

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Office of AIDS Research

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**JUSTIFICATION
OFFICE OF AIDS RESEARCH**

Budget Authority:

| | FY 2003 | | |
|------------------------|---------------------------------------|-------------------------|---------------------------------|
| FY 2002 Actual | Amended President's Budget | FY 2004 Estimate | Increase or Decrease |
| \$2,499,458,000 | \$2,759,940,000 | \$2,869,858,000 | +\$109,918,000 |

INTRODUCTION

The Global HIV/AIDS Pandemic

| Group | People Newly Infected in 2002 | People Living with HIV/AIDS in 2002 | AIDS Deaths in 2002 |
|-----------------------|--|--|--------------------------------|
| Adults | 4.2 Million | 38.6 Million | 2.5 Million |
| <i>Women</i> | <i>2.0 Million</i> | <i>19.2 Million</i> | <i>1.2 Million</i> |
| Children | 800,000 | 3.2 Million | 610,000 |
| Total | 5.0 Million | 41.8 Million | 3.1 Million |
| <i>Source: UNAIDS</i> | | | |

According to a new CIA report, “The HIV/AIDS pandemic continues to spread around the world at an alarming rate, and the number of people with the disease will grow significantly by the end of the decade, as it becomes more geographically diffuse. By 2010, we estimate that five countries of strategic importance to the United States – Nigeria, Ethiopia, Russia, India, and China – collectively will have the largest number of HIV/AIDS cases on earth.” (1) The dramatic global implications of this “next wave” (2) of the epidemic are stated in stark terms in a recent article in *Foreign Affairs* magazine: “The spread of HIV/AIDS through Eurasia, in short, will assuredly qualify as a humanitarian tragedy – but it will be much more than that. The pandemic there stands to affect, and alter, the economic potential – and by extension, the military power – of the region’s major states. And the disease will do more damage to some big countries than to others. Over the decades ahead, in other words, HIV/AIDS is set to be a factor in the very balance of power within Eurasia – and thus in the relationship between Eurasian states and the rest of the world.”

Dramatic increases in HIV infection also are occurring in Eastern Europe, Central Asia, Latin America, and the Caribbean.

HIV has already infected more than 60 million people around the world, and AIDS has surpassed tuberculosis and malaria as the leading infectious cause of death worldwide (3). In sub-Saharan Africa, UNAIDS/World Health Organization (WHO) estimated that 29.4 million adults and

children were living with HIV/AIDS at the end of 2002. Women represented 58 percent of the adults living with HIV disease in sub-Saharan Africa. An article in the *New York Times* recently added another horrifying dimension to the epidemic in Africa: "As a result of HIV, the worst-hit African countries have undergone a social breakdown that is now reaching a new level: African societies' capacity to resist famine is fast eroding. Hunger and disease have begun reinforcing each other." (4) Young adults, especially women, who tend the fields and bring in the harvest, are becoming sick and dying. The resulting malnutrition, in turn, accelerates HIV disease progression.

Curbing the transmission of HIV from infected mother to infant is an especially compelling challenge in resource-poor countries. The coexistence of other endemic diseases widely prevalent in developing countries, such as respiratory and gastrointestinal infections, complicate treatment and pose additional problems for medical personnel caring for HIV-infected individuals. Attitudes, beliefs, and taboos surrounding sex, the status of women and children, and the source and etiology of HIV can complicate attempts to control transmission and provide appropriate prevention and treatment.

The Epidemic in the United States

The HIV/AIDS epidemic in the United States continues to evolve. According to CDC statistics, the incidence of new AIDS cases has declined, due largely to expanded use of new antiretroviral therapies (ART) that prevent progression of HIV infection to AIDS. However, the decline in death rates observed in the late 1990s has now leveled off and, more disturbingly, the rate of new HIV infections has not changed since 1990, remaining constant at about 40,000 new infections each year, according to CDC estimates. This means that the overall epidemic is continuing to expand (5,6,7). In addition, use of ART has now been associated with a series of side effects and long term complications that may have a negative impact on mortality rates. HIV infection rates are continuing to climb among women, racial and ethnic minorities, young homosexual men, individuals with addictive disorders, and people over 50 years of age (5, 8). The appearance of multi-drug resistant strains of HIV presents an additional serious public health concern (9, 10, 11,12,13). These data forebode an epidemic of even greater magnitude in the coming years.

According to CDC reports, approximately one quarter of the HIV-infected population in the United States also is infected with hepatitis C virus (HCV). HIV/HCV co-infection is found in 50 to 90 percent of injecting drug users (IDUs). HCV progresses more rapidly to liver damage in HIV-infected persons and may also impact the course and management of HIV infection, as HIV may change the natural history and treatment of HCV (14).

AIDS disproportionately affects African Americans and Hispanics. According to CDC figures through December 2001, approximately 64 percent of newly infected women are African American and 17 percent are Hispanic. Among newly infected men, approximately 43 percent are African American and 20 percent are Hispanic (15).

Setting the AIDS Research Priorities

To respond to this pandemic, the NIH has developed a comprehensive biomedical and behavioral research program to better understand the basic biology of HIV, develop effective therapies to treat and control HIV disease, and design interventions to prevent new infections from occurring.

The Office of AIDS Research (OAR) develops an annual *NIH Plan for HIV-Related Research* that is based on the most compelling scientific priorities that will lead to better therapies and prevention strategies for HIV infection and AIDS. The Plan serves as the framework for developing the annual NIH AIDS budget; for determining the use of NIH AIDS-designated dollars; for tracking and monitoring expenditures; and for informing the scientific community, the public, and the AIDS-affected community about NIH AIDS research priorities. OAR has established an effective model for developing a consensus on the scientific priorities of the Plan, utilizing planning Groups composed of NIH scientists and experts from academia and industry, as well as representatives from the AIDS community, who meet together in workshops to develop each section of the Plan.

Historically, the Plan has established the NIH AIDS research agenda in the following Scientific Areas of Emphasis: Natural History and Epidemiology, Etiology and Pathogenesis, Therapeutics, Vaccines, and Behavioral and Social Science. As the epidemic evolved, OAR recognized the need to bring additional focus to a number of cross-cutting areas. Thus, the Plan now also addresses the areas of Racial and Ethnic Minorities; Women and Girls; Microbicides; HIV Prevention Research; International Research; Training, Infrastructure, and Capacity Building; and Information Dissemination. In collaboration with the Director of NIH, the OAR determines the total annual AIDS research budget. Within that total, the OAR establishes the AIDS research budgets for each NIH Institute and Center, in accordance with the priorities and objectives of the plan.

