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National Institutes
of Health
Fiscal Year 2002
Plan for HIV-Related
Research

PREPARED BY THE DIRECTOR
OFFICE OF AIDS RESEARCH
NATIONAL INSTITUTES OF HEALTH

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Foreword

It is the mandate of the Office of AIDS Research (OAR) to set the scientific agenda for the large and diverse NIH AIDS research program. To this end, we develop the annual comprehensive NIH HIV-related research Plan and budget, based on the most compelling scientific priorities that will lead to better therapies and prevention strategies for HIV infection and AIDS. Those priorities are determined through a collaborative process involving the NIH institutes and non-Government experts from academia and industry, with the full participation of AIDS community representatives. The contributions of this diverse group of experts are crucial to the planning process, and I am grateful to each of them for the time and careful consideration they devoted to the development of this Plan.

Four major themes frame this research Plan: international research priorities, particularly to address needs in developing countries; research targeting the disproportionate impact of AIDS on minority populations in the United States; therapeutic research to treat those who are already infected; and prevention research to reduce HIV transmission here in the United States and around the world.

Since the development of last year's Plan, critical attention has been brought to the international dimension of the AIDS epidemic, catalyzing efforts across the Government to address AIDS globally. In January 2000, the United Nations Security Council declared that AIDS represents a new kind of threat to political stability and thus an issue of national security. As more than 90 percent of new infections occur in developing countries,

where therapeutic interventions are unaffordable and undeliverable, NIH is increasing its international research portfolio to pursue interventions that can be implemented in these resource- and infrastructure-deprived nations. Thus, this FY 2002 Plan includes a new section within the areas of special interest that details our international research agenda. To facilitate this critical area of research, the OAR established the International AIDS Research Collaborating Committee, bringing together all of the Departments of the U.S. Government conducting research, along with international partners such as the Joint United Nations Programme on AIDS and the World Bank.

The disproportionate impact of the HIV/AIDS epidemic on communities of color in the United States remains a key research priority. The scientific agenda for research targeting minority communities is also highlighted among the areas of special interest in this plan. To advise us on the scientific priorities for this critical research area, the OAR established the Ad Hoc Working Group on Minority Research. We are directing increased resources toward new interventions that will have the greatest impact on these groups, and we are making significant investments to improve research infrastructure and training opportunities for minorities. The participation of minority subjects in AIDS clinical trials as well as in natural history, epidemiologic, and prevention studies remains a priority.

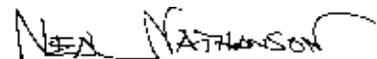
Several NIH-supported research efforts have demonstrated differences in viral dynamics between women and men. These recent findings provide new avenues for investigation that may have important implications about disease progression and treatment in women. Another high-priority research area for women is the development of physical and chemical barriers, including topical microbicides, to prevent HIV transmission. In March 2000, the OAR supported the first international conference on microbicides to stimulate new research initiatives and international collaboration in this critical area of our prevention science agenda.

The development of protease inhibitors has had a significant impact on the length and quality of life for many HIV-infected individuals in the U.S. But the long list of serious problems for patients receiving these HIV therapies includes: (1) failure to obtain a satisfactory reduction in viral load even for patients who comply with treatment regimens; (2) toxicities; (3) metabolic and cardiac complications, including diabetes and fat redistribution; (4) drug resistance; and (5) complicated and expensive regimens that make compliance difficult. These problems require the development and testing of new, simpler, less toxic, and cheaper anti-HIV drugs.

Primary prevention of new HIV infections is the most effective means of controlling the spread of the epidemic in the United States and globally. Both behavioral and biomedical efforts are critical to this effort. In the United States, regimens of antiretroviral drugs resulting from NIH-supported research have dramatically reduced transmission from infected mother to infant. However, the complexity of administration and high cost make the regimens used in industrialized countries impractical for much of the developing world. Therefore we are continuing a major research effort to develop affordable methods to prevent perinatal transmission and to better understand the mechanisms involved in HIV transmission through breast-feeding.

To control the pandemic for all individuals, communities, and nations at risk, a safe and effective vaccine is the critical missing element in our armamentarium. The NIH has made enormous strides to invigorate and reorganize our AIDS vaccine efforts, and we will intensify our support for HIV vaccine research both intramurally and in extramural sites around the world, consistent with the President's challenge to the nation in 1997 to develop an AIDS vaccine.

The wise investment of resources, based on the scientific priorities of our annual planning process, has reaped rewards. But as we make these scientific strides, we cannot afford to leave anyone behind. This Plan, developed with the assistance of hundreds of scientists, experts, and AIDS community representatives, will shape our investments in biomedical and behavioral research and provide the framework to translate our research findings to benefit populations desperately in need, both here in our country and abroad.



Neal Nathanson, M.D.

Director, OAR

June 2000

Legislative Mandate

The National Institutes of Health Revitalization Act of 1993 (Public Law 103-43) provided that the Director of the Office of AIDS Research (OAR) “shall plan, coordinate and evaluate research and other activities conducted or supported” by NIH. The Director of OAR “shall act as the primary Federal official with responsibility for overseeing all AIDS research conducted or supported by the National Institutes of Health” and shall “establish a comprehensive plan for the conduct and support of all AIDS activities of the agencies of the National Institutes of Health...; ensure that the Plan establishes priorities among the AIDS activities that such agencies are authorized to carry out; ensure that the Plan establishes objectives regarding such activities...; and ensure that the Plan serves as a broad, binding statement of policies regarding AIDS activities of the agencies, but does not remove the responsibility of the heads of the agencies for the approval of specific programs or projects, or for other details of the daily administration of such activities, in accordance with the Plan.” The law further provides that “the Director of the Office shall ensure that the Plan provides for basic research; provides for applied research; provides for research that is supported and conducted by the agencies; provides for proposals developed pursuant to solicitations by the agencies and for proposals developed independently of such solicitations; and provides for behavioral research and social science research.”

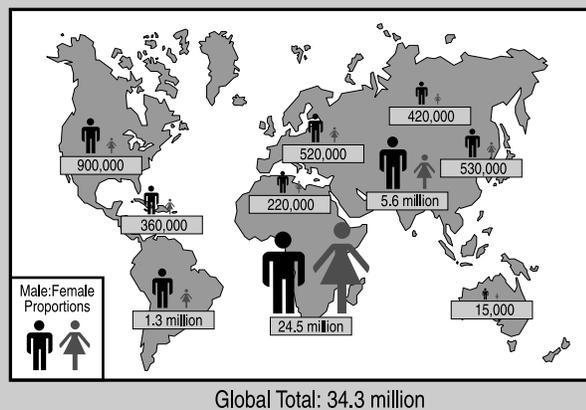
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Executive Summary

By every definition, AIDS is the great plague of the 20th century. The impact of AIDS on developing nations and many former communist countries is staggering, with even greater potential disaster to come. As a growing threat to global security, AIDS is reversing decades of progress in public health and significantly affecting international economies. The cost in lost productivity and profitability, sickness and death, and a significant reduction in the skilled workforce in developing countries will have economic effects worldwide.

Estimated Number of Persons Living With HIV/AIDS, December 1999



Source: UNAIDS, 2000

In the United States, the incidence of new AIDS cases and AIDS deaths has declined, due largely to the expanded use of new antiretroviral therapies that prevent the progression of HIV infection to AIDS; however, the decline in AIDS-related death rates has leveled off. Most significantly, the rate of new HIV infections has been constant since 1990, with no decline, indicating that we have not yet begun

to reduce the epidemic in the United States. HIV infection rates are continuing to climb in two major groups: women and minority populations. HIV/AIDS

affects the disenfranchised in our society—the poor, the homeless, and those with addictive or mental disorders. AIDS also is increasing in young homosexual men and people over 50 years of age. Further, HIV drug-resistant strains present a very serious public health concern.

These data forebode an epidemic of even greater magnitude in the years ahead and shape our most urgent research priorities. These priorities address two critical populations—those living in developing countries and the minority populations of the United States. Thus, our research agenda is two-pronged: therapeutic research to treat those who are already infected and prevention research to reduce HIV transmission. The prevention agenda includes both vaccine and non-vaccine strategies, such as behavioral research, development of topical microbicides, and prevention of perinatal transmission.

STRUCTURE OF THE PLAN

The FY 2002 NIH Plan for HIV-Related Research is divided into five Scientific Areas of Emphasis and four Areas of Special Interest. *Scientific Areas of Emphasis* are Natural History and Epidemiology, Etiology and Pathogenesis, Therapeutics, Vaccines, and Behavioral and Social Science. *Areas of Special Interest*, which cross-cut all of the scientific areas, are Racial and Ethnic Minorities; International Research Priorities; Training, Infrastructure, and Capacity Building; and Information Dissemination. This format is intended to provide a comprehensive framework that defines the scope of NIH-supported HIV-related research. The process for development of the annual comprehensive plan is explained in the Introduction.

PRIORITIES FOR FUTURE RESEARCH

The following are some of the high-priority research areas deemed most worthy of new or expanded funding, based on the current scientific knowledge, opportunities, and gaps. These priorities will help guide the development of the FY 2002 AIDS budget and to adjust the FY 2001 AIDS budget as needed.

SCIENTIFIC AREAS OF EMPHASIS

Natural History and Epidemiology

- Determine the mechanisms and develop interventions to prevent postpartum transmission (i.e., resulting from breast-feeding).
- Evaluate the net impact of antiretroviral therapies on HIV transmission.

- Determine the biological characteristics, sociocultural factors, and health services issues that alter the dynamics of transmission and disease progression in men and women, as well as in the various racial and ethnic groups.
- Characterize the relative importance of alcohol and drug use in the acquisition and subsequent transmission of HIV in order to identify and apply appropriate alcohol and drug use interventions as public health measures.

Etiology and Pathogenesis

- 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 cofactors may influence the process of virus transmission.
- Investigate the mechanism 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 reconstruction of T-cell populations in response to therapy.
- 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 an era of increasingly effective therapies.

Therapeutics

- Advance the discovery of new anti-HIV agents by facilitating research on new or understudied viral and host targets, and develop new models and methodologies for predicting the effects and efficacy of anti-HIV agents in humans.
- Develop and evaluate therapeutic approaches that will enhance, restore, or maintain the immune systems of HIV-infected individuals.
- Conduct clinical studies to identify more effective, less toxic, and easier-to-take drug regimens; determine when antiretroviral regimens should be initiated or switched for optimal patient care; and evaluate the long-term effects of antiretroviral therapy.

- Develop and test safe, effective, and feasible microbicides and other chemical and physical barriers to halt sexual transmission of HIV and sexually transmitted diseases (STDs).

Vaccines

- Continue to expand core programs in HIV/AIDS vaccine research and development to ensure that the research pipeline for vaccine research and development is robust.
- Conduct clinical trials of promising vaccine candidates in both domestic and international settings: conduct Phase I and II trials of products, moving new concepts and products into human testing as rapidly as possible; and enable the conduct of efficacy trials with sufficient lab support to define correlates of immunity.
- Expand immunological assessment of vaccines: ensure that standardized assays are developed that are precise, sensitive, and practical; develop and provide resources and appropriate reagents for these assays; strengthen the immunological assessment of clinical vaccine trials; study the immune responses in neonates and infants to assure development of appropriate vaccine products for breast-feeding populations.
- Invest in the development of critical vaccine research capabilities, information dissemination, and education to conduct vaccine trials in populations with a high incidence of HIV infection, in both the United States (including minority populations, adolescents, and women) and in international settings.

Behavioral and Social Science

- Monitor, understand, and address the disparate risks and impact of HIV infection, as well as the disparate access to, and utilization and quality of, prevention and care services according to race/ethnicity, gender, age and socioeconomic status.
- Identify and address psychological, social, cultural, and ethical issues related to the initiation, maintenance, sustainability, replicability, and durability of effective HIV prevention, testing, counseling, and care efforts within communities over time, including efforts targeting HIV-infected individuals.

- Investigate the social and environmental factors that contribute to HIV infection, behaviors after infection, and co-occurring conditions (e.g., substance use, mental illness, homelessness, hepatitis, STDs, tuberculosis [TB]), including the causes and implications of stigma.
- Investigate both the facilitators and the barriers to policy decisions and public health implementation informed by behavioral and social science findings, including the development of interventions targeting the attitudes, capacities, and resources of HIV service providers and selected institutional settings (e.g., prisons, schools).

AREAS OF SPECIAL INTEREST

Racial and Ethnic Minorities

- Recruit sufficient candidates to increase the pool of minority investigators for increased efficacy in HIV research.
- Decrease health disparities among racial and ethnic minorities with respect to HIV infection, as well as in comparison to majority populations.
- Promote the inclusion of racial and ethnic minorities in prevention, therapeutic, and clinical trials in numbers that are reflective of the incidence data.

International Research Priorities

- Establish centers of excellence in international settings that will provide an environment that promotes the development of true and equal partnerships between U.S. and foreign investigators. These centers will support basic research and long-term cohort studies, serve as loci for studies of efficacy of biomedical and behavioral prevention interventions (including Phase I, II, and III vaccine trials), function as training centers for investigators from throughout the region, and serve as bridges in providing services.
- Conduct studies relevant to the geographic areas of the world and specific populations hardest hit by the epidemic.
- Enhance translation of research results into action that will improve patient management, develop prevention programs appropriate to the setting, and effect policy changes.

- Continue to enhance training for research needs, clinical capability, and technology transfer, building bridges with programs providing services where possible.

Training, Infrastructure, and Capacity Building

- 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.

Information Dissemination

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

Introduction

Introduction

HIV/AIDS: A GLOBAL PERSPECTIVE

By every definition, AIDS is the great plague of the 20th century. HIV has infected more than 50 million people around the world. AIDS already has killed more than 16 million people, surpassing tuberculosis and malaria as the leading infectious cause of death worldwide, according to recent data released

by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO). In 1999, a record 2.8 million people died—more than in any prior year—and an estimated 5.4 million people contracted HIV.

“What began as a handful of recognized cases among homosexual men in the United States has become a global pandemic of such proportions that it clearly ranks as one of the most destructive microbial scourges in history. We are at a pivotal point in the evolution of this historic event as we enter the new millennium.... Unless methods of prevention, with or without a vaccine, are successful, the worst of the global pandemic will occur in the 21st century.” Fauci AS. The AIDS Epidemic—Considerations for the 21st Century. *N Engl J Med* 1999; 341:1046-1050.

Ninety-five percent of HIV infections occur in developing countries. The impact on these nations is staggering, with even greater potential disaster to come. In Africa, the epicenter of the pandemic, AIDS is killing 10 times as many people as war, sabotaging economic development, leading to massive social breakdown, and creating a generation of orphans.

Given the continuing loss of its skilled and unskilled workers, this region is struggling to save its economic, social, political, educational, and military infrastructures from collapse.

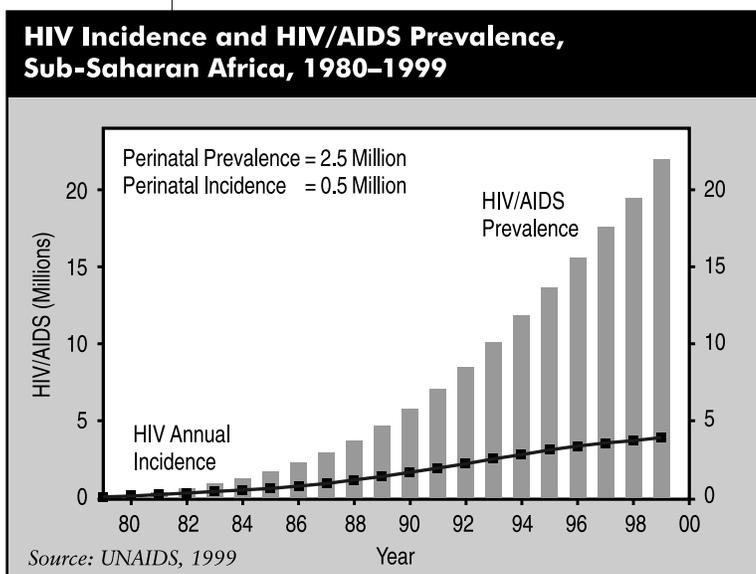
The Exploding Global HIV/AIDS Pandemic				
Group	People Newly Infected in 1999	People Living With HIV/AIDS	AIDS Deaths in 1999	Cumulative AIDS Deaths
Adults	4.7	33.0	2.3	15.0
<i>Women</i>	2.3	15.7	1.2	7.7
Children	0.62	1.3	0.50	3.8
Total	5.4	34.3	2.8	18.8

** all numbers are in millions
Source: UNAIDS, 2000.*

“It [AIDS] is taking away both the breadwinner and those who look after the young, the old, and the infirm. It is destroying the very fabric of society. It is not only taking away Africa’s present, it is taking away Africa’s future.”
U.N. Secretary-General Kofi Annan, at a New York town hall meeting organized by African Amicale, 2/07/00

The seriousness of the crisis in Africa was dramatized in January 2000 when the United Nations Security Council highlighted the growing epidemic and declared that AIDS has become an issue of national security, representing a new kind of threat to political

stability. It was the first time the Security Council placed a health issue on its agenda and the first time a sitting U.S. Vice President addressed the Security Council.



If the global spread of HIV/AIDS continues unchecked, South and Southeast Asia, and perhaps China, will follow the disastrous course of sub-Saharan Africa. Currently, there are an estimated 5.6 million HIV-infected people in South and Southeast Asia. In India alone, UNAIDS estimates that between 3 and 5 million of its nearly 1 billion population are infected, and the number

of new infections is continuing to double every 14 months. Rapid increases also are occurring in Eastern Europe and Central Asia, and AIDS remains

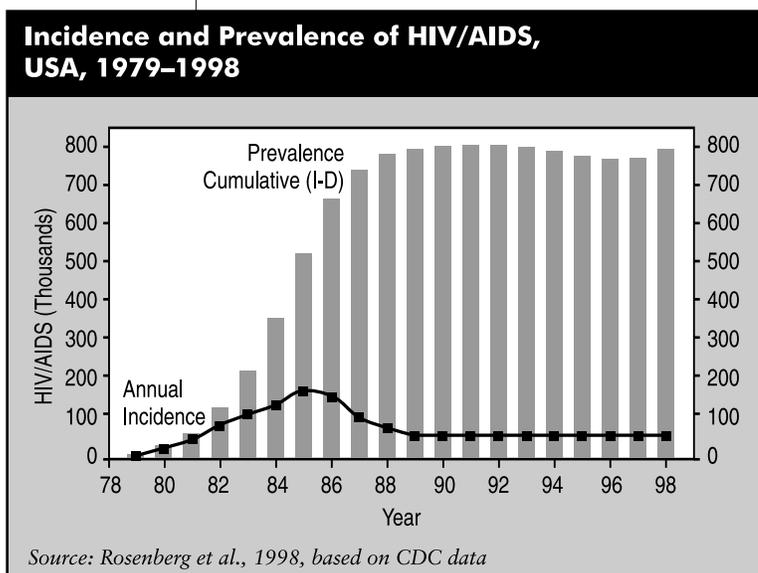
a serious threat in Latin America and the Caribbean. HIV infections in the former Soviet Union have doubled in just 2 years.

Recent data indicate that worldwide there are now almost equal numbers of men and women infected with HIV. In sub-Saharan African, UNAIDS/WHO estimated that more women than men were living with HIV/AIDS at the end of 1999: 12.2 million women and 10.1 million men between the ages of 15–49. Curbing the transmission of HIV from infected mother to infant is an especially compelling challenge in developing countries.

The coexistence of other endemic diseases widely prevalent in developing countries, such as respiratory and gastrointestinal infections, complicates treatment and poses additional problems for medical personnel caring for HIV-infected individuals. Of particular note is the parallel epidemic of tuberculosis in the developing world. Attitudes, beliefs, and taboos surrounding sex, the status of women and children, and the source and etiology of AIDS can complicate attempts to control transmission and provide appropriate prevention and treatment.

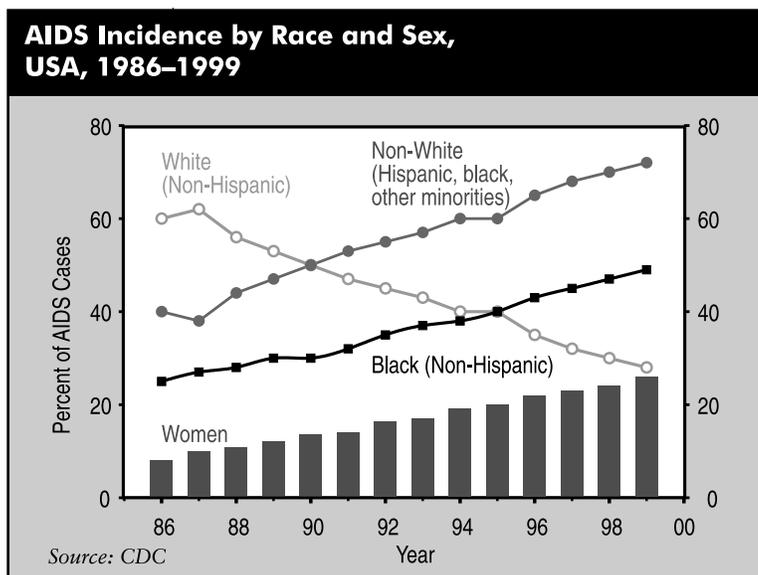
HIV/AIDS IN THE UNITED STATES

In the United States, the HIV/AIDS epidemic continues to evolve. Although the incidence of new AIDS cases has declined, attributed largely to expanded use of new antiretroviral therapies that prevent progression of HIV infection

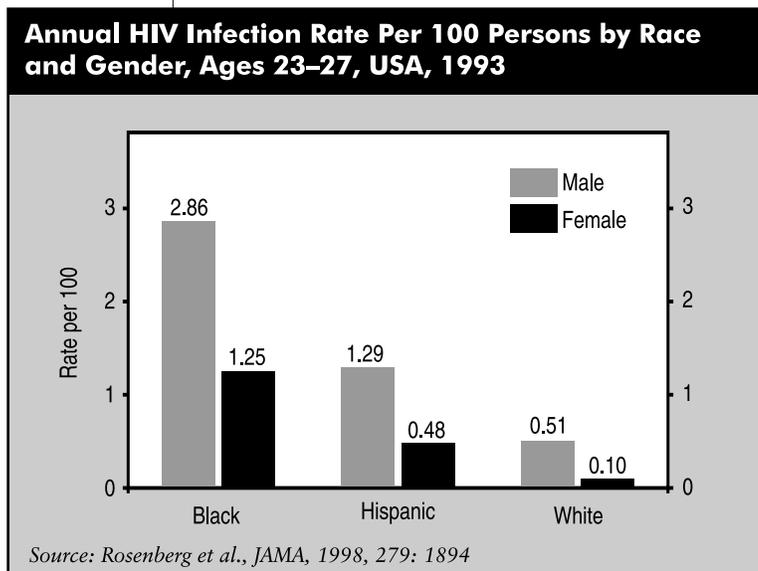


to AIDS, the decline in death rates observed in the late 1990s has leveled off. Further, according to the Centers for Disease Control and Prevention (CDC), the rate of new HIV infections has been constant, at approximately 40,000 new cases each year since 1990, meaning that the overall epidemic is continuing to expand. In fact, HIV infection rates are continuing to climb in a number of subpopulation

groups, such as women, racial and ethnic minorities, young homosexual men, individuals with addictive disorders, and people over 50 years of age. The recent appearance of multi-drug-resistant strains of HIV presents a serious public health concern. These data forebode an epidemic of even greater magnitude in the coming years.



AIDS disproportionately affects African Americans and Hispanics. They account for 45 percent and 20 percent, respectively, of all persons newly diagnosed with AIDS during 1998. CDC’s HIV/AIDS Surveillance Report of June 1999 states that among women with AIDS, minorities account for 80 percent of cases; among men, minorities account for 61 percent of cases. Addressing these racial disparities is a high priority for the NIH.



THE NIH AIDS RESEARCH AGENDA

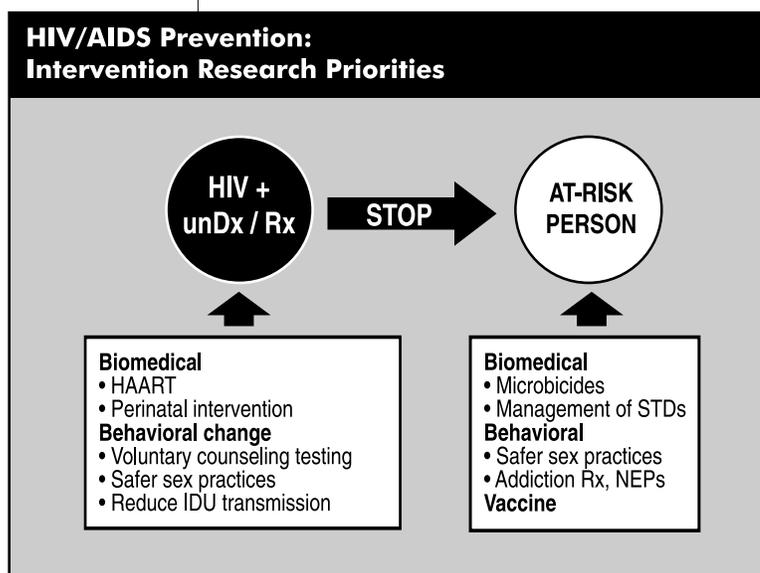
In response to this pandemic, NIH has developed a comprehensive biomedical and behavioral research program to better understand the basic biology of HIV, develop effective therapies to treat it, and design interventions to prevent new infections from occurring. It is the role of the Office of AIDS Research (OAR) to plan and coordinate this research program, sponsored by all 25 NIH Institutes and Centers (ICs). The changing demographics in the epidemic demand careful consideration in planning our research agenda, since different prevention and intervention strategies must be applied to each subepidemic.

The transmissible nature of HIV makes it radically different from non-transmissible diseases such as heart disease and cancer. The

transmissibility of HIV—between individuals and across borders and populations—is what most defines the global pandemic and makes it imperative that the United States help address prevention and treatment needs worldwide. The transmissibility of the infection means that there is the potential for unlimited global spread. But it also means that, with the development of appropriate biomedical and behavioral interventions, there is the possibility for dramatic reductions in new infections—and ultimate control of the pandemic—in a way that will not be possible for noninfectious diseases.

Prevention Research

NIH supports a comprehensive approach to HIV prevention research that includes contributions from the biomedical, behavioral, and social sciences.



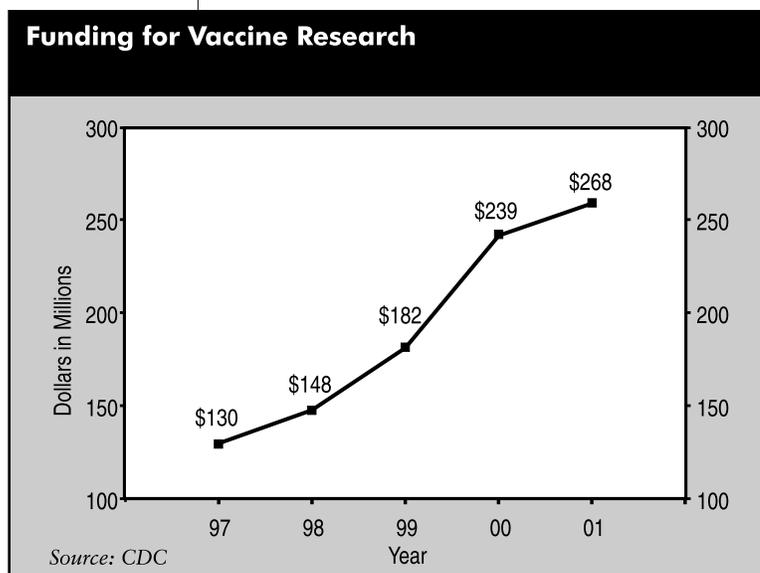
The OAR prevention science research agenda targets interventions to both infected and uninfected at-risk individuals to reduce HIV transmission. Our biomedical prevention research priorities include the development of topical microbicides, strategies to prevent perinatal transmission (including a better understanding of risk-associated breast-feeding), and management of sexually transmitted diseases (STDs).

