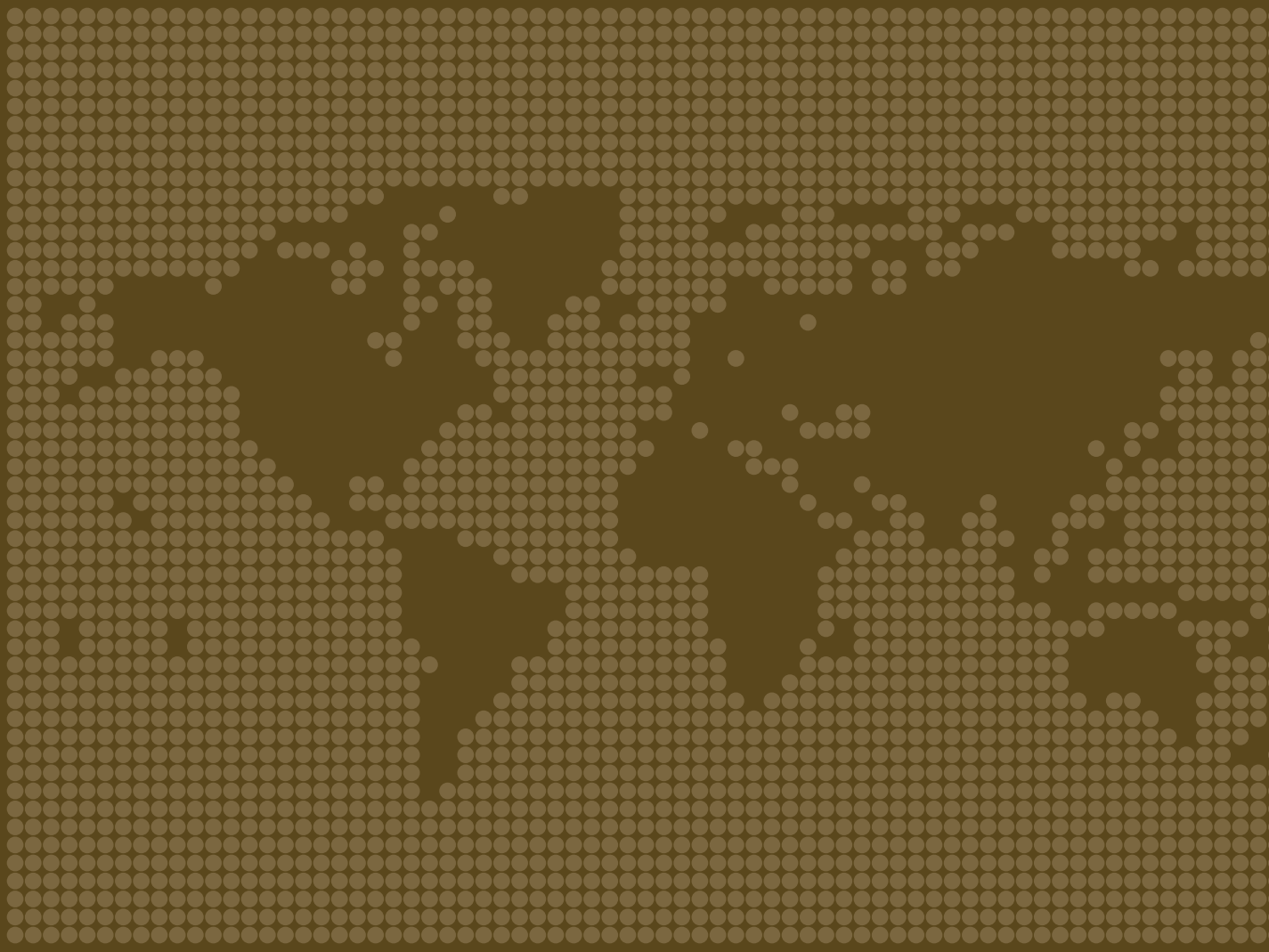
FISCAL YEAR 2010



NATIONAL INSTITUTES OF HEALTH

TRANS-NIH AIDS RESEARCH BY-PASS BUDGET ESTIMATE

Prepared by the Office of AIDS Research
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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
Office of AIDS Research

FY 2010 Trans-NIH AIDS Research By-Pass Budget Estimate

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LEGISLATIVE MANDATE

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."

INTRODUCTION

The Office of AIDS Research (OAR) is the only National Institutes of Health (NIH) programmatic office that is legislatively mandated to develop an annual Presidential By-Pass budget. Only the National Cancer Institute has a similar authority. In accordance with the law, OAR has developed this fiscal year (FY) 2010 AIDS Research By-Pass (Professional Judgment) Budget Estimate to carry out the scientific priorities established in the FY 2010 Trans-NIH Plan for HIV-Related Research. The By-Pass budget is based solely on scientific opportunity and the commitment and urgent need to support the highest quality research.

This By-Pass budget request:

- Addresses critical new 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 of the United States; and
- Begins to restore vital resources that have been drained by the dual effects of inflation and a flat budget.

THE HIV/AIDS PANDEMIC

Over 25 years since the recognition of AIDS and the identification of HIV as its causative agent, the HIV/AIDS pandemic has become a global scourge that affects people in 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] 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 the years 2001 and 2007, the number of people living with HIV in Eastern Europe and Central Asia more than doubled.[2] As a result of programs in low- and middle-income countries, almost 3 million people now have access to antiretroviral drug treatment. However, for every one person who starts taking antiretroviral drugs, another three become infected.

THE HIV/AIDS PANDEMIC

Worldwide in 2007 [1]

- Approximately 33 million people were living with HIV/AIDS infection.
- An estimated 2.7 million new HIV infections occurred.
- Approximately 2 million people died from AIDS.

In the United States in 2006 [3]

- Approximately 1.1 million people were living with HIV/AIDS.
- Approximately 56,300 new infections occurred.
- More than 14,000 died of AIDS.
- More than 950,000 people had been diagnosed with AIDS since 1981, of whom 565,000 had died.
- Minority racial and ethnic populations are disproportionately affected by HIV/AIDS.

In the United States, HIV/AIDS remains an unrelenting public health crisis, disproportionately affecting minority racial and ethnic populations, women of color, young adults, and men who have sex with men (MSM). The Centers for Disease Control and Prevention (CDC) reports that in the United States, more than a million people are infected with HIV. CDC has released new statistics showing 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. From the beginning of the AIDS epidemic through 2006, there were more than 565,000 cumulative AIDS deaths.[3]

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1 Report on the Global AIDS Epidemic. UNAIDS. Available at *http://www.unaids.org/en/KnowledgeCentre/HIVData/GlobalReport/2008/*. Accessed September 8, 2008.

