FY 2013

National Institutes of Health

TRANS-NIH AIDS RESEARCH BY-PASS BUDGET ESTIMATE

and

TRANS-NIH PLAN FOR HIV-RELATED RESEARCH

Prepared by the Office of AIDS Research
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NIH Associate Director for AIDS Research and
Director, Office of AIDS Research

The cover photo shows a 3-D model of HIV, depicted as orange threads, attacking and fusing with an immune cell, depicted as the gray surface.

Constructed by a Russian team of scientists, the image won first place for illustrations in the 2010 International Science and Engineering Visualization Challenge sponsored by the journal *Science* and the National Science Foundation.

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Dr. Edward Handelsman at the Liquid Camp for HIV-positive teens, where he served each summer as the camp's Medical Director.

Dedicated to the memory and legacy of

DR. EDWARD LOUIS HANDELSMAN

Chief of the International Maternal, Adolescent, and Pediatric Branch
Division of AIDS
National Institute of Allergy and Infectious Diseases
National Institutes of Health

His intelligence, passion, commitment, and heart
made him a champion for maternal, pediatric, and adolescent
AIDS research, prevention, and care.

FY 2013 Trans-NIH AIDS Research By-Pass Budget Estimate

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FY 2013 Trans-NIH AIDS Research By-Pass Budget Estimate

Legislative Mandate

AUTHORIZING LEGISLATION

BY-PASS BUDGET

Section 2353 of the Public Health Service Act requires that "the Director of the Office of AIDS Research (OAR) establish a comprehensive plan for the conduct and support of all AIDS activities of the agencies of the National Institutes of Health (NIH)." 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."

STRATEGIC PLAN

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

In accordance with the law, the NIH Office of AIDS Research, a component of the NIH Office of the Director, has developed this document that includes both the *Fiscal Year (FY) 2013 Trans-NIH AIDS Research By-Pass (Professional Judgment) Budget Estimate* and the *FY 2013 Trans-NIH Plan for HIV-Related Research*.

Introduction

The Office of AIDS Research (OAR) 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. This by-pass budget estimate is based solely on the current scientific opportunities and the commitment and urgent need to support the highest quality research to carry out the *Trans-NIH Plan for HIV-Related Research*.

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—and eventually a cure—are developed and universally available. The by-pass budget request:

- Addresses critical scientific needs;
- Addresses gaps in our understanding through an 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; and
- Addresses the key themes of the Director of the NIH.

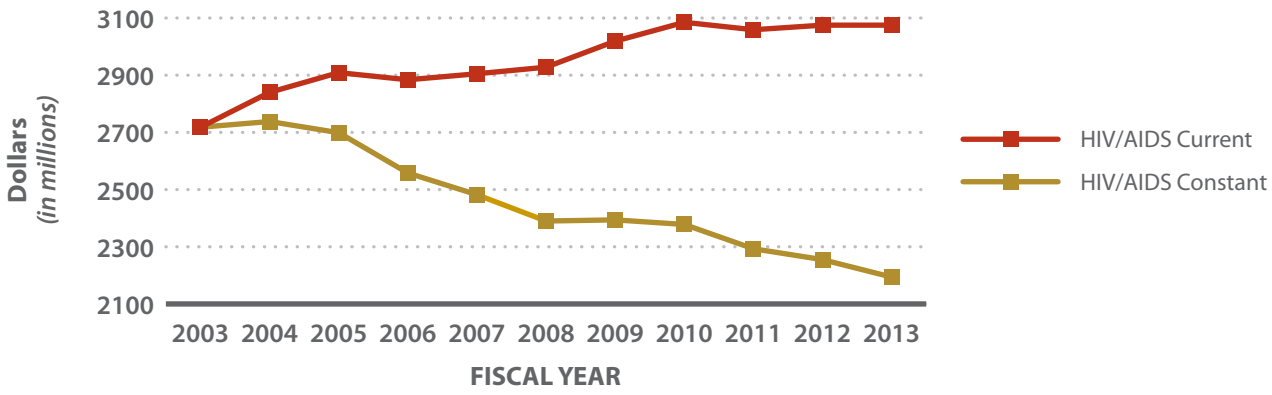
This by-pass request and strategic Plan establish the critical priorities for trans-NIH AIDS research. These include:

- **INVESTING IN BASIC RESEARCH:** OAR will increase support for basic research that will underpin further development of critically needed *vaccines and microbicides*.
- **ENCOURAGING NEW INVESTIGATORS AND NEW IDEAS:** OAR will provide additional support for innovative multidisciplinary research and international collaborations to develop novel approaches and strategies to eliminate viral reservoirs that could lead toward *a cure for HIV*.
- **ACCELERATING DISCOVERY THROUGH TECHNOLOGY:** OAR will increase funds to support critical studies in the area of *therapeutics as a method to prevent infection,* including treatment to prevent HIV infection after exposure; pre-exposure prophylaxis (PrEP); a potential prevention strategy known as "test and treat," to determine whether a community-wide testing program with treatment can decrease the overall rate of new HIV infections; and improved strategies to prevent mother-to-child transmission. A key priority is to evaluate prevention interventions that can be used in combination in different populations, including adolescents and older individuals.
- **IMPROVING DISEASE OUTCOMES:** OAR will target funding for NIH research focused on developing better, less toxic treatments and investigating 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. Studies will address the increased incidence of malignancies, cardiovascular and metabolic complications, and premature aging associated with long-term HIV disease and antiretroviral therapy.
- **ADVANCING TRANSLATIONAL SCIENCES:** OAR will ensure adequate resources for research on the feasibility, effectiveness, and sustainability required to scale up interventions from a structured behavioral or clinical study to a broader "real world" setting.

The FY 2013 by-pass budget request for NIH AIDS research is $3.598 billion, which represents a 17 percent increase over the FY 2012 enacted level. The total for AIDS research is reported in a different manner than NIH funding for other disease research, as 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, as well as the wide spectrum of AIDS-associated malignancies, opportunistic infections, coinfections, and clinical complications.

This increase represents an investment that must be sustained 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 budget at the 2012 enacted level is approximately equivalent in constant dollars to the FY 2001 appropriation. Further, there is projected to be a 19.3 percent loss in buying power for NIH AIDS research between 2003 and 2013.

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



30 YEARS OF EXTRAORDINARY NIH AIDS RESEARCH ACCOMPLISHMENTS

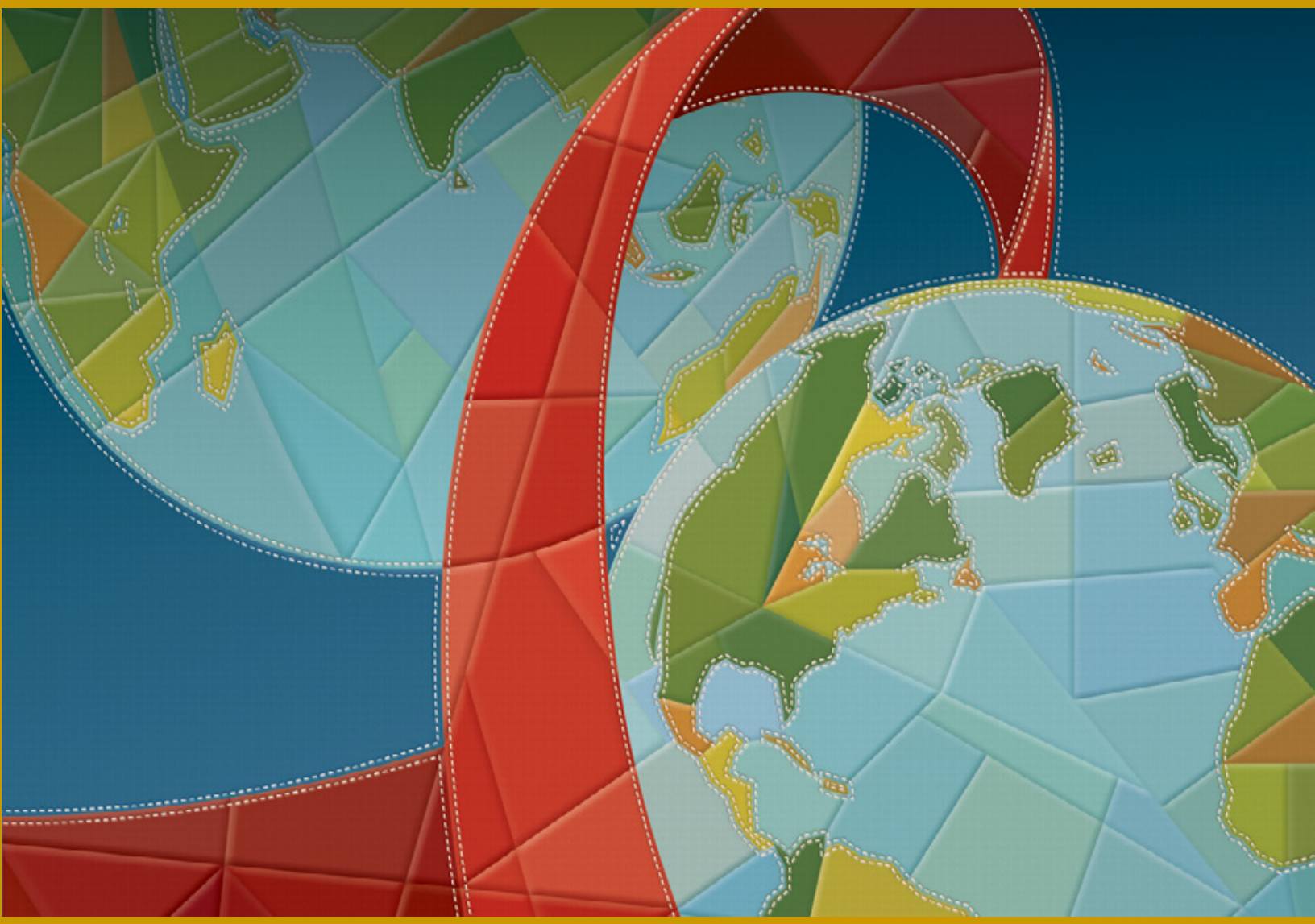
In the three decades since AIDS was first recognized—through the develop ment of effective combination therapies, to today's research to determine whether a vaccine, microbicide, or eventual cure for AIDS will one day be possible—the U.S. National Institutes of Health has been the global leader in research to understand, prevent, diagnose, and treat HIV and its many related conditions. This investment in HIV research has transformed the disease from a mysterious and uniformly fatal infection into one that can be accurately diagnosed and effectively managed with appropriate treatment. A recent study estimated that 14.4 million life years have been gained among adults around the world since 1995 as a result of AIDS therapies developed through NIH-funded research.[1]

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

- Co-discovery of HIV, the virus that causes AIDS;
- Development of the first blood test for the disease, which has allowed diagnosis of infection as well as ensured the safety of the blood supply;
- The critical discovery of key targets to develop antiretroviral therapies and multidrug regimens that have resulted in improved life expectancy for those with access to and who can tolerate these drugs, and the development of treatments for many HIV-associated coinfections, comorbidities, malignancies, and clinical manifestations, with benefits for patients also suffering from those other diseases;
- Groundbreaking strategies for the prevention of mother-to-child transmission, which have resulted in dramatic decreases in perinatal HIV in the United States;
- Demonstration that the use of male circumcision can reduce the risk of HIV acquisition;
- The first step in proving the concept that a vaccine to prevent HIV infection is feasible, and discovery of two potent human antibodies that can stop more than 90 percent of known global HIV strains from infecting human cells in the laboratory;
- Demonstration of the first proof-of-concept for the feasibility of a microbicide gel capable of preventing HIV transmission;

1 *Sexually Transmitted Infections*. 2010 Dec; 86 Suppl 2:ii67–71.

- Demonstration that the use of therapy by infected individuals can dramatically reduce transmission to an uninfected partner;
- Demonstration of the potential feasibility of PrEP, that long-term use of antiretroviral treatment regimens by some groups of high-risk uninfected individuals can reduce risk of HIV acquisition;
- Discovery that genetic variants may play a role in protecting some individuals, known as "elite controllers," who have been exposed to HIV over an extended period, from developing symptoms and enabling them to control the infection without therapy;
- Critical basic science discoveries that continue to provide the foundation for novel research; and
- Progress in both basic and treatment research efforts aimed at eliminating viral reservoirs in the body, which, for the first time, is leading scientists to design and conduct research aimed at a cure.



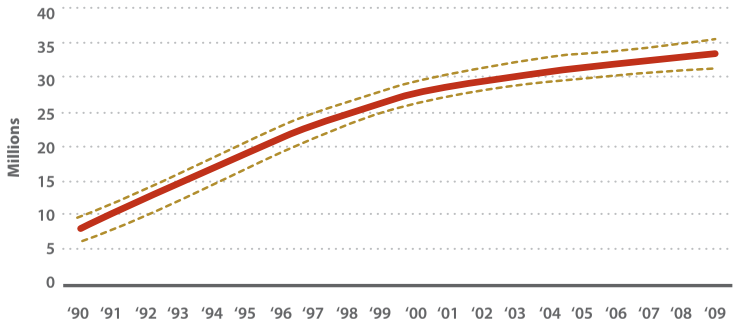
HIV/AIDS Pandemic

Despite these important advances, the HIV/AIDS epidemic continues to expand. The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that in 2010, more than 34 million people were living with HIV/AIDS; 2.7 million were newly infected; and 1.8 million people died of AIDS-related illnesses. In the United States, the Centers for Disease Control and Prevention (CDC) estimates that more than 1.2 million people are HIV-infected, and someone is infected with HIV every 9½ minutes.

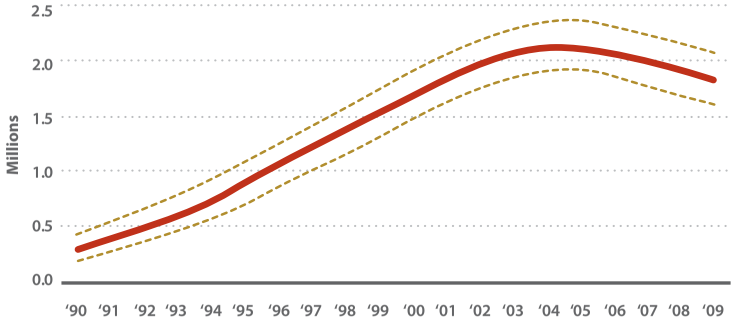
Global HIV Trends, 1990 to 2009

Gold, dashed lines represent ranges; solid red lines represent the best estimate.

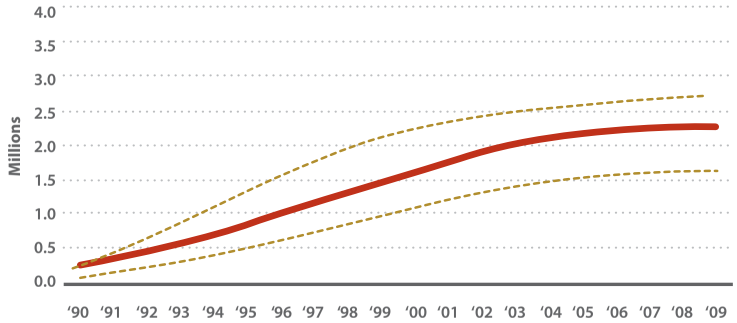
Number of people living with HIV



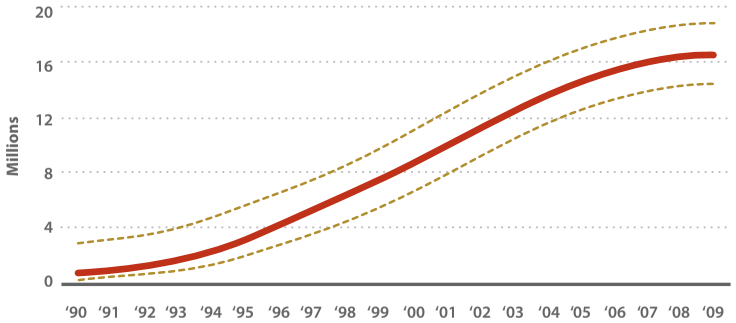
Adult and child deaths due to AIDS



Number of children living with HIV



Number of orphans due to AIDS



Source: UNAIDS

AIDS disproportionately affects racial and ethnic populations, women of color, young adults, and men who have sex with men (MSM). The AIDS pandemic has devastating consequences around the world in virtually every sector of society. Further research to improve prevention and treatment is urgently needed. Advances in prevention and treatment also will have extensive economic benefits.

AIDS AND AGING

The populations affected by AIDS continue to shift. HIV/AIDS began its deadly course in the United States mostly as a disease of young men, but today the epidemic touches people of all ages, including adults aged 50 and older. With the advent of potent, multidrug therapy against HIV in the mid-1990s, many HIV-infected Americans are living into their 50s and well beyond. In addition, an increasing proportion of new infections are occurring in older adults. Further, HIV disease itself and/or its treatment appear to affect the process of aging or the development of illnesses associated with aging. The NIH-sponsored Multicenter AIDS Cohort Study has shown that HIV disease accelerates the development of chronic diseases. The CDC estimates that by 2015, half the people living with HIV infection in the United States will be 50 years of age or older. Older adults with long-term or new HIV infection experience complex interactions with HIV, antiretroviral therapy (ART), age-related changes to the body, and, often, treatment for illnesses associated with aging.

The NIH 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. The maturing U.S. epidemic has the potential to generate concentric mini-epidemics of liver disease, tuberculosis, cardiovascular disease, and other HIV-associated comorbidities, foreshadowing an epidemic of greater complexity in the coming years.

DISEASE BURDEN WORLDWIDE

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.

The majority of cases worldwide are the result of heterosexual transmission.

Women represent approximately 50 percent of all of those living with HIV infection, but in some sub-Saharan countries, women are more than 60 percent of the epidemic.

Global mother-to-child transmission rates in the absence of antiretroviral drug administration to the mother and infant are 15–30 percent, and increase to 45 percent with breastfeeding.

Each day about 1,000 children—the majority of whom are newborns—become infected with HIV.

An estimated 390,000 children became infected with HIV in 2010—which is 21 percent below the number of new infections at the peak of the epidemic in 1997.

WOMEN AND AIDS

A recent NIH-funded study (HPTN 064) revealed that HIV infection rates among black women in some parts of the United States are similar to the incidence in some countries in sub-Saharan Africa. This rate is five times higher than previous estimates. The data underscore the need for continued research to identify the biological, behavioral, social, and economic factors related to vulnerability to infection, including issues related to drug use, stigma, and domestic violence; prevention and treatment of unique clinical complications; factors related to response to therapy; and issues related to adherence to therapy and prevention strategies.

IN THE UNITED STATES

- Gay and bisexual men of all races and ethnicities, African American men and women, and Hispanic men who have sex with men (MSM) are the most affected groups.
- Sixty-one percent of all new infections in 2009 occurred in MSM.
- In 2009, blacks accounted for 44 percent of all new infections, even though they comprise only 14 percent of the total U.S. population. Moreover, the rate of new HIV infections among black men was more than 6½ times higher than for Caucasian men.
- At the end of 2008, Hispanics/Latinos represented 16 percent of the population but accounted for an estimated 17 percent of people living with HIV and 20 percent of new infections. The rate of new HIV infections among Hispanic/Latino men was more than 2½ times that of white men, and the rate among Hispanic/Latina women was nearly 4½ times that of white women.
- In 2008, an estimated 29 percent of HIV-infected adults in the United States were at least 50 years old, and in 2009 individuals 50 years of age and older accounted for approximately 17 percent of all new HIV infections.
- Among adolescents aged 13–19 years, 2,057 were diagnosed with HIV infection in 2009.
- As a result of NIH-supported research, the rate of mother-to-child transmission of HIV in the United States has dropped from more than 25 percent to less than 2 percent during the past two decades, resulting in fewer than 100 cases per year.
- Heterosexuals and injection drug users continue to be affected by HIV: Individuals infected through heterosexual contact accounted for 27 percent of new HIV infections in 2009, and 28 percent of people living with HIV in 2008.
- Women represent 24 percent of adults living with AIDS in the United States.
- HIV/AIDS remains one of the most serious medical consequences of drug and alcohol abuse, and its link goes well beyond injection drug use to risky sexual behaviors brought on by intoxication or addiction.
- Approximately 25 percent of HIV-infected individuals also are infected with hepatitis C virus (HCV), a rate that increases to 80 percent among injection drug users.
- Neuropsychological impairment was detected in 52 percent of HIV-infected individuals in the United States receiving combination ART.

SOURCE: Heaton RK, Clifford DB, Franklin DR Jr, et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology* 2010 Dec 7; 75(23):2087-96. Available at *http://www.ncbi.nlm.nih.gov/pubmed/21135382.*

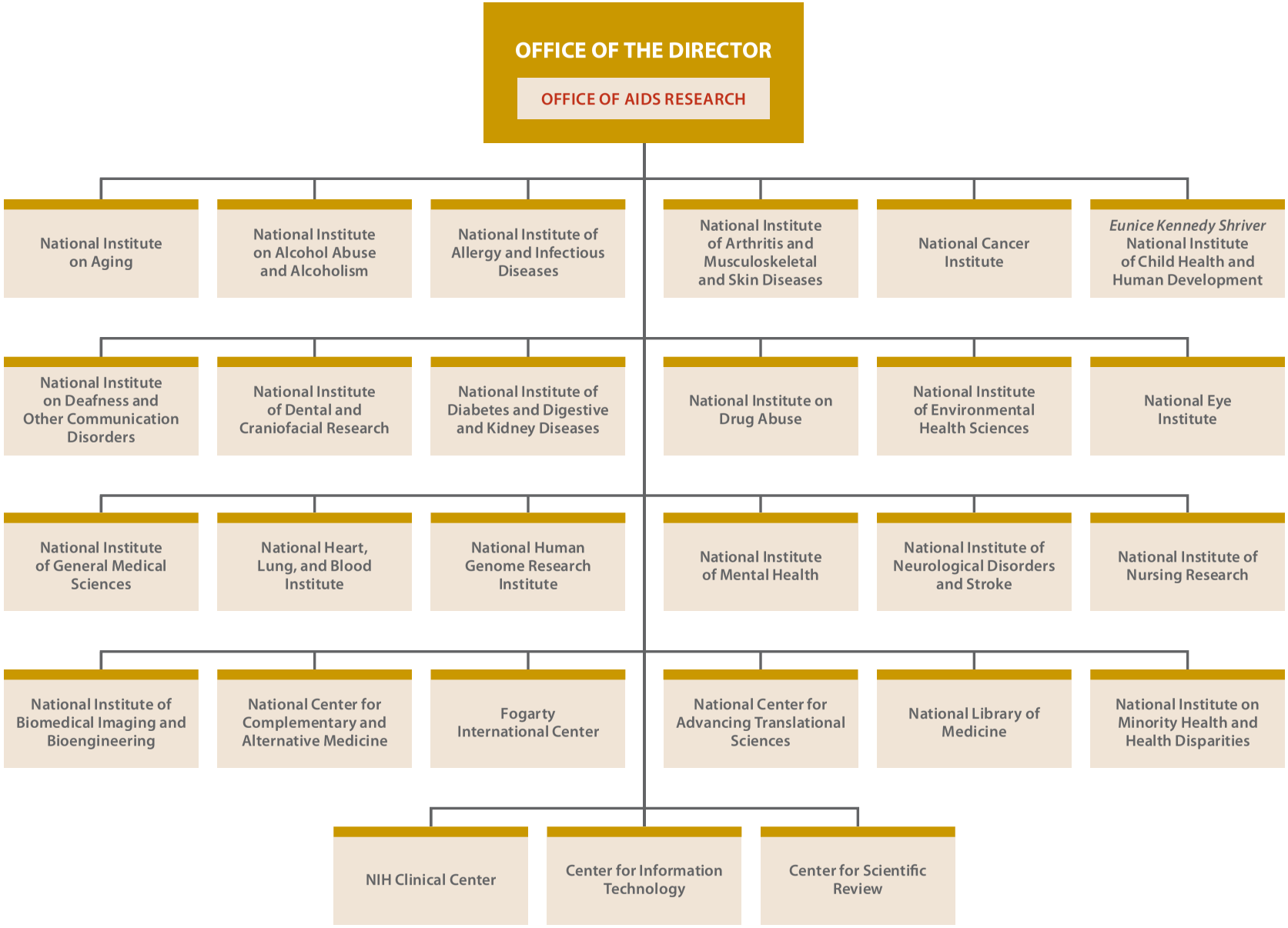
NIH AIDS Research Program

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

NIH AIDS RESEARCH PROGRAM

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

NATIONAL INSTITUTES OF HEALTH



NIH Office of AIDS Research

The Office of AIDS Research (OAR) *(http://www.oar.nih.gov/)*, established in 1988, has unique legislative authorities unlike any other NIH entity to plan, coordinate, evaluate, and budget the entire $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 Institute and Center (IC). This diverse research portfolio demands an unprecedented level of trans-NIH scientific coordination and management of research funds. OAR coordinates the scientific, budgetary, legislative, and policy elements of the NIH AIDS research portfolio and sets the trans-NIH scientific priorities for this large and diverse program. Utilizing its legislative authorities, OAR has established comprehensive trans-NIH planning, budgeting, and portfolio analysis processes to: identify the highest priority areas of scientific opportunity, enhance collaboration, minimize duplication, and ensure that precious research dollars are invested effectively and efficiently.