NIH also supports behavioral research strategies, including prevention interventions related to drug and alcohol use and risky sexual behaviors. Efforts continue to identify the most appropriate intervention strategies for different populations and subepidemics in the United States and around the world. The OAR Prevention Science Working Group continues to provide advice about HIV prevention research priorities.

Vaccines

A safe and effective HIV preventive vaccine is essential for the global control of the AIDS pandemic. In 1997, the President challenged the nation to develop an AIDS vaccine. Consistent with this challenge, NIH funding for HIV vaccine research increased by more than 100 percent between FY 1997 and FY 2000, resulting in the award of new grants to foster

innovative research on HIV vaccines, including vaccine design and development and the invigoration and reorganization of the NIH vaccine clinical trials effort. Construction of the new intramural Vaccine Research



Center will be completed by mid-2000. In February 1999, NIH-supported investigators initiated the first AIDS vaccine trial in Africa. The AIDS Vaccine Research Committee, chaired by Nobel laureate Dr. David Baltimore, continues to provide critical advice on all aspects of the NIH AIDS vaccine development program. The changes implemented in this area over the past few years have

enormous significance, not only for AIDS research but for other diseases as well, as progress made in the development of an AIDS vaccine will have implications for vaccines against other life-threatening illnesses.

Behavioral and Social Science Research

Studies have demonstrated that behavioral change can successfully prevent or reduce the spread of HIV infection in both domestic and international settings. Prevention programs resulting from such studies have altered sexual and drug-using behaviors and have reduced the risk of transmission in many communities and subgroups. 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.

Microbicides

The vulnerability of women to acquiring HIV infection demands the development of effective and acceptable female-controlled chemical and physical barrier methods, such as topical microbicides, to reduce HIV transmission. To enhance and stimulate research in this area, OAR cosponsored the first international conference devoted to all aspects of microbicide research and development. The conference, Microbicides 2000,

included more than 600 participants from 45 nations. NIH is supporting Phase I, Phase II, and Phase III trials of various topical microbicides. NIH also supports behavioral and social research on the acceptability and use of microbicides among different populations.

Mother-to-Child Transmission

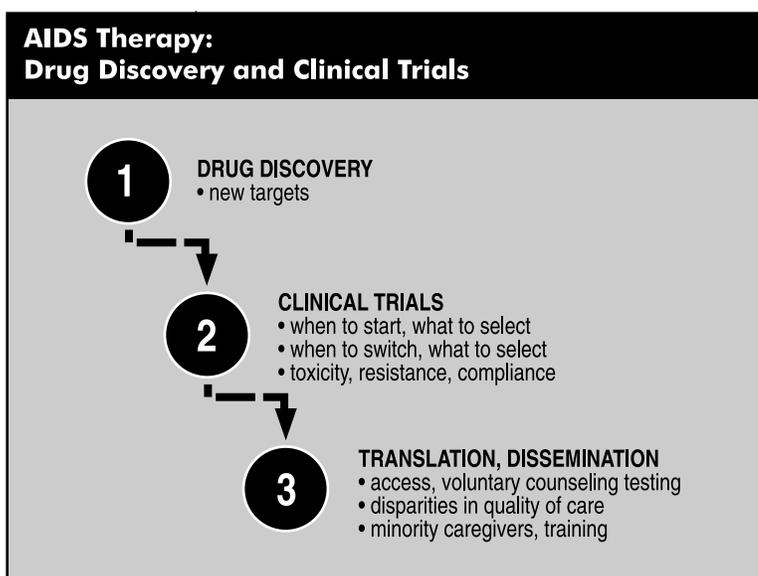
In the United States, regimens of antiretroviral drugs resulting from NIH-supported research have dramatically reduced transmission from infected mother to infant. However, the complexity of administration and high cost make this option impractical for much of the developing world. For example, NIH-supported clinical trials in Uganda recently demonstrated that a single dose of the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine—given to women during labor and followed by a single dose administered to their newborns, at a total cost of approximately \$4—reduced transmission by half, compared with a similar and considerably more costly short course of AZT. This advance can substantially lower the cost barrier that has kept many countries from adopting drug strategies that prevent perinatal HIV transmission. However, lack of health care infrastructure or access to other health care services may still affect the ability of developing countries to implement this regimen. Further research on this and other low-cost alternatives is included in this Plan. Another key research issue is the need for better methods for the reduction of HIV transmission through breast-feeding.

TREATMENT RESEARCH

Highly Active Antiretroviral Therapy (HAART)

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, highly active antiretroviral therapy (HAART) 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 the high cost of approximately \$15,000 per year. Others fail to obtain a satisfactory reduction in viral load, even while adhering to treatment regimens.

In addition, metabolic complications—such as hypercholesterolemia, hypertriglyceridemia, insulin resistance, and body composition changes inclusive



of deforming deposits of abdominal adipose tissue—have emerged in individuals who have been on long-term antiretroviral regimens. Finally, an increasing number of treatment failures are linked to the increasing emergence of drug-resistant HIV.

The need for simpler, less toxic, and cheaper drugs and drug regimens to treat HIV infection and its associated opportunistic infections (OIs), malignancies, and

other complications, continues to be a high 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 to address these issues 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.

Basic Science

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 attending 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. In addition, basic behavioral and social science studies are also needed to provide further information on risk factors and behaviors and the identification of populations at risk. These areas of investigation, driven by investigator-initiated research, have provided the constantly advancing knowledge base that permits the development of new applications for the prevention and treatment of HIV/AIDS. Thus, a substantial portion of NIH AIDS-related research will continue to be devoted to fundamental biomedical, behavioral, and social science research.

SPECIAL AREAS OF INTEREST

Racial and Ethnic Minorities

Research to address the disproportionate impact of the HIV/AIDS epidemic on U.S. racial and ethnic minority communities continues to be a high priority. OAR has established the Ad Hoc Working Group on Minority Research to provide advice on scientific priorities in this critical research area, which are reflected in this Plan.

NIH is directing increased resources toward 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 ensure the participation of minority subjects in AIDS clinical trials as well as in natural history, epidemiologic, and prevention studies. In response to the Congressional Black Caucus initiative, OAR 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 was a Training and Career Development Workshop for racial and ethnic minority investigators. This workshop provided minority investigators with an opportunity to learn about available NIH funding mechanisms and to meet and network with senior minority investigators who receive significant levels of NIH funding.

International Research Priorities

The exploding nature of the epidemic globally, particularly in the poorest parts of the world, has escalated the urgency of improved intervention strategies. For this reason, NIH will continue to significantly increase its investments in international studies in the coming year. NIH supports a growing portfolio of research conducted in collaboration with investigators in developing countries. Results of this research benefit the people in the country where the research is conducted, as well as people affected by HIV/AIDS worldwide. For example, NIH collaborates with UNAIDS, host country governments, and in-country scientists for vaccine development and in preparations for efficacy trials. NIH-sponsored programs target studies on factors related to HIV transmission and the pathogenic mechanisms associated with HIV disease progression through a number of studies in Africa, Asia, and Latin America. These studies focus on the biologic determinants of infectiousness and susceptibility and behavioral factors involved in HIV transmission.

It is critical to the success of international studies that foreign scientists be full and equal partners in the design and conduct of collaborative studies and that they have full responsibility for the conduct of studies in-country. To that end, NIH supports international training programs and initiatives that help to build infrastructure and laboratory capacity in developing countries where the research is conducted.

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 and development to treat viral infections. For example, the drug known as 3TC, developed to treat 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 is also providing new understanding of the relationship between viruses and cancer.

THE NIH AIDS RESEARCH PROGRAM

The Role of the Institutes

Each NIH component supports HIV/AIDS-related research activities, consistent with its individual mission. A list of the NIH ICs is found in

Appendix A of this Plan. The ICs whose research programs are most heavily concerned with HIV, AIDS, and their sequelae are the National Institute of Allergy and Infectious Diseases (NIAID), the National Cancer Institute (NCI), the National Institute on Drug Abuse (NIDA), the National Institute of Mental Health (NIMH), the National Center for Research Resources (NCRR), the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute of Child Health and Human Development (NICHD). A table of expenditures by IC appears in Appendix B. The Warren Grant Magnuson Clinical Center provides the infrastructure for intramural clinical studies sponsored by the ICs.

The Role of the Office of AIDS Research

OAR was established in 1988 by the Director of NIH and the Department of Health and Human Services (DHHS) Assistant Secretary of Health to coordinate the AIDS research effort across NIH and serve as a focal point for AIDS policy and budget development. The NIH Revitalization Act of 1993 (Public Law 103-43) gave broad new authorities to the office. OAR is responsible for the annual comprehensive planning and budgeting process for all NIH AIDS research and for preparation of a Presidential bypass budget. The law also requires OAR to evaluate the AIDS activities of each of the ICs, as well as provide for the periodic reevaluation of such activities. OAR maintains a discretionary fund, and the appropriations committees have provided OAR with transfer authority permitting it to move up to 3 percent of AIDS research funds among Institutes. The OAR monitors and fosters plans for NIH involvement in international AIDS research activities.

OAR has established and supported the efforts of five trans-NIH Coordinating Committees in the following areas: Natural History and Epidemiology, Etiology and Pathogenesis, Therapeutics, Vaccines, and Behavioral and Social Science. The Committees represent those Institutes with the most significant research portfolios in these areas. The Committees foster collaboration and coordination and assist in the development of the NIH Plan and budget for AIDS research. In addition, OAR established the Ad Hoc Minority Working Group in 1999. Composed of NIH staff and non-NIH scientists and experts, this group advises the OAR Director on needed research and research-related efforts specifically targeted to these populations.

OAR also established the International AIDS Research Collaborating Committee to bring together all of the Departments of the U.S. Government conducting AIDS research, along with international partners such as the UNAIDS and the World Bank, to facilitate international research efforts.

To carry out its activities, OAR depends upon the expert advice of several committees. Each of these committees includes AIDS community representatives. The OAR Advisory Council (OARAC) is composed of non-Government experts from a broad array of disciplines, as well as AIDS community representatives. OARAC reviews the annual Plan and discretionary fund disbursements. A list of current OARAC members is included as Appendix C. OAR also has established the Prevention Science Working Group and the Therapeutics Research Working Group to provide advice in these critical scientific areas.

OAR directly supports several programs and initiatives. These include the Intramural AIDS Targeted Antiviral Program (IATAP) and the NIH AIDS Research Loan Repayment Program (LRP). In addition, OAR recognizes the critical need to ensure that research results are translated into effective prevention programs and into clinical practice. To accomplish this goal, OAR supports a number of activities to promote the distribution of research information to researchers, physicians, institutions, and communities.

OVERVIEW OF THE PLAN

The Planning Process

OAR has established a unique and effective model for developing a consensus on scientific priorities for the annual comprehensive NIH Plan for HIV-Related Research. To develop the FY 2002 Plan, OAR sponsored a Planning Workshop to seek the input of non-NIH experts, including scientists from academia, foundations, and industry, and community representatives. These experts participated with NIH scientific and program staff in Planning Groups for Natural History and Epidemiology; Etiology and Pathogenesis; Therapeutics; Vaccines; Behavioral and Social Science; Research Related to Racial and Ethnic Minorities; and International Research Priorities. A list of participants may be found in Appendix D. Participants in each Planning Group were asked to review and revise the objectives and strategies of the draft Plan, based on the state of the science, and to identify a set of priorities for their area. All groups were asked to address needs in the areas of information dissemination, training, infrastructure and capacity building related to their area. The resulting draft Plan was then provided to each Institute and Center Director and AIDS Coordinator for recommendations and comments. Finally, the Plan was reviewed by the Office of AIDS Research Advisory Council.

OAR continues to reassess the planning process and make refinements in order to better capture the broadest range of expertise and community

participation and to facilitate the identification of specific scientific priorities. This year, a new section has been added to the Plan, focusing on International Research Priorities.

Structure of the Plan

The Plan is divided into five Scientific Areas of Emphasis and four Areas of Special Interest. *Scientific Areas of Emphasis* are Natural History and Epidemiology; Etiology and Pathogenesis; Therapeutics; Vaccines; and Behavioral and Social Science. *Areas of Special Interest*, which cross-cut all of the scientific areas, are Racial and Ethnic Minorities; International Research Priorities; Training, Infrastructure, and Capacity Building; and Information Dissemination.

Scientific Issues and Priorities

This section provides a scientific overview and specific priorities identified by the planning groups for each area. These priorities narrowly define a few high-priority areas deemed *most worthy of new or expanded funding*, based on the current scientific knowledge, opportunities, and gaps. They will be used to guide the development of the FY 2002 AIDS budget and to adjust the FY 2001 AIDS budget as needed. It is expected that these priorities will change from year to year, and thus expenditures in these areas will not be tracked over time.

Objectives and Strategies

Objectives consist of a comprehensive list, in priority order, of the scientific questions to be addressed for each Scientific Area of Emphasis or Area of Special Interest. Under each Objective is a set of Strategies that provide examples of avenues and approaches that may be pursued.

Uses of the Plan

The Plan serves several purposes:

- As the framework for developing the NIH AIDS budget. A chart showing the interaction between the planning and budget process may be found in Appendix E.

- For determining the use of NIH AIDS-designated dollars and for tracking and monitoring those expenditures. The Plan thus defines those research areas for which AIDS-designated funds may be allocated.
- As a document that provides information to the public, the scientific community, Congress, and the AIDS-affected communities about the NIH AIDS research agenda. OAR distributes the annual comprehensive Plan to a wide audience, and it appears on the OAR Web site: <http://www.nih.gov/od/oar/>.

Progress on Implementation of the 1996 Levine Report Recommendations

In 1996, the NIH AIDS Research Program Evaluation Working Group, convened by OARAC and chaired by Dr. Arnold Levine, issued its report and recommendations on the NIH AIDS research program. The Working Group and its Area Review Panels conducted an in-depth analysis of all aspects of HIV/AIDS research at the NIH. Appendix F includes a summary of the “Levine Report” recommendations and the current status of their implementation.

Scientific Areas of Emphasis

Natural History and Epidemiology

SCIENTIFIC AREA OF EMPHASIS:

Natural History and Epidemiology

SCIENTIFIC ISSUES

While recent epidemiologic research indicates that there is an ongoing HIV/AIDS epidemic among minorities, women, adolescents, drug users, and heterosexuals in the United States, other recent findings signal a continuing and significant HIV/AIDS epidemic among men who have sex with men. Urban, minority, and disenfranchised communities need to respond to the intersecting epidemics of HIV/AIDS, sexually transmitted diseases (STDs), tuberculosis (TB), and drug use. Communities of men who have sex with men need to respond to multiple issues, including those involving HIV-positive and minority men. Globally, the HIV/AIDS epidemic continues to spread, with significant focal points in sub-Saharan Africa, India, and Southeast Asia.

To address these communities and populations, diverse longitudinal and cross-sectional samples of HIV-negative and HIV-positive individuals need to be studied, in natural history and epidemiology investigations, in both domestic and international settings. Continuing research needs to examine topics in HIV transmission, HIV/AIDS disease progression, malignancies, metabolic complications, neurological and behavioral dysfunctions, and the development of other HIV/AIDS-related conditions. Further studies are needed to investigate the effects of viral, host, and other factors on transmission and disease progression. Results from these studies will provide new directions and improvements in HIV/AIDS prevention and care.

**MOTHER-TO-CHILD
TRANSMISSION**

Although mother-infant HIV transmission is not the predominant source of HIV infections worldwide, it is the primary way that children become infected and has resulted in a large number of infected children. UNAIDS estimates that during 1999, 1.2 million children were living with HIV/AIDS, and 570,000 children were newly infected. These infections are having an effect on overall child health and survival.

It is currently estimated that in breast-feeding populations, one-sixth of the infections occur before delivery (prepartum), one-half during labor and delivery (intrapartum), and one-third postpartum during breast-feeding. Advances have been made in understanding and preventing prepartum and intrapartum transmission. Current prevention strategies include the use of various combinations of antiretrovirals during pregnancy and during labor and delivery. However, less is known about postpartum transmission. Studies of postpartum transmission are needed to determine the risks and mechanisms involved and to develop effective interventions. For example, it would be important to gain a better understanding of the net impact on HIV transmission of such factors as the timing and duration of breast-feeding, the timing and severity of the mother's infection, the timing of the introduction of other foods, and the use of antiretrovirals, such as nevirapine.

PRIORITY FOR FUTURE RESEARCH:

- **Determine the mechanisms and develop interventions to prevent postpartum transmission (i.e., resulting from breast-feeding).**

**THE EFFECT OF
ANTIRETROVIRAL
THERAPIES ON HIV
TRANSMISSION**

In the United States and other developed countries, the use of antiretroviral combination therapies since the mid-1990s has ushered in a new phase of the HIV/AIDS epidemic, one in which more HIV-infected individuals are living longer. The new antiretroviral therapies have had many effects, which not only include decreases in HIV/AIDS morbidity and mortality but also include increases in numbers of drug-resistant strains of the virus.

The effects of the new antiretroviral therapies on HIV transmission are not completely understood. A few studies suggest that individuals on antiretroviral therapy may be less likely to transmit HIV infection because they have lower viral loads after treatment. The result of this phenomenon may be a decrease in the rates of transmission and HIV incidence. However, the net effect of the perception that individuals on antiretrovirals may be less likely to transmit HIV infection may be that more people are taking greater sexual risks. Thus, the paradoxical consequence of the lower viral

loads that result from antiretroviral therapies may be *higher* rates of HIV transmission and infection. Because biological, pharmacological, psychological, and behavioral factors all potentially influence the impact of antiretroviral therapies on HIV transmission, there is a need to evaluate the specific contributions of these factors and their net impact on HIV transmission.

PRIORITY FOR FUTURE RESEARCH:

- **Evaluate the net impact of antiretroviral therapies on HIV transmission.**

SEX AND RACE/ETHNICITY DIFFERENCES IN TRANSMISSION AND DISEASE PROGRESSION

Like many other diseases in the United States, HIV/AIDS has become concentrated in urban, disenfranchised communities of low socioeconomic status, as well as in certain racial and ethnic minority groups (i.e., African Americans and Hispanics). There are also continuing reports about male/female differences in transmission and disease progression. Thus, a determination of 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 race/ethnicity groups is needed for developing appropriate prevention and treatment strategies across at-risk populations in domestic and international settings.

PRIORITY FOR FUTURE RESEARCH:

- **Determine the biological characteristics, sociocultural factors, and health services issues that alter the dynamics of transmission and disease progression in men and women, as well as in the various racial and ethnic groups.**

ALCOHOL AND DRUG USE

HIV can be directly transmitted when individuals mingle their blood with the blood of others while sharing needles, syringes, and other injecting-drug-use equipment. However, alcohol and drug use (both injecting and non-injecting) is also a complex cofactor of HIV transmission: people using drugs may become infected or infect others through sexual transmission. For example, drugs can alter thought processes about sex (e.g., increasing sexual drive, decreasing sexual inhibitions, etc.). Alcohol and drug-using environments, like bars or dance clubs, may increase the likelihood that individuals will have sex with new partners. To design better HIV prevention efforts, studies are needed to gain a better understanding of the roles and relationships of alcohol and drug use in HIV transmission.

Better HIV prevention efforts could also be developed by adapting current alcohol and drug use prevention models and programs and including HIV prevention as an objective. Prior research has led to effective alcohol and drug use interventions that now need to be identified, characterized, and translated into interventions that can have an impact on a population-level (public health) scale, thereby affecting HIV dynamics at the community, regional, and national levels.

PRIORITIES FOR FUTURE RESEARCH:

- **Characterize the relative importance of alcohol and drug use in the acquisition and subsequent transmission of HIV.**
- **Identify successful alcohol and drug risk-reduction models, and then determine how to apply them as public health interventions in domestic and international settings.**

METHODS FOR MEASURING HIV INCIDENCE

HIV incidence (i.e., the number of new HIV infections in a population during a specified period of time) is the best measure of the current dynamics of the HIV epidemic in a population or a particular group. Understanding the current stage and future directions of the HIV epidemic in a population or group makes it possible to design and evaluate timely and appropriate HIV prevention programs. However, traditional HIV incidence studies are complicated to conduct, since they involve the monitoring of study participants over time and then testing them for HIV at different points in time, to determine whether they seroconvert from HIV-negative to HIV-positive. The consequence of this study design—the followup cohort study—means that HIV incidence results may not be available for months or years. Therefore, new laboratory and statistical methods are needed to measure HIV incidence in populations and groups.

PRIORITY FOR FUTURE RESEARCH:

- **Develop methods (e.g., laboratory, statistical) to determine and project HIV incidence in populations in both domestic and international settings.**

METHODS FOR ACCESSING HARD-TO-REACH GROUPS

Epidemiologic research indicates an ongoing HIV/AIDS epidemic among minorities, women, adolescents, drug users, heterosexuals, and men who have sex with men in the United States. Some of the subgroups involved (e.g., young men who have sex with men, the homeless, drug users, minorities) are hard to reach using traditional household-oriented and institution-based sampling methods. Also, even when it is possible to contact

the individuals in these subgroups by using innovative sampling methods, it may be difficult to enroll these people in research studies. Thus, to gain a better understanding of the current dynamics of the HIV epidemic in these groups, it is important to continue to develop methods for reaching individuals in these groups and encouraging their participation in research studies.

PRIORITY FOR FUTURE RESEARCH:

- **Develop and evaluate methods for more successful recruitment and enrollment of hard-to-reach and difficult-to-enroll groups into research studies.**

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE:

Develop and evaluate biomedical and behavioral prevention strategies for HIV-infected and at-risk populations to prevent transmission and acquisition of HIV, in both domestic and international settings.

1.A

STRATEGIES:

- Identify adolescents, young adults, minorities, women, and substance users in the United States and throughout the world with incidence and prevalence suitable for recruitment into vaccine and other intervention trials for preventing HIV transmission.
- Develop and maintain the infrastructure in HIV epicenters for conducting vaccine, behavioral, and other intervention trials.
- Develop and evaluate methods to access, recruit, and retain at-risk populations, including minorities, adolescents, women, substance users, and the mentally ill, for preventive intervention studies.
- Develop strategies and conduct studies, in a manner relevant to the developed and developing world, to evaluate vaccines, drugs, and other interventions that may prevent perinatal transmission.
- Develop and assess the effectiveness of various strategies to reduce HIV transmission via breast-feeding.
- Develop and assess the effectiveness of utilizing multiple approaches, both individually and in combination, that may decrease HIV transmission among adolescents and substance users.
- Develop and evaluate biomedical and behavioral interventions for controlling STDs as a means of preventing HIV transmission.
- Evaluate the potential risks and benefits of providing prophylaxis against infection after occupational and nonoccupational exposures to HIV.
- Evaluate differences in the use of antiretroviral prophylaxis as a function of type of exposure.
- Evaluate the effects of sexual activity, hygiene practices, and contraception choices on STD/HIV transmission.

- Evaluate the effects of access to, acceptability of, and compliance with prevention interventions on perinatal, sexual, and drug-use-associated transmission of HIV.
- Examine the impact of population-level interventions on HIV transmission in international and domestic communities, such as social normative behavior changes, economic opportunities for women, mass or syndromic approaches to STD control, early treatment of HIV infection, and use of family planning programs to diagnose and treat STDs.
- Evaluate new, improved, and cost-effective methods to prevent HIV transmission via blood transfusion in developing and developed countries.
- Evaluate the potential long-term complications of vaccines, antiviral therapy, and other therapies used to reduce HIV transmission on the development of chromosomal damage, mutagenesis, or carcinogenesis.
- Examine the ability of vaccines, antiretrovirals, STD therapy, and nutritional supplementation to decrease infectiousness among persons who subsequently become HIV-infected despite the administration of vaccines.

OBJECTIVE:

Characterize the risk factors and mechanisms of HIV transmission in both domestic and international populations, with the goal of preventing transmission.

1.B

STRATEGIES:

- Evaluate the impact of antiretroviral therapies on HIV infectiousness and transmission.
- Evaluate HIV transmission and acquisition in relation to the following:
 - ▶ Viral factors, such as viral concentration in blood, genital, and oral secretions, and at mucosal sites; characteristics of HIV (genotype, phenotype, and drug resistance); and HIV infection stage;
 - ▶ Host intrinsic factors, such as menstrual cycle, cervical ectopy, pregnancy, menopause, circumcision, mucosal immunity, and immunologic and genetic determinants;
 - ▶ Extrinsic factors, including intercurrent STDs, exogenous irritants, other causes of oral and anogenital inflammation, contraceptive use, nutrition, hormonal replacement therapy, drug use, and preexisting infection with other microbial agents;
 - ▶ Therapeutic factors, such as immunomodulators, antibiotics for other infectious agents, and vaccines; and
 - ▶ Social and ecologic factors associated with infection, including demographic variables such as socioeconomic status, race, ethnicity, culture, age, community and neighborhood, physician expertise, and access to health care.
- Investigate the impact of intensive combination or new antiretroviral regimens, during all phases of HIV infection, on risk behavior and HIV transmission.
- Further define the timing, mechanisms, and risk factors in perinatal and postnatal transmission, including concurrent STDs, bacterial vaginosis, chorioamnionitis, nutritional deficiencies, mode of delivery, and breast-feeding.
- Evaluate the occurrence of transient HIV infection and the mechanisms by which it may occur.

- Conduct studies on the molecular epidemiology and effects on HIV transmission of infection with different subtypes, multiple subtypes, and recombinant viruses.
- Identify and characterize the factors related to resistance to HIV infection, including genetic, immunologic, virologic, and nutritional factors, in persons who remain uninfected despite perinatal, breast-feeding, sexual, or parenteral exposure.
- Develop appropriate nonhuman primate animal models to study the biology of transmission, so that these studies will be more directly relevant to HIV transmission in humans.

OBJECTIVE:

Use epidemiologic research, in international and domestic settings, to identify virologic, immunologic, host, co-infectious, therapeutic, and other biological and behavioral factors that influence disease progression and health outcomes, and to assess how interventions alter disease progression and health outcomes.

1.C**STRATEGIES:**

- Elucidate the pathogenic mechanisms mediating HIV disease progression in well-defined population subgroups.
- Investigate the role of potential cofactors, correlates, and mediators of disease progression, including gender, immunological factors, infectious agents, hormonal factors, nutritional factors, drug use, reexposure to HIV, and interventions such as nutritional supplementation, exercise, and other health-enhancing behaviors.
- Develop approaches for identifying recently exposed and newly infected infants, adolescents, and adults for studies on the pathogenesis of early infection.
- Investigate how different patterns of adherence to drug regimens in treatment-experienced and -unexperienced populations contribute to HIV drug resistance and affect disease progression.
- Study the effectiveness of compliance/adherence interventions in minority, adolescent, drug-using, mentally ill, and international populations.
- Study the effects of nutritional deficiencies, oxidative stress, and body composition on HIV disease progression.
- Develop and evaluate counseling procedures for prognostic and diagnostic tests.
- Investigate the influence of HIV viral factors, including genotype, phenotype, and HIV drug resistance, on disease progression.
- Study HIV-infected infants, children, and adolescents to determine (1) factors related to divergent rates of disease progression, (2) mechanisms that contribute to impaired growth and neurodevelopment, (3) the physical and emotional impact of childhood infectious diseases and the safety and efficacy of immunizations for these diseases, (4) childhood- and adolescent-specific complications, and (5) the impact

of medical and behavioral treatment interventions on the items listed above.

