

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 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate	Increase or Decrease
Budget Authority	\$2,920,551,000	\$2,903,664,000	\$2,888,492,000	-\$15,172,000

INTRODUCTION

The Global HIV/AIDS Pandemic

The AIDS pandemic will wreak devastating consequences around the world for decades to come for virtually every sector of society. The pandemic affects the future of families, communities, agriculture, business, healthcare, child development, education, national security, military preparedness, political stability, and national economic growth in countries around the globe. AIDS is the deadliest epidemic of our generation. The United Nations General Assembly's Declaration of Commitment on HIV/AIDS states, "...the global HIV/AIDS epidemic, through its devastating scale and impact, constitutes a global emergency and one of the most formidable challenges to human life and dignity, as well as to the effective enjoyment of human rights, which undermines social and economic development throughout the world and affects all levels of society..."¹ Laurie Garrett, in *Foreign Affairs*, states: "First, HIV/AIDS is the most complex disease humanity has ever faced and presents it with unprecedented challenges of research and analysis. Second, new threats to stability and security may emerge as the pandemic escalates. Third, a well-conceived campaign to curtail the virus, particularly through the development of an effective HIV vaccine, could short circuit the attendant security concerns."²

GLOBAL AIDS PANDEMIC, AS OF THE END OF 2005

- More than 40 million people worldwide are living with HIV/AIDS;
- Approximately 2.3 million are children under the age of 15 years;
- About half of the infected adults are women;
- An estimated 4.9 million people (adults and children) acquired HIV in 2005;
- The global HIV/AIDS epidemic killed more than 3.1 million people in 2005; and
- More than 25 million people have died since the beginning of the epidemic.

Source: UNAIDS

¹The Impact of AIDS (Department of Economic and Social Affairs, United Nations, 2004).

²Garrett, L., The Lessons of HIV/AIDS, *Foreign Affairs*, July/August 2005.

The Epidemic in the United States

The HIV/AIDS epidemic in the United States continues to expand.³ 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.⁴ In addition, use of antiretroviral therapy is now associated with a series of side effects and long-term complications that may have a negative impact on mortality rates. The appearance of multi-drug resistant strains of HIV presents an additional serious public health concern.⁵ 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). HCV progresses more rapidly to liver damage in HIV-infected persons and may also impact the course and management of HIV infection; and HIV may change the natural history and treatment of HCV.⁶

The NIH AIDS Research Program

NIH is the world's leader in AIDS research. NIH supports a comprehensive program of basic, clinical, and behavioral research on HIV infection, its associated co-infections, opportunistic infections, malignancies, and other complications. This represents a unique and complex multi-institute, multi-disciplinary, global research program with the ultimate goals 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. Perhaps no other disease so thoroughly transcends every area of clinical medicine and basic scientific investigation, crossing the boundaries of the NIH Institutes and Centers. This diverse research portfolio demands an unprecedented level of scientific coordination and management of research funds to identify the highest priority areas of scientific opportunity, enhance collaboration, minimize duplication, and ensure that precious research dollars are invested effectively and efficiently. It is the unique role of the Office of AIDS Research (OAR), part of the Office of the Director, to: coordinate the scientific, budgetary, and policy elements of the NIH AIDS program; prepare an annual comprehensive trans-NIH strategic plan and budget for all NIH-sponsored AIDS research; evaluate the AIDS research portfolio; identify and facilitate multi-institute participation in priority areas of research; and facilitate NIH involvement in international AIDS research activities. As such, the OAR represents the roadmap for NIH AIDS research, allowing NIH to pursue a united research front against the pandemic.

Setting the AIDS Research Priorities: Comprehensive Strategic Plan

The 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. 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. The Plan

³Cases of HIV Infection and AIDS in the United States, 2004, CDC HIV/AIDS Surveillance Report (2005).

⁴A Glance at the AIDS Epidemic, CDC (2005).

⁵World Health Report on Infectious Diseases: Overcoming Antimicrobial Resistance," (WHO, 2000).

⁶NIH Consensus Conference Statement: Management of Hepatitis C: 2002, p 76-77.

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. The over-arching themes of the AIDS research plan are: a strong foundation of basic science; research to prevent and reduce HIV transmission, including vaccines, microbicides, and behavioral interventions; research to develop better 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. The Plan establishes 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. The Plan also addresses the crosscutting areas of: Racial and Ethnic Minorities; Women and Girls; Microbicides; HIV Prevention Research; International Research; Training, Infrastructure, and Capacity Building; and Information Dissemination.

Trans-NIH AIDS Research Portfolio Analysis

Last year, OAR initiated a unique, innovative, and essential multi-tiered comprehensive trans-NIH review of all grants and contracts supported with AIDS-designated funds scheduled to re compete in FY 2006. OAR also convened a group of eminent non-government experts to assist in this task, taking into account the evolving scientific opportunities to address the domestic and international AIDS epidemic. This highly successful review provided a new model to ensure that research dollars support the highest priority science. As a result of this review, OAR directed the transfer of funds to better manage the AIDS research portfolio. This process has now been implemented as an integral component of the annual OAR strategic planning and budget processes. In preparation of this FY 2007 budget request, a review was conducted of all grants eligible for renewal in FY 2007. This will allow OAR to further redirect funds to support the highest scientific priorities.

Critical Priorities for FY 2007: Prevention Research

Through the planning and portfolio analysis processes, OAR determined that the highest priorities in FY 2007 are in the area of prevention research. This budget request places the highest priority on prevention research, including development of vaccines and microbicides. The experts who assisted in the portfolio analysis recommended that OAR redirect funds to support new innovative "second generation" prevention strategies, providing seed funds to newer areas of promising investigation to prevent HIV transmission, such as circumcision, early treatment of co-infections, use of antiretroviral therapy as prevention, cervical barrier methods, addiction treatment/substitution therapy, and combination prevention strategies. OAR will provide additional funds to the NIH Institutes and Centers for these new prevention projects.