OFFICE OF AIDS RESEARCH MISSION

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

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

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

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

Trans-NIH Strategic Plan

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

OAR requires ICs to report all AIDS-related expenditures, including extramural, intramural, and research management and support, on a quarterly basis, to the OAR trans-NIH AIDS Research Information System (ARIS) database. 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 (RCDC) system. This process 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

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, the Food and Drug Administration, the U.S. Agency for International Development, the Department of Veterans Affairs, and the Department of Defense, respectively.

OAR Budget Development Process

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

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

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

OAR BUDGET DEVELOPMENT PROCESS

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

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

OAR also has a 3 percent transfer authority to move dollars across ICs during the fiscal year.

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 that will facilitate the implementation of the President's 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 both to 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

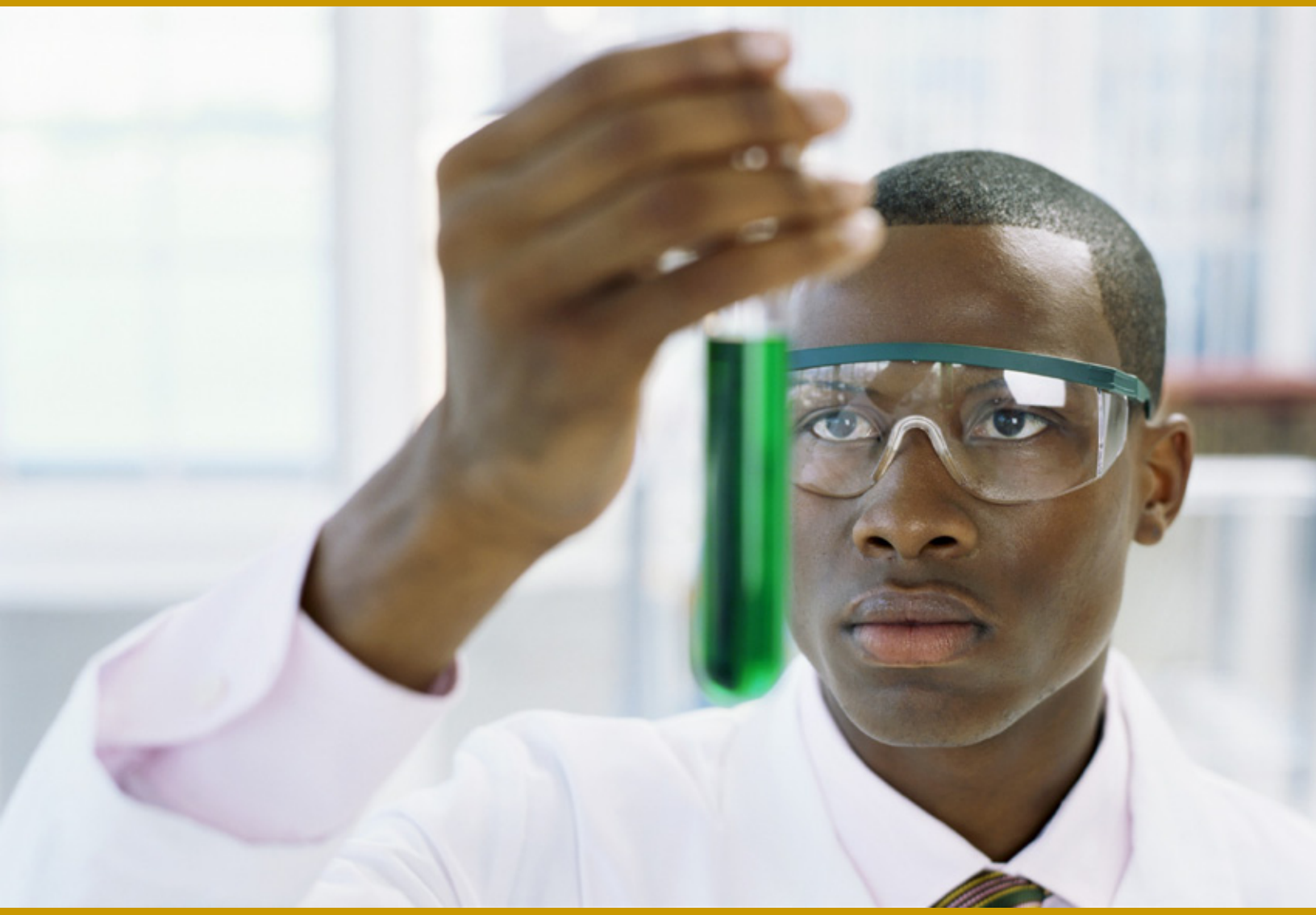
The critical priorities of this by-pass budget estimate are aligned and in concert with the major goals of the President's National HIV/AIDS Strategy.

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 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, providing new and exciting research opportunities in the search for strategies to prevent and treat HIV infection. 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.

ADVANCES IN TREATMENT AS PREVENTION

HIV PREVENTION TRIALS NETWORK (HPTN) 052—Scientific Breakthrough of the Year: In the past year, clinical results from a large NIH-sponsored Phase III, two-arm, multisite international clinical trial showed that early initiation of antiretroviral treatment of HIV-infected heterosexual individuals resulted in a reduction in sexual transmission of HIV to their uninfected partners. The interim efficacy analysis in April 2011 revealed a 96 percent reduction in HIV transmission for participants who received antiretroviral therapy (ART) immediately with CD4 counts of 350–550 as compared with those participants who were in the ART-delayed arm (start ART at CD4 of 250). The study is continuing in order to assess the durability of the HIV prevention benefit. The journal *Science* selected HPTN 052 as the 2011 Breakthrough of the Year.[2]

NEW REGIMENS FOR PREVENTION OF MOTHER-TO-CHILD TRANSMISSION: Two recent studies have demonstrated the effectiveness of new multidrug antiretroviral regimens for the prevention of HIV mother-to-child transmission during pregnancy and breastfeeding.[3]

PRE-EXPOSURE PROPHYLAXIS (PREP): The study known as iPrEX cosponsored by the NIH and the Gates Foundation found that a daily dose of an oral antiretroviral drug approved to treat HIV infection reduced the risk of HIV acquisition among men who have sex with men by 44 percent. Even higher rates of effectiveness, up to 73 percent, were found among study participants who adhered most closely to the daily drug regimen. Additional and continued research is needed to determine whether PrEP will be similarly effective at preventing HIV infection in other at-risk populations.[4]

ADVANCES IN RESEARCH TOWARD A CURE

PROGRESS IN BOTH BASIC SCIENCE AND TREATMENT RESEARCH aimed at eliminating viral reservoirs and eradicating persistent/latent HIV has for the first time led scientists to plan and conduct research aimed at a cure.[5]

ADVANCES IN GENETICS/GENOMICS RESEARCH

NIH-SPONSORED RESEARCHERS MADE AN IMPORTANT DISCOVERY RELATED TO THE GENETICS OF AN INDIVIDUAL'S IMMUNE SYSTEM that appears to offer some protection from 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.[6]

2 Available at *http://www.hptn.org/research_studies/hptn052.asp; http://www.nejm.org/doi/full/10.1056/NEJMoa1105243; http://www.sciencemag.org/content/334/6063/1628.*

3 Kesho Bora study: Available at *http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(10)70288-7/abstract*; Botswana study: Available at *http://www.nejm.org/doi/full/10.1056/NEJMoa0907736.*

4 Grant RM, Lama JA, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *New England Journal of Medicine* 2010 Dec 30;363(27):2587-99. [Epub 2010 Nov 23.] Available at *http://www.nejm.org/doi/full/10.1056/NEJMoa1011205); http://www.nejm.org/doi/pdf/10.1056/NEJMe1012929.*

5 Siliciano RF and Greene WC. HIV latency. Cold Spring Harbor Perspectives in Medicine. 2011; 1:a007096:1-19. Available at *http://www.perspectivesinmedicine.org/content/1/1/a007096.full.pdf+html;* Choudhary SK and Margolis DM. Curing HIV: Pharmacologic approaches to target HIV-1 latency. Annual Review of Pharmacology and Toxicology. 2011 Feb 10; 51:397-418. Available at *http://www.annualreviews.org/doi/full/10.1146/annurev-pharmtox-010510-100237?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed&.*

6 International HIV Controllers Study. The major genetic determinants of HIV-1 control affect HLA class I peptide presentation. *Science.* 2010 Dec 10; 330(6010):1551-57. [Epub 2010 Nov 4.] Available at *http://www.sciencemag.org/content/330/6010/1551.full.*

NIH SCIENTISTS REACTIVATE IMMUNE CELLS EXHAUSTED BY CHRONIC HIV: National Institute of Allergy and Infectious Diseases (NIAID) scientists have demonstrated why certain immune cells chronically exposed to HIV shut down, and how they can be reactivated. The investigators used small interfering RNAs (siRNAs), which acted at the genetic level to prevent exhausted B cells from replenishing inhibitory receptors. The new siRNA-based approach may hold promise for scientists seeking to develop therapies to improve the human antibody response against HIV and other pathogens by altering the expression of specific B-cell genes.[7]

NIH SCIENTISTS UNVEIL CHARACTERISTIC OF HIV EARLY IN TRANSMISSION: A new finding from NIAID scientists could advance efforts to design vaccines and other prevention tools to block HIV in the early stages of sexual transmission, before infection takes hold. The researchers have helped to explain genetic differences that can distinguish some early-transmitting viruses found in an infected individual within the first month after infection from forms of HIV isolated later in infection. These genetic features help HIV bind tightly to a molecule called integrin α4β7 and likely enhance the ability of HIV to complete the many steps of sexual transmission and become the "founder" virus that establishes infection in an individual. Given the new finding that certain early-transmitting isolates of HIV can have an affinity for α4β7, investigators believe that it is likely that CD4+ T cells with the α4β7 receptor play an important role in the sexual transmission of HIV.[8]

7 Kardava L, Moir S, Wang W, et al. Attenuation of HIV-associated human B cell exhaustion by siRNA downregulation of inhibitory receptors. *The Journal of Clinical Investigation.* 2011 Jul 1; 121(7):2614-24. Available at *http://www.jci.org/articles/view/45685. DOI:10.1172/jci45685.*

8 Nawaz F, Cicala C, Van Ryk D, et al. The genotype of early-transmitting HIV gp120s promotes α4β7 reactivity, revealing α4β7+/CD4+ T cells as key targets in mucosal transmission. *PLoS Pathogens.* 2011 Feb 24. Available at *http://www.plospathogens.org/article/info%3Adoi%2F10.1371%2Fjournal.ppat.1001301.*

ADVANCES IN HIV VACCINE RESEARCH

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.[9]

AN EXTENSIVE COLLABORATIVE EFFORT IS UNDERWAY TO IDENTIFY CORRELATES OF RISK using blood samples from the RV144 HIV vaccine clinical trial. These efforts have already yielded findings that may provide important direction for extending the efficacy of the candidate vaccine in RV144, and inform the field in general.[10]

NIH-LED TEAM MAPS ROUTE FOR ELICITING HIV NEUTRALIZING ANTIBODIES—NEW TECHNIQUE CAN BE USED WIDELY TO DEVELOP VACCINES: Some HIV-infected individuals develop broadly neutralizing antibodies over a period of several years. To better understand how these antibodies develop, a collaborative research team led by investigators at the NIAID Vaccine Research Center (VRC) exploited structure-based and genomics approaches for dissecting common pathways of antibody binding and sequence maturation. Structural data showed convergent binding of diverse antibodies to the same invariant viral structure (the CD4-binding site), and deep sequencing of thousands of specific families of heavy- and light-chain sequences revealed common antibody maturation intermediates in developing broadly neutralizing antibodies. Further, these technologies provide not only a means to identify the sequences of such intermediates but also a means to facilitate their detection in people. Thus, structure-based and functional genomics data

9 Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *New England Journal of Medicine.* 2009 Dec 3; 361(23):2209-20. Available at *http://www.nejm.org/doi/full/10.1056/NEJMoa0908492.*

10 Available at *http://www.hivvaccineenterprise.org/conference/2011/detailed-program; http://www.nejm.org/doi/full/10.1056/NEJMoa0908492.*

are providing a roadmap of B-cell maturation necessary for generating broadly neutralizing antibodies, and thereby may help to guide more effective design of protective AIDS vaccine immunogens.[11]

NIH SCIENTISTS IDENTIFY ANTIBODIES THAT HELP PROTECT MONKEYS FROM HIV-LIKE VIRUS: Using a monkey model of AIDS, scientists at the NIAID VRC have identified a vaccine-generated immune-system response that correlates with protection against infection by simian immunodeficiency virus (SIV). The study showed that neutralizing antibodies generated by immunization were associated with protection against SIV infection and provides evidence that neutralizing antibodies are an important part of the immune response needed to prevent HIV infection. The ability of the vaccine regimen to protect monkeys from SIV infection is comparable to the results seen in the RV144 Thai trial. The new research also provides an animal model to better understand the immune basis for vaccine protection against lentiviruses. This knowledge will help guide strategies for the future development of AIDS vaccines for humans.[12]

NEW VACCINE RESEARCH IN MONKEYS suggests that scientists are homing in on the critical ingredients of a protective HIV vaccine and identifying new HIV vaccine candidates to test in human clinical trials. In the study, co-funded by NIAID, scientists report that several SIV prime-boost vaccine regimens demonstrated partial protection against acquisition of infection by a virulent, tough-to-neutralize SIV strain that is different from the strain used to make the vaccine—a scenario analogous to what people might encounter if an HIV vaccine were available. The experimental vaccine regimens reduced the monkeys' likelihood of becoming infected per exposure to SIV by 80 to 83 percent compared with a placebo vaccine regimen. Further, in those monkeys that did become infected, the experimental vaccine regimens substantially reduced the amount of virus in the blood compared with controls. Plans are underway for early-stage clinical trials of a human-adapted version of one of the study's prime-boost vaccine combinations.[13]

NIH-FUNDED RESEARCHERS SHOWED THAT RHESUS MACAQUES COULD BE PROTECTED FROM CHALLENGE WITH A HIGHLY PATHOGENIC SIV using vaccine vectors based on rhesus cytomegalovirus to deliver SIV antigens. Despite being infected with the challenge virus, macaques that were vaccinated were able to control the infection for more than 1 year. At necropsy, cell-associated SIV was only occasionally measurable at the limit of detection with ultrasensitive assays, observations that indicate the possibility of eventual viral clearance. Protection was shown to be associated with induction of effector memory CD8+ T cells.[14]

NIH SCIENTISTS IDENTIFY SEVERAL LINES OF EVIDENCE THAT IMPLICATE AMINO ACIDS IN THE V1/V2 VARIABLE LOOPS OF HIV GP120 AS IMPORTANT FOR PROTECTIVE IMMUNE RESPONSES AND FOR VIRAL EVASION OF IMMUNE CONTROL: A collaborative research group led by investigators at the NIAID VRC solved the crystal structure of this viral protein region when bound by the broadly neutralizing monoclonal antibody PG9. This work provided the first atomic-level resolution of the structure of a protective gp120 epitope and provided

11 Wu X, Zhou T, Zhu J, et al. Focused evolution of HIV-1 neutralizing antibodies revealed by structures and deep sequencing. *Science*. 2011 Sept 16; 333(6049):1593-1602. [Epub 2011 Aug 11.] Available at *http://www.sciencemag.org/content/333/6049/1593. DOI:10.1126/science.1207532.*

12 Letvin NL, Rao SS, Montefiori DC, et al. Immune and genetic correlates of vaccine protection against mucosal infection by SIV in monkeys. *Science Translational Medicine.* 2011 May 4; 3(81):81. Available at *http://stm.sciencemag.org/content/3/81/81ra36.abstract. DOI:10.1126/scitranslmed.3002351.*

13 Barouch DH, Liu J, Li H, et al. Vaccine protection against acquisition of neutralization-resistant SIV challenges in rhesus monkeys. *Nature*. 2012 Feb 2; 482(7383):89-93. [Epub 2012 Jan 4.] Available at *http://www.nature.com/nature/journal/v482/n7383/full/nature10766.html. DOI:10.1038/nature10766.*

14 Hansen SG, Ford JC, Lewis MS, et al. Profound early control of highly pathogenic SIV by an effector memory T-cell vaccine. *Nature.* 2011 May 26; 473(7348):523–27. [Epub 2011 May 11.] Available at *http://www.nature.com/nature/journal/v473/n7348/full/nature10003.html. DOI:10.1038/nature10003.*

the basis for understanding which conserved substructures in this highly variable region represent productive targets for immune protection.[15]

NIH SCIENTISTS EXPLORE THE MECHANISM FOR VRC01 NEUTRALIZATION OF HIV: NIAID VRC researchers found that the broadly neutralizing antibody VRC01 partially mimics the interaction of the primary virus receptor, CD4, with the gp120 protein of the virus, but displays some key differences. VRC01 achieves potent neutralization by precisely targeting a highly conserved region of the CD4 binding site without requiring the alterations of the Env functional spike configuration that occur upon CD4 ligation.[16]

ADVANCES IN PREVENTION AND TREATMENT OF HIV-ASSOCIATED COINFECTIONS, COMORBIDITIES, MALIGNANCIES, AND COMPLICATIONS

NIH SCIENTISTS ANALYZE EMERGING CANCER PATTERNS IN THE CHRONICALLY INFECTED AND AGING HIV-INFECTED POPULATION IN THE UNITED STATES: ART has dramatically prolonged the survival of HIV-infected patients, and the HIV-infected population in the United States is rapidly aging. With these trends, an increase in the incidence of non-AIDS-defining cancers, such as lung cancer, anal cancer, and Hodgkin's lymphoma, has been documented, and the number of cases of key malignancies determined.[17]

15 McLellan JS, Pancera M, Carrico C, et al. Structure of HIV-1 gp120 V1/V2 domain with broadly neutralizing antibody PG9. *Nature*. 2011 Dec 15; 480(7377):336-43. [Epub 2011 Nov 23.] Available at *http://www.nature.com/nature/journal/v480/n7377/full/nature10696.html. DOI:10.1038/nature 10696.*

16 Li Y, O'Dell S, Walker LM, et al. Mechanism of neutralization by the broadly neutralizing HIV-1 monoclonal antibody VRC01. *Journal of Virology*. 2011 Sept; 85(17):8954-67. Available at *http://jvi.asm.org/content/85/17/8954.full?view=long&pmid=21715490. DOI:10.1128/JVI.00754-11.*

17 Shiels MS, Pfeiffer RM, Gail MH, et al. Cancer burden in the HIV-infected population in the United States. *Journal of the National Cancer Institute*. 2011 May 4; 103(9):753-62. [Epub 2011 Apr 11.] Available at *http://www.ncbi.nlm.nih.gov/pubmed/21483021.*

NIH-FUNDED SCIENTISTS TARGET INTERVENTIONS FOR OPTIMUM IMPACT: A study sponsored by the National Institute on Drug Abuse (NIDA) successfully demonstrated a unique and innovative intervention aimed at reducing substance use and HIV health disparities among Hispanic youth. Familias Unidas, a Hispanic-specific, parent-centered program, is the only published behavioral intervention with demonstrated efficacy in preventing both substance use and unprotected sexual behavior among Hispanic youth. It is now being translated to community practice.[18]

NIH-SUPPORTED RESEARCH PROVIDES NEW HOPE FOR PEOPLE COINFECTED WITH HIV AND TUBERCULOSIS (TB): Findings from the Cambodia-based study known as CAMELIA, co-funded by NIAID and the French National Agency for Research on AIDS and Viral Hepatitis, demonstrated that there was a significant increase of 33 percent survival in untreated, HIV-infected adults with very weak immune systems and newly diagnosed TB when they started ART 2 weeks after beginning TB treatment, rather than waiting 8 weeks, as had been standard. TB accounts for half a million deaths worldwide every year for people living with AIDS.[19]

NIH-SPONSORED SCIENTISTS MADE SIGNIFICANT ADVANCES IN UNDERSTANDING THE PATHOGENESIS OF HIV-RELATED NEUROLOGICAL DISORDERS: Researchers supported by the National Institute of Mental Health (NIMH), using an *in vitro* model of the blood-brain barrier, showed that even a small number of HIV-infected astrocytes were able to disrupt the barrier in a manner dependent on gap junctions. Migration of HIV across the blood-brain

18 Information available at *http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3131683/?tool=pubmed.*

19 Blanc F-X, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *New England Journal of Medicine*. 2011 Oct 20; 365(16):1471-81. Available at *http://www.nejm.org/doi/full/10.1056/NEJMoa1013911.*

barrier is thought to be responsible for bringing virus into the brain and establishing chronic neuroinflammation.[20]

AN NIH-SUPPORTED VIRAL GENETIC STUDY MADE A KEY FINDING THAT HIV VARIANTS IN SPINAL FLUID MAY HOLD CLUES IN DEVELOPMENT OF HIV-RELATED DEMENTIA: NIMH-sponsored analysis of HIV-1 replication in the brain showed that genetically distinct variants of HIV were present in the spinal fluid and absent in the blood. These HIV variants may play a role in the development of HIV-associated dementia and related neurological disorders.[21] HIV-infected subjects were shown to be the same as uninfected subjects who were 15–20 years older when functional brain demands were measured by neuroimaging, indicating diminished capacity in the brains of older HIV-infected adults.[22]

HUMAN PAPILLOMAVIRUS (HPV) VACCINE GARDASIL® RECOMMENDED FOR THE PREVENTION OF HPV-RELATED CANCERS: The incidence of anal cancer is rising very rapidly in the HIV-infected population. The 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 neoplasia 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.[23]

NIH-FUNDED RESEARCHERS DEVELOP IMPROVED THERAPY FOR AIDS-RELATED LYMPHOMA: The development of new regimens for the treatment of lymphoma and the tailoring of these regimens to specific tumor types has 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.[24]

ADVANCES IN THE DEVELOPMENT OF MICROBICIDES TO PREVENT HIV INFECTION

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. The CAPRISA 004 study, conducted by the Centre for the AIDS Programme of Research in South Africa (CAPRISA), and sponsored by USAID, found 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.[25]

20 Eugenin EA, Clements JE, Zink MC, et al. Human immunodeficiency virus infection of human astrocytes disrupts blood-brain barrier integrity by a gap junction-dependent mechanism. *Journal of Neuroscience*. 2011 June 29; 31(26):9456-65. Available at *http://www.ncbi.nlm.nih.gov/pubmed/21715610.*

21 Schnell G, Joseph S, Spudich S, et al. HIV-1 replication in the central nervous system occurs in two distinct cell types. *PLoS Pathogens.* 2011 Oct; 7(10). [Epub 2011 Oct 6.] Available at *http://www.ncbi.nlm.nih.gov/pubmed/22007152.*

22 Ances BM, Vaida F, Yeh MJ, et al. HIV and aging independently affect brain function as measured by functional magnetic resonance imaging. *Journal of Infectious Diseases*. 2010 Feb 1; 201(3):336–40. Available at *http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2804778/?tool=pubmed. DOI:10.1086/649899.*

23 Advisory Committee on Immunization Practices. Recommendations on the use of quadrivalent human papillomavirus vaccine in males. *Morbidity and Mortality Weekly Report*. 2011 Dec 23; 60(50):1705-08. Available at *http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6050a3.htm?s_cid=mm6050a3_e.*

24 Dunleavy K, Little RF, Pittaluga S, et al. The role of tumor histogenesis, FDG-PET, and short-course EPOCH with dose-dense rituximab (SC-EPOCH-RR) in HIV-associated diffuse large B-cell lymphoma. *Blood*. 2010 Apr 15;115(15):3017-24. [Epub 2010 Feb 3.] Available at *http://bloodjournal.hematologylibrary.org/cgi/content/full/115/15/3017. DOI:10.1182/blood-2009-11-253039.* Sparano JA, Lee JY, Kaplan LD, et al. Rituximab plus concurrent infusional EPOCH chemotherapy is highly effective in HIV-associated B-cell non-Hodgkin lymphoma. *Blood*. 2010 Apr 15;115(15):3008-16. [Epub 2009 Dec 18.] Available at *http://bloodjournal.hematologylibrary.org/cgi/content/full/115/15/3008. DOI:10.1182/blood-2009-08-231613.*

25 Karim QA, Karim SA, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science*. 2010 Sept 3; 329(5996):1168-74.[Epub 2010 Jul 19.] Available at *http://www.sciencemag.org/content/329/5996/1168.full. DOI:10.1126/science.1193748.*