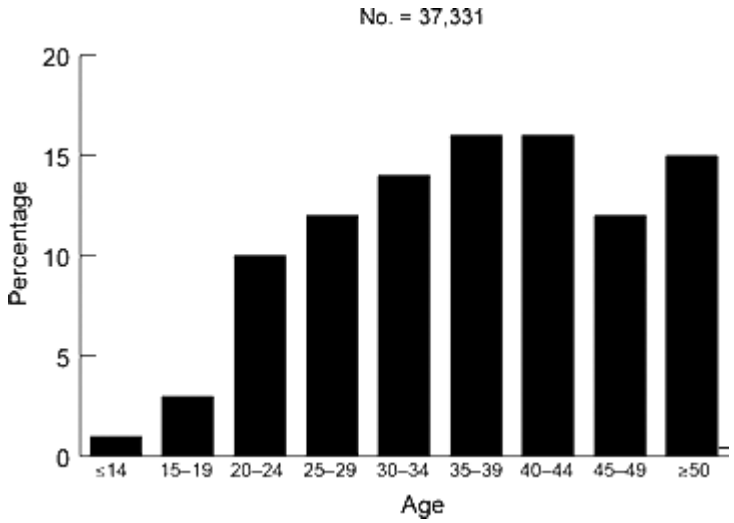
2 2008 Report on the Global AIDS Epidemic. UNAIDS. Available at *http://www.unaids.org/en/KnowledgeCentre/HIVData/GlobalReport/2008/*. Accessed September 8, 2008.

3 Centers for Disease Control and Prevention. Cases of HIV Infection and AIDS in the United States and Dependent Areas, 2006. Available at *http://www.cdc.gov/hiv/topics/surveillance/resources/reports/2006report/default.htm*. Accessed September 9, 2008.

According to the new 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 13 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. For example, the number of individuals aged 50 years and older who are living with HIV/AIDS has been increasing in recent years, due in part to antiretroviral therapy, which has made it possible for many HIV-infected persons to live longer, but also due to new infections in persons over the age of 50. In fact, as of 2005, persons aged 50 and older accounted for 15 percent of new HIV/AIDS diagnoses; 24 percent of persons living with HIV/AIDS (increased from 17 percent in 2001); 19 percent of all AIDS diagnoses; and 35 percent of all deaths of persons with AIDS. The rates of HIV/AIDS among persons 50 and older were 12 times as high among blacks (51.7/100,000) and 5 times as high among Hispanics (21.4/100,000) as those of whites (4.2/100,000).

Figure 1. Estimated Numbers of Cases of HIV/AIDS, by Age, 2005



Based on data from 33 States with long-term, confidential name-based HIV reporting.

The maturing U.S. epidemic has the potential to generate concentric mini-epidemics of liver disease, tuberculosis (TB), 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 universally available.

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[4] U.S. Census 2000. Available at *http://www.census.gov/main/www/cen2000.html*. Accessed September 23, 2008.

OAR requires ICs to report all AIDS-related expenditures on a quarterly basis to an OAR trans-NIH database, coded to the corresponding objectives of the Plan, thus permitting OAR to review and analyze the total intramural and extramural AIDS research program.

OAR BUDGET DEVELOPMENT PROCESS

The legislative authorities require OAR to allocate all appropriated NIH AIDS research funds to the ICs according to the *Trans-NIH Plan for HIV-Related Research*. Thus, the Plan provides the framework for the annual budget development and allocation process. The trans-NIH AIDS research budget (*http://www.oar.nih.gov/budget/*) is developed by OAR in partnership with the ICs and is explicitly tied to the objectives of the strategic Plan. Each year, OAR reviews IC AIDS budget requests in relation to the scientific priorities and objectives articulated in the Plan, and to other IC submissions. Dollars are not allocated to the ICs based on a formula, but rather on the priorities of the Plan, scientific opportunities, and the capacity of individual ICs to invest resources in the most meritorious science. The comprehensive budget is allocated by IC, by Scientific Area of Emphasis of the Plan, and by mechanism. The careful determination of the balance of the research budget—among ICs, among areas of science, between AIDS and non-AIDS research, 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 IC portfolios. This process reduces redundancy, promotes harmonization, and assures cross-IC collaboration.

OAR BUDGET DEVELOPMENT PROCESS

- Institutes and Centers (ICs) develop new/expanded program initiatives, with budget requests, for each scientific area.
- OAR reviews IC initiatives in relation to the Plan and OAR priorities.
- Consultations are ongoing between the ICs and the OAR throughout the process.
- The budget is developed in consultation between the OAR Director and the NIH Director.
- OAR allocates budget levels to each IC.

OAR identifies emerging scientific opportunities and public health challenges that require focused attention; manages and facilitates multi-IC and trans-IC 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. For example, OAR has focused increased emphasis on microbicide research and established the Microbicide Research Working Group, *http://www.oar.nih.gov/initiatives/mrgw.asp*, an external panel of experts to advise NIH and other entities that support microbicide research and development. OAR also shifted funds to provide significant increases to this research area, even in years of flat budgets.

THE NIH OFFICE OF AIDS RESEARCH

OAR *(http://www.oar.nih.gov/)*, established in 1988, has unique legislative authorities unlike those of any other Office of the Director programmatic office, to plan, coordinate, evaluate, and budget the entire $2.9 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 (DHHS), other Federal agencies, and domestic and international governmental and nongovernmental organizations on behalf of NIH AIDS-related research.

OAR'S MISSION

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

- An annual trans-NIH strategic planning process to identify the 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; and
- Facilitation and implementation of domestic and international collaborative AIDS research agreements.

Perhaps no other disease so thoroughly transcends every area of clinical medicine and basic scientific investigation, crossing the boundaries of nearly every Institute and Center (IC). This diverse research portfolio demands an unprecedented level of 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, which is conducted or supported by nearly every IC. Utilizing its legislative authorities, OAR has established comprehensive trans-NIH planning, portfolio analysis, and budgeting 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.

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 NIH, 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 assessed, and scientific opportunities 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; 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. The strategic Plan is a unique and critical document, because it serves because the framework for developing the annual AIDS research budget for each IC; for determining the use of AIDS-designated dollars; and for tracking and monitoring all NIH AIDS research expenditures.

