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

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## 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.

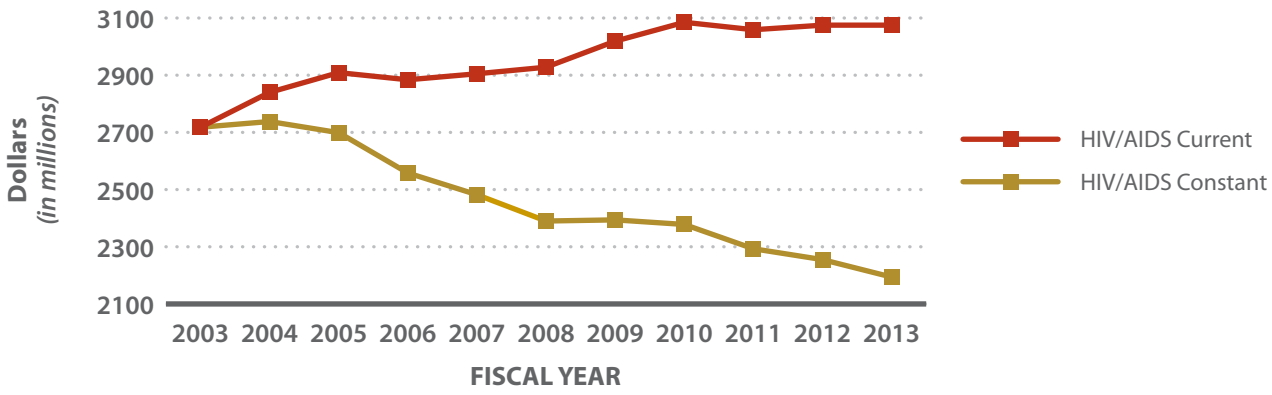
This by-pass request and strategic Plan establish the critical priorities for trans-NIH AIDS research. These include:

- **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

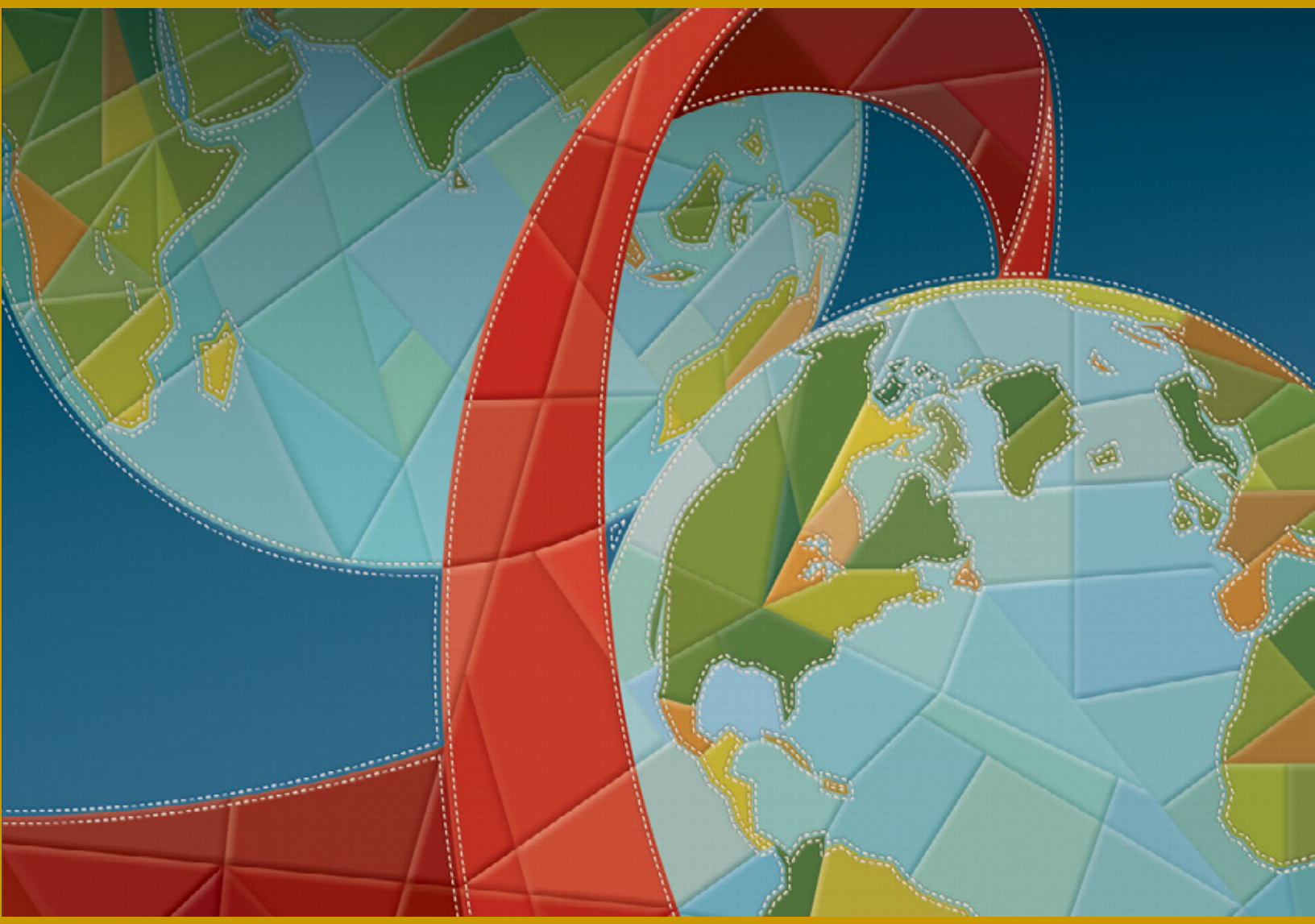
In the three decades since AIDS was first recognized—through the develop ment of effective combination therapies, to today's research to determine whether a vaccine, microbicide, or eventual cure for AIDS will one day be possible—the U.S. National Institutes of Health has been the global leader in research 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.