ADVANCES IN PROMOTING HIV TESTING AND DETECTION

NIH-SPONSORED TRIAL OF COUNSELING AND TESTING STRATEGY: The large-scale NIMH-funded Project Accept trial was conducted in four countries and determined that mobile, community-based voluntary HIV counseling and testing was four times more likely to identify individuals living with HIV infection than standard clinic-based HIV testing. The study investigators are currently determining if wide-scale mobile HIV testing and community mobilization activities can reduce HIV incidence.[26]

NIH-SPONSORED STUDY OF RAPID HIV TESTING STRATEGY: Findings from a recent NIDA-sponsored study demonstrated that nurse-initiated routine screening with rapid HIV testing and streamlined counseling in a primary-care population resulted in increased rates of testing and receipt of test results, and was cost-effective compared with traditional HIV testing strategies. This study showed that rapid HIV testing can be successfully implemented in community treatment drug abuse centers and primary care settings, thus contributing to more comprehensive health care for specific high-risk populations.[27]

ADVANCES IN PREVENTING AND TREATING HIV IN CHILDREN AND ADOLESCENTS

NIH-SPONSORED STUDIES OF SIDE EFFECTS OF ANTIRETROVIRAL DRUGS IN CHILDREN: Anti-HIV drug treatment in children is life-saving, yet it also can carry inherent risks or side effects, including the development of high lipid levels. In research studies co-funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), elevated cholesterol levels associated with ART in HIV-infected children were observed in HIV-infected infants as well as older children. These levels remained elevated in children even at a 2-year followup examination. Therefore, treatment of HIV-infected children with current anti-HIV therapies may place them at increased risk for cardiovascular diseases associated with high cholesterol that can develop later in life.[28]

ANOTHER NICHD-FUNDED STUDY DEMONSTRATED THAT HIV-INFECTED CHILDREN have higher levels of biomarkers of vascular dysfunction than do HIV-exposed but uninfected children. Risk factors associated with higher biomarkers include unfavorable lipid levels and active HIV replication.[29]

26 Sweat M, Morin S, Celentano D, et al. Community-based intervention to increase HIV testing and case detection in people aged 16-32 years in Tanzania, Zimbabwe, and Thailand (NIMH Project Accept, HPTN 043): A randomised study. *The Lancet Infectious Diseases*. 2011 Jul 1;11(7): 525-532. [Epub 2011 May 4.] Available at *http://globalhealth.med.ucla.edu/publications/lancetid.pdf. DOI:10.1016/s1473-3099(11)70060-3.*

27 Sanders GD, Anaya HD, Asch S, et al. Cost-effectiveness of strategies to improve HIV testing and receipt of results: Economic analysis of a randomized controlled trial. *Journal of General Internal Medicine*. 2010 Jun;25(6):556-63. [Epub 2010 Mar 4.] Available at *http://www.ncbi.nlm.nih.gov/pubmed/20204538.*

28 Hazra R, Cohen RA, Gonin R, et al. Lipid levels in the second year of life among HIV-infected and HIV-exposed uninfected Latin American children. *AIDS*. 2012 Jan 14;26(2):235-40. Available at *http://www.ncbi.nlm.nih.gov/pubmed/22008654.*

29 Miller T, Borkowsky W, Dimeglio L, et al. Metabolic abnormalities and viral replication are associated with biomarkers of vascular dysfunction in HIV-infected children. *HIV Medicine*. 2012 May;13(5):264-75. [Epub 2011 Dec 4.] Available at *http://www.ncbi.nlm.nih.gov/pubmed/22136114. DOI: 10.1111/j.1468-1293.2011.00970.x.*

NIH-FUNDED INVESTIGATORS STUDY LANGUAGE AND HIV EXPOSURE IN HIV-EXPOSED, UNINFECTED CHILDREN: Children exposed to HIV before birth but who are not infected are at risk for language impairments. NICHD-funded researchers found that, in a group of school-age children born to HIV-infected women, 35 percent have difficulty understanding spoken words and expressing themselves verbally.[30]

NIH-FUNDED CLINICAL TRIAL NETWORK STUDIES LINKAGE OF HIV-INFECTED ADOLESCENTS TO CARE: Approximately one-third to one-half of new HIV infections in the United States occur in adolescents and young adults (12 to 24 years old), and almost-two thirds of HIV-infected youth are unaware they are infected. NICHD's Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) is the only national research network devoted to the health and well-being of these age groups of young people who are HIV-infected or at risk of HIV infection. A program has been established linking the existing ATN research and treatment network with Centers for Disease Control and Prevention (CDC)-funded HIV counseling and testing programs that reach out to potentially HIV-infected adolescents and young adults. This new ATN/CDC collaboration seeks to enhance methods of linking these youth with treatment and encouraging them to remain in care so they can continue to receive their life-saving therapy and management of any co-occurring conditions.

30 Rice ML, Buchanan AL, Siberry GK, et al. Language impairment in children perinatally infected with HIV compared to children who were HIV-exposed and uninfected. *Journal of Developmental & Behavioral Pediatrics.* 2012 Feb; 33(2):112-23. [Epub 2011 Dec 15.] Available at *http://www.ncbi.nlm.nih.gov/pubmed/22179050.*

AIDS Research Benefits Other Diseases

AIDS is one of the most complex diseases ever targeted by biomedical research. Investments in HIV research have transformed the disease from a mysterious and uniformly fatal infection into one that can be accurately diagnosed and effectively managed with treatment. Research also has led to the development of numerous approaches to slow the epidemic's spread.

Similarly, AIDS research pays extensive dividends in multiple other areas of biomedical research, including in the prevention, diagnosis, and treatment of many other infectious, malignant, neurologic, autoimmune, and metabolic diseases, and in deepening our understanding of immunology, virology, microbiology, molecular biology, and genetics. This overview provides just a few examples of how investments in HIV research advance other areas of scientific research.

IMPROVING THERAPIES FOR OTHER DISEASES

AIDS treatment research has accelerated efforts to develop more effective drugs for multiple bacterial, mycobacterial, and fungal diseases. AIDS research has fostered significant improvements in drug design technologies such as **X-ray crystallographic methodologies, nuclear magnetic resonance techniques, computational approaches to medicinal chemistry**, and **new animal models of viral diseases** that are advancing efforts to develop new drugs for other diseases, including:

- Chronic **hepatitis B virus** (HBV) infection: Previously, HBV infection could be treated only with injections of alpha-interferon, and many HBV-infected persons progressed inexorably to cirrhosis, liver failure, and liver cancer, which affect 300 million people worldwide. The HIV drug lamivudine (3TC) is now FDA-approved for the treatment of chronic HBV infection, and is expected to lead to the development of more effective therapies to treat, and perhaps even cure, chronic HBV infection. Another HIV treatment, tenofovir (Viread), is also now approved to treat chronic HBV disease.
- **Hepatitis C virus** (HCV): Experience with HIV protease inhibitors and nucleoside polymerase inhibitors has informed the development of HCV inhibitors that are transforming HCV care.
- **Breast Cancer:** HIV drugs that block the CCR5 receptor on cells also may help prevent aggressive breast cancers from metastasizing.
- **Osteoporosis:** Experience gained from the development of HIV protease inhibitors is being applied to efforts to combat osteoporosis and the heart muscle damage that can result from a heart attack.
- **Smallpox:** Experience gained from the development of HIV protease inhibitors also is being applied to efforts to develop antiviral drugs against smallpox.
- **Cytomegalovirus (CMV):** Techniques used to derive inhibitors of HIV protease are leading to new candidate drugs to treat CMV, a significant cause of birth defects.
- **Influenza:** Techniques developed and validated through HIV drug development are leading to progress in inhibiting influenza.
- **Malaria:** A recent study in Uganda also showed that protease inhibitors significantly increase the effectiveness of drugs used to prevent malaria in children. Malaria is the leading cause of death in children in many malaria-endemic areas and a significant cause of illness and death in people living with HIV.

UNDERSTANDING THE ORIGINS AND MANIFESTATIONS OF OTHER DISEASES

- **Cancer:** Strategies to block natural body hormones called growth factors, which promote the activity of HIV, also are helping researchers understand how to inhibit the growth of certain cancers.
- **Cervical cancer:** Studies of HIV-associated cervical cancer have stimulated new research and therapeutic strategies that likely will benefit all women at risk of cervical cancer.
- **Cancer cachexia:** Approaches developed to treat HIV-associated wasting may benefit persons with cancer-related weight loss and wasting.

- **Diabetes:** Studies of metabolic abnormalities associated with HIV disease and treatment may provide crucial insights into type 2 diabetes and obesity and advance efforts to prevent **cardiovascular disease** in patients with diabetes.
- Research into HIV disease provides new information on viral latency and the susceptibility of the nervous system to infection and inflammatory processes, with important implications for research on **Alzheimer's disease**, **dementia**, **multiple sclerosis**, **neuropsychological disorders**, **encephalitis**, and **meningitis**.
- Research to support AIDS vaccine studies and other large-scale clinical trials in developing countries builds research capacity to address a broad variety of health conditions; produces valuable information on the prevalence and incidence of other diseases beyond HIV; adds to strategies to address hard-to-reach populations; provides valuable data on health and risk-taking behaviors; and helps to shape a broad range of health interventions and policies.

ADVANCING UNDERSTANDING OF THE HUMAN IMMUNE SYSTEM

- HIV research has greatly advanced our understanding of the **human immune system** and has allowed more effective approaches to treat diseases in which dysregulated immune responses are either the actual cause of, or a substantial contributing factor to, the fundamental disease process, including **allergies**, **multiple sclerosis**, **juvenile diabetes**, **heart disease**, **rheumatoid arthritis**, and **systemic lupus erythematosus**.
- The development of effective drugs to prevent and treat opportunistic infections in HIV disease has led to the development of new approaches to reduce illness and save lives among people undergoing **cancer chemotherapy** or receiving immunosuppressive therapy to prevent the rejection of **transplanted organs or tissues.**

ENHANCING OUR PREPAREDNESS FOR EMERGING AND REEMERGING INFECTIOUS DISEASES

- Studies of HIV infection are improving our understanding of how viral infections cross species to enter human populations (**zoonotic infection**), and how this process can be prevented.
- Studies of HIV-infected individuals have led to the discovery of a number of important new infectious agents, including human herpesvirus 6 (HHV6), which causes illnesses such as **exanthem subitum** in children; human herpesvirus 7 (HHV7); human herpesvirus 8 (HHV8 or KSHV), the likely causative agent of Kaposi's sarcoma; bacteria of the genus *Rochalimaea*, also known as *Bartonella*, which causes **bacillary angiomatosis** and "**cat scratch fever**"; and many others.
- Molecular diagnostic techniques developed in the study of HIV helped Centers for Disease Control and Prevention researchers to rapidly identify **hantavirus** as the cause of an outbreak of fatal pneumonia in the southwestern United States a few years ago, determine its origin in local mice populations, and limit its spread among humans.
- Computational methods and mathematical modeling developed to study HIV transmission also are being used to track the transmission and dissemination of **bovine spongiform encephalopathy** (mad cow disease) and will benefit the study of other infectious agents as well.
- New international collaborations developed to track the natural history and epidemiology of HIV will be of significant value should new epidemic diseases emerge in the future.

IMPROVING THE DIAGNOSIS OF OTHER INFECTIONS

- The polymerase chain reaction test used to diagnose HIV infection is now also used routinely to rapidly diagnose other infectious diseases, including **HCV**, **tuberculosis**, **chlamydia**, **Lyme disease**, and a variety of **fungal infections**.
- The development of tests to screen blood for HIV has stimulated advances in **blood safety** technologies to screen the blood supply for other serious infectious diseases, such as HCV, HBV, HTLV-1, and HTLV-2—viruses that are associated with the development of **leukemia** and serious **neurologic diseases**.

EXPANDING THE BASIC SCIENCE KNOWLEDGE BASE

- Biotechnology companies are capitalizing on new basic biomedical information provided by AIDS research, most notably new findings regarding chemokines and **novel proteins as targets for drug and vaccine development**.
- The discovery by AIDS researchers that a large protein molecule can kill HIV-infected cells may lead to similar approaches to **destroy cancer cells** and cells infected with HCV, herpesvirus, and other infectious agents.
- Improved understanding of the mechanism that HIV uses to infect target cells may advance gene therapy for **hemophilia** and other **genetic diseases**.

ENHANCING HEALTH PROMOTION AND DISEASE PREVENTION

- Increased awareness of and attention to sexual behavior and drug use related to HIV transmission have led to improvements in our understanding of the determinants and consequences of sexual initiation and sexual practices in a range of populations, and have laid the groundwork for improved understanding and more effective prevention of addiction-related behaviors.
- Increased attention to the design and implementation of interventions to prevent HIV-related risk behaviors also has expanded strategies to promote a range of health-improving behaviors, such as **better nutrition**, **adherence to drug therapies**, **prevention of unwanted pregnancy**, and **reductions in smoking and alcohol and drug use**.
- The development of improved methods of measuring and assessing sensitive sexual and drug-using behaviors and the social and sexual networks in which such behaviors occur—which have been instrumental in charting the movement of HIV epidemics in different social groups and communities—is advancing understanding of the social dynamics of sexually transmitted infections, substance abuse, fertility, and family planning, and advancing **social science and behavioral epidemiology** related to other infectious and noninfectious diseases.

IMPROVING MATERNAL AND CHILD HEALTH IN LOW-RESOURCE COUNTRIES

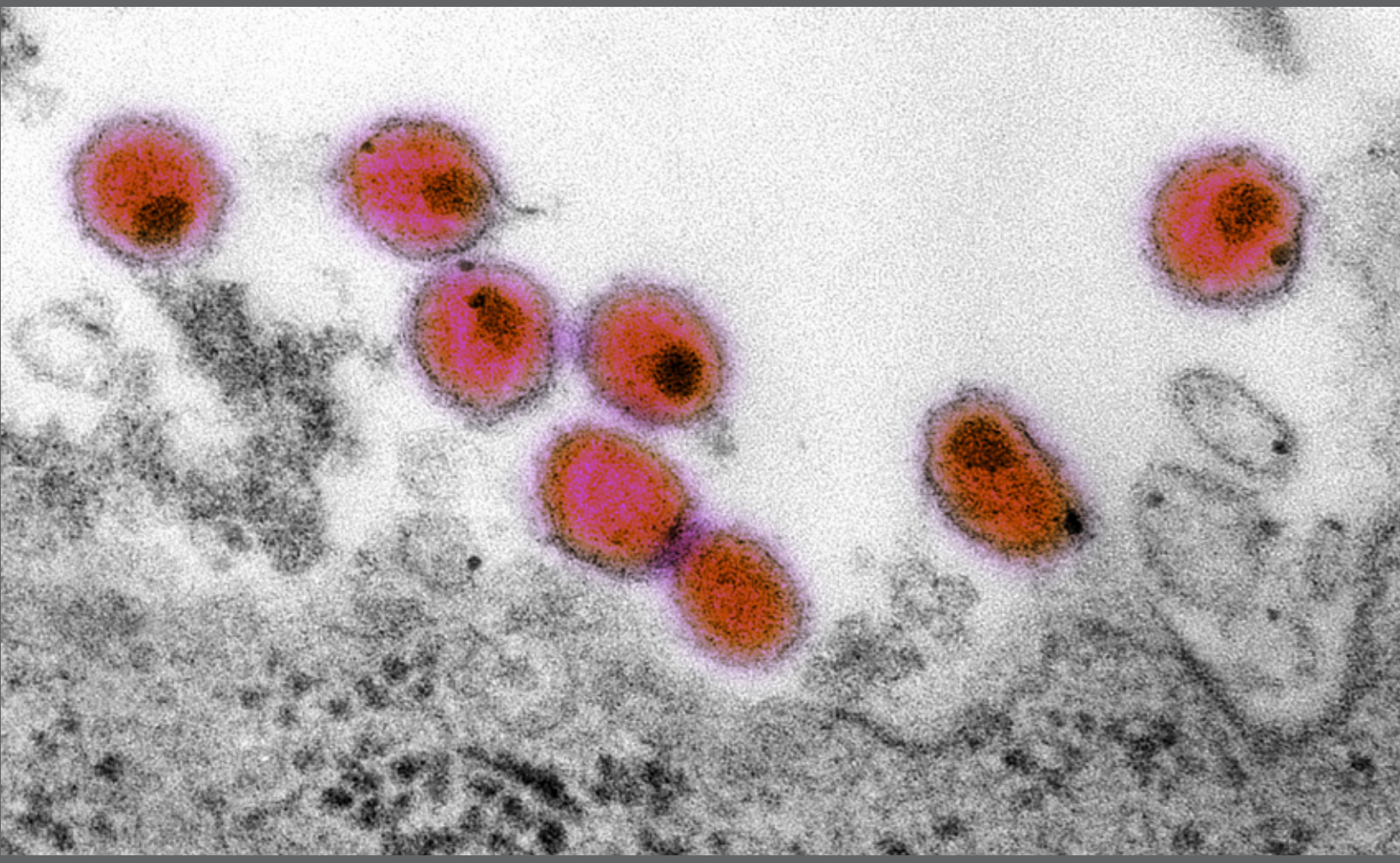
Research on HIV in children and the prevention of mother-to-child HIV transmission, and the integration of HIV services into maternal-child health settings, have improved maternal-child care and outcomes in developing countries. The benefits from AIDS research and care delivery include:

- **Improved delivery of preventive care to children and prenatal care** in developing countries.
- **Increased understanding of the importance of breastfeeding to infant survival** in developing countries and an **increased focus on optimizing infant nutrition**.
- Development of **new tools to assess neurodevelopment in children** in developing countries.

NEW APPROACHES TO DRUG TRIALS

AIDS research has led to new models to test treatments for other diseases in faster, more efficient, and more inclusive clinical trials. Advances pioneered in AIDS research include:

- **Community-based clinical trials,** which capture the expertise of community physicians.
- **"Parallel-track"** mechanism, which permits preapproval access to promising drug treatments for individuals who would not otherwise qualify for specific clinical studies.
- **Community advisory boards**, which are now used to help ensure close coordination between clinical trial sites and community constituency groups in multiple disease areas.
- **Ancillary services**—such as general health care, transportation, obstetrical care, daycare for children, and other related services—to recruit and ensure the continued participation of women, children, adolescents, and minorities in clinical trials.



FY 2013 Trans-NIH AIDS Research Priorities

The research priorities of the *FY 2013 Trans-NIH Plan for HIV-Related Research* and the *Trans-NIH AIDS Research By-Pass Budget Estimate* represent the most critical and promising areas of research to address the continuing pandemic.

PRIORITY:
Investing in Basic 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, address critical gaps, and capitalize on emerging scientific opportunities. Progress in basic science provides the building blocks to progress across all other scientific areas and 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 the transmission, acquisition, establishment, and maintenance of HIV infection and the causes of its associated profound immune deficiency and severe clinical complications. Research on basic HIV biology and AIDS pathogenesis has revolutionized the design of drugs, methodologies for diagnosis of HIV infection, and tools for monitoring disease progression and the safety and effectiveness of antiviral therapies. Groundbreaking strides have been made toward understanding the fundamental steps in the life cycle of HIV, the host-virus interactions, and the clinical manifestations associated with HIV infection and AIDS.

Additional research is needed to further the understanding of the virus and how it causes disease, including studies to delineate how sex, gender, age, ethnicity, race, pregnancy, nutritional status, and other factors interact to influence vulnerability to infection and disease progression and affect treatment success or failure, including immune dysregulation and inflammation, and the development of HIV-associated comorbidities, malignancies, coinfections (including tuberculosis and hepatitis C), and cardiovascular, neurological, and other clinical complications. Additional research examining the genetic determinants associated with HIV susceptibility, disease progression, and treatment response also is needed and 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 and genes associated with susceptibility to HIV infection in a small subset of individuals already have been identified.

Research examining the mechanisms by which HIV establishes and reactivates latent reservoirs of infection, and studies that further understanding of factors that are associated with the ability of the host to restrict HIV infection and/or mitigate HIV disease progression, also are high priorities for the NIH. A better understanding of these processes could help identify key targets for the development of new therapeutic strategies to prevent or control HIV infection or possibly lead to a cure for HIV disease.

The FY 2013 by-pass budget request for this area is $816 million, which is an increase of 13 percent over the FY 2012 enacted level. 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 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, vaccine, and pre-exposure prophylaxis 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 transverses mucosal surfaces; and the establishment and maintenance of latent viral reservoirs. The NIH will provide increased resources for research on the biology of HIV transmission, which will be of importance for all HIV prevention research. Basic research to better understand HIV coinfections, comorbidities, and malignancies, as well as factors related to premature aging and other complications, will be priorities. Funds also will be provided for research to better understand the differences in HIV transmission, treatment, and progression in women compared with men, as well as the unique clinical manifestations of HIV disease in women.

Research Toward a Cure

An important new priority area will focus on issues related to the potential for a cure or lifelong remission of HIV infection, including studies on viral persistence, latency, immune activation, and inflammation. 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.

Eradication of Viral Reservoirs: Toward a Cure

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

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 the best hope for ending the HIV pandemic, but researchers 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, as reducing HIV incidence inevitably will require a combination of various biomedical, behavioral, and structural interventions, not just a single "silver bullet." For example, an HIV vaccine, a microbicide, and/or pre-exposure prophylaxis with antiretroviral (ARV) 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 men who have sex with men.

VACCINES

The best long-term hope for controlling the AIDS pandemic is the development of safe, effective, and affordable AIDS vaccines that may be used in combination with other prevention strategies. The NIH supports a broad AIDS vaccine research portfolio encompassing basic, preclinical, and clinical research, including studies to identify and better understand potentially protective immune responses in HIV-infected individuals and studies of improved animal models for the preclinical evaluation of vaccine candidates. Information gained from these studies is being used to inform the design and development of novel vaccine strategies. Since the announcement of the results of the RV144 trial in Thailand, the NIH has supported an unprecedented collaborative effort with investigators around the world to identify clues about the necessary immune responses required to protect against HIV acquisition. To take advantage of the knowledge gained, it now will be essential to conduct additional clinical trials in other populations and in other parts of the world. The recent release of data from this and several vaccine Phase I and Phase II clinical studies presents new scientific opportunities for investigation.

The FY 2013 by-pass budget request for this activity is $757 million, an increase of 38 percent over the FY 2012 enacted level. Vaccine research in the past 2 years has resulted in critical advances that provide new targets and scientific opportunities in this essential area, leading to renewed excitement in this field.

Basic research studies, particularly those using samples from ongoing 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 the development of improved animal models to conduct preclinical evaluations of vaccine candidates. In FY 2013, the NIH will fund additional basic research in these areas, as well as the design and development of new vaccine concepts and the preclinical/clinical development of vaccine candidates in the pipeline.

At the by-pass level, resources are essential to ensure the pursuit of new opportunities and will be directed toward:

- Development and testing of improved vaccine candidates in additional clinical studies, both in the United States and abroad, building on the results of the recent Phase III vaccine trial in Thailand;

- New initiatives to integrate systems biology with HIV vaccine discovery and for additional research involving nonhuman primates; and
- Initiatives to build on the partial protection and newly identified markers that may be related to the early protection observed in the trial conducted in Thailand and develop new test systems to measure immune responses to the vaccine that will integrate preclinical animal and human clinical studies.

New Opportunities in Vaccine Research

- Characterization of "transmitted/founder" HIV variants
- New immunologic assays for T cells and antibodies
- Genetic analysis of virus from infected vaccinees
- Development of alternative animal models
- New designs of vaccines ready for testing
- Advancement of HIV vaccine candidates to efficacy testing

MICROBICIDES

A safe and effective microbicide may be the best hope for woman-controlled HIV prevention. Microbicides are antimicrobial agents and other products that could be applied topically and used alone or in combination with other strategies to prevent transmission of HIV and other sexually transmitted infections. Microbicides represent a promising approach to primary prevention. The NIH supports a comprehensive and innovative microbicide research program that includes the screening, discovery, development, preclinical testing, and clinical evaluation of microbicide candidates. The NIH supports basic science aimed at understanding how HIV crosses 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 menopause; studies in adolescents and in men who have sex with men; and implementation research to better understand how to integrate a potential product into community prevention practices. Basic science and clinical studies have shown promise for the use of ARV-based microbicides as HIV prevention strategies. Followup studies testing different ARV- and non-ARV-based microbicide candidates are underway or being developed.

The FY 2013 by-pass budget request for this area is $146 million, which represents an increase of 14 percent over the FY 2012 enacted level for this high-priority area of research. In FY 2013, the NIH will continue to support the discovery, design, development, and evaluation of microbicide candidates. Key ongoing activities include support for the microbicide clinical trials network and the necessary infrastructure to conduct microbicide trials. Research activities will be designed to build on recent research advances; develop innovative, novel, and high-risk/high-reward approaches for the discovery, development, and testing of microbicide candidates and microbicide delivery systems; develop criteria for selecting potential microbicides to be advanced through the different phases of preclinical and clinical studies, including clinical effectiveness studies; and research on ethics, adherence, and other behavioral and social science issues that can have an impact on clinical trials and product use. Through a number of trans-Governmental working groups and nongovernmental expert consultations, OAR will continue to foster coordination and collaboration in innovative microbicide research leading to the development and testing of novel potential candidates that can prevent HIV transmission and acquisition.