- Evaluate the rate of HIV disease progression in conjunction with the effects of feasible interventions for delaying or preventing progression in international settings or populations with different viral clades and possible cofactors such as nutrition and opportunistic infections (OIs).
- Study the molecular epidemiology and effects on HIV disease progression of infection with different subtypes, multiple subtypes, and recombinant viruses.
- Study the effects of host genetic differences on disease progression.
- Assess the effectiveness and impact of immunizations and co-infections with hepatitis C, TB, and other infectious agents on disease progression in HIV-infected populations.
- Develop new and maintain long-term followup of, cohorts, including observational cohorts and intervention populations, and specifically in HIV-infected populations, to determine the changing spectrum of disease, especially in minority populations.
- Study the emergence and reemergence of infectious diseases and the development of antimicrobial-resistant infections, such as multidrug-resistant TB, in HIV-infected populations.
- Examine the impact of access to health care and of compliance/adherence to therapy regimens on health outcomes in HIV-infected populations.
- Consider the possible interaction of highly active antiretroviral therapy (HAART), treatment for drug use/abuse, and other infections (e.g., hepatitis C virus [HCV]) on HIV disease progression and resulting treatment recommendations.
- Explore low-cost, low-technology interventions for preventing HIV disease progression in developing countries, including nutritional interventions and better prophylaxis and treatment of OIs.
- In HIV-infected populations, evaluate risk factors and develop and assess interventions that reduce or prevent the following:
 - ▶ Infectious diseases;
 - ▶ Malignancies and associated oncogenic infections;

- ▶ Negative consequences of treatment interventions; and
- ▶ Other HIV-associated diseases, including central and peripheral nervous system diseases, cardiovascular manifestations, oral and mucosal lesions, and wasting and other metabolic disorders.

OBJECTIVE:

Develop and evaluate improved methods and resources for epidemiologic and clinical studies, including culturally relevant recruitment and retention approaches; new laboratory, sampling, and statistical methods; and informatics.

1.D

STRATEGIES:

- Develop and evaluate accurate, reproducible, and inexpensive virologic, immunologic, bacteriologic, and genetic assays suitable for large-scale epidemiologic research.
- Develop and evaluate low-cost virologic, immunologic, bacteriologic, and genetic assays suitable for epidemiologic research in developing nations.
- Develop telephone and face-to-face survey and sampling methods for at-risk subpopulations.
- Develop new biostatistical techniques to better characterize transmission dynamics, monitor and interpret disease trends, and study disease progression.
- Develop innovative approaches to link records, in a manner respectful of participant privacy, to facilitate better studies of HIV-associated diseases and mortality.
- Develop, maintain, and effectively utilize national specimen repositories and databases for interdisciplinary HIV-related studies.
- Enhance the application of informatics to facilitate the conduct of HIV research in managed care settings as well as in developing countries.
- Develop rapid, inexpensive, and noninvasive diagnostic assays for STDs, other OIs, and AIDS-related malignancies.
- Integrate assays from animal studies, so that findings are more applicable to studying the disease in humans.
- Develop and evaluate mechanisms for effective dissemination of HIV information to researchers, community-based organizations, health care providers, and the general public that affect prevention and disease progression in developed and developing countries.

- Support a comprehensive program of interdisciplinary methods research on statistical design and analysis of clinical trials with multiple interventions, community randomized HIV prevention trials, and studies on the role of social networks in HIV transmission.

Etiology and Pathogenesis

SCIENTIFIC AREA OF EMPHASIS:

Etiology and Pathogenesis

SCIENTIFIC ISSUES

In the quest for vaccines to prevent HIV infection and for more effective drugs to contain the infection and treat the opportunistic infections (OIs), tumors, and other manifestations of a dysfunctional immune system, a better understanding is needed of how HIV infection is established and what causes the profound immune deficiency and terrible complications that accompany this infection. 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 disturbances that characterize AIDS? These outstanding questions define the central contemporary issues encompassed within the area of etiology and pathogenesis research.

HIV BIOLOGY

Since the initial isolation of HIV in 1983 and its identification as the causative agent of AIDS shortly thereafter, tremendous progress has been made in understanding the genetic structure and variability of the viral genome, the critical aspects of the virus life cycle, and the functions of viral gene products and their interaction with the host. The knowledge

that has emerged from basic research in these areas provides the foundation for all efforts to develop current therapies to treat HIV infection, particularly the elucidation of the structure and function of two of the critical viral enzymes, reverse transcriptase and protease. Similar insights from basic research into the mechanisms of viral entry and the mechanisms by which the infection becomes established and spreads also are crucial for vaccine development efforts.

The challenge remains to develop drugs for the treatment of HIV infection that are cheaper, easier to take, more potent, and with fewer adverse effects, along with microbicides to prevent sexual transmission of HIV infection; and to identify immunogens able to elicit strong neutralizing responses for the development of an effective vaccine.

Recent scientific advances in AIDS research, such as the resolution of the crystal structure of gp41 and gp120 bound to CD4 and a neutralizing antibody, the delineation of many of the molecular interactions between virally encoded regulatory proteins and host cell factors, recent insights into critical requirements for viral replication, and the identification of conserved structural intermediates of gp41 that might be able to elicit a strong and cross-reactive neutralizing response are affording us the opportunity to identify these new viral and cellular targets.

PRIORITY FOR FUTURE RESEARCH:

- **Facilitate the translation of new insights into HIV biology to develop novel interventions for the prevention and treatment of HIV infection.**

Emphasis should be placed on the elucidation of structures and a better understanding of the biochemistry, interaction, and biologic function of relevant virus and host cell constituents. These studies should focus on defining the roles of specific host cell and viral gene products in HIV replication, persistence, and pathogenesis. The NIH also should play an instrumental role in facilitating collaborative research aimed at developing and implementing biologically relevant validated assays for drug screening.

TRANSMISSION, ESTABLISHMENT, AND SPREAD OF HIV INFECTION

In spite of the tremendous scientific advances in AIDS research, the factors that determine the transmissibility of HIV and the variables that may influence a person's susceptibility to HIV infection following exposure have yet to be clearly understood. The observed resistance to HIV-1 infection of multiply-exposed subjects bearing a homozygous deletion in one of the genes encoding a coreceptor for primary HIV-1 isolates highlighted the importance of coreceptor utilization in HIV-1 transmission. More important

is that these findings also suggested that the early interaction of HIV with target cells at the portal of entry is critical for the subsequent establishment and spread of infection. Prospective studies in discordant couples have recently provided evidence that peripheral blood viral load is the most important predictor of the risk of heterosexual transmission of HIV. These findings have important implications for the development of prevention strategies, since they suggest that reducing viral load in HIV-infected persons will result in decreased infectiousness. In the same studies, circumcision also appeared to prevent acquisition of HIV, highlighting the role of biologic factors as well as behavior in HIV transmission.

NIH-funded research is giving special emphasis to studies aimed at defining the role of components of the mucosal compartment, cellular and molecular aspects of mucosal innate and adaptive immunity, viral and host genetic factors, and cofactors such as other infectious agents, sexually transmitted diseases (STDs), and local inflammatory processes, on HIV-1 acquisition and transmission. This basic knowledge is crucial for our efforts to develop effective vaccines and microbicides. In the developing world, where infection rates have climbed to 25 percent in some countries and few people can afford antiretroviral drugs, the main issue continues to be how to stop transmission of the virus.

PRIORITY FOR FUTURE RESEARCH:

- **Elucidate the biologic determinants of HIV transmission between individuals and define the mechanisms by which host factors, viral factors, and cofactors may influence the process of virus transmission.**

Emphasis should be placed on studies focused on cohorts that are most representative of the expanding HIV epidemic. This can be facilitated by studies whose design reflects the collaborative interaction of basic scientists and population-based researchers.

Efforts should be directed at understanding the relative efficiency of transmission of cell-free and cell-associated virus in various bodily fluids at different portals of entry (particularly mucosal), mechanisms of initial entry and the cells that represent the first target of infection, mechanisms of virus compartmentalization in genital secretions, the relationship between biologic findings and the anatomical organization of mucosal tissue, and the role of viral genotypes/phenotypes and dose on HIV entry and establishment of infection. There also should be an emphasis on enabling the availability of emerging technologies in genetics, functional genomics, and the assessment of host immune responses for studies of the biology of HIV transmission.

**PATHOGENIC
MECHANISMS OF
HIV INFECTION**

Ongoing research at NIH on the molecular, cellular, and organ system levels is elucidating the pathogenic mechanisms of HIV infection. Research at the cellular and molecular levels includes studies of the mechanisms by which HIV infects various cell types, the interaction between the viral regulatory elements and host cell factors that appear to be directed at maintaining a persistent infection, and the viral- and host-mediated mechanisms that influence the level of viral expression seen in successive stages of HIV disease. Since HIV so profoundly affects the immune system, ongoing research also is aimed at elucidating the viral- and immune-mediated pathogenic processes that result in the severe loss of immune function, the inappropriate immune activation, and the disruption of immunomodulatory cytokine expression and production observed in HIV infection and disease.

NIH-supported investigators have demonstrated that significant levels of virus are present in plasma during all stages of HIV infection, including the clinically asymptomatic phase, and that active virus replication is directly linked to the depletion of T-cell populations in infected individuals and correlates with progression to disease. This understanding of the magnitude and dynamics of HIV replication *in vivo* has had great implications for understanding AIDS pathogenesis and for the management of HIV-infected patients.

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, recent 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 able to drive viral load below the limits of detection. The continuous ongoing viral replication might explain the apparent long half-life of the latently infected reservoir, since this could be continuously reseeded from activated CD4 T cells and monocytes/macrophages newly infected with HIV. Monocytes also appear to represent a significant reservoir for viral replication in patients on antiretroviral therapies. A better understanding of the different mechanisms of viral persistence is needed 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.

PRIORITY FOR FUTURE RESEARCH:

- **Investigate the mechanisms of persistence of HIV infection.**

Research efforts should focus on the explication of the cells and tissue reservoirs of persistent virus replication and their rates of turnover, the mechanisms of viral latency and reactivation, the impact of low-level viral replication on virus transmissibility, and the ability of natural and induced immunity to control and eliminate persistent infections.

The new emphasis on the dynamic and quantitative aspects of HIV replication is also paralleled by new efforts to quantitate T-cell population dynamics *in vivo* during different stages of HIV infection and disease. These efforts have great implications for understanding the mechanism behind the most central and unresolved issues in HIV-mediated immunopathogenesis: the depletion of CD4+ T cells and the failure of the regenerative capacity of the immune system to compensate for virus-induced damage. Several mechanisms, either direct or indirect, have been suggested; however, the critical mechanism remains to be elucidated. New technological developments that permit investigators to measure lymphocyte population dynamics and numbers of cells recently emigrated from the thymus during HIV infection, disease, and therapy may provide valuable insights into this pathogenic process.

PRIORITY FOR FUTURE RESEARCH:

- **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.**

Elucidation of these mechanisms will be critical for generating new therapeutic principles and approaches that will take into account both viral and cellular kinetic parameters. Potential compensatory mechanisms to replenish the lost T cells include peripheral expansion of residual memory cells and increased production of naive cells by the thymus. Current effective antiretroviral therapies lead to a rapid increase in memory CD4 and CD8 T cells, probably due to redistribution from lymphoid organs, a decrease in cell death, and peripheral expansion. However, regeneration of the T-cell repertoire is generally delayed for many months and will ultimately require production of new T cells from the thymus.

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 phenomenal discoveries in immunology of the last decades have been built on studies of the mouse immune system. While important lessons can be learned from these experimental studies, not all findings from the mouse model can be directly translated to the human system because of its heterogeneity and complexity.

PRIORITY FOR FUTURE RESEARCH:

- **Enhance and expand innovative studies of human immunology to guide vaccine development and immune reconstitution efforts.**

Emphasis should be placed on a better understanding of the elicitation and maintenance of immunologic memory. Emphasis also should be given to the definition and validation of markers and assays that will enhance our understanding of and ability to study immune function in humans, especially those approaches that permit the study of the *in vivo* regulation and function of the immune system. Recent technological breakthroughs are affording us the opportunity to more accurately assess the quantity and function of T cells in HIV infection. These are the tetramer technique that allows the analysis of antigen-specific CD8 T cells during the infection process, the nonradioactive method that directly measures lymphocyte turnover in humans, the ELISPOT assay that measures the secretion of cytokines in response to an antigenic stimulus, the single-cell intracellular cytokine production assay, and the deletion circles technique that identifies T cells recently emigrated from the thymus. The use of these innovative techniques is already providing HIV investigators with critical insights into the effects of HIV infection, antiretroviral therapy, and potential preventive or therapeutic vaccines on the immune system. Our attempts at preserving or reconstituting immune function in HIV-infected persons also will benefit from focused efforts directed at elucidating the homeostatic and regenerative mechanisms of lymphocyte populations, the markers for true thymic-derived cells, the factors that may influence T-cell proliferative capacity or survival in the normal state and with HIV disease, the immunological impact of long-term therapies, and potential interventions to improve thymic function and the generation of naive T cells. Likewise, focused efforts directed at functionally characterizing CD8 effector cells, at analyzing humoral and cellular immunity at mucosal sites, and at a better understanding of mechanisms leading to maintenance of immunological memory will greatly benefit research aimed at developing effective HIV vaccines.

**HIV
PATHOGENESIS
AFFECTING
WOMEN AND
MATERNAL-FETAL
TRANSMISSION**

Continued support of *in vivo* research is a high priority at NIH in order to further an understanding of the interaction between the virus and host immune system response. NIH-sponsored longitudinal cohort studies constitute a major resource for pathogenesis research. Specific cohorts, such as long-term nonprogressors, HIV-exposed but uninfected individuals, and rapid progressors, will provide clues for treatment and vaccine research by helping to characterize immune response profiles and providing information on correlates of immunity. *In vivo* research into mechanisms of virus-mediated immunopathogenesis also utilizes animal models. All the available animal models contribute to our understanding of disease mechanisms.

In response to the changing demographics of HIV infection, studies have been designed to elucidate the pathogenic mechanisms more commonly observed in women, children, and adolescents infected with HIV. As part of this effort, NIH supports a number of epidemiologic cohort studies focused specifically on women, adolescents, and children. The study of patient samples and of data generated by these cohorts is providing critical information about the mechanisms of transmission, the course of disease progression, and response to therapy in these populations.

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. Current basic research studies relevant to HIV-infected women focus on the characterization of cells susceptible to HIV infection in both the lower and upper reproductive tracts, the influence of hormonal modulation on viral infectivity and vaginal immunity, and the gynecological manifestations attending HIV infection.

Epidemiological studies performed to date have shown that HIV-infected women experience the same HIV-related signs and symptoms that have been observed in men, and few gender differences have been found in terms of OI incidence and AIDS progression. However, more recent studies have highlighted differences in viral dynamics in women compared with men. HIV-1 viral load has been found to be significantly lower in women than men at the time of seroconversion, and while plasma viral load at seroconversion predicted progression to AIDS in men, it failed to do so in women until 2 years afterward. Further studies are warranted to elucidate the biological underpinnings for these findings.

Some of the gender studies compared factors other than sex in patients. Women also were more likely to be poor, to belong to racial minorities, and to use injection drugs. Thus, analyses of gender differences should take into account other factors that have important effects on health outcomes. Age also is emerging as an important factor to consider, due to the increased survival of HIV-infected persons and the increase in newly HIV-infected individuals at different life stages.

PRIORITY FOR FUTURE RESEARCH:

- **Investigate the impact of gender, race, and age on the biology of HIV infection and on the responses to therapies and vaccines.**

In the area of maternal-fetal transmission, studies have demonstrated that the transmission rate of HIV from mother to infant is between 20 and 35 percent. Transmission of HIV-1 from a mother to her infant may occur *in utero* through transplacental passage of virus, during delivery, or postnatally through breast-feeding.

Many basic issues associated with maternal-fetal transmission remain unclear and are actively under investigation. These include the specific mechanism involved and the point in time at which HIV transmission occurs between mother and infant; whether specific strains (macrophage tropic or T lymphocyte tropic) of the virus are more likely to be transmitted; the possible correlation between elevated maternal HIV-1 ribonucleic acid (RNA) levels in plasma or vaginal secretions and an increased risk of neonatal infection; delineation of the role of maternal immunity in preventing transmission of HIV to the fetus; and the role of cofactors, such as substance abuse and concomitant infections, in the efficiency of transmission.

DISEASE MANIFESTATIONS

HIV infection affects the functioning of virtually all the organ systems within the body. Current NIH-supported basic and clinical studies are focused on the characterization of HIV/AIDS-associated diseases and on the assessment of their relative contribution to the overall disease progression in AIDS. NIH is striving to enhance the bidirectional flow between basic and clinical observations and intervention programs on HIV-related complications.

The availability of new and more effective antiviral drugs and treatment modalities is having a beneficial effect on the course of HIV infection and has altered the incidence and nature of some of its manifestations. The influence of new antiretroviral therapies, which are able to lower viral

load to undetectable levels, on the natural history of AIDS is providing an unprecedented opportunity to gain insights into the pathogenic mechanisms underlying the disease manifestations associated with HIV infection and AIDS. Unfortunately, use of these therapies also is associated with a series of side effects and complications that we are just starting to appreciate and study.

Metabolic and Body Composition Changes

The study of HIV-associated manifestations is rapidly changing as a result of the introduction of effective antiretroviral therapies and the concomitant decline in the incidence of OIs. The incidence of wasting has declined, and insulin resistance, hypercholesterolemia, hypertriglyceridemia, and abnormal fat distribution (either depletion or accumulation) have been described in HIV-infected individuals taking antiretroviral therapies. These manifestations are a real cause for concern with broad public health implications. Patients are experiencing problems in adhering to regimens when these symptoms occur, some stop taking medications, and others are not initiating therapies due to the possible occurrence of disfiguring physical changes and the long-term risk of cardiovascular complications. These changes were initially considered a single syndrome commonly referred to as lipodystrophy. Recent data are instead suggestive of multiple syndromes with different etiologies. Protease inhibitors were first associated with these metabolic and body composition changes, but recent data have indicated that HIV patients treated with only nucleoside reverse transcriptase inhibitors (NRTIs) also develop these symptoms. In addition to the direct effects of these drugs, age, duration of therapy, HIV disease, and return to health following suppression of viral replication also may play a role in the development of these abnormalities. With the longer duration of therapy, many other complications have been reported in association with current anti-HIV treatment including osteopenia, lactic acidosis, pancreatitis, and liver toxicities. Mitochondrial damage and depletion resulting from the inhibitory activity against gamma DNA polymerase of some of these drugs could potentially be involved in the etiology of these complications.

PRIORITY FOR FUTURE RESEARCH:

- **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 an era of increasingly effective therapies.**

Elucidation of the factors contributing to metabolic and body composition changes, toxicities, and long-term consequences of antiretroviral therapy will allow effective therapies to be tailored to the specific mechanism by

which they occur, with the potential for enhancing quality of life in HIV-infected persons.

Although the incidence of wasting has declined, it remains one of the most devastating aspects and one of the major causes of morbidity and mortality in individuals who do not respond or lack access to potent antiretroviral therapies, such as those in the developing countries. Weight loss in AIDS results in a significant reduction in survival, independent of other influencing factors, including CD4 cell count and history of infection or malignancy. AIDS patients with wasting illness escape a homeostatic control system and fail to generate normal responses to weight loss. The etiology of wasting associated with AIDS is complex and multifactorial. Alterations in energy expenditure, metabolic and endocrine abnormalities, and cytokine dysregulation have all been implicated in the pathogenic mechanisms underlying the wasting syndrome.

AIDS-Related Malignancies

AIDS is associated with a broad spectrum of neoplasms, including Kaposi's sarcoma (KS), lymphomas, human papillomavirus (HPV)-related cervical and anogenital carcinomas, Castleman's disease, leiomyomas, leiomyosarcomas, and hepatitis B-related hepatocellular carcinomas. Because HIV causes immunosuppression and because 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. NIH-supported investigators are trying to clarify the mechanistic role of chronic stimulation mediated by viral and cellular proteins, high levels of growth-promoting cytokines present in HIV-infected subjects, and human DNA and RNA viruses and their direct or indirect interaction with HIV in the development of AIDS-associated malignancies. Studies of AIDS-related KS have highlighted the potential causative role of a newly discovered human herpesvirus (HHV-8), angiogenic growth factors, and HIV proteins released in the extracellular milieu in the etiology of this neoplasm. Elucidation of the interactive factors involved in the pathogenesis of AIDS-associated malignancies will possibly translate to the identification of new targets for prevention and treatment.

Following the introduction of effective antiretroviral therapies, preliminary studies have shown a dramatic decline in the incidence of KS, but no decrease in non-Hodgkin's lymphoma (NHL) or other AIDS-related malignancies has been reported. More extensive followup is needed to clearly discern the impact of effective therapy and prolonged survival of HIV-infected persons on their risk of developing cancer.

Neuropathogenesis

Neurological disease and neurobehavioral dysfunction associated with HIV infection cause considerable morbidity and mortality in afflicted children and adults. These manifestations include diseases associated with opportunistic infection of the brain resulting from the underlying immunodeficiency and the AIDS dementia complex, a disorder that is unique to HIV infection. HIV enters the central nervous system (CNS) very early during infection, although manifestation of neurologic impairment occurs in late-stage HIV infection. Intense research efforts have focused on elucidating the role of HIV persistence in the brain parenchyma in the development of CNS disease. The cells expressing HIV or simian immunodeficiency virus (SIV) in patients or monkeys with AIDS have been found to be primarily perivascular macrophages, that is, cells derived from monocytes trafficking to the brain that have a very rapid turnover. These findings raise the intriguing possibility that the viral reservoir in the CNS is not composed of persistently or latently infected cells but of cells undergoing continual turnover. NIH-supported research is directed at understanding how HIV infection contributes to nervous system damage through direct interaction of HIV with neuronal and nonneuronal cells and indirect mechanisms, such as those mediated by cytokines, chemokines, and neurotoxins released in response to the infection or the local inflammatory response to the infection. Important areas of ongoing research include the determination of how HIV enters and establishes infection in the different compartments of the CNS and the correlation between the extent of HIV replication *in vivo* and the incidence and severity of neurologic complications. The possible role of the CNS as a reservoir of HIV infection in the setting of antiviral therapies with limited CNS bioavailability is also under investigation. Special emphasis in all these studies is given to *in vivo* models of neuropathogenesis and to the integration of basic research studies on the neurologic complications of AIDS with natural history studies and ongoing clinical trials.

Opportunistic Infections

HIV infection results in 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-1-infected individuals. OIs 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. Currently supported research is directed toward developing methods to culture and grow these

pathogens *in vitro*, developing animal models to study disease pathogenesis, sequencing these infectious microorganisms' genomes, identifying new targets for therapeutic interventions, and facilitating discovery and development of prophylactic and therapeutic agents. Special emphasis is given to the interactions between the pathogen and the host and its immune system. This research will permit a better understanding of the establishment of infection, mechanisms of immune control by the host, evasion by the pathogen, and the contribution of the host immune response to disease.

The use of potent antiretroviral therapies has resulted in a dramatic decline in the incidence of OIs, suggesting that the increase in the number of immune cells that follows effective antiretroviral therapies is accompanied by the recovery of functional responsiveness to antigens of several important opportunistic pathogens. However, development of OIs during the first 2 months of effective antiretroviral therapy has also been described, suggesting that the restoration of immune function may be partial or delayed. New manifestations also have been reported in HIV-infected persons taking anti-HIV drugs as a result of reconstitution of their immune responses.

OIs remain the most important complication of HIV infection and the principal cause of death in AIDS patients. Understanding the fundamental biology and pathogenesis of these organisms, their interaction with the host immune system, and the effect of therapy-associated immune reconstitution on the clinical course and manifestations of OIs will translate into new or more rational approaches to the prevention and treatment of OIs in patients on antiretroviral therapy, as well as in patients who lack access to or who are not responding to antiretroviral therapies.

Organ System-Specific Complications of HIV Infection

Organ system-specific manifestations also attend HIV infection and disease. Gastrointestinal dysfunction and malabsorption are commonly observed in HIV-infected subjects. The gastrointestinal tract is one of the most important routes of transmission of HIV and appears to be a major site of viral replication and the major site of CD4+ T-cell depletion in early stages of infection in the SIV model. NIH-supported researchers are investigating the contribution of OIs, of micronutrient deficiencies, of acquired deficiencies in intestinal enzymes, of malignancies, and of potential HIV infection of cells in the gastrointestinal tract to the gastrointestinal complications observed in HIV-infected individuals. HIV infection is also associated with multiple endocrine alterations, probably reflecting critical interaction between the endocrine and the immune systems. HIV-associated hematologic, pulmonary, heart, renal, and mucocutaneous complications

also represent a cause of morbidity in infected subjects. The pathogenic mechanisms involved in all 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.

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE: (The scientific objectives 2.A and 2.B are of equal weight.)

Delineate the viral and host mechanisms involved in the transmission, establishment, and spread of HIV infection in adults and children.

2.A

STRATEGIES:

- Delineate the relative efficiency of transmission of cell-free and cell-associated virus in various bodily fluids at different portals of entry.
- Delineate the molecular mechanisms by which virus-encoded genes, viral gene products, and host cellular factors regulate HIV replication and influence transmission, establishment, and spread of HIV infection.
- Determine the role of viral phenotype/genotype and dose on transmission of cell-free and cell-associated virus, in various bodily fluids.
- Determine the structures of viral and host proteins important for the transmission, establishment, and spread of HIV infections.
- Determine the cell or tissue types that serve as the portals of entry and support subsequent spread of HIV.
- Determine the mechanisms by which STDs and other processes may influence HIV transmission, establishment, and spread.
- Identify host factors that mediate resistance or sensitivity to infection, and delineate their mechanisms of action.
- Identify viral and host factors that influence the ability of an HIV-infected person to transmit HIV infection to others.
- Define the cellular and immune mechanisms that inhibit/enhance the early events in the transmission, establishment, and spread of HIV infection.
- Evaluate the influence of effective antiretroviral therapies on the early events in HIV transmission, establishment, and spread.
- Study the biology of the mucosal immune system, including the cellular elements and regulatory processes responsible for the generation of immune responses.

- Investigate transmission, establishment, and spread of HIV upon re-exposure in previously infected individuals.
- Identify the biologic, environmental, social, gender-related, and host factors that determine the relative efficiency of HIV transmission in various populations, especially developing versus developed country populations.
- Elucidate unique aspects of the biology of HIV transmission in diverse settings (domestic and international) and in underresearched populations in both genders.

To facilitate the research goals listed above:

- Further develop and utilize experimental human, nonhuman, *ex vivo*, and theoretical/mathematical models to study the transmission and establishment of lentiviral infections with emphasis on models of direct relevance to human HIV infection and models that address important issues not readily approachable in human subjects.
- Promote augmented access to and sharing of key patient samples, animal model resources, laboratory reagents, new technologies and equipment, information databases, and quantitative virologic and immunologic assays.

OBJECTIVE: (The scientific objectives 2.A and 2.B are of equal weight.)

Delineate the viral and host mechanisms associated with the pathogenesis of immune dysfunction and disease progression in HIV-infected adults and children.

2.B**STRATEGIES:**

- Determine the impact of early events in the establishment and systemic spread of HIV infection on the clinical course of the disease.
- Define the virologic, host, pharmacologic, and environmental factors that contribute to disease progression and nonprogression.
- Define the virologic and host factors that enable HIV to establish and maintain a persistent infection *in vivo* in the setting of both drug-naive and drug-treated individuals.
- Delineate the mechanisms of host immune control of HIV replication and how the effectiveness of immune control may vary depending upon the identity and location of infected host cells.
- Delineate the molecular mechanisms by which virus-encoded genes, viral gene products, and host cellular factors regulate HIV replication and influence pathogenesis.
- Determine the structures of viral and host proteins involved in the processes that underlie disease progression.
- Delineate the direct and indirect mechanisms underlying HIV-induced depletion and dysfunction of immune target cells/tissues, focusing on:
 - ▶ The loss of specific CD4+ T lymphocyte subpopulations and clones;
 - ▶ The impact of HIV infection on T-cell population numbers, specificities, and functions;
 - ▶ Virally triggered immunopathogenesis, including immune activation, induction of nonresponsiveness, dysregulation in the number and function of immune effector cells other than T lymphocytes, and production of host factors, including cytokines and other mediators;
 - ▶ The structural and functional compromise of primary and secondary lymphoid organs, including hematopoietic precursor cells and their microenvironment;

- ▶ Influences on the developing immune system; and
- ▶ Disruption of host compensatory mechanisms that govern the generation, regeneration, and homeostasis of T-cell populations.
- Evaluate whether and to what extent viral-induced damage to the immune system can be reversed following suppression of HIV replication by therapeutic interventions.
- Determine the life span and developmental and regenerative pathways of T lymphocytes; elucidate the mechanisms that regulate the size and composition of T-cell populations and how these may change with age.
- Define markers and functional assays that will enhance our understanding of and ability to study immune function in humans, especially those approaches that permit study of the *in vivo* activity of the immune system.
- Elucidate the unique aspects of the biology of disease progression in both genders and in diverse and underresearched populations.
- Determine the impact of reinfection by HIV on the clinical course of the disease.
- Define the reservoirs of virus infection that permit HIV persistence in the setting of effective antiretroviral therapies.
- Determine the viral and host factors associated with clinical response and lack of response to therapeutic interventions in HIV-infected subjects.