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

Dr. Jack Whitescarver serves as both the NIH Associate Director for AIDS Research and the Director of OAR. He has served in a leadership role in OAR since its establishment in 1988 *(http://www.oar.nih.gov/about/director.asp)*.

THE NIH AIDS RESEARCH PROGRAM

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 nearly all the NIH ICs in accordance with their missions, in both intramural and extramural programs.

NIH AIDS RESEARCH PROGRAM

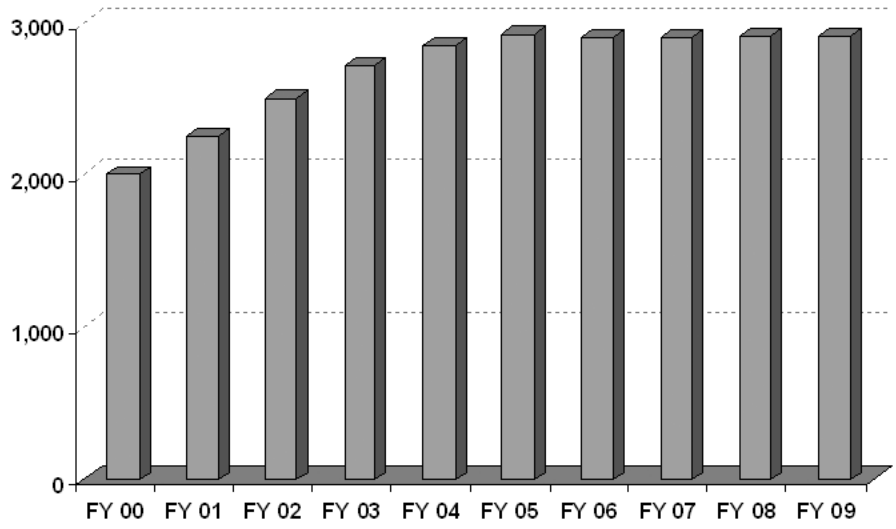
- Largest public investment in AIDS research in the world
- Encompasses nearly all NIH ICs
- Transcends every area of clinical medicine and basic scientific investigation
- Comprehensive program of basic, clinical, and behavioral research on HIV infection, its associated coinfections, opportunistic infections, malignancies, and other complications
- Research or training projects in over 100 countries
- Requires unprecedented scientific coordination and management of research funds.

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. In addition, NIH research has led to the development of treatments for some HIV-associated coinfections and comorbidities, including malignancies, neurological complications, TB, and other clinical manifestations. NIH research also has led to 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.

Figure 2. Total NIH AIDS Research Budget (dollars in millions), FY 2000 Through FY 2009



OAR BY-PASS BUDGET ESTIMATE

The FY 2010 By-Pass budget request for NIH AIDS research is $3.35 billion, which represents a 15 percent increase over the FY 2009 Continuing Resolution (CR) level. This 15 percent increase represents an initial investment—a down payment—that must be maintained and enhanced to address the impact of the erosion of buying power on critical research programs, to restore lost opportunity, and to take advantage of emerging scientific advances. This amount includes the total trans-NIH support for intramural and extramural research; research management support; research centers; and basic and clinical research on HIV/AIDS, as well as the wide spectrum of AIDS-associated malignancies, opportunistic infections, coinfections, and clinical complications.

Figure 3. Current and Constant Projections of NIH HIV/AIDS Research Dollars (in millions), FY 2003 Through FY 2009

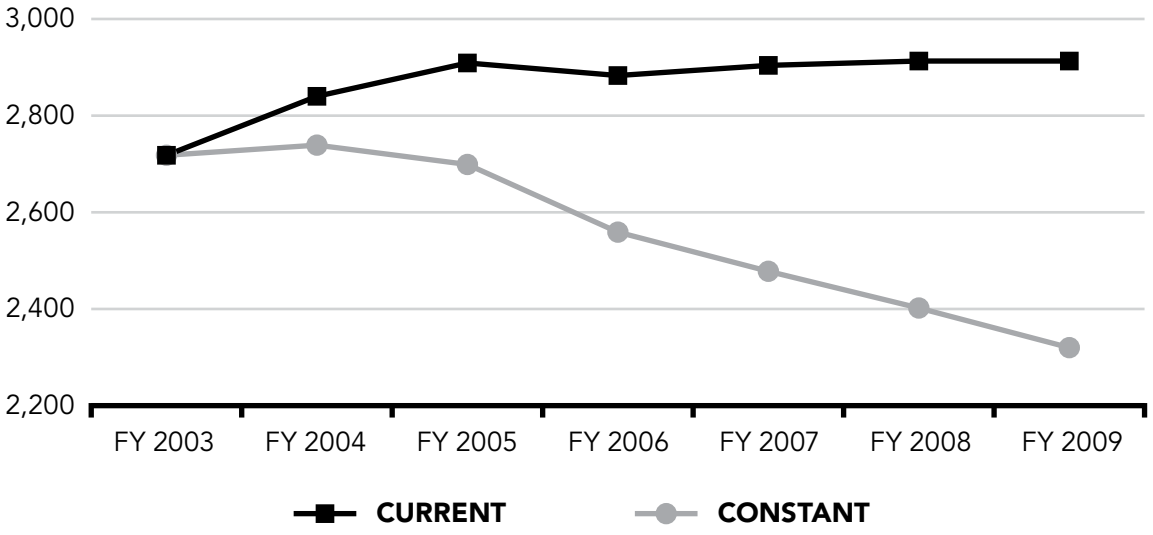


Figure 3 demonstrates the serious impact of inflation, as measured by the Biomedical Research and Development Price Index (BRDPI), and the flattening of the NIH AIDS budget over the past 5 years on the buying power of the NIH AIDS research program. Together, these factors have effectively reversed the doubling of the budget that occurred between fiscal years 1998 and 2003.