BEHAVIORAL AND SOCIAL SCIENCE

The NIH supports research to better understand the risk behaviors and social contexts that lead to HIV infection and disease progression, how to change those behavioral and social contexts, and how to maintain protective behaviors once they are adopted. Studies are developing and evaluating interventions directly targeted to substance abuse and sexual behaviors associated with HIV transmission. Social and environmental factors associated with infection and disease outcomes are being studied, including housing, employment, health care access, stigma, and interpersonal networks. An important area of research is determining effective strategies to test HIV-infected persons, link them to care, and promote adherence to antiretroviral therapy. Studies have shown that early access to medical care substantially reduces direct medical treatment expenditures. Other research aims toward better understanding and changing the environmental, social, and cultural factors associated with HIV infection and disease outcomes, including stigma.

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 and retention in clinical 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 2013 by-pass budget request for this area is $487 million, which is an increase of 15 percent over the FY 2012 enacted level. The NIH will continue to fund research to reduce HIV-related risk behaviors and to better understand social factors contributing to HIV transmission, with an emphasis on racial and ethnic communities most affected by HIV. Resources will be directed toward several new prevention initiatives, addressing the challenges of 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. The NIH will support initiatives to better understand the multiple factors related to adherence, utilizing novel ways to ensure that patients take their medications and use prevention strategies appropriately.

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 men who have sex with men, older individuals, and adolescents, particularly among racial and ethnic populations.

TREATMENT AS PREVENTION

A critical new area of prevention research is the study of treatment strategies as a method to prevent new HIV infections. This approach builds on NIH-sponsored landmark clinical trials that demonstrated that treatment of HIV-infected pregnant women could significantly reduce transmission of HIV from mother to child. Recent groundbreaking studies have demonstrated the successful use of antiretrovirals to prevent transmission of HIV in specific populations. Clinical results from a large NIH-sponsored international clinical trial (HPTN 052) showed that early initiation of antiretroviral treatment of HIV-infected heterosexual individuals resulted in a 96 percent reduction in sexual transmission of HIV to their uninfected partners. Another major NIH-sponsored clinical trial (iPrEx) demonstrated that use of an antiretroviral drug by some high-risk uninfected men could reduce their risk of acquiring HIV. The findings from this study showed proof-of-concept and the effectiveness of a novel HIV prevention strategy known as pre-exposure prophylaxis (PrEP). However, these findings have not been replicated in women.

The FY 2013 by-pass budget request for this area is $89 million, which is an increase of 17 percent over the FY 2012 enacted level.

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:

- Discovery and testing of the next generation of antiretroviral drugs that may be used in potential new strategies for PrEP (therapeutic regimens for uninfected at-risk individuals), particularly for women and adolescents;
- 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; and
- 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.

PRIORITY:
Improving Disease Outcomes for HIV-Infected Individuals

DRUG DISCOVERY, DEVELOPMENT, AND TREATMENT

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. ART also has delayed the progression of HIV disease to the development of AIDS. Unfortunately, the treatment is beginning to fail in an increasing number of patients who have been on ART. These patients are experiencing serious drug toxicities and developing drug resistance. Recent epidemiologic studies have shown that the incidence of coinfections, comorbidities, AIDS-defining and non-AIDS-defining malignancies, and complications associated with long-term HIV disease and ART are increasing. These include tuberculosis, hepatitis C, metabolic disorders, cardiovascular disease, conditions associated with aging, and neurologic and neurocognitive disorders.

The NIH supports a comprehensive therapeutics research program to design, develop, and test drugs and drug regimens. Under development are drugs to maintain undetectable viral load, to overcome drug resistance and treatment failure, and to prevent and treat HIV-associated coinfections, comorbidities, and other complications. 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. The program also is focused on developing drugs and other strategies that can eradicate persistent viral reservoirs that may lead to a functional cure for HIV disease.

The FY 2013 by-pass budget request for this area is $691 million, which represents an increase of 11 percent over the FY 2012 enacted level. Improved therapeutic regimens for the treatment of HIV and its associated coinfections, comorbidities, and complications are urgently needed, especially regimens that can be implemented in resource-limited settings. Over the past several years, 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 and novel cell- and immune-based approaches 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, including 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 "therapeutics as prevention" strategies.

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 infrastructure, equipment, shared instrumentation, tissue and specimen repositories, and capacity-building support for the conduct of AIDS-related research, including preclinical and clinical studies. The expansion of NIH-funded HIV research globally has necessitated the development of research training, infrastructure, and capacity-building efforts in many resource-limited settings throughout the world. 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. These efforts are integral to strengthening the quality and capacity of HIV/AIDS research, both domestically and internationally.

The FY 2013 by-pass budget request for this area is $246 million, which represents an increase of 11 percent above the FY 2012 enacted level. The NIH will support training programs for U.S. and international researchers to build the critical capacity to conduct AIDS research both in racial and ethnic communities in the United States and in developing countries. The NIH will continue to support ongoing efforts to increase the supply of nonhuman primates and other animal models, particularly rhesus and pigtail macaques, for AIDS research and other areas of biomedical research both in the United States and abroad. 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.

HIV Research in Women and Girls

Worldwide, women represent approximately 50 percent of the epidemic; in the United States, women are 24 percent of the adults living with HIV. Sixty-six percent of HIV-infected women in the United States are African American; 15 percent are Hispanic/Latina. HIV-infected African American women have twice the risk of dying from AIDS compared with their white counterparts. The NIH places high priority on research to address the unique needs of women, including:

- Basic sciences: Differences between men and women, including mucosal immunology and HIV-risk differences across the life cycle
- Physiologic and pathogenesis differences, including metabolic issues, ARV side effects, and hormonal effects
- Epidemiology: HPTN 064 (ISIS): defining HIV risk in U.S. women; found that HIV seroincidence in some communities of African American women is similar to women in some African countries
- Women's Interagency HIV Study (WIHS): Long-term followup study of HIV pathogenesis and unique manifestations of HIV disease in women
- PROMISE, IMPAACT: Studying mother-to-child transmission, pregnancy, maternal health, and breastfeeding
- Microbicide Trials Network (MTN): Oral and topical biomedical prevention in women, including during pregnancy, adolescence, and menopause
- HIV Vaccine Trials Network (HVTN): Clinical trials of vaccine candidates
- HIV Prevention Trials Network (HPTN): Behavioral and social sciences
- Clinical trials to treat HIV disease in adults and adolescents (ACTG, INSIGHT, ATN)
- PrEP and Treatment as Prevention
- Integrated research: Biomedical, behavioral, and social science research on risk and prevention, adherence
- Multipurpose prevention technology: Preventing HIV, pregnancy, and sexually transmitted infections
- Clinical trial participants: Females, 45.7 percent; males, 48.9 percent

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 on HIV/AIDS is critical to the monitoring of epidemic trends, to the evaluation of prevention modalities, to characterization of the clinical manifestations of HIV disease and related comorbidities, and to measurement of the effects of treatment regimens at the population level. Multisite epidemiologic studies in the United States are identifying new HIV-related comorbidities and helping to differentiate effects related to HIV treatment from those related to HIV disease itself. As the AIDS epidemic evolves, there is a crucial need for epidemiologic studies in domestic and international settings. The NIH supports a comprehensive research portfolio in both settings to study the epidemiologic characteristics of populations in which HIV is transmitted and the changing spectrum of HIV-related disease (including the occurrence of coinfections, malignancies, metabolic, cardiovascular, neurological, skeletal, and other complications). These studies have delineated the significant health disparities that are critical factors in the epidemic (e.g., racial and ethnic disparities in the United States, between industrialized and resource-constrained nations, between men and women, within younger and older age groups, and health disparities based on sexual identity).

AIDS and Aging Research Priorities

- Investigate issues related to cardiovascular, liver, and renal disease; cancers; osteoporosis; and neurocognitive decline in HIV-infected individuals
- Study unifying aging mechanisms in persons with HIV, including immunosenescence, inflammation, and hypercoagulability
- Study these mechanisms in light of the complex and mutually reinforcing effects of HIV infection, antiretroviral therapy (ART), and aging
- Study multimorbidity and polypharmacy, which are frequently observed in HIV-infected aging individuals
- Develop biomarkers and clinical indices to predict conditions leading to morbidity and mortality and to test interventions for such conditions
- Conduct studies of sociobehavioral issues and community support to specifically address AIDS and aging issues

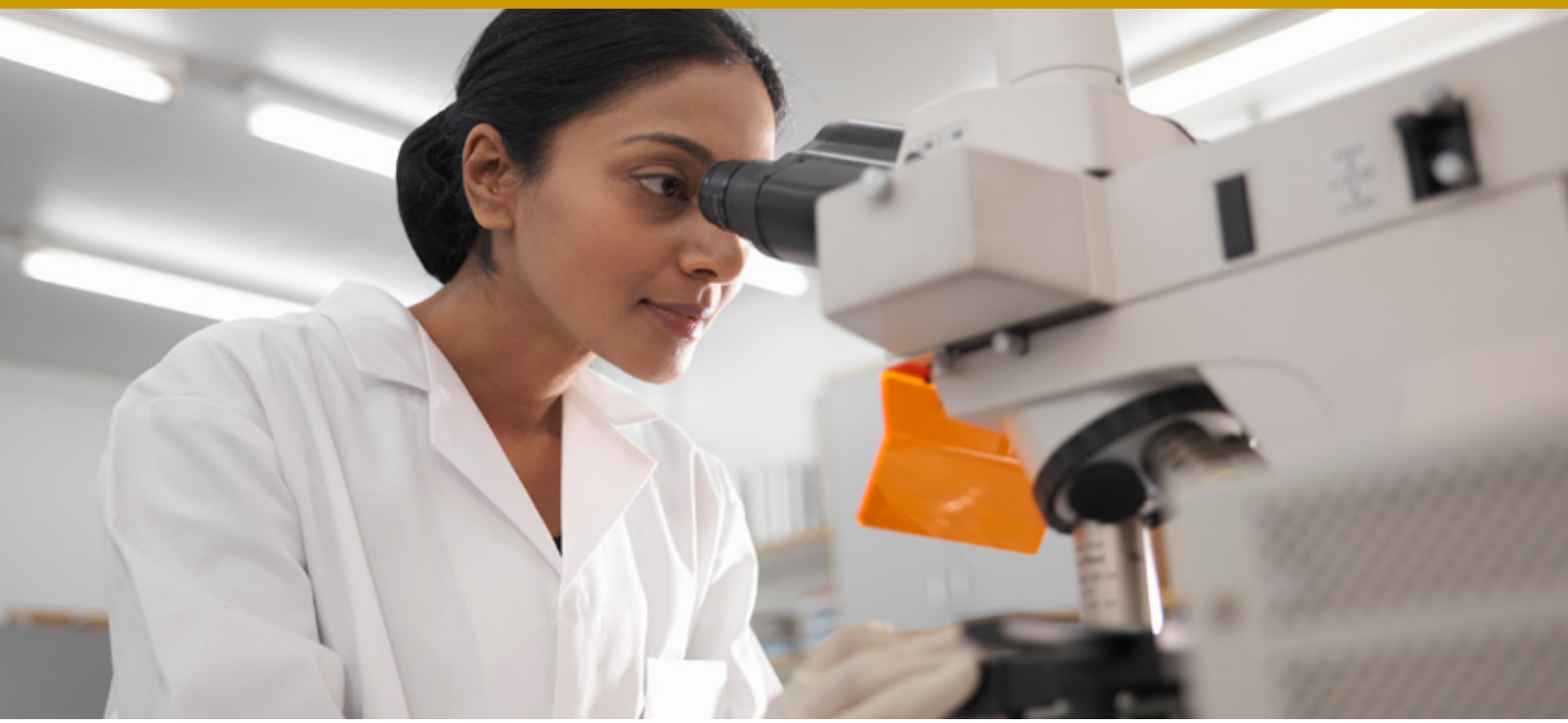
The FY 2013 by-pass budget request for this area is $313 million, which represents an increase of 11 percent above the FY 2012 enacted level. The NIH will continue to provide support for high-priority epidemiology studies of groups and populations affected by HIV and at high risk of infection, including individuals over 50 years of age, men who have sex with men (MSM), especially MSM of color, women, and adolescents. The NIH also will increase support for critical studies of the specific role of race and gender, the effects of increased HIV testing and linkage to care on HIV spread, the impact of therapy in changing the spectrum of HIV disease, and the preventable causes of death. In addition, resources will be provided for studies of HIV in aging populations and for implementation science, including how to implement strategies to scale up cost-effective interventions that may accelerate the progress toward an AIDS-free generation. As the AIDS epidemic continues to evolve, there is a crucial need to continue to conduct epidemiologic studies in both domestic and international settings. The NIH will continue to place high priority on understanding the causes of HIV-related health disparities, both in the United States and around the world, their role in disease transmission and acquisition, and their impact on treatment access and effectiveness.

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 2013 by-pass budget request for this area is $53 million, which represents an increase of 6 percent above the FY 2012 enacted level. As the number and complexity of clinical studies increases, 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 ART, 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 *(http://www.aidsinfo.nih.gov)* and its Spanish language site *(http://infosida.nih.gov/)*.



Conclusion

The recent scientific advances resulting from NIH-funded research represent a turning point for AIDS research. New avenues for discovery have been identified, providing possibilities for the development of new strategies to prevent, treat, and potentially cure HIV. This by-pass budget provides the resources necessary to capitalize on those advances, to move science forward, and to begin to turn the tide against this pandemic.

Over the past several years, OAR has used its authorities to shift AIDS research program priorities and resources to meet the changing epidemic and scientific opportunities. Even in years of flat budgets, OAR has provided increases to high-priority prevention research in the areas of microbicidies, vaccines, and behavioral and social science research and has preserved funding for the critical basic science base that supports research on AIDS and its associated diseases and conditions. However, in order to provide those increases, OAR has had to reduce and redirect funds from other important research in other areas, including therapeutics, natural history and epidemiology, and training and infrastructure support.

The NIH 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. This budget request is designed to support critical research to find new tools to begin to turn the tide 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 2011 Actual Budget Authority	FY 2012 Enacted Level	FY 2013 By-Pass Estimate	Percent Change FY 2012 to FY 2013
Etiology and Pathogenesis	$731	$723	$816	13.0%
Vaccines	549	550	757	38.0
Microbicides	121	128	146	14.0
Behavioral and Social Science	412	424	487	15.0
Treatment as Prevention	65	76	89	17.0
Drug Discovery, Development, and Treatment	615	620	691	11.0
Total Therapeutics	680	696	780	12.0
Training, Infrastructure, and Capacity Building	233	222	246	11.0
Natural History and Epidemiology	279	282	313	11.0
Information Dissemination	54	50	53	6.0
TOTAL	$3,059	$3,075	$3,598	17.0%

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

	FY 2011 Actual Budget Authority		FY 2012 Enacted Level		FY 2013 By-Pass Estimate		Percent Change FY 2012 to FY 2013
	NO.	AMT.	NO.	AMT.	NO.	AMT.	
RESEARCH PROJECTS							
Noncompeting	1,784	1,354	1,691	1,318	1,675	1,279	-3.0
Administrative supplements	(76)	8	(50)	8	(48)	7	-13.0
Competing	559	296	646	322	866	648	101.0
Subtotal, RPGs	2,343	1,658	2,337	1,648	2,541	1,934	17.0
SBIR/STTR	71	35	74	38	175	94	147.0
Total, RPGs	2,414	1,693	2,411	1,686	2,716	2,028	20.0
RESEARCH CENTERS							
Specialized/comprehensive	73	135	82	142	80	157	11.0
Clinical research	1	56	1	56	1	62	11.0
Biotechnology	0	5	0	5	0	6	20.0
Comparative medicine	12	57	9	55	10	63	15.0
Research centers in minority institutions	3	14	3	15	3	19	27.0
Subtotal, Centers	89	267	95	273	94	307	12.0
OTHER RESEARCH							
Research careers	240	43	242	43	228	46	7.0
Cancer education	0	0	0	0	0	0	—
Cooperative clinical research	12	17	12	18	9	11	-39.0
Biomedical research support	2	2	3	3	3	3	—
Minority biomedical research support	0	0	0	0	0	0	—
Other	140	63	132	62	136	72	16.0
Subtotal, Other Research	394	125	389	126	376	132	5.0
Total, Research Grants	2,897	2,085	2,895	2,085	3,186	2,467	18.0
TRAINING	**FTTPs**		**FTTPs**		**FTTPs**		
Individual	84	3	73	3	74	4	33.0
Institutional	669	33	661	34	648	36	6.0
Total, Training	753	36	734	37	722	40	8.0
Research and development contracts	133	411	130	428	122	515	20.0
(SBIR/STTR)	(1)	(1)	(1)	(1)	(1)	(1)	—
Intramural research	—	339	—	337	—	370	10.0
Research management and support	—	125	—	124	—	136	10.0
Office of the Director—Appropriation	—	144	—	144	—	158	10.0
Office of the Director—Other	—	63	—	64	—	70	9.0
ORIP and SEPA	—	81	—	80	—	88	10.0
TOTAL, Budget Authority	—	**$3,059**	—	**$3,075**	—	**$3,598**	**17.0%**

FY 2013 Trans-NIH Plan for HIV-Related Research

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FY 2013 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

FY 2013 RESEARCH PRIORITIES

- Further the understanding of fundamental viral and host mechanisms associated with the acquisition, replication, and persistence of HIV at the cellular and organism level and determinants of disease progression, including intrinsic cellular restrictions, and the mechanisms and role of immune activation and inflammation.
- Identify the sites, mechanisms of persistence, and strategies for eradication of reservoirs of HIV infection.
- Develop novel strategies to treat and prevent HIV using knowledge gained from studies on HIV reservoirs, host mechanisms involved in acquisition and inhibition of HIV infection, and immune activation and inflammation.
- Study the interaction of aging with HIV infection and the mechanisms responsible for the pathogenesis of comorbid conditions 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.
- Elucidate the mechanisms associated with the pathogenesis of HIV/AIDS-related coinfections and HIV/AIDS-associated malignancies, and the effect of these conditions on HIV pathogenesis, as well as the impact of HIV on the progression of these diseases.

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.
- Elucidate the genetic complexity, molecular features, and biological characteristics of HIV variants that are transmitted to the naive host.
- Determine the mechanisms by which virus-encoded genes or viral gene products regulate and influence transmission, establishment, and dissemination of HIV infection.
- Determine the cell subsets and tissue types at portals of entry responsible for the acquisition, replication, and dissemination of HIV during the initial stages of infection.
- Delineate the mechanisms and impact of genetic, metagenomic, viral and host epigenetics, and 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 and organs 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, Viral Pathogenesis, and Viral Persistence

Delineate the viral and host mechanisms associated with HIV replication and dissemination, and those that influence viral setpoint, disease progression, and viral persistence 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 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.
- Elucidate mechanisms by which epigenomic modifications of HIV interact with and enable host immune responses to control viral replication, setpoint, spread, and disease progression, and that prevent immune dysfunction, aberrant immune activation, and inflammation.
- 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, genitourinary, and respiratory 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, metagenomic, viral and host epigenetic, and environmental risk factors, as well as mechanisms of immune dysfunction, associated with the susceptibility to, the development of, and the progression of OIs and coinfections.
- Elucidate the mechanisms of innate and adaptive immune function that mediate protection against OIs and the effect of these mechanisms on HIV infection.
- Study the effects of HIV therapy on the clinical course and manifestation of OIs and coinfections, including pathogenesis of immune reconstitution inflammatory syndrome, 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 therapy (ART).
- Define the molecular and phylogenetic characteristics of major HIV-associated OIs and pathogens, and integrate strain-specific characterization of data into studies of the pathogenesis, mechanisms of transmission, and epidemiology of OIs.
- Determine biomarkers and factors associated with clinical response 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, pulmonary, 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, pulmonary, 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, pulmonary, and atherosclerotic cardiovascular disease.
- Study the influence of the gut microbiome and other microbiota in conjunction with metabolic abnormalities, body composition changes, and cardiovascular and pulmonary 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 patients.

OBJECTIVE–G: Pathogenesis of Neurological Disease

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

STRATEGIES

- Define the neurobiological, immunological, and molecular basis of HIV- or ART-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 mechanisms and determinants of HIV neuroinvasion (e.g., via blood-brain barrier), spread, persistence, and latency within the CNS.
- Determine the host and viral factors influencing independent evolution of drug-resistant HIV strains in the CNS compartment as well as its functional consequences.
- 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

FY 2013 RESEARCH PRIORITIES

- Continue to explore new concepts for rapidly inducing and maintaining effective immune responses to prevent HIV transmission and control HIV replication. Utilize combination approaches not only of priming with a viral vector and boosting with a second vector or protein, but also novel approaches to engage relevant B-cell populations for long-term protective antibody production to HIV.

  Because we have not yet attained highly effective HIV vaccine-induced protection against infection and/or disease progression, it is essential to support truly novel alternative approaches to HIV vaccines. In particular, these include approaches to induce effective long-term protective antibody responses to HIV envelope as well as broad-based T-cell immune responses to the most conserved regions of HIV proteins. Studies of adjuvant-enhanced immune responses in nonhuman primates (NHPs) and human volunteers are particularly needed because of the documented differences observed in small animal models. Studies of immunogen designs that incorporate repetitive motifs may be needed for strong and stable protective antibody responses. Further studies of cytokine and chemokine induction, along with other host factors in selected subsets of cells or mucosal tissues, may enable improved assessment of vaccine-induced adaptive and innate protective responses.

- Develop and refine animal models to accurately reflect sexual transmission and dissect vaccine-induced responses in clinical trials and in animal models in parallel.

  Considering the limited number of transmitted/founder virions of HIV that appear to successfully establish infection in humans, it is important to develop models that will examine transmission both in an immunologically "inflamed" environment and a "normal" mucosal environment. Animal models that can directly test HIV strategies directed at HIV envelope, as well as surrogate simian immunodeficiency virus (SIV) models, need to be further refined to query different modes of transmission. Chimeric simian/human immunodeficiency virus (SHIV) models that can test the diverse HIV clades also need to be developed to study the breadth of protection achieved by different HIV vaccine approaches. It is of utmost importance to bridge between the animal models and clinical HIV vaccine studies during product testing and immune analyses to define correlates of protection.

- Develop clinical products, design further immune correlate analyses, and actively move toward initiation of expanded clinical trials to test potential efficacy as rapidly as possible to confirm and improve upon the limited efficacy observed in the HIV vaccine trial of avipox-vectored HIV antigens plus HIV envelope proteins conducted in Thailand.

  Current Phase I and Phase II HIV vaccine clinical trials would enable the advanced study of several products and vaccination strategies starting in 2013. Continued monitoring and engagement of potential clinical cohorts will be essential for rapid enrollment and conduct of clinical trials. Efficacy trials will become increasingly large and complex with the success and further implementation of other successful prevention

strategies such as circumcision, antiretroviral treatment, and microbicides. It is essential that populations with different modes of transmission be included in testing HIV vaccines to determine the limits and ability of various vaccine concepts to effect protection. Because of the expense and complexity of product development for clinical trials, it is important for the NIH to engage in partnerships at multiple levels to enable the study of several products that will test different strategies or potential correlates of immune protection.

OBJECTIVE–A: Adaptive and Innate Host Defense Mechanisms

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

STRATEGIES

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

- Define the heterogeneity of specific responses to vaccine immunogens, specifically those derived from HIV, SIV, and SHIV, within diverse tissue compartments, and identify factors that confer protection from infection by various routes, including vaginal, rectal, oral, and parenteral exposure.

- Determine which factors promote development of particular human anti-HIV effector cell types; promote production of antiviral substances, including chemokines; or enhance non-antigen-specific innate protective mechanisms.

- Define the basis for adaptive, antigen-specific immune reactivity (humoral, cellular, and other) across divergent HIV types (clades and biological phenotypes or immunotypes); study clinical samples from human volunteers participating in HIV vaccine trials to determine the extent of cross-reactive immune responses that can be achieved with different candidate vaccines.

- Determine whether HIV immune responses that can contribute to immune enhancement of viral replication *in vitro* can interfere with induction or propagation of vaccine-induced effector responses *in vivo*.

- Seek new clues for correlates of immune protection and vaccine design by studying HIV-infected or highly exposed but seronegative individuals across the lifespan, and SIV or SHIV NHP lentivirus models, by conducting the following research:

  - Study acutely HIV-infected individuals, 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 might inform HIV vaccine studies.

  - Monitor the effects on immune activation with intercurrent sexually transmitted diseases (STDs), malaria, tuberculosis (TB), hepatitis B and C, human papillomavirus (HPV), and other infectious diseases, and with administration of drugs of abuse or effects of antiretroviral therapy (ART) on HIV shedding in vaccinated subjects. Model these confounding elements in NHP.