FY 2004 Plan and Budget Request for HIV-Related Research: Research Priorities

This budget request is framed on the scientific priorities and objectives of the NIH FY 2004 Plan for HIV-Related Research. The entire plan can be found on the OAR web site: <http://www.nih.gov/od/oar/public/public.htm#PLAN>. The FY 2004 research agenda continues the following over-arching themes: research to prevent and reduce HIV transmission, including vaccines, microbicides, and behavioral interventions; research to develop therapies for those who are already infected; international research, particularly to address the pandemic in developing countries; and biomedical and behavioral research targeting the disproportionate impact of AIDS on minority populations in the United States. These efforts all require a strong foundation of basic science. The key priorities for each research area of the plan and directions for future research are summarized below.

1. "Intelligence Community Assessment: The Next Wave of HIV/AIDS: Nigeria, Ethiopia, Russia, India, and China." (CIA, 2002).
2. "The Future of AIDS," *Foreign Affairs*, November/December 2002.
3. "Report on the Global HIV/AIDS Epidemic: July 2002," (UNAIDS/WHO, Geneva, Switzerland, 2002).
4. A. de Waal, "What AIDS Means in a Famine," *New York Times*, 11/19/02.
5. *Morbidity and Mortality Weekly Report*, 50, 434 (CDC, 2001).
6. "Centers for Disease Control and Prevention HIV Prevention Strategic Plan Through 2005," (CDC, 2001).
7. "HIV/AIDS Update – A Glance at the HIV Epidemic," (CDC, 2001).
8. "U.S. HIV and AIDS Cases Reported through June 2000," *CDC HIV/AIDS Surveillance Report, Vol. 12* (2000).
9. N. Loder, *Nature* 407, 120 (2000).
10. H. Salomon et al., *AIDS* 14, 17 (2000).
11. Y.K. Chow et al., *Nature* 361, 650 (1993).
12. M. Waldholz, "Drug Resistant HIV Becomes More Widespread," *Wall Street Journal*, 2/5/99.
13. "World Health Report on Infectious Diseases 2000: Overcoming Antimicrobial Resistance," (WHO, Geneva, 2000).
14. "Frequently Asked Questions and Answers About Coinfection with HIV and Hepatitis C Virus" (CDC, 2002).
15. "U.S. HIV and AIDS Cases Reported through Dec. 2001," *CDC HIV/AIDS Surveillance Report, Vol. 13* (2001).

THERAPEUTICS

Research Priorities of the FY 2004 Plan

Development of New Therapeutic Agents and Approaches:

- Advance the discovery and validation of new viral and cellular targets.
- Develop new therapeutic agents that: target drug-resistant virus; have activity in viral reservoirs and cellular compartments; and have improved pharmacologic properties.
- Develop and evaluate therapeutic approaches that will improve and sustain immune function or prevent transmission of HIV infection.

Treatment of Co-Infection:

- Evaluate the effects of co-infection especially with hepatitis B virus (HBV), HCV, or TB, on the management of HIV.

Clinical Evaluation of Therapies:

- Determine optimal therapeutic strategies including when to start (early versus late), change, sequence, or interrupt therapies and evaluate therapeutic drug monitoring strategies.
- Identify regimens with improved toxicity, efficacy, pharmacokinetics, activity in viral reservoirs, adherence potential, and reduced cost.
- Target populations, especially women, IDUs, children, adolescents, older adults, and across racial/ethnic groups. Conduct studies that permit evaluation of potential differences in response to therapy due to gender and/or racial/ethnic differences.
- Perform studies to evaluate the impact of treatment regimens to prevent HIV transmission.

Prevention of Mother-to-Child Transmission:

- Develop safe, effective, feasible, and conveniently administered strategies to interrupt mother-to-child transmission of HIV, including emphasis on transmission through breast-feeding.
- Conduct studies to evaluate and reduce short- and long-term toxicity of antiretroviral drugs in women during pregnancy and their offspring who were perinatally exposed.

International Clinical Research:

- Design and conduct clinical studies that are appropriate for diverse international settings, including studies to improve and facilitate the delivery of therapeutic interventions for HIV disease.
- Evaluate the clinical and public health impact of prophylactic and therapeutic interventions for co-infections/opportunistic infections endemic to international settings.

The development of therapeutics for HIV/AIDS has long been a focus of NIH. Today, many HIV-infected people are living with the benefits resulting from NIH-supported research in this area. The development of combination regimens including protease inhibitors has extended the length and quality of life for many HIV-infected individuals in the United States and Western Europe. Unfortunately, however, antiretroviral therapy (ART) has failed to eradicate HIV, and a growing proportion of patients receiving therapy experience treatment failure. Some patients find it difficult or impossible to comply with arduous treatment regimens, develop toxicities and side-effects, or cannot afford their high cost. Others fail to obtain a satisfactory reduction in viral load

even while adhering to treatment regimens. An increasing number of treatment failures are linked to the increasing emergence of drug-resistant HIV. In addition, metabolic complications, including insulin resistance, and body composition changes such as deforming deposits of abdominal adipose tissue, have emerged in individuals who have been on long-term antiretroviral regimens. These side-effects and complications appear to be increasing as HIV-infected patients continue on the drug regimens. More deaths occurring from liver failure, kidney disease, and cardiovascular complications are being observed in this patient population.

The need for simpler, less toxic, and cheaper drugs and drug regimens to treat HIV infection and its associated coinfections, opportunistic infections (OIs), malignancies, and other complications, continues to be a critical priority. This includes the discovery and development of the next generations of antiviral drugs directed against new cellular and viral targets. Clinical trials will help to better define when to begin and/or switch drugs within a regimen, as well as to identify regimens for treatment-experienced individuals who no longer respond to these anti-HIV drugs. Antiretroviral and OI prophylaxis regimens are becoming increasingly complex with respect to drug-drug interactions and adherence. Protease inhibitors, in particular, interact with each other and many other medications commonly used by HIV-infected individuals. Additional research is under way and planned with the goal of minimizing viral replication and delaying disease progression, drug resistance, and development of manifestations such as metabolic complications and body composition changes. Important studies are planned to evaluate delayed and long-term effects of these antiretroviral drugs.