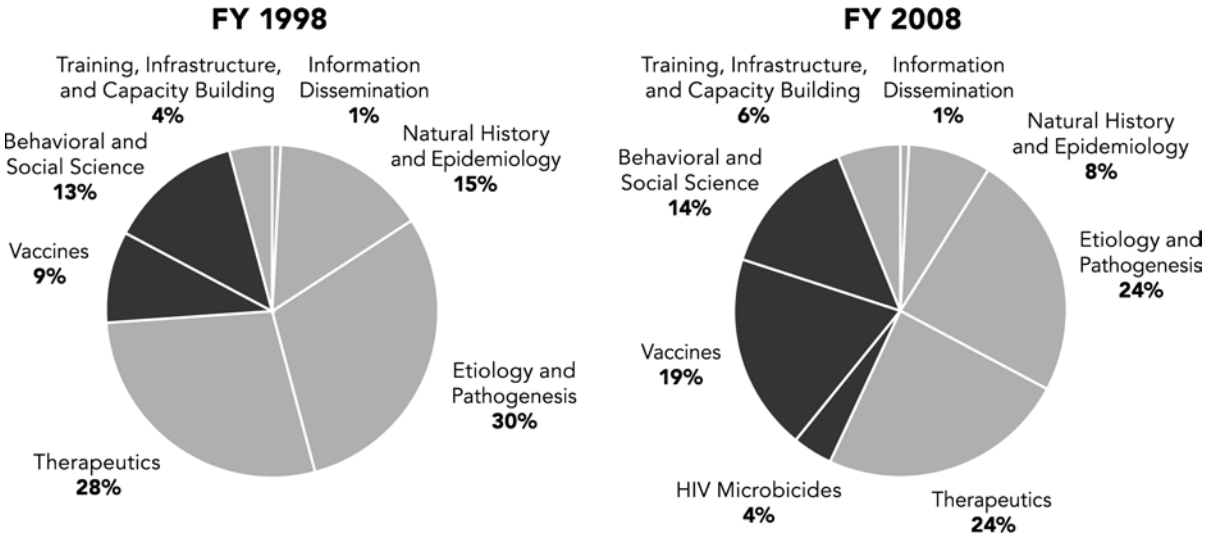
The decline of the U.S. dollar has further eroded buying power for AIDS researchers conducting studies in international settings. AIDS research represents the largest proportion of the total NIH international research portfolio. As the dollar has declined against the currencies in many countries where AIDS research is ongoing, the value or purchasing power of NIH awards for research in international settings has diminished over the past several years.

It is important to note that these budgetary constraints have occurred during a time of significant public health need and scientific opportunity. Increased demand and urgency for Government funding is further necessitated by concurrent significant reductions in pharmaceutical and biotechnology company investment in basic and clinical AIDS biomedical research. This budget request takes all these factors into account.

CONTINUED EMPHASIS ON PREVENTION RESEARCH

Over the past 10 years, OAR has increasingly focused on prevention research, shifting dollars to meet the critical needs in prevention, as indicated in Figure 4 in darker gray:

Figure 4. Actual Spending, by Scientific Area of Emphasis



OAR ADDRESSING THE U.S. EPIDEMIC

OAR supports a multifaceted initiative to address the U.S. epidemic, particularly in minority racial and ethnic populations. Included in OAR's efforts are activities addressing African Americans, Native populations, and populations in the Caribbean region. OAR has launched 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, involving both intramural and extramural NIH program staff, CDC, the Health Resources and Services Administration, District of Columbia government officials, 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 nations.

HIV/AIDS IN THE DISTRICT OF COLUMBIA (D.C.)

- The AIDS case rate is 9 times the national average.
- One in 20 D.C. residents has HIV infection; one in 50 has AIDS.
- More than 80 percent of recent HIV/AIDS cases were among African Americans.
- Heterosexual contact accounted for 37 percent of newly reported infections.
- D.C. accounted for 9 percent of all U.S. pediatric AIDS cases in 2005.

TRANS-NIH AIDS RESEARCH PRIORITIES FOR FY 2010

During the development of the Plan, the Planning Groups for each Scientific Area of Emphasis were asked to identify the most critical research priorities in their Area. In the distillation of all the suggested priorities, two clear, overarching priorities emerged to focus research across all the Areas: (1) prevention of acquisition and transmission of HIV and (2) prevention and treatment of HIV-associated comorbidities, comortalities, and coinfections.

In addition, the Planning Groups identified several specific priorities that transcended all Scientific Areas of Emphasis of the Plan. These include:

- The application of genetics, genomics, proteomics, systems biology, and other related technologies to the study of HIV/AIDS and the host immune response;
- The interrelatedness of HIV/AIDS and nutrition; and
- The development and testing of research models, methods, and measures to accurately assess risk and protective behaviors in the evolving and diverse populations at risk.

All these priorities are essential to address the epidemic both in the United States and in international settings, requiring interventions that are gender- and age-appropriate, and culturally sensitive.

The overarching priorities are described in more detail below.

1. PREVENTION OF ACQUISITION AND TRANSMISSION OF HIV

Prevention of HIV infection is the NIH's highest priority for AIDS-related research. There is an urgent need to expand the range of interventions for preventing HIV transmission beyond those currently available. The NIH AIDS prevention research portfolio includes basic, clinical, and translational studies on all aspects of biomedical and behavioral and social science research. This research may lead to the development of improved strategies for the prevention of HIV infection.

The disappointing results from recent clinical studies of HIV vaccine and microbicide candidates underscore the need for additional discovery (basic) research on HIV and the host immune response. Although NIH-funded AIDS research has yielded an impressive foundation of knowledge about the host response to HIV, the results from the recent trials indicate that a better understanding of the natural history, epidemiology, etiology, and pathogenesis of all phases of HIV infection and the host immune response is needed to enable the development of novel products that prevent the acquisition and/or transmission of HIV.

There is increasing recognition that biology and behavior interact in complex ways to affect HIV transmission and acquisition. For example, it is now clear that the probability of transmitting HIV very early in infection is higher than later in infection, when viral load is lower due to antiretroviral therapy, even given the same risk behaviors at both time points. Less clear are the complex interactions of behavioral and cellular events and the potential differential of susceptibility between individuals of different racial and ethnic backgrounds. The use of alcohol or drugs of abuse also may have both behavioral and health consequences that relate to susceptibility to infection.

Behavioral research studies have demonstrated that a number of existing interventions can have an impact upon HIV risk in targeted populations. The intensity of effort required to implement these interventions, as well as concerns about the sustainability of modified behavior, are concerns vis-à-vis large-scale implementation. There is a pressing need for research to determine the best means to scale up implementation and to determine where and when to best utilize existing prevention strategies.