Trans-NIH AIDS Research Budget

In collaboration with the Director of NIH, the OAR determines the total annual NIH AIDS research budget. Within that total, the OAR establishes the AIDS research budget for each NIH Institute and Center, in accordance with the annual strategic plan. This FY 2007 budget request is framed on the scientific priorities and objectives of the *NIH FY 2007 Plan for HIV-Related Research*, which can be found in its entirety on the OAR Web site:

http://www.nih.gov/od/oar/public/pubs/fy2007/0_Preface.pdf. The key research priorities in each area of the plan follow.

SCIENCE ADVANCES AND NEW INITIATIVES

VACCINES

RESEARCH PRIORITIES OF THE FY 2007 PLAN

- Maintain a vigorous program of basic and preclinical HIV vaccine research emphasizing research on vaccines designed to induce broad immune responses to the HIV envelope.
- Support research on protective immune responses. Develop resources to facilitate comparative vaccine studies.
- Conduct appropriate preparative work in vaccine clinical trial sites, particularly in international settings and minority communities in the United States.
- Provide critical viral and immunological information to inform vaccine trial design while helping to educate communities and high-risk populations while developing a strong, sustainable research infrastructure.

Safe and efficacious vaccines are essential for global control of the AIDS pandemic. As a result of increased NIH vaccine research funding, many new approaches are being pursued. Basic research in vaccine design, studies of immune responses in small animals and non-human primates, and 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.

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. In FY 2005, the NIH funded a new consortium, the Center for HIV/AIDS Vaccine Immunology, to identify the protective immune responses and to test vaccine strategies that might induce protective immune responses. In addition, NIH-funded independent investigators are pursuing many different HIV vaccine approaches. Initial studies are leading to improved vaccine candidates that may provide better protection. NIH has now conducted or initiated approximately 80 Phase I and two Phase II clinical trials of nearly 50 vaccine candidates, individually or in combination, in human volunteers in collaboration with academic investigators and industry co-sponsorship, and with the support of communities and government officials where the trials are being conducted.

Although production of candidate vaccines for clinical study has proceeded slowly in the past, 12 new Phase I and II trials were begun in 2005 that included 5 new products. Several new combinations of products, which are expected to provide better immune responses, are being tested in Phase I or II trials. At least 4-6 new candidate vaccines will enter Phase I trials in the next 2 years. The HIV Vaccine Trials Network working with the NIH Dale and Betty Bumpers Vaccine Research Center recently launched a Phase II clinical trial of a multi-clade, multi-gene vaccine candidate in the Americas. Additional sites in Africa as part of the Partnerships for AIDS Vaccine Evaluation will also study these vaccine candidates, including a site in Kenya supported by the U.S. Military HIV Research Program and a site in Rwanda funded by the International AIDS Vaccine Initiative. Along with multiple collaborators, NIH has initiated a Phase IIb, "proof of concept" trial that will enroll about 3,000 people in the U.S., Caribbean, and the Americas. The Phase III trial of a canarypox vector with a boost of HIV envelop proteins has enrolled more than 14,000 volunteers who will be studied for an additional 2-3 years.

HIV VACCINE RESEARCH ACCOMPLISHMENTS

- More than 50 products or combinations tested in over 80 Phase I and II trials
- More than 17,500 volunteers have participated in HIV vaccine studies
- New vaccine designs developed; 4-6 to enter Phase I clinical trials within 2 years
- A "proof of concept" Phase IIb trial with non-replicating Adenovirus vector and a Phase III trial with a canarypox vector in Thailand are ongoing.
- First multi-gene, multi-clade Phase II trial launched by HIV Vaccine Trials Network and NIH Vaccine Research Center

A key priority for testing candidate vaccines before they enter clinical trials continues to be a resolution of the crisis in the supply of monkeys available for HIV vaccine studies. The supply of non-human primates, particularly rhesus macaques, for AIDS research and other areas of biomedical research remains a 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 studies of new concepts in HIV vaccines. NIH continues to work toward solutions to these obstacles.

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.

THERAPEUTICS

RESEARCH PRIORITIES OF THE FY 2007 PLAN

- Discover and develop new therapeutic agents and regimens that are less toxic, have fewer side effects, permit easier compliance, and are less expensive.
- Determine optimal treatment regimens, including when to start (early versus late), change, sequence, or interrupt therapies and evaluate therapeutic drug monitoring strategies.
- Increase enrollment in clinical trials of women, injecting drug users, children, adolescents, older adults, and racial/ethnic groups. Conduct studies to determine potential differences in response to therapy due to gender and/or racial/ethnic differences.
- Evaluate the long-term effects of therapy and the implications of these findings on public health.
- Develop safe and effective, strategies to interrupt mother-to-child transmission of HIV with a focus on resource-limited settings and on breastfeeding.
- Conduct studies on short- and long-term toxicity of anti-HIV drugs used to prevent HIV transmission in women during pregnancy, and their babies.
- Evaluate the effects of and develop treatments for HIV coinfections, especially hepatitis B virus, hepatitis C virus, tuberculosis, and malaria, on the management of HIV disease.
- Design and conduct clinical studies that are appropriate for diverse international settings.

Many HIV-infected people are living with the benefits resulting from NIH-supported therapeutics research. 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. The use of antiretroviral therapy continues to result in the significant reduction of viral load, increased CD4 cell counts, decreased coinfections, opportunistic infections and certain malignancies, and improved immune function in patients who are able to adhere to the treatment regimens and tolerate the toxicities associated with antiretroviral drugs. A high priority of NIH-sponsored AIDS therapeutics research continues to be the development of better 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. Research is addressing the metabolic complications, including insulin resistance, and body composition changes such as deforming deposits of abdominal adipose tissue, that have emerged in individuals who have been on long-term antiretroviral regimens. More deaths occurring from liver failure, kidney disease, and cardiovascular complications are being observed in this patient population. The global impact and continued spread of the AIDS pandemic in both developed and developing nations underscore the urgent need to develop therapeutic regimens that can be implemented in international settings.