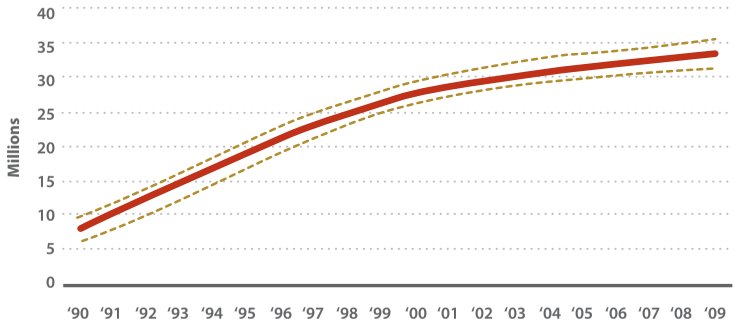
# HIV/AIDS Pandemic

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.

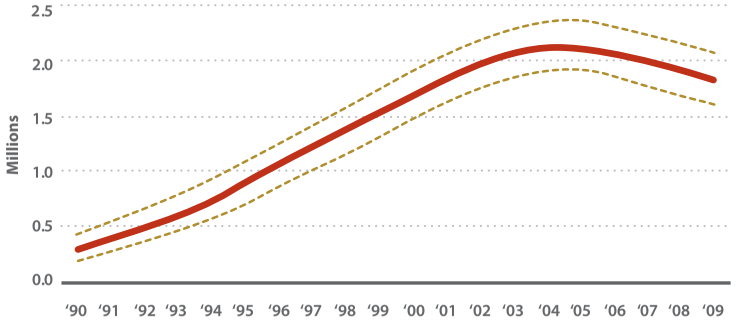
# Global HIV Trends, 1990 to 2009

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