The NIH recognizes that while HIV transmission and acquisition are fundamentally processes that occur at the individual level, they must be considered at the community level and within specific populations (e.g., MSM, racial and ethnic populations, women, adolescents, etc.). There is a continuing need to better understand how HIV is transmitted in the course of human relationships, occurring 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, particularly interventions that target MSM, as well as men and women from racial and ethnic populations. To advance AIDS prevention research, additional innovative studies are needed on environmental modifications, network perturbations, policy interventions, and other broad-scale prevention methods.

With this By-Pass budget, NIH will give highest priority to research that will:

- Advance understanding of the etiology and pathogenesis of HIV, including:
  - The host response to HIV and the overall capacity and complexity of the human immune system.
  - Genetic and biological mechanisms that govern the entry of HIV into target cells, particularly in relation to the interactions of HIV envelope, cell receptors, and mucosal surfaces.
  - 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 biomarkers and bioassays of HIV-host interaction at various stages throughout the entire course of HIV disease that are predictive of the efficacy and safety of biomedical interventions, including vaccines and microbicides.
- Develop and validate animal models that can be used in the preclinical evaluation of biomedical strategies for preventing the acquisition and/or transmission of HIV.
- Apply knowledge from basic research on HIV pathogenesis to the development of behavioral strategies and social interventions that prevent the establishment and spread of HIV between individuals and within communities.
- Develop and evaluate novel biomedical strategies, including vaccines and microbicides, along with existing strategies, in clinical trial settings to inform and optimize future product design and application.
- Develop and test methods of intervening at structural, environmental, and community levels to reduce acquisition and transmission of HIV. Focus attention on prevention strategies that can be implemented in racial and ethnic communities and in populations with a high incidence of HIV infection, such as MSM.

2. PREVENTION AND TREATMENT OF HIV-ASSOCIATED COMORBIDITIES, COMORTALITIES, AND COINFECTIONS

The landmark development of combination therapies for the treatment of HIV disease has resulted in extended survival and improved quality of life for those individuals who have access to antiretroviral drugs, can adhere to complicated treatment regimens, and can tolerate their toxicities and side effects. However, recent epidemiologic studies and clinical reports have shown an increasing number of malignancies, as well as cardiovascular and metabolic complications, associated with long-term HIV disease and antiretroviral therapy.

Basic research is needed to better understand the pathogenesis of HIV disease, and the mechanisms of toxicity of antiretroviral drugs that contribute to the development of HIV-associated comorbidities and comortalities. Epidemiologic studies are needed to determine the incidence and prevalence of those associated with long-term HIV disease and antiretroviral therapy in various populations, as well as to determine, monitor, and evaluate the effects of sex, gender, race, age, pregnancy status, nutritional status, and other factors on these antiretroviral therapy complications. Clinical protocols that integrate studies on metabolic, endocrine, cardiovascular, neurologic, renal, and bone parameters are essential to better define these potential complications of antiretroviral therapy and to develop regimens to prevent and treat these comorbidities.

Additional research is needed to define the mechanisms responsible for treatment failure and the development of strategies to maintain long-term undetectable viral load in HIV-infected individuals in the United States and internationally. This includes expanding research programs on drug resistance, drug toxicities, pharmacogenomics, nutrition, and adherence. Findings from these studies may benefit the development of improved strategies to prevent HIV transmission.

Recent advances in genomics have made it possible to identify genetic determinants associated with HIV disease progression and treatment response. Pharmacogenomics studies are needed to examine the inherited variations in genes that dictate an individual's response to antiretroviral therapies. In addition, studies are needed to explore how genetic variations can be used to predict the efficacy of and tolerability of antiretroviral medications in individual patients. Such studies might allow the development of future therapeutic regimens that can be custom formulated for an individual patient based on his or her genetic sequence.

The development of optimal strategies for the prevention and treatment of HIV coinfections (including TB, hepatitis C, 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 antiretrovirals and agents used to prevent and treat coinfections associated with HIV.

This By-Pass budget request gives highest priority to research that will:

- Develop and evaluate new agents and drug regimens to prevent and treat comorbidities and comortalities (malignancies, cardiovascular diseases, metabolic disorders, and other complications) associated with long-term HIV disease and antiretroviral treatment.
- Develop and evaluate new strategies to prevent and treat HIV coinfections, including multi-drug-resistant and extensively drug-resistant TB, hepatitis C, and malaria.
- Identify genetic determinants of disease progression and treatment response and develop methods to optimize therapeutic regimens based on an individual's genomic sequence.
- Identify and evaluate the viral and host factors associated with antiretroviral therapy failure.

NIH RESEARCH TO ADDRESS THESE PRIORITIES

The FY 2010 NIH By-Pass budget request for HIV/AIDS research responds to these critical priorities in each of the following key areas:

Microbicides

Around the world, most HIV infections are spread through heterosexual transmission, and half of all infected adults are women. Women have no means to protect themselves from HIV infection if their partners do not use a condom or allow a female condom to be used. Prevention methods such as abstinence or being faithful will not protect married women or those who are sexually abused. A safe and effective microbicide would provide women a means to protect themselves from HIV.

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. In addition, the NIH supports behavioral and social science research on the acceptability and use of microbicides among different populations. NIH has undertaken a sustained effort over the years to attract investigators into this field.

The NIH has initiated a series of administrative steps to increase the level of awareness and focus on microbicide research, including: the establishment of a Microbicide Research Working Group, comprised of non-Government experts who will play a unique and essential role in guiding the formulation of the NIH microbicide agenda; establishment of a new microbicides section within OAR; establishment of a new microbicide research branch at the National Institute of Allergy and Infectious Diseases; and support for the multi-IC Microbicide Innovation Program, designed to accelerate the discovery and development of single and/or combination microbicides.

Recent clinical trial results of microbicide candidates have been disappointing, and demonstrate the need for renewed and intensified efforts to fund additional research to better understand and answer basic science questions and to develop new approaches to designing potential microbicides.

BUDGET POLICY This By-Pass budget places high priority on microbicide research, requesting $133 million in this area, representing a $15 million (12.7 percent) increase over the FY 2009 CR level. The NIH is unable to adequately address this important area of investigation without additional funds above the FY 2009 CR level. Therefore, this By-Pass budget requests increased support for basic science initiatives on the mechanisms to interrupt HIV transmission.