To facilitate the research goals listed above:

- Further develop and utilize experimental human, nonhuman, *ex vivo*, and theoretical/mathematical models to study the pathogenesis of lentiviral infections with emphasis on models of direct relevance to human HIV infection and models that address important issues not readily approachable in human subjects.
- Promote augmented access to and sharing of key patient samples, animal model resources, laboratory reagents, new technologies and equipment, information databases, and quantitative virologic and immunologic assays.

OBJECTIVE: (The scientific objectives 2.C through 2.F are of equal weight.)**Elucidate the etiology and pathophysiology of HIV infection- and treatment-related metabolic and body composition changes in adults and children.****2.C****STRATEGIES:**

- Investigate the direct and indirect mechanisms by which antiviral therapies and/or suppression of HIV replication may affect metabolism, body composition, and long-term risk of atherosclerotic cardiovascular disease.
- Define the etiologic and pathogenic mechanisms of HIV-related metabolic and body composition changes (including studies performed on appropriate animal models) that may be operative at various stages of disease and in individuals of different ages, genders, and races.
- Elucidate the virologic and host consequences of HIV infection that result in metabolic changes, alterations in body composition and nutritional status, impaired growth and development, malabsorption, and anorexia.
- Elucidate the pathogenic mechanisms by which OIs, hormonal dysregulation, and other consequences of HIV infection lead to metabolic and body composition changes, impaired growth and development, malabsorption, and anorexia.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms of HIV-associated metabolic and body composition changes and impaired growth and development; evaluate how HIV-associated metabolic and body composition changes and impaired growth and development are altered by such therapies.
- Determine factors associated with clinical response and lack of response to therapeutic interventions against AIDS-associated metabolic and body composition changes and impaired growth and development.

To facilitate the research goals listed above:

- Transfer expertise from the endocrine and metabolic research field to the HIV field and promote linkage between HIV researchers and established individuals and centers of excellence in metabolic and endocrine research.

- Promote programs to facilitate augmented access to and sharing of key patient samples, *in vivo* and *in vitro* metabolic research techniques, animal model resources, laboratory reagents, new technologies and equipment, information databases, modeling and calculation tools used in metabolic research, and quantitative virologic and immunologic assays.

OBJECTIVE: (The scientific objectives 2.C through 2.F are of equal weight.)

Elucidate the etiologic factors, cofactors, and mechanisms in the pathogenesis of HIV-related malignancies in adults and children.

2.D**STRATEGIES:**

- Elucidate the role of HIV infection and its associated immune dysfunction in the development of HIV-associated malignancies.
- Elucidate the role of infectious agents other than HIV, including novel pathogens, in the development of HIV-associated malignancies, and develop new methodologies for novel pathogen identification.
- Define the biologic processes underlying transmission and pathogenesis of infectious pathogens associated with AIDS-related malignancies.
- Identify the mechanisms by which immune dysregulation, oncogenes, suppressor genes, carcinogens, and non-HIV viral and other microbial genes and proteins contribute to the development of HIV-associated malignancies; correlate these molecular factors with epidemiologic studies.
- Identify the characteristics of the host that predispose to development of HIV-associated malignant disease.
- Determine the role of immunologic control to infectious etiologic agents in their susceptibility to AIDS-associated malignancies.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms of HIV-related malignancies, and evaluate how the manifestations of HIV-associated malignancies are altered by such therapies.
- Determine factors associated with clinical response and lack of response to antineoplastic therapeutic intervention in HIV-infected subjects.

To facilitate the research goals listed above:

- Promote programs to facilitate the development of and augmented access to *in vivo* animal models, patient specimens for HIV-associated malignancies, sharing of key patient samples, laboratory reagents, new technologies and equipment, information databases, and quantitative virologic and immunologic assays.

OBJECTIVE: (The scientific objectives 2.C through 2.F are of equal weight.)**Elucidate the mechanisms underlying HIV-associated neurological disease and neurobehavioral dysfunction in adults and children.****2.E****STRATEGIES:**

- Determine the cellular and molecular bases and pathogenic mechanisms involved in HIV-associated neurobehavioral and neurological dysfunction, including:
 - ▶ Identifying how HIV enters, establishes infection, spreads, and persists in the CNS;
 - ▶ Examining the effects of HIV infection on specific cell populations and regions of the nervous system;
 - ▶ Investigating the connection between blood-brain barrier dysfunction and neuronal injury;
 - ▶ Determining the relationship of virologic, host (including gender-specific differences), pharmacologic, and environmental factors to HIV-associated CNS dysfunction;
 - ▶ Determining the consequences of the biologic activity of cytokines, other mediators, and their receptors on the CNS in the context of HIV infection; and
 - ▶ Developing methods to monitor the levels of HIV replication and consequences of HIV infection within the CNS in living subjects.
- Determine the impact of HIV/CNS infection on systemic disease progression.
- Determine the role of the CNS as a reservoir of, and sanctuary for, persistent HIV infection.
- Define mechanisms of immunologic control of HIV and OIs in the CNS.
- Develop methods to investigate, diagnose, and monitor HIV-associated neurological and neurobehavioral disorders.
- Investigate aspects of HIV infection that uniquely influence the developing nervous system.

- Delineate the role of OIs and drug treatment in neurologic and neurobehavioral complications of AIDS, including CNS dysfunction and peripheral neuropathies.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms of HIV-associated neurologic diseases and neurobehavioral dysfunction; evaluate how the manifestations of HIV-associated neuropathogenesis are altered by such therapies.
- Determine factors associated with clinical response and lack of response to therapeutic interventions for neurologic and neurobehavioral complications of HIV disease.

To facilitate the research goals listed above:

- Develop and employ appropriate animal models (e.g., nonhuman primate models) of CNS-lentivirus infection that best reflect specific aspects of the human HIV/CNS disease course or treatment that are crucial to understanding neurobehavioral and neurologic disorders.
- Ensure that information, materials, and specimens needed for neuro-AIDS research are appropriately collected, catalogued, classified, stored, and distributed, and promote access to and sharing of new technologies and equipment.
- Encourage new multidisciplinary approaches to investigate HIV-associated neurological disease and neurobehavioral dysfunction.

OBJECTIVE: (The scientific objectives 2.C through 2.F are of equal weight.)**Elucidate the pathogenic mechanisms of HIV-related OIs in adults and children.****2.F****STRATEGIES:**

- Conduct studies of the basic biology and pathogenic mechanisms of opportunistic pathogens and their interactions with the host, including definition of:
 - ▶ Portals of entry of opportunistic pathogens into the human host;
 - ▶ Processes that underlie the establishment and spread of infection; and
 - ▶ Mechanisms of tissue and organ system damage.
- Develop *in vitro* techniques and animal models to propagate and define the life cycles of the opportunistic pathogens associated with HIV disease.
- Develop and validate diagnostic assays for the reliable and rapid identification of HIV-associated OIs.
- Identify and elucidate the genetic and environmental risk factors associated with susceptibility to and development and progression of OIs.
- Study the effects of OIs on immune dysfunction and HIV disease progression.
- Elucidate the mechanisms of immune function that mediate protection against OIs.
- Study the effect of coexisting infections on the course and manifestations of HIV disease.
- Study the effects of therapy-associated immune reconstitution on the clinical course and manifestations of OIs.
- Develop and validate assays of opportunistic pathogen-specific immune responses.
- Characterize the molecular and phylogenetic relationships of major AIDS OI pathogens; standardize and improve techniques of phylogenetic analysis; and integrate strain-specific characterization data into

studies of the pathogenesis, mechanisms of transmission, and epidemiology of OIs.

- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms of HIV-associated OIs, and evaluate how the causes, agents, and manifestations of HIV-associated OIs are altered by such therapies.
- Determine factors associated with clinical response and lack of response to therapeutic interventions against OIs in HIV-infected subjects.
- Study clinical syndromes seen in HIV-infected persons that are not associated with known opportunistic pathogens in order to identify novel pathogens and characterize their biology and pathogenic mechanisms.

OBJECTIVE:

Elucidate the etiology and pathogenesis of HIV-related disorders in adults and children: gastrointestinal, pulmonary, hematologic, renal, endocrine, cardiovascular, cutaneous, oral, and other diseases.

2.G**STRATEGIES:**

- Investigate the etiologic and pathogenic mechanisms of HIV-associated gastrointestinal disease, including those responsible for varying manifestations of disease in diverse populations.
- Identify the etiologic and pathogenic mechanisms of HIV-associated nephropathy, including those responsible for varying manifestations of disease in diverse populations.
- Investigate the etiology and pathogenesis of endocrine dysfunction and the role of alteration in the endocrine/immune axis in progression of HIV disease.
- Investigate the etiologic and pathogenic mechanisms of HIV-associated hematologic disorders.
- Investigate the etiologic and pathogenic mechanisms of HIV-associated pulmonary disorders.
- Investigate the etiology and pathogenesis of additional HIV-related disorders including autoimmune disorders and cardiovascular, cutaneous, oral, and other organ/tissue-specific disorders, as these disorders compromise organ system development and function.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms of HIV-related organ/tissue-specific complications, and evaluate how the manifestations of HIV-related organ/tissue-specific complications are altered by such therapies.
- Determine factors associated with clinical response and lack of response to therapeutic interventions against HIV-related disorders.
- Employ animal models to investigate the etiology and pathogenesis of lentivirus-associated disorders in the above systems.

Therapeutics

SCIENTIFIC AREA OF EMPHASIS:

Therapeutics

SCIENTIFIC ISSUES

Scientific findings from basic research have significantly advanced the discovery, development, and clinical evaluation of drugs against HIV infection and its associated opportunistic infections (OIs) and malignancies. Most important of these advances has been the demonstration that multidrug combinations of antiretroviral agents significantly reduce the viral load in many patients to undetectable levels. This reduction in HIV is accompanied by increases in CD4 cell counts and, in many cases, the amelioration of HIV-related symptoms. These effects have been observed in individuals with advanced HIV disease and/or OIs. The improvements seen with highly active antiretroviral therapy (HAART) now permit the elimination of some drugs previously required for HIV-infected individuals for prophylaxis against certain OIs.

Further research is needed to identify therapeutic regimens that are less toxic, limit development of drug resistance, enter viral reservoirs to inhibit viral replication, permit easier adherence, and are more readily accessible. The scientific agenda for this area of research is focused on answering the following questions:

When should antiretroviral (HAART) therapies be initiated?

- How long can successful therapies maintain decreased viral loads, increased CD4 counts, and improved clinical outcomes?
- When should antiretroviral therapies be changed?

- 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 HAART?
- 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?

The development of new agents that are designed to inhibit one or more of the regulatory or enzymatic proteins of HIV is a priority for NIH-sponsored research. 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.

NIH sponsors an active and comprehensive drug discovery and drug development program that permits the design and identification of new, safe, and more effective drugs that can (1) enter host compartments that serve as viral reservoirs, (2) produce less toxicity and fewer side effects, (3) eliminate viral mutation that results in drug resistance, (4) permit increased compliance with treatment regimens, and (5) be more readily accessible.

A better understanding of the molecular mechanisms involved in viral entry into host cells may permit the design and development of new and more effective antiretroviral drugs. The identification of new viral and host/cellular targets permits the ongoing development of agents that block or inhibit infection of host cells. Recent studies have led to the development of potential gp41 fusion inhibitors, as well as the identification of several potential integrase inhibitors and promising protease inhibitors capable of crossing the blood-brain barrier.

PRIORITY FOR FUTURE RESEARCH:

- **Advance the discovery and validation of new targets and the discovery of new agents. Identify and validate new or insufficiently studied viral and host targets for anti-HIV therapy. Develop agents targeted at drug-resistant virus. Develop new methodologies for predicting biologic properties, including metabolic abnormalities and cellular toxicities, of new and existing compounds in humans.**

NIH-sponsored programs provide resources for conducting preclinical testing of potential compounds against HIV infection and its sequelae. Further development of *ex vivo* and animal models to evaluate agents for their potential pharmacologic properties and toxic effects is important to accelerate the identification of new and better compounds for entry into clinical trials. Coordination of and collaboration between Government-sponsored programs with the pharmaceutical and biotechnology industries is essential to advancing potential agents through this stage of the drug development process.

PRIORITY FOR FUTURE RESEARCH:

- **Stimulate research to support the preclinical development of agents. Develop *ex vivo* and/or animal models to evaluate the biological properties of drugs, including their pharmacology and toxicology. Create an environment that will foster drug development, including the coordination of government and industrial resources for drug synthesis and formulations development.**

The discovery, development, and testing of microbicides and of other chemical and physical barriers to provide viable and affordable methods to halt the sexual transmission of HIV and sexually transmitted diseases (STDs) are critical priorities for NIH. Effective microbicides have the potential to greatly reduce the spread of HIV infection in developing countries and in populations in this country where the epidemic is increasing. NIH recently collaborated with other domestic agencies and international organizations to convene the Microbicides 2000 Conference, which assessed the state-of-the-science and strengthened collaborations between developed and developing nations in this critical area of research. Additional efforts are essential to accelerate microbicides research and to ensure a comprehensive program for screening, discovery, development, preclinical testing, and clinical evaluation of potential spermicidal and nonspermicidal topical agents and other barrier methods.

PRIORITY FOR FUTURE RESEARCH:

- **Develop and test safe, effective, and feasible microbicides and other methods to halt sexual transmission of HIV. Support the discovery, development, and preclinical and clinical testing of improved, acceptable, effective, and safe physical and chemical barrier methods—including topical microbicides, other agents, and other methods—to reduce sexual transmission of HIV and STDs in developed and developing nations.**

Recent insights into HIV biology and HIV/host interactions have led to the development of treatment strategies involving combinations of antiretroviral drugs that can result in prolonged and significant suppression of detectable HIV replication in many HIV-infected individuals. Studies have shown that the viral load rapidly increases when individuals stop taking the antiretrovirals. Although there is evidence of immune reconstitution in some HIV-infected individuals who receive antiretroviral therapy, it is still not known whether the immune function of individuals on therapeutic regimens can be restored without additional interventions.

Findings from cohort studies of long-term nonprogressors indicate that HIV-1-specific CD4 T-cell responses are able to control HIV infection. In a few cases, individuals who have stopped taking antiretrovirals, then restarted medications, and then terminated them entirely have remained disease-free, with some residual virus in the blood. These findings raise the possibility that CD4 cells can be triggered to control the viral load. These studies have important implications for the development of new immune therapeutic strategies. Structured treatment interruptions, which involve the intermittent removal of drug therapies for brief periods of time, may allow for a brief burst of HIV replication to trigger a potent immune response to HIV infection. Further studies of this approach are necessary to determine its validity, safety, and efficacy. Because the current antiretrovirals have limitations (toxicities, side effects, strict dosing requirements, development of drug resistance, and inability to enter viral reservoirs for complete eradication of HIV), immune-based and immune-restorative therapies are needed, especially for individuals with more advanced disease and immune depletion.

PRIORITY FOR FUTURE RESEARCH:

- **Develop and evaluate therapeutic approaches that will enhance, restore, induce, and/or maintain the immune systems of HIV-infected individuals and extend our understanding of immunopathogenesis.**

High levels of viral replication occur during acute infection and the long period of clinical latency. The development of HAART has permitted innovative studies on the immunopathogenesis of HIV disease. Studies are needed to determine if the virus could be eradicated by initiating HAART shortly after an individual is newly infected. While complete eradication of HIV may not be possible with existing therapeutic regimens, viral suppression, improved immune responses, and delay in disease progression may be possible as a result of early treatment. In addition, studies are urgently needed to determine when agents in multiple drug combinations should be switched to maintain low viral loads, sustain improvements in immune responses, and further delay disease progression. The routine use of genotypic and phenotypic testing in the clinical setting may permit the selection of more effective and individualized therapeutic regimens, as well as further characterization of drug-sensitive/drug-resistant strains and the monitoring of emerging strains of drug-resistant HIV.

PRIORITIES FOR FUTURE RESEARCH:

- **Conduct clinical studies to determine when antiretroviral therapy should be initiated, so as to produce extended periods of viral suppression, improved immune function, and delayed disease progression.**
- **Conduct strategy trials to determine optimal use of antiretroviral treatment such as sequencing of antiretroviral therapy (including definitions of treatment failure) and when to switch agents. Conduct clinical trials to determine optimal use of antiretroviral therapy so as to produce extended periods of viral suppression, improved immune function, and delayed disease progression.**

One of the highest priorities of NIH-sponsored research is the clinical evaluation of potential agents against HIV infection and its associated OIs and malignancies. Current therapeutic regimens are extremely complex; patients may experience drug-drug interactions as well as difficulties in adhering to rigid dosing schedules that can lead to drug-resistant strains. In addition, there are limitations to HAART, including the persistence of HIV reservoirs and ongoing viral replication; toxicities and side effects, including metabolic complications and body composition transformations; rigid dosing regimens; and high cost. Ongoing and planned research is evaluating new and better drugs and drug combinations to reduce and overcome these limitations, so that HIV-infected individuals can live longer, with improved quality of life and delayed disease progression.

As the AIDS epidemic has evolved in the United States, the disease has increasingly affected diverse groups, including women, racial and ethnic minorities, adolescents, injecting drug users (IDUs), and older adults. A high priority for NIH-sponsored research is the recruitment and retention of individuals from these affected populations in clinical trials. NIH also supports clinical studies in international settings. Such studies require the direct involvement of host-nation researchers in the design, conduct, and analysis of clinical trial protocols. This approach ensures the host nation's involvement in the study, as well as in the implementation of the therapeutic interventions after the study is completed. NIH will continue to develop and evaluate therapeutic regimens that can be implemented in developed and developing nations to prevent, treat, and control HIV disease.

Studies on the long-term effects of antiretrovirals are essential. Metabolic complications, body transformations, and mineral and bone loss have been associated with some of the drugs used in HAART. Ongoing studies are evaluating these adverse reactions and the potential drug-drug interactions that may result from current treatment regimens. Further studies are needed to evaluate delayed and long-term effects of these antiretrovirals as well as to determine the mechanisms/pathophysiology of these effects.

PRIORITIES FOR FUTURE RESEARCH:

- **Conduct clinical studies to evaluate new and existing treatment regimens. Identify regimens with improved toxicity, efficacy (including disease progression), pharmacodynamics (including modeling simulation), activity in viral reservoirs, and adherence potential.**
- **Enhance efforts to better understand new and existing drug treatment regimens in women, adolescents, children, older adults, racial and ethnic groups, and IDUs. Targeted studies conducted in developing nations should take into account underlying diseases and malnutrition as well as the ability to implement interventions in limited-resource settings.**
- **Evaluate the long-term effects of antiretroviral therapy. Enhance the capabilities for long-term followup studies of individuals on antiretroviral therapy. Assess delayed or late toxic effects, including hepatotoxicity, carcinogenicity, metabolic/endocrine abnormalities, cardiovascular complications, neurological disorders, and musculoskeletal abnormalities. Determine the mechanisms/pathophysiology of these effects, such as mitochondrial disorders.**

The evaluation of potential therapies for the treatment of HIV infection and its associated OIs, malignancies, and other complications is a high priority for NIH-sponsored research. Significant increases in the incidence of hepatitis C virus (HCV), hepatitis B virus (HBV), tuberculosis (TB), and multidrug-resistant TB in the setting of HIV infection are occurring both globally as well as in U.S. minority, urban, and drug-using populations. Antiretroviral and OI prophylaxis regimens are becoming increasingly complex with respect to adherence and drug-drug interactions. Ongoing and planned research is needed to address these issues, with the goal of better understanding the effects of co-infection on viral replication, disease progression, development of HIV-related complications, and understanding treatment interactions.

PRIORITY FOR FUTURE RESEARCH:

- **Evaluate the effect of co-infection (e.g., HBV, HCV, and TB) on management of HIV and vice versa. Determine the bidirectional effects of co-infection on disease progression and interaction of therapy.**

The prevention of maternal-fetal transmission is critical to the reduction of the primary source of HIV transmission in children. Previous NIH studies have demonstrated that the use of zidovudine administered antepartum, intrapartum, and to the neonate has significantly reduced perinatal transmission in the United States and Europe. Recent findings from the HIV Network for Prevention Trials (HIVNET) 012 study have shown that a simplified, less costly (\$4) regimen of nevirapine could successfully reduce the rate of maternal-infant transmission by nearly 50 percent in a developing nation. A single oral dose of nevirapine provided to the HIV-infected pregnant women at the onset of labor and to the infant within 72 hours of birth may represent a viable strategy for decreasing perinatal transmission in developing nations. Current guidelines recommend treatment of the pregnant woman with HAART for maternal indications, preferably with a regimen that includes zidovudine. Perinatal and pediatric clinical trials in domestic and international settings are needed to determine the safety and pharmacokinetics of combination therapy. NIH also continues to support studies of other strategies that may halt maternal-fetal transmission in diverse cultural and economic settings. These include studies on breast-feeding practices that will provide important information on the timing, risk factors, and potential approaches to blocking this mode of HIV transmission.

Also important is long-term followup of infants exposed *in utero* and for postnatal periods to antiretroviral agents for possible adverse consequences. NIH and the Centers for Disease Control and Prevention (CDC) recently completed a thorough review of the records of 15,000 uninfected children enrolled in NIH- and CDC-sponsored perinatal transmission studies for the last decade. None of the 43 deaths that occurred have been attributed to mitochondrial disease resulting from perinatal exposure to zidovudine. Additional investigations are underway in the United States and abroad to search for symptoms of mitochondrial disorders among living children with and without exposure to antiretroviral agents. Thus far, there is no clinical evidence that *in utero* exposure to antiretroviral agents is harmful to either the fetus or infant. NIH will continue to monitor the health outcomes in infants exposed to antiretroviral drugs and will remain vigilant in monitoring for possible late events as a greater number and variety of antiretroviral agents are routinely used in pregnant women.

PRIORITY FOR FUTURE RESEARCH:

- **Develop therapeutic regimens to block perinatal transmission that can be implemented in developed and developing nations. Develop safe, effective, feasible, and conveniently administered strategies to interrupt maternal-fetal transmission of HIV. Evaluate the safety and pharmacokinetics of antiviral agents in pregnant and breast-feeding women, including studies on the transplacental passage of the agents and safety for the fetus; evaluate pharmacokinetics, metabolism, tissue absorption, and drug elimination in the newborn. Conduct studies on the long-term effects on infants exposed *in utero*, and for postnatal periods, to antiretrovirals.**

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE: (The scientific objectives of 3.A and 3.B are of equal weight.)

Increase the understanding of viral and cellular functions required for reproduction of HIV and identify and validate new targets for their inhibition; discover and develop novel agents and therapeutic strategies directed against viral and/or host factors involved in HIV infection.

3.A

STRATEGIES:

- Identify and characterize new or understudied viral and host targets for anti-HIV therapy; define the cell-specific factors leading to viral fusion, entry, integration, transcription, replication, assembly, budding, and infectivity; define molecular and cellular determinants affecting HIV virulence and pathogenicity; develop predictive test models, including appropriate lentivirus systems, to aid in the identification of agents and strategies active against these targets.
- Acquire structural information on HIV constituents and host cell components that can be used to design potent therapeutic agents with activity against drug-resistant strains; make resolved structures available to publicly accessible databases in a timely manner.
- Integrate genomics and informatics paradigms, concepts, and methodologies (microchip-based screens and analyzers) into mainstream drug discovery and development research.
- Develop analytical methods and chemical formulations of new compounds and combinations of compounds, including those derived from the screening of natural products.
- Develop agents or treatment strategies to destroy or inhibit the expression of HIV in latently infected cells and anatomical and organ reservoirs.
- Conduct preclinical studies of potential agents—when they cannot be done by industry—to assess immunologic effects, pharmacokinetics and pharmacodynamics, toxicity, teratogenicity, transplacental carcinogenicity, and effects on fertility.
- Employ whole animal and *ex vivo* organ models of lentivirus infections to study the biologic and pharmacologic characteristics of therapeutic compounds.

- Evaluate the intracellular pharmacokinetics and activity of antiretroviral agents in various cell types and in different stages of the cell cycle in all age groups, including newborns; correlate intracellular pharmacokinetic parameters with drug efficacy/toxicity.
- Develop agents with desirable biopharmaceutical characteristics, such as improved bioavailability and tissue penetration to the central nervous system (CNS) and other sanctuary sites; develop drug delivery devices or systems that improve the pharmacokinetic profile of therapeutic agents to target specific organs or tissues, improve adherence to therapeutic regimens, and reduce toxicities and adverse metabolic effects.
- Study the mechanisms and implications of drug resistance and viral fitness; evaluate the early markers and genotypic mutations that lead to resistance and cross-resistance.
- Emphasize basic and applied research to advance gene-based strategies to treat HIV infection and its complications; support the development of new approaches and technologies to optimize gene delivery and allow for stable and persistent gene expression; continue the development of *ex vivo* approaches to gene therapy while advancing new concepts, strategies, and vectors for direct *in vivo* delivery that eliminate the need for *ex vivo* manipulations of cells.
- Develop formulations of existing and experimental agents that are suitable for infants and children; develop novel delivery strategies and formulations of existing and experimental agents that facilitate adherence.
- Develop enabling technologies to accelerate and optimize the discovery and development of therapeutic entities and strategies; establish the infrastructure to provide services and reagents needed by the scientific community.
- Explore and develop, as appropriate, mechanistic mathematical and computer models of HIV infection and therapeutic interventions that may enable simulations for the purpose of predicting *in vivo* efficacy and toxicity and other outcomes of clinical trials.
- Investigate the host cell effects of antiretroviral drugs.
- Investigate therapies to modulate cellular bystander apoptosis induced directly or indirectly by HIV.

- Cooperate with the private sector to increase involvement and investment in HIV drug discovery and development research, especially in areas where public health needs are substantial; assume full responsibility, when necessary, for the development of potential therapies with high public health relevance and need.

OBJECTIVE: (The scientific objectives of 3.A and 3.B are of equal weight.)

Conduct clinical trials and develop new methodologies to evaluate the short- and long-term safety and efficacy of therapeutic agents and strategies against HIV infection; optimize clinical efficacy and proper use of available modalities to treat HIV infection in treatment-naïve and in treatment-experienced HIV-infected individuals; define, evaluate, and mitigate factors that adversely affect the success of therapeutic strategies against HIV infection (including nonadherence and resistance); advance the understanding of disease pathogenesis and progression as part of the design and conduct of clinical trials; develop appropriate partnerships to design and conduct clinical studies domestically and internationally.

3.B**STRATEGIES:**

- Conduct clinical trials of potential therapeutic agents and combinations of agents in adults and children to determine pharmacokinetics and tissue bioavailability, antiviral activity, effects on the immune system, safety, and clinical efficacy.
- Enhance efforts to evaluate new and existing drug treatment regimens in women, adolescents, children, older adults, racial and ethnic groups, and IDUs as reflected by demographics of the epidemic. When appropriate, evaluate potential gender-, race-, ethnicity-, and age-specific differences in drug efficacy and safety, including pharmacokinetics, metabolism, tissue absorption, and drug elimination.
- Evaluate combinations of antiretroviral agents that are synergistic, complementary, toxicity-sparing, and non-cross-resistant in individuals with prior antiretroviral drug experience, including pretreated individuals with advanced disease.
- Support long-term clinical trials to study the timing, selection, and strategic sequencing of antiretroviral agents to optimize clinical outcomes.
- Conduct clinical studies using structured treatment interruptions to determine their effects on virologic and immunologic responses to HIV infection, viral containment, and disease progression.
- Develop a coordinated plan to evaluate the long-term efficacy of therapeutic strategies and to facilitate cross-protocol analyses and meta-analyses.