Studies are answering the following questions: When should ART be initiated? When should they be changed? How long can successful therapies maintain decreased viral loads, increased CD4 counts, and improved clinical outcomes? What is the basis for the emergence of drug resistance, and how can it be prevented? What are the long-term clinical efficacy and tolerability associated with ART? Can treatment strategies be developed for patients who no longer respond to current regimens? Can immune-restorative/immune-enhancing approaches rebuild the immune system, so that disease progression is delayed? Can treatment strategies be developed to eliminate HIV, so that it is not transmitted from an infected individual to others?

Recent advances in therapeutics research underscore the importance of continued and further collaboration of Government- and industry-sponsored drug development research and clinical trials with the common goal of developing therapeutic regimens that slow disease progression, extend life spans, and improve the quality of life for HIV-infected individuals.

ETIOLOGY AND PATHOGENESIS

Research Priorities of the FY 2004 Plan

- Facilitate the translation of new insights into HIV biology to develop novel interventions for the prevention and treatment of HIV infection.
- Elucidate the biologic determinants of HIV transmission between individuals and define the mechanisms by which host factors, viral factors, and co-factors may influence the process of virus transmission.
- Characterize the dynamics of virus-host interaction through the course of HIV infection.
- Investigate the mechanisms of persistence of HIV infection.
- Define the direct and indirect mechanisms that lead to T-cell depletion following HIV infection and the factors that determine numerical and functional reconstitution of T-cell populations in response to therapy.
- Enhance and expand innovative studies of human immunology to guide vaccine development and immune reconstitution efforts.
- Investigate the impact of gender, health status, race, and age on the biology of HIV infection and on the responses to therapies and vaccines.
- Advance the understanding of the mechanisms responsible for the toxicities and long-term complications of ART and the factors that underlie changes in the causes of morbidity and mortality in an era of increasingly effective therapies.

Of paramount importance in our fight against HIV/AIDS is maintaining a strong commitment to basic research. Tremendous progress has been made in understanding the fundamental steps in the life-cycle of HIV, the host-virus relationship, and the clinical manifestations associated with HIV infection and AIDS. Groundbreaking research on basic HIV biology and AIDS pathogenesis has revolutionized the design of drugs, the methodologies for diagnosis, and the monitoring for efficacy of antiviral therapies. In spite of these achievements, we still do not have a clear understanding of major aspects of the virus interaction with the infected individual, the nature of the immune response to the virus, how the virus establishes infection and spreads throughout the body, and its mechanisms of pathogenesis. This basic knowledge is critical for our efforts to prevent and control HIV infection and disease progression. A substantial portion of NIH AIDS-related research will continue to be devoted to basic research. This area of investigation, driven by investigator-initiated research, has provided the constantly advancing knowledge base that permits the development of new applications for the prevention and treatment of disease.

Some of the outstanding questions within the area of etiology and pathogenesis research include: What role do the specific products of HIV (the viral genes and their protein products) play in the viral life cycle in individual cells and within the body of infected individuals? How is HIV transmitted between cells and between individuals? What contribution does the immune system make to controlling the infection and to the disease process? What mechanisms are involved in cell injury and death in the immune, nervous, and other systems that HIV afflicts? What host

factors and cofactors influence the course and outcome of HIV infection? What is the relationship of HIV infection to the associated malignancies, OIs, neurological impairments, and metabolic abnormalities that characterize AIDS?

The dramatic success of effective antiretroviral therapies in reducing plasma viremia to undetectable levels had raised the intriguing possibility that prolonged therapy might lead to virus eradication. However, data have indicated that the virus can persist in the body of HIV-infected patients for almost a lifetime. HIV can persist in a latent reservoir of resting memory CD4 T cells that is established very early after infection and by continuously replicating, albeit at very low levels, even in the presence of antiretroviral therapies that can drive viral load below the limits of detection. Research is focusing on the different mechanisms of viral persistence to understand the reasons for drug failure, to design rational approaches for virus eradication, and to better assess the impact of persistence on HIV transmission and its implications for HIV prevention.

Understanding the normal development and functioning of the human immune system is crucial to our ability to understand the effects of HIV on the immune system and the pathogenesis of AIDS. This understanding also holds the key to designing rational immune reconstitution approaches in persons undergoing antiretroviral treatment and identifying the characteristics of the immune response that are needed for a protective vaccine.

The basic science underlying HIV etiology and pathogenesis research is generally gender neutral. Basic mechanisms of viral replication and pathogenesis are not expected to differ in women and men. However, there are differences in the way HIV infection is transmitted and how the disease is manifested in women and men. Studies have been designed to elucidate the pathogenic mechanisms more commonly observed in women, children, and adolescents infected with HIV. Transmission of HIV from a mother to her infant may occur *in utero* through transplacental passage of virus, during delivery, or after birth through breast-feeding. Many basic research questions associated with maternal-fetal transmission remain unclear and are actively under investigation.

AIDS is associated with a broad spectrum of cancers and tumors. As HIV causes immunosuppression and most AIDS-associated malignancies are strongly associated with viruses, HIV infection provides a unique model to study the interplay of viruses, a dysfunctional immune system, and the development of cancers. Elucidation of the interactive factors involved in the pathogenesis of AIDS-associated malignancies will possibly translate into the identification of new targets for prevention and treatment.

HIV infection results in the progressive damage of the immune systems of infected individuals and makes them susceptible to a diverse collection of bacteria, viruses, fungi, and protozoa that represent the major causes of suffering and death for HIV-infected individuals. Opportunistic infections can affect virtually every tissue and organ system in the body, resulting in severe functional compromise. NIH currently supports a comprehensive portfolio of basic research on the pathogenesis of AIDS-associated OIs.

NATURAL HISTORY AND EPIDEMIOLOGY

Research Priorities of the FY 2004 Plan

- Structure epidemiological studies in domestic and international communities to characterize risk factors for transmission and assess the impact of interventions (antiviral therapy, prevention programs, etc.) on HIV incidence, risk behaviors, and outcomes of infection in adult and pediatric populations.
- Develop and implement studies to provide epidemiologic data that will serve as the basis for intervention trials in domestic and international locales.
- Develop and evaluate accurate, reproducible, and affordable virologic, immunologic, pharmacologic, and genetic assays; measures of adherence to therapy; and markers of recent infection for large-scale use in domestic and international settings.
- Develop, maintain, and effectively utilize domestic and international cohorts, repositories, and nested studies among populations experiencing emerging and ongoing HIV epidemics. Use this approach to increase the understanding of natural history and pathogenesis of HIV infection and disease, including adverse events in the presence of interventions.
- Enhance our understanding of the interactions between the epidemiology, prevention, treatment, and management of HIV and concomitant infections and disorders. Investigate the implications of concomitant infections on immunogenicity and efficacy of HIV vaccine candidates.