It is critical for the NIH to increase collaborations with academia, industry, and foundations to identify and explore new and existing compounds as potential microbicidal agents. Without this By-Pass budget request level, the NIH will be unable to: provide adequate funds to support the evaluation of novel lead candidates in animal models with unique mechanisms of action; expand the initiative for development of new innovative microbicide concepts; or accelerate the integrated preclinical/clinical program for development of lead microbicide candidates. This By-Pass budget also requests additional funds for the development of standardized criteria for selecting potential products for evaluation in clinical trials and for advancing them through the different phases of preclinical and clinical studies. Additional funds are requested to provide essential support for the Microbicide Trials Network and the infrastructure necessary to conduct microbicide trials, especially in developing countries, as well as to fund important research on ethical, adherence, and behavioral issues impacting these clinical trials. A number of working groups, conferences, workshops, and symposia also will be supported to foster innovative microbicide research that can lead to the development of potential products that prevent HIV transmission and acquisition.

Vaccines

The best long-term hope for controlling the AIDS pandemic is the development of safe, effective, and affordable HIV/AIDS vaccines. AIDS vaccine research remains a high priority to ensure that new and innovative concepts continue to advance through the pipeline. The NIH supports a broad HIV vaccine research portfolio encompassing basic, preclinical, and clinical research.

Two large studies conducted by the NIH in partnership with Merck & Co., Inc., were halted by the Data and Safety Monitoring Board in 2007, after interim analyses of data demonstrated that the vaccine candidate did not prevent HIV infection. Although disappointing, the results from these clinical studies underscore the critical need to reinvest in basic research 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. As a result of these findings, the clinical protocol design for the planned clinical trial of the NIH Dale and Betty Bumpers Vaccine Research Center (VRC) candidate is being extensively modified with additional monitoring and immunologic testing of study volunteers, adding additional cost to this large NIH-sponsored study. Without additional funds, the study will be severely impacted.

BUDGET POLICY This By-Pass budget requests $616 million for this area, an increase of $56 million (10 percent) over the FY 2009 CR level. This request provides additional funds above the FY 2009 CR level to support basic research studies in vaccine development. One such important

study is ongoing at the VRC. NIH intramural scientists at the VRC determined the long-sought configuration of the precise interaction of the HIV surface protein gp120 as it looks when bound to an infection-fighting antibody, a finding that could have profound implications for HIV vaccine design. In addition, researchers at the NIH-sponsored Center for HIV/AIDS Vaccine Immunology have reported significant findings from genomics experiments comparing the genome of long-term nonprogressors to those who experienced rapid disease progression.

These results highlight the urgent need for an increased emphasis on genomic studies of the human immune system. Without the additional funds requested in this By-Pass budget, the NIH will be unable to fund additional basic research on HIV and host immune responses. Findings from this important research could provide new information for the design and development of new vaccine concepts and the preclinical/clinical development of vaccine candidates in the pipeline. These funds are critically needed to support these changing priorities in HIV/AIDS vaccine research.

Behavioral and Social Science

Behavioral studies and social science research are essential components of the NIH prevention science agenda. 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, if the virus is still viable at undetectable levels.

BUDGET POLICY This By-Pass budget requests $490 million in this area, an increase of $79 million (19.2 percent) over the FY 2009 CR level. This request provides additional support for expansion of ongoing research to develop and test effective HIV-related interventions that build on studies of substance addiction and the complex interaction of alcohol use, drug use, and disinhibition. This request also includes additional funds that would permit the NIH to support new global partnership initiatives for social science research on AIDS and studies on the role of behavioral and social networks in HIV transmission. Without these additional funds, the NIH will be unable to support the development and evaluation of effective interventions to prevent HIV transmission and acquisition by reducing HIV-related risk behaviors and increasing protective behaviors. Additional funding requested in this By-Pass budget would permit the NIH to sponsor studies of prevention strategies

that could be implemented in racial and ethnic communities with high incidence of HIV infection and in groups disproportionately affected, such as young women of color and MSM. Additional funds also are needed to allow adequate support for implementation or operational research to foster the scale-up and use of existing efficacious HIV prevention interventions.

Therapeutics

The NIH supports a comprehensive therapeutics research program to design, develop, and test drugs and drug regimens to prevent and treat HIV infection and its associated coinfections and comorbidities. NIH-supported research demonstrated the effectiveness of antiretroviral therapy to reduce mother-to-child HIV transmission. As a result of the implementation of these regimens, fewer than 200 HIV-infected babies are born each year in the United States. The NIH is continuing to develop regimens that can be implemented in resource-constrained nations, including strategies to prevent transmission associated with breastfeeding.

Antiretroviral treatment has resulted in improved immune function in patients who are able to adhere to the treatment regimens and tolerate the toxicities associated with antiretroviral drugs; and it has delayed the progression of HIV disease, extending the time between initial infection and the development of AIDS. However, epidemiologic studies have demonstrated that HIV-infected individuals are experiencing coinfections, including TB and hepatitis C, and comorbidities associated with long-term HIV disease, such as malignancies, metabolic disorders, cardiovascular disease, and neurologic disorders. These complications result in more deaths occurring from liver failure, kidney disease, cardiovascular complications, and malignancies in this patient population compared to uninfected individuals.

BUDGET POLICY This By-Pass budget requests $751 million for HIV therapeutics research, a $73 million increase (10.8 percent) over the FY 2009 CR level. This request increases funds for research aimed at establishing a better understanding of the underlying biology of these HIV-associated conditions. This research is critical to the development of better prevention and treatment strategies. At the FY 2009 CR level, the NIH will be unable to provide necessary funding for basic and clinical studies on the increasing incidence of AIDS-related cardiovascular disease, diabetes, and malignancies, additional studies on the pathogenesis of HIV and hepatitis C coinfection, and critical studies on metabolic abnormalities associated with HIV disease and long-term antiretroviral treatment.

Although improved therapeutic regimens for the treatment of AIDS and AIDS-associated coinfections and comorbidities are urgently needed, particularly regimens that can be deployed in resource-limited settings, funding levels in this area have been significantly decreased over the past several years in order to provide increased funding for HIV prevention research. This By-Pass budget requests additional funds to begin to restore those funds and expand support for the

development of better lead compounds, drugs, and therapeutic regimens that are less toxic and have fewer side effects, limit the development of drug resistance, enter viral reservoirs to inhibit viral replication, promote easier adherence, and are more readily accessible.

Additional funds are critical for the development of therapeutic regimens that can be implemented in international settings to address the global impact and continued spread of the AIDS pandemic in both developed and developing nations. Thus, this By-Pass budget requests additional funds to support the infrastructure necessary for the conduct of perinatal, pediatric, and maternal clinical studies, including studies in developing nations.

