and impact of alcohol, tobacco, and other substance use in women and girls in HIV-related therapeutics trials.
- Study the effects of ART on HPV-associated disease.
- Study the effect of the HPV vaccine on HIV disease and the reduction of HPV-related lesions in HIV-infected women and girls.
- Study viral-specific and ART-associated changes in the onset of puberty, the menstrual cycle, fertility, and sexual function and dysfunction.
- Study the effect of ARVs and other HIV-related therapies on HIV viral dynamics, tissue distribution, and replication in blood and viral reservoirs in women of varied race and ethnicity across the life cycle.

- Study how treatment interventions in acute and chronic HIV infection, including treatment during pregnancy, affect short- and long-term 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 quality-of-care guidelines on the community- and country-level health status of women and girls.
- Study the impact of stigma on access to and use of health services and HIV treatment.
- Study the impact of access to care for women on family health.
- 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.

## **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 clinical trial participants.
- Investigate the unintended social and community consequences of policies and practices (including research practices) that provide special benefits, including treatment for HIV-infected individuals.
- Investigate unintended harmful and beneficial consequences for women and girls, their families, their partners, 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.
- 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

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**FY 2012 RESEARCH PRIORITIES**

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- Develop in-country leadership and support sustainable capacity in HIV/AIDS research in low- and middle-income countries through strengthened research training in all relevant disciplines, by building research infrastructure, and through implementation and evaluation of new training methodologies (such as Web-based distance learning), in collaboration with other partners.
- Design and evaluate effective and sustainable biomedical and behavioral interventions at multiple levels (including complex, combined approaches), with a particular emphasis on social and structural interventions and implementation science, to prevent HIV transmission.
- Identify more effective care and treatment approaches, integrated with prevention and operational strategies based on implementation science research, to reduce HIV-related morbidity and mortality.
- Develop, refine, and validate assays and approaches to identify recent HIV infection, and develop cross-sectional measures of incidence densities across HIV-1 subtypes, host populations, and epidemic stages.

## OBJECTIVE–A: Capacity Building

Develop a sustainable, collaborative research environment by utilizing existing scientific and public health structures and enhancing in-country capacity.

### STRATEGIES

#### Site Development

- Assess existing international study sites supported by the NIH, and, as needed, further develop sustainable sites, or establish new in-country sites as rapidly as possible to address urgent and emerging scientific opportunities, while coordinating with ongoing NIH-funded research programs.
- Enhance capacity for the conduct of basic and applied prevention and treatment research, with emphasis on maintaining and developing both Good Laboratory Practice and Good Clinical Practice 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 diagnostic and clinical capabilities through research training and “hands-on” research experiences;
  - ▶ developing affordable alternatives to viral load, CD4+ cell counts, resistance testing, and other expensive laboratory tests used for monitoring treatment efficacy and toxicity;
  - ▶ developing alternative technologies and assays for the diagnosis and monitoring of HIV-related coinfections (e.g., tuberculosis) in resource-limited settings, with a goal to be more affordable, simpler (i.e., not requiring electricity, refrigeration, and/or computer), requiring less operator training, and environmentally more durable (i.e., withstanding high ambient temperature, humidity, and dust) than current technologies;
  - ▶ enhancing existing anatomic pathology and histopathology laboratory practices to develop more accurate (differential) diagnosis, ascertainment, and research capabilities of HIV-associated comorbidities, particularly in regions such as sub-Saharan Africa;
  - ▶ supporting the analysis of scientific and research-based international databases and developing common laboratory information management systems;
  - ▶ enhancing capabilities in medical records management, data analysis, and biostatistics;
  - ▶ addressing barriers in maintaining, optimizing the use of, and ensuring human subject protections related to repositories of biological specimens in resource-constrained countries;
  - ▶ developing and testing strategies that support the recruitment and retention of participants in prevention, treatment, and care studies;
  - ▶ optimizing epidemiological assessments of targeted 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, men who have sex with men, prisoners, and others at risk.
  - ▶ 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;
  - ▶ addressing regulatory issues and oversight mechanisms related to biomedical and behavioral clinical research;

- ▶ conducting research on the feasibility, success, and sustainability of rapid scale-up of 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 in intended populations;
- ▶ enabling communities to participate in the development and design of HIV-related research (including clinical trials) as well as in the translation of research results into community-relevant programs, standards of care, and practices;
- ▶ enhancing mechanisms for information exchange among investigators, including enhanced electronic communication;
- ▶ strengthening library services and access to scientific resources; and
- ▶ strengthening capabilities of in-country staff in financial/grants management, administrative practices, and scientific/peer review.
- Build global capacity to conduct implementation science (i.e., operational) research, including outcome and cost-effectiveness studies and modeling, to rapidly address emerging priorities in prevention, treatment, and care.
- Conduct studies on HIV 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.
- Foster regional approaches to research in order to enhance communication, avoid duplication of effort, achieve economies of scale, help establish new collaborations, and address common issues and needs (i.e., gap analysis) related to HIV-related research among countries in a given region, such as:
  - ▶ conducting regional meetings and training workshops;
  - ▶ facilitating the sharing of resources across regional sites; and/or
  - ▶ developing regional centers for advanced medical technology and/or training in foundation specialties (e.g., pathology, cytology, and radiology) to build workforce capacity.

### Collaboration and Coordination

- Ensure the leadership role of in-country investigators, community-based and indigenous leaders, and other stakeholders 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, data collection and analysis, publication, and presentation of research results to government and other relevant stakeholders and audiences.
- Encourage the integration and coordination of research projects being conducted by NIH-funded U.S. researchers in resource-limited countries with established in-country programs, while collaborating with local investigators on strategic planning for research, to ensure project relevance and to optimize the research effort.
- Encourage the continued development of research collaborations between international and U.S. investigators, 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.
- Coordinate with other U.S. Government agencies, foreign governments, and international organizations to help identify and support priorities for research infrastructure and capacity building in developing countries.
- Explore and assess the efficacy of collaborations with non-physician health professionals (e.g., nurses, pharmacists, and health aides) and community members (including faith and religious communities, elders, indigenous/traditional healers, student leaders, peer educators, and at-risk populations) to identify practices that may add value in treating and preventing diseases in diverse geographical settings and to facilitate their involvement as partners in AIDS research, prevention, and care, including the optimization of antiretroviral (ARV) rollout in settings with limited numbers of physicians and/or resources.