A goal of therapeutic research is to minimize viral replication and delay disease progression, drug resistance, and development of clinical

THERAPEUTICS RESEARCH ACCOMPLISHMENTS

- Extended and improved quality of life for many HIV-infected individuals
- Reduced AIDS deaths
- Decreased morbidity due to opportunistic infections
- Reduced pediatric mortality
- Demonstration that combinations of antiretroviral agents can significantly reduce viral load in many patients to undetectable levels and increase CD4 counts
- Revolution in design and testing of drugs and diagnostic methodologies benefits other diseases
- Findings contributed to approval of AIDS-related therapies by FDA and development of guidelines for their optimal use

complications. Important studies are planned to evaluate delayed and long-term effects of these antiretroviral drugs. An additional challenge is that regimens for antiretroviral therapy and opportunistic infection prophylaxis 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.

The scientific agenda for NIH AIDS therapeutics research is focused on the following questions: Are there new viral and cellular targets against which therapies can be directed? What therapeutic agents and regimens can be developed that target drug-resistant virus? What are the optimal approaches for management of HIV infection, including when to start, change, sequence, or interrupt therapy? What are the effects of these drugs in pregnant and breastfeeding women, and what impact does this have upon the fetus? What is the impact of coinfection or cancer on disease progression and treatment of both HIV and comorbidities such as hepatitis B virus, hepatitis C virus, tuberculosis, or malaria? What are the clinical and public health ramifications of administering antiretroviral therapy in developing countries? Collaboration between Government- and industry-sponsored drug development research and clinical trials is critical to achieve 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 2007 PLAN

- Elucidate the biologic determinants of HIV transmission, and define the mechanisms by which host factors, viral factors, and cofactors may influence the process of virus transmission and dissemination.
- Understand the dynamics of virus-host interaction through the course of HIV infection.
- Investigate the mechanisms of persistence of HIV infection.
- Develop innovative technologies in human and nonhuman primate immunology to guide HIV prevention and immune reconstitution efforts in at-risk and HIV-infected individuals.
- Advance the understanding of the mechanisms responsible for the toxicities and long-term complications of antiretroviral therapy and the factors that underlie changes in the causes of morbidity and mortality in HIV-infected patients in an era of increasingly effective therapies.

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. Maintaining a strong commitment to basic research is of paramount importance in our fight against HIV/AIDS. This research is focused on gaining a better understanding in two areas: (1) how HIV infection is established and maintained; and (2) what causes the profound immune deficiency and severe clinical complications that accompany this infection.

Critical questions in this area are: What role do specific HIV proteins play in the viral life cycle in individual cells and within the bodies of infected individuals? What are the primary modes of HIV transmission 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 organ systems affected by HIV? What host factors and cofactors influence primary infection and the course and outcome of HIV infection? What is the relationship of HIV infection to the associated malignancies, opportunistic infections and coinfections, neurological impairments, and metabolic disturbances that characterize AIDS? This basic knowledge is critical for our efforts to prevent and control HIV infection and disease progression.

ETIOLOGY AND PATHOGENESIS ADVANCES

- Identification of key HIV components as drug targets
- Identification of macromolecular structure of viral components for drug design
- Identification of chemokines as co-receptors
- Identification of viral reservoirs as sites of latent infection

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 viral persistence on HIV transmission and its implications for HIV prevention. 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.

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 system 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 remain one of the most important complications of HIV infection and the principal cause of death in AIDS patients. HIV infection is also associated with multiple endocrine alterations, probably reflecting critical interaction between the endocrine and the immune systems. HIV-associated hematologic, pulmonary, cardiac and vascular, renal, mucocutaneous, bone, and liver complications also represent causes of morbidity in infected subjects. Some of these complications are disproportionally affecting racial groups. The pathogenic mechanisms involved in all of these AIDS manifestations are not well understood and are under investigation. Their definition will permit a more rational approach to both preventive and therapeutic interventions.

NATURAL HISTORY AND EPIDEMIOLOGY

RESEARCH PRIORITIES OF THE FY 2007 PLAN

- Sponsor epidemiologic investigations into the interactions between HIV genetic variability, host genetics, and other factors that influence disease morbidity and mortality, with special emphasis on routes of transmission, chronic and infectious comorbidities and malignancies, and long-term use of antiretroviral therapies.
- Develop, maintain, and effectively utilize domestic and international study populations, repositories, and nested studies of populations experiencing emerging and ongoing HIV epidemics.
- Implement epidemiologic and simulation studies among HIV-infected individuals and appropriate control populations to inform, monitor, and evaluate intervention strategies, including initiation of treatment programs, in domestic and international settings.
- Continue improving key measures to diagnose and monitor HIV/AIDS in diverse settings by encouraging development of and evaluating late-generation laboratory assays. These include accurate, reproducible, and affordable virologic, immunologic, pharmacologic, and genetic assays; measures of adherence to therapy; and markers of toxicity and comorbidity for use in domestic and international settings.

The demographics of the AIDS epidemic in the United States, and in many other industrialized countries, have changed. New HIV infections now occur more frequently in racial and ethnic minorities, groups with high-risk sexual behaviors, injecting drug users, and adolescents. The use of potent antiretroviral therapy has delayed the progression of HIV disease, extending the time between HIV infection and development of AIDS. A more complex pathology, however, is being uncovered as HIV-infected people live longer and develop age-related comorbidities. In addition, while effective in improving the health of many HIV-infected people, antiretroviral therapy has been associated with a wide variety of undesired effects in many organ systems. Epidemiologic research has been instrumental in identifying and describing such effects, disentangling effects related to treatment from those related to HIV disease itself. Since the beginning of the HIV epidemic, NIH-supported epidemiologic research has also played a key role in elucidating the interplay of virus, host, and environment. However, the changing face of the epidemic, with new

NATURAL HISTORY AND EPIDEMIOLOGY RESEARCH ACCOMPLISHMENTS

- CD4 and viral load established as biomarkers for disease progression and response to therapy
- Gender differences in disease progression: women progress to AIDS at lower viral load levels than men
- Regimens to prevent opportunistic infections initiated at 200 CD4 level or less
- Presence of hepatitis G virus predicts survival

groups and populations being affected, requires that rigorous epidemiologic studies be conducted in those different settings.