Etiology and Pathogenesis

The NIH supports a comprehensive portfolio of research focused on gaining a better understanding of how HIV infection is established and maintained, and what causes the associated profound immune deficiency and severe clinical complications. Research on basic HIV biology and AIDS pathogenesis has revolutionized the design of drugs, methodologies for diagnosis, and monitoring of the safety and effectiveness of antiviral therapies.

Although 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 gender, age, ethnicity, and race influence vulnerability to infection and HIV-disease progression. The results from recent microbicide and vaccine clinical studies have revealed gaps in the knowledge and understanding of HIV etiology and pathogenesis, particularly with regard to host immune responses and how HIV interacts with and transverses mucosal surfaces.

BUDGET POLICY This By-Pass budget requests $849 million for this essential area of research, representing a $140 million increase (19.7 percent) over the FY 2009 CR level. Without the funds requested in this budget, the NIH will be unable to provide additional support for essential investigator-initiated basic research, including initiatives addressing the important pathogenic mechanisms more commonly observed in women, children, and adolescents infected with HIV. The results of such studies are critical for our efforts to prevent and control HIV infection and disease progression.

This By-Pass budget requests additional funds above the FY 2009 CR level to support an expansion of research to pursue novel ideas to better understand the normal development and functioning of the human immune system. These studies are crucial to answering essential questions about HIV pathogenesis and disease progression and the development of new and better treatments and prevention strategies. Without these additional funds, research will be inadequate to address these questions, including the role of specific HIV proteins in the viral life cycle; the primary modes of HIV transmission between cells and between individuals; how the immune system controls the infection and disease progression; the mechanisms involved in cell injury and death in the immune, nervous,

and other organ systems; host factors and cofactors that influence primary infection and disease course; and the relationship of HIV infection to its associated malignancies, opportunistic infections and coinfections, neurological impairments, and metabolic disturbances.

NIH-supported genomics studies recently identified genetic factors influencing the rate of viral suppression and the pace of HIV disease progression. This By-Pass budget requests funding to launch a major new multiyear intramural/extramural program devoted to research on HIV and the human genome. This new program would allow the NIH to capitalize on these new research findings and other recent advances in genomic and proteomic technologies that could lead to improved HIV therapies and provide new targets for vaccine, microbicide, and therapeutics development. The NIH will be unable to initiate this critical multiyear program without a significant increase in funds.

Natural History and Epidemiology

Natural history and epidemiologic 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, disentangling effects related to treatment from those related to HIV disease itself.

NIH researchers in two clinical trials demonstrated that heterosexual HIV acquisition was reduced by 50 percent in adult males who had been medically circumcised. These findings are of significant public health importance for HIV prevention. Ultimately, increased adult male circumcision could lead to fewer infections in women in those areas of the world where HIV is spread primarily through heterosexual intercourse.

BUDGET POLICY This By-Pass budget requests $259 million in this scientific area, a $34 million (15.1 percent) increase over the FY 2009 CR level. These funds will support 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. This budget requests additional funds for translational research in international settings to define the optimal parameters of treatment and care to achieve the best outcomes. Funds also are requested to support an evaluation of the community effectiveness of HIV prevention interventions.

Funding has been significantly decreased in this area over the past several years in order to provide increased funding for HIV prevention research. This By-Pass budget requests additional funds to begin to restore those funds and expand support for critical additional support for epidemiologic studies to investigate the mechanisms of disease progression, the impact of therapy in changing the spectrum of HIV disease, and the causes of death. Additional funding also is requested to address the urgent need to identify and enroll new clinical study participants, particularly those manifesting new complications of long-term infection and therapy, in the Multicenter AIDS Cohort Study. Sufficient funding is not possible for these important studies without an increase over the FY 2009 CR level. Increased funds also are requested in this budget to continue to conduct research on circumcision as well as the development of other new and novel prevention strategies.

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. In addition, the NIH Loan Repayment Program has attracted health professionals to the NIH to engage in AIDS-related research. The NIH is working to improve international research and training to better address the challenges of the AIDS pandemic in resource-constrained nations. One example is a trans-NIH initiative involving both intramural and extramural scientists to establish partnerships with scientists at Indian research institutions, particularly partnerships focusing on HIV prevention research.

BUDGET POLICY This By-Pass budget requests $201 million for training, infrastructure, and capacity building, an increase of $32 million (18.9 percent) over the FY 2009 CR level. This budget requests additional funds to 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. Additional funds also are requested to continue the expansion of NIH-funded HIV research globally, which has necessitated the development of research infrastructure in many locations, including resource-limited settings in Africa, the Caribbean, India, and Asia.

Additional funds also are requested to support efforts to increase the supply of nonhuman primates, particularly rhesus macaques, for AIDS research and other areas of biomedical research both in the United States and abroad. In particular, this By-Pass budget requests critical additional funds for construction and renovation of the primate research centers, which are national resources.