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### **Ethical Issues**

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- Ensure that research projects are designed to benefit the communities in which the research is being conducted by 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 culturally relevant issues in developing countries.
  - Identify ways to improve the application of ethical principles in the conduct of research in varied cultural settings by encouraging countries to develop their own set of ethical guidelines and procedures, to include the principles of respect for persons, beneficence, and justice, and the application of informed consent, assessment of risks and benefits, and selection of subjects.
  - Ensure that ethical review mechanisms, such as informed consent forms, are relevant and appropriate to the country where the research is conducted and are placed in an appropriate cultural context (including low literacy and local languages).
  - Ensure that all research is conducted in accordance with international standards of human rights principles and in accord with the dignity of persons.
- Provide improved access to information concerning treatment and prevention guidelines and research results through enhanced information technology.
  - Transfer clinical, laboratory, and public health technologies that may be sustained and used for implementation of prevention, symptoms management, clinical training, and patient care programs after research studies are completed.
  - Support operational research based on implementation science and innovative research designs not limited to randomized clinical trials (RCTs).

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### **Technology Transfer and Translation of Research Results**

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- Ensure that research 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 effective technologies to enhance communication of research results and translation into prevention, treatment, and care programs.

## 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.

### STRATEGIES

- Provide sustainable research career development opportunities, with incentives for working in-country, for new, junior, mid-career, and senior investigators 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.
- 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 (including non-physician professionals, such as nurses, midwives, and pharmacists), social and behavioral scientists, clinical pathologists, biostatisticians, public health professionals, community health workers, and other researchers from developing nations to enhance the conduct of research on HIV/AIDS, other sexually transmitted infections (STIs), and HIV-related coinfections, malignancies, and comorbidities.
- Provide training in data collection, management, and analysis for in-country research personnel.
- Provide training in the ethical conduct of research, including application of informed consent, establishment of community advisory boards, and other topics related to the protection of human subjects.
- Develop and provide training at international sites conducting vaccine studies on the role and responsibilities of an institutional biosafety committee.
- Enhance training in implementation science research (i.e., translational, operational, and health services research), including training in cost-effectiveness analysis.
- Provide training in all aspects of grantsmanship, including preparation of grant proposals, registration for electronic submission, grants management, reporting requirements, research administration, and fiscal accounting.
- Support research efforts to develop and assess the impact of novel training technologies with applications in low-resource settings, such as Web-based and distance learning, video conferencing, handheld platforms, and other innovative training tools.

## OBJECTIVE—C: Structural Interventions

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

### 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 behaviors and substance use in settings with varying levels of HIV seroprevalence;
  - ▶ assess approaches to 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 strategies 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.
- Evaluate the various approaches used by different countries for implementing structural interventions and investigate how these approaches may be systematically facilitated.
- Investigate the effectiveness of structural interventions for HIV, STI, and tuberculosis (TB) prevention, treatment, and care among incarcerated populations.
- Evaluate the effectiveness of interventions targeted to drug users and other at-risk populations.
- Develop and test strategies for encouraging voluntary and safe partner notification within the context of families and couples counseling.
- Evaluate the effectiveness and consequences of expanded access to male circumcision programs to implement such expanded interventions.
- Assess and determine optimal combinations of different interventions for specific populations at high risk, as no single intervention is likely to eliminate HIV transmission in all groups.
- Conduct empirical data analysis and modeling to determine required coverage levels for different interventions in order to attain basic efficiencies and maximal effectiveness for specific populations.
- Assess and determine optimal methodologies for evaluation of various structural interventions and their impact, encouraging the use of innovative study designs not limited to RCTs.

## OBJECTIVE–D: Interventions to Alleviate Stigma and Discrimination

Develop and test interventions that address the issues of sex/gender, age, power relationships, stigma, and discrimination.

### STRATEGIES

- Conduct research on sex/gender identity and age differences and their impact on inequities in access to and use of resources, prevention and care services, and adherence issues, particularly in settings where rights of minorities or vulnerable populations are limited and/or where stigma persists.
- 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 age-, sex-, and gender-related social, behavioral, and biological factors affecting susceptibility to HIV infection and its acquisition or transmission, including:
  - ▶ use of medications and/or contraceptives;
  - ▶ presence of gender-specific conditions, such as human papillomavirus (HPV) infection and cervical cancer;
  - ▶ intimate partner violence; and
  - ▶ the conflicting demands of childbearing and avoidance of disease.
- 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, stigma, and discrimination associated with HIV and AIDS, with particular emphasis on children infected with or affected by HIV.
- 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-TB drug regimens; and participate in HIV/AIDS research studies.
- Support the training of community leaders to become role models in the implementation of such strategies and interventions.
- Develop and strengthen innovative research methods, including measures and study designs, for investigating the impact of stigma and discrimination (and interventions to decrease stigma) on HIV prevention, care, and treatment-seeking behavior.
- Evaluate attitudes (e.g., stigma) of health care providers regarding HIV-infected individuals and the effect of these attitudes on provision of care and treatment.
- Study how stigmatization within small social networks (e.g., ostracism and interpersonal violence) can be minimized in order to increase utilization of counseling, testing, and ART, and to reduce further transmission.

## **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.

### **STRATEGIES**

- Develop and test sustainable interventions at multiple levels (e.g., individual, couple, group, and society) that address multiple risk factors of HIV acquisition and transmission, targeting both HIV-infected and -uninfected individuals in specific populations.
- Develop and test prevention strategies that reflect regional aspects of the epidemic.
- 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 of HIV.
- Study risk behaviors and prevention of such behaviors among individuals with perinatally acquired HIV who are surviving into adolescence and young adulthood.
- Study the movement of the HIV epidemic across borders and regions, and evaluate the effects of various policies and structural interventions related to migration and immigration on HIV transmission.
- Identify the most effective strategies to reach and prevent HIV transmission among mobile or at-risk populations.
- Develop analytical tools and support innovative methodologies, including ethnographic studies, to better understand and evaluate risk behaviors within social networks.
- 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 (e.g., drug and alcohol users and individuals with physical and/or mental disabilities) 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.
- 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 substance use initiation, dependence, and transition to riskier drug practices, such as initiating drug injection and sharing of injection equipment.



## OBJECTIVE–F: Biomedical Prevention Interventions

Develop and evaluate the application of complex and combined biomedical prevention interventions and strategies.

### 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, including treatment as prevention.
- Study and integrate the behavioral aspects of complex, combined 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.
- Conduct research to better understand coverage of available prevention interventions and barriers to their access.
- 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 acceptability of male circumcision.
- 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.
- Evaluate whether circumcision is associated with behavioral disinhibition.

### Antiretroviral Use

### Male Circumcision

- Determine the durability of effectiveness (i.e., sustainability) 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.
- Determine the effectiveness of pre- and postexposure ARV prophylaxis in prevention of sexual and blood-borne HIV transmission, while continuing to study and monitor drug resistance.
- Determine the most effective ARV agents, formulations, or combinations of agents to reduce transmission risk.
- Focus on compartments including ARV optimization in genital secretions and in the anorectal and gut mucosa.
- If proven effective, determine the social, cultural, and practical factors affecting ARV use and/or providing barriers to implementation of pre- and postexposure prophylaxis.