- Evaluate potential delayed or late toxic effects of antiretroviral therapy (e.g., hepatotoxicity; carcinogenicity; and metabolic/endocrine, musculoskeletal, and neurological abnormalities) following short-term administration of prophylaxis regimens and during chronic treatment.
- Develop and evaluate standardized virologic, immunologic, and clinical markers to assess drug activity; determine and validate the prognostic value of surrogate markers in response to various therapeutic interventions.
- Support research and development of more relevant clinical trial design, statistical methodology, and the selection and investigation of biologic markers, surrogates, and/or other outcomes to evaluate the safety, efficacy, and reasons for failure of new agents and strategies for the treatment of HIV disease.
- Explore the utility of real-time antiretroviral phenotypic and genotypic assays in managing antiretroviral therapy across a broad spectrum of patients.
- Determine the relationship between drug exposure (pharmacokinetics) and outcomes (antiviral effect and immune function) to facilitate rational dosing strategies within clinical trials and individual patient management (therapeutic drug monitoring).
- Identify and evaluate the viral and host factors that influence disease progression during antiretroviral treatment, including malabsorption, drug resistance, and suboptimal adherence.
- Evaluate the presence and persistence of HIV in different tissue compartments during HAART; investigate the possible role of HIV compartmentalization in the development of HIV drug resistance, transmission, and establishment of long-term reservoirs; and evaluate regimens to diminish or eradicate this viral pool.
- Develop more accurate and simple approaches to quantify HIV replication in different tissues and body compartments.
- Evaluate the impact of transmission of drug-resistant HIV strains on disease progression and therapy.
- Support research on the effectiveness of pharmacologic, behavioral, and other approaches to facilitate better adherence to antiretroviral regimens, including the development of drugs and drug combinations

that are more potent, longer acting, less toxic, less likely to induce resistant strains of HIV, and with less potential for drug-drug interactions.

- Determine the factors influencing adherence to multidrug regimens in IDUs and other special populations; develop better methods to assess adherence to treatment regimens across a variety of affected populations; compare and validate adherence measures in the context of HIV treatment; evaluate the impact of improved adherence on the clinical effectiveness of antiretroviral regimens.
- Investigate drug-drug interactions among commonly used treatments for HIV-related disease and its complications, as well as other substances that may be used by HIV-infected individuals (e.g., drug-abuse treatment medications, oral contraceptives, other prescription drugs, nonprescription drugs, alternative or complementary therapies, and substances of abuse, including alcohol).
- Design and implement clinical trials to evaluate the long-term effects of antiretroviral treatment of primary infection in adults (horizontal transmission) and neonates (vertical transmission), including assessment of the course of subsequent clinical disease using virologic and immunologic markers.
- Investigate immunologic and virologic dynamics during primary perinatal infection; use this information, as appropriate, to investigate potential surrogate outcomes in pediatric trials.
- Evaluate the safety of antiviral agents in pregnant women, including transplacental passage of the agents and safety for the fetus; evaluate pharmacokinetics, metabolism, tissue absorption, and drug elimination in the newborn.
- Evaluate the role of antiretroviral therapy or other treatment modalities administered in the immediate post-HIV-exposure period in preventing the establishment of HIV infection in persons exposed under a variety of circumstances, such as sexual, injection related, mother to infant (e.g., breast-feeding), mucosal, and broken skin.
- Support clinical trials to evaluate the safety and efficacy of gene therapy.
- Support studies that combine novel therapeutic modalities (e.g., cell-based, gene-based, and therapeutic vaccine approaches) with state-of-the-art antiretroviral therapies.

- Evaluate the impact of potent antiretroviral therapy on the reactivation of hepatitis viruses, the potential need for treatment of viral hepatitis in coinfecting patients, and the development of late-stage complications of viral hepatitis.
- Design methods to improve the retention of patients in clinical trials.
- Develop, incorporate, and validate appropriate quality-of-life parameters in clinical trials of antiretroviral agents.
- Determine the global patterns of resistance to antiretroviral therapies and how these patterns could reduce the long-term effectiveness of antiretrovirals.
- Enhance the development of international collaborations that will assist in addressing important therapeutic research questions by including populations of HIV-infected individuals outside the United States.
- Assist developing nations, as appropriate, in technology transfer to facilitate the evaluation of antiretroviral agents and other therapies in local settings.

OBJECTIVE:

Develop and evaluate new compounds to inhibit sexual transmission of HIV, including topical microbicides, HIV-specific virucides, biologic approaches, and systemic agents.

3.C**STRATEGIES:**

- Support the discovery, development, and preclinical evaluation of new, improved, acceptable, effective, and safe chemical and physical barrier methods, including topical microbicides and other methods, to reduce sexual transmission of HIV and STDs in developed and developing nations.
- Support the evaluation of existing chemical and physical barriers to reduce sexual transmission of HIV and STDs in developed and developing nations.
- Develop formulations and vehicles suitable for the genitourinary tract and gastrointestinal tract.
- Develop and support animal models to evaluate the safety and efficacy of chemical and physical barriers, including topical microbicides, for prevention of mucosal HIV transmission.
- Develop and validate sensitive, specific, and reproducible methods for quantifying HIV in genital secretions.
- Study the relationship between viral characteristics (quantitative, qualitative, drug resistance, phenotype/genotype) of both cell-free and cell-associated HIV in genital secretions and their association with risk of sexual transmission.
- Conduct clinical testing of microbicides and other chemical and physical barriers to demonstrate safety and efficacy in reducing sexual transmission of HIV.
- Cooperate with the private sector to increase involvement and investment in the discovery, development, and evaluation of microbicides, especially in areas where public health needs are substantial; assume full responsibility, when necessary, for the development of potential microbicides with high public health relevance and need.

OBJECTIVE:

Develop, evaluate, and implement strategies for interrupting vertical transmission of HIV from mother to child, including breast-feeding, in developed and developing countries; evaluate short- and long-term effects of these regimens; and extend the understanding of the pathogenesis of perinatal transmission and early infection.

3.D**STRATEGIES:**

- Use and/or develop suitable animal models to evaluate novel strategies to prevent transplacental and postpartum transmission of lentivirus, and to evaluate transplacental passage of antiretroviral agents and their effects on placental function and on fetal development and viability.
- Investigate the mechanisms and timing of perinatal HIV transmission (*in utero*, intrapartum, and postpartum via breast milk) to facilitate and develop targeted drugs/strategies to decrease perinatal transmission.
- Develop and evaluate strategies for reducing the risk of vertical transmission of HIV from pregnant women to their offspring without compromising treatment of the pregnant women; such strategies may include antiviral agents, anti-HIV immunoglobulin, monoclonal antibodies, agents targeted to cellular targets (e.g., blocking cytokine receptors), cell- and gene-based strategies, vitamin supplementation, HIV vaccines, adjuvants, and virucides, alone or in combination.
- Advance cell- and gene-based therapies in neonates and young children that may restore immune function and control viral load.
- Evaluate the short- and long-term toxicities, pharmacokinetics, and antiretroviral activity of agents and combinations of agents in pregnant women and their neonates.
- Determine the characteristics of transplacental transfer of anti-HIV drugs from mother to infant.
- Evaluate the risk of vertical transmission of drug-resistant strains of HIV.
- Evaluate the influence of drug-resistant virus in the mother on the efficacy of regimens to prevent perinatal transmission.

- Study the effect of antiretroviral regimens used for maternal health indications on the risk of vertical transmission and on other outcomes, including developmental milestones in offspring.
- Investigate interactions between drugs of abuse and HIV therapeutics in pregnant women; evaluate the impact of such interactions on vertical transmission of HIV and maternal disease progression.
- Investigate interactions between HIV therapeutics and anti-addiction therapy in pregnant women; evaluate the impact of such interactions on the maintenance of anti-addiction therapy and on vertical transmission of HIV.
- Support the long-term followup of women and children (including children ultimately found to be uninfected) who participate in perinatal trials to evaluate possible late effects of antepartum antiretroviral therapy.
- Evaluate the potential mechanism for possible carcinogenic or mutagenic effects of *in utero* antiretroviral exposure.
- Support collaborative analyses of existing databases to evaluate potential obstetric interventions to prevent vertical transmission, such as cesarean deliveries and other aspects of intrapartum care.
- Further evaluate the risk and benefit of cesarean delivery for reducing transmission, e.g., evaluate the risk of postpartum morbidity in infected women with elective cesarean delivery and determine whether additional benefit of cesarean delivery for preventing transmission accrues in women receiving HAART.
- Support research and development of new, more relevant clinical trial designs and statistical methodologies and the selection and investigation of biologic markers, surrogates, and/or other outcomes to evaluate the activity, clinical efficacy, and reasons for failure of new agents and approaches in the treatment of pregnant women and their offspring.
- Improve the sensitivity and specificity of diagnostic procedures that are accessible and cost-effective to permit the earliest possible determination of HIV infection in infants born to HIV-infected mothers.
- Develop criteria to define early identification of infant infection in perinatal trials conducted in breast-feeding and non-breast-feeding

populations; determine if antiretroviral and/or immunopreventive therapies affect the timing and sensitivity of these assays for diagnosis.

- Develop reproducible, sensitive, specific, low-technology, and cost-effective assays to detect and quantitate the amount of cell-free and cell-associated virus in breast milk.
- Support international collaborative efforts to conduct perinatal trials.
- Develop and evaluate strategies to prevent transmission of HIV through breast milk.
- Develop safe and conveniently administered strategies to interrupt maternal-fetal transmission of HIV using interventions that are widely affordable in developing and resource-poor nations.
- Develop, incorporate, and validate appropriate quality-of-life parameters in clinical trials of HIV-infected pregnant women.

OBJECTIVE: (The scientific objectives of 3.E and 3.F are of equal weight.)**Develop strategies for the evaluation and management of antiretroviral therapy-related complications and advance the understanding of their pathogenesis.****3.E****STRATEGIES:**

- Evaluate potential delayed or late-toxic effects of antiretroviral therapy (e.g., hepatotoxicity; carcinogenicity; and metabolic/endocrine, neurological, and musculoskeletal abnormalities) following short-term administration of prophylaxis regimens as well as during chronic treatment.
- Support research on the pathogenesis and mechanisms of the complications of therapeutic regimens used to treat HIV disease and its associated disorders.
- Develop and test approaches to prevent or reverse potential metabolic abnormalities (e.g., changes in body composition, development of atherogenicity and endocrine disorders, and changes in bone and muscle structure) based on an understanding of the mechanisms by which antiviral therapies and/or suppression of HIV replication may affect metabolic processes.

OBJECTIVE: (The scientific objectives of 3.E and 3.F are of equal weight.)

Discover and validate potential molecular targets and discover and develop agents for prevention and treatment of HIV-associated infections while improving the understanding of the biology and pathogenesis of HIV-associated opportunistic microorganisms. Develop and evaluate new agents and strategies for preventing and treating OIs and other co-infections.

3.F**STRATEGIES:**

- Improve our understanding of the interplay between HIV-associated immune deficits and the onset of infectious complications.
- Delineate the structure and function of potential molecular targets of HIV-associated opportunistic microorganisms. Support preclinical drug development programs to develop therapies against opportunistic pathogens, especially *Cryptosporidium*, *Mycobacterium avium* complex (MAC), multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB), microsporidia, JC virus (JCV) (the etiologic agent of progressive multifocal leukoencephalopathy [PML]), cytomegalovirus (CMV), human papillomavirus (HPV), and azole-resistant fungi, with emphasis on innovative approaches and agents with favorable bioavailability and pharmacokinetics.
- Develop *in vitro* culture systems for opportunistic microorganisms such as *Pneumocystis carinii*, cryptosporidia, and microsporidia; develop animal models that predict the efficacy of potential agents for preventing and/or treating OIs.
- Support and encourage mechanism-based screening of novel synthetic compounds and natural products to identify candidate agents used for treating OIs; provide support for medicinal chemistry, structural databases, resynthesis, and toxicity testing.
- Determine the high-resolution molecular structures for proteins from OI microorganisms; utilize these structures in the design of inhibitors; provide coordinates for resolved structures in publicly accessible databases in a timely manner; determine structures of other OI macromolecules (e.g., surface glycoproteins) as potential targets.
- Conduct preclinical studies of anti-OI drugs—when they cannot be done by industry—to assess their immunologic effects, pharmacokinetics and pharmacodynamics, toxicity, teratogenicity, transplacental carcinogenicity, and effects on fertility.

- Conduct clinical trials to evaluate agents for the prophylaxis and treatment of HIV-associated OIs; target OIs shown to cause significant morbidity by epidemiological studies, including MDR-TB, MAC disease, CMV disease, HPV disease, cryptosporidiosis, microsporidiosis, cryptococcosis, azole-resistant fungal disease, toxoplasmosis, *Pneumocystis carinii* pneumonia (PCP), acyclovir-resistant herpes simplex and varicella zoster virus infections, PML, bacterial infections, and other infections made worse by HIV-induced immunosuppression.
- Support clinical trials that assess the impact of new antiretroviral regimens on the risks for and manifestations of OIs associated with HIV/AIDS in adults and children.
- Develop better strategies for simultaneous prevention of multiple OIs in the context of antiretroviral treatment; determine the optimal timing for initiating/discontinuing prophylaxis for different OIs; develop improved OI strategies to minimize toxicities and the development of drug-resistant microorganisms.
- Develop more precise tools to identify those patients at high risk for development of specific OIs in order to improve the efficiency of clinical trial design and to improve the risk/benefit ratio of the drugs in clinical use for prophylaxis and for treatment.
- Support research on the effectiveness of pharmacologic and other approaches to facilitate better adherence to anti-OI regimens.
- Support clinical research in the context of drug abuse treatment to reduce OIs among HIV-infected drug users; develop and evaluate interventions to facilitate better adherence to therapies among populations with HIV infection and substance abuse and/or mental illness.
- Study the bidirectional interaction of HIV infection and OI microorganisms on pathogenesis, presentation, and disease outcomes in adults and children in the context of clinical trials of antiretroviral agents and OI drugs; study the bidirectional effects, including pharmacologic interactions, of anti-OI therapies with antiretrovirals.
- Study the differential impacts of primary acquisition of OI pathogens compared to reactivation of latent infections on disease manifestations and treatment.

- Determine the role of preexisting immunity in controlling OIs; evaluate immune-based therapies as adjuncts for treating OIs.
- Support research and development of new, more relevant clinical trial designs, statistical methodologies, and selection and investigation of biologic markers, surrogates, and/or other outcomes to evaluate the safety, efficacy, and reasons for failure of new agents and approaches in the treatment and prophylaxis of opportunistic complications of HIV disease.
- Develop clinically useful assays and methodologies for early and rapid diagnosis of OIs, quantitative assessment of microbiological responses, and drug sensitivity testing of opportunistic microorganisms, especially *M. tuberculosis*, *M. avium*, enteric pathogens, *P. carinii*, CMV, fungi, toxoplasma, and JCV.
- Develop OI-specific vaccines; determine the ability of HIV-infected adults and children to respond to current and new vaccines against OIs throughout the course of their HIV infection.
- Support clinical trials to evaluate the safety and pharmacokinetics of existing and experimental agents intended to treat or prevent OIs in HIV-infected infants, children, and pregnant women.
- Develop formulations, routes of administration, and delivery systems for existing and experimental anti-OI drugs appropriate for use in infants, children, and other populations.
- Develop, incorporate, and validate appropriate quality-of-life parameters in clinical trials of agents used to prevent or treat OIs.
- Cooperate with the private sector to increase involvement and investment in OI drug discovery and development research, especially in areas where public health needs are substantial; assume full responsibility, when necessary, for the development of potential therapies with high public health relevance and need.

OBJECTIVE:

Develop and evaluate therapeutic approaches that will enhance, restore, induce, and/or maintain the immune systems of HIV-infected individuals and extend our understanding of immunopathogenesis.

3.G**STRATEGIES:**

- Study the therapeutic mechanisms of action of immunomodulating agents; proceed with preclinical studies of the most promising approaches.
- Evaluate immunoactive strategies and approaches to immune restoration in clinical trials, taking advantage of opportunities to test specific hypotheses of HIV immunopathogenesis.
- Evaluate the ability of the immune system to maintain or repair itself after maximal viral suppression has been achieved through HAART.
- Develop, validate, and standardize new methods for evaluating immune function in clinical trials that enroll adults and children.
- Accelerate the preclinical and clinical testing of cytokines, modulators of cytokines, and other immunoactive agents to prevent further immune deterioration and to reconstitute deficient immune systems in HIV-infected individuals.
- Develop and evaluate active and passive immunotherapeutic approaches for the treatment of HIV infection and its sequelae.
- Support research on the effectiveness of pharmacologic and other approaches to facilitate better adherence to immunoactive regimens.
- Evaluate the safety and efficacy of administering cellular elements in an autologous, syngeneic, allogeneic, or xenogeneic fashion, including use of expanded peripheral blood T cells, bone marrow, cord blood stem cell transplantation, and thymic transplantation.
- Develop new therapeutic strategies based on gene therapy approaches to protect mature, hematopoietic stem cells, and stromal elements for replacing immune functions from destruction by HIV.
- Evaluate the potential for inhibiting HIV replication and spread by modifying chemokine receptor expression and/or chemokine levels and by developing agents capable of blocking HIV binding to co-receptors.

- Explore the feasibility and utility of the storage of lymphocytes and/or stem cells from HIV-infected individuals; support the development of a cord blood bank of cells from infants born to HIV-infected mothers in anticipation of future gene therapy trials.
- Develop, incorporate, and validate appropriate quality-of-life parameters in clinical trials of immunoactive agents.

OBJECTIVE:

Develop strategies for assessing, preventing, and treating HIV nervous system infection and central and peripheral nervous system disorders in HIV-infected individuals; advance our understanding of the pathogenesis of the HIV-associated neurologic complications.

3.H**STRATEGIES:**

- Develop and evaluate novel strategies and agents, such as neuroprotective agents, that are active against putative pathways of HIV-induced CNS dysfunction in adults and children.
- Develop and utilize *in vitro* and animal models of CNS lentivirus infections and CNS injury in order to identify therapeutic agents for the nervous system complications of HIV infection.
- Assess the pathogenic role of viral sequestration in the CNS, including its potential role as a reservoir of viral persistence and as a site of independent selection of antiviral drug-resistant strains and other mutants.
- Design and conduct clinical trials addressing nervous system complications of HIV infection in adults and in children.
- Develop objective quantitative assessments (e.g., surrogate markers in cerebrospinal fluid [CSF], neuroimaging) of treatment effects.
- Develop therapeutic agents to block HIV entry into the CNS and treat HIV in the CNS; evaluate their safety and efficacy in clinical trials.
- Develop better strategies to prevent, diagnose, and treat peripheral neuropathies in HIV-infected persons while improving the basic understanding of pathogenesis.
- Characterize the CNS pharmacokinetics and pharmacodynamics of antiretroviral drugs; determine the importance of CNS drug penetration, particularly penetration of the blood-brain barrier, in reducing CNS infection in neurologically symptomatic and asymptomatic subjects.
- Conduct studies to determine drug-drug interactions among commonly used treatments for HIV disease and its complications with drug abuse treatment medications.

- Validate and enhance the efficiency of neuropsychological and neurologic tests performed in the context of clinical trials to identify those tests most capable of determining treatment-related changes in different age and cultural groups.
- Determine the prevalence, causes, and pathogenesis of pain in HIV-infected individuals and develop optimal therapies to control pain.
- Monitor CSF for HIV viral load and immune activation markers in patients enrolled in studies of HAART.
- Further elucidate the correlation among CSF HIV viral load, chemokine levels, proinflammatory cytokines, and markers of immune activation with CNS disease in the setting of clinical trials.
- Support research and development of new, more relevant clinical trial design and statistical methodologies and the selection and investigation of biologic markers, surrogates, and/or other outcomes to evaluate the safety and clinical efficacy of new agents and approaches in the treatment of neurologic complications of HIV disease.
- Support research on the effectiveness of pharmacologic and other approaches to facilitate better adherence to therapeutic regimens in neurologically impaired individuals with HIV infection.
- Develop, incorporate, and validate functional neurologic and quality-of-life scales that are aimed at measuring the impact of the nervous system complications of HIV infection in clinical trials.
- Selectively incorporate neurologic and neuropsychological assessments into other HIV-related clinical trials.

OBJECTIVE: (The scientific objectives of 3.I and 3.J are of equal weight.)**Discover, develop, and evaluate improved strategies for the assessment, treatment, and prevention of HIV-associated malignancies.****3.I****STRATEGIES:**

- Identify novel mechanisms and targets (e.g., cytokines, angiogenesis factors, hormones) for treatment and prevention of HIV-associated tumors such as Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL), and HPV malignancies, including anogenital dysplasias and cancers; develop new therapeutic strategies based on these findings.
- Promote screening, discovery, and development of novel therapeutic agents with activity against HIV-associated malignancies, including pathogenesis-based strategies, agents with better CNS penetration, and agents with better safety profiles.
- Develop therapeutic and prevention strategies for HIV-associated malignancies based on an improved understanding of the role of infectious agents (e.g., KSHV/HHV-8 and Epstein-Barr virus [EBV], HPV, and hepatitis B virus) in their pathogenesis.
- Use rational drug design approaches based on structural biologic and biochemical information to develop therapeutic agents for the treatment of HIV-associated malignancies by targeting pathogenic mechanisms.
- Develop preclinical and *in vivo* models (e.g., severe combined immuno deficiency-human [SCID-hu] mice) for the testing of potential therapeutic strategies against HIV-associated malignancies.
- Develop *in vitro* models of KS and assays for angiogenesis inhibitors.
- Improve methods for early diagnosis of malignancies and for early detection of recurrent cancer.
- Design and conduct clinical trials to evaluate novel approaches for the treatment of HIV-associated malignancies and to evaluate the interactions between treatment of malignancies and treatment of the underlying HIV infection.
- Develop, incorporate, and validate clinical trial methodologies to correlate tumor-specific responses with clinical benefit; develop a staging system indicative of prognostic response and survival.

- Encourage collaborative studies within clinical trials networks to develop mechanisms for early identification of patients at high risk for malignancy and to develop and assess interventional strategies to reduce the risk or prevent the development of malignancies.
- Study the role of immunomodulating agents in the treatment and prevention of AIDS-related tumors.
- Encourage clinical studies of HIV-infected patients with non-AIDS-defining malignancies, emphasizing the evaluation of diagnostic and management challenges and the impact of therapy on virologic, immunologic, tumor parameters, and drug-drug interactions.
- Explore strategies for attenuating or preventing toxicities associated with therapy, and study the effects of such strategies on virologic and immunologic parameters.
- Support research on the effectiveness of pharmacologic and other approaches to facilitate better adherence to complex therapeutic regimens in individuals with HIV-associated malignancies.

OBJECTIVE: (The scientific objectives of 3.I and 3.J are of equal weight.)

Develop and evaluate better therapies for the treatment and prevention of serious HIV-associated complications, including wasting syndrome and growth failure, and hematologic, dermatologic, renal, metabolic, pulmonary, cardiac, gastrointestinal, endocrinologic, psychiatric, and oral manifestations.

3.J**STRATEGIES:**

- Develop and evaluate therapeutic strategies for preventing and treating complications of HIV infection while increasing knowledge of their pathogenesis.
- Develop and evaluate conventional and nonconventional chemopreventive approaches, including those containing quantifiable doses of micronutrients (such as vitamins and trace elements) and macronutrients, to delay the development of wasting and other complications of HIV disease in infected individuals who may be at risk of malnourishment, including those who use illicit drugs.
- Develop and evaluate new agents and approaches to prevent, treat, and reverse wasting syndrome, growth retardation and failure, and other complications of HIV infection; optimize clinical trial designs, statistical methodologies, and biologic markers, surrogates, and/or other outcomes used to evaluate the safety and clinical efficacy of new agents and approaches to treat and prevent these complications.
- Support research on the effectiveness of pharmacologic and other approaches to facilitating better adherence to therapeutic regimens.
- Develop, incorporate, and validate appropriate quality-of-life parameters in clinical trials of wasting and other complications of HIV infection.
- Evaluate the safety and efficacy of alternative and complementary therapies—including nonpharmacologic interventions such as exercise, nutrition, and sleep hygiene—in the management of HIV disease and its complications.
- Evaluate drug-drug interactions with potential clinical significance for patients with HIV infection, particularly the interactions between antiretroviral agents and psychotropic medications; develop strategies to avoid or minimize the clinical impact of these interactions.

Vaccines

SCIENTIFIC AREA OF EMPHASIS:

Vaccines

SCIENTIFIC ISSUES

As a result of new scientific findings and new funding in the area of HIV vaccines, many new approaches to HIV vaccines are being pursued from the basic research level through vaccine product development. In the past several years, investigators have determined that several AIDS vaccine strategies have been able to decrease the level of the virus that was established shortly after challenge in animal models. Even though these vaccines have not been totally effective in preventing virus infection, the concept that control of viral load may be an equally important vaccine outcome has been recognized because of data that suggest that partners of HIV-infected subjects become infected far less frequently when there is a reduced level of HIV transmission. The one thing that all of these vaccine strategies appear to have in common is their ability to induce, at least to some level, cytotoxic T lymphocytes (CTL) specific for viral antigens.

**BASIC RESEARCH IN
VACCINE DESIGN
AND TESTING****Animal Model Development**

New chimeric viruses made from the envelope gene of HIV and the core and replication genes of simian immunodeficiency virus (SIV) (i.e., SHIV viruses) have been produced and adapted for growth in macaque models with differential pathogenicity. One of these, SHIV-SF162, a macrophage-tropic virus that utilizes the CCR5 co-receptor, has shown a pathogenicity that reflects a rapid loss of T cells in the gastrointestinal tract with a slower loss of peripheral CD4 T cells. A second SHIV chimera,

SHIV-SF33, with a strong T-cell tropism, results in a dramatic and rapid depletion of peripheral T cells, with a slower loss of CD4 cells from the mucosal sites. Attempts to create new SHIV viruses that can express the envelope gene from HIV isolates of different genetic clades are being developed to help in the evaluation of vaccines that are based on envelope products from different regions of the world.

Attenuated Vaccines

Continued followup of the rare individuals who had received attenuated forms of HIV and of nonhuman primates that have received attenuated virus with *nef* gene alterations reveals that many have progressed to disease years after infection, leading to increasing concern as to whether an attenuated vaccine for HIV will be possible. Investigators have continued to evaluate new mutations that might cripple the virus in ways that make defective proteins or substitute nonpathogenic genetic variants for both structural and other regulatory genes.

Correlates of Immune Protection

Exposed individuals that have remained seronegative despite high risk of HIV exposure have been documented in groups of individuals that have been studied in various parts of the world and in the United States. Concerns have been raised about the possibility of a hidden virus infection that may become apparent if the repeated exposure either continues so that a pathogenic recombinant forms or a protective immune state wanes so that an individual is no longer protected.

Long-term survivors of HIV infection have contributed important information about the complexity of the immune response that may be needed for effective vaccine protection. Studies within the past few years have indicated that T cell help for maintenance of HIV-specific CTLs may be extremely important for effective control of viral load. Parallel assessment in animal models has indicated that this will be an important parameter to induce in HIV vaccines.

Structure of the HIV Envelope

Continued studies of the structure and function of the HIV envelope have led several groups of researchers to pursue vaccine designs that remove the carbohydrate sites from HIV-envelope protein. Deglycosylated envelope gp120 and gp140 proteins are currently under study in macaques. It is hoped that these proteins will be more immunogenic and induce high titers of antibody that can neutralize a broad range of HIV isolates. With this same

goal in mind, new approaches to configure fully native trimeric gp160 or partially truncated gp140 proteins are also underway. Many of these new approaches to seek more immunogenic forms of HIV envelope are using envelope genes that are derived from CCR5-using, nonsyncytium-inducing (NSI) isolates that appear to have some early outgrowth advantage in HIV-infected individuals.