- Develop *in vitro* experimental approaches for analysis of HIV vaccine responses that will combine sensitivity, specificity, high throughput, and the ability to use small sample volumes; develop *in vitro* and *in vivo* tools to study systemic and mucosal immune mechanisms of control of virus for analysis of vaccinated individuals (across 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-naive, HIV- or SIV-vaccinated, or SHIV- or SIV-infected animals to provide a resource for assay development in parallel with human studies.
  - Develop improved methodologies and assays to measure HIV neutralization; explore the mechanisms of virus neutralization and the reason(s) for the relative difficulty 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 and utilize system biology approaches, including functional genomics to characterize vaccine-induced protective immune responses.
  - Develop or improve sensitive quantitative measures of HIV (and SIV) in body fluids and low-level tissue reservoirs, including genital secretions, oral fluids, and breast milk, to assess the effectiveness of vaccines designed to lower viral load and interrupt transmission or prevent disease progression.

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

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

STRATEGIES

- Multiple parallel approaches to development and testing of candidate HIV/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;

- 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 innate and 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 ART 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 integrity of the mucosal surface or the inductive ability of HIV vaccines.

- Support development of reagents and standardized methods to assess specific HIV or SIV vaccine-induced immune responses in NHP animal models and humans, including infants, for both humoral and cellular aspects of systemic and mucosal immunity. This includes:
  - Developing and refining assays to distinguish between serological and cellular responses due to immunization versus those due to HIV, SIV, or SHIV infection;
  - Characterizing and evaluating potential negative side effects of candidate HIV/SIV vaccine designs, including the potential to increase the susceptibility to infection or the rate of disease progression in NHP animal models;
  - Standardizing and validating assays to assess potency of candidate HIV vaccines;
  - Standardizing and validating assays to be used as Phase III study endpoints; and
  - 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 the 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 naive 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, innate, and mucosal immune parameters; and the efficacy of different preventive vaccine candidates. This includes the following:
  - Develop and implement strategies to coordinate studies in 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 by studying initially concordant HIV-uninfected couples at high risk or discordant couples or by studying subsequent transmission from vaccinated individuals who become infected after administration of the trial vaccine to new partners identified via partner tracing). This includes the following areas of trial design research:

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

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

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

    - Consider the impact of 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 the feasibility of vaccine studies in appropriate cohorts or populations.

STRATEGIES

- Identify and develop potential domestic and foreign sites with a high HIV seroincidence and improve access to populations at high risk for acquiring HIV infection, where vaccine or other prevention research activities may be feasible. This includes the following activities:
  - Track the course of the epidemic by applying newer epidemiologic tools for estimating the HIV incidence in various populations with documented high-risk behaviors in the United States and worldwide; improve methods to identify and evaluate emerging risk groups and those groups most likely to be informed, willing, and able participants in HIV vaccine clinical trials.
  - Identify and address barriers to participation in clinical trials among all at-risk groups, so that all relevant populations, especially women and adolescents, are included in HIV vaccine clinical trials.
  - Develop and apply new laboratory diagnostic tools, including rapid, point-of-care tools, that can be adapted for high throughput to detect, characterize, and amplify virus in blood and mucosal fluids from individuals with new HIV infections and allow distinction between 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; and 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

FY 2013 RESEARCH PRIORITIES

- Develop and maintain a robust and diverse pipeline of topical microbicide candidates and standard protocols for efficiently advancing candidates through the pipeline.
- Develop and test animal and tissue models that are predictive of microbicides safety and efficacy.
- Develop biomarkers for the assessment of adherence and sexual activity in microbicides studies.
- Design and conduct microbicides studies that integrate the biological, behavioral, and social sciences.
- Define normal and abnormal male and female genital tract and anal/rectal immune physiology and function and their impact on HIV risk and acquisition.
- Develop standard pharmacokinetic/pharmacodynamic (pK/pD) correlates of efficacy for microbicides studies.

OBJECTIVE–A: Basic Mechanisms of Mucosal Transmission

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

STRATEGIES

- Identify, investigate, and characterize new and understudied viral and host targets and kinetic sequencing of infection important for the early dissemination and transmission of HIV in the upper and lower genital tracts and the anus/rectum.
- Develop and study exploratory techniques and systems biology approaches to better characterize the functions of genital and anus/rectum immune and mucosal epithelial cells.
- Investigate the importance of innate, adaptive, and maladaptive host defenses that enhance susceptibility to or protect against HIV transmission and acquisition. Explore strategies to harness these defenses to protect against HIV acquisition.
- Study the interactions between topical candidate microbicides and innate and adaptive genital tract physiology, microbiology, immunology, viral population dynamics, and mucosal secretions and surfaces.
- Study how semen may affect the genital tract and anus/rectum physiology and discern how this affects HIV transmission, acquisition, and susceptibility, and the safety, efficacy, and acceptability of, and adherence to, microbicides.
- Study the tissue and physiology that supports entry or facilitates transport processes that disseminate HIV in humans, and simian immunodeficiency virus (SIV) or chimeric simian/human immunodeficiency virus (SHIV) in nonhuman primate models of infection.
- Determine the role of viral phenotype, genotype, clade, and resistance patterns on the efficiency of transmission of cell-free and cell-associated HIV in secretions and tissues in the genital tract and anus/rectum.
- Investigate the effect of variations in male and female endogenous hormonal status on HIV susceptibility, transmission, and acquisition.

OBJECTIVE–B: Discovery, Development, and Preclinical Testing

Support the discovery, development, and preclinical evaluation of microbicide candidates.

STRATEGIES

- Support the development, validation, and standardization of reproducible methods to assess the antimicrobial and contraceptive activity of microbicide candidates.
- Develop and validate biomarkers and other methods to assess the safety, efficacy, and genital pharmacodynamics of topical microbicide candidates; determine product use and adherence; and document the sexual activity and viral exposure of participants in clinical studies.
- Determine dynamic changes of the genital and rectal microbiome associated with the use of and adherence to topical microbicide candidates.
- Support the development, validation, and standardization of explant and cell culture models to investigate the very early events in HIV or SIV/SHIV transmission and the activity, safety, and toxicity of microbicides.
- Support the development, validation, and standardization of new cellular, tissue, and animal models for HIV and other sexually transmitted infection (STI) susceptibility that closely reflect the dynamics of sexual transmission.
- Evaluate the efficacy of topical microbicides against a variety of HIV viral resistance types, subtypes, and clades.
- Develop methods to facilitate the advancement of microbicide candidates through the preclinical pathway by providing support for Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP), design, and scale-up.
- Collaborate with the Food and Drug Administration to accelerate the pace of development of combination topical microbicides.
- Develop and test specific assays and algorithms that will inform which candidate microbicides should be advanced through the pipeline.
- Support the development of contraceptive and non-contraceptive microbicide candidates.

OBJECTIVE–C: Formulations and Modes of Delivery

Develop and evaluate safe and acceptable topical microbicide formulations and modes of delivery.

STRATEGIES

- Develop coitally dependent and independent microbicide formulations, and delivery systems for optimal dosing that reduce or eliminate tissue toxicity and trauma while maintaining product effectiveness, acceptability, and adherence.
- Develop multifunctional topical microbicide formulations that prevent HIV and other STIs.
- Study the systemic and tissue-level dose-response and bioavailability of topical microbicides in varied formulations and delivery systems.
- Identify and validate methods that improve the understanding of rheological and physical properties of microbicide candidate formulations before, during, and after intercourse.
- Develop, standardize, and validate methods to relate local and systemic microbicide concentrations to product safety and efficacy for varied formulations and delivery methods.
- Develop and incorporate age-appropriate and culturally sensitive measures of acceptability during the discovery and development of new microbicide formulations and delivery systems.
- Develop, validate, and standardize methodologies to analyze properties of candidate microbicides formulated as individual and combination products.
- Evaluate the interaction of genital and anal/rectal practices on the safety, efficacy, and rheologic properties of microbicide candidates in a variety of formulations and delivery systems.

OBJECTIVE–D: Conduct Topical Microbicide Clinical Trials

Conduct clinical studies to assess the safety, efficacy, acceptability of, and adherence to candidate topical microbicides used to reduce the transmission of HIV and other STIs in at-risk female and male populations.

STRATEGIES

- Design and implement effective translational research strategies to develop criteria for the movement of candidate microbicides from preclinical to clinical studies.
- Identify populations in domestic and international settings with sufficient current HIV seroincidence to meet the power threshold for the conduct of clinical efficacy studies.
- Develop, implement, and evaluate novel testing assays and seroincidence assessments to provide current data that will identify appropriate communities for clinical studies.
- Assess and integrate community-level cultural beliefs, practices, and expectations in the design, development, and implementation of microbicide clinical trials.
- Integrate and analyze the impact of behavioral and social science HIV prevention interventions on community- and individual-level risk behaviors in microbicides clinical trials.
- Develop and implement the use of standardized measures to optimize the validity and comparability of study outcomes.
- Conduct and evaluate novel culturally appropriate strategies to recruit and retain participants in clinical studies.
- Conduct clinical studies in at-risk and HIV-infected populations, including adolescents, pregnant women, and menopausal women, to evaluate the pharmacokinetics, safety, efficacy, acceptability of, and adherence to microbicide candidates.
- Design and evaluate culturally appropriate behavioral and biomedical tools that measure product use, acceptability, and adherence within and outside the clinical study environment.
- Address the ethical and legal challenges inherent in the inclusion of adolescents and pregnant women as participants in microbicides research.
- Conduct clinical research on the acceptability, adherence to, and efficacy of microbicide candidates, used alone and in combination with other biomedical, behavioral, and community-level HIV prevention interventions.
- Conduct followup research with participants who seroconvert while participating in microbicide clinical trials to assess the impact of product use on HIV pathogenesis, drug resistance, and other adverse events.
- Conduct Phase IV postmarketing surveillance studies on microbicide candidates.
- Study contraceptive and non-contraceptive properties of candidate microbicides *in vivo* and the impact of product exposure on fertility; fetal and childhood development; and maternal, infant, and pregnancy outcome.
- Develop pK/pD correlates of microbicide clinical efficacy.

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

Conduct basic and applied behavioral and social science research to inform and optimize the development, testing, acceptability, and use of and adherence to topical microbicides.

STRATEGIES

- Develop and study epidemiological models of risk perception and the use of protection within community- and population-level social and cultural contexts that can be used to inform research on the acceptability of and adherence to microbicides.
- Conduct behavioral and social science research with individuals, their partners and families, and communities to improve microbicide acceptability and adherence.
- Support operations and cost analysis research on the implementation of behavioral and social science interventions designed to support microbicide use and adherence.
- Evaluate the effects of social and community norms on the use or nonuse of candidate microbicides.
- Evaluate the impact of microbicide clinical trials on individual and community-level HIV-risk behaviors.
- Determine the optimal combinations of biomedical, behavioral, and social science intervention strategies that decrease HIV acquisition and risk.

OBJECTIVE–F: Topical Microbicide Infrastructure

Establish and maintain the infrastructure needed to conduct microbicide research.

STRATEGIES

- Establish and strengthen training and infrastructure for the development of domestic and international institutional capacity for the discovery, development, and clinical study of candidate microbicides.
- Provide research training and career development opportunities to foster and develop the skills of new investigators in microbicide research.
- Support the dissemination of standardized microbicide-related discovery and development strategies that will assist the advancement of the microbicides field.
- Develop, support, and evaluate strategies for the collaborative involvement of domestic and international community representatives and leaders and researchers in the planning and implementation of microbicide research projects.
- Support the development of GLP and GMP production systems for the early clinical testing of candidate microbicides.
- Develop and evaluate appropriate community communication strategies to introduce microbicide clinical trials 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 research and development activities with external organizations' activities to facilitate the cost-effective use of available resources to accelerate microbicide development.

AREA OF EMPHASIS

Behavioral and Social Science

FY 2013 RESEARCH PRIORITIES

- Develop further understanding of HIV risk that reflects complex biological–behavioral and social/environmental interactions (including political, economic, and natural events, as well as more localized phenomena) affecting changes in transmission risks over the course of HIV exposure, acute infection, chronic infection, and treatment, and promote the development and use of research methods needed to understand these complex models, using community-based participatory research where appropriate.

- Conduct translational research (i.e., dissemination, implementation, or operational research) to foster and optimize the use of existing efficacious biomedical, behavioral, and social interventions to prevent and treat HIV infections.

- Study the continued disparities in HIV infection rates, access to care, and treatment outcomes that are manifest among racial and ethnic communities and socioeconomically disadvantaged communities in the United States and among similarly disproportionately affected populations in international settings to identify epidemiologic, sociocultural, psychosocial, and structural factors in these communities that could explain the disparities, and suggest opportunities for novel and targeted interventions.

- 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 and the role of stigma in prevention strategies for specific communities, such as racial and ethnic communities, men who have sex with men (MSM), youth, women, transgender individuals, young adults in high-prevalence or high-risk areas, and older adult populations engaging in risk behaviors.

- Evaluate the use of social media and other rapidly changing forms of communication technologies to reduce HIV acquisition and transmission through sexual behavior, drug use, and alcohol use, recognizing the interdependencies among these and the need to address multiple levels of interventions.

- Advance research on adolescents' development of healthy relationships and sexual functioning to elucidate factors reducing risk of HIV infection.

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

- Evaluate approaches to maintaining the highest ethical standards in the conduct of HIV prevention science 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.

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 to maximize their potential, when deployed singly or in combination, for preventing HIV infections. Apply basic behavioral and social science research to optimize intervention strategies.
- 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.
- Develop and evaluate behavioral and social interventions to improve "Seek, Test, Treat, and Retain" programs and to enhance the use of HIV treatment for prevention purposes.

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 and acquisition (e.g., MSM, transgender individuals, ethnic minority heterosexuals, injection drug users, and migrants).
- Continue development of interventions for persons with comorbid psychiatric and physical disorders.
- Conduct studies on medication-assisted substance abuse treatment modalities and access to care (e.g., methadone maintenance, buprenorphine/naloxone, modafinil, naltrexone, and antabuse), alone or in combination with mental health and behavioral interventions, as HIV interventions.
- Examine the impact of widespread antiretroviral therapy (ART) availability on willingness to be tested for HIV, willingness to provide HIV testing, and decreased stigma associated with HIV.
- Support research on populations in which epidemiological evidence suggests a need for more effective HIV prevention interventions.
- 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 and scale-up of effective HIV interventions, particularly research on the diffusion, adoption, adaptation, and maintenance of efficacious HIV interventions. Evaluate novel interventions identified as high priority by HIV community-planning groups and other service providers.
- 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 genetic, epigenetic, neurobiological, cognitive, motivational, and other mechanisms that underlie HIV-risk behaviors and health decisionmaking.
- Develop new models of behavior change that integrate biological, psychological, and social perspectives to explain and predict the adoption and maintenance of HIV-risk and HIV-protective behaviors among vulnerable populations.
- 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 (nonintervention) research on the decisionmaking processes and behaviors of health care workers regarding the offering of HIV counseling, testing, and other prevention services, as well as the prescription of HIV disease treatments, to those in need of HIV services and care; investigate the relationships between the health care workers' decisions and those of patients, family members, and community members.
- Conduct research concerning the health and life course of children, including orphans, affected by HIV. This research should include early identification and assessment of affected children for physical, psychological, and social consequences.
- Identify the neurobiological, behavioral, cognitive, social, and economic consequences of HIV disease for HIV-seropositive individuals (including children), their support systems (e.g., partners, family members, and other caregivers), health care systems, and communities.
- 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.

Prevention

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

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

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

- 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, also should be addressed.

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

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

- Study the social, structural, cultural, and demographic factors (e.g., socioeconomic status, marital status, ethnicity, sexual identification, 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.

- Conduct research that identifies the social and behavioral factors affecting recruitment, retention, and adherence to prevention interventions, including clinical trials of HIV-related vaccines, microbicides, and therapeutics.

- 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 dissortative 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 the care of older seropositives.

Biopsychosocial Consequences

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

- Test interventions designed to support formal and informal caregivers and family members of HIV-infected persons 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

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

Modeling

- Develop and refine mathematical models for linking behavioral change interventions with a reduction in HIV transmission at different levels of seroprevalence.
- Improve methods for forecasting and modeling AIDS caseloads, health care needs, and health care utilization under different treatment and survival scenarios and for forecasting and modeling prevention services needs. Greater consideration needs to be given to probabilistic relationships among risk factors and other contributing variables, as well as practical constraints in the implementation and uptake of interventions.
- Develop and refine models of potential efficacy of environmental-level (e.g., laws and policies) interventions for reducing HIV risk.
- Develop and refine models of potential efficacy of network and dyad-level interventions for reducing HIV risk.

Design and Statistical Analysis

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

Ethics and Other Issues

- Evaluate the effects of legal and ethical constraints on methods of HIV research and service delivery, particularly among vulnerable or special populations.
- Use behavioral and social research methods to investigate factors associated with particular ethical and legal principles in research design (e.g., competence to provide consent, prevalence of adverse events, and associated remedies).
- Develop and refine research techniques to advance new studies as required by epidemiologic findings on HIV transmission. Encourage secondary data analysis; develop approaches to protect and document confidentiality.
- Develop and test an ethical framework for the use of biomedical interventions (e.g., ART) for HIV prevention that encompasses 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.
- Evaluate the ethical considerations related to control groups and various approaches for comparison groups in clinical trials, examining the content and constructs utilized.

AREA OF EMPHASIS

Treatment as Prevention

FY 2013 RESEARCH PRIORITIES

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

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

OBJECTIVE–A: Approaches to Interrupt Vertical Transmission

Develop and assess strategies to prevent mother-to-child transmission (MTCT), applicable to resource-limited and resource-rich countries, with emphasis on strategies to prevent transmission through breastfeeding and short- and long-term effects of interventions for preventing MTCT on the health of women and infants.

STRATEGIES

Mechanisms of Transmission

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

Interventions and Trials to Evaluate Interventions to Prevent Transmission

- Develop and evaluate novel strategies for preventing transmission of HIV from pregnant women to their offspring, and evaluate the impact of those strategies on maternal health treatment options; such strategies may include long-acting antiviral agents, novel delivery methods, anti-HIV immunoglobulin, monoclonal antibodies, agents targeted to cellular targets (e.g., blocking cytokine receptors), cell- and gene-based strategies, HIV vaccines, and adjuvants.
- Develop safe, affordable, and conveniently administered strategies to prevent MTCT in resource-limited nations, including specific strategies to maintain HIV-free survival of breastfeeding infants.
- Evaluate the pharmacokinetics and safety of antiretroviral (ARV) drugs in pregnant women and their fetuses/infants, and the penetration of ARV drugs into breast milk and genital fluids.
- Evaluate strategies for reducing MTCT when maternal antepartum and intrapartum antiretroviral therapy (ART) is not given or available (e.g., postpartum prophylaxis of the infant only) and for preventing MTCT in the setting of acute maternal infection during pregnancy or breastfeeding.
- 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 mother-to-child transmission (PMTCT).
- Use and/or develop suitable animal models to evaluate novel strategies to prevent transplacental and postpartum breastfeeding transmission of HIV, and to evaluate transplacental passage of ARV agents and their effects on placental function and on fetal development and viability.
- Develop strategies for PMTCT for pregnant women during acute infection and lactation.

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 in their infants, and the kinetics and durability of such resistance in cell-free and cell-associated virus in plasma, breast milk, and genital secretions.
- 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, including the impact on PMTCT for future pregnancies.
- Evaluate effective, safe, simple, and short alternative ARV regimens that have lower risk of inducing drug 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 the emergence of drug resistance 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 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 discontinue ARVs after delivery or after breastfeeding cessation.
- 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 feasibility 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.

OBJECTIVE–B: Therapeutic Approaches to Prevent Horizontal Transmission

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

STRATEGIES

Mechanisms of Transmission

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

Interventions to Reduce Transmission

- Support domestic and international collaborative efforts to conduct trials of ARV, immunotherapeutic, and other treatment interventions with an endpoint of horizontal transmission in acute and chronic infection, including studies in adolescents/young adults.
- Develop and evaluate strategies for reducing the risk of sexual transmission of HIV without compromising treatment of the HIV-infected individual; such strategies may include ARVs, therapeutic vaccines, anti-HIV immunoglobulin, monoclonal antibodies, and immunotherapeutic agents, alone or in combination.
- Develop delivery systems for non-topical agents to prevent HIV transmission, including postexposure prophylaxis (PEP), 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.
- 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.
- Develop implementation strategies to assess feasibility and sustainability of PrEP within specific high-risk target populations, including studies on cultural barriers and facilitators, factors affecting adherence, treatment effectiveness, and cost-effectiveness.

PRIORITY:

Improving Disease Outcomes for HIV-Infected Individuals

Drug Discovery, Development, and Treatment

Research Toward A Cure

AREA OF EMPHASIS

Drug Discovery, Development, and Treatment

FY 2013 RESEARCH PRIORITIES

- Accelerate the discovery and validation of therapeutic strategies, including new and existing viral and cellular targets, to provide safe, tolerable, maximally long-term suppressive viral activity.
- Support research on the mechanisms of HIV persistence and develop strategies to prevent the establishment of, decrease, or eliminate the viral reservoirs despite optimal treatment.
- Advance the discovery and validation of therapeutic strategies to prevent progression of HIV and its associated comorbidities, coinfections, and other clinical complications in HIV-infected individuals, across the lifespan including in older adults.

OBJECTIVE–A: Discover and Develop Anti-HIV Treatments

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

STRATEGIES

- Identify, characterize, and validate viral and host targets for anti-HIV therapy. Develop predictive test models, including appropriate lentivirus animal models, to aid in identifying agents and strategies active against these targets.
  - Develop new agents and treatment strategies that target, inhibit, and clear HIV in cellular, anatomical, and organ reservoirs and sanctuaries, including agents (e.g., biologics) 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 or approaches that target and eliminate reservoirs.
  - Characterize potential antiviral agents with respect to their preclinical, immunologic, pharmacokinetic, pharmacodynamic, toxicity, and teratogenicity profiles.
  - Develop new drugs, biologics, extended-release formulations, and novel routes of administration to increase safety, tolerability, durability, and ease of use of therapeutic agents.
  - Employ whole animal and *ex vivo* organ or tissue models of lentivirus infections to study the biologic and pharmacologic characteristics of therapeutic agents.
  - Acquire structural information on HIV 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 and improve public awareness of such technologies.
  - 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 and 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, tissue penetration, and long-acting formulation) with enhanced capability for ease in adherence measurement and detection; develop drug delivery devices or systems that improve the pharmacokinetic profile of therapeutic agents, target specific organs or tissues, reduce toxicities and adverse effects, and result in improved adherence to therapeutic regimens.

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

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

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

- Study the effects of recombination within and between HIV clades on the evolution of drug resistance.

- Develop and evaluate interventions aimed at reducing 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 and geriatric populations.

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

- Develop therapeutic agents for the treatment of HIV/AIDS that do not interact with psychotropic medications, drugs of abuse, 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 novel strategies against acute, established or latent, HIV infection, viral reservoirs, and transmission in treatment-naive and treatment-experienced HIV-infected individuals, across the lifespan 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 novel therapeutic strategies;
    - timing, selection, and strategic sequencing of ARV agents to optimize clinical outcome in relevant populations;
    - simplified and maintenance regimens;
    - optimal treatment for heavily ARV-experienced individuals with treatment failure;
    - 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 and long-acting ARVs in all age groups.
  - Investigate the effects of class-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.

Clinical Trial Methodology

- Develop and evaluate standardized virologic, immunologic, and clinical markers to assess drug activity; determine and validate surrogate markers in response to various therapeutic interventions, including those most applicable to resource-limited settings.
- Develop novel inexpensive and rapid platforms, as well as point-of-care assay systems, for detection and quantification of HIV, diagnosis of recent HIV infection, ARV resistance testing, adherence to therapy, biomarker evaluation, and genetic testing for both *in vitro* and *in vivo* evaluations.
- Develop, incorporate, and validate appropriate quality-of-life parameters and patient-reported outcome instruments in clinical trials of ARV agents.
- Develop 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.
- Develop a better framework for the conduct of clinical trials through research on bioethics.

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 response to therapy.

Mechanisms of Treatment Failure

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

Adherence and Retention

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

International

- Expand the development of international collaborations that will assist in addressing relevant therapeutics 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 ARVs 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 assess the validity of 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, including HIV drug resistance, as well as adherence to therapy, that can be used in resource-limited settings.
- Develop standardized clinical indicators to determine how and when to initiate ART, to monitor responses to therapy, and to determine when to change therapy.
- Determine acceptable laboratory monitoring 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.

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

Develop strategies to predict, evaluate, treat, and prevent complications of long-term HIV disease and toxicities of ART, and the interaction of comorbidities and immune reconstitution inflammatory syndrome (IRIS) in HIV infection in domestic and international settings.