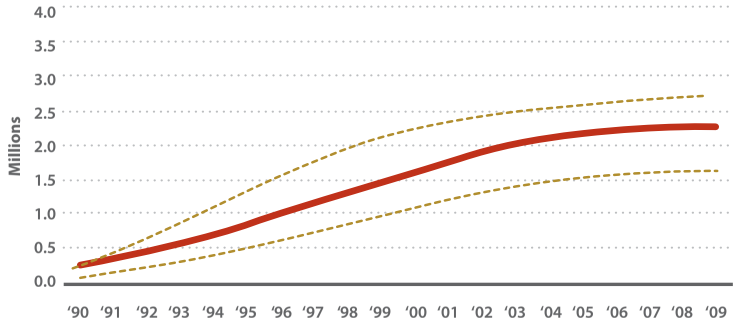
## Number of people living with HIV



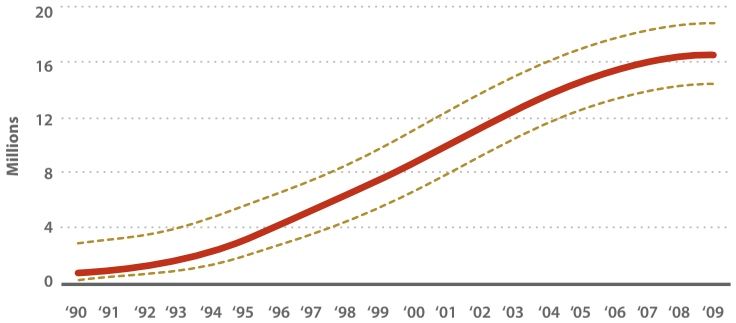

## Adult and child deaths due to AIDS




## 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.*

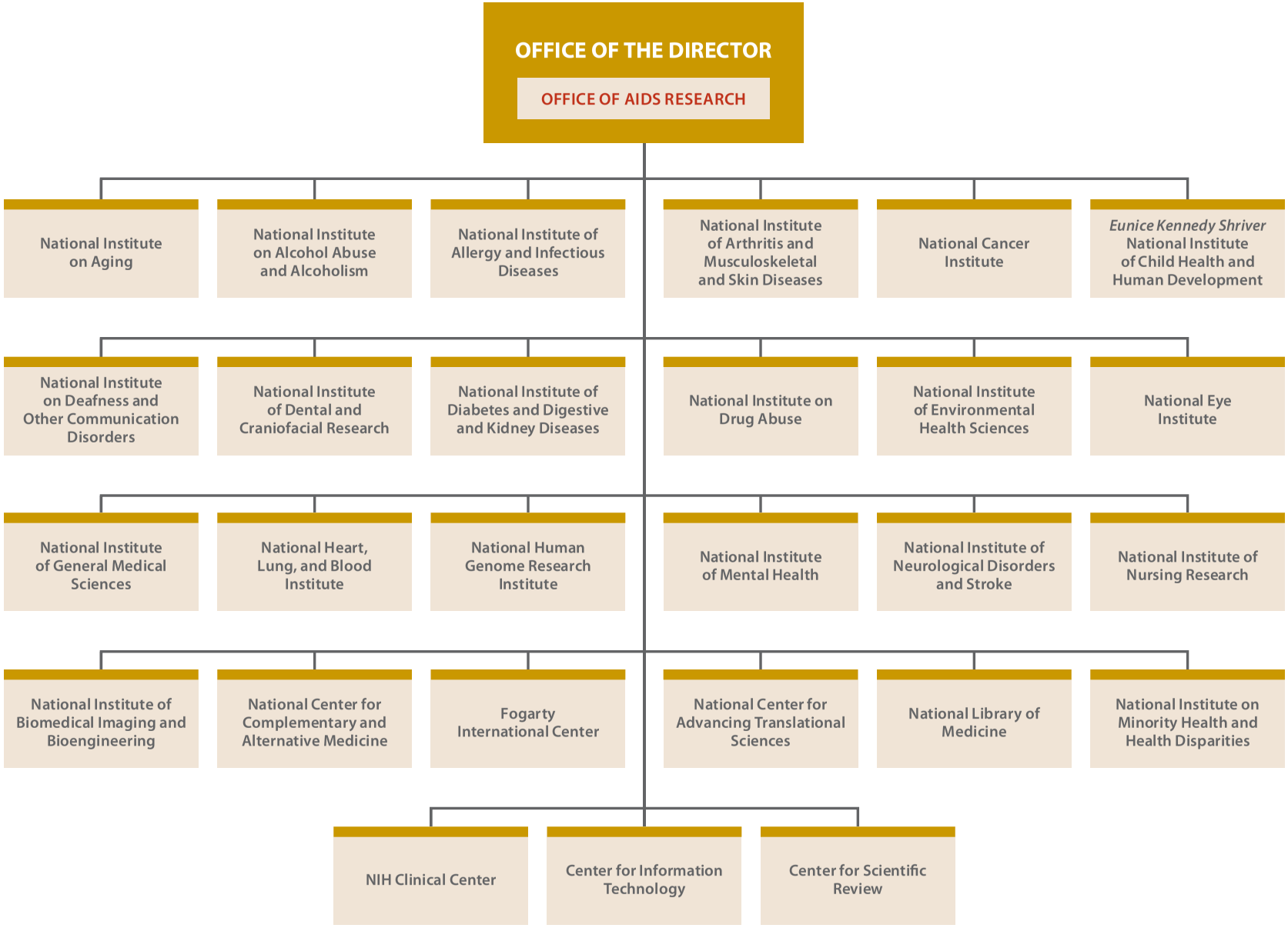