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. NIH will continue to support research to examine topics in HIV transmission, HIV/AIDS disease progression (including the occurrence of OIs), malignancies, metabolic complications, neurological and behavioral dysfunctions, and the development of other HIV/AIDS-related conditions. Domestically, as well as internationally, the populations affected by HIV/AIDS are also those most severely affected by the spreading epidemics of sexually transmitted diseases (STDs), TB, and other co-morbidities, such as Hepatitis C. Researchers are studying the effects of viral, host, and other factors on transmission and disease progression. Since biological, pharmacological, psychological, and behavioral factors all potentially influence the impact of antiretroviral therapies on HIV transmission, researchers are evaluating the specific contributions of these factors and their net impact on HIV transmission. Research also is focusing on determining the biological characteristics, sociocultural factors, and health services issues that contribute to the differential dynamics of HIV transmission and disease progression in men, women, and in different racial/ethnic groups. Results from these studies will provide new directions and improvements in HIV/AIDS prevention and care.

NIH will continue to emphasize the importance of epidemiologic cohort studies to investigate the mechanisms of disease progression, the causes of death, and the impact of therapy in changing the

spectrum of HIV disease. The expansion of existing cohorts in the United States will allow the identification of long-term effects of HIV therapy. The assembly of new, representative cohorts, specimen repositories, and databases in developing countries will be important to study key co-factors (e.g., infectious and nutritional) that modify HIV disease. In addition, NIH will foster basic and applied research that will develop inexpensive virologic, immunologic, and genetic assays for use in both domestic and developing country settings.

BEHAVIORAL AND SOCIAL SCIENCE

Research Priorities of the FY 2004 Plan

- Better understand and address through interventions the psychological, social, economic, and cultural dynamics of gender and sexuality that play a role in promoting sexual health or conferring sexual risk related to HIV transmission.
- Investigate new and changing patterns, contexts, and kinds of substance use (injection and other forms of drugs and alcohol) and their implications for HIV transmission, with an emphasis on associated sexual risk-taking behaviors.
- Understand and address the disparate risks and consequences of HIV infection, as well as access, utilization, and quality of prevention and health care services among individuals and groups differing by socioeconomic status, geographic location, gender, sexual orientation, age, and ethnicity.
- Identify and address issues related to the initiation, sustainability, and renewal of HIV/AIDS risk reduction efforts at the individual, dyadic, group, and community levels over time, including changing perceptions and risk behaviors associated with the development of new HIV treatments, healthcare services, and prevention technologies.
- Conduct and support operational and health services research to better understand and address, through interventions, barriers to, and facilitators of, the implementation of science-based HIV/AIDS interventions at the local community level.
- Support research on the social, structural, and environmental factors and contexts that contribute to the co-occurrence of HIV/AIDS, other infectious diseases (e.g., TB, STDs, hepatitis), substance use, mental illness, and homelessness; and support intervention research to address such co-occurring conditions.
- Support the development of methods and models for assessing the synergistic effects of HIV preventive interventions in a community or society.

NIH supports research to further our understanding of how to change the behaviors that lead to HIV transmission—including preventing their initiation—and how to maintain protective behaviors once they are adopted in all populations at risk. NIH also supports research on preventing and mitigating the psychosocial consequences of HIV/AIDS on individuals and communities. NIH sponsors research related to: developing, implementing, and evaluating behavioral and social interventions to reduce HIV transmission in a range of populations and settings; strengthening our understanding of the determinants, trends, and processes of

HIV-related risk behaviors and the consequences of HIV infection; developing and evaluating behavioral strategies for preventing or ameliorating the negative physical, psychological, and social consequences of HIV infection; and improving the research methodologies employed in behavioral and social science research.

A better understanding of social and cultural factors that contribute to HIV risk or protection, particularly in minority communities, will contribute to the successful implementation of a broader range of preventive or therapeutic measures. Drug users and their sex partners are the fastest growing segment of AIDS cases in the U.S. and in many other countries. Priority is being given to research that bridges and builds upon studies of the phenomenon of addiction itself, the complex interaction of alcohol use, drug use, and poor impulse control, and to developing effective HIV-related interventions from that knowledge base.

The development of new and more effective anti-HIV drugs and drug combinations has raised a host of behavioral issues with significant implications for HIV prevention and treatment. The number of drugs and frequency of dosing require strict adherence to regimens that may be difficult for many people to achieve. Lack of complete adherence 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. These issues highlight the importance of research on how best to ensure adherence to both pharmacological and behavioral HIV-related interventions.

VACCINES

Research Priorities of the FY 2004 Plan

- Test novel approaches to induce broadly cross-reactive antibodies against HIV-1 envelope in small animals and in human clinical trials; advance promising candidates into comparative testing; develop new facilities to produce candidates in accordance with Good Manufacturing Processes (GMP).
- Establish infrastructure to enroll study populations in vaccine clinical trials, including adolescents; address ethical and legal concerns; and foster academic-private sector partnerships.
- Expand access to nonhuman primates for studies of HIV/AIDS vaccines, with emphasis on models that employ alternatives to rhesus macaques; support collaborative studies and reagent development in additional species.
- Examine multi-clade and clade-specific HIV vaccines to ensure world-wide efficacy; evaluate cross-clade immune responses; develop standardized assays, quality assurance programs, and quality control of reagent panels for preclinical and clinical studies.

Safe and efficacious vaccines to prevent HIV infection and disease and/or transmission are essential for global control of the AIDS pandemic. As a result of increased funding from NIH in the area of HIV vaccines, many new approaches to HIV vaccines are being pursued. Basic research in vaccine design and studies of immune responses in small animals and nonhuman primates (NHP) as well as vaccine product development are underway. Recent HIV vaccine research studies in animal models have provided strong scientific rationales to further explore and develop several vaccine concepts and to move additional candidate vaccines into clinical testing. Although production of candidate vaccines for clinical study has proceeded slowly, at least 10 new candidate vaccines will enter Phase I trials in the next 2 years. Several new combinations of products, which are expected to provide better immune responses, also will be tested in Phase I or II trials. The Dale and Betty Bumpers Vaccine Research Center recently launched the first Phase I clinical trials of a multi-clade, multi-gene vaccine candidate.