STRATEGIES

- Develop and evaluate therapeutic strategies for preventing and treating complications of HIV infection or its treatment.
- Evaluate potential delayed or late effects of ART following short-term administration of prophylactic regimens (e.g., for prevention of mother-to-child transmission), or chronic drug administration.
- Develop standards and definitions to allow better comparisons of late complications across clinical trials (i.e., meta-analysis between studies, efficacy of interventions in clinical trials versus effectiveness in public health practice).
- Support research on the pathogenesis and mechanisms of toxicity of drugs used to treat HIV disease.
- Develop and test approaches to prevent, reverse, or reduce potential metabolic abnormalities (e.g., changes in body composition, development of atherogenicity and endocrine disorders, and changes in bone and muscle structure) 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, central nervous system (CNS), bone, and other complications of ART and/or long-term survival with HIV disease.
- Integrate metabolic, endocrine, cardiovascular, neurologic, renal, liver, and musculoskeletal studies into ongoing and planned clinical studies, which may provide an opportunity to answer important questions related to HIV disease and the potential complications of ART.
- 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.
- Evaluate the impact of nutrition and nutritional interventions, provided concurrently with ART, on improved clinical outcomes in undernourished populations or lactating mothers.
- 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 in various populations, including geriatric populations and individuals with altered drug metabolism.
- 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, inflammation, and/or immune senescence associated with HIV disease and treatment.
- Evaluate the pathogenesis, diagnosis, and treatment of immune reconstitution inflammatory syndromes associated with the unmasking or paradoxical worsening of opportunistic infections following initiation of ART.
- Develop novel tools (including nanotechnology, proteomics, metabolomics, and immunotechnology) for rapid DNA sequence identification to facilitate toxicogenomic research and applications.
- 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

Preclinical Discovery and Development

- 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 (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.
- Utilize mechanism-based screening of novel synthetic compounds and natural products to identify candidate agents for treating the most significant coinfections; provide support for medicinal chemistry, structural databases, 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, adults, and pregnant women.
- Develop novel platforms for fast, accurate, and cost-effective detection and diagnosis of pathogenic organisms and related biomarkers.
- Develop novel delivery methods to both enhance the efficacy and decrease the toxicity of currently existing and future therapeutic agents.
- Support development of nano-targeting modalities to selectively infiltrate and treat infected compartments, tissues, and cells.

Clinical Trials of Preventive and Therapeutic Regimens

- Assess the impact of new ARV regimens on the risks for and manifestations of infections associated with HIV disease 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 or discontinuing prophylaxis for different OIs and coinfections, particularly in resource-limited countries; 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.
- Investigate the effects of maternal immunization for opportunistic infections on pregnant women and on their infants for infant protection.

Detection of HIV Coinfections

- Develop clinically useful assays and methodologies for early and rapid diagnosis of OIs, coinfections (particularly TB), and febrile illnesses (besides TB and malaria), 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

- 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 coinfected with HIV and TB (both active and latent infection). Evaluate safety and efficacy of treatment regimens in coinfected individuals. Determine optimal length of treatment. Evaluate regimens in the context of degree of immunosuppression.
- Investigate surrogate markers of TB disease that could distinguish between latent, active, and eradicated infection in coinfected individuals; determine how each infection influences or alters the other disease in respect to progression and response to therapy.
- Support clinical trials investigating the efficacy and risks of treatment of HCV in individuals who are coinfected with HIV; determine how each infection influences or alters the other disease in respect to progression and response to therapy.
- Study the interaction of coinfections with HIV transmission (e.g., placental malaria and perinatal infections) and effects on HIV disease progression.
- Investigate the role of HIV-associated coinfections with pregnancy outcomes.

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.
- Support research on the interactions between ART and treatments for coinfections.

Adherence and Self-Management

- Support research on the effectiveness of 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 HIV-infected individuals with co-occurring substance abuse and/or mental illness.

- Investigate strategies for managing symptoms that are attributed to HIV infection, coinfection, and/or therapy, and investigate the relationship between symptom management and improved adherence to ARV regimens. This may include self-management or combined biobehavioral approaches.

International

- Conduct clinical trials in adults (including pregnant women) and children to evaluate agents for the prophylaxis and treatment of HIV-associated 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.
- Optimize and utilize *in vitro, ex vivo,* and animal models of CNS lentivirus infections and CNS injury to identify therapeutic agents (tailored for needs during neurodevelopmental and mature brain periods) for the nervous system complications of HIV infection.
- Assess the pathogenic role of viral sequestration in the CNS, including its potential role as a reservoir of viral persistence and as a site of independent selection of antiviral drug-resistant strains and other mutants.
- Evaluate strategies to reduce or eliminate HIV reservoirs in the CNS.
- Assess the interactions between chronic HIV infection, HIV-associated neurocognitive disorders, and aging-related neurodegenerative disease.
- Develop objective quantitative assessments (e.g., surrogate markers in cerebrospinal fluid [CSF] and neuroimaging) of HIV disease progression and treatment effects as they relate to the nervous system.
- Characterize the CNS pharmacokinetics (pK) and pharmacodynamics (pD) of ARVs; determine the importance of CNS drug penetration, particularly penetration of the blood-brain barrier, in reducing CNS infection in neurologically symptomatic and asymptomatic subjects.
- Develop novel bioimaging applications and bioassays to facilitate assessment of compartmental pK/pD.
- Develop strategies for manipulating drug transporters at the blood-brain barrier to facilitate entry of ARVs into the CNS compartment.
- Develop novel tools (e.g., nanotechnology) to facilitate and modulate delivery of ARVs 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.
- Conduct studies on the effectiveness of approaches to facilitate better adherence to therapeutic regimens in neurologically impaired individuals.
- Evaluate the effectiveness of reducing HIV-associated CNS disease burden by therapeutic agents currently used to treat other neurologic diseases (e.g., Parkinson's and Alzheimer's disease) that may share pathophysiologic features with HIV-associated neurologic disease.

- Assess the incidence and prevalence of 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 its 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 with both immunomodulatory and neuroprotective functions to reduce comorbid psychiatric conditions (markedly depression and anxiety disorders) in HIV-infected individuals.
- Develop novel or adapt existing rehabilitative strategies to ameliorate HIV-associated CNS disease manifestations that affect social-emotional, motor, sensory, cognitive, and daily functioning.

Clinical Neuroassessment, Methodologies, and Trials

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

OBJECTIVE–F: Treatment of AIDS-Related Cancers

Develop and evaluate improved strategies for the assessment, treatment, and prevention of cancer-specific manifestations of HIV disease and 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, agents with better safety profiles, and agents that are optimal in resource-limited settings.
- 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 (including in resource-limited settings) 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 HPV-induced cervical, anal, and oral cancer in HIV-infected populations, including adolescents.
- Evaluate novel approaches for the treatment of AIDS-defining and other HIV-associated malignancies through clinical trials, and evaluate the interactions between treatment of malignancies and treatment of the underlying HIV infection.
- 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, such as interventions in the premalignant stages.

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

- Support clinical studies of HIV-infected individuals with non-AIDS-defining malignancies in order to define the best treatment of these malignancies 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.

- Develop and assess preventive and therapeutic strategies that are appropriate 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 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: Management of HIV Disease with Nonpharmacologic and Complementary and Alternative Modalities

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

STRATEGIES

- Develop and evaluate conventional and nonconventional chemopreventive approaches, including those containing quantifiable doses of micronutrients (such as vitamins and trace elements) and macronutrients to delay the development of wasting and other HIV-associated manifestations.
- Evaluate the safety and efficacy of nonpharmacologic and complementary and alternative medicine approaches, such as exercise, nutrition, and sleep cycles, in the management of HIV disease and its associated manifestations.
- Evaluate the benefits or risks 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.

AREA OF EMPHASIS

Research Toward A Cure

FY 2013 RESEARCH PRIORITIES

- Further the understanding of fundamental viral and host mechanisms associated with the control and persistence of HIV at the cellular, tissue, and organism level, and identify the sites, mechanisms of persistence, and strategies for immune containment and eradication of HIV reservoirs in the presence and absence of antiretroviral therapy (ART).

- Design and conduct clinical trials to evaluate novel approaches to eliminate viral reservoirs and persistent virus, as well as strategies to control viral pathogenesis. Identify translational research methods to foster scale-up and optimize the use of existing efficacious strategies to eradicate HIV.

- Develop and test behavioral and social science interventions to improve adherence to therapeutic regimens, as well as strategies that would optimize implementation of eradication strategies and cure approaches.

- Identify and validate novel assays to measure latently infected cells, viral reactivation, and persistent HIV infection. Develop and test animal and tissue models that are predictive of HIV eradication.

OBJECTIVE–A: Biology of HIV Infection

Delineate the viral, host, and immune mechanisms involved in HIV infection, persistence, and dissemination, and the establishment and maintenance of the viral reservoir. Identify factors involved in the control of HIV disease progression and host restriction in the presence and absence of ART.

STRATEGIES

Basic Research on the Establishment of HIV Infection

- Identify and validate viral and host cellular functions required for HIV replication that can be targeted for viral inhibition and eradication of latent and persistent virus.
- Determine structural information on HIV and cell constituents involved in HIV infection for the design of potent and selective therapeutic agents and therapeutic vaccine candidates.
- Conduct studies to identify and estimate the prevalence and correlates of divergent viral genotypes, and neutralization profiles and their temporal trends.
- Characterize how different HIV types, subtypes, and recombinant forms influence routes and modes of HIV transmission, superinfection, response to ART and pre-exposure prophylaxis, and emergence of drug-resistant viruses.
- Determine the mechanisms by which host and virus-encoded genes or viral gene products regulate and influence establishment of HIV infection, including integration of the virus into the host cell genome.

Inhibiting HIV Replication and Viral Dissemination

- Characterize new and understudied viral and host targets and kinetic sequencing of infection important for the early dissemination of HIV.
- Evaluate the role and mechanisms of preventing or enhancing HIV replication and dissemination by soluble factors contained within bodily fluids, including breast milk.
- Investigate the role of immune activation, inflammation, and their mediators in various tissues on the establishment and dissemination of HIV infection.
- Delineate innate and adaptive immune responses to HIV in tissue reservoirs.
- Explore mechanisms of the host response to HIV or simian immunodeficiency virus (SIV) infection that involve the interface between innate and adaptive immunity.
- Determine the impact of host immunity on viral evolution and fitness, and the influence of viral factors on host immunity.
- Identify immunological predictors of *in vivo* immune control of viral replication.
- Determine the correlates of immune control by studying HIV-infected or highly exposed but seronegative individuals, across the lifespan, and SIV or chimeric simian/human immunodeficiency virus nonhuman primate models.
- Delineate the mechanisms and impact of genetic or environmental factors on immune responses that influence HIV replication, establishment, and dissemination to lymphoid and other tissues and reservoirs.
- Define the molecular mechanisms and pathogen-host interactions underlying infection and replication at the cellular and molecular levels, including viral gene products and their interactions with cellular cofactors and host restriction factors.

Establishment of Latent HIV Reservoirs

- Identify the tissue and cellular reservoirs of latent HIV *in vivo*.
- Define whether HIV clade differences play a role in establishing latent reservoirs.
- Develop tools to measure and quantify HIV in reservoirs, such as novel imaging techniques.
- Develop novel strategies to inhibit HIV integration into host DNA and prevent the establishment of latency, and define the molecular mechanisms that lead to the initial establishment, subsequent maintenance, and reactivation of latently infected cells.
- Develop and evaluate novel mechanisms to eliminate HIV reservoirs or prevent viral reactivation in latently infected cells.
- Assess the pathogenic role of viral sequestration in the central nervous system (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.
- Define the sites and mechanisms of latent/persistent HIV infection in patients on suppressive therapy, and the mechanisms by which reservoirs are established and maintained in the presence of ART.
- Examine the effects of discontinuation of ART on HIV reservoirs in individuals who have stopped therapy.

Disease Progression and Pathogenesis

- Delineate mechanisms responsible for the differences between pathogenic and nonpathogenic HIV infection in humans and nonhuman primates.
- Elucidate the mechanisms of CD4+ T-cell depletion in the infected host.
- Examine the role of immune activation, inflammation, and dysfunction/dysregulation in HIV or SIV pathogenesis, and delineate the mechanisms leading to pathological immune activation and autoimmunity in HIV or SIV infection.
- Define the sites of infection and replication in the untreated host at the cellular and cell subset level, both anatomically and functionally, and how cell subset targeting determines disease progression or non-progression.
- Identify the host immune responses to HIV-1 and HIV-2, as well as the viral or host factors that enhance or reduce the amounts of circulating virus and influence disease course in long-term non-progressors and elite controllers.
- Delineate the mechanisms by which sexually transmitted infections, other coinfections, and the microbiome (bacterial, fungal, and viral) influence HIV replication and dissemination and contribute to HIV persistence and pathogenesis.

Methodology and Animal Models

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

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

Identify and validate viral and host cellular factors and functions required for HIV replication that can be targeted for eradication of persistent virus. Discover and develop novel agents and virological, immunological, and cellular therapeutic strategies that are effective in eradicating HIV.

STRATEGIES

- Develop new agents and treatment strategies that target, inhibit, and clear HIV in cellular, anatomical, and organ reservoirs and sanctuaries, including agents that can suppress HIV in non-T-cell reservoirs.
- Evaluate the intracellular pK and activity of antiretrovirals (ARVs) in different tissue and cell types, different stages of the cell cycle, and across the lifespan. Correlate intracellular pK parameters with drug efficacy and toxicity.
- Develop agents and delivery systems to eradicate HIV with desirable biopharmaceutical characteristics (e.g., improved bioavailability; tissue penetration; targeted to specific tissues, cells, organelles, proteins, and/or nucleic acids; reduced toxicities and adverse effects; and long-acting formulation) to facilitate uptake, adherence, and adherence monitoring.
- Develop cell-based models of the blood-brain barrier in order to test transport efficiencies of ARVs and transport of HIV into the CNS.
- Develop therapeutic agents to block HIV entry into the CNS, and design novel tools (e.g., nanotechnology) to facilitate and modulate delivery of ARVs into the CNS compartments to treat HIV infection.
- Advance gene-based strategies to treat HIV infection and to protect mature, hematopoietic stem cells, hematopoietic pluripotent cells, neurons, and stromal cell elements from destruction by HIV.
- Develop and evaluate interventions aimed at reducing HIV-related immune activation.
- Determine the mechanisms of action of immunomodulating agents, and develop the most promising approaches.
- Support the design, development, production, and preclinical testing of novel active and passive HIV therapeutic vaccine candidates for safety and for their ability to control or eliminate viral reservoirs.
- Identify mechanisms of protective immunity to HIV in newborns and infants, and support the development of distinct study designs for safe and effective early ART as well as therapeutic vaccine strategies and passive immune interventions, alone or in combination with other interventions, for controlling HIV infection in this population worldwide.

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

Assess the short- and long-term efficacy and effectiveness of therapeutic agents and novel strategies against acute, persistent, or latent HIV infection and viral reservoirs in HIV-infected individuals across the lifespan, including in older individuals, through the conduct of clinical trials and cohort-based studies in domestic and international settings.

STRATEGIES

- Develop domestic and international partnerships to design and conduct clinical studies.
- Conduct Phase I, II, and III clinical trials of potential therapeutic agents and combinations of strategies in adults, including older populations, pregnant women, adolescents, and children, to determine pK, tissue bioavailability, antiviral activity, effects on the immune system, safety, and clinical efficacy.
- Support clinical trials to study long-term effectiveness (including toxicities) of novel therapeutic strategies.
- Evaluate coformulated and long-acting ARVs across the lifespan.
- Quantitate persistent HIV in different tissue compartments during effective ART, and evaluate strategies to reduce or eradicate such reservoirs.
- Evaluate the penetration of ARVs and other agents into various body fluids and tissue compartments, including the cerebrospinal fluid as a surrogate marker for the CNS.
- Assess the impact of transmission of drug-resistant strains of HIV on disease progression or response to therapy.
- Investigate the pK and safety of ARVs in pregnant women and their fetuses/infants, and the penetration of ARVs into breast milk and genital fluids.
- Determine the pK/pD of ARVs in the CNS; determine the importance of CNS drug penetration, particularly penetration of the blood-brain barrier, in reducing CNS infection/reservoirs in neurologically symptomatic and asymptomatic individuals.
- Develop and assess therapeutic approaches that will restore, sustain, and enhance the immune system in HIV-infected individuals.
- Advance clinical testing of cytokines, modulators of 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.
- Evaluate the immune system after partial restoration by ART. Define qualitative and quantitative differences between the restored immune system and the naive immune system to determine if identified deficiencies can be diminished by immunoactive agents.
- Assess immune-based therapy as an adjunct to salvage therapy strategies and/or reservoir elimination.
- Evaluate the extent to which HIV or SIV-related immunopathogenesis can be prevented or reversed by therapeutic interventions.
- Investigate the impact of cancer therapy, immunosuppressive agents, and other immunomodulatory and myeloablative therapy on virologic, immunologic, and tumor parameters, including viral reservoirs; assess the toxicity of anticancer modalities in HIV-infected patients; and evaluate the pK of anticancer agents in HIV-infected patients, including a study of drug-drug interactions.

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

- Conduct Phase I, II, and III HIV therapeutic vaccine clinical trials that will determine short- and long-term safety; immunologic responses measured by a broad range of humoral, cell-mediated, and mucosal immune parameters; and the efficacy of different vaccine candidates.

OBJECTIVE–D: Behavioral and Social Science Research

Support behavioral, social, structural, and environmental research to inform the development, testing, and implementation of HIV eradication and cure approaches, and to develop and test interventions to strengthen the reach and impact of HIV eradication and cure strategies.

STRATEGIES

- Conduct studies on psychosocial and ethical issues associated with research toward a cure at both the individual and population levels, including the acceptability of risks and benefits associated with HIV eradication and cure approaches in relationship to existing HIV treatment.
- Develop better behavioral methods to assess and enhance adherence to treatment and prevention regimens across a variety of affected populations in an effort to inform adherence assessments in HIV eradication and cure research; compare and validate adherence measures in the context of HIV treatment and prevention; closely monitor adherence to HIV eradication and cure strategies during clinical trials; and examine the association between adherence and trial outcomes.
- Conduct assessment of social and behavioral factors (e.g., risk perception and risk behavior) during clinical trials of strategies to eradicate HIV to identify and evaluate any changes in those factors as a result of participation in a clinical trial.
- Conduct behavioral research on individuals who become reinfected during clinical trials to identify interventions that may prevent high-risk behaviors and nonadherence in future clinical studies.
- Examine the relationship between ART availability and HIV testing, as well as the role of HIV-associated stigma on HIV testing and ART uptake.
- Conduct studies to identify key components of efficacious behavioral interventions that facilitate behavior change that could be scaled up in the context of an effort to eradicate HIV.
- Study the acquisition and maintenance of HIV-related risk and protective behaviors associated with 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 and progression as related to cultural norms that affect disempowerment of and violence toward women.

OBJECTIVE–E: Implementation Science

Establish a collaborative research enterprise in order to advance HIV/AIDS cure research as well as translational research to enhance the uptake of strategies to eradicate HIV/AIDS.

STRATEGIES

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

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

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

PRIORITY:

Reducing HIV-Related Disparities

Special Populations:

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

Training, Infrastructure, and Capacity Building

AREA OF EMPHASIS

Racial and Ethnic Populations

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A: System Determinants of Health

Support research that examines the impact of policies, organizations, financing, and delivery of HIV/AIDS-related prevention, care, treatment, and support services in disproportionately affected racial and ethnic populations, including those demonstrably at highest risk for HIV infection.

STRATEGIES

- Identify and modify system-level factors that mitigate or create barriers to HIV prevention, care, and treatment for incarcerated racial and ethnic minorities when they return to their communities.
- Explore the systems of care available to seasonal workers and what factors facilitate and prevent engagement in HIV testing, care, and treatment.
- Identify and modify system-level factors that mitigate or create barriers to HIV testing, care, and treatment for aboriginal individuals, including the role of traditional and/or indigenous medicine.
- Utilize implementation science to identify the essential components of HIV prevention interventions and mechanisms for efficient and rapid translation among racial and ethnic minority populations.
- Develop, pilot, and test synergistic prevention interventions for high-risk HIV-uninfected individuals within health care systems.
- Examine the influence of stigma, racism, prejudice, and homophobia within health care systems, and the impact of these biases upon HIV prevention behaviors (including HIV testing) among racial and ethnic populations.
- Identify venues that can effectively deliver acceptable, efficient, and dependable HIV testing for racial and ethnic populations.

OBJECTIVE–B: Environmental and Social Determinants of Health

Encourage research that identifies 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) adoption and incorporation of effective prevention and therapeutic interventions for those at highest risk for HIV infection.

STRATEGIES

- Explore the intersections of the social determinants of health (such as poverty, residential segregation, and incarceration), and their effects upon HIV transmission across the lifespan.
- Identify synergistic effects of the provision of stable housing, treatment, and prevention interventions upon HIV-risk behavior, disease outcome, and treatment.
- 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 intersections of poverty, racism, substance abuse, and historical displacement upon HIV-risk behavior and HIV resiliency in indigenous populations,
- Study the impact of social, sexual, alcohol, and drug networks upon the HIV risk among racial and ethnic youth.
- Develop culturally and racially appropriate HIV testing and prevention interventions targeting adolescents and youth for dissemination in their social and sexual networks.
- Explore the impact of immigration status, including seasonal population migrations (e.g., migrant workers), upon HIV-risk behavior and comorbid sexually transmitted infections (STIs).
- Identify HIV prevention interventions for rural undocumented immigrant communities.
- Examine the impact of prejudice, racism, stigma, and racial stereotyping by health care providers on access to HIV prevention, care, and treatment.

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

Expand 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 (traditional and indigenous), and community-level factors associated with HIV infection, risk of infection, and related health outcomes in racial and ethnic populations.

STRATEGIES

- Identify practical, cost-effective, sustainable, and scalable community-level HIV prevention interventions for racial and ethnic communities, including sexual minorities.
- 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 measures of community engagement (e.g., with leaders and organizations) that predict readiness for, and acceptance of, 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 interventions and evaluation into community-based participatory research, especially in communities disproportionately affected by HIV.
- Incorporate implementation science in the development of HIV prevention interventions to facilitate prompt translation, scale-up, and delivery of effective interventions.
- Examine the impact of existing and evolving social and sexual norms and community-derived responses to the HIV epidemic on changing patterns of sexual risk behavior.

OBJECTIVE–D: Individual-Level Determinants of Health

Develop and conduct research that focuses on individual-level determinants of HIV risk, including biologic factors, resiliency, and cultural and social norms, in disproportionately affected populations.

STRATEGIES

- Develop, pilot, and test synergistic prevention interventions for high-risk HIV-uninfected individuals within health care systems.
- Identify factors (e.g., health literacy and HIV awareness) that increase HIV risk among disproportionately affected populations, and examine the impact of HIV preventions that reduce or eliminate those factors.
- Identify the behavioral, biological, cultural, and social factors that affect older women and affect their risk of HIV acquisition and transmission.
- Conduct basic research on and develop interventions that address the social and ecological determinants of sexual health and HIV risk in disproportionately affected populations and their social networks.
- Determine the impact of personal trauma (e.g., gender-based violence and childhood abuse) upon the adoption and maintenance of HIV prevention strategies in racial and ethnic populations, with particular attention to adolescents and sexual minorities.
- Study the biological (including genetic), physiological, and environmental factors that affect HIV acquisition, transmission, and disease progression among racial and ethnic minority individuals.

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.
- Fund initiatives to 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 for 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.
- 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

Support behavioral, intervention, and implementation research that: (1) creates and tests interventions to modify the factors that prevent access to care, treatment adherence, and care maintenance; (2) examines biological and individual factors that affect response to HIV treatment and its associated complications and comorbidities; and (3) determines critical junctures where effective interventions will result in improved treatment outcomes in disproportionately affected racial and ethnic populations.

STRATEGIES

- Advance the study of the biology of HIV infection among racial and ethnic populations:
  - Evaluate the effect of race, ethnicity, and gender upon immune response to combination antiretroviral therapy.
  - Determine the effect of race, ethnicity, and gender upon immune dysregulation and the development of opportunistic infection and malignancies.
- Determine the impact of race and ethnicity on risk of HIV acquisition, rate of HIV disease progression, and HIV disease manifestations in understudied indigenous populations, including Native Americans, Alaska Natives, Pacific Islanders, and Native Hawaiians.
- Create and test effective interventions designed to increase the uptake of HIV care and enhance the quality of HIV care among racial and ethnic populations.
- Examine the effect of perceived and enacted HIV stigma, as well as homophobia and institutionalized racism, upon access to care, HIV care seeking, care retention and maintenance, and treatment adherence.
- Develop and evaluate therapeutic strategies to prevent and treat the most prevalent complications and comorbidities of HIV infection among racial and ethnic populations.
- Create, test, and disseminate effective multidisciplinary interventions that reduce barriers to HIV care and treatment.
- Enhance and expand research collaborations with tribal entities, community-based organizations, and nontraditional community partners to conduct treatment and treatment adherence research in racial and ethnic populations.
- Enhance and expand recruitment and retention efforts to increase the participation and retention of migrant workers in HIV clinical trials, with a specific focus upon HIV prevention, treatment access, treatment adherence, and retention in care.