# NIH AIDS Research Program

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

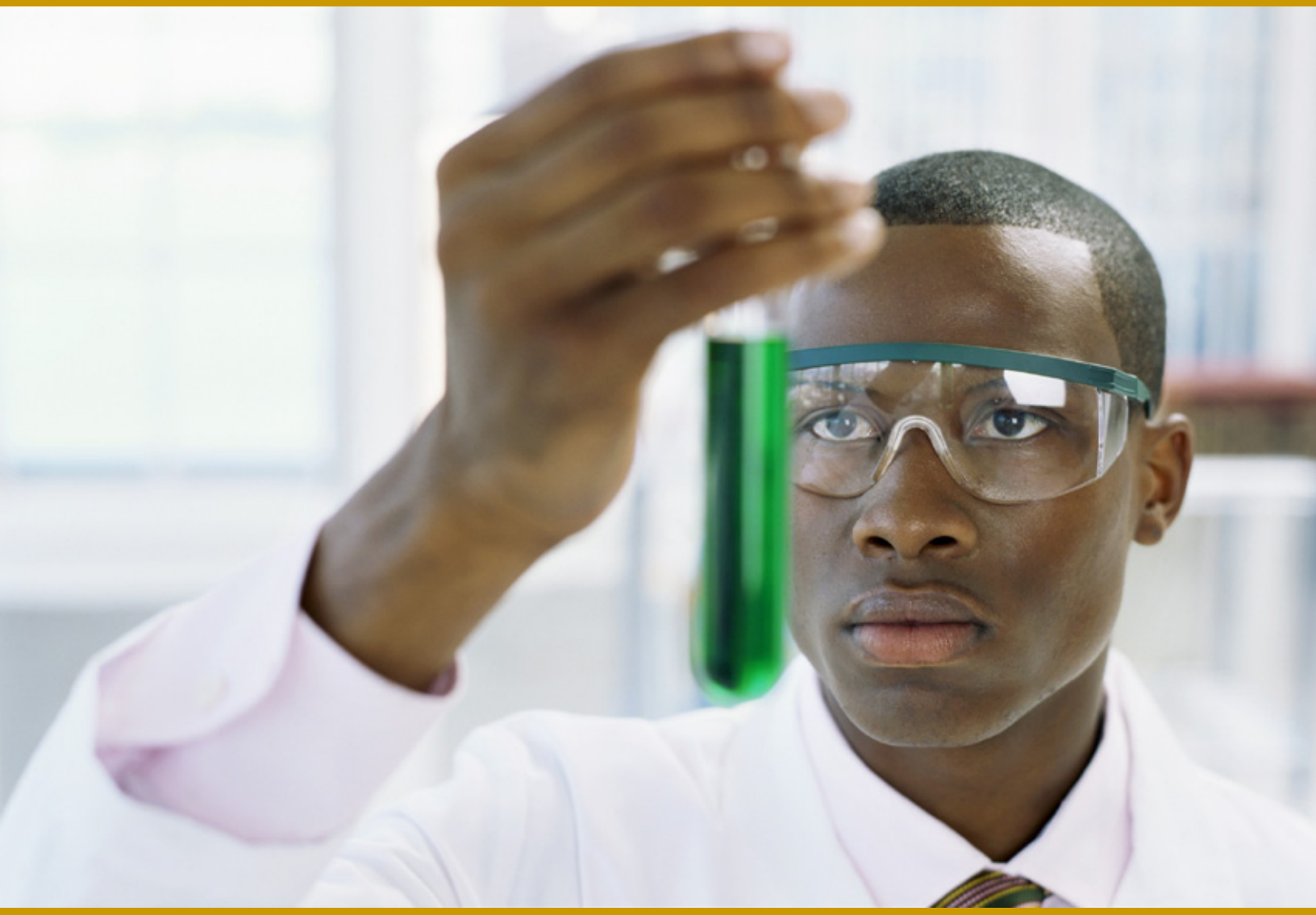
*The critical priorities of this by-pass budget estimate are aligned and in concert with the major goals of the President's National HIV/AIDS Strategy.*