Information Dissemination

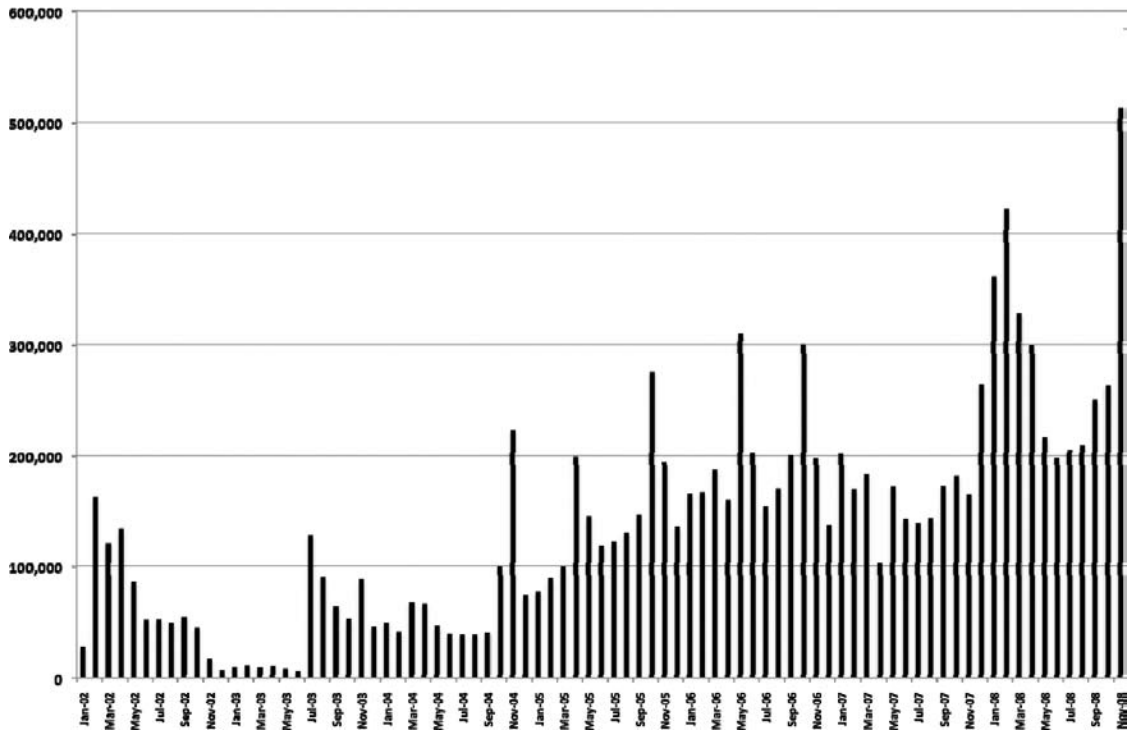
Effective information dissemination approaches are integral to HIV prevention and treatment efforts and critical in light of the continuing advent of new and complex antiretroviral treatment regimens, issues related to adherence to prescribed treatments, and the need to translate behavioral and social prevention approaches into practice. The changing pandemic and the increasing number of 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.

BUDGET POLICY This By-Pass budget requests $51 million for information dissemination efforts, an increase of $8 million (18.6 percent) over the FY 2009 CR level. 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 minorities. Funds will allow expansion of OAR's efforts to provide community outreach and support to address the AIDS epidemic in racial and ethnic populations in the United States, particularly African American and Latino populations.

This By-Pass budget also requests additional funds for a program to develop specialized tools for HIV sequence analysis through the National Center for Biotechnology Information. At the FY 2009 CR level, the NIH is unable to provide increased funds to enable additional researchers to access these important resources and more fully utilize data from genomics studies.

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. Guidelines are updated and posted on a continual basis. In the past year, the guidelines were downloaded approximately 4.4 million times, an increase of 27.2 percent over the previous year. *AIDSInfo* also provides information about participation in HIV therapeutics, vaccine, and microbicide clinical trials. In 2007, the Web site received more than 6 million page views. In FY 2008, *AIDSInfo* added a number of new Spanish-language features about HIV/AIDS clinical trials and treatment information to its companion site, *infoSIDA*, with more than 1 million pages accessed.

Figure 5. DHHS Adult and Adolescents Antiretroviral Guidelines Download, January 2002 Through November 2008



CROSS-OVER 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 provide benefit to 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. 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.

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.

SUPPORTING DOCUMENTS

OAR is providing the following materials in support of this request:

- NIH AIDS Research Funding Table by Scientific Area of Emphasis
- NIH AIDS Research Mechanism Table
- *FY 2010 Trans-NIH Plan for HIV-Related Research*

Table 1. Funding by Scientific Areas of the Trans-NIH Plan for HIV-Related Research (dollars in millions)

			OAR REQUEST		
AREA OF EMPHASIS	FY 2008 Actual Budget Authority	FY 2009 Estimate	FY 2010 By-Pass	Dollar Change FY 2009 to FY 2010	Percent Change FY 2009 to FY 2010
HIV Microbicides	$115	$118	$133	$15	12.7%
Vaccines	556	560	616	56	10.0
Behavioral and Social Science	413	411	490	79	19.2
Therapeutics	698	678	751	73	10.8
Etiology and Pathogenesis	704	709	849	140	19.7
Natural History and Epidemiology	228	225	259	34	15.1
Training, Infrastructure, and Capacity Building	172	169	201	32	18.9
Information Dissemination	42	43	51	8	18.6
TOTAL	$2,928	$2,913	$3,350	$437	15.0%

Table 2. FY 2010 Funding by Research Mechanism (dollars in millions)

	FY 2008 Actual Budget Authority		FY 2009 Estimate		FY 2010 By-Pass		FY 2010 over FY 2009
	NO.	AMT.	NO.	AMT.	NO.	AMT.	PCT.
RESEARCH PROJECTS							
Noncompeting	1,859	$1,296	1,796	$1,252	1,799	$1,259	0.6
Administrative supplements	(166)	27	(118)	35	(93)	35	—
Competing	640	297	676	310	1,022	516	66.5
Subtotal, RPGs	2,499	1,620	2,472	1,597	2,821	1,810	13.3
SBIR/STTR	87	35	84	34	79	42	23.5
Total, RPGs	2,586	1,655	2,556	1,631	2,900	1,852	13.5
RESEARCH CENTERS							
Specialized/comprehensive	58	123	58	129	59	144	11.6
Clinical research	5	49	5	51	5	58	13.7
Biotechnology	—	3	3	4	3	4	—
Comparative medicine	18	61	15	60	15	67	11.7
Research centers in minority institutions	4	11	3	9	4	50	455.6
Subtotal, Centers	85	247	84	253	86	323	27.7
OTHER RESEARCH							
Research careers	270	39	270	38	280	42	10.5
Cancer education	—	—	—	—	—	—	—
Cooperative clinical research	15	25	15	22	18	28	27.3
Biomedical research support	—	2	1	2	1	2	—
Minority biomedical research support	—	—	—	—	—	—	—
Other	141	55	126	56	147	72	28.6
Subtotal, Other Research	426	121	412	118	446	144	22.0
Total, Research Grants	3,097	2,023	3,052	2,002	3,432	2,319	15.8
TRAINING	**FTTPs**		**FTTPs**		**FTTPs**		
Individual	85	3	85	3	89	4	33.3
Institutional	715	32	685	32	810	37	15.6
Total, Training	800	35	770	35	899	41	17.1
Research and development contracts (SBIR/STTR)	161	398	156	422	243	491	16.4
	—	—	—	—	—	—	—
Intramural research	—	304	—	291	—	324	11.3
Research management and support	—	106	—	101	—	108	6.9
Construction	—	—	—	—	—	—	—
Office of the Director	—	62	—	62	—	67	8.1
Buildings and Facilities	—	—	—	—	—	—	—
TOTAL, Budget Authority	—	$2,928	—	$2,913	—	$3,350	15.0

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