### HIV Vaccine Development

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

### Microbicides and Barrier Methods

- Discover and develop candidate microbicides (including ARV-based microbicides) and other physical/chemical barrier methods to prevent sexual HIV transmission.
- Conduct Phase I, Phase II, and Phase III clinical trials of suitable candidate microbicides in diverse international settings for safety and efficacy.
- 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 (particularly female-controlled 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, acquisition, and disease progression.
- Determine the role of sexually transmitted coinfections on HIV transmission, acquisition, and disease progression.

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### Substance Abuse

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- Develop and evaluate innovative, culturally relevant, contextually appropriate alcohol and drug abuse treatment programs for their utility as HIV and hepatitis C virus (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, including those in high-income social strata.

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### Mother-to-Child Transmission: Considerations for the Mother, Child, Adolescent, and Family

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- Develop and evaluate strategies:
  - ▶ for primary prevention, i.e., prevention of HIV acquisition by adolescent girls and women;
  - ▶ to evaluate reproductive decisionmaking and improve reproductive health in serodiscordant couples, including HIV-risk reduction during *in vitro* fertilization; and
  - ▶ for prevention of unintended pregnancy by HIV-infected adolescent girls and women, and study factors associated with unintended pregnancy.

- Investigate the mechanisms of and risk factors for *in utero*, intrapartum, and postnatal mother-to-child transmission (MTCT) of HIV.
- Develop new effective, safe, and feasible strategies to further decrease vertical transmission of HIV, particularly postnatal (breast milk) transmission, or provide alternatives to currently identified effective strategies.
- Further evaluate and adapt known efficacious interventions in infants, mothers, or both to prevent MTCT (i.e., ARV prophylaxis, cesarean section before labor and before ruptured membranes, complete avoidance of breastfeeding, exclusive breastfeeding, and ARV prophylaxis to breastfeeding infants and/or lactating mothers).
- Evaluate the effects of perinatally acquired HIV infection in adolescent girls who become pregnant and receive treatment regimens to prevent MTCT.
- Evaluate acquisition of HIV infection during pregnancy:
  - ▶ quantify more precisely the risk of MTCT when maternal HIV infection is acquired during pregnancy; and
  - ▶ develop strategies for detecting or reducing maternal incident infection during pregnancy.
- 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 -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.
- Conduct implementation science research on identifying barriers to developing effective strategies for scale-up and delivery of successful interventions for prevention of MTCT of HIV, in view of the new World Health Organization (WHO) recommendations on prevention of MTCT and infant feeding.
- 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.

## 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.

### STRATEGIES

- Characterize the clinical course of HIV infection in diverse geographic settings.
- Conduct research on biological, behavioral, and psychosocial effects related to the treatment and care of HIV disease among children and adolescents (both horizontally and perinatally infected).
- Develop and evaluate suitable and sustainable approaches for the diagnosis of HIV infection, especially for children under the age of 18 months.
- Collaborate with clinicians from resource-limited countries to identify, recruit, and retain individuals with acute and early HIV infection in treatment research programs.
- Identify affordable, safe, and effective ARV regimens, including timing of initiation and durability of initial treatment, and study the 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 settings.
- Develop appropriate pharmacovigilance systems to evaluate short- and long-term effects of treatments provided to HIV-infected individuals (including special populations such as children, adolescents, pregnant women, and alcohol and substance users).
- 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 (on 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 in pregnant women.
- Evaluate and monitor treatment effectiveness, adherence, drug–drug interactions, drug resistance, 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 ART).
- Develop and test region-specific strategies, including promotion of treatment literacy for health care workers, people living with HIV/AIDS, and family and community members, to support adherence to medication regimens in adults, adolescents (including those who acquired HIV through perinatal transmission), and children 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.

- 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, and determine whether expanded ART care leads to a decrease in HIV-associated stigma.
- 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.
- Evaluate the effectiveness of different approaches to task shifting for HIV care and treatment from physicians to non-physician staff.

## OBJECTIVE–H: Endemic Diseases, Comorbidities, and HIV

Study the interactions between HIV infection, endemic diseases, and the entire spectrum of comorbidities (including alcohol and substance use, psychiatric illness, and other organ system disorders), with a particular focus on diseases that affect HIV care, and develop strategies to optimize their integrated prevention, diagnosis, treatment, and care.

### 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 and urologic diseases; musculoskeletal and skin disorders; 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 responses 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 coinfections, opportunistic infections (OIs), and comorbidities.
- Identify affordable strategies to target high-risk patients for initiation of prophylaxis for HIV-related coinfections, OIs, and comorbidities.
- Develop and test new, low-cost, effective, and rapid diagnostic tools and drug susceptibility tests for comorbid diseases, including TB and malaria.
- Examine the role of coinfections 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 in HIV-infected patients.
- Develop and study feasible and effective strategies for prevention of transmission of drug-susceptible and drug-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 HIV-infected adult, pediatric, and adolescent populations, 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 in HIV-infected adult, pediatric, and adolescent populations, including pregnant women.

- 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 the development of resistance to ARV and anti-TB drugs in clinical study participants.
- 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 coinfecting 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 to develop adequate clinical approaches to the management of such cancers in regional settings.



## 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.

### 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 and entry into care and treatment in various communities.
- Determine how availability of ARV prophylaxis for prevention of MTCT affects entry into antenatal care (ANC) and utilization of VCT within ANC.
- Develop effective strategies to integrate the delivery of HIV care with other medical and social services, while enhancing and optimizing linkages among interdependent programs, such as those for control and management of TB and other comorbid conditions, alcohol/substance abuse or dependence treatment programs, maternal and child health services and family planning, and support services for the elderly.
- Evaluate the interactions of ARVs with alcohol, psychoactive drugs, or medications used for the treatment of substance abuse, and investigate the effects of these comorbid conditions (and their integrated treatment) on HIV disease progression, adherence to treatment regimens, and clinical outcomes.
- Determine how ART affects breastfeeding behaviors.
- Identify comorbidities 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.
- Develop biomarkers that can serve as surrogates for measurement of HIV-risk behaviors and can be used to predict and monitor rapid escalation of HIV subepidemics (i.e., in local areas or in high-risk groups).
- 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 and test optimal strategies to integrate ART treatment programs with region- and/or country-specific cancer services for diagnosis and management of HIV-associated malignancies to allow a continuum of care and enhanced outcomes of comprehensive HIV care.
- Develop demonstration programs that simultaneously address prevention, care, and treatment.
- Examine the potential use of HIV therapeutic vaccines.
- 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 and strengthen existing infrastructure that simultaneously address multiple health outcomes.



## AREA OF EMPHASIS

# Training, Infrastructure, and Capacity Building

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## SCIENTIFIC OBJECTIVES AND STRATEGIES

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### OBJECTIVE–A: Research Training

Provide training in biomedical, social and behavioral, and intervention research on HIV and its associated complications, coinfections, and comorbidities, with an emphasis on multidisciplinary research in gender-diverse and racially and culturally diverse and marginalized populations domestically and in developing countries with high HIV incidence and/or high prevalence of HIV infection.