*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

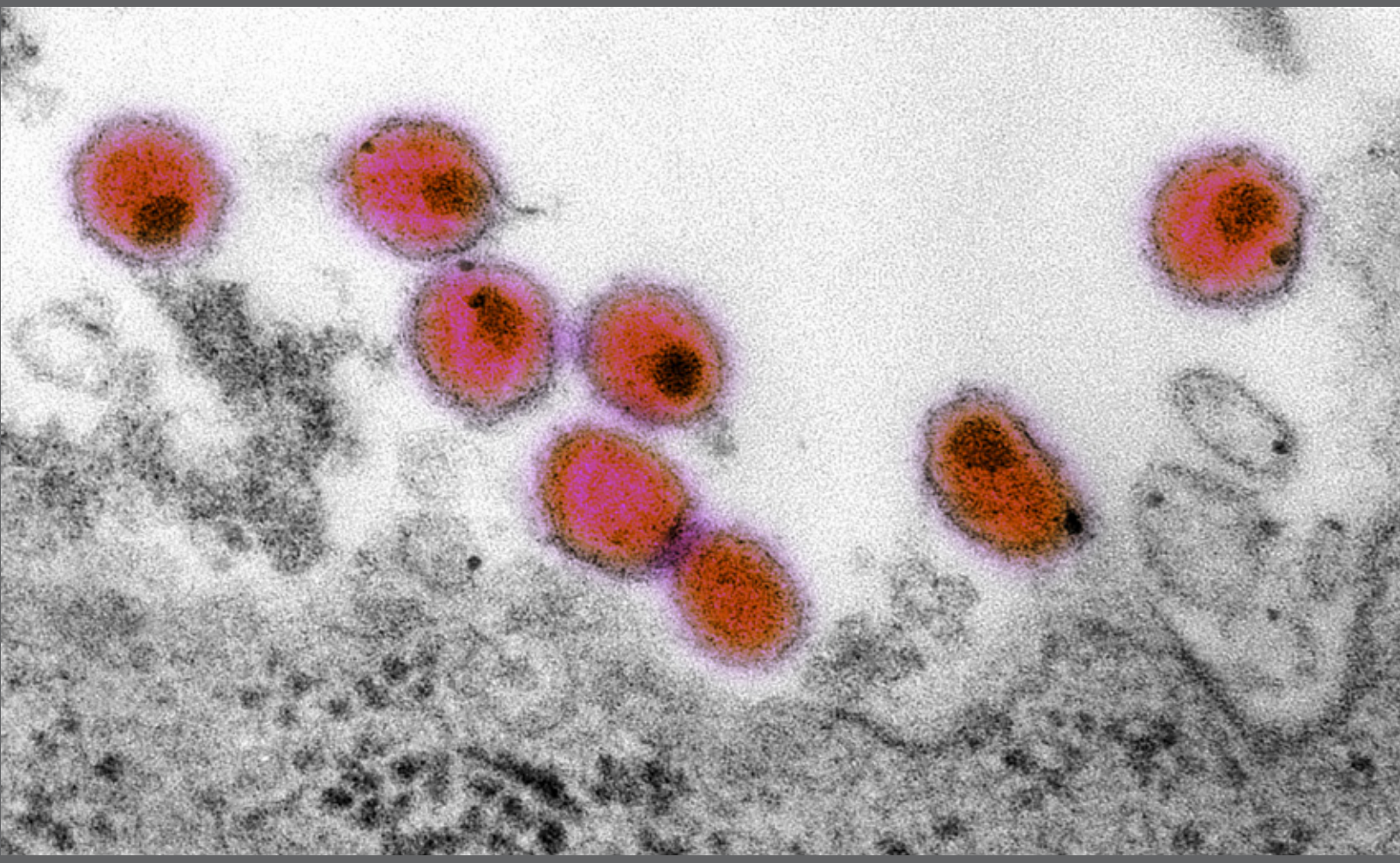
Research on HIV in children and the prevention of mother-to-child HIV transmission, and the integration of HIV services into maternal-child health settings, have improved maternal-child care and outcomes in developing countries. The benefits from AIDS research and care delivery include:

- **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

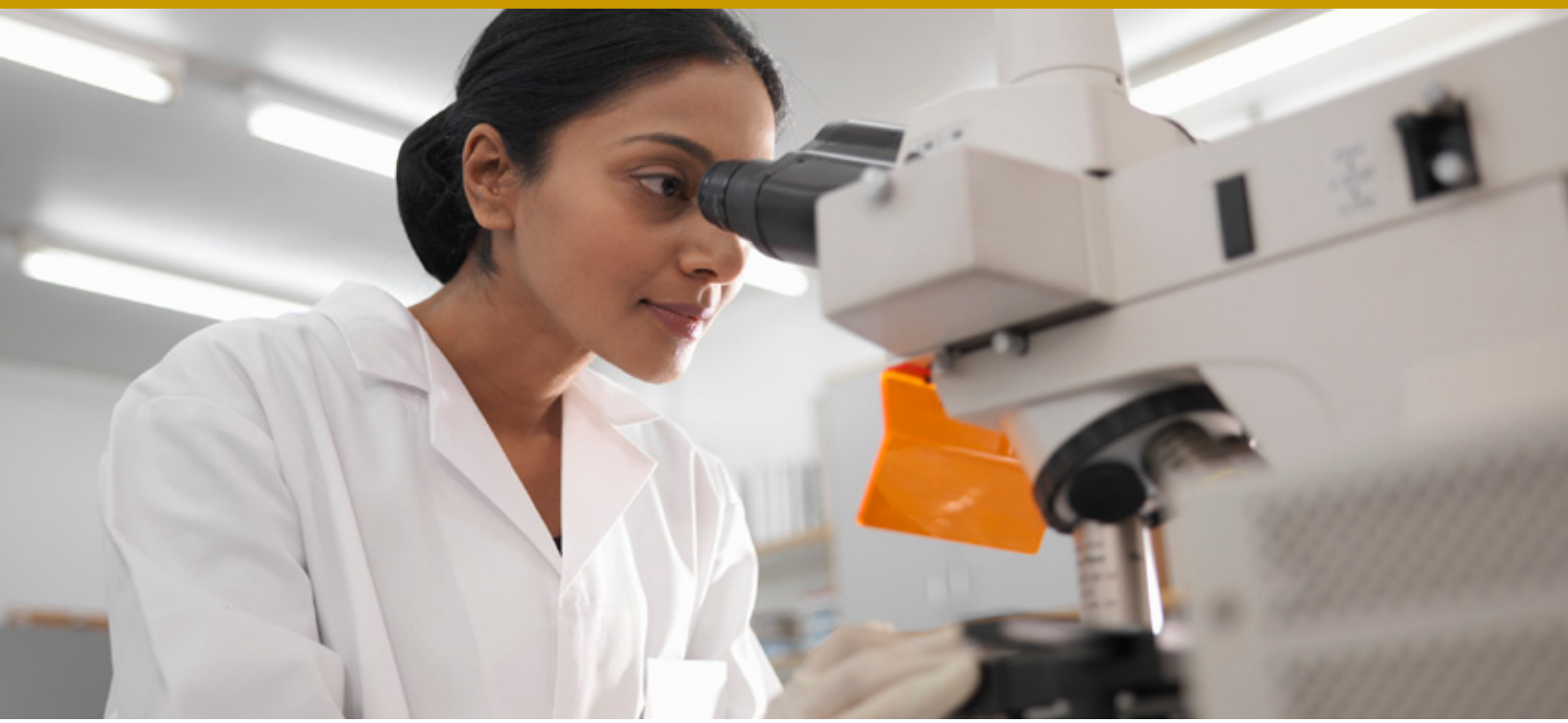
The FY 2013 by-pass budget request for this area is $313 million, which represents an increase of 11 percent above the FY 2012 enacted level. The NIH will continue to provide support for high-priority epidemiology studies of groups and populations affected by HIV and at high risk of infection, including 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%** |