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 opportunistic infections), malignancies, metabolic complications, neurological and behavioral dysfunctions, and the development of other HIV/AIDS-related conditions.

Worldwide, studies have shown a global spread of an epidemic mostly fueled by heterosexual transmission and, in some geographic areas, augmented by injecting drug use. The rollout of antiretroviral treatment initiatives is slowly increasing. Thus, antiretroviral treatment is now becoming a more frequent backdrop in places where research on HIV/AIDS is being conducted. NIH-supported research on HIV/AIDS can play a major role in providing the scientific basis for the implementation of treatment and prevention programs. Well-designed epidemiological studies are a key component of such research, as they help to characterize local epidemics; the respective effects of viral, host, and environmental factors on HIV transmission and disease progression; and the measurable effects of antiretroviral therapy. In addition, translational research will help define the optimal parameters of treatment and care to achieve the best outcomes. NIH will continue to emphasize the importance of epidemiologic studies to investigate the mechanisms of disease progression, the causes of death, and the impact of therapy in changing the spectrum of HIV disease.

MICROBICIDES

RESEARCH PRIORITIES OF THE FY 2007 PLAN

- Foster the development of chemically and biologically derived microbicides that have the potential to interact with the pathways involved in HIV transmission across the epithelia.
- Identify and standardize methodologies to assess safety and activity of microbicides.
- Foster the development of combination approaches and of microbicides containing multiple active compounds with different chemical classes, specificities, and mechanisms of action.
- Promote innovative methods to develop and assess formulations and modes of delivery for microbicides.
- Expand capacity (infrastructure and human resources) and strengthen coordination to conduct Phase I/II/III microbicides clinical trials.
- Conduct social and behavioral research in concert with microbicides clinical trials, including research on product use, user acceptability, sexual behaviors, and the identification and development of reliable and valid behavioral tools and measurement techniques for use in trials.
- Promote innovative mechanisms of funding to attract additional investigators to undertake multidisciplinary research on microbicides discovery and development.

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 microbicidal agents.

The Office of AIDS Research coordinates microbicide research across the NIH, and with other federal agencies providing administrative accountability and funding coordination for this important research area.

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.

RESEARCH PRIORITIES OF THE FY 2007 PLAN

- Develop and test comprehensive behavioral models for risk of HIV transmission and acquisition.
- Elucidate new and changing patterns, contexts, and kinds of drug and alcohol use and their implications for HIV transmission and acquisition, either directly or as mediators of sexual behavior.
- Develop and evaluate methods of intervening to reduce HIV acquisition and transmission associated with drug and alcohol use.
- Develop and evaluate methods of intervening to reduce HIV acquisition and transmission associated with sexual behavior, using methods that recognize the implications of technological advances in medicine (e.g., rapid HIV testing, medications to treat sexual dysfunction) and changes in medical practice (e.g., simplified dosing regimens, routine and universal testing).
- Support research on the interactions among factors that contribute to the concurrence of HIV/AIDS and other medical disorders (e.g., infectious diseases, substance abuse) and social problems, and develop interventions to address the co-occurring conditions.
- Improve understanding of health disparities in consequences and of care for HIV infection in various subpopulations and of the stigma associated with HIV/AIDS.

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 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 methodologies employed in behavioral and social science research. A better understanding of social and cultural factors associated with HIV risk or protection, particularly in minority communities, will contribute to the successful implementation of a broader range of preventive or therapeutic measures. 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. 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. These issues highlight the importance of research on how best to ensure adherence to both pharmacological and behavioral HIV-related interventions.

PREVENTION RESEARCH

RESEARCH PRIORITIES OF THE FY 2007 PLAN

- Examine social, economic, cultural, and environmental conditions, including stigma and discrimination, that contribute to, or create sources of, HIV-related risk; and develop interventions based on this understanding.
- Examine factors associated with the initiation and sustainability of HIV prevention efforts among individuals and communities over time, as well as factors that may impede consistent HIV risk reduction practices.
- Elucidate the effects of HIV/AIDS treatment availability, delivery, success, and failure on HIV transmission and acquisition, and the integration of prevention into clinical care.
- Further develop and evaluate alternative methods to the randomized controlled trial (RCT) for testing the efficacy of multidisciplinary HIV preventive interventions when RCTs are inappropriate or impossible to conduct.
- In collaboration with other governmental and nongovernmental organizations, enhance support for operations, health services, and evaluation research on the design, adaptation, testing, and implementation of evidence-based HIV prevention strategies; and assess the impact of such strategies on risk behaviors at the population level.

NIH supports a comprehensive prevention science research agenda that 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 HIV risk associated with breast-feeding), and management of sexually transmitted diseases. NIH behavioral research strategies include 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.

These 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 HIV-infected individuals 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.

PREVENTION RESEARCH AGENDA

- Vaccines
- Microbicides
- Behavioral research
- Reducing transmission due to substance abuse
- Sexually transmitted diseases control
- Prevention of mother-to-child transmission
- Antiretroviral therapy as prevention
- "Second generation" prevention strategies

RACIAL AND ETHNIC MINORITIES

RESEARCH PRIORITIES OF THE FY 2007 PLAN

- Include racial and ethnic minorities in clinical research in numbers that reflect their representation in the HIV epidemic.
- Enhance the capacity of minority investigators, minority institutions, and minority community-based organizations to conduct multidisciplinary HIV research
 - Identify biomedical, sociocultural, and structural determinants, pathways, and mechanisms that maintain or perpetuate health disparities.
- Develop and test innovative models, research methods, and measures of risk behavior in racial and ethnic minority areas.
- Identify and address the specific aspects and impact of HIV infection upon Native American and Alaska Native communities, with particular attention to the epidemiologic, sociocultural, and psychosocial antecedents and effects.
- Examine the effectiveness of therapeutic interventions in racial and ethnic minorities, as well as adherence to therapeutic regimens within the sociocultural context of the populations affected.