Targeting Antigen Presentation with Vectors and DNA Approaches

Several newer vaccine strategies are targeting dendritic cells, either through vaccine delivery or the use of viruses for vectors that do so naturally. The alphavirus family, which includes Venezuelan equine encephalitis virus (VEE), Sindbis virus, and Semliki Forest virus, may have a natural propensity to move to antigen-presenting cells or dendritic cells. Making a vaccine that uses the outer coat of the alphavirus to carry copies of HIV protein genes, in a product called VEE replicons, has been shown to induce immune responses and effect reduced virus load in macaques challenged with pathogenic virus. In addition, some investigators have developed DNA vaccines that have incorporated non-methylated CpG motifs that appear to also target dendritic cells.

Vaccine Designs

New vaccine approaches that focus on non-envelope proteins and, in particular, the exploration of HIV tat protein as a target for early immune intervention, have been under investigation in several centers. Finally, new approaches to investigate whole killed virus that has been genetically and/or chemically inactivated have also been linked with the concept that presentation of the immune system with an appropriately configured virus particle could present a better surface to induce neutralizing antibody.

In summary, many new vaccine concepts are being explored at the basic research level. These concepts are bolstered by new scientific findings on the immune response to HIV and new insights that have been revealed from the structure and function relationships of the HIV virion itself. To be certain that this kind of scientific base continues to fill the gaps in HIV/AIDS vaccine research, the following priority for AIDS-related research was identified.

PRIORITY FOR FUTURE RESEARCH:

- **Continue to expand core programs in HIV/AIDS vaccine research and development to ensure that the research pipeline for vaccine research and development is robust.**
 - **Encourage studies that will identify immunotypes, define the significance of genetic variation, and assist in the selection of products that may induce broadly protective immune responses.**
 - **Continue to explore different combinations of vaccine products and schemes of priming and boosting with different products to optimize both quality and duration of the immune responses.**
 - **Enable testing in the most relevant animal models (e.g., models that reflect kinetics of human HIV infection).**

CLINICAL TRIALS

NIH has now conducted more than 50 Phase I and two Phase II clinical trials of nearly 30 vaccine products, individually or in combination, in human volunteers in collaboration with academic investigators and company co-sponsorship. Many of the early trials involved recombinant HIV envelope protein, the outer coating of the virus. However, complex vaccine products and products that contain other components of HIV have been included in a large number of these trials in the past few years.

Phase I trials have provided extensive safety information, as well as immunogenicity data from human volunteers in whom different vectors and adjuvants were studied. An ongoing Phase II clinical trial of a canarypox vector carrying copies of genes for several HIV proteins that was being administered alone or concurrently with a recombinant HIV envelope protein in one of the study arms is nearly completed. Preliminary information from this trial (released in mid-1999) indicated that whereas infections occurred in a few individuals because of risky behavior, about the same number of infections occurred in the placebo group as in the vaccine groups, but there were twice as many vaccine recipients. The number of participants in this Phase II trial is too small to draw efficacy conclusions, but these data are consistent with observations in related animal studies. Ongoing trials continue to evaluate alternate vectors and recombinant envelope protein products that might provide improved responses.

The first trial of an HIV vaccine in Africa is examining whether cross-type CTL are generated by Ugandan individuals in response to a vaccine that is derived from an HIV type that is common in the United States and Europe but less common in other parts of the world. CTL from HIV-infected

individuals recognize conserved regions of amino acids that are common between different HIV subtypes. It is unknown whether individuals from very different genetic backgrounds and environments will be able to generate CTL in response to HIV vaccines. If CTL recognition of different viral subtypes is a common event, then vaccines that have been developed for clade B in the United States and Europe may be used in broader international settings without re-design and additional testing.

PRIORITY FOR FUTURE RESEARCH:

- **Conducting clinical trials of promising vaccine candidates in both domestic and international settings is a top priority for the vaccine field. Current plans for expanded trials will require an initial expansion for the vaccine trials network to be undertaken in FY 2001, and this effort will need to be further expanded in FY 2002 to conduct efficacy trials. Clinical trials are expected to be iterative and allow for comparison of vaccine candidates.**
 - **Conduct Phase I and II trials of products, moving new concepts and products into human testing as rapidly as possible.**
 - **Enable the conduct of efficacy trials with sufficient lab support to define correlates of immunity.**

THERAPEUTIC VACCINATION IN SETTINGS WITH IMMUNE RECONSTITUTION

An area that has gained substantial momentum is therapeutic HIV vaccines. With the advent of effective antiretroviral therapy that can control virus replication, it may be possible to obtain the regeneration of effective T-helper responses with vaccines. The careful exploration of potential therapeutic vaccines, particularly in adolescents and young persons who would face long-term antiretroviral therapy, has gained a lot of interest. New trials to address the effectiveness of HIV therapeutic vaccines for persons already on highly active antiretroviral therapy (HAART) have been started, and others are being designed with long-term reduction in viral load and clinical benefit as potential outcomes. Careful assessment of these trials for immune correlates may permit prophylactic vaccine design.

PASSIVE IMMUNITY

Important observations using passive transfer of antibody have been published within the past year. Combining selected anti-HIV monoclonal antibodies, with or without purified HIV immunoglobulin (HIVIG) that could be administered by intravenous route, protected against oral exposure in infant macaques or against vaginal exposure in adult female macaques. The monoclonal antibodies that were used can neutralize HIV isolates from a number of individuals, in particular, isolates that are able to grow out

early in infection, that utilize the CCR5 chemokine receptor, and that demonstrate a macrophage-tropic NSI phenotype.

Data have been published from the clinical trial of zidovudine (ZDV) plus intravenous HIVIG to prevent transmission from mothers to infants. This trial was begun in 1993, was closed to accrual in 1997, and completed the 24-month followup of infants in 1999. In this study, no infants born to mothers who received HIVIG were HIV positive by virus culture or HIV RNA testing at birth. Whereas, about half of the infected infants, whose mothers received intravenous Ig (IVIG) in the trial, were virus culture-positive at birth. By 6 weeks, most of the infants, who were eventually diagnosed as HIV positive, had been detected by viral culture in both arms of the trial, and there was no statistically significant difference in the HIV transmission. Because so few infants became infected, this trial was closed before target enrollment was reached. Analysis of transmission within subgroups within the trial suggested that the infants, born to women with lower CD4 count and/or prior ZDV use because of their health, may have benefitted from the HIVIG administration.

ADVANCES IN HUMAN IMMUNE RESPONSES

Clinical trials of vaccines in human subjects have been instrumental in rapidly adapting and utilizing technology for functional assessment of immune lymphocytes raised by vaccines. Techniques that measure individual cells and quantify immune responses, as well as define T-cell specificity, have been developed for HIV-infected individuals in preparation for assessment of HIV vaccines in human clinical trials.

Parallel evaluation of immune parameters in macaque vaccine studies may identify the best way to measure the immune responses that correlate with protection for human clinical trials. The immunological assessment of HIV/AIDS vaccines and of correlates of immune protection is a future research priority.

PRIORITY FOR FUTURE RESEARCH:

- **Expand immunological assessment of vaccines. This priority is deemed to be a critical element that underlies the evaluation of vaccines at multiple levels and is reflected in the following initiatives:**
 - **Ensure that standardized assays with high throughput for both animal and human studies are developed that are precise, sensitive, and practical. Develop and provide resources and appropriate reagents for these assays to enable a number of laboratories to work in parallel in different animal models as well as clinical trials.**

PRIORITY FOR FUTURE RESEARCH (CONTINUED):

- ▶ **Strengthen the immunological assessment of clinical vaccine trials, including therapeutic vaccine trials, and ensure linkage with development of the therapy aspects to understand principles and mechanisms of priming and boosting of the immune response.**
- ▶ **Study the immune responses in neonates and infants as a special case to assure development of appropriate vaccine products for breast-feeding populations where safe alternatives to breast-feeding are not readily available.**

PRIMATE RESOURCES

The need for increased primate resources appropriate for conducting vaccine studies already is impacting the ability to address questions of vaccine effects. The extent of this problem needs to be defined as quickly as possible so that comparative vaccine studies with adequate numbers of animals can be performed that will be informative for vaccine candidate development. Related studies of macaque genetics, particularly for the major histocompatibility complex (MHC) region that has defined roles in restriction of the immune response, should be implemented.

PRIORITY FOR FUTURE RESEARCH:

- **Increase AIDS-dedicated nonhuman primate resources for breeding and holding. NIH should immediately initiate a survey to define the extent of needs for nonhuman primates. A major program to assure the availability of pedigreed, specific pathogen-free (SPF) nonhuman primates designated for AIDS-related research that deals with several specific aspects relevant to vaccines should be implemented as quickly as possible.**
 - ▶ **Because of the impact of MHC genes on immune responses to vaccines, this program should incorporate characterization of the MHC haplotypes in macaques and other nonhuman primates that will permit functional programs for genetic typing of animals assigned to vaccine studies.**
 - ▶ **Increase availability of neonatal as well as adult animals for vaccine studies.**

INFORMATION, EDUCATION, AND INFRASTRUCTURE NEEDS

To move forward in large-scale vaccine or prevention studies will require major efforts in communities that may be rarely involved in medical research. Development of infrastructure may need to be undertaken, as well as information dissemination and education of staff, potential participants, and community leaders of the groups that will participate in vaccine research.

PRIORITY FOR FUTURE RESEARCH:

- **Invest in the development of critical vaccine research capabilities, information dissemination, and education to conduct vaccine trials in populations with a high incidence of HIV infection. As HIV infections continue to move deeper into minority populations, adolescents, and women in the United States who often do not perceive risk, new efforts must be developed for enabling partnerships and full participation of volunteers from these groups. Similarly, in international settings, increased attention must be paid to building the capability and infrastructure in populations in the sites identified for future efficacy trials; to provide a solid scientific knowledge base (incidence, viral subtypes, MHC types, natural history) to justify clinical trials; and to conduct vaccine trials in these sites and communities according to the highest clinical and ethical standards. This includes a broad range of activities:**
 - › **The transfer of information, development of scientific expertise, and training in all aspects of clinical trials to individuals in the populations identified for potential vaccine trials.**
 - › **To enable full participation for long-term trials and for international vaccine studies, especially in developing countries, this may require development of information and skills that will contribute to infrastructure development.**

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE:

Increase scientific knowledge through basic research on protective immune responses and host defenses against HIV to facilitate the development of vaccines and other biomedical intervention strategies to prevent and/or control HIV infection.

4.A

STRATEGIES:

Define the mechanisms underlying protective systemic and mucosal immunity to HIV and other lentiviruses by pursuing research that includes the following areas of interest:

- Determine the mechanisms of immunologically mediated control of infection with HIV and other related lentiviruses, including the role of specific and nonspecific cellular and biochemical immunity in inhibiting viral replication, to provide a basis for optimal vaccine design.
- Define the structure-function relationships and the antigenicity and immunogenicity of HIV proteins, including transient and conformational domains induced by virus interacting with CD4, chemokine, and other cellular receptors to improve vaccine designs to more effectively induce immune responses to block infection by active and passive immunity.
- Define and characterize viral B-cell and T-cell epitopes that induce protective immunity in HIV or related disease; utilize structure and antigenicity to determine whether and how their immunogenicity can be improved and exploited in vaccine development.
- Understand how and why HIV and related lentiviruses evade or escape from humoral and cellular arms of the immune response; design vaccine approaches to prevent this; and define conserved epitopes in which genetic substitutions cannot be tolerated by the virus.
- Characterize pathways of antigen processing of HIV proteins, including envelope glycoproteins, for presentation by MHC class I and class II molecules. Investigate the interaction of HIV proteins with antigen processing mechanisms that enhance or inhibit specific epitope presentation to the immune system.

- Study immunological memory and long-term protective function of different subsets of human lymphocytes in HIV-related disease; define factors that favor establishment and maintenance of memory cells able to generate effective recall to vaccine antigens, particularly HIV and related viral antigens, and development of long-term protective immunity, particularly in human subjects.
- Study the mechanism of action of vaccine adjuvants and enhanced modes of HIV and related lentivirus antigen presentation to induce different cytokine or chemokine responses; carry out translational research in nonhuman primates and human vaccinees.
- Determine how chronic infection with one strain of HIV or related lentivirus, including attenuated viruses, confers protection against subsequent infection or reduces viral replication of a second pathogenic virus strain; define the properties of the virus and of the immune system that are responsible for lack of disease induction and protection from challenge with wild-type virus; and determine the protective mechanism, duration, and extent of cross-protection.
- Define the heterogeneity of specific responses to vaccine immunogens, particularly HIV, within diverse tissue compartments, and identify factors that confer protection from infection by various routes including vaginal, rectal, oral, and parenteral.
- Determine which factors promote development of particular human effector cell types, promote production of antiviral substances including chemokines, or enhance non-antigen-specific protective mechanisms.
- Define the basis for immune reactivity (both humoral and cellular) across divergent HIV types (clades and biological phenotypes or immunotypes).
- Determine whether HIV immune responses that can contribute to immune enhancement of viral replication *in vitro* can interfere with induction or propagation of vaccine-induced effector responses *in vivo*.

Seek new clues for correlates of immune protection from HIV-infected or highly exposed but seronegative individuals, both adults and infants, and from lentivirus models that will provide the basis for further design of candidate vaccines by conducting the following studies:

- Study acutely infected individuals, exposed/seronegative, or possibly transiently infected humans, including uninfected children born to

HIV-infected mothers, individuals with controlled therapy interruptions, HIV-infected individuals vaccinated while on antiviral therapy, nonprogressors, and recipients of therapeutic vaccines to define immune responses to HIV-1 and HIV-2, potential vaccine-inducible host immune responses, and viral factors (or viral attenuations) that reduce the amounts of circulating virus and influence disease course.

- Elucidate the important mechanisms for protective immunity against HIV, including identification of specific responses by passive transfer of antibody or immune cells and deletion of selected immune subsets in nonhuman primate models.
- Investigate the sequence of events required for mucosal transmission/infection of HIV and other lentiviruses at different portals of entry to define how and where specific immune effector mechanisms can impede viral entry and/or prevent establishment of infection.
- Study mucosal immunity to viral and microbial antigens in relevant animal models and humans to develop optimal vaccine strategies for HIV antigen delivery and effective immune-based prevention of HIV transmission.
- Explore the molecular epidemiology, humoral, and cell-mediated immune response to HIV-1; acquire clinical specimens from populations relevant to vaccine trials for laboratory studies; and acquire appropriate epidemiological information to enable interpretation of these analyses.
- Monitor the effects on immune activation with intercurrent sexually transmitted diseases (STDs), administration of drugs of abuse, or effects of antiretroviral therapy on viral shedding in vaccinated subjects. Model these confounding elements in nonhuman primates.

Develop *in vitro* experimental approaches for analysis of vaccines that will combine sensitivity, high throughput, and the ability to use small sample volumes; develop *in vitro* and *in vivo* tools to study systemic and mucosal immune mechanisms of control of virus for analysis of vaccinated individuals (both adults and infants) and protected animals by undertaking the following research activities:

- Develop and improve animal models of lentivirus infection that are practical and representative of the spectrum of HIV infections and development of AIDS, including use of appropriate HIV cellular receptors and different modes of transmission; develop genetically

defined and histocompatible nonhuman primate models to facilitate immune cell transfer studies; in general, make models amenable to use in evaluating protection by vaccines or other biomedical interventions.

- Develop and standardize immunological reagents, improved methodologies, and assays to measure viral neutralization; explore the mechanisms of virus neutralization and the reason(s) for the relative difficulty to neutralize primary isolates.
- Study the function of CTLs, T-helper and viral suppressive immune responses, and develop and apply high-throughput assays with specificity for primary virus isolates.
- Develop or improve sensitive quantitative measures of HIV (and SIV) concentration in body fluids and low-level tissue reservoirs, including genital secretions and breast milk, to assess the effectiveness of vaccines designed to lower viral load and interrupt transmission or prevent disease progression.

OBJECTIVE:

Design viral antigens and vaccine delivery methods that elicit long-lasting protective immune responses against a broad range of HIV isolates by applying findings from basic, epidemiologic, and clinical research; facilitate development and preclinical evaluation of vaccine strategies in laboratory studies and animal models; and foster early and continued collaboration between academicians and industry in the research and development of candidate vaccines to test a broad array of vaccine concepts and combinations of different approaches for development of potential HIV vaccine products, including vaccines for particular populations.

4.B**STRATEGIES:**

Multiple parallel approaches to development and testing of candidate HIV/AIDS vaccines will be investigated to provide complementary and comparative preclinical data on safety and immunogenicity questions about HIV vaccines. Such studies should achieve the following:

- Support the design, development, production, and testing of novel HIV/AIDS vaccine candidates for safety and their ability to elicit appropriate antiviral immune responses. This may include, but is not limited to:
 - ▶ Virus-like particles containing one or more virus proteins, peptides, or antigens;
 - ▶ Whole-inactivated HIV rendered noninfectious by chemical and/or genetically engineered deletions of pathogenic viral elements;
 - ▶ Naturally occurring and genetically engineered, live-attenuated strains of HIV;
 - ▶ DNA or RNA coding for viral proteins;
 - ▶ Live, recombinant viral and bacterial vectors engineered to express one or more HIV proteins with attention to vectors that might provide dual benefit for HIV and some other pathogen or to vaccine vectors that target mucosal immune responses;
 - ▶ Viral replicons or other strategies to target dendritic cells;
 - ▶ Recombinant HIV viral protein subunits produced by a variety of methods, with an emphasis on retention or exposure (e.g., through deglycosylation) of critical nonlinear structural epitopes for induction of effective antibody responses;

- ▶ Structurally constrained viral protein fragments, peptides, mimetopes, or complex peptides capable of inducing and boosting cellular or humoral immunity to HIV; and
- ▶ Cell surface components carried on the viral surface.
- Foster collaboration between academic investigators, industry sponsors, NIH, and the Food and Drug Administration (FDA) on research and development of novel vaccine design concepts. These collaborations should
 - ▶ Enable production of pilot lots of vaccine candidates for testing in nonhuman primates and human subjects;
 - ▶ Develop programs to design and conduct comparative testing of vaccine approaches with industry and academic partners that will permit long-term followup to assess disease progression in animal models; and
 - ▶ Develop infrastructure; address scientific, legal, and regulatory issues to foster and encourage participation by, and collaboration between, academic investigators, industry, and other agencies in the research, development, production, and clinical testing of candidate vaccines.
- Foster the development of vaccines to optimize characteristics appropriate for broad international use, including designs exhibiting stability and ease of administration. This may include
 - ▶ Combined use of two or more vaccine strategies with mixed modalities to boost the same component and/or to engage different components of the immune response; and
 - ▶ Multivalent vaccine candidates incorporating different genetic clades and antigenic types to increase breadth of immune responses.
- Support design, development, and incorporation of methods to improve or modulate immune responses (qualitatively or quantitatively) in vaccine approaches, including
 - ▶ Novel adjuvants and delivery methods that might enhance effective dendritic cell antigen presentation;
 - ▶ Agents that stimulate or modulate mucosal immune responses or other host defenses, including cytokines or chemokines;
 - ▶ Vaccines formulated with cytokines or incorporating cytokine genes in vectors or other biologically active molecules; and

- ▶ Other novel strategies, including nutritional supplementation and treatment of underlying infections and/or diseases that might have an impact on vaccine responses.
- Evaluate the efficacy of vaccine and other immune prevention strategies in animal models of HIV and related lentiviruses by
 - ▶ Testing vaccine and other biomedical prevention strategies in animal models that most closely mimic HIV infection in humans;
 - ▶ Determining *in vitro* correlates of an *in vivo* protective immune response;
 - ▶ Determining the effect of vaccine formulation, site of delivery, and regimen, as well as the nature, timing, phenotype, and route of infectious virus challenge on the effectiveness of the vaccine-induced immunity;
 - ▶ Defining the impact of different vaccine approaches on kinetics of immune responses, kinetics and localization of viral replication, long-term followup of disease progression with low-level chronic infection and concomitant diseases (e.g., tuberculosis, hepatitis, or autoimmune diseases), and biologic characteristics of breakthrough virus including transmissibility;
 - ▶ Determining the impact of genetic factors and age on vaccine responses and on protection against virus at various challenge sites;
 - ▶ Studying the efficacy of the immune response in the face of viral mutation and variation; and
 - ▶ Investigating vaccines and other biomedical prevention strategies with attention to potential cofactors such as changes in vaginal/cervical epithelium during puberty, hormonal changes during pregnancy, use of contraceptives or hormonal replacement therapy, and presence of STDs; wherever possible, study potential concomitant effects on the genital tract immune system and inflammatory activity that might compromise integrity of the genital tract or the inductive ability of vaccines.
- Support development of reagents and standardized methods to assess specific vaccine-induced immune responses in animal models and humans, including infants, for both humoral and cellular aspects of systemic and mucosal immunity. This includes:

- ▶ Developing and refining assays to distinguish between serological and cellular responses due to immunization and those due to viral infection;
 - ▶ Characterizing and evaluating the potential negative side effects of candidate vaccine designs, including the potential to increase the susceptibility to infection or the rate of disease progression in animal models; and
 - ▶ Standardizing and validating assays to be used as Phase III study endpoints.
- Foster research on the safety and regulatory considerations of candidate HIV/AIDS vaccines
 - ▶ Whose production utilizes human-derived tumor cell and other continuous cell lines; and
 - ▶ That have the potential to integrate into the host chromosome or have the potential for chronic expression.

OBJECTIVE:

Identify mechanisms of protective immunity to HIV in newborns and infants, and support the development of distinct study designs for safe and effective vaccine strategies and passive immune interventions, alone or in combination with other interventions, for preventing or controlling HIV infection in this population worldwide.

4.C**STRATEGIES:**

Investigate the unique immune status and develop immune interventions in both pregnant women and infants to interrupt HIV transmission. Active and passive HIV vaccine strategies need to be modeled and evaluated, particularly in infants, in parallel to studies in uninfected adults. To accomplish this goal, it is important to develop research that will achieve the following:

- Develop relevant animal models of maternal-fetal and maternal-infant perinatal transmission that can
 - ▶ Determine preclinical safety and immunogenicity of various HIV vaccines and adjuvants, particularly in primates;
 - ▶ Determine safety of various monoclonal and polyclonal antibody preparations;
 - ▶ Determine the best immunization routes or protocols to induce antibodies in milk and other secretions;
 - ▶ Evaluate efficacy of vaccines and passive immunotherapy for prevention of perinatal or breast-feeding transmission; determine whether there is attenuation of disease progression among neonatal animals that become infected despite immune intervention; determine correlates of protective immunity; and
 - ▶ Evaluate the effect of antiviral drugs in combination with immune prevention strategies.
- Determine virologic and nonimmunologic host factors that influence transmission of HIV-1 from mother to infant that would have an impact on selection of viral antigens for the design of an HIV vaccine or for identifying the target of immune-based intervention to prevent perinatal transmission. This includes
 - ▶ Determining the importance of viral load and viral phenotypes and genotypes in perinatal or early infant HIV transmission and

what viral factors are associated with differences in perinatal transmissibility;

- ▶ Developing standardized methods to detect, characterize, and quantify HIV in cervico-vaginal secretions and in breast milk to determine their potential relevance in mother-to-child transmission; and
- ▶ Determining if virus in maternal genital secretions or breast milk is distinguishable from virus found in blood and which type is transmitted from mother to fetus and mother to infant.
- Identify maternal and infant immune responses that might control viral replication in either the mother and/or the infant and prevent transmission of HIV or establishment of infection in infants.

Define immune approaches that will provide specific and sustained protection against HIV transmission; develop the products necessary to achieve these goals; and develop the capacity to evaluate their safety in human subjects. This research includes the following activities:

- Determine specific immune strategies for perinatal intervention that blocks interaction of HIV with its receptors and coreceptors and/or to target infected cells.
- Characterize the transmitted viral subtypes and monitor changes that may occur in proposed trial sites; evaluate the impact that genetic polymorphism in different racial or ethnic backgrounds might have on receptor usage or immune responsiveness.
- Evaluate, in Phase I and Phase II studies, the safety and immunogenicity of various HIV vaccines, adjuvants, vaccine administration regimens, and the pharmacokinetics of passive antibody preparations among both HIV-infected pregnant women and newborns exposed to HIV (born to HIV-infected women).

Test the safety and efficacy of active and passive HIV vaccine interventions alone or in combination with other modes of intervention, particularly in the international setting. This testing includes the following activities:

- Identify and characterize the important issues to consider in the development of criteria for advancement of candidate vaccines, adjuvants, and passive antibody preparations from Phase I and Phase II to Phase III clinical trials in pregnant HIV-infected women and/or HIV-exposed children.

- Develop the capacity in domestic and foreign trial sites necessary to enroll mothers and infants in trials of vaccines, passive immunity, and other perinatal interventions with prospective long-term followup—for vaccines, this should include both the assessment of duration of detectable humoral immune responses as well as memory or recall responses in the cellular immunity compartment(s).
- Conduct Phase III clinical trials for evaluation of efficacy of the most promising candidate vaccines and/or passive antibody preparations that meet established criteria in pregnant HIV-infected women and/or children exposed to HIV.
- Develop criteria to define infant infection status as a perinatal intervention trial endpoint in countries where breast-feeding is recommended despite maternal infection status, including type of diagnostic tests, timing of the tests, and length of followup.
- Study viral isolates and the immune response in infants who become infected despite administration of active and/or passive immunization to evaluate the effects of immune intervention on the characteristics of transmitted (escape) virus and on the quality and quantity of the infected infant's antiviral responses.
- Study the impact of early antiviral therapy and HIV vaccines, given while on effective antiretroviral therapy, on the maintenance or regeneration of antiviral immune responses of HIV-infected infants.

OBJECTIVE:

Conduct Phase I, Phase II, and Phase III trials for safety, immunogenicity, and efficacy with suitable candidate vaccines or concepts in domestic and international settings.

4.D**STRATEGIES:**

Support the conduct of Phase I, II, and III clinical trials that will determine long-term and short-term safety, evaluate efficacy, and compare immunologic responses to different preventive vaccine candidates by evaluating a broad range of humoral, cell-mediated, and mucosal immune parameters. This includes the following tasks:

- Design and conduct Phase I and Phase II trials using promising HIV vaccine candidates. Trials should test immunogenicity of vaccine concepts, and address questions about optimal vaccine strain selection, (i.e., the properties of a strain [immunologic, genotypic, or phenotypic]) that make it optimal for use in a selected population. Trials also should include an appropriate representation of ethnic and racial minority populations affected by HIV and be of an appropriate size to provide data on the frequency of immune responses to facilitate decisions regarding initiation and evaluation of larger “proof of concept” or efficacy trials.

Develop a comprehensive plan for conducting vaccine trials with a high level of retention and adequate followup of vaccinees to reach predefined endpoints, as follows:

- Prepare for adequate long-term followup of volunteers in HIV vaccine clinical trials to determine the durability of immune response, the correlates of immune protection, long-term safety, the impact of participation on risk-taking behavior, and vaccine-related reduction (or enhancement) of disease progression and HIV transmission.
- Conduct large-scale efficacy trials of preventive vaccine candidates that have proven promising, safe, and immunogenic in Phase II trials and that meet appropriate criteria by
 - ▶ Evaluating HIV vaccine candidate efficacy against infection, disease, and/or transmission;
 - ▶ Evaluating additional virologic, immunologic, and behavioral outcomes, particularly potential correlates of protective immunity;

- ▶ Ensuring that trials are conducted with the highest regard for social and ethical standards and in populations that reflect the racial and ethnic burden of the HIV disease;
 - ▶ Ensuring access to achievable, sustainable, and culturally appropriate best practices to prevent HIV exposure; and
 - ▶ Developing, adapting/modifying, and coordinating educational and information programs about HIV and HIV vaccines suitable for the individual participants and communities of different ethnic, racial, and cultural backgrounds that will be involved in trials.
- Characterize the clinical course, immune responses, and other characteristics of vaccinees (e.g., risk of infection) who become HIV-infected; isolate and characterize viral isolates from participants in vaccine trials with intercurrent HIV infections to explore the possible effects of vaccination on the characteristics of escape (transmitted) viruses.
 - Continue to use existing strategies to avert social harm and develop additional strategies to complement existing mechanisms at the local and national levels to reduce the risk of social and economic harm to volunteers in Phase I, II, and III trials.
 - Conduct behavioral research during vaccine trials, particularly with Phase II and Phase III trial participants, to identify changes in risk behavior as a result of participation in a vaccine trial; develop, test, and ensure access to interventions to prevent high-risk behaviors; conduct behavioral research with specific emphasis on individuals who become infected during trials to identify interventions that may prevent high-risk behaviors.
 - Closely coordinate the evaluation of research findings on prophylactic AIDS vaccines with preclinical research and immunotherapeutic interventions.