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

Explore the interrelationship between HIV infection and a broad range of comorbidities in racial and ethnic populations to: (1) determine their impact upon HIV care, treatment adherence, care retention, and disease progression; (2) modify the impact upon adherence to HIV treatment and the comorbid condition(s); (3) reduce their negative impact upon retention in care; and (4) improve health outcomes for this population.

STRATEGIES

- Determine the impact of alcohol, drug use, and chronic medical and neuropsychiatric comorbidities upon HIV health care behavior, including medication adherence and retention.
- Delineate the impact of substance use and chronic mental health comorbidities (including chronic pain states) upon HIV disease progression, morbidity, and mortality.
- Determine the impact of treatment interventions upon progression of HIV disease and HIV-associated coinfections and comorbidities, such as hepatitis B and C infection, tuberculosis (TB), STIs, and malignancies.
- Create, test, and disseminate cost-effective provider- and patient-targeted interventions that facilitate access to HIV care and treatment and retention in care.
- Examine the impact of incarceration upon stage at presentation for care, disease progression, and morbidity and mortality of HIV and other comorbid diseases.
- Evaluate the impact of underlying cardiovascular, endocrine, metabolic, neurologic, psychiatric, and renal disorders upon treatment readiness, acceptance, and effectiveness.
- Determine the impact of combination antiretroviral therapy (ART) in late testers on the progression of comorbid conditions, especially hepatitis B and C infection, TB, and malignancies.
- Examine the response to combination ART by race and gender to determine if differences exist and, if present, the causes of these differences and potential interventions.

OBJECTIVE–H: Enhancing and Expanding Capacity for NIH-Funded HIV Research

Enhance and expand the capacity for NIH-funded HIV research by and for individuals from diverse groups disproportionately affected by HIV infection, *and* underrepresented groups such as tribes and tribal entities.

STRATEGIES

For the investigator:

- Promote and expand predoctoral opportunities for the recruitment, training, and retention of investigators from underrepresented racial and ethnic backgrounds.
- Improve HIV/AIDS research capabilities by establishing a national mentorship network to recruit, train, and retain investigators from groups underrepresented in the biomedical sciences.
- Support senior investigators with robust research infrastructures to mentor prospective researchers from underrepresented groups in the biomedical sciences, in culturally and contextually appropriate HIV/AIDS research.
- Through existing funding mechanisms, provide incentives for the development, recruitment, and retention of intramural and extramural investigators from underrepresented groups in the biomedical sciences.

For the institution:

- Utilize existing HIV/AIDS Centers of Excellence and networks for training and mentorship of postdoctoral fellows, as well as M.D.–Ph.D. fellows from groups underrepresented in biomedical sciences.
- Support collaborative efforts among research-intensive and non-research-intensive institutions to encourage and enhance interest in the conduct of HIV/AIDS research.
- Support activities and programs (e.g., workshops, curriculum improvements, and seed support) in HIV/AIDS to strengthen the representation of disproportionately affected populations in pipeline programs throughout all levels of the institution.
- Support community–academic partnerships and coalitions, as well as partnership-building activities with other agencies across the U.S. Department of Health and Human Services, to strengthen strategic collaborative HIV/AIDS research efforts in disproportionately affected populations.

For the community:

- Develop processes that facilitate the incorporation of new scientific findings into ongoing HIV prevention programs.
- Promote organizational capacity to enhance participation of tribes and tribal entities, and other racial and ethnic community groups, in decision-making to influence programmatic adaptation of new scientific findings.
  - Fund community-based and community-driven participatory research to facilitate: (1) community capacity development, (2) bidirectional transfer of knowledge and observations of interest to both the community and the investigator(s), and (3) culturally and contextually appropriate translation of these findings into community programs.

For systems:

- Determine the impact of system-level factors such as health provider attitudes that prevent HIV-infected individuals from seeking and obtaining needed services.
- Support aspects of the health system composition (e.g., service delivery, convenience of location, hours of operation, and availability of ancillary services) that facilitate accessing health care.
- Identify, implement, and support information-sharing capabilities to promote the development of evidence-based HIV service delivery models for disproportionately affected populations.

AREA OF EMPHASIS

Women and Girls

FY 2013 RESEARCH PRIORITIES

- Design and conduct studies that integrate the biological, behavioral, and social sciences to explain factors that influence HIV risk, pathogenesis, and prevention in women, girls, and infants.
- Define the normal and abnormal biology of the genital and anal/rectal tract across all age groups (including, but not limited to, the changing immunologic and hormonal status), and its relationship to HIV risk, acquisition, and treatment.
- Define the impact of host and viral factors on comorbidities in women and girls.
- Study interactions of HIV and HIV treatment with reproductive health, reproductive technology, and family planning.
- Design and conduct studies that assess the impact of social and behavioral aspects of stigma, discrimination, and disenfranchisement on HIV testing, treatment, and care uptake and delivery across the life cycle.
- Evaluate methods to accurately assess current HIV seroincidence and seroprevalence of women and girls.

OBJECTIVE–A: Determinants of HIV Transmission

Define the mechanisms by which innate and biologic targets for intervention and adaptive viral and host immune factors influence HIV transmission, acquisition, and resistance to infection.

STRATEGIES

- Evaluate the role of viral characteristics and host immune function in 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 anal/rectum and genital tract physiology, innate and adaptive immunity, microbiology, and concomitant infections on cellular and other tissue mechanisms on HIV transmission, acquisition, and prevention.
- Study the role of genetic factors in HIV transmission, acquisition, and resistance to infection.
- Study the factors associated with sexual activity on HIV susceptibility, transmission, acquisition, and resistance to infection.
- Study the impact of antiretroviral therapy (ART) on genital tract and anal/rectum viral dynamics and immune function on HIV transmission, acquisition, and resistance to infection.
- Identify and study appropriate animal models to explain female-specific, host-viral-immune interactions and mechanisms of infection in women and girls.
- Develop standardized assays and techniques for sampling upper and lower genital tract, anus/rectum, and oral mucosa to assess host and viral immune factors and physiology that affect HIV transmission, acquisition, and resistance to infection.

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

Conduct and support integrated biomedical, behavioral, and social science interventions research to prevent HIV transmission, acquisition, and resistance to treatment.

STRATEGIES

- Support integrated approaches to combination HIV, sexually transmitted infection (STI), and family planning prevention research that consider the social and cultural context of the population in which the interventions will be applied.
- Support integrated research to understand how health care services, including reproductive health and social services, affect HIV risk, transmission, acquisition, and resistance to infection.
- Analyze the impact of community-level social and behavioral norms on the acceptability and efficacy of and adherence to 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 recruit and retain women and girls who are demographically representative of the populations at risk for HIV infection into HIV prevention studies.
- Support research to identify effective methods to improve the translation and implementation of female-focused, effective HIV prevention technologies.
- Support research to identify and develop methods to overcome barriers to enrolling girls under the age of 18 and hard-to-reach populations into HIV prevention intervention trials.
- Develop and evaluate interventions that target HIV-serodiscordant couples to prevent HIV and STI transmission and prevent or allow pregnancy.
- Investigate the interaction between HIV-risk perception and sexual behaviors and activity, on the use and effectiveness of HIV prevention methods.
- Conduct and support intervention research to address the couple-specific dynamics that affect HIV risk, acquisition, and transmission.
- Develop, evaluate, and implement culturally focused prevention interventions for populations traditionally perceived to be at low risk for HIV infection.
- 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 and acquisition for women and girls globally.
- Conduct research on the dynamics of sex- and gender-specific stigma and discrimination, and its impact on HIV risk and prevention.
- Conduct research on the dynamics of sex- and gender-specific violence on HIV/STI risk and prevention.
- Develop, evaluate, and implement HIV/STI prevention interventions that decrease the impact of violence and power discordance on HIV/STI risk.
- Develop and evaluate interventions to reduce or prevent adverse psychological and social consequences for women and girls infected with or affected by HIV/AIDS.

OBJECTIVE–C: Biology of HIV Disease

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

STRATEGIES

- Develop and evaluate innovative and rapid testing strategies in diverse settings to identify acute and chronic HIV infection and HIV-related coinfections in women and girls.
- Identify the mechanisms specific to women and girls that mediate virus/host interactions and affect disease progression, including, but not limited to:
  - Endogenous and exogenous hormones;
  - Intermittent ART for the prevention of perinatal transmission; and
  - Genetic factors.
- Elucidate the sex-specific risks, etiologies, and pathogenesis of HIV disease, disease manifestations, and interactions between HIV and non-HIV-related diseases and conditions.
- Investigate the impact of HIV and HIV-related coinfections and therapy on fetal, infant, and childhood development.
- Evaluate the impact of maternal HIV and ART on breast milk and on breastfed infants.
- 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 and support research to inform the diagnosis, care, and treatment of HIV-infected women and girls across the life cycle.

STRATEGIES

- Develop and evaluate innovative combination strategies in diverse settings to diagnose, link, and maintain HIV-infected women and girls in HIV care and treatment.
- Study the effect of receiving an HIV-positive test result on HIV-risk behaviors, seeking access to and participating in HIV treatment and care, and in reproductive health.
- Study the pharmacokinetics, pharmacodynamics, toxicity, and success and failure of therapeutics for HIV, opportunistic infections, and other comorbidities in women and girls.
- Evaluate the short- and long-term effects of anti-HIV therapy on health, fertility, morbidity, and mortality in women and girls across the life cycle.
- Study factors that affect adherence to HIV therapeutic regimens and care, and develop and evaluate interventions to improve adherence.
- Evaluate the impact of comorbidities, including substance abuse and mental health disorders, on morbidity, mortality, access to health care, and the enrollment of women and girls in clinical trials.
- Support multidisciplinary research to identify unmet needs and barriers for women and girls to achieving optimal HIV/AIDS care, support, treatment, and prevention services.
- Study the interrelationships between HIV and human papillomavirus (HPV), as well as HIV and HPV vaccination, on HIV risk and pathogenesis.
- Study how treatment interventions in acute and chronic HIV infection, including treatment during pregnancy, affect short- and long-term HIV disease progression.
- Identify appropriate female-specific HIV quality-of-care indicators and study the impact of implementing quality-of-care guidelines on community and country-level health status of women and girls.
- Study the issues relevant to stigma and discrimination and comorbidities that affect women and girls' access and use of health services, including HIV treatment.
- Develop and evaluate accessible assisted reproductive technologies designed to assist in meeting fertility desire without vertical or horizontal HIV transmission.
- Investigate the interaction between HIV, its treatment, and aging and age-related conditions or comorbidities.
- Develop treatment and technological interventions to prevent mother-to-child transmission (MTCT) of HIV through breastfeeding.
- Study the impact of interventions to prevent MTCT and HIV-related comorbidities on the health of women and infants/children, including maternal and infant morbidity and mortality, and on long-term morbidity and mortality.

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 strategies to facilitate obtaining fully informed consent from potential clinical trial participants.
- Investigate the unintended consequences of policies and practices for women and girls as a result of their participation in research.
- 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.
- Study the ethical issues related to HIV-specific prevention, diagnostic, and therapeutic strategies implemented during pregnancy and lactation.
- Study the ethical issues related to providing reproductive health 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

FY 2013 RESEARCH PRIORITIES

- Continue to develop in-country leadership and support sustainable capacity in HIV/AIDS research in low- and middle-income countries through strengthened research training, building of research infrastructure, and implementation and evaluation of new training methodologies (such as Web-based and distance learning) in cross-disciplinary collaboration with other partners.

- Design and evaluate the integrated application of effective tools and sustainable approaches, in combination and at multiple levels, with a particular emphasis on sociobehavioral and structural interventions targeted to specific settings and/or populations at risk, to prevent HIV infection and transmission.

- Identify more effective care and treatment approaches, integrated with prevention and operational strategies based on implementation science and evaluation research, to ensure epidemic control, reduce HIV-related morbidity and mortality, and maximize cost-effective health outcomes in affected individuals and communities.

- Strengthen in-country laboratory capacity, particularly to refine and validate assays and approaches to identify recent HIV infection and develop accurate incidence density measures across HIV-1 subtypes, host populations, and epidemic stages, and to improve diagnostics for HIV-related coinfections and comorbidities.

OBJECTIVE–A: Capacity Building

Continue to strengthen sustainable and collaborative research environments by building on existing scientific and public health institutions and enhancing in-country leadership and research capacity.

STRATEGIES

Site Development

- Monitor existing international study sites supported by the NIH, and, as needed, further develop sustainable sites, or establish new in-country sites, to address urgent or unmet needs and emerging scientific opportunities, in coordination with ongoing NIH-funded research programs.
- Enhance capacity for the conduct of basic and applied prevention and treatment research through:
  - strengthening laboratory capacity through the provision of required equipment and human resource development with appropriate quality assurance and training;
  - maintaining and developing both Good Laboratory Practice and Good Clinical Practice requirements for large-scale clinical trials;
  - developing diagnostic and clinical capabilities through research training and "hands-on" research experiences;
  - developing affordable, effective 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) and opportunistic infections (OIs) in resource-limited settings, with a goal to be more affordable, simpler (i.e., not requiring electricity, refrigeration, and/or computer), more environmentally durable (i.e., withstanding high ambient temperature, humidity, and dust) than current technologies, and requiring less operator training;
  - enhancing existing pathology practices to permit use of updated disease classification in the diagnosis, ascertainment, and research 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;
  - addressing barriers in establishing, maintaining, optimizing, 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 approaches to population-based recruitment of hard-to-reach populations, such as respondent-driven sampling, venue-time sampling, and Internet-based sampling;
  - 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 appropriately and meaningfully in the development and design of HIV-related research (including clinical trials), as well as in the translation of research results into community-relevant programs, standards of care, and practices;

  - enhancing capabilities in medical records management, data analysis, and biostatistics;
  - strengthening library services, access to scientific resources, and enhanced information exchange, including electronic communications; and
  - strengthening capabilities of in-country staff in financial/grants management, administrative practices, and scientific/peer review.

- Continue to strengthen the capacity to conduct implementation science and operational research, including outcome studies, cost-effectiveness analysis, and modeling to rapidly address emerging priorities in prevention, treatment, and care in low- and middle-income countries.

- 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.

Collaboration and Coordination

- Ensure the leadership role of in-country investigators, academic leadership, community-based and indigenous leaders, and other stakeholders by involving them in all stages of research, including conceptualization of the research question, study design, development of protocols, study implementation, data collection and analysis, publication, and presentation of research results to government and other relevant stakeholders and audiences.

- Encourage the integration and coordination of research projects being conducted by NIH-funded researchers in resource-limited settings with established in-country programs, while collaborating with local investigators, to ensure project relevance and to optimize the research effort.

- Encourage the continued development of research collaborations between U.S. and low- and middle-income institutions and investigators into more equal partnerships, including strategic planning for research.

- Coordinate with other U.S. Government agencies, foreign governments, universities, and international organizations to help identify and support priorities for research infrastructure and capacity building in developing countries.

- Continue to collaborate with nonphysician 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 therapy (ART) rollout in settings with limited numbers of physicians and/or resources.

- Foster regional approaches to research in order to enhance communication, 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.

Ethical Issues

- Ensure that research projects are designed to benefit and engage the communities in which the research is being conducted by addressing locally relevant scientific questions and capacity needs.

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

- Strengthen the capacity of institutional review boards (IRBs), including information-sharing between IRBs, updates on recent developments, and monitoring of approved protocols.

- Ensure collaboration between resource-limited countries' ethical review committees and U.S. IRBs, and inform U.S. IRBs about culturally relevant issues in developing countries.

- 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 respecting the dignity of persons.

Technology Transfer and Translation of Research Results

- Support operational research based on implementation science and innovative research designs not limited to randomized clinical trials (RCTs).

- Ensure 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 personnel in relevant Ministries.

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

- Provide improved access to information concerning treatment and prevention guidelines and 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.

OBJECTIVE–B: Mentoring and Training Investigators

Continue to 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 both developed and developing countries to collaborate together on research projects in low- and middle-income countries and spend significant amounts of time working together 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 faculty and mentors for others.
- Continue to support research training, including degree training where appropriate, of clinicians and nonphysician professionals (such as nurses, midwives, and pharmacists), social and behavioral scientists, clinical pathologists, biostatisticians, public health professionals, and 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 bioethics to strengthen in-country capacity for 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.
- Support programs to develop and provide training in the responsible conduct of research in low- and middle-income countries.
- Develop and provide training at international sites conducting clinical trials 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 to better respond to needed adaptation to local epidemics and local social and cultural issues.
- 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.
- Identify barriers that international investigators encounter in the NIH application submission process through *www.grants.gov*, and work with relevant agencies to address the barriers that prevent application submissions.

OBJECTIVE–C: Interventions to Alleviate Stigma and Discrimination

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

STRATEGIES

- Design and evaluate culturally appropriate strategies to reduce stigma and discrimination and increase willingness of individuals to enter into voluntary counseling and testing (VCT); identify and implement alternative infant-feeding practices; receive and adhere to ART and anti-tuberculosis (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.
- Study age-, sex-, and gender-related social, behavioral, and biological factors affecting susceptibility to HIV infection and its acquisition or transmission, including intimate partner violence, the conflicting demands of childbearing, and avoidance of disease.
- Develop interventions to mitigate the negative social consequences of HIV infection related to AIDS stigma and discrimination, with particular emphasis on children infected with or affected by HIV.
- 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, 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 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 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–D: 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 and reflecting 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.
- 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 and test prevention strategies 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 injection equipment.
- Develop and test strategies specifically targeted to preventing transmission in serodiscordant couples.

OBJECTIVE–E: Structural Interventions

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

STRATEGIES

- 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.
- Determine barriers and facilitators to acceptance of VCT, and develop more comprehensive and integrated health system-level approaches to the provision of VCT, including:
  - assessing 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;
  - assessing approaches to integrate VCT into other existing health services, including TB and STI clinics, family planning, maternal and child health care, and child immunization services;
  - changing community norms for seeking VCT that encourage knowledge of one's status, help mitigate social harm, and reduce HIV stigma; and
  - developing and testing strategies for encouraging voluntary and safe partner notification within the context of families and couples counseling.
- 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, in particular:
  - identify the most effective and sustainable strategies for schools, leisure locations, and worksites to support behavior change interventions; and
  - examine structural interventions for HIV, STI, and TB prevention, treatment, and care among incarcerated populations.
- Conduct empirical data analysis and modeling to determine required coverage levels for different interventions in order to attain basic efficiencies and maximal effectiveness targeted to specific populations, including drug users and other at-risk groups.
- Evaluate the various approaches used by different countries for implementing structural interventions and investigate how these approaches may be systematically facilitated.

OBJECTIVE–F: Prevention Approaches

Design and evaluate the integrated application of effective and sustainable prevention tools and approaches in combination and at multiple levels, including synergistic biomedical, behavioral, and structural strategies, targeted to specific settings and populations at risk.

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, including infants born to HIV-infected mothers receiving antiretroviral (ARV) drugs during pregnancy or breastfeeding, for treatment or prevention of mother-to-child transmission (PMTCT).
- Develop and evaluate methods for increasing access to, acceptability of, and adherence to biomedical interventions, including ARV-based prevention, such as pre-exposure prophylaxis or treatment as prevention.
- Study and evaluate products that require minimal adherence, such as patches, vaginal rings, or longer-acting ARVs.
- Study and integrate the behavioral aspects of complex, combined biomedical interventions and strategies.
- Assess optimal combinations of existing prevention interventions for specific populations at high risk, as no single intervention is likely to eliminate HIV transmission in all groups.
- Examine novel study designs to evaluate the synergistic effects of combination prevention approaches, which permit attribution to specific components of the regimen.
- 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.

Male Circumcision

- Determine the effectiveness, sustainability, and durability of male circumcision in reducing HIV transmission risk from men to women and men to men.
- Develop and evaluate innovative strategies for the safe and effective delivery of male circumcision and other male-oriented prevention services to prevent or reduce HIV transmission.
- Study the sociocultural aspects and other factors that may inhibit or encourage the use of male circumcision or affect its acceptability.
- 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.
- Examine methods to increase uptake and demand for this service and evaluate best methods for scale-up, such as mobile clinics, task shifting, and others.
- Evaluate the effectiveness and consequences of expanded access to male circumcision programs.

Antiretroviral Use

- Determine the effectiveness of pre- and postexposure ARV prophylaxis in the 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.
- Conduct research on ARV optimization in genital secretions and in the anorectal, oropharyngeal, and gut mucosa.
- Determine the social, cultural, and practical factors affecting the provision of ARV-based prophylaxis and/or understanding the barriers to implementation of pre- and postexposure prophylaxis.
- Examine strategies to increase long-term adherence and examine product formulations that do not require daily adherence.

Oral and Topical Microbicides and Barrier Methods

- Discover and develop candidate oral and topical microbicides and other physical/chemical barrier methods (particularly female-controlled methods) to prevent sexual HIV transmission, and identify barriers to long-term adherence.
- Conduct Phase I, Phase II, and Phase III clinical trials of suitable candidate oral and topical microbicides (including ARVs) in various international settings and in diverse populations, including pregnant women, for safety and efficacy.
- Develop appropriate biological and surrogate markers of safety or protection.
- Study the sociocultural and behavioral concerns related to partner involvement and acceptance of microbicide use, or covert use in the absence of partner willingness or acceptance.
- Determine the cost-effectiveness of microbicides and other physical/chemical barrier methods in limiting transmission and curtailing the expansion of the epidemic.

HIV Vaccine Development

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

- Examine relevant behavioral issues related to the conduct of HIV vaccine research and its acceptability in diverse populations.
- Conduct research on the potential social and economic effects, including cost-effectiveness, of the use of HIV vaccines.

Sexually Transmitted Infections 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 human papillomavirus (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 and opportunistic infections on HIV transmission, acquisition, and disease progression.

Substance Abuse

- Develop and evaluate innovative, culturally relevant, and 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 and in developing countries.

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

- 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 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.
- Conduct implementation science research focused on the cascade of steps for prevention of MTCT beginning at prenatal care and extending to adherence at delivery, and examine ways to prevent loss to followup at any point.
- Evaluate strategies to ensure linkage of sites (and data from sites) conducting prevention of MTCT with sites providing maternal ART treatment and with pediatric health clinics.

OBJECTIVE–G: Optimal Use of Antiretroviral Treatment and Other Interventions for HIV Epidemic Control

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

- Develop and test region-specific strategies 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, in particular:
  - promote treatment literacy for health care workers, people living with HIV/AIDS, and family and community members;
  - evaluate the effectiveness of different approaches to task shifting for HIV care and treatment from physicians to nonphysician staff;
  - determine the role of pharmacogenetics/pharmacokinetics and identify appropriate ARVs that can be used in specific populations throughout the life course;
  - develop appropriate pharmacovigilance systems to evaluate short- and long-term effects of treatments provided to HIV-infected individuals (including special populations such as pregnant women and alcohol or substance users); and
  - 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) and provision of care to targeted groups, such as health care workers, security forces, and teachers.
- Develop and evaluate public health models, such as family and community models of care that integrate HIV/AIDS care and other existing health services for infants to older adults in a single setting to maximize outcomes and avoid duplication of effort, including:
  - evaluating and monitoring treatment effectiveness, adherence, drug-drug interactions, drug resistance, and toxicity of ARVs and prophylaxis medications against major coinfections and opportunistic infections in pediatric, adolescent, and adult populations (including over age 50 and pregnant women) in resource-constrained settings; and
  - developing and evaluating the use of HIV treatment as a component of prevention interventions.
- Assess the cost-effectiveness of ARVs in resource-limited settings, in particular:
  - identify affordable, safe, and effective ARV regimens, including timing of initiation and durability of initial treatment;
  - develop and evaluate suitable and sustainable approaches to monitoring the effectiveness and safety of HIV treatment, especially with regard to affordable technologies to measure CD4+ cell counts and viral load (or appropriate alternatives) and validate low-cost monitoring technology; and
  - determine the minimal level and methods of targeted drug-resistance monitoring necessary in those failing therapy and pregnant women.

- Conduct research on biological, behavioral, and psychosocial effects related to the diagnosis, treatment, and care of HIV disease among children and adolescents (both horizontally and perinatally infected), in particular:
  - develop and evaluate suitable and sustainable approaches for the diagnosis of HIV infection, especially for children under the age of 18 months; and
  - support the long-term followup of children exposed to ART *in utero* and/or postpartum in resource-limited settings to evaluate possible late effects of ARV exposure.
- Characterize the clinical course of HIV infection in diverse geographic settings and determine the efficacy of ARV regimens on various clades prevalent around the world.
- 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.
- Conduct community-based studies that assess the effect of community mobilization on VCT and treatment success.
- 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.
- Collaborate with clinicians from resource-limited countries to identify, recruit, and retain individuals with acute and early HIV infection in treatment research programs.
- Conduct basic research on latency and eradication of viral reservoirs that could lead toward a functional or actual cure of HIV.