NIH continues to increase support for a broad program encompassing basic, preclinical, and clinical research on candidate vaccine products. As promising candidates move further in the vaccine pipeline, expanded trials with populations at increased risk for HIV infection will become increasingly important. HIV/AIDS vaccine research requires trained health care, medical research, and prevention specialists, as well as populations at risk who will be integrally involved in the development of vaccine candidates and clinical vaccine and prevention trials. International and domestic sites are being developed, including a cadre of trained personnel, to conduct vaccine trials.

One of the foremost priorities for testing candidate vaccines continues to be a resolution of the crisis in the supply of monkeys available for HIV/AIDS vaccine studies. The supply of NHP, particularly rhesus macaques, for AIDS research and other areas of biomedical research remains a major problem for NIH-funded investigators. Both the supply of animals and the available space for conducting experiments that require adequately controlled biosafety housing are limiting and impeding exploration of new concepts in HIV vaccines. NIH is working to find solutions to these obstacles.

The development of an HIV vaccine is a complex research challenge because HIV is unusually well-equipped to elude immune defenses, as exemplified by its ability to vary extensively, to persist in viral reservoirs, and to eventually overcome the immune system. Many different vaccine approaches are being pursued. Initial studies are leading to more advanced vaccine candidates that may provide better protection. NIH has now conducted, in collaboration with academic investigators and industry co-sponsorship, more than 50 Phase I and two Phase II clinical trials of more than 30 vaccine products, individually or in combination, in human volunteers in collaboration with academic investigators and industry co-sponsorship.

MICROBICIDES

Research Priorities of the FY 2004 Plan

- Foster the development of varieties of endogenous and exogenous microbicide products that are based on specific biological and physiological pathways involving mucosal routes of HIV transmission.
- Promote innovative mechanisms of funding to attract additional investigators to undertake multidisciplinary research on the discovery and development of microbicides.
- Identify relevant practical and accessible methodologies to assess preclinical/clinical safety and activity of microbicides in a standardized manner.
- Foster the development of combination approaches in acceptable formulations to prevent transmission and acquisition of HIV and other sexually transmitted diseases, such as chemical and physical barriers, and microbicides with different specificities and mechanisms of action.
- Promote innovative methods to develop and assess acceptable formulations and modes of delivery for microbicides, bridging knowledge and applications from multiple scientific disciplines.
- Expand capacity (infrastructure and human resources) and strengthen coordination to conduct Phase II/III microbicide clinical trials.
- Conduct social and behavioral research in concert with microbicide clinical trials, including research on product use, sexual behaviors, and the identification of reliable and valid behavioral assessments for the use of microbicides in trials.

The vulnerability of women to acquiring HIV infection requires the development of effective and acceptable female-controlled chemical and physical barrier methods, such as topical microbicides, to reduce HIV transmission. NIH supports a comprehensive research program that includes the screening, discovery, development, preclinical *in vitro* and *in vivo* testing, and clinical evaluation of compounds with the potential to act as antimicrobial agents with both spermicidal and nonspermicidal activity. NIH closely collaborates with academia and industry to identify and explore new and existing compounds as potential topical microbicide agents.

Animal model testing and toxicity studies of potential candidate compounds are conducted through NIH-sponsored contracts before these agents are considered for clinical trials. NIH also supports Phase I, II, and III clinical trials of various topical microbicides, as well as behavioral and social research on the acceptability and use of microbicides among different populations. Important areas of research include the establishment of clinical trial sites and the necessary infrastructure to conduct those trials, especially in developing countries; the development of criteria for selecting potential products to be evaluated in clinical trials and for advancing them through the different phases of clinical studies; and research on ethical and behavioral issues impacting clinical trials.

PREVENTION RESEARCH

Research Priorities of the FY 2004 Plan

- Examine the ways in which social, economic, cultural, and environmental conditions, especially stigma and discrimination, contribute to, or create sources of, HIV-related risk; and develop interventions based on this understanding.
- Elucidate the effects of HIV/AIDS treatment availability, delivery, success, and failure—including associated drug adherence and drug resistance—on HIV transmission and acquisition.
- Support research on methodologies for developing, implementing, and assessing multidisciplinary, multilevel, multimethod, and cross-cultural HIV preventive interventions.
- Investigate the psychological, social, and other variables that contribute to the maintenance or erosion of protective attitudes, beliefs, and behaviors previously achieved through HIV prevention efforts.
- Further explore, develop, and evaluate alternative methods to the randomized controlled trial (RCT) for testing the efficacy of HIV preventive interventions when RCTs are inappropriate or impossible to conduct; and develop guidelines for the appropriate use of such methods.
- In collaboration with other governmental and nongovernmental organizations, enhance support for operations research and health services research on the design, adaptation, testing, and evaluation of evidence-based strategies to deliver HIV prevention services.

NIH supports a comprehensive approach to HIV prevention research that includes contributions from the biomedical, behavioral, and social sciences. The NIH prevention science research agenda targets interventions to both infected and uninfected at-risk individuals to reduce HIV transmission.

Biomedical prevention research priorities include the development of topical microbicides, strategies to prevent mother-to-child transmission (including a better understanding of risk associated breast-feeding), and management of sexually transmitted diseases. NIH also supports behavioral research strategies, including prevention interventions related to drug and alcohol use and risky sexual behaviors. Research efforts continue to identify the most appropriate intervention strategies for different populations and sub-epidemics in the United States and around the world.

NIH's HIV prevention research activities include both basic and intervention studies. Research that elucidates the fundamental mechanisms of human behavior and disease transmission and progression provides the essential basic knowledge needed for the development of testable interventions. Studies examine the range and interaction of biological, neurological, psychological, familial, social network, and other environmental factors that have an impact on HIV transmission, acquisition, or protection. While the focus of the NIH HIV prevention research program is on primary prevention of new HIV infections, it also addresses secondary prevention, that is, prevention of the negative physiological, psychological, and social consequences of disease among individuals already infected with HIV and their families, networks, and communities. This includes identifying potential co-factors, correlates, and mediators of disease progression, and developing biomedical and/or psychosocial interventions to address them.