### STRATEGIES

- Increase opportunities for prebaccalaureate, undergraduate, predoctoral, doctoral, postdoctoral, and advanced research training across a broad range of AIDS-related scientific disciplines, and support research to better understand the barriers and incentives along the research career pathways for investigators.
- Expand the NIH AIDS Loan Repayment Program to encourage promising U.S. scientists and physicians from disadvantaged backgrounds and from racial and ethnic populations to pursue HIV-related research careers.
- Establish mentoring networks to improve the supply of trained mentors for the development and retention of new investigators in all aspects of AIDS research, and 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 programs to improve recruiting, training, mentoring, and retaining investigators in AIDS research, especially those from diverse scientific backgrounds, including biomedical, behavioral, and social scientists.
- Provide new incentives and research training opportunities to attract newly trained investigators and established researchers from other fields to pursue AIDS research.
- Support the development and sharing of novel techniques from relevant research fields to the HIV field, including structural biology, computational biology, and systems biology to understand HIV-associated disorders. Encourage and facilitate collaborative and interdisciplinary research in these areas.
- Implement new research training programs for non-physician professionals (e.g., physician assistants, nurse practitioners, and laboratory staff) in resource-limited settings and at domestic sites to increase the diversity of the pool of AIDS researchers.
- Develop collaborative evaluation research programs to assess the efficacy of strategies to shift HIV care tasks in resource-limited settings to non-physician-professional trained individuals.
- Strengthen cultural competency training and ethics training for the conduct of HIV/AIDS research in vulnerable populations, in both domestic and international settings.

- Expand training programs to increase the capacity for basic and clinical research on HIV and HIV-related complications, coinfections, and comorbidities in domestic and resource-limited countries, including tuberculosis, hepatitis B virus, and hepatitis C virus.
- Develop research training programs in the area of blood safety to develop improved blood screening strategies and technologies and appropriate use of transfusions.
- Support training programs for pediatricians in HIV prevention, diagnosis, manifestations, complications, and treatment.
- 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 training programs for veterinarian scientists conducting AIDS research using animal models, including nonhuman primates (NHPs).
- Provide training in Good Laboratory Practices/ Good Clinical Practices for staff in domestic and international settings where clinical research on HIV/AIDS is being conducted.
- Support training opportunities in the use of advanced computer and information technologies for HIV-related biomedical and behavioral research, and support access to appropriate tools and equipment at the end of training.
- Support analysis of distance learning used to teach research and research-related topics, to assess and better understand the acquisition of research skills and competency.
- Develop new models of integrated training and mentoring that focus on the protection of human and animal subjects in AIDS research.
- Support training programs for personnel in institutions in resource-limited settings to strengthen the administrative and financial management capacity needed to conduct AIDS-related research.
- Expand programs that provide support for international AIDS researchers trained in NIH-sponsored programs to continue their studies in their home countries.
- Expand programs that utilize the infrastructure at NIH-sponsored AIDS clinical trial sites for training programs in the design and conduct of clinical research.
- Further develop, validate, and utilize experimental animal models, *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.

## 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

- Enhance and improve research capacity and infrastructure to advance research on HIV and HIV-associated coinfections, comorbidities, and other complications.
- Enhance and improve the infrastructure to conduct clinical trials of prevention and therapeutic strategies in domestic and international sites, including laboratory capacity, trained scientists and other personnel, appropriate participant cohorts, and establishment of local institutional review boards to address bioethical issues.
- Support the infrastructure necessary for producing AIDS vaccine candidates under Good Manufacturing Practices for preventive and therapeutic vaccine clinical trials.
- Develop, maintain, and effectively utilize domestic and international cohorts, repositories, and nested studies among populations experiencing emerging and ongoing HIV epidemics, and maintain updated databases, allowing their broader and more efficient use by the scientific community, when appropriate.
- Establish and support quality-controlled repositories, biobanks, and well-characterized panels of reagents to ensure access by qualified scientists to human blood and tissue specimens from clinical trials and cohorts. Improve and disseminate the process of requesting, prioritizing, and receiving these specimens to allow timely and equitable access.
- Promote Internet connections, cell-phone-based communication, and online social networks, including those with virtual worlds for training, infrastructure, and treatment. Ensure availability of pertinent information technology at health science centers, hospitals, outpatient clinics, community-based organizations (CBOs), and other access points, both domestically and internationally, for HIV-related research and patient care.
- Develop statistical sampling methodologies, data collection protocols, and statistical analysis tools that are easy to use and adaptable to different settings; facilitate efficient statistical analysis and report generation and enhance standardization, when appropriate, in the context of AIDS research.
- Promote research in, and application of, medical informatics (e.g., high-performance computing) for AIDS research and clinical practice in resource-limited settings, both domestically and internationally.
- Develop efficient and effective systems for collecting and managing HIV/SIV/SHIV (chimeric simian/human immunodeficiency virus) multiple-center and single-site clinical and animal model trial data, and ensure timely and accurate dissemination of clinical and animal model trial information.
- Increase collaborations between CBOs and other Government-supported health care service providers and academic researchers to improve the quality and capacity of HIV/AIDS research in health care service settings.

### DOMESTIC

- Support enhanced research infrastructure at U.S. minority-serving institutions to improve capacity to support AIDS research.
- Support HIV/AIDS research planning and organizational initiatives targeting domestic minority institutions and minority-serving communities, with emphasis on initiatives that develop academic–community partnerships.
- Expand opportunities for institutions serving specific diverse populations at risk for HIV/AIDS to develop equal and productive partnerships with U.S. majority institutions.

- Develop programs to sustain human capacity and to link U.S. AIDS research scientists, industry partners, and relevant institutions with each other and with investigators and institutions in both resource-developed and -developing countries.
- Develop strategies to promote the infrastructure for bidirectional translational science by enhancing national capacity for clinical and translational HIV research; supporting team-building, consortium collaborations; and facilitating the use of national data-sharing HIV networks.
- Support and expand adequate facilities and resources, including BSL-2/3 (Bio Safety Level 2/3) facilities for studies in NHPs, and provide appropriate ethical and procedural training to house and breed NHPs for use in AIDS research.
- Expand the breeding of genetically defined specific pathogen-free NHPs, with emphasis on Indian-origin rhesus macaques.
- Develop and characterize appropriate reagents for use in HIV-related research conducted in different species of macaques and other NHPs.
- Support programs that enhance the current AIDS research infrastructure, such as the Centers for AIDS Research, the Research Facilities Improvement Program, and the National Primate Research Centers.
- Support the Biomedical Technology Research Centers Program for structural studies of HIV proteins and host proteins.
- Develop and improve conventional and electronic systems for documentation of medical care and tracking of HIV/AIDS in low-resource settings to improve epidemiologic research.
- Increase population-based cancer registration in resource-limited countries to allow for a better understanding of cancer rates in HIV-infected persons in these locations.

