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

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Legislative Mandate

Authorizing Legislation:

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

Appropriations Language:

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

Introduction

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

This by-pass budget estimate:

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

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

HIV/AIDS Pandemic

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

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

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

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

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

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

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

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

2 Ibid.

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

4 Ibid.

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

NIH AIDS Research Program

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

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

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

NIH AIDS RESEARCH PROGRAM

Represents the largest public investment in AIDS research in the world

Encompasses all NIH Institutes and Centers

Transcends every area of clinical medicine and basic scientific investigation

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

Includes research or training projects in more than 100 countries

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

NIH Office of AIDS Research

OAR *(http://www.oar.nih.gov/),* established in 1988, has unique legislative authorities unlike those of any other NIH entity to plan, coordinate, evaluate, and budget the entire $3 billion NIH AIDS research program, which represents approximately 10 percent of the total NIH budget—the largest and most significant public investment in AIDS research in the world. OAR serves as the principal liaison with the U.S. Department of Health and Human Services, other Federal agencies, and domestic and international governmental and nongovernmental organizations, on behalf of NIH AIDS-related research.

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

Perhaps no other disease so thoroughly transcends every area of clinical medicine and basic scientific investigation, crossing the boundaries of every IC. This diverse research portfolio demands an unprecedented level of trans-NIH scientific coordination and management of research funds. OAR coordinates the scientific, budgetary, legislative, and policy elements of the NIH AIDS research portfolio, and sets the trans-NIH scientific priorities for this large and diverse program. Utilizing its legislative authorities, OAR has established comprehensive trans-NIH planning, budgeting, and portfolio analysis processes to identify the highest priority areas of scientific opportunity, to enhance collaboration, to minimize duplication, and to ensure that precious research dollars are invested effectively and efficiently.

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

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

OFFICE OF AIDS RESEARCH MISSION

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

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

Trans-NIH Strategic Plan

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

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

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

Developing the annual AIDS research budget for each IC

Determining the use of AIDS-designated dollars

Developing the annual Presidential by-pass budget estimate

Tracking and monitoring all NIH AIDS research expenditures.

OAR Budget Development Process

OAR is mandated to develop the annual trans-NIH AIDS research budget *(http://www.oar.nih.gov/budget/)* in partnership with the ICs and explicitly tied to the objectives of the Strategic Plan. The law provides that OAR "shall receive directly from the President and Director of the OMB all funds available for AIDS activities of the NIH" for allocation to the ICs in accordance with the Plan. Subsequently, however, an agreement with Congress established the tradition that rather than receiving a separate, single appropriation, OAR would determine each IC's AIDS research allocation to be included within the IC total appropriation. It also was agreed that AIDS and non-AIDS appropriations would grow at approximately the same rate; that is, as an "institute without walls," AIDS research, as determined by OAR, would receive the same increase as the other ICs. Thus, AIDS research has historically represented approximately 10 percent of the total NIH budget.

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

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

OAR BUDGET DEVELOPMENT PROCESS

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

President's National HIV/AIDS Strategy

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

Reducing HIV incidence

Increasing access to care and optimizing health outcomes

Reducing HIV-related health disparities

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

FY 2011 Trans-NIH AIDS Research Priorities

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

Expanding basic discovery research

Reducing new HIV infections

Improving disease outcomes for HIV-infected individuals

Reducing HIV-related disparities

Translating research from bench to bedside to community

PRIORITY:

Expanding Basic Discovery Research

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

ETIOLOGY AND PATHOGENESIS: Groundbreaking strides have been made toward understanding the fundamental steps in the life cycle of HIV, the host-virus interactions, and the clinical manifestations associated with HIV infection and AIDS. However, additional research is needed to further the understanding of the virus and how it causes disease, including studies to delineate how gender, age, ethnicity, and race influence vulnerability to infection and HIV disease progression.

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

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

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

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

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


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PRIORITY:

Reducing New Infections

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

PRIORITY:

Improving Disease Outcomes for HIV-Infected Individuals

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

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

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

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

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

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

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

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

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

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

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

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

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

PRIORITY:

Reducing HIV-Related Disparities

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

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

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

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

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

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

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

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

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

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

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

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

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

PRIORITY:

Translating Research From Bench to Bedside to Community

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

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

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

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

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

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

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

Crossover Benefits

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

Conclusion

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

Budget Tables

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

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

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

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