RACIAL AND ETHNIC MINORITIES

Research Priorities of the FY 2004 Plan

- Increase research on the causes of health disparities in HIV/AIDS and develop effective interventions to reduce these disparities.
- Increase the number of NIH-funded minority investigators in HIV/AIDS research to expand their critical mass.
- Increase the capacity for multidisciplinary HIV/AIDS research in minority institutions and minority communities through a sustained and developmentally staged program.
- Include racial and ethnic minorities in prevention, therapeutic, and vaccine clinical trials in numbers that reflect the current epidemic trends and that address the research questions relevant to racial and ethnic minorities.
- Develop, pilot, and evaluate effective interventions to prevent and reduce HIV transmission and its comorbidities, as well as HIV-related health disparities in racial and ethnic minorities.
- Increase information dissemination and technology transfer to racial and ethnic minority communities and community-based organizations, with the explicit goal of increasing their capacity to utilize HIV-related research in meeting their specific needs.
- Study approaches to treatment and adherence that impact health outcomes in racial and ethnic minority communities.

HIV infection, like many other disease states, reflects the ongoing health disparity among racial and ethnic minority communities. HIV seroprevalence in racial and ethnic minority communities is disproportionately higher than in majority communities. In many U.S. urban centers, HIV seroprevalence mimics rates found in the developing world. These findings, along with the resurgence of sexually transmitted infections and associated high-risk behaviors, demonstrate the need for comprehensive strategies to decrease HIV transmission in affected vulnerable populations, and improve treatment options and treatment outcomes.

NIH is directing increased resources toward research to develop new interventions that will have the greatest impact on these groups. These include interventions that address the co-occurrence of other STDs, hepatitis, drug abuse, and mental illness; and interventions that consider the role of culture, family, and other social factors in the transmission and prevention of these disorders in minority communities. NIH is making significant investments to improve research infrastructure and training opportunities for minorities and will continue to assure the participation of minority participants in AIDS clinical trials, as well as in natural history, epidemiologic, and prevention studies. NIH has provided additional funds to projects aimed at increasing the number of minority investigators conducting behavioral and clinical research; targeting the links between substance abuse, sexual behaviors, and HIV infection; increasing outreach education programs targeting minority physicians and at-risk populations; and expanding the portfolio of population-based research. One of these projects is a series of Training and Career Development Workshops for racial and ethnic minority investigators. These workshops provide minority investigators with an opportunity to learn more about available NIH funding mechanisms and to meet and network with senior minority investigators who receive significant levels of NIH funding.

NIH supports a broad array of behavioral intervention studies with specific focus on African American populations. These studies are characterizing the disease process in drug users, factors influencing disease progression, consequences of multiple co-infections, effectiveness of therapeutic regimens, and the impact of health care access and adherence to therapeutic regimens on disease outcomes. The increasing number of minority AIDS cases underscores the importance of research to define and utilize cultural, social, and contextual factors that affect HIV risk behaviors. The role of alcohol and drug use in facilitating HIV transmission through social networks in all communities also is being explored within these social frameworks.

WOMEN AND GIRLS

Research Priorities of the FY 2004 Plan

- Study the biology of the reproductive tract of HIV-infected and uninfected women and girls, integrating studies of physiology, immunology, and anatomy.
- Elucidate a range of host-virus interactions through the course of HIV infection (in particular, during primary HIV infection) and across the life cycle in women and girls.
- Develop and conduct clinical studies including biological, therapeutic, vaccine, natural history, epidemiological, behavioral, and social science to ascertain the effects of sex and gender in HIV infection among women and girls.
- Enhance basic behavioral and social science research (theoretical and methodological) on gender construction, maintenance, dynamics, and consequences; and integrate this work into the design and evaluation of HIV prevention and care interventions.
- Conduct research on stigma and discrimination associated both with being female and with HIV/AIDS; and integrate this work into interventions to reduce such stigma and its consequences for HIV prevention and care.
- Explore factors that influence adoption, use, and effectiveness of women-controlled methods (including physical and chemical barrier methods), alone or in combination, for preventing HIV transmission and acquisition.
- Support research to identify effective strategies to improve dissemination and uptake of information from HIV/AIDS research to women and girls and to individuals, communities, and organizations.
- Enhance opportunities and mechanisms for recruiting and training biomedical, behavioral, and social scientists in the conduct of interdisciplinary sex and gender analyses in HIV/AIDS research.

Women experience HIV/AIDS differently from men both physiologically and socially. NIH research has demonstrated that women progress to AIDS at lower viral load levels and higher CD4 counts than do men. This finding may have implications for care and treatment of HIV-infected women, particularly with ART. Women's childbearing capacity also differentiates their HIV/AIDS experiences from men's, as HIV-infected pregnant women may transmit the virus to their fetuses and infants. Women in most societies are the primary care providers for children and older people, so their early deaths from AIDS and its complications often leave dependents with no one to care for them. NIH researchers are studying the ways in which sex and gender confer vulnerability to, or protection from, HIV infection and AIDS among women and girls—in general, and relative to men—in diverse geographical settings and during different stages of the life course. There are many research questions that remain unanswered about specific anatomical and physiological characteristics of women and girls that might play a role in transmission, acquisition, or resistance to

HIV infection. Studies will focus on factors in HIV acquisition, including the influence of hormonal modulation on viral replication and immune responses in the reproductive tract, and co-factors, such as coincident infections with other STD pathogens.

INTERNATIONAL AIDS RESEARCH

Research Priorities of the FY 2004 Plan

- Develop in-country research and training infrastructure for the conduct of effective prevention and treatment interventions research, integrating new activities into existing health care and prevention services where possible.
- Facilitate the rapid initiation of studies on the rational use and feasibility of ART in resource-diverse settings.
- Define the spectrum of HIV-related illness in diverse geographic settings and develop effective prevention and treatment interventions to limit its impact.
- Support studies to develop prevention interventions, addressing drug and alcohol use and their associated risks in transmitting and acquiring HIV infection.
- Study the interrelationships between stigma and health behaviors, such as seeking and/or utilizing prevention and treatment interventions, and devise strategies to improve access to and uptake of interventions.
- Develop capacity and support for operational and health services research to facilitate the translation of research findings to clinical practice and public health programs in resource-diverse settings.
- Address ethical, legal, and human rights challenges in research and implementation of research findings in resource-diverse settings.