HIV infection, like many other disease states, reflects the ongoing health disparities among racial and ethnic minority communities. Prevalence of HIV infection in racial and ethnic minority communities is disproportionately higher than in majority communities. In many U.S. urban centers, the prevalence of HIV infection mimics rates found in the developing world. These findings, along with the resurgence of sexually transmitted diseases (that have been shown to increase the risk of HIV transmission and acquisition) and associated high-risk behaviors, underscore 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 interventions that will have the greatest impact on these groups. These include interventions that address the co-occurrence of other sexually transmitted diseases, 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.

NIH is making significant investments to improve research infrastructure and training opportunities for minorities and will continue to assure the participation of minorities 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.

INITIATIVES TARGETING MINORITY COMMUNITIES

- Minority-targeted research, primarily prevention
- Initiatives to increase minority enrollment in clinical studies
- Minority training, infrastructure, and research capacity-building initiatives
- Grantsmanship workshops for minority researchers
- Regional Technology Transfer Program
- Community outreach programs

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 AIDS cases among minorities 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 2007 PLAN

- Study the biology of the reproductive tract of HIV-infected and HIV-uninfected women and girls, integrating studies of physiology, pharmacology, immunology, microbiology, and anatomy.
- Elucidate a range of host-virus interactions through the course of HIV infection in women and girls.
- Develop and continue clinical studies to ascertain the effects of sex and gender in HIV infection and response to treatment among women and girls.
- Explore factors that influence development, adoption, use, and effectiveness of women-controlled methods for preventing HIV transmission and acquisition.
- Integrate basic behavioral and social science research on gender into the design and evaluation of HIV prevention and care interventions.
- 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 antiretroviral therapy. 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 sexually transmitted disease pathogens.

INTERNATIONAL AIDS RESEARCH

RESEARCH PRIORITIES OF THE FY 2007 PLAN

- Develop in-country research and training infrastructure.
- Conduct research to identify a comprehensive set of effective, appropriate, and sustainable interventions to curtail HIV transmission.
- Conduct both experimental and observational research to identify appropriate care and treatment strategies to limit the impact of HIV-related disease.
- Examine the interactions among aspects of treatment and prevention, including the impact of therapy on the HIV epidemic.

Since the early days of the epidemic, NIH has supported research efforts in countries affected 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 AIDS research portfolio. NIH has expanded its research effort to encompass approximately 90 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-sponsored 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; therapeutics for HIV-related coinfections and other conditions; and approaches to using antiretroviral therapy 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. To establish efficacy, large numbers of at-risk study participants are necessary. Because of the large populations at high risk of infection, prevention studies can be more efficiently conducted in those settings.

NEW CHALLENGE: CLINICAL EVALUATION OF THERAPIES IN INTERNATIONAL SETTINGS

- Expand therapeutic studies into international sites
- Develop research capacity and infrastructure
- Design studies to improve and facilitate delivery of therapeutic interventions
- Evaluate clinical and public health impact of antiretroviral treatment
- Integrate therapeutic regimens and prevention interventions

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.

Development of a research infrastructure is essential to these research 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.

TRAINING, INFRASTRUCTURE, AND INFORMATION DISSEMINATION

RESEARCH PRIORITIES OF THE FY 2007 PLAN

- Continue to support training of domestic and international biomedical and behavioral AIDS researchers.
- Continue to support improvement of infrastructure of research sites for the conduct of domestic and international AIDS research, including support of facilities for animal model research.
- Continue to support effective information dissemination approaches among researchers, health care providers, and affected communities to rapidly translate research findings into practice.

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 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 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.

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 DISEASE RESEARCH EFFORTS

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.

Program Assessment Rating Tool (PART): Assessment of NIH AIDS Program

The NIH AIDS research program received an overall score of 83 in the OMB's FY 2005 Program Assessment Rating Tool (PART). This score included a 100 percent in the Program Purpose and Design section. PART demonstrated that NIH provides effective scientific coordination and management of this diverse AIDS research portfolio through a comprehensive planning and budget development process, which was utilized to develop this FY 2007 budget request. Through the OAR, NIH is enhancing collaboration, minimizing duplication, and ensuring that precious research dollars are invested in the highest priority areas of scientific opportunity that will allow NIH to meet its scientific goals.

CROSS-OVER BENEFITS

- New paradigm for viral research and drug design
- Established concept of "prophylaxis" of opportunistic infections in immuno-suppressed persons
- Unique model to study the role of the immune system in the emergence of cancers, and to test novel approaches by which immune responses can be modified to help treat malignancies (Kaposi's sarcoma, non-Hodgkin's lymphoma, cervical cancer)
- New approaches for rapid and sensitive diagnosis of disease and monitoring of treatment applicable to other infectious diseases
- Understanding of HIV-associated wasting benefits persons with cancer and other diseases
- 3TC and other drugs and drug combinations developed for HIV now standard of care for hepatitis B and C
- Drugs for opportunistic infections used for transplant or immuno-suppressed patients
- Design of clinical trials, including community involvement
- Understanding of immune response to pathogens
- Insight into neurological, autoimmune, and metabolic diseases