OBJECTIVE–H: 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 related to HIV/AIDS into existing health service delivery programs.

STRATEGIES

- Develop effective strategies for and evaluate the integration of the delivery of HIV care with primary care and 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, in particular:
  - 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;
  - examine novel strategies to increase uptake of routine HIV testing;
  - examine the potential use of HIV therapeutic vaccines;
  - 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; and
  - develop strategies to control the HIV epidemic and strengthen existing infrastructure that simultaneously address multiple health outcomes.
- Assess the biological, social, psychological, societal, and economic impacts of ART on risk behaviors, HIV transmission, and prevalence, including associated behavior change, in individuals across the lifespan, families, and various communities, in particular:
  - study the 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;
  - evaluate the interactions of ARVs with alcohol, psychoactive drugs, traditional medicines, 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;
  - 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; and
  - determine how ART affects breastfeeding behaviors.
- Examine innovative ways to measure HIV incidence at a community level.
- 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, in particular:
  - develop demonstration programs that simultaneously address prevention, care, and treatment;
  - prior to the scale-up of HIV prevention, care, and treatment programs in a limited-resource context, determine how limited resources can best be utilized to attain required coverage levels;
  - evaluate the impact of scale-up of HIV prevention, care, and treatment programs at a population level to determine the most opportune time for evaluation of national-level interventions; and
  - ensure that implementation research is adapted to address the local epidemic.
- 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.

OBJECTIVE–I: 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.
- 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.
- 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.
- Identify comorbidities in HIV-exposed, uninfected infants and young children, using appropriate control populations, in resource-constrained settings.
- Investigate operational strategies for responding to the converging epidemics of HIV, TB, alcohol and substance abuse, and other comorbidities, while considering issues relevant to long-term treatment specific to the regional epidemic.
- Develop simple clinical algorithms for guiding initiation of prevention or treatment of HIV-related coinfections, OIs, malignancies, and other 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 and conditions, including TB, malaria, and early precancerous lesions.
- 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.
- Study the association between HIV, aging, and the development of AIDS-related comorbidities throughout the lifespan.
- 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 of HIV disease with prevention and treatment of OIs, endemic diseases, and comorbidities, especially TB, including clinical research to assess clinical outcomes 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 coinfected individuals.

- Develop and test the feasibility of low-cost assays for early diagnosis of viral cancers, particularly oral and 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.

AREA OF EMPHASIS

Training, Infrastructure, and Capacity Building

SCIENTIFIC OBJECTIVES AND STRATEGIES

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 populations that are diverse with respect to gender, race, and culture, including marginalized populations domestically and internationally, particularly in countries with high HIV incidence and/or high prevalence of HIV infection.

STRATEGIES

- 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.
- Enhance programs that improve recruiting, training, mentoring, and retaining investigators—especially those from diverse scientific backgrounds, including biomedical, behavioral, and social scientists—in AIDS research.
- Increase opportunities for highly trained specialists to develop skills in AIDS research, such as, but not limited to:
  - Opportunities for pediatricians, adolescent medicine specialists, and geriatricians in HIV prevention, diagnosis, manifestations, complications, and treatment.
  - Opportunities for HIV prevention researchers interested in adding specific methodological skills to their research expertise.
  - Opportunities for related specialists such as pharmacologists and dental scientists to develop skills in AIDS research.
  - Opportunities for veterinarian scientists conducting AIDS research using animal models, including nonhuman primates (NHPs).
- Implement new research training programs for non-physician professionals—such as 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.
- Support and expand training programs for basic and clinical/applied researchers across disciplines:
  - Provide training and promote standardized certification in Good Laboratory Practice/Good Clinical Practice for staff in domestic and international settings where clinical research on AIDS is being conducted.

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

- Support training opportunities for tested and emerging research methodologies relevant to HIV such as 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/systems analysis.
- Expand the NIH AIDS Loan Repayment Program to encourage promising U.S. scientists and physicians to pursue HIV-related research careers, placing an emphasis on those from disadvantaged backgrounds and/or from racial and ethnic minority populations.
- 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 best practices and the knowledge base of educational and social science research.
- Strengthen cultural competency training and ethics training for the conduct of AIDS research in vulnerable populations, in both domestic and international settings.
- Develop research training programs in the area of blood safety to develop improved blood screening strategies and technologies and appropriate use of transfusions.
- Develop new models of integrated training and mentoring that focus on the protection of human and animal subjects in AIDS research.
- Support the development and sharing of novel techniques from relevant research fields to the HIV/AIDS field, including structural biology, computational biology, genomics, metabolomics, proteomics, and systems science to understand HIV/AIDS-associated disorders. Encourage and facilitate collaborative and interdisciplinary research in these areas.
- Support development and analysis of distance learning used to teach research and research-related topics as well as to assess and better understand the acquisition of research skills and competency.

OBJECTIVE–B: Infrastructure and Capacity-Building Development

Establish and maintain the appropriate infrastructure and capacity needed to conduct AIDS research domestically and internationally, with emphasis on 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 in appropriate numbers, 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 AIDS 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.
- Develop, validate, and utilize experimental animal models, *ex vivo*, and theoretical/mathematical models to study the transmission and establishment of HIV/SIV/SHIV (chimeric simian/human immunodeficiency virus) infections, with emphasis on models of direct relevance to human HIV infection and models that address important issues not readily approachable in human subjects.
- Promote Internet connections, cell-phone-based communication, and online social networks, including those with virtual worlds for training, infrastructure, and treatment, taking into consideration appropriate levels of confidentiality/security. Ensure availability of pertinent and secure information technology at health science centers, hospitals, outpatient clinics, community-based organizations (CBOs), and other access points, both domestically and internationally, for HIV-related research and patient care.
- Develop statistical sampling methodologies, data collection protocols, and statistical analysis tools that are easy to use and adaptable to different settings; and facilitate efficient statistical analysis and enhance report generation and standardization when appropriate in the context of AIDS research.
- Promote research in, and application of, medical informatics (e.g., high-performance computing) for AIDS research and clinical practice in resource-limited settings, both domestically and internationally.
- Develop efficient and effective systems for collecting and managing HIV/SIV/SHIV multiple-center and single-site clinical and animal model trial data, and ensure timely and accurate dissemination of clinical and animal model trial information.
- Increase collaborations between CBOs/nongovernmental organizations and other Government-supported health care service providers and academic researchers to improve the quality and capacity of AIDS research in health care service settings.

Domestic

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

International

- Enhance and improve research infrastructure and capacity in resource-limited settings with high HIV incidence, with particular emphasis on facilities for research on HIV prevention, therapeutics, and behavioral interventions.
- Enhance coordination and collaboration among NIH-supported investigators, other U.S. Government agencies, and other international agencies conducting AIDS research in the same countries.
- Enhance opportunities to evaluate successful HIV prevention and therapeutic strategies in resource-limited countries that also could be used in the United States.
- Develop and improve conventional and electronic systems for documentation of medical care and tracking of HIV infection and AIDS in low-resource settings to improve epidemiologic research.
- Increase population-based cancer registration in resource-limited countries to allow for a better understanding of cancer rates in HIV-infected persons in these locations.

PRIORITY:

Translating Research From Bench to Bedside to Community

Natural History and Epidemiology

Information Dissemination

AREA OF EMPHASIS

Natural History and Epidemiology

FY 2013 RESEARCH PRIORITIES

- Develop and evaluate novel methods for HIV testing, linkage to and retention in care, adherence to treatment, and monitoring response to care for use in domestic and international settings. This priority activity includes conducting research on: (1) accurate, reproducible, and affordable virologic, immunologic, pharmacologic, and genetic assays, and behavioral assessments; (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 viral suppression at a population level; and (6) novel strategies for identifying HIV-infected persons who are unaware of their status.

- Conduct studies that improve the uptake, implementation, and translation of research findings into health care practices involving HIV/AIDS and related conditions. This priority includes implementation science research studies that address the multiple and diverse issues being encountered in the scale-up of prevention and treatment interventions, particularly in resource-limited settings, and evaluative research leading to more effective and cost-effective public health interventions.

- Conduct studies that assess the epidemiologic aspects of HIV infection in aging populations, including risk factors for HIV acquisition and transmission, and the long-term effects of HIV disease and its treatment, in aging individuals.

- 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 best practices for the collection, analysis, and sharing of data from these studies.

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

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

STRATEGIES

- Study the feasibility and acceptability of the seek, test, treat, and retain approach, both alone and in combination with other prevention interventions, in the United States and internationally, using clinical and mathematical models and cost-effectiveness analyses.
- Utilize existing cohorts, and develop new cohorts of selected subpopulations (especially newly emerging, vulnerable groups), to employ novel methods (e.g., social/sexual network analysis, molecular epidemiology and epigenetics, temporal phylogenetic analyses, and geographic information systems), alone and in combination, to further assess the magnitude of HIV incidence 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) and societal/structural factors (e.g., stigma, community cohesion, and conflict) on the risk of HIV acquisition and to assess the impact of in-country resource capacities, allocation, and availability on HIV progression and outcomes.
- Conduct molecular epidemiology studies to identify and estimate the incidence, 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), pre-exposure prophylaxis (PrEP), postexposure prophylaxis, and other biomedical interventions; 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 prevention and therapy.
- Refine epidemiologic and mathematical models to improve estimates of per-exposure risk of HIV transmission and to develop estimates of population-attributable risk, based on type of sexual and/or other exposure; characteristics of the infected and uninfected partners (e.g., plasma and/or anogenital tract viral load, host genetics, and coinfections); cofactors (e.g., substance use, psychiatric comorbidities, and ART); and biomedical interventions (e.g., oral PrEP, topical microbicides, male circumcision, and vaccines).

Strategies Related to Transmission and Its Prevention

- Investigate viral, host, and environmental characteristics that distinguish high-efficiency transmitters and nontransmitters of HIV, through studies of serodiscordant couples, sexual and/or molecular network-based studies, and other strategies.
- 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, gingival crevicular fluid, and semen), and mucosal compartments such as the oral mucosa, the female genital tract, and the anorectal mucosa;

- Host factors such as age, sex, race, socioeconomic status, functional capacity, hormonal status, strength and breadth of immune response, comorbid diseases, coinfections, transfusion and transplant history, and host genetics;
- Modifiable factors such as diet and nutritional status; 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 hepatitides;
- 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, men who have sex with men [MSM] in developing countries, and racial/ethnic minorities); and
- Sexual activity, abstinence, pregnancy, sexual networks, partner choice (i.e., serosorting or choosing partners from high- versus low-prevalence populations), partner concurrency, partner fidelity, duration of partnership, sex trade, control of STIs, hygienic practices such as douching, contraception practices, cultural practices such as the use of traditional vaginal preparations and male circumcision, venues for meeting sexual partners, 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:
  - Assessing the clinical outcomes, cost, and cost-effectiveness of different strategies for prevention of mother-to-child transmission (PMTCT), and determining predictors of success in countries in which the elimination of perinatal HIV transmission is being pursued as a public health goal;
  - 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 health of women and their infants, on the emergence of ARV drug resistance in the mother and in those infants who become infected despite prophylaxis, and on programmatic uptake, adherence, and costs;
  - Studying the safety and effectiveness of sustainable approaches to PMTCT of HIV, including the access and provision of maternal ART, successful breastfeeding weaning strategies, improved safety of formula feeding, longitudinal 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 further optimization of ART for 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, including maternal testing, receipt of test results, provision of PMTCT regimens, retention in care, and infant testing; and
  - Assessing the impact of perinatal treatment and prophylaxis regimens on community-wide HIV incidence, resistance to ARVs, and costs of care and treatment; 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; orphanhood; and pediatric neurobehavioral development.

Strategies Related to Prevention and Treatment

- Conduct studies to assess the individual and public health value of programs to promote widespread, frequent HIV testing, including couples counseling and partner notification with immediate linkage to counseling, care, and ART.

- Assess the efficacy and effectiveness and long-term sustainability of individual and various combinations of prevention strategies (e.g., behavioral changes, partner testing and notification, ART, biomedical interventions, and treatment for coinfections and comorbidities) in different populations.

- Conduct epidemiologic modeling studies on the aggregate impact of ART, oral PrEP, topical microbicides, and male circumcision on HIV transmission in the presence or absence of other biomedical, behavioral, and structural interventions, particularly in settings with endemic, generalized, hyper-endemic, and emerging epidemics.

- Study the impact of widespread ART availability, adherence, pre-ART and ART care, 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 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 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 HIV transmission to uninfected female and male partners, with consideration of the timing of male circumcision and other factors that increase or decrease transmission.

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, response to ART, and development of non-AIDS-defining chronic conditions, 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 the roles of host and viral genetic characteristics and differences by route of exposure, and continue to characterize the epidemiology 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 and laboratory monitoring overall and by sex and age groups.

- Characterize global patterns of innate and acquired viral resistance to ART and how these patterns are influencing the long-term effectiveness and cost-effectiveness of monitoring strategies and therapies.

- Characterize the changing spectrum of clinical outcomes, causes of morbidity and mortality, complications of ART, (e.g., cardiovascular disease), and cost patterns associated with evolving therapeutic strategies, domestically and internationally, in relation to person, medication, and system-level factors.

- Use observational studies in resource-limited settings to estimate the HIV prevalence, incidence, and correlates of treatment failure in first-line, second-line, and subsequent treatment regimens.

- Assess the effect of ART on the incidence, pathogenesis, and presentation of cancers in the 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, oral, and liver disease) in HIV-infected individuals. Use mathematical models to project the frequency, outcomes, and treatment costs of these comorbidities in HIV survivors.

- Characterize 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.

Strategies Related to Comorbidities

- Expand research on the spectrum of HIV-associated malignancies and on malignancies not associated with HIV that may develop in HIV-infected patients who have responded to ART and are living longer with immune deficiency.
- Identify effective and cost-effective screening strategies for such malignancies in HIV-infected populations.
- Investigate the role of risk factors such as chronic inflammation in the development of malignancies and metabolic, cardiovascular, musculoskeletal, renal, and liver disorders in HIV-infected individuals, and how cumulative and current ART use might mediate or mitigate the effects of chronic inflammation.
- Establish standards in different resource-limited regions 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 and herpes viruses, and helminthic infections) on such standard values.
- Assess the ability of health care systems in resource-limited settings to screen, diagnose, and treat AIDS-defining and non-AIDS-defining malignancies.
- 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 coinfected 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-coinfected 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 methods of integrating TB and HIV diagnostics and care and their effects 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-coinfected patients.
- Evaluate the clinical and economic impact of treatment of smoking; alcohol and illicit drug use, abuse, and dependence; 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.
- Study 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 and anal cancer and high-grade dysplasia as well as oral cancer in HIV-infected individuals.
- Evaluate different cervical and anal dysplasia and cancer identification and treatment methods in HIV-infected individuals for sensitivity, specificity, cost-effectiveness, and appropriateness in both international and domestic settings.
- Evaluate the effectiveness of HPV vaccines among HIV-infected individuals (female and male) from geographically diverse regions.
- Assess the effect of primary care screening and interventions (e.g., statin use; hypertension management; smoking cessation; alcohol/drug use screening, treatment of depression, STIs, and viral hepatitis; and cancer screening and treatment) on HIV disease outcomes, survival, and costs of care.
- Investigate hemostatic disturbances in HIV-infected individuals and the role of coagulation and fibrinolytic mechanisms in risk of vascular events and other complications.
- Examine the impact of cryptococcal disease on early mortality 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 Mother-to-Child Transmission and Pediatric HIV Infection

- Evaluate the differences in adherence, treatment response, drug resistance, 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 children 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.
- 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.

Strategies Related to Aging

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

- Study the incidence and determinants of physical, neurologic, and cognitive changes by age group and by duration of HIV infection among HIV-infected individuals and the effect of frailty and functional impairment on HIV, ART use and response, and self-care behaviors.

- Study the epidemiologic association between immunologic and virologic responses to treatment and adverse effects of HIV and ART in aging populations, including those with coexisting morbidities 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, development and progression of comorbid conditions, and mortality in older versus younger adults receiving ART to refine treatment guidelines for older HIV-infected patients.

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 prevention, diagnosis, and treatment and AIDS in diverse domestic and international populations.
- Evaluate study designs, including adaptive trial designs, to more efficiently assess the effectiveness of prevention and treatment interventions.
- Develop and assess strategies to increase the participation of underrepresented groups in epidemiology, prevention, and therapeutics research.
- 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.
- Promote the development and dissemination of simple point-of-care tools appropriate for both industrialized and resource-limited settings to standardize the diagnosis and monitoring of treatment-limiting or life-threatening complications of chronic HIV infection and ART.
- 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 underserved areas and in stigmatized populations.
- Investigate the use of Internet-based methods of recruitment, risk assessment, and preventive interventions for HIV.

Strategies Related to Natural History/Diagnosis and Monitoring

- Further develop epidemiologic, laboratory-based, and simulation modeling methods in conjunction with prospective cohort studies, domestically and internationally, to monitor HIV incidence, response to ART, and the incidence of complications 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, TB screening, 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.

Strategies Related to Research on Design and Analysis of Epidemiologic Data

- Develop new epidemiological designs and statistical methods, including development of informatics tools and simulation, to better characterize transmission dynamics and monitor long-term trends in disease progression and development of toxicities in the setting of potent ART.
- Continue to develop and improve upon quantitative methods for making effective and appropriate use of data from 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;
  - Validation of methods for imputing ART status in HIV surveillance registries that do not collect information on ART use;
  - Methods for sampling hidden populations (e.g., venue-based, Internet-based, snowball, mixed method, respondent-driven, and time-location sampling);
  - Methods for standardizing the reporting of results from studies that are Internet-based or use respondent-driven sampling;
  - Models and inferential methods for characterizing multiple/comorbid disease processes and events;
  - Methods for linking cohort data to health care utilization and cost data to address health policy questions;
  - Methods for compiling and linking blood donation data across blood centers, and estimating trends in incidence and transfusion-transmitted risks for HIV;
  - Methods for simultaneously addressing more than one hypothesis or intervention, including the use of factorial randomized trials and quasi-experimental designs;
  - Methods for collecting and analyzing spatio-temporal data (including geo-sentinel mapping), especially as they relate to transmission and spread of HIV infection;
  - Methods for multilevel analysis of population-based HIV/AIDS surveillance data; and
  - Methods to assess the role and effectiveness of social media use in different populations to enhance HIV prevention, care, and treatment.
- 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.

- Conduct studies that make innovative use of existing data (e.g., cohorts, surveillance data, routinely collected service delivery data, blood donor screening programs, and data from monitoring and evaluation systems) for well-designed, rigorous analyses, hypothesis generation, and hypothesis testing.
- Design data collection and evaluation to accurately assess "community viral load."
- 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.

Strategies Related to Interventions

- Study and evaluate prevention packages that combine multiple strategies into one intervention, especially those that combine behavioral, biological, and/or structural interventions.
- Develop studies to compare the effectiveness, efficacy, and cost-effectiveness of various HIV prevention strategies (e.g., opt-out testing, secondary prevention, oral PrEP, topical microbicides, male circumcision, and immediate ART) between populations with generalized versus concentrated epidemics.
- Assess optimal algorithms for HIV diagnosis, including point-of-care algorithms, and strategies for diagnosis of acute HIV 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.
- Assess the effectiveness of strategies designed to reduce the impact of comorbidities, including smoking cessation, medication-assisted treatment for substance abuse, hepatitis C virus treatment, vaccination against HBV and HPV-16/18, and cytologic screening for cervical and anal cancers.
- Adapt interventions initially developed in older adults to HIV-infected individuals with multiple comorbidities, functional impairments, polypharmacy, cognitive decline, and/or who are at risk of adverse outcomes common in geriatric populations (e.g., falls, fractures, and functional decline).

Strategies Related to Implementation

- Evaluate the various operational strategies that can be employed for the implementation and dissemination of efficacious, preventive (e.g., male circumcision, oral PrEP, and topical microbicides), or therapeutic interventions, and evaluate countrywide ART programs, including the use of implementation science research and integrated observational databases, to evaluate effectiveness at community and population levels.
- Evaluate novel methods for rapid dissemination of successful and reproducible findings for implementation into the field, and improve understanding of how to efficiently deliver effective interventions, develop standardized

methodologies to transfer interventions from one setting or population to another, and make informed choices among different interventions.

- Design and implement evaluations of both targeted and 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.

- Support implementation science studies and population-based research necessary for translating epidemiology findings into guidelines for health care practices.

- Assess the use of "community viral load" (CVL) as a population-level marker of program effectiveness. Establish the CVL sensitivity, specificity, and predictive value in tracking the epidemic, allocating resources, and evaluating the effectiveness of HIV prevention and treatment efforts.

- Support the use of implementation science to investigate barriers and facilitators to the efficient implementation of empirically tested prevention and adherence strategies in different environments.

- Design and evaluate implementation of system-level approaches for management of complex HIV-associated comorbidities in settings or populations with resource-limited available care.

- Evaluate different models of approaching a continuum of screening, prevention, treatment, and care and the impact of expanded intervention availability, access, and coverage in various settings and populations.

AREA OF EMPHASIS

Information Dissemination

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A: Disseminate Information to All Constituencies

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

STRATEGIES

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

- Work with community-based organizations (CBOs), nongovernmental organizations (NGOs), and local agencies to develop and promote effective methods of information dissemination on treatment, prevention, and research in target populations to increase awareness and clinical trial participation and to reduce stigma.
- Support dissemination of research findings to community representatives, study participants, health care practitioners, 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, including cancer trials, to increase awareness about research in these areas and the importance of supporting and participating in clinical studies.
- Evaluate the effectiveness of communication efforts by appropriate means, including obtaining feedback from target audience members through methods such as usability testing of paper and computer interfaces (see *www.usability.gov*) and information dissemination intermediaries, such as journalists and health educators.
- Promote wide dissemination of the annual *Trans-NIH Plan for HIV-Related Research* and other HIV-related reports as they become available.
- Promote and enhance the exchange of scientific information and communication between public and private research enterprises, such as enhancing communication with the pharmaceutical industry concerning research on the development of therapeutics, vaccines, and microbicides, and working with industrial scientists to make information concerning basic science and HIV protein structures available to the general scientific community.
- Communicate and exchange information internationally on topics such as prevention and treatment; patient management, including comorbidities and prevention guidelines; and research results that improve the care of HIV-infected individuals, including those in developing countries.
- Support the exchange of basic and applied research information at community, regional, national, and international conferences and workshops.
- Support the cross-collaborations of HIV and AIDS information providers to develop more integrated and comprehensive information dissemination approaches.
- Provide support for online access to presentation materials and other information (e.g., slides, graphics, and plenary presentations) from scientific meetings.
- Develop HIV/AIDS training materials using a variety of current technologies most appropriate for specific audiences, as well as materials adapted for local languages.

OBJECTIVE–B: Develop New Communication Strategies

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

STRATEGIES

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

OBJECTIVE–C: Coordination and Collaboration Efforts

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

STRATEGIES

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

Appendices

A. Planning Groups

B. NIH Institutes and Centers

C. List of Acronyms

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APPENDIX B

NIH Institutes and Centers

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

APPENDIX C

List of Acronyms

AIDS	acquired immunodeficiency syndrome
ANC	antenatal care
ART	antiretroviral therapy
ARV	antiretroviral
CAB	community advisory board
CBO	community-based organization
CDC	Centers for Disease Control and Prevention
CNS	central nervous system
CMV	cytomegalovirus
CSF	cerebrospinal fluid
CVL	community viral load
DC	dendritic cell
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HHV	human herpesvirus
HIV	human immunodeficiency virus
HPV	human papillomavirus
HSV-2	herpes simplex virus type 2
ICs	Institutes and Centers
IRB	institutional review board
IRIS	immune reconstitution inflammatory syndrome
KSHV	Kaposi's sarcoma herpesvirus

KSHV/HHV-8	Kaposi's sarcoma herpesvirus/human herpesvirus type 8
MDR-TB	multi-drug-resistant TB
MHC	major histocompatibility complex
MRSA	methicillin-resistant *Staphylococcus aureus*
MSM	men who have sex with men
MTCT	mother-to-child transmission
NGO	nongovernmental organization
NHP	nonhuman primate
NIH	National Institutes of Health
OAR	Office of AIDS Research, NIH
OI	opportunistic infection
pD	pharmacodynamics
PEP	postexposure prophylaxis
pK	pharmacokinetics
PMTCT	prevention of mother-to-child transmission
PrEP	pre-exposure prophylaxis
RCTs	randomized clinical trials
SHIV	chimeric simian/human immunodeficiency virus
SiRNA	small interfering RNA
SIV	simian immunodeficiency virus
STD	sexually transmitted disease
STI	sexually transmitted infection
TB	tuberculosis
TOC	test of concept
VCT	voluntary counseling and testing
VRC	Vaccine Research Center
WHO	World Health Organization
XDR-TB	extensively drug-resistant TB

NIH...Turning Discovery Into Health

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