The UNAIDS report, *AIDS Epidemic Update: December 2001*, states that “AIDS has become the most devastating disease humankind has ever faced.” HIV/AIDS is the fourth largest killer worldwide; in sub-Saharan Africa, it is the leading cause of death. The impact of AIDS on the developing nations of Africa, Asia, Europe, and Latin America is staggering, with even greater potential disaster to come. The cost in lost productivity and profitability, sickness and death, and a significant reduction in the skilled workforce in developing countries will have major economic impact for the United States and the world economy and security.

Since the early days of the epidemic, NIH has supported research efforts in countries impacted by HIV and AIDS. Beginning in 1984 with a research project in Haiti and the establishment of Projet SIDA in 1985 in what was then Zaire, NIH has maintained a strong international research portfolio. NIH has expanded its research effort to encompass approximately 85 countries around the world. Results of this research benefit not only the people in countries where the research is conducted, but people affected by HIV/AIDS worldwide. NIH international research includes efforts to develop: HIV vaccine candidates and chemical and physical barrier methods, such as microbicides, to prevent sexual transmission; behavioral strategies targeted to the individual, family, and community to alter risk behaviors associated with sexual activity and drug and alcohol use; drug and non-drug

strategies to prevent mother-to-child transmission (MTCT); therapeutics for HIV-related co-infections and other conditions; and approaches to using ART in resource-poor settings. Before prevention and treatment interventions can be implemented in different geographic settings, their safety must be confirmed and efficacy demonstrated in such settings through clinical trials and other intervention research.

To develop vaccines and other prevention strategies that will be effective globally, phase I safety studies are first conducted in small populations in the U.S. However, in order to establish efficacy, large numbers of at-risk study participants are necessary. Around the world, the predominant mode HIV transmission is heterosexual. Among heterosexuals in the United States, the rate of HIV infection is estimated to be approximately 1.5 percent. In some developing country populations, the rate of heterosexual HIV infection is 13-25 percent. Because of the large populations at high-risk of infection, prevention studies can be more efficiently conducted in developing countries.

Although industrialized nations have experienced a dramatic decrease in transmission of HIV from infected mother to her child, preventing this transmission is a significant challenge in resource-poor settings of the world; strategies that can effectively be used in such settings continue to be pursued. Research also is needed to devise strategies to decrease transmission in medical settings.

Development of a research infrastructure is essential to these programs. Specific international infrastructure needs include: (1) developing research sites through establishment of stable, targeted cohorts, development of recruitment strategies, and enhancement of laboratory, clinical, and data management capabilities; (2) increasing the number of scientists, clinicians, and health care workers trained in basic, clinical, and behavioral research, data management, and ethical considerations; (3) developing research collaborations; and (4) transferring appropriate clinical and laboratory technologies.

The Global AIDS Research Strategy Group, co-chaired by the Director of OAR and the Director of NIAID, provides a forum for discussion of current and planned international HIV research efforts, key scientific policy and bioethics issues in international research, and exchange of scientific information. The Group includes representatives of the NIH institutes with major international AIDS research portfolios, other federal agencies, departments, and international organizations.

TRAINING, INFRASTRUCTURE, AND CAPACITY BUILDING

Research Priorities of the FY 2004 Plan

- Continue to support training of domestic and international biomedical and behavioral AIDS researchers, including programs designed to recruit individuals from minority communities into research careers and to build research infrastructure in minority institutions.
- Continue to support improvement of facilities and equipment for the conduct of domestic and international AIDS research, including support of animal facilities for animal model research.

The NIH will continue to support training of domestic and international biomedical and behavioral AIDS researchers, as well as the improvement of facilities and equipment for the conduct of AIDS-related research, including support of animal facilities for animal model research. Numerous NIH-funded programs have increased the number of training positions for AIDS-related research, including programs specifically designed to recruit individuals from minority communities into research careers and to build research infrastructure in minority institutions. The NIH Loan Repayment Program (LRP) was mandated by Congress under Public Law 100-607 in 1988 and authorized under 42 USC 288-1 to encourage health professionals to engage in AIDS-related research at the NIH. NIH also sponsors programs to train scientists in developing countries to undertake AIDS research. The National Primate Research Centers (NPRC) Program, provides specialized facilities, scientific and technical personnel, animal models research and breeding, and a wide variety of non-human primate species to support diverse requirements for AIDS-related research.

INFORMATION DISSEMINATION

Research Priorities of the FY 2004 Plan

- Continue to support effective information dissemination approaches among researchers, health care providers, and affected communities to rapidly translate research findings into practice.

Effective information dissemination approaches will continue to be integral to HIV prevention and treatment efforts. Such programs are critical in light of the continuing advent of new and complex antiretroviral treatment regimens, the adherence issues related to HIV/AIDS treatment, the need for research communities to work and communicate globally, 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 minorities and women, also underscore the need to disseminate HIV research findings and other related information to communities at risk. The flow of information among researchers, health care providers, and the affected communities represents new opportunities to rapidly translate research results into practice and to shape future research directions.

AIDS Research Benefits Other Diseases

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.