NATIONAL INSTITUTES OF HEALTH

Office of AIDS Research SUMMARY BY BUDGET MECHANISM

MECHANISM	FY 2005 Actual		FY 2006 Appropriation		FY 2007 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Grants:						
Research Projects						
Nonecompeting	2,080	\$1,013,328,000	2,060	\$1,018,338,000	1,964	\$1,181,937,000
Administrative supplements	(197)	268,524,000	(123)	25,477,000	(106)	22,439,000
Full Funded	0	0	0	0	0	0
Single Year	656	269,990,000	649	490,720,000	714	286,075,000
Subtotal, competing	656	269,990,000	649	490,720,000	714	286,075,000
Subtotal, RPGs	2,736	1,551,842,000	2,709	1,534,535,000	2,678	1,490,451,000
SBIR/STTR	64	30,262,000	62	27,271,000	67	28,551,000
Subtotal, RPGs	2,800	1,582,104,000	2,771	1,561,806,000	2,745	1,519,002,000
Research Centers						
Specialized/comprehensive	58	113,005,000	57	110,940,000	58	120,174,000
Clinical research	0	44,643,000	0	44,243,000	0	44,243,000
Biotechnology	0	4,007,000	0	3,647,000	0	3,647,000
Comparative medicine	16	50,119,000	7	53,771,000	7	54,781,000
Research Centers in Minority Institutions	0	11,017,000	0	10,119,000	0	10,111,000
Subtotal, Centers	74	222,791,000	64	222,720,000	65	232,956,000
Other Research						
Research careers	314	41,312,000	317	41,543,000	311	40,830,000
Cancer education	0	37,000	0	37,000	0	37,000
Cooperative clinical research	17	33,046,000	17	32,998,000	17	33,054,000
Biomedical research support	0	1,262,000	0	1,460,000	0	1,460,000
Minority biomedical research support	2	703,000	2	705,000	2	702,000
Other	112	59,694,000	114	63,966,000	115	62,930,000
Subtotal, Other Research	445	136,054,000	450	140,709,000	445	139,013,000
Total Research Grants	3,319	1,940,949,000	3,285	1,925,235,000	3,255	1,890,971,000
Ruth L. Kirschstein Training Awards:	FTEPs		FTEPs		FTEPs	
Individual awards	90	3,660,000	89	3,754,000	88	3,672,000
Institutional awards	702	33,473,000	664	32,659,000	661	32,502,000
Total, Training	792	37,133,000	753	36,413,000	749	36,174,000
Research & development contracts (SBIR/STTR)	211 (3)	471,296,000 (1,315,000)	210 (3)	480,814,000 (1,302,000)	225 (3)	501,183,000 (1,296,000)
Intramural research		300,694,000		293,638,000		292,222,000
Research management and support		98,164,000		99,898,000		101,200,000
Construction		3,966,000		0		0
Library of Medicine		7,450,000		7,376,000		7,452,000
Office of the Director		60,899,000		60,290,000		59,290,000
Total, NIIH Budget Authority		2,920,551,000		2,903,664,000		2,888,492,000

NATIONAL INSTITUTES OF HEALTH

Office of AIDS Research

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

Research Area	FY 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate	Change
Natural History and Epidemiology	\$297,070	\$282,189	\$271,837	(\$10,352)
Etiology and Pathogenesis	741,688	698,835	689,357	(9,478)
Therapeutics	732,159	692,658	681,003	(11,655)
Vaccines	510,943	602,237	620,584	18,347
Behavioral and Social Science	416,857	405,466	399,339	(6,127)
Training and Infrastructure	179,069	181,945	188,248	6,303
Information Dissemination	42,765	40,334	38,124	(2,210)
Total, Budget Authority	2,920,551	2,903,664	2,888,492	(15,172)

National Institutes of Health

Office of AIDS Research

AIDS Funding by Institute and Center

Institute/Center	FY 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate
NCI	\$265,907,000	\$253,666,000	\$244,104,000
NHLBI	74,690,000	67,351,000	65,094,000
NIDCR	24,985,000	19,688,000	18,601,000
NIDDK	31,151,000	30,898,000	30,674,000
NINDS	47,364,000	46,351,000	45,731,000
NIAID	1,459,642,000	1,489,424,000	1,491,573,000
NIGMS	54,632,000	53,485,000	53,485,000
NICHD	132,992,000	133,555,000	133,435,000
NEI	12,562,000	10,585,000	9,451,000
NIEHS	8,702,000	7,513,000	7,235,000
NIA	5,459,000	5,389,000	5,294,000
NIAMS	6,697,000	4,866,000	4,652,000
NIDCD	1,734,000	1,412,000	1,412,000
NIMH	182,615,000	178,558,000	177,581,000
NIDA	313,137,000	300,073,000	299,266,000
NIAAA	27,166,000	26,942,000	26,942,000
NINR	12,236,000	12,114,000	12,114,000
NHGRI	6,862,000	6,835,000	6,835,000
NIBIB	1,048,000	1,038,000	700,000
NCRR	156,858,000	160,992,000	162,044,000
NCCAM	2,778,000	2,285,000	2,124,000
NCMHD	---	---	---
FIC	22,985,000	22,978,000	23,403,000
NLM	7,450,000	7,376,000	7,452,000
OD	60,899,000	60,290,000	59,290,000
B&F	---	---	---
TOTAL, Budget Authority	2,920,551,000	2,903,664,000	2,888,492,000

NATIONAL INSTITUTES OF HEALTH

Office of AIDS Research

SIGNIFICANT ITEMS IN HOUSE and SENATE APPROPRIATIONS COMMITTEE REPORTS

FY 2006 House Appropriations Committee Report Language (H.Rpt.109-143)

Item

Pediatric HIV research - The Committee recognizes the importance of research into the long-term health implications of preventive HIV drug regimens in children, the psychological and social needs of HIV-infected children and appropriately targeted prevention services. The Committee requests the Director to identify the resources necessary for domestic and international research on the long-term effects of preventive drug regimens on HIV-exposed pediatric populations; the long-term health, psychosocial, and prevention needs for pediatric populations perinatally HIV-infected; the transition to adulthood for HIV-infected pediatric populations; and safer and more effective treatment options for pediatric populations with HIV disease. (p. 102)

Action taken or to be taken

The NIH is deeply committed to domestic and international research in HIV, its complications, and long-term outcomes in infants, children, and adolescents. The dramatic reductions in U.S. mother-to-child HIV transmission rates, and increases in the number of HIV-infected children surviving into adolescence are largely attributed to NIH-funded research demonstrating the efficacy of anti-HIV drugs. There is little information currently available on the long-term safety, in uninfected children, of the antiretroviral drugs given to their mothers and to the children as newborns. For HIV-infected children whose lives are prolonged with drug treatments, there also is little information about the effects of the infection and its treatments on growth, development, immune status, bone health, and other biological and psychosocial aspects of their health. The National Institute of Child Health and Human Development (NICHD), with co-funding from the National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Mental Health (NIMH), National Institute on Deafness and Other Communication Disorders (NIDCD), and the National Institute on Drug Abuse (NIDA), have begun a new initiative, the Pediatric HIV/AIDS Cohort Study (PHACS). This study will address two critical research questions for HIV-infected children: 1) the long-term effects of fetal exposure to antiretroviral drugs; and 2) the clinical course of HIV infection through adolescence.

The Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN), a domestic multi-center network funded by the NICHD, NIMH and NIDA, conducts the full spectrum of HIV research for youth: from studies of primary prevention for at-risk youth to trials of clinical management of youth with HIV.

NICHD and NIAID support pediatric and adolescent clinical trials networks with international sites that collaboratively conduct trials on the treatment of HIV infection and its complications in

infants, children and adolescents. For example, the International Site Development Initiative, conducted in Latin America and the Caribbean, includes a pediatric observational study that is evaluating 1) long-term outcomes in uninfected children exposed to antiretroviral drugs while in their mother's womb or during birth; and 2) toxicity from antiretroviral treatment in infected children. The NIH is also moving proactively to meet future research needs in resource-poor countries, by developing additional networks of sites with clinicians trained to conduct clinical trials. Already, studies conducted in such networks have led to FDA approval of the use of several new antiretroviral drugs for children at the same time the drugs were approved for adults. Other international studies are also specifically assessing the behavioral and psychiatric aspects of pediatric HIV disease and adherence to therapy, taking into account different cultural and community expectations.

Microbicides for the Prevention HIV/AIDS –The Committee urges strengthened funding for microbicide research and development at NIH. In addition, the Committee has long advocated that NIAID establish a dedicated microbicide unit with clearly identified leadership to accelerate microbicide research. The Committee understands that NIAID has established the Microbicide Team in the Division of AIDS (DAIDS), which also coordinates a broader NIAID group with representatives from DAIDS and the Division of Microbiology and Infectious Diseases (DMID). The Office of AIDS Research, within the Office of Director, is continuing to coordinate microbicide research across the NIH. Greater leadership and coordination on this issue is especially critical given that consideration is being given to the possibility of a microbicide-specific clinical trial network. (p.106)

Action taken or to be taken

The NIH Office of AIDS Research (OAR) has set microbicides research among the as a high priority and serves as the coordinating office for all federally-funded microbicide research conducted at the NIH; as well as coordinating NIH efforts with activities at other federal agencies such as the Centers for Disease Control and Prevention (CDC) and the United States Agency for International Development (USAID). The OAR convenes the Trans-NIH Topical Microbicide Working Group, which includes representatives from eight NIH Institutes and Centers (ICs) involved in topical microbicide-related research. The National Institute of Allergy and Infectious Diseases (NIAID), through its Division of AIDS (DAIDS) and Division of Microbiology and Infectious Diseases (DMID), supports the most extensive microbicide research efforts at NIH.

The microbicide research programs within DAIDS and DMID are designed to be complementary and to integrate into NIH-wide efforts related to microbicide research. At the Institute level, microbicide research is further coordinated by a cross-divisional Topical Microbicide Working Group led by DAIDS. This Group has met monthly for several years under the leadership of the Topical Microbicide Team Leader in DAIDS. NIAID continues its efforts to increase the number of staff devoted to microbicide research and to facilitate integration across its Divisions. The establishment of a microbicide branch, however, may compromise NIAID's multidisciplinary approach that encompasses research on both HIV and sexually transmitted infections, which cross different components of the Institute.

In planning future clinical research efforts, NIAID has identified microbicide research as a high priority area for its re-structured HIV/AIDS clinical research networks. Awards are planned in fiscal year (FY) 2006 for new Network Leadership Groups which could help to further microbicide research through maximizing efficiency, increasing collaboration, and integrating prevention and treatment research. In FY 2004, NIAID released a request for proposals for Microbicide Design and Development Teams (MDDT). These teams are designed to engage industry in the development of candidate microbicides. One award was made in FY 2005 to a pharmaceutical company. An expansion of this program is planned for FY 2007.

Finally, OAR and NIAID are working together with the National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH) to coordinate the new Microbicide Innovation Program (MIP) which is designed to identify innovative concepts and discoveries relevant to topical microbicides. The Program will support research through NIH Phased Innovation Awards based on the merit of the concept for advancement along the product development path. Awards are planned for FY 2006.

Programs and initiatives in microbicides research, both in progress and planned for the future, will enable NIH to continue to strategically build on the coordinated portfolio of research currently in progress and lead to the translation of discoveries into candidate microbicides suitable for evaluation in clinical trials.

Item

Public-private partnerships in support of microbicides to prevent HIV/AIDS - There is an urgent need to expand the development pipeline with more microbicide candidate products, particularly those that target HIV in new ways. In addition to candidates that may arise from NIH-funded basic research efforts, possibilities may be found within pharmaceutical companies where there are potential compounds already developed as therapeutics that could be tested as potential microbicides. NIH has mechanisms in place to encourage partnerships among researchers in academia, government and the private sector. The Committee strongly urges the leadership at NIH to support the microbicide field by encouraging partnering with the pharmaceutical industry and non-governmental organizations. In the past year, the International Partnership for Microbicides has entered into agreements with leading pharmaceutical companies to jointly test and develop leading AIDS drugs as microbicides. More partnerships like these between the pharmaceutical industry and the non-profit community in collaboration with NIH will be critical, and should receive the active support of NIH leadership. (p. 106-107)

Action taken or to be taken

Topical microbicides represent an important potential strategy for preventing the sexual transmission of HIV, and the National Institutes of Health (NIH) continues to support research and development, through public-private partnerships, toward an effective microbicide.

In fiscal year (FY) 2004, the National Institute of Allergy and Infectious Diseases (NIAID) announced the Microbicide Design and Development Teams program to partner with industry in

the streamlined development of microbicide candidates, emphasizing combination products with multiple active agents. One award was made in FY 2005 to a pharmaceutical company to develop a novel dendrimer-based microbicide candidate). Additional awards are expected in FY 2006.

NIH's Integrated Preclinical/Clinical Program for HIV Topical Microbicides program continues through 2006. This program is designed to stimulate iterative preclinical and clinical research for novel microbicide strategies against HIV infection and benefits from the involvement of the private sector as a component of the award. The program now supports nine multi-project microbicide development efforts for novel single and combination microbicides. These efforts include pilot Phase I clinical trials.