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## INTERNATIONAL

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- Enhance and improve research capacity and infrastructure in resource-limited settings with high HIV incidence, with particular emphasis on facilities for research on HIV prevention, therapeutics, and behavioral interventions.
- Enhance coordination and collaboration among NIH-supported investigators, other U.S. Government agencies, and other international agencies conducting HIV/AIDS research in the same countries.







**PRIORITY:**

Translating Research  
From Bench to Bedside  
to Community

Natural History and Epidemiology

Information Dissemination



## AREA OF EMPHASIS

# Natural History and Epidemiology

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### FY 2012 RESEARCH PRIORITIES

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- Integrate data from clinical trials and observational studies with simulation, mathematical modeling, and other advanced statistical methods with the goal of assessing the short- and long-term effects of preventive and therapeutic interventions, including multicomponent intervention strategies, in domestic and international settings.
- Develop, maintain, and effectively utilize research resources, such as domestic and international observational and intervention studies, collaborative networks, databases, and biological sample repositories from populations experiencing emerging, re-emerging, and ongoing HIV epidemics.
- Encourage development and evaluation of novel methods for HIV testing, linkage and retention to care, and for monitoring response to care for use in domestic and international settings. This priority activity would include conducting research on: (1) accurate, reproducible, and affordable virologic, immunologic, pharmacologic, and genetic assays; (2) measures of the outcomes of HIV testing programs; (3) accurate and cost-effective point-of-care diagnostics and monitoring technologies; (4) assays to determine HIV incidence at the population level; (5) methods for evaluating the outcomes of initiation of antiretroviral therapy at a population level; and (6) methods for measuring, preventing, and treating comorbidities.

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

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

### STRATEGIES

- Utilize existing cohorts, and develop new cohorts of novel subpopulations (especially newly emerging, vulnerable groups), to employ novel methods (e.g., social/sexual network analysis, molecular epidemiology, temporal phylogenetic analyses, and geographic information systems), alone and in combination, to further assess the magnitude of and risk factors for HIV transmission.
  - Optimize the use of existing cohort data to evaluate the impact of differing demographics (e.g., socioeconomic status, race, ethnicity, gender, age, and sexual orientation) on the risk of HIV acquisition and to assess the impact of in-country resource capacities and availability on HIV progression and outcomes.
  - Conduct molecular epidemiology studies to identify and estimate the prevalence and correlates of divergent viral genotypes, drug resistance, and neutralization profiles and their temporal trends; characterize how different HIV types, subtypes, and recombinant forms influence routes and modes of HIV transmission, superinfection, natural history, response to antiretroviral therapy (ART), response to pre-exposure prophylaxis, and emergence of antiretroviral (ARV)-resistant viruses.
  - Conduct studies on the clinical and public health 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.
  - Refine epidemiologic and mathematical models 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 (e.g., drug use, psychiatric comorbidities, and ART).
  - Examine the test-and-treat concept in the United States and internationally, using both clinical and mathematical models, focusing on test-and-treat both alone as a form of prevention and also as part of a larger scale prevention package.
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- ### Strategies Related to Transmission and Its Prevention
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- Investigate viral, host, and environmental characteristics that distinguish individuals who have not become infected with HIV despite intensive or prolonged exposure to the virus.
  - Evaluate the risk of sexual and blood-borne HIV transmission in relation to the following:
    - ▶ Viral factors such as viral quantity, diversity, coreceptor usage, genotype (e.g., types, subtypes, recombinants, and resistant 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 factors such as age, sex, race, socio-economic status, country of origin, hormonal status, strength and breadth of immune response, comorbid chronic diseases, coinfections, and host genetics;
    - ▶ Modifiable factors such as diet and nutritional status (including food insecurity); geographic location (urban, rural, and mobility); drug, alcohol, and tobacco use and/or treatment; mental health; housing; circumcision status; behavioral interventions; and access to and use of health care;
    - ▶ Other infections, 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, behavioral, social, cultural, geographic, and structural determinants of susceptibility to HIV acquisition among hard-to-reach and vulnerable populations (e.g., transient and mobile populations; sex workers; injection and noninjection drug users; and racial/ethnic minorities); and
  - ▶ Sexual activity, abstinence (including during the postoperative period after male circumcision), pregnancy, sexual networks, partner choice (i.e., serosorting or choosing partners from high–low-prevalence populations), partner concurrency, partner fidelity, duration of partnership, sex trade, control of STIs, hygienic practices such as douching, contraception choices, cultural practices such as the use of traditional vaginal preparations and male circumcision, and use of drugs/alcohol during sexual activity.
- Further refine the timing, mechanisms, and risk factors in perinatal and postnatal transmission, including HIV testing and treatment of the mother, infant feeding modalities, fertility interventions, child spacing, physiology of lactation, long-term effects of perinatal interventions, maternal and infant genetic variation, and kinetics of viral resistance. These studies include:
- ▶ Studying practices and barriers to HIV testing of the mother during prenatal care, during labor, and of the infant after birth;
  - ▶ Assessing the impact of maternal and infant ARV regimens of different potency and duration on mother-to-child transmission (MTCT) of HIV, 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 access and provision of maternal ART, identification of successful breastfeeding weaning strategies, methods for improving the safety of formula feeding, ongoing HIV testing of the child, and determining the effects of such approaches on infant morbidity and mortality;
  - ▶ Evaluating maternal HIV risks during pregnancy, including the optimization of maternal HIV testing, behavioral and hormonal risks, risk of MTCT during incident infection or after pregnancy, and optimization of ART for prevention of MTCT (PMTCT);
- ▶ Assessing the impact of maternal and infant adherence to ART on the risk of subsequent ARV resistance, clinical outcomes, and the effectiveness of ART in mothers and their children;
  - ▶ Assessing the clinical and economic impact of investments in alternative components of the PMTCT cascade, from maternal testing to receipt of test results, provision of PMTCT regimens, retention in care, and infant testing;
  - ▶ Assessing the impact of perinatal treatment and prophylaxis regimens on community-wide HIV resistance to ARVs, future regimens, and costs of care;
  - ▶ 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; orphans; and pediatric neurobehavioral development; and
  - ▶ Assessing the clinical outcomes, cost, and cost-effectiveness of different strategies for prevention of MTCT.
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- Strategies Related to Prevention and Treatment**
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- Conduct epidemiologic modeling studies on the aggregate impact of ART on HIV transmission in the presence or absence of other biomedical and behavioral interventions, particularly in settings with endemic, high-prevalence, and emerging epidemics.
  - Study the impact of widespread ART availability, adherence, HIV-related comorbidities, and patterns of ARV resistance on HIV prevalence, incidence, community-level viral load, risk behaviors, and the transmission of resistant HIV strains.
  - Conduct studies to assess the clinical (i.e., individual) and public health value of programs to promote widespread, frequent HIV testing with immediate linkage to care and ART.