OBJECTIVE:

Develop strategies, infrastructure, and collaborations with governments, researchers, communities, and industry that are necessary to ensure adequate performance of vaccine trials, while balancing the prevention needs of the at-risk populations; identify domestic and foreign populations, and perform necessary research to define seroincidence and viral subtypes and to determine and optimize feasibility of vaccine studies in appropriate cohorts.

4.E**STRATEGIES:**

Identify and develop potential domestic and foreign sites with a high seroincidence and access to populations at high risk for acquiring HIV infection, where vaccine or other prevention research activities may be feasible. This includes the following activities:

- Track the course of the epidemic by studying HIV incidence in cohorts of individuals with high-risk behavior to monitor changes in the risk profiles and infection rates (seroincidence) of various populations in the United States and worldwide; improve methods to identify and evaluate emerging risk groups and those groups most likely to be informed, willing, and capable participants in vaccine trials.
- Analyze MHC genetic differences and other relevant genetic or medical factors of populations at potential trial sites that might affect the qualitative or quantitative levels of immune responses to candidate HIV vaccines, or of infection or of viral load.
- Acquire and analyze HIV isolates from mucosal sites, as well as blood from recently infected persons representative of potential efficacy trial populations, so that genetic and antigenic information about viruses being transmitted in the population can be obtained.
- Develop and maintain the necessary immunology and virology laboratory infrastructure for conducting domestic and international vaccine efficacy trials. This includes education and training of personnel from international sites hosting vaccine trials, development of laboratory infrastructure, and participation of trained personnel in studies related to the trial.

Establish, build, and nurture linkages with communities and community organizations where vaccine trials might be conducted to optimize education, recruitment, and followup activities; listen to and address

community concerns, resolve social issues, and ensure ethical conduct of AIDS vaccine efficacy trials. This includes the following:

- For all vaccine trials, enlist participation of local representatives or community advisory boards (CABs) in the development of appropriate trial protocols as well as responsive mechanisms to inform and educate the participating individuals; establish networks within the community that will effectively, and on a continuing basis, address the social and medical concerns of the participants; establish mechanisms to provide ongoing information and open discussions concerning the scientific rationale of the study.
- Develop mechanisms to engage collaboration and to provide education and the means to inform communities, and particularly individuals participating in the trials through CABs, on a continuing basis so that social as well as medical concerns are addressed; work to establish trust through open discussions of scientific rationale, expectations, and concerns.
- For international trials, in addition, work closely with national (host) governmental and regulatory authorities, collaborating institutions or agencies, local community representatives, vaccine manufacturer(s), and the United Nations Joint Programme on AIDS (UNAIDS) to prepare for, plan, and conduct vaccine trials adhering to the highest ethical and scientific standards.

In collaboration with Government agencies, institutions, nongovernmental organizations, and communities being identified as potential collaborators, explore behavioral and social issues and prevention activities that might have a substantial impact on either the design or the conduct of a trial. This includes the following research:

- Evaluate other biomedical and behavioral interventions that could prove of benefit in decreasing the incidence of HIV infection in the populations identified for future vaccine efficacy trials; address their potential impact on the evaluation of vaccine efficacy.
- Conduct behavioral research in populations at high risk for HIV infection to determine, for example, appropriate risk-reduction interventions and to estimate risk behavior and recruitment, adherence, unblinding, and retention strategies pertinent to the design and execution of a successful efficacy trial, especially for populations that have been historically under-represented in clinical trials and where the epidemic is expanding disproportionately.

- Determine possible adverse social, economic, behavioral, or legal consequences of participation in clinical trials; develop broadly applicable strategies for mitigating potential harm.
- Determine optimal methods of achieving informed consent for vaccine efficacy trials.

Explore innovative trial designs to improve efficiency of vaccine efficacy studies (e.g., determine the impact of HIV vaccines on subsequent transmission from vaccinated individuals who become infected after administration of the trial vaccine or utilizing initially concordant negative couples at high risk or discordant couples). This includes the following areas of trial design research:

- Consider the use of secondary endpoints, particularly immune correlates of protection, surrogates of disease progression and clinical outcomes, and the benefit of long-term followup.
- Consider the impact of early antiretroviral therapy on HIV infections in complex trial designs.
- Encourage linkage between vaccine preparedness studies in high-risk populations and other research activities, including research on tuberculosis and STDs; integrate research on vaccines against opportunistic infections, as appropriate.

Behavioral and
Social Science

SCIENTIFIC AREA OF EMPHASIS:**Behavioral and Social Science****SCIENTIFIC ISSUES**

At present, the most effective way to prevent or reduce the spread of HIV/AIDS is through behavioral change. The majority of AIDS cases both in the United States and globally result from two activities: (1) unprotected sexual intercourse with an HIV-infected person and (2) the use of HIV-contaminated injection drug equipment. The primary goal of NIH-sponsored AIDS-related behavioral and social science research is to discover how to change the behaviors that lead to HIV transmission—including preventing their initiation—and how to maintain protective behaviors once they are adopted. An additional goal is to reduce the negative impact of HIV on individuals with HIV infection, on their families, on the health care system, and on society. Three themes cross-cut, and are implicit in, priority areas in AIDS-related behavioral and social science: addressing ethical considerations in the conduct of research; further developing appropriate research methods; and investigating issues in both domestic and international settings, as appropriate.

**UNDERSTANDING
AND INTERVENING
IN HIV
TRANSMISSION**

Current research priorities in the behavioral and social sciences reflect a number of recent and significant developments. First, there has been a notable shift in the demographics of the HIV/AIDS epidemic in the United States over the past decade. An increasing proportion of new HIV and AIDS diagnoses is occurring among women, racial/ethnic minorities (principally African American and Latino/Hispanic), and people older than 50 years of age; and, increasingly, HIV is transmitted through heterosexual

contact in the context of drug and alcohol use. These changes require the development and refinement of behavioral and social interventions that take into account the complex interplay of gender, age, cultural context, and HIV risk. It is important to improve knowledge about how cultural beliefs and institutional arrangements contribute to access to and utilization of prevention and care services, as well as the relative effectiveness of individual behavioral-change interventions and community-based prevention strategies.

PRIORITIES FOR FUTURE RESEARCH:

- **Monitor, understand, and address the disparate risks and impacts of HIV infection, as well as the disparate access to, and utilization and quality of, prevention and care services according to race/ethnicity, gender, age, and socioeconomic status.**
- **Better understand and address, through interventions, the psychological, social, economic, and cultural factors that underlie the relationship between substance abuse (alcohol and other drugs) and HIV transmission.**
- **Improve the development and integration of theoretical and methodological work on gender and sexuality, to better understand and address the psychological, social, economic, and cultural dynamics that play a role in promoting sexual health or conferring HIV risk, including the impact of abuse, sexual development, gender norms and identity, and gender inequality.**
- **Investigate changing patterns, contexts, and tools of substance use (alcohol and other drugs) and their implications for HIV transmission, including factors that contribute to specific risks related to injecting or noninjecting drug use, as well as those that link substance use and sexual risks.**

Second, the development of new and more effective drug therapies—in particular, combination therapies—for combating HIV infection has raised a host of behavioral questions that have significant implications for HIV prevention and treatment. With combination therapies, 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 resistant strains of HIV, which could have devastating effects on our ability to stem transmission and treat HIV-infected individuals. In addition, as HIV-infected individuals experience improved health and a decline in detectable virus in their bodies as a result of taking the new combination therapies, they may believe 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, as well as research on the sustainability of HIV prevention efforts over time. It is essential to improve knowledge about how best to provide individual and community support for primary prevention efforts among HIV-infected individuals and how best to ensure societal commitment to HIV prevention for the duration of the epidemic.

PRIORITY FOR FUTURE RESEARCH:

- **Identify and address psychological, social, cultural, and ethical issues related to the initiation, maintenance, sustainability, replicability, and durability of effective HIV prevention, testing, counseling, and care efforts within communities over time, including efforts targeting HIV-infected individuals.**

A third important recent development is the recognition that large-scale HIV prevention strategies adopted by national and local governments have been effective in reducing transmission in many countries and cities. Policy changes related to promoting access to and utilization of known HIV-prevention measures, including condoms, sterile injection equipment, and delaying or abstaining from sexual intercourse, have resulted in documented declines in HIV incidence, even in settings with high seroprevalence rates. This suggests the advisability of further study into the impact of economic, legal, and policy changes on stemming the AIDS epidemic through behavioral and social change. It also highlights the urgency of widely disseminating efficacious, science-based HIV prevention interventions for the maximum impact on public health. Concurrent with this dissemination, it is important to identify and address cultural, ethical, and logistical issues (e.g., infrastructure-building, cost, training) that arise in replicating and/or adapting interventions with different populations and in different settings.

PRIORITIES FOR FUTURE RESEARCH:

- **Investigate both the facilitators and the barriers to policy decisions and public health implementation informed by behavioral and social science findings, including the development of interventions targeting the attitudes, capacities, and resources of HIV service providers and selected institutional settings (e.g., prisons, schools).**
- **Investigate the micro- and macro-economic conditions and interventions that contribute to HIV prevention or transmission, including access to, and quality and financing of, health care.**

AMELIORATING THE CONSEQUENCES OF HIV INFECTION AND AIDS

There has been a growing recognition that many individuals who become HIV-infected also have, or are vulnerable to, a host of co-morbid conditions, including other infectious diseases (e.g., hepatitis, sexually transmitted diseases [STDs], tuberculosis [TB]), substance abuse, mental illness, and homelessness. Both the risks and the consequences of HIV infection for these individuals must be evaluated and addressed in the context of these other conditions. Studies are needed that test the efficacy and effectiveness of interventions that simultaneously address multiple diagnoses and risks, improve HIV treatment adherence, and/or have an impact on other health outcomes among multiply diagnosed individuals.

PRIORITY FOR FUTURE RESEARCH:

- **Investigate the social and environmental factors that contribute to HIV infection, behaviors after infection, and co-occurring conditions (e.g., substance use, mental illness, homelessness, hepatitis, STDs, TB), including the causes and implications of stigma.**

RESEARCH AND EVALUATION METHODOLOGIES

Rapid advancement of meaningful and effective HIV-related behavioral and social science research requires further development of methodological tools, including those for evaluating HIV prevention interventions. As methodology represents the essential building blocks of both basic and intervention research, it must be given special attention at NIH. Current needs in the behavioral and social sciences include assessing the viability, advantages, and disadvantages of including both behavioral and biological outcomes in individual studies and developing methods for rapid assessment and intervention in community settings.

With these recent developments and current priorities in mind, NIH will continue to sponsor research related to the following: 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.

The idea that HIV-related behavior and behavior change must be viewed within a human developmental framework cuts across these issues, as does recognition of the role that cultural and socioeconomic factors play in

diverse geographic and resource settings. Accordingly, research must address emerging issues at different points along the developmental trajectory from childhood through old age (including middle childhood, adolescence, young adulthood, and middle age) and in diverse geographic settings. Also cutting across priorities in the behavioral and social sciences is a continued commitment to fostering better linkages among researchers, communities most affected by HIV and AIDS, and organizations responsible for providing HIV prevention and health care services.

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE:

Support research to develop, evaluate, and diffuse effective behavioral, social, environmental, and economic interventions to prevent HIV transmission and acquisition by reducing HIV-related risk behaviors and increasing protective behaviors. Interventions should address the social and cultural contexts within which risks occur (e.g., social class, gender, race, age, and ethnicity) and attend to ethical issues, both domestically and internationally.

5.A

STRATEGIES:

- Develop and evaluate the efficacy, effectiveness, and cost-effectiveness of demographically and culturally appropriate behavioral and social interventions in different domestic and international settings and populations to reduce high-risk HIV-related sex and drug use behaviors and HIV transmission.

Populations and Contexts

- Develop and test interventions targeted at HIV-infected persons to reduce their risky sexual and drug use behaviors.
- Support intervention research that addresses the impact of alcohol and/or drugs on sexual encounters that may contribute to HIV transmission.
- Continue development of interventions targeting at-risk populations (e.g., injecting drug users [IDUs], other drug users, partners of drug users, men who have sex with men), with particular emphasis on drug use and sex-related risks.
- Support domestic and international intervention research to enhance healthy sexual development and responsible protective behaviors (including access to and use of barrier methods, avoidance of too-early or nonconsensual sex, and abstinence from unsafe sexual behavior) throughout one's lifetime.
- Support interventions for populations that are currently low risk or that perceive themselves to be low risk for HIV infection, but that may be susceptible to engaging in high-risk behaviors (e.g., non-sexually active, non-drug-using adolescents; heterosexual men and women; and middle-aged and older populations).

- Support intervention research that identifies effective attention to contextual risk factors for groups disproportionately affected who continue to demonstrate high-risk behaviors. This research also should identify which public health applications most effectively attend to cultural contexts.
- Investigate the interaction of behavioral and pharmacologic therapies for drug and alcohol addiction and mental health disorders in those at risk of becoming HIV infected or already HIV infected.
- Develop, test, and evaluate interventions that target individuals both within prisons and returning to society from the prison system—strategies include increasing access to education, information, therapeutic care, prevention services, and clinical trials.
- Support the capacity to develop rapid-response domestic and international intervention studies.

Effectiveness

- Develop, test, and evaluate interventions that target a range or combination of levels of social organization—individual, dyad, family, network, community, institution, and society—and that examine how these levels interact to affect HIV risk and protective behavior and HIV transmission in different cultural contexts.
- Support research to increase the effectiveness, cost-effectiveness, and cost-utility of interventions for HIV-related drug abuse, mental health, alcoholism treatment, and family planning and to improve access to these treatments and interventions—such research may include the development of new pharmacotherapies and behavioral therapies to reduce HIV-related risk behavior and HIV transmission in different settings and populations.
- Support research in the United States and abroad to improve the transfer of effective HIV interventions to and from the community; support research on the adoption and adaptation of efficacious HIV interventions by communities (including studies of diffusion processes and the exchange of knowledge between service providers and researchers)—this includes research on the maintenance of effective interventions as well as assessing the generalizability of interventions with diverse populations.

- Evaluate novel interventions identified as high priority by HIV community planning groups and other service providers.

Systems

- Support research that investigates the impact of laws and policies on HIV transmission.
- Support research to understand and improve the organization, financing, management, access, delivery, cost-effectiveness, and cost-utility of health care, family planning, and social services that reduce HIV risk behaviors and HIV transmission.
- Support interdisciplinary and cross-national behavioral research.
- Support research to understand and improve linkage, coordination, and integration among primary medical care; drug, alcohol, and mental health treatment; STD treatment; reproductive health and family planning services; social services; and community-based HIV prevention services.
- Support research to integrate HIV risk-reduction goals and assessments into existent models of drug abuse treatment (e.g., methadone maintenance, outpatient drug-free, inpatient, and therapeutic community treatment programs).
- Support intervention research on strategies for changing the willingness of communities to support and adopt primary prevention interventions.

Methods

- Design and test behavioral interventions to increase recruitment, retention, and adherence to protocols for HIV prevention research, including trials for prophylactic vaccines, microbicides, and other biomedical prevention methods.
- Encourage, where appropriate, the use of quasi-experimental designs and the evaluation of natural experiments in domestic and international HIV preventive intervention research.
- Support behavioral intervention studies that include HIV seroincidence data and other biologic markers as outcome measures.

OBJECTIVE: (The scientific objectives 5.B and 5.C are of equal weight.)

Support basic social and behavioral research to strengthen understanding of the determinants, processes, and cultural and contextual issues influencing HIV-related risk and protective behaviors and the consequences and impact of HIV disease, including treatment for and management of HIV infection. This includes domestic and international research that examines the societal, community, organizational, social network, dyadic, and individual barriers and facilitators to the adoption and utilization of effective preventive and treatment interventions across the life course.

5.B**STRATEGIES:****Emerging Priorities**

- Conduct basic research to better understand the impact of HIV therapeutic regimens on adherence, sexual risk behaviors, drug-related risk behaviors, and psychosocial adaptation (i.e., people feeling better and healthier).
- Develop new models of behavioral change that integrate biological, psychological, and social perspectives to explain and predict the acquisition and maintenance of HIV-related behaviors among vulnerable individuals and understudied groups domestically and internationally; support theory-building studies developed in the context of HIV prevention research, including studies that adopt a developmental and life-course perspective.
- Support research to better monitor the epidemic and risk behaviors to identify emerging needs for basic behavioral and intervention research.

Consequences

- Support research on the decision-making processes and behaviors of health care workers regarding the offering of HIV counseling, testing, and other prevention services, as well as the prescription of HIV disease treatments.
- Conduct research on children affected by HIV, including early identification and assessment.
- Identify the neurobiological, behavioral, cognitive, social, and economic consequences of HIV disease for HIV-seropositive individuals (including children), their support systems (e.g., partners, family members, and other caregivers), health care systems, and communities.

- Support research on the economic and social implications for retired and older individuals who provide support and care to younger family members or friends with HIV/AIDS and their dependents.
- Support interdisciplinary research, involving behavioral and biomedical scientists, to determine whether a bidirectional relationship between stress, depression, immune system functioning, and HIV infection exists and, if so, to examine the psychosocial and physiological factors affecting that relationship.
- Support studies on animal models of behavior and behavioral change relevant to HIV infection and prevention; in particular, conduct behavioral neuroscience and neuropsychological research to determine the brain/behavior changes associated with exposure to HIV, the effects of HIV exposure upon social behaviors (e.g., mother–infant attachment, peer interactions), and behavioral changes in relation to comorbidities of HIV and substance use and addiction.

Prevention

- Study the acquisition and maintenance of HIV-related risk and protective behaviors associated with HIV transmission or progression in specific social and cultural contexts, such as the sexual dyad, peer groups, social and substance-using networks, families, and communities; study how HIV risk might change over time as a function of developmental and life-course events, such as adolescence, childbearing, marriage, divorce and separation, and aging.
- Conduct research on decision-making processes that relate to sexual and drug-related risk taking across the life course, e.g., individual and dyadic decision processes concerning whether and under what circumstances to have sexual intercourse; risk assessment of self and partner; the weighing of pregnancy prevention, HIV prevention, and relationship goals in choosing to use a condom and/or other method; and decision processes related to sharing needles or other drug paraphernalia and having sex with someone who may be infected.
- Support multidisciplinary research that investigates the biobehavioral and sociobehavioral determinants and mechanisms of sexuality, including processes of sexual and gender identity formation.
- Conduct research on partner selection and relationship dynamics, including studies of how partner choice, partner formation, relationship development, and partner stability change over the life course and

affect health-related behavior—studies should examine psychological, cultural, and social factors that influence these phenomena.

- Support multidisciplinary research that investigates biobehavioral and sociobehavioral determinants of injection drug use and the transition from noninjection to injection drug use as they relate to HIV transmission—such research may also include studies that investigate the relationship between any drug use and sexual risk behaviors.
- Conduct research on individual social and cultural differences in human sexuality that have an impact on the sexual transmission of HIV—such research may include studies that examine how sexual behavior is affected by substance use and abuse, sexual abuse or coercion, developmental processes, and the formation and dissolution of intimate relationships.
- Study the social, structural, cultural, and demographic factors—such as socioeconomic status, marital status, ethnicity, sexual identification, age, and gender—that influence HIV-related behavior across the life course and in diverse geographic regions, affect access and delivery of care (including cost-effectiveness and cost-utility of behavioral change interventions), and influence the implementation of intervention strategies.
- Support research to understand how and whether communities engage in HIV preventive interventions; determine how to better ensure the use of prevention research by communities, public health entities, and policy planners in the United States and abroad.
- Conduct research that identifies the social and behavioral factors affecting recruitment, retention, and adherence to prevention and treatment interventions, including clinical trials of HIV-related vaccines, microbicides, and therapeutics.
- Support behavioral and social research on the acceptability and use of biomedical HIV prevention methods (e.g., condoms, microbicides, and vaccines).
- Support basic and preintervention research on behavior modification and maintenance of new behavioral patterns for developing prevention and intervention strategies.

OBJECTIVE: (The scientific objectives 5.B and 5.C are of equal weight.)

Support research for the development, evaluation, diffusion, and adoption of strategies to increase early identification, to improve treatment adherence, and to prevent or minimize the negative physical, psychological, cognitive, and social consequences of HIV, including stigmatization of persons with or at risk for HIV infection. Support research strategies for promoting effective health care utilization among all persons with HIV infection and for promoting modifications in the health care delivery system to develop more effective, socially appropriate, and culturally sensitive methods to better serve treatment needs of infected populations domestically and internationally.

5.C**STRATEGIES:****Treatment and Care**

- Develop and test interventions to modify the practice behaviors of health care providers to improve the quality of screening, counseling, and treatment services for HIV-positive persons and persons at risk for HIV infection.
- Support research on adherence to treatment regimens, including communication techniques to improve shared decision making between health care providers and HIV-infected individuals, on issues such as how and when to initiate therapy, and behavioral strategies to manage symptoms secondary to treatment protocols.
- Promote research to identify and remove barriers to effective health care utilization among persons with or at risk of HIV infection, including access, engagement, followup, and adherence to health and social services across the care continuum (e.g., early identification of HIV infection, testing and counseling, health care-seeking behavior, adherence, case management, and home/hospice care) and across the life course (i.e., from childhood to old age).
- Develop and test interventions to increase recruitment, adherence, and retention in HIV/AIDS clinical trials and care by HIV-infected persons from all vulnerable populations, with special attention to developmental and life-course issues.
- Support research on the decision-making processes of health care workers in screening and identifying HIV cases, especially cases of early and acute infection.

- Support health services research and evaluation research to determine the impact of changes in the health care delivery system on HIV/AIDS care.
- Support research to foster more effective participation in treatment planning, decision making, and formulating advanced directives by patients and families.

Biopsychosocial Consequences

- Develop and evaluate interventions to prevent the adverse psychological and social consequences of HIV infection and to assist HIV-affected populations to cope with HIV infections, maintain quality of life, and avoid engaging in HIV-related risk behaviors.
- Test interventions to address the neuropsychological, neurodevelopmental, and psychiatric sequelae of HIV infection.
- Develop and evaluate interventions to minimize the impact of stigmatization on HIV-infected persons, including decisions regarding treatment and quality of life.
- Test interventions designed to support formal and informal caregivers and family members of HIV-infected persons in order to prevent, for example, depression and burnout.
- Support research to enhance the quality of life and minimize the impact of pain, fatigue, physical symptoms, and treatment side effects and to integrate effective palliative care throughout the course of treatment for all people living with HIV and AIDS.

OBJECTIVE:

Support research to advance innovative quantitative and qualitative methodologies to enhance behavioral and social science on HIV prevention and care, and to address pressing ethical issues in the conduct of such research.

5.D**STRATEGIES:****Measurement**

- Develop improved methodologies—including methods for obtaining and validating self-report data, culturally appropriate standardization of measurement tools for surveys, and the measurement of change over time—based on an assessment of the current status of qualitative and quantitative methodologies for studying behavioral and social factors associated with HIV and AIDS.
- Develop and strengthen culturally, linguistically, and age-sensitive and -appropriate research instruments for subpopulations (e.g., HIV-infected children, the elderly, and prisoners).
- Develop and refine techniques for measuring social networks associated with HIV transmission.
- Support research to determine under what circumstances each of the following outcome measures—alone or in combination—is appropriate to use: self-report measures, HIV infection, and other disease outcomes such as other STDs and blood-borne diseases.
- Develop improved qualitative approaches to theory building and to measurement of HIV-related behaviors, behavioral change, and factors that influence behavior and behavioral change.
- Develop improved triangulated approaches to formulate, integrate, and analyze theories from qualitative and quantitative observations.
- Support research to determine how self-reported outcome measures are affected by “response shift,” including the effects of disease progression and treatment on the criteria individuals use to appraise their quality of life, and the impact of interventions on participants’ standards for judging their degree of risk, level of skills, and adequacy of support and care.
- Develop and refine outcome measures and indicators appropriate for the evaluation of social policy and the societal impact of HIV prevention interventions.

- Develop and refine research techniques for measuring responses by organizations to HIV and for characterizing organizations working in the HIV field.

Modeling

- Develop and refine mathematical models for linking behavioral change interventions with a reduction in HIV transmission at different levels of seroprevalence.
- Improve methods for forecasting and modeling the AIDS caseload, health care needs, and health care utilization under different treatment and survival scenarios and for forecasting and modeling prevention services needs.

Design and Statistical Analysis

- Develop improved sampling strategies for subpopulations (e.g., children, drug users, the elderly, and gay men of color).
- Develop improved and innovative methods and techniques for conducting and analyzing longitudinal studies of HIV-vulnerable and -infected populations, including improved followup methodologies, methods to increase followup rates, and methods for dealing with subject attrition, missing data, and non-normal distributions.
- Foster the development and dissemination of design alternatives to the randomized controlled trial that permit cost-effective evaluation of intervention strategies at the individual, group, and community levels.

Ethics and Other Issues

- Evaluate the effects of legal and ethical constraints on methods of HIV research and service delivery, particularly among adolescents, children, psychiatric populations, prisoners, immigrants, and other vulnerable or special populations.
- Develop and refine research techniques to advance multisite, intercultural, and international studies.
- Encourage secondary data analysis; develop approaches to protect and document confidentiality.
- Develop and evaluate mechanisms for dissemination of behavioral research findings to the HIV/AIDS research and service communities.

Areas of Special Interest

Racial and Ethnic Minorities

SCIENTIFIC AREA OF EMPHASIS:

Racial and Ethnic Minorities

SCIENTIFIC ISSUES

For over two decades, the disproportionate impact of HIV infection upon racial and ethnic minority communities has presented a significant challenge to biomedical, behavioral, social, and clinical research. The complex interplay of cultural, economic, political, macrostructural, and individual forces in general, and especially within racial and ethnic minority communities, necessitates not only creative interventions, but also greater emphasis on the training of minority scientists. The paucity of minority scientists participating in HIV/AIDS research, when compared with the demographics of the epidemic, highlights the health disparities that occur at every level in racial and ethnic minority communities, however such a community is defined. Within these communities, the main routes of HIV transmission—unprotected sexual intercourse and substance abuse—are inextricably linked to underlying community and social factors. These include, but are not limited to, racism, poverty, homophobia, social apathy, immigration, and homelessness. Although the goal of NIH-sponsored research in racial and ethnic minority communities is to discover the contexts within which risk behavior occurs, as well as to determine the impact of interventions, without significant and ongoing attention to the development of minority investigators (and the infrastructure of the institutions that can produce these investigators), a key component of the most effective response to the epidemic is missing.

The pivotal roles of social forces and cultural contexts in HIV transmission among racial and ethnic minority communities cannot be overemphasized. These forces include gender roles and sexual orientation, as well as religion, violence, social stigma, and acculturation. The history of these forces within the community, as well as individuals' experience in interacting with mainstream society, further circumscribes risk behaviors, as well as the individual perceptions of, and community norms that pertain to, that behavior.

MINORITY INVESTIGATORS

The demographics of the HIV epidemic, as contrasted with the demographics of HIV/AIDS researchers, continues to show marked underrepresentation of racial and ethnic minority scientists. Creative strategies to increase the numbers of racial and ethnic minorities who participate in clinical research and behavioral intervention studies, without a sustained and ongoing program to increase the number of minority investigators, cannot achieve their full impact. The legacy of mistrust of research in racial and ethnic communities, combined with the variable levels of cultural sensitivity and cultural competence in NIH-funded research, has been a barrier to participation. Community mistrust and suspicion are further heightened by the paucity of minority investigators visible to the communities that are participating in these research studies. Increasing the number of minority scientists is a long-term investment that will require ongoing commitment and oversight. In addition to recruiting and training minority scientists, opportunities to support the transition from trainee to independent investigator, as well as mentoring, will be essential. Developing and monitoring partnerships at the institutional level, as well as a sustained commitment to infrastructure development, are needed to further enhance these training efforts.