NATIONAL INSTITUTES OF HEALTH

Office of AIDS Research
SUMMARY BY BUDGET MECHANISM

| MECHANISM | FY 2002 Actual | | FY 2003 Amended President's Budget | | FY 2004 Estimate | |
|---|----------------|--------------------------|---------------------------------------|--------------------------|------------------|--------------------------|
| | No. | Amount | No. | Amount | No. | Amount |
| Research Grants: | | | | | | |
| <u>Research Projects</u> | | | | | | |
| Noncompeting | 2,170 | \$1,089,975,000 | 2,256 | \$1,156,699,000 | 2,349 | \$1,208,036,000 |
| Administrative supplements | (215) | 24,465,000 | (121) | 18,444,000 | (114) | 18,383,000 |
| Full Funded | 0 | 0 | 0 | 0 | 4 | 2,539,000 |
| Single Year | 741 | 315,181,000 | 852 | 371,991,000 | 748 | 338,388,000 |
| Subtotal, competing | 741 | 315,181,000 | 852 | 371,991,000 | 752 | 340,927,000 |
| Subtotal, RPGs | 2,911 | 1,429,621,000 | 3,108 | 1,547,134,000 | 3,101 | 1,567,346,000 |
| SBIR/STTR | 79 | 25,713,000 | 95 | 29,711,000 | 96 | 30,856,000 |
| Subtotal, RPGs | 2,990 | 1,455,334,000 | 3,203 | 1,576,845,000 | 3,197 | 1,598,202,000 |
| <u>Research Centers</u> | | | | | | |
| Specialized/comprehensive | 58 | 92,036,000 | 57 | 97,001,000 | 59 | 104,180,000 |
| Clinical research | 0 | 41,461,000 | 0 | 41,581,000 | 0 | 43,081,000 |
| Biotechnology | 0 | 5,568,000 | 0 | 7,918,000 | 0 | 8,058,000 |
| Comparative medicine | 12 | 41,069,000 | 13 | 42,274,000 | 14 | 45,774,000 |
| Research Centers in Minority Institutions | 0 | 8,936,000 | 0 | 10,732,000 | 0 | 11,336,000 |
| Subtotal, Centers | 70 | 189,070,000 | 70 | 199,506,000 | 73 | 212,429,000 |
| <u>Other Research</u> | | | | | | |
| Research careers | 209 | 25,547,000 | 220 | 27,458,000 | 220 | 28,628,000 |
| Cancer education | 0 | 9,000 | 0 | 25,000 | 0 | 50,000 |
| Cooperative clinical research | 22 | 31,626,000 | 22 | 33,446,000 | 22 | 34,052,000 |
| Biomedical research support | 2 | 3,364,000 | 1 | 1,892,000 | 1 | 1,892,000 |
| Minority biomedical research support | 2 | 1,158,000 | 2 | 1,168,000 | 2 | 1,192,000 |
| Other | 98 | 56,512,000 | 107 | 67,331,000 | 115 | 70,793,000 |
| Subtotal, Other Research | 333 | 118,216,000 | 352 | 131,320,000 | 360 | 136,607,000 |
| Total Research Grants | 3,393 | 1,762,620,000 | 3,625 | 1,907,671,000 | 3,630 | 1,947,238,000 |
| <u>Training</u> | <u>FTTPs</u> | | <u>FTTPs</u> | | <u>FTTPs</u> | |
| Individual awards | 55 | 1,999,000 | 59 | 2,107,000 | 59 | 2,179,000 |
| Institutional awards | 754 | 29,740,000 | 751 | 30,774,000 | 751 | 31,875,000 |
| Total, Training | 809 | 31,739,000 | 810 | 32,881,000 | 810 | 34,054,000 |
| Research & development contracts (SBIR/STTR) | 149 (2) | 279,882,000 (508,000) | 179 (3) | 343,428,000 (600,000) | 187 (3) | 406,364,000 (600,000) |
| Intramural research | | 277,326,000 | | 315,463,000 | | 320,852,000 |
| Research management and support | | 85,032,000 | | 91,280,000 | | 92,931,000 |
| Cancer prevention & control | | 0 | | 0 | | 0 |
| Construction | | 2,803,000 | | 4,000,000 | | 0 |
| Library of Medicine | | 6,677,000 | | 7,177,000 | | 7,477,000 |
| Office of the Director | | 53,379,000 | | 58,040,000 | | 60,942,000 |
| Total, NIH Budget Authority | | 2,499,458,000 | | 2,759,940,000 | | 2,869,858,000 |

NATIONAL INSTITUTES OF HEALTH

Office of AIDS Research

**Spending by the NIH Plan for HIV-Related Research
(dollars in thousands)**

| Research Area | FY 2002 | FY 2003 Amended | FY 2004 | Change |
|---|------------------|-------------------------------|------------------|----------------|
| | Actual | President's Budget | Estimate | |
| Natural History and Epidemiology | \$278,016 | \$301,501 | \$307,930 | \$6,429 |
| Etiology and Pathogenesis | 684,014 | 735,127 | 754,503 | 19,376 |
| Therapeutics | 689,076 | 740,136 | 758,787 | 18,651 |
| Vaccines | 329,423 | 413,607 | 456,291 | 42,684 |
| Behavioral and Social Science | 344,661 | 373,961 | 390,325 | 16,364 |
| Training and Infrastructure | 120,796 | 137,745 | 141,871 | 4,126 |
| Information Dissemination | 53,472 | 57,863 | 60,151 | 2,288 |
| Total, Budget Authority | 2,499,458 | 2,759,940 | 2,869,858 | 109,918 |

National Institutes of Health

Office of AIDS Research

AIDS Funding by Institute and Center

| Institute/Center | FY 2002 Actual | FY 2003 Amended President's Budget | FY 2004 Estimate |
|--------------------------------|-----------------------|---|-------------------------|
| NCI | \$254,252,000 | \$265,009,000 | \$269,615,000 |
| NHLBI | 70,906,000 | 75,380,000 | 75,524,000 |
| NIDCR | 23,267,000 | 24,737,000 | 25,357,000 |
| NIDDK | 25,925,000 | 29,708,000 | 31,024,000 |
| NINDS | 42,166,000 | 45,562,000 | 47,456,000 |
| NIAID | 1,185,660,000 | 1,345,004,000 | 1,407,356,000 |
| NIGMS | 48,391,000 | 52,385,000 | 54,894,000 |
| NICHD | 115,647,000 | 125,985,000 | 131,133,000 |
| NEI | 12,730,000 | 12,777,000 | 12,746,000 |
| NIEHS | 8,248,000 | 8,589,000 | 8,789,000 |
| NIA | 4,985,000 | 5,320,000 | 5,519,000 |
| NIAMS | 6,302,000 | 6,621,000 | 6,759,000 |
| NIDCD | 1,737,000 | 1,738,000 | 1,758,000 |
| NIMH | 163,007,000 | 175,996,000 | 182,390,000 |
| NIDA | 278,372,000 | 303,487,000 | 315,011,000 |
| NIAAA | 23,950,000 | 25,886,000 | 26,944,000 |
| NINR | 10,978,000 | 11,877,000 | 12,155,000 |
| NHGRI | 6,247,000 | 6,641,000 | 6,925,000 |
| NIBIB | 972,000 | 972,000 | 1,062,000 |
| NCRR | 134,791,000 | 146,920,000 | 153,464,000 |
| NCCAM | 2,552,000 | 2,718,000 | 2,818,000 |
| NCMHD | --- | --- | --- |
| FIC | 18,317,000 | 21,411,000 | 22,740,000 |
| NLM | 6,677,000 | 7,177,000 | 7,477,000 |
| OD | 53,379,000 | 58,040,000 | 60,942,000 |
| B&F | --- | --- | --- |
| TOTAL, Budget Authority | 2,499,458,000 | 2,759,940,000 | 2,869,858,000 |