- Conduct research to increase the uptake of and adherence to all steps of the testing and treatment process (testing, linkage to care, initiation of ART, and adherence to ART), with the goal of reducing community-level viral loads.
- Conduct studies of male circumcision as an HIV risk-reduction strategy, including:
  - ▶ Assessing the impact of adult male circumcision on HIV incidence in circumcised men and their partners, and on 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 prevention and risk-reduction 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, with consideration of the timing of male circumcision.
- Develop and evaluate the effectiveness of individual-, couple-, network-, and community-based interventions for HIV-infected and at-risk persons and their partners to sustain behavioral change and prevent acquisition and transmission of HIV, especially in racial and ethnic minorities, injection drug users, and men who have sex with men (MSM).
- Assess the effectiveness and long-term sustainability of various combinations of prevention strategies (e.g., behavioral changes, ART, biomedical interventions, and treatment for coinfections and comorbidities).

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

Use epidemiological research in domestic and international settings to identify the effectiveness, impact, and interactions of HIV-related therapeutics (e.g., ART and opportunistic infection [OI] prophylaxis), biological factors (e.g., age, host genetics, coinfections, comorbidities, HIV types and subtypes, and viral genetic variation), and behaviors (e.g., health care system use; adherence; sexual activity; and smoking, alcohol and drug use) in relation to HIV progression and response to ART, as indicated by virologic, immunologic, and clinical outcomes.

### 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 to determine the changing spectrum of HIV disease; identify highly exposed uninfected persons, long-term non-progressors, and elite suppressors; and evaluate interventions, especially in aging and minority populations, in resource-limited countries, and in emerging epidemic zones.
- 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 or no exposure to ART, those with virologic and/or immunologic responses to ART, and those who have experienced ART failure.
- Determine, using different epidemiologic study designs, the effects on disease progression of cumulative and current ART exposure to specific drugs; classes of drugs; drug combinations, including drugs for coinfections; and treatment strategies, overall and by age group.
- Investigate the effect on disease progression of viral factors, including viral type, subtype, and genetic variation; 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 and cost-effectiveness of these therapies.
- Characterize the changing spectrum of clinical outcomes, causes of morbidity and mortality, complications of ART, and cost patterns associated with evolving therapeutic strategies, domestically and internationally.
- Use observational studies in resource-limited settings to estimate the HIV prevalence, incidence, and correlates of treatment failure.
- Assess the effect of ART on the incidence, pathogenesis, and presentation of cancers in domestic and international settings, and use mathematical models to project the frequency, outcomes, and costs of treatment for these cancers.
- Define the prevalence, incidence, predictors, potential treatments, and consequences of diabetes and other diseases (e.g., cardiovascular, musculoskeletal, skin, renal, and liver disease) in HIV-infected individuals. Use mathematical models to project the frequency, outcomes, and costs of treatment for these comorbidities in HIV survivors.
- Characterize in a prospective manner the long-term effect of HIV infection on the central nervous system, including the effect of viral burden in the cerebrospinal fluid, its effect on white matter degeneration, and the role of ART in reducing the neurocognitive burden of disease, and differentiate these changes from other neurocognitive diseases, such as dementia and Alzheimer's disease.

- Evaluate and characterize immune reconstitution inflammatory syndrome (IRIS), including modifiable (e.g., the microbiome) and nonmodifiable predictors of immune recovery, and determine best treatment practices for IRIS in diverse populations.
- 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.

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### Strategies Related to Comorbidities

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- Expand research on the spectrum of HIV-associated malignancies and on the spectrum of malignancies not associated with HIV that may develop in HIV-infected patients who have responded to ART and thus are living longer with immune deficiency.
- Investigate the role of risk factors such as 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.
- 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 (e.g., 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 and retention in care of patients in high-prevalence settings who are coinfecting with HIV and TB.
  - ▶ Develop novel TB diagnostics for use with HIV-infected patients in order to rapidly identify undiagnosed active TB, latent TB, and MDR/XDR-TB in HIV/TB-coinfecting populations.
- ▶ 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.
- ▶ Assess outcomes related to methods of integrating TB and HIV care on survival, quality of care, cost, and cost-effectiveness of care.
- ▶ Investigate the feasibility, effectiveness, and cost-effectiveness of treating latent TB on the epidemiology of HIV/TB coinfection in endemic countries.
- ▶ Conduct implementation science research to understand barriers to implementation of preventive therapy and treatment of active TB in HIV/TB-coinfecting patients.
- Evaluate the clinical and economic impact of treatment of smoking, 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 (e.g., cancer, TB, transplant, and mortality) to enhance the understanding of HIV/AIDS outcomes in populations and in standard-of-care cohorts.
- Identify, characterize, and determine the frequency, changing manifestations, and effects of HIV-related respiratory disease (e.g., recurrent bacterial pneumonia; drug-resistant TB, MDR-TB, and XDR-TB/HIV cases; immune reconstitution syndromes affecting the lungs, including sarcoidosis and other immune-mediated and smoking-related diseases; HIV-related pulmonary hypertension; accelerated emphysema; and lung cancer) on morbidity, mortality, and HIV disease progression, in both untreated patients and those receiving ART.
- Study the emergence and reemergence of infectious diseases and the clinical and epidemiological characteristics of antimicrobial-resistant infections



in HIV-infected populations (e.g., MDR-TB, sulfa-resistant malaria, antibiotic-resistant pneumococcal pneumonia, cotrimoxazole-resistant *Pneumocystis jirovecii* pneumonia, methicillin-resistant *Staphylococcus aureus* [MRSA] infections, and lamivudine-resistant hepatitis B virus [HBV] infections).

- Estimate the prevalence of specific human papillomavirus (HPV) types associated with cervical cancer and high-grade dysplasia in HIV-infected women and in MSM.
- Evaluate the effectiveness of HPV vaccines among HIV-infected individuals (female and male) from geographically diverse regions.
- Evaluate different cervical dysplasia and cancer identification methods in HIV-infected women for sensitivity, specificity, cost-effectiveness, and appropriateness.
- Assess the effect of primary care screening and interventions (e.g., statin use; hypertension management; smoking cessation; treatment of depression, STIs, and viral hepatitis; and cancer screening and treatment) on HIV disease outcomes, survival, and costs of care. Use these assessments to guide the development of improved interventions and to inform recommendations for adoption and prioritization of primary care guidelines tailored to patients living with HIV infection.
- Investigate hemostatic disturbances in HIV-infected individuals and the role of coagulation and fibrinolytic mechanisms in risk of vascular events and other complications.
- Examine the impact of cryptococcal disease on early mortality in international settings, and evaluate potential effective and cost-effective strategies for prevention and early detection of cryptococcal disease in HIV-infected individuals.