In FY 2005, NIAID entered into an agreement with the International Partnership for Microbicides (IPM) to share information and expertise in the effort to develop a vaginal microbicide. This partnership pairs NIAID's expertise in topical microbicide discovery and early product development with IPM's capacity to design optimal microbicide formulations, manufacture clinical lots for testing, and conduct clinical trials. The relationship between NIAID and IPM will accelerate the advance of candidate microbicides in the development pipeline. NIAID's partnership with IPM facilitated a recent agreement between IPM and leading pharmaceutical companies for further development of three microbicide candidate. Initial development of these products was supported by NIAID's Microbicide Development Program and the Integrated Preclinical/Clinical Program for HIV Topical Microbicides.

In FY 2005, a Phase II/Ib safety and effectiveness trial of two candidate microbicides began at sites in Africa and the United States. The NIH HIV Prevention Trials Network (HPTN), a network of academic clinical trial sites, is evaluating PRO 2000 and BufferGel in partnership with two different pharmaceutical partners. The trial will enroll over 3,000 women and is expected to be completed in FY 2008.

In FY 2005, NIAID made five awards under the Partnerships for Topical Microbicides program. Each Partnership award joins industry and academic or other non-profit organizations together to develop and bring promising topical microbicide candidates from concept stage through pre-IND development, and helps prepare them for clinical trials.

NIH is developing a new microbicide research initiative to foster the translation of microbicide innovations to preclinical development. The Microbicide Innovation Program (MIP) is a novel, milestone-driven program. The MIP will identify innovative microbicide concepts and then advance them toward development. The first awards are expected in FY 2006.

To enhance global collaboration and coordination, NIH is actively involved in the Microbicides Coordinating Board convened by the Bill and Melinda Gates Foundation and the Alliance for Microbicide Development. The board is a coordinating mechanism intended to facilitate and execute a range of international activities aimed at moving the microbicide field forward through collaborative efforts.

FY 2006 Senate Appropriations Committee Report Language (S. Rpt. 109-103)

Item

Microbicides to Prevent HIV/AIDS – Given current scientific advancements, an effective microbicide could be developed by the end of the decade, and once available, could well change the course of the epidemic. According to NIH, “the U.S. Government is firmly committed to accelerating the development of safe and effective microbicides to prevent HIV” because microbicides may provide “one of the most promising prevention interventions that could be inexpensive, readily available, and widely acceptable” (U.S. Government Strategic Plan for Microbicides). Despite these statements, NIH continues to spend barely 2 percent of its HIV/AIDS research budget on microbicides. The Committee strongly urges greater funding for microbicide research and development at NIH. (p. 160-161)

Action taken or to be taken

NIH funding for microbicide research has more than tripled since FY 2000, making NIH the single largest public funder of microbicides in the world. The U.S. government dominates public sector funding for microbicides and committed about 74% (\$ 92 million) of the total global funds invested by the public sector in 2004. Within the U.S. government, the primary source of funding is NIH, which accounted for 72% (\$ 66.2 million) of U.S. public sector funding in 2004, or 53% of total global public sector investment.

NIH also strives to increase the number of investigators interested in microbicides research and development by identifying and addressing opportunities to strengthen and expand its research portfolio. NIH is developing a new broadly based microbicide program, the Microbicide Innovation Program (MIP), to foster the translation of innovative ideas to preclinical development. This novel, milestone-driven program is aimed at enlarging the microbicide pipeline, facilitating technologic/methodologic design and development that may advance the field as a whole, and paving the way for an understanding of how vaccines and microbicides may be exploited in combination as an effective and comprehensive prevention strategy. The OAR will provide funding to the Institutes and Centers for this program, and the first awards are expected in FY 2006.

To enhance global collaboration and coordination, NIH is actively involved in the Microbicides Coordinating Board convened by the Bill and Melinda Gates Foundation and the Alliance for Microbicide Development. The board is a coordinating mechanism intended to facilitate and execute a range of international activities aimed at moving the microbicide field forward through collaborative efforts.

Item

Partnerships for Microbicide Development - In addition, this Committee has long advocated that NIH establish a dedicated microbicide unit with clearly identified leadership to accelerate and coordinate federally supported microbicide research, and is concerned that no significant progress has been made toward this goal. Greater leadership and coordination on this issue is especially critical given that consideration is being given to the possibility of a microbicide-specific clinical trial network. If this evolves, the notion of a dedicated microbicide unit at the NIH would be essential. (p.161)

Action taken or to be taken

See House Report response, page 25 of this document

Item

Public-private partnerships in support of microbicides to prevent HIV/AIDS - There is an urgent need to expand the development pipeline with more microbicide candidate products, particularly those that target HIV in new ways. In addition to candidates that may arise from NIH-funded basic research efforts, possibilities may be found within pharmaceutical companies where there are potential compounds already developed as therapeutics that could be tested as potential microbicides. NIH has mechanisms in place to encourage partnerships among researchers in academia, government and the private sector. The Committee strongly urges the leadership at NIH to support the microbicide field by encouraging partnering with the pharmaceutical industry and non-governmental organizations. In the past year, the International Partnership for Microbicides has entered into agreements with leading pharmaceutical companies to jointly test and develop leading AIDS drugs as microbicides. More partnerships like these between the pharmaceutical industry and the non-profit community in collaboration with NIH will be critical, and should receive the active support of NIH leadership. (p. 161)

Action taken or to be taken

See House Report response, page 26 of this document

Item

Pediatric HIV research - The Committee recognizes the importance of research into the long-term health implications of preventive HIV drug regimens in children, the psychological and social needs of HIV-infected children and appropriately targeted prevention services. The Committee requests the Director to identify the resources necessary for domestic and international research on the long-term effects of preventive drug regimens on HIV-exposed pediatric populations; the long-term health, psychosocial, and prevention needs for pediatric populations perinatally HIV-infected; the transition to adulthood for HIV-infected pediatric populations; and safer and more effective treatment options for pediatric populations with HIV disease. (p. 161)

Action taken or to be taken

See House Report response, page 24 of this document