### 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.
- Assess the long-term impact of *in utero* HIV and ART exposure in HIV-uninfected infants and children born to HIV-infected mothers.
- Study the effect of the health status of HIV-infected mothers and of ART during pregnancy, lactation, and early child life on survival, quality of life, and care costs of their HIV-infected and -uninfected children and on maternal outcomes.
- 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.
- Develop appropriate epidemiologic and surveillance studies to assess the immunologic responses to routine vaccinations of childhood and adolescence and the need for altered vaccine schedules in HIV-infected youth.
- Assess the risk factors for acquisition and natural history of HPV infection, and the impact of HPV vaccines in HIV-infected children and adolescents.

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### Strategies Related to Aging

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- 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, pulmonary disease, diabetes, hypertension, arthritis, osteoporosis, anemia, and dyslipidemia), as they affect disease outcomes and survival.
- Study the incidence and determinants of physical, neurologic, and cognitive decline in aging HIV-infected individuals and the effect of frailty and functional impairment on HIV, ART, and self-care behaviors.
- Study the epidemiologic association between immunologic and virologic responses to treatment and adverse effects of HIV and ART in aging populations, including those with coexisting morbidities and/or who receive numerous medications.
- Examine the impact of polypharmacy in elderly HIV-infected patients, including its effect on adherence and prioritization of the most critical drug regimens.
- 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.

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### Strategies Related to Adherence, Linkage to Care, Retention in Care, and Quality of Life

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- 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 linkage and access to care, retention in care, and improving HIV-related outcomes.
- Examine predictors of successful care outcomes, including linkage to and retention of HIV-infected patients in care, from the time of HIV testing through 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 policies and guidelines.

### STRATEGIES

- Evaluate and promote the use of multiple study designs that incorporate appropriate ethical, cultural, and policy context for studies of HIV disease and AIDS in diverse domestic and international populations.
- Continue to support local, regional, and international collaborations to integrate, harmonize, and utilize existing data for rigorous scientific investigations.
- Capture and utilize 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, persons from geographical regions most affected by the epidemic, adolescents and young adults, MSM, racial and ethnic populations, drug and alcohol users, and persons affected by other comorbidities.
- Ensure that studies reflect the needs and priorities of the countries or regions in which they are conducted and produce results that are quantifiable and applicable to diverse circumstances and geographic areas.
- Use mathematical models to assist in trial design to project value of information and to assess which trials are most feasible and cost-effective.
- When feasible and appropriate, involve representatives of the community and study participants in all phases of research planning, design, management, approval, and reporting, and promote and support academic/community-based research collaborations.
- Assess different strategies to improve community education about research and community involvement in planning, interpretation, implementation, and dissemination of research.
- Promote study designs that provide the highest degree of human subject protection and benefit possible, according to U.S. Government requirements, as well as local requirements in the case of international research.
- Promote the development and dissemination of simple point-of-care tools appropriate for both industrialized and resource-limited settings to standardize the objective diagnosis and monitoring of treatment-limiting or life-threatening complications of chronic HIV infection and ART.
- Explore expanded utilization of new diagnostics designed for use at the point of care (e.g., low-cost mobile devices or inexpensive disposable diagnostics), which have potential to address access, disparity, and confidentiality issues for people at risk for or infected with HIV disease, especially in remote or otherwise underserved areas.

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### Strategies Related to Natural History/ Pathogenesis

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- Develop epidemiologic, laboratory-based, and simulation modeling methods in conjunction with prospective cohort studies, domestically and internationally, to monitor HIV incidence, response to ART, and the incidence of complications 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 OI prophylaxis, viral hepatitis testing, HIV resistance testing, and assays for STIs and other coinfections.

- ▶ Maintain and effectively utilize ongoing and newly developed cohort studies, domestic or international specimen repositories, and databases for interdisciplinary HIV-related studies to address short-, medium-, and long-term outcomes. 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 and made available for other researchers to assess, validate, and use.
- ▶ Develop new and evaluate existing assays to accurately measure HIV incidence at a population level, using rapid, inexpensive, and reproducible measures, including methods appropriate for 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 nucleic acid tests are not readily available.

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

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- Continue to develop and improve upon quantitative methods for making effective and appropriate use of data from local, State, and national HIV/AIDS surveillance systems and 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;
  - ▶ Methods for collecting and analyzing spatio-temporal data, especially as they relate to transmission and spread of HIV infection; and
  - ▶ Methods for multilevel analysis of population-based HIV/AIDS surveillance data.
- Encourage research on innovative design and analysis through interdisciplinary collaboration between methodologists from different fields, such as epidemiology, biostatistics, econometrics, computer science, biomathematics, decision sciences, implementation science research, health services research, behavioral and social sciences, and demography.

- Support studies that make innovative use of existing data (e.g., cohorts, surveillance data, routinely collected service delivery data, and data from monitoring and evaluation systems) for well-designed, rigorous analyses, hypothesis generation, and hypothesis testing.
- Promote collaborative studies using genetic epidemiology methods (e.g., genome-wide association studies) applied to large, diverse populations to elucidate mechanisms of HIV infection, disease progression, and complications.

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### Strategies Related to Interventions

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- Study and evaluate the various operational strategies that can be employed for the implementation and dissemination of efficacious, evidence-based preventive or therapeutic interventions (e.g., male circumcision) and to evaluate countrywide ART programs, including the use of implementation science research and integrated observational databases, to evaluate treatment effectiveness and cost-effectiveness at the individual, community, and population levels.
- Improve understanding of how best to disseminate effective interventions, deliver effective interventions most efficiently, transfer interventions from one setting or population to another, and make informed choices among available interventions.
- 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, efficacy, and cost-effectiveness of various HIV prevention strategies (e.g., opt-out testing, secondary prevention, and immediate ART) between populations with generalized versus concentrated epidemics.
- 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, cost-effective, and affordable in various international settings.
- Use appropriate clinical and laboratory definitions of short- and longer-term ART failure, and mechanisms for monitoring drug resistance evolution in HIV types, subtypes, and variants, in domestic as well as international populations.
- 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, older adults, racial and ethnic populations, and populations in diverse domestic and 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 community-wide morbidity and mortality.
- Assess the effectiveness of strategies designed to reduce the impact of comorbidities, including smoking cessation, vaccination against HBV and HPV-16/18, and cytologic screening for cervical and anal cancers.

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### Strategies Related to Implementation

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- Design and implement evaluations of large-scale HIV testing and treatment programs, with attention to clinical outcomes, HIV incidence rates, viral resistance, long-term dynamics of the HIV epidemic, and comparative costs for the programs relative to present-day strategies.
- Utilize implementation science to improve the operations and efficiency of a proven strategy or treatment and to determine to what degree it is applicable across a broad range of target populations.
- Evaluate the long-term clinical and public health impact, cost, and health care utilization ramifications of different strategies for care, including treatment of HIV-associated conditions and comorbidities, ART, and complications of ART.
- Assess the 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

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## SCIENTIFIC OBJECTIVES AND STRATEGIES

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### OBJECTIVE—A: Disseminate Information to All Constituencies

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

### STRATEGIES

- Rapidly disseminate new basic, translational, and clinical research findings, including information on the potential implications for HIV prevention, care, and treatment, using existing and innovative methods.
- Promote study designs that include plans for dissemination of appropriate and relevant findings to study participants, health care practitioners, community representatives, policymakers, and the public while ensuring that confidentiality of efficacy and safety data is maintained during the conduct of clinical trials.
- Facilitate the update and dissemination of HIV prevention and treatment guidelines based on the latest clinical research findings.
- Utilize computer and other information dissemination technology (including the Internet) to disseminate up-to-date HIV and AIDS information; information about HIV therapeutic, vaccine, microbicide, and other prevention trials; and information about HIV training programs.
- Expand access to and education about 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, as well as information concerning 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 datasets 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 the importance of clinical trials participation, ongoing clinical trials, and trial results.
- Improve outreach and support access to AIDS information resources (including computers) by community groups, health care providers, and community-based AIDS service organizations, including those serving racial and ethnic populations.



- Work with community-based organizations (CBOs), nongovernmental organizations (NGOs), and local agencies to develop and promote effective methods of information dissemination on treatment, prevention, and research in target populations to increase awareness and clinical trial participation and to reduce stigma.
- Support dissemination of research findings to community representatives, study participants, health care practitioners, payors, policymakers, AIDS community organizations, and the public, in culturally and linguistically appropriate ways.
- Develop and disseminate educational information to enhance understanding of HIV and basic and clinical research processes by health care providers, community-based AIDS service organizations, social service organizations, policymakers, and persons with HIV and AIDS.
- Develop and disseminate information resources about HIV prevention, microbicide, vaccine, and treatment clinical trials to increase awareness about research in these areas and the importance of supporting and participating in clinical studies.
- Evaluate the effectiveness of communication efforts by appropriate means, including obtaining feedback from target audience members through methods such as usability testing of paper and computer interfaces (see [www.usability.gov](http://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 and prevention guidelines, and research results that improve the care of HIV-infected individuals, including those in developing countries.
- Support the exchange of basic and applied research information at community, regional, national, and international conferences and workshops.
- Support the cross-collaborations of HIV and AIDS information providers to develop more integrated and comprehensive information dissemination approaches.
- Provide support for online access to presentation materials and other information (e.g., slides, graphics, and plenary presentations) from scientific meetings.
- Develop HIV/AIDS training materials using a variety of current technologies most appropriate for specific audiences, as well as materials adapted for local languages.



## **OBJECTIVE–B: Develop New Communication Strategies**

Support research to identify existing gaps in communication approaches, identify and evaluate existing strategies, and develop and test new and innovative communication strategies that will improve access to and use of state-of-the-art HIV information by all relevant target audiences, domestically and internationally.

### **STRATEGIES**

- Continue to assess the changing information needs and resources used by various audiences, including biomedical and behavioral research communities, health care providers, service providers, persons living with HIV and their advocates, at-risk populations, scientific and lay media, and the general public.
- Identify obstacles to information dissemination and develop, test, and evaluate possible ways to overcome these obstacles.
- Develop, test, and evaluate innovative strategies for effectively reaching specific audiences (e.g., racial and ethnic populations, adolescents, drug users, other hard-to-reach populations, and health care providers) with relevant HIV information.
- Investigate how and under what circumstances different communication and dissemination strategies influence the adoption of scientifically based HIV behavior-change interventions and clinical practices in specific audiences.
- Promote 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 communication activities across NIH Institutes and Centers (ICs), among other Federal and non-Federal groups, and with international partners.

### **STRATEGIES**

- Promote and foster information dissemination regarding research and programmatic efforts across the ICs, among U.S. Government agencies, and with international partners.
- Promote collaboration among all ICs in providing information about their HIV/AIDS clinical trials to *AIDSinfo* and *ClinicalTrials.gov*.
- Build and enhance partnerships among CBOs/NGOs and basic, clinical, and behavioral researchers to encourage exchange of information and experience.
- Continue collaborations with the Joint United Nations Programme on HIV/AIDS, the Pan American Health Organization, and other international AIDS agencies or societies on information/communication 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.





# Appendices

- A. Planning Groups
- B. NIH Institutes and Centers
- C. List of Acronyms



## APPENDIX A

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## APPENDIX B

# NIH Institutes and Centers

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





## APPENDIX C

# List of Acronyms

<b>AIDS</b>	acquired immunodeficiency syndrome
<b>ANC</b>	antenatal care
<b>ART</b>	antiretroviral therapy
<b>ARV</b>	antiretroviral
<b>CAB</b>	community advisory board
<b>CBO</b>	community-based organization
<b>CNS</b>	central nervous system
<b>CSF</b>	cerebrospinal fluid
<b>DC</b>	dendritic cell
<b>EBV</b>	Epstein-Barr virus
<b>GLP</b>	Good Laboratory Practice
<b>GMP</b>	Good Manufacturing Practice
<b>Gyn</b>	gynecologic
<b>HBV</b>	hepatitis B virus
<b>HCV</b>	hepatitis C virus
<b>HIV</b>	human immunodeficiency virus
<b>HPV</b>	human papillomavirus
<b>HSV-2</b>	herpes simplex virus type 2
<b>ICs</b>	Institutes and Centers
<b>IRB</b>	institutional review board
<b>IRIS</b>	immune reconstitution inflammatory syndrome
<b>KSHV</b>	Kaposi's sarcoma herpesvirus
<b>KSHV/HHV-8</b>	Kaposi's sarcoma herpesvirus/human herpesvirus type 8
<b>MDR-TB</b>	multi-drug-resistant TB
<b>MHC</b>	major histocompatibility complex
<b>MRSA</b>	methicillin-resistant <i>Staphylococcus aureus</i>
<b>MSM</b>	men who have sex with men

<b>MTCT</b>	mother-to-child transmission
<b>NGO</b>	nongovernmental organization
<b>NHP</b>	nonhuman primate
<b>NIH</b>	National Institutes of Health
<b>OAR</b>	Office of AIDS Research, NIH
<b>OI</b>	opportunistic infection
<b>PMTCT</b>	prevention of mother-to-child transmission
<b>PrEP</b>	pre-exposure prophylaxis
<b>RCTs</b>	randomized clinical trials
<b>SHIV</b>	chimeric simian/human immunodeficiency virus
<b>SIV</b>	simian immunodeficiency virus
<b>STD</b>	sexually transmitted disease
<b>STI</b>	sexually transmitted infection
<b>TB</b>	tuberculosis
<b>TOC</b>	test of concept
<b>VCT</b>	voluntary counseling and testing
<b>WHO</b>	World Health Organization
<b>XDR-TB</b>	extensively drug-resistant TB





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