PRIORITY FOR FUTURE RESEARCH:

- **Recruit sufficient candidates to increase the pool of minority investigators, for greater efficacy in HIV research. Develop strategies to recruit adequate numbers of mentors, as well as train minority investigators for HIV research domestically and internationally.**

HEALTH DISPARITIES

That health disparities exist for racial and ethnic minorities has been clearly and repeatedly demonstrated. HIV disease is but one of many diseases that exhibit health disparities. Gaps in care, treatment, and research, in conjunction with the barriers to health care access that racial and ethnic minorities encounter, further exacerbate these disparities. However, these

gaps do not occur in isolation but, rather, in the broader context of the society and culture within which these gaps occur. The continued and ongoing impact of inadequate drug treatment and the impact of comorbidities—such as sexually transmitted diseases and hepatitis C—on racial and ethnic minorities prompt a number of clinical research questions. Ongoing support is needed of basic and clinical research to understand the influence of cultural, economic, biological, behavioral, gender, and age factors on health disparities in HIV disease. Factors that promote, as well as impede, early access to care and treatment must be identified. Interventions that are both culturally and contextually appropriate, accounting for the many macrostructural forces that affect these communities alone, will be insufficient. These interventions, if successful, must be replicated to ensure their durability, as well as their generalizability within racial and ethnic minority communities.

PRIORITY FOR FUTURE RESEARCH:

- **Decrease health disparities among racial/ethnic minorities, as well as in comparison to the majority population.**

PARTICIPATION IN CLINICAL TRIALS

Minority participation in clinical trials must continue to reflect minority representation in the epidemic; participation rates should reflect incidence, rather than prevalence, data. To achieve this extent of participation, innovative and creative strategies must be incorporated into clinical trials, to identify not only barriers, but also the appropriate inducements, to participation. Development of population-specific recruitment activities and outreach, in conjunction with community research partnerships, is one of many approaches to this challenge. Such partnerships are most likely to be productive when there is *equal* input and recognition from both sides of the partnership.

Community input through such partnerships alone, however, is insufficient. Ongoing community participation through community advisory boards, as well as community-level assessments to identify community norms with respect to prevention and treatment, will also be an important ingredient. Exploration of the basic racial/ethnic science, of gender difference on transmission, of side effects, of body composition, and of drug treatment will also be essential.

Analyses of the impact of adjunctive/alternative therapies used in conjunction with traditional therapies in this population will also be key. Risk-benefit analyses of the timing of antiretroviral therapy that addresses initiation, adherence, and long-term drug effects in minority populations are also needed.

PRIORITY FOR FUTURE RESEARCH:

- **Promote the inclusion of racial/ethnic minorities in prevention, therapeutic, and clinical trials in numbers that reflect the current incidence data.**

PREVENTION INTERVENTIONS

The ongoing transmission of HIV infection within communities of color, and their increasing representation among the new cases of HIV infection, provides a real-time reflection of the impact of prevention messages within these communities. Understanding the extant social networks, and the likely routes of HIV transmission through these networks in minority communities, can only be useful if the interventions designed are relevant to the target population. Thus, knowledge of the specific cultural issues and contexts of the population is an important component of intervention development. Some of the anthropological, behavioral, and social science research needed to identify these issues and contexts is best conducted through institutions, some nontraditional, that can serve as not only entry points to the community but can also serve to validate the importance of the research to the community. Nevertheless, the paucity of minority investigators involved in such research undermines the long-term investment and may result in continued short-term strategies. If the goal is to go beyond reaching marginalized communities and establishing a research presence to identify which interventions are most effective in decreasing primary and secondary HIV transmission, then social marketing alone is insufficient. Representation of the community in all areas of the research effort will be crucial.

PRIORITY FOR FUTURE RESEARCH:

- **Develop, test, evaluate, and sustain prevention interventions in racial and ethnic minority communities to prevent primary and secondary HIV transmission.**

ADHERENCE TO THERAPY

Despite significant changes in HIV therapy, issues of adherence to treatment regimens persist in all communities, but especially in racial and ethnic minority communities. Novel therapies, more potent formulations, and increasing once-a-day dosing regimens have yielded

benefits; however, the benefits achieved with these therapies have not been uniformly distributed. In addition to access-to-care issues and barriers to treatment, there remain other factors that affect adherence, which suggests a number of research questions. The impact of maturational differences, as well as individual cultural/social beliefs and value systems, on adherence requires further study. Development of culturally appropriate and population-specific models of adherence for racial and ethnic minority communities is one step toward the qualitative studies needed to evaluate the area of adherence. The interplay of social and cultural forces, superimposed on individual stages of behavior change with respect to adherence, is a fertile area for additional research. Such research, if conducted with cultural awareness and by culturally competent investigators/teams, could make a significant contribution in this area. Beyond identification of the interplay of these social and cultural forces is the development and testing of models that promote adherence.

PRIORITY FOR FUTURE RESEARCH:

- **Promote and increase adherence to treatment regimens among racial and ethnic minorities.**

SCIENTIFIC PRIORITIES AND RESEARCH APPROACHES

PRIORITY FOR FUTURE RESEARCH:

- **Recruit sufficient candidates to increase the pool of minority investigators, for greater efficacy in HIV research. Develop strategies to recruit adequate numbers of mentors, as well as train minority investigators for HIV research domestically and internationally.**

RESEARCH APPROACHES:

- Recruit at many levels, including:
 - ▶ High school, college, predoctoral, and postdoctoral levels.
 - ▶ Individual-scholar level, through support for research, meeting attendance, or mentoring programs.
 - ▶ Through productive collaborations (i.e., partnerships between minority and majority institutions).
 - ▶ Outside of the traditional sources.
- Ensure that information dissemination about the opportunities for minorities reaches the target populations and is appropriate for the preferred communication modalities of that population.
 - ▶ Provide information to the appropriate “gatekeepers,” in a variety of formats.
 - ▶ Provide information to the Association of Minority Health Professional Schools, the American Psychological Association (APA) Office of Ethnic Minority Research, the Association of Black Psychologists, Historically Black Colleges and Universities (HBCUs), the National Association for Equal Opportunity in Higher Education (NAFEO), and others, for dissemination to the target population.
- Develop opportunities to support the transition from trainee to independent status (investigator, clinician, academician).
 - ▶ Assure compliance, through the guidance given to study sections, with NIH regulations for including minorities in training grants.
 - ▶ Create cultural competency training for study section members.
 - ▶ Encourage mentoring through training, guidelines, and incentives.
 - ▶ Make and sustain investments in career development in both trainees and research infrastructures.

OUTCOMES:

- Ensure long-term investment in infrastructure development, both at the institutional as well as the individual level, to foster the development of basic scientists as well as clinical researchers.
- Provide international research opportunities for minority investigators.
- Monitor the number of minority participants who serve on study sections.
- Monitor the semiannual or quarterly support of minority investigators.
- Monitor the number of minorities in the training pipeline, and note how many of these persons complete NIH-sponsored programs.
- Monitor the mentoring process, including the partnerships between minority and majority institutions, for number of minority scientists trained, scientific productivity of the trainees, and opportunities afforded to trainees for collegial inclusion in research and/or supplemental projects.

PRIORITY FOR FUTURE RESEARCH:

- **Decrease health disparities among racial/ethnic minorities, as well as in comparison to the majority population.**

RESEARCH APPROACHES:

- Encourage and support basic and clinical research to understand the influence of cultural, economic, biological, behavioral, gender, and age factors to racial and ethnic minority health disparities.
 - ▶ Unravel the complex interplay of macrostructural forces such as poverty, racism, homophobia, and homelessness in creating the health disparities observed among racial/ethnic minorities.
 - ▶ Study the influences of macrostructural forces on the individual and community behavior, with respect to HIV infection.
 - ▶ Examine the mechanisms of resistance to, as well as facilitation of, transmission and disease progression in racial and ethnic minorities.
 - ▶ Identify the impact of other co-morbid disease states including, but not limited to, hepatitis C, cardiovascular disease, chronic mental illness, diabetes, asthma, and substance abuse on the health outcomes of racial and ethnic minorities.
- Identify the barriers within racial and ethnic minority communities that contribute to these health disparities, and study the effectiveness of various strategies to reduce or eliminate these barriers.
 - ▶ Identify and study the effectiveness of culturally relevant interventions for primary and secondary prevention in racial and ethnic minority communities.
 - ▶ Identify the factors that promote early access to care, treatment, and interventions.
 - ▶ Identify the factors that impede early access to care, treatment, and interventions.
- Review and consider, based upon observational studies, the ethics of interventions in racial and ethnic minority communities that do not have enough resources to develop the infrastructure needed to support ongoing interventions against HIV/AIDS.

PRIORITY FOR FUTURE RESEARCH:

- **Promote the inclusion of racial/ethnic minorities in prevention, therapeutic, and clinical trials in numbers that reflect the current incidence data.**

RESEARCH APPROACHES:

- Develop population-specific recruitment activities and outreach, especially for the newly infected.
 - ▶ Increase emphasis upon the conduct of clinical trials where individuals get their care.
 - ▶ Include community input, through community advisory boards.
 - ▶ Encourage and support community-level assessment to identify community norms with respect to treatment, within the stages of change continuum.
- Increase emphasis on the basic science of the impact of racial/ethnic/gender differences on transmission, side effects, body composition, etc. (pathogenesis, drug treatment, clades).
- Block/reserve spaces for minority participants to ensure that participation reflects local incidence data, and to achieve sufficient statistical power for data analysis of trends/effects/outcomes specific to minority participants.
 - ▶ Conduct studies of adjunctive/alternative therapies that may be used in conjunction with “traditional” therapies.
 - ▶ Conduct risk-benefit analyses of the timing for initiating antiretroviral therapy that address efficacy, adherence, and long-term drug effects in minority populations.

OUTCOME:

- Monitor AIDS Clinical Trials Group (ACTG), Community Programs for Clinical Research on AIDS (CPCRA), and Veterans’ Administration (VA) accrual yearly.
 - ▶ For women, monitor and compare minority participation rates in primary treatment and perinatal transmission trials.

PRIORITY FOR FUTURE RESEARCH:

- **Develop, test, evaluate, and sustain prevention interventions in racial and ethnic minority communities to prevent primary and secondary HIV transmission.**

RESEARCH APPROACHES:

- Continue basic science research to identify the specific mechanisms of transmission, and the critical factors that influence transmission, among racial/ethnic minorities.
 - ▶ Identify the significant macrostructural forces (e.g., stigma, poverty, racism, sexism, violence, homophobia) that interfere with prevention messages.
 - ▶ Improve the research conducted with the multiply diagnosed (HIV/AIDS, mental disorders, alcohol/substance abuse, medical disorders), including the interplay of methods, the multitude of risk factors, integrated interventions, and the spectrum of care systems.
 - ▶ Develop productive community-based partnerships that will enable their programmatic input and participation in the intervention strategies that will be tested in racial and ethnic minority communities.
 - ▶ Develop and support innovative models to conduct outcome evaluations in racial/ethnic minority communities, to determine the relative success or failure of each intervention.
 - ▶ Ensure that the standardized scales to be used in studies have been validated in minority populations.
 - ▶ Increase community-level awareness of how to prevent HIV transmission through closer collaboration between NIH and all of the Department of Health and Human Services (DHHS) agencies charged with decreasing HIV transmission through increased awareness.
 - ▶ Reduce or eliminate language barriers for communities where English is not the primary language.
 - ▶ Identify community-specific issues that will lead to behavior change.
 - ▶ Work with science museums, as well as other less traditional community partners for science education, including the dissemination of information on HIV/AIDS, in racial and ethnic minority communities.

- ▶ Improve NIH support of research in racial and ethnic minority communities by:
- ▶ Assuring compliance with regulations;
- ▶ Providing adequate review of innovative applications through culturally competent study section members by requiring training.

PRIORITY FOR FUTURE RESEARCH:

- **Promote and increase adherence to treatment regimens among racial and ethnic minorities.**

RESEARCH APPROACHES:

- Increase basic science research into formulation and combination therapies, to simplify the current regimens.
 - ▶ Increase basic science studies of metabolic and body composition differences in racial/ethnic minorities that could be turned to therapeutic advantage.
 - ▶ Improve research on the impact of maturational differences on treatment response.
 - ▶ Study the short- and long-term effects of failure to adhere to treatment regimens in racial/ethnic minority communities (e.g., the emergence of drug-resistant HIV, multidrug resistant tuberculosis [MDR-TB], opportunistic infections [OIs]).
 - ▶ Explore multifactor interventions that involve cultural/social beliefs and value systems, conducted with cultural awareness and by culturally competent investigators/teams.
 - ▶ Review the long-term impact of decreased adherence in women postpartum.
- Develop culturally appropriate and population-specific models of adherence for racial and ethnic minority communities.
 - ▶ Promote the qualitative studies needed to evaluate the impact of adherence.
 - ▶ Identify the effects of knowledge, attitude, and behavior on adherence.
 - ▶ Identify the complex interplay of macrostructural forces on adherence in racial/ethnic minorities, including individuals' current status in regard to the continuum of behavior change.
 - ▶ Review/evaluate adequacy of funding for adherence.
 - ▶ Encourage and promote innovative models for interventions to increase adherence.
 - ▶ Encourage study of the impact of short- and long-term side effects on adherence (e.g., the impact of cosmetic changes associated with antiretroviral therapy).

International Research Priorities

AREA OF SPECIAL INTEREST:**International Research Priorities****SCIENTIFIC ISSUES**

To date, HIV has infected more than 50 million people around the world. Already, AIDS has killed more than 16 million people, surpassing tuberculosis and malaria mortality to become the leading infectious cause of death worldwide, according to recent data released by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO). In 1999, a record 2.8 million people died from AIDS—more than in any prior year. New epidemics are rapidly spreading in Russia, Eastern Europe, and Central Asia, and there are now warning signs of newly emerging HIV/AIDS epidemics in the Middle East. UNAIDS estimates that in India, between 3 and 5 million people are now infected, with the number of new infections doubling every 14 months. AIDS remains a serious threat in Latin America: the scope of the epidemics in Central America and the Caribbean is escalating. Africa remains the epicenter of the pandemic, bearing the heaviest burden of disease. Africa has 71 percent of all the people living with AIDS, worldwide; 83 percent of global AIDS deaths; and 95 percent of the world's AIDS orphans.

From a global perspective, the major modes of acquiring HIV infection are heterosexual transmission and transmission by injecting drug users (IDUs). The vast majority of infections occur through heterosexual transmission, and approximately 46 percent of all of the HIV-infected people in the world are women. Because of the high level of HIV infection among women, the potential exists for large numbers of infected children, since infants can become infected with HIV, from infected mothers *in utero*, at birth, or

during breast-feeding. Mother-to-child transmission accounts for 90 percent of infection among children, worldwide. In the worst-affected countries in the world, between 20 and 45 percent of pregnant women are HIV positive, and one-third of their babies are infected. Injecting drug use is fueling epidemics in Central and Eastern Europe and some countries of Asia; it is also a major concern in industrialized nations and the Middle East. In 1999, the world's most rapidly accelerating epidemic was in the newly independent states of the former Soviet Union, where the proportion of the population living with HIV doubled between end-1997 and end-1999.

The NIH collaborates with UNAIDS, host country governments, and in-country scientists in prevention research and preparation for efficacy trials of various interventions. Significant efforts have been undertaken, particularly with Kenya, Malawi, South Africa, Uganda, Zambia, and Zimbabwe in Africa; Brazil, Haiti, and Trinidad and Tobago in Latin America; and India and Thailand in Asia. In total, NIH-supported research studies are ongoing in approximately 50 countries around the world.

**CENTERS OF
EXCELLENCE FOR
INTERNATIONAL
COLLABORATION**

Because more than 90 percent of new infections occur in developing countries, where current therapies are unaffordable and/or undeliverable, it is critical to conduct research that can help address the epidemics in these countries. NIH has long supported a portfolio of international AIDS research, with an emphasis on (1) describing the nature of HIV/AIDS in different geographical regions and (2) developing prevention interventions that can be implemented in resource-poor and infrastructure-deprived settings. These studies have been conducted through collaborative relationships between U.S. and foreign scientists. NIH plans to further enhance its international efforts.

Ethical considerations must be paramount in the development of international collaborations. The fundamental step in addressing ethical considerations, critical to the success of international studies, is to ensure that foreign scientists are full and equal partners in the design and conduct of collaborative studies: they have full responsibility for the conduct of studies in-country. This responsibility should include full participation in the conceptualization of the research; development of protocols; study implementation and collection of data; data processing and analysis; and dissemination of information about the research and its results, through the lay press, professional meetings, and publications in scientific journals. A second step in addressing ethical considerations is to assist developing countries acquire the internal capability and the capacity to conduct independent ethical and scientific review. Proposed studies must receive

full ethical review and approval in the country where the research will be conducted, as well as in the United States, and the studies should fully conform with the ethical principles that prevail in both countries. Finally, study participants and the communities from which they come in host countries must have maximum possible access to any preventive or therapeutic products developed during the course of research. This consideration should be an essential element in the discussion as the research is being developed.

Equally important to an international research effort is the need to expand and sustain laboratory capacity in developing countries, to improve clinical capabilities, and to develop a cadre of trained scientists. These improvements will help ensure that the research conducted is of high quality, will facilitate the transfer of sustainable technologies, and will make it easier to translate the results of the research to the affected populations. Thus, the research effort must focus on strengthening institutions and building capacity, in addition to the biomedical research question under investigation.

PRIORITY FOR FUTURE RESEARCH:

- **Establish centers of excellence in international settings that will provide an environment that promotes the development of true and equal partnerships between U.S. and foreign investigators. These centers will support basic research and long-term cohort studies, serve as loci for studies of efficacy of biomedical and behavioral prevention interventions (including Phase I, II, and III vaccine trials), function as training centers for investigators from throughout the region, and serve as bridges with programs that provide services.**

RESEARCH TO ADDRESS LOCAL EPIDEMICS

To effectively address their epidemics, developing countries need a great deal of information. Research conducted in developing countries provides: (1) information that can be used to establish programs to prevent HIV infection in the community; (2) information relevant to the development of a safe and effective vaccine that can be used for the populations participating in the research; and (3) information useful to providers of health care and other services to help them care for their patients who are infected and to help families and others who are affected by HIV/AIDS.

Prevention of infection in diverse populations, and in diverse settings globally, is of highest concern. Issues of relevance to developing countries include heterosexual transmission; mother-to-child transmission (MCT); transmission through use of injection drugs; and transmission in health care settings. Strategies

are needed to prevent blood-borne transmission in health care settings, including blood screening strategies and technologies and the role (i.e., use/misuse) of transfusion and injections. Also needed are behavioral and other interventions to address the risk of acquiring HIV through injecting drug use.

Since most HIV infection in the world is acquired through sexual transmission, it is critical to develop the best sustainable, behavioral, economic, and environmental interventions for reducing sexual transmission in both men and women. Because of the tremendous cultural diversities found throughout the world, it is not possible to simply transplant interventions developed for one cultural setting to a new one. It is necessary to conduct research to identify the specific cultural and social variables that must be considered so that interventions can be adapted to new settings, and to provide a foundation for the development of new interventions specifically designed for a particular cultural and social context. In this regard, efforts will be targeted toward selected populations at risk, especially adolescents.

Globally, women are at high risk for becoming infected, perhaps because of both biological and socioeconomic factors. It is critical to develop biomedical strategies to prevent heterosexual transmission, with particular emphasis on women, such as microbicides, barrier methods, and syndromic management of sexually transmitted diseases (STDs). To further this effort, it will be necessary to identify the biological determinants of infectiousness and susceptibility in both men and women. Several international cohorts provide unique opportunities for such research. In April 2000, NIH convened a "Biology of Transmission Think Tank" to identify future directions for research in this important area. There are several issues of concern: whether women who use hormonal contraceptives are at increased risk for acquiring HIV infection; the role of the mucosal surface in transmission; the role of viral subtypes in transmission; and the role of STDs in transmission.

There is a global need to develop safe, effective, and acceptable topical microbicides to protect women around the world from sexual transmission of HIV. Currently, 60 microbicide candidates are under development, 23 of which are at the clinical testing stage. To further enhance the microbicide research effort, this year NIH sponsored Microbicides 2000, an international conference with the objectives of (1) establishing a global dialogue to enhance knowledge about microbicides; (2) identifying new research opportunities, including related methodological and behavioral issues; and (3) improving understanding of the cultural, ethical, and economic obstacles to development and use of a microbicide. With a specific focus on including

participants from developing countries, the conference provided researchers and public health workers from diverse regions with an opportunity to gain practical knowledge and to develop international research collaborations.

In addition, some complications of HIV are unique to, or more prevalent in, women than in men. Studies are needed to examine the possible effects of hormones on infectiousness and progression of disease in women. Another question is the impact of HIV on cervical cancer, because co-infection with human papillomavirus (HPV) is common in HIV-infected women. These and other issues are being studied in international cohorts.

Transmission of HIV from infected mother to child has severely affected many developing countries. Initiation of treatment with zidovudine before birth, during delivery, and to the infant has significantly reduced the incidence of MCT in the United States. However, this protocol is not easily applied in most developing countries, because it is expensive and the health care infrastructure may not be adequate. More recently, findings from an NIH-supported trial in Uganda demonstrated that a single oral dose of nevirapine to the infected woman at the onset of labor, combined with a single dose of oral nevirapine to her infant within 72 hours of birth, reduced the risk of transmission by nearly 50 percent. This simplified, low-cost regimen has significant international implications. Nonetheless, more study is warranted concerning the safety of nevirapine for this use. In addition, it is critical to further identify cost-effective drug and nondrug approaches for preventing MCT. These include development of alternatives to breast-feeding, treatment of chorioamnionitis, and the use of caesarean section in some circumstances.

A safe and effective preventive vaccine is essential for the global control of the AIDS pandemic. The President has made discovery of an AIDS vaccine a national research priority. Consistent with this challenge, NIH has moved forward aggressively to build a comprehensive vaccine research enterprise. In recognition of the need to develop vaccines that are efficacious against a variety of strains found around the world, it is critical that NIH enhance international research efforts to analyze the genetic and antigenic variations of HIV and to target efforts toward eliciting cross-reactive immune responses. It will also be necessary to address the behavioral issues that pertain to conducting vaccine trials and those that pertain to the various groups' willingness to be vaccinated, once a product is available. Since such issues will likely vary greatly from region to region and country to country, they will need to be addressed within the context of each individual country.

In the developed world, the advent of antiretroviral therapy has extended the length, and improved the quality, of life for many HIV-infected people. However, these drugs are expensive, difficult to administer and monitor, and entail significant challenges in patients' adherence. In the absence of antiretroviral therapy in much of the world, it is necessary to develop approaches to treat and prevent the opportunistic infections (OIs) that are the cause of morbidity and mortality, as well as to develop strategies for palliative care. As a foundation for development of such interventions, it is critical to characterize the nature, prevalence, and course of disease of the OIs found in diverse geographic settings and develop diagnostic methods to detect them. For mid-level income countries with a basic health care infrastructure, low-cost, alternative antiretroviral approaches may be feasible and should be investigated, including intermittent-treatment regimens and lower-cost antivirals and treatment combinations.

Recent studies of “therapeutic vaccines” that do not prevent infection, but can prevent or delay disease progression in animal models, offer opportunities for additional intervention strategies. The use of such a vaccine, in the context of at least some antiviral therapy, could potentially benefit humans, and it is a priority of the NIH vaccine program to pursue research in this area.

Globally, HIV/AIDS is the cause of much suffering—for those infected with HIV, for their families and friends, and for members of communities affected by AIDS. Research is needed to develop interventions to mitigate the negative consequences of HIV infection, particularly among AIDS orphans, including AIDS stigma.

The implementation of ethical considerations in international research, to the satisfaction of both the United States and the host country, can be a complex task, because of differences in areas such as law, regulation, and public policy; organizational structure; and cultural background. Research on ethical issues will help to identify how best to apply ethical principles in the design and conduct of intervention studies and in the implementation of results.

PRIORITY FOR FUTURE RESEARCH:

- **Conduct studies relevant to the geographic areas of the world and specific populations hardest hit by the epidemic.**

TRANSLATION OF RESEARCH RESULTS

To combat the raging pandemic, it is essential to implement the results of research that have an impact on the affected populations in developing countries. Further, ethical issues must be considered in planning for implementation of research results. Accomplishing these goals requires that research results be made available to policy makers in foreign governments, as well as to nongovernmental organizations and international organizations that develop programs to deliver health care, prevention, and other services. In addition, the research results must be interpreted in the context of the host country's social, cultural, economic, and political situation. To facilitate this process, the conduct of translational research is of critical importance, to better understand how to develop and implement programs in the relevant developing country context. Areas where translational research are urgently needed include strategies to reduce MCT, such as drug options and modification of breast-feeding practices, and the role of syndromic management of STDs.

To enable the widest possible dissemination of information to scientists and service providers, it will be necessary to improve access to such information through enhanced information technology. NIH's electronic information services currently are available through the Internet, and literature databases reflect the world's literature. Currently NIH is working to upgrade electronic communications in Africa.

The role of the mass media also needs to be considered, in creating an environment in host countries conducive to the conduct of research, and in assisting foreign governments and in-country organizations to implement the HIV-related programs that devolve from research. For example, the media can (1) inform the public about the role research plays in addressing the country's epidemic, (2) have a role in helping recruit study populations for studies such as trials of vaccines and other interventions, and (3) help inform target groups and the public about intervention programs such as condom campaigns, school-based educational programs, and MCT programs. Promoting this role for the media will require sustained efforts to educate the press, with ethical considerations chief among the issues to be addressed.

PRIORITY FOR FUTURE RESEARCH:

- **Enhance the translation of research results into action that will improve patient management, develop prevention programs appropriate to the setting, and effect policy changes.**

TRAINING OF FOREIGN SCIENTISTS

A cadre of trained investigators is a critical component of the infrastructure needed for conducting research in developing countries. This training will facilitate international collaborative research, as well as increase the capability of foreign investigators, institutions, and governments to independently conduct research to address their epidemics and to translate research results into clinical and public health practice. Areas of focus for training include epidemiology, development and testing of a wide variety of behavioral and biomedical prevention strategies, vaccine development, and development of indigenous substances as therapeutics. To build this capacity, NIH funds the AIDS International Training and Research Program (AITRP), which provides research training for scientists, health care providers, and public health workers from developing countries. The objectives of AITRP are to (1) increase the capacity of developing countries to deal with the AIDS epidemic through research and (2) stimulate cooperation and sharing of research knowledge by scientists worldwide. The AITRP provides training through grants to U.S. institutions; U.S. investigators develop relationships with in-country investigators and institutions. This program continues to link with the international research programs of the Institutes so that training supports the NIH research effort. Additional international training is conducted as an integral part of ongoing research programs such as the Centers for AIDS Research (CFARs), other HIV centers, the Prevention Trials Network, and the Vaccine Trials Network.

Although much of the training has, in the past, consisted of training foreign scientists in the United States, it is increasingly recognized that highly trained investigators who have returned to their home countries can serve as a training resource for other scientists in their own countries and geographic regions. Such “south-to-south” training should be encouraged to further increase the numbers of scientists who conduct high-quality research. In addition to being cost-effective, similarities in language, geography, cultural backgrounds, social contexts, and political and economic situations help to ensure that the training is relevant to the country and region.

For international research to be of high quality, it must meet the highest ethical standards. In this regard, it is essential to provide training for foreign scientists and members of ethical review committees in ethical issues related to the conduct of research.

PRIORITY FOR FUTURE RESEARCH:

- **Continue to enhance training for research needs, clinical capability and for technology transfer, building bridges with programs providing services, where possible.**

SCIENTIFIC PRIORITIES AND RESEARCH APPROACHES

PRIORITY FOR FUTURE RESEARCH:

- **Establish centers of excellence in international settings that will provide an environment that promotes the development of true and equal partnerships between U.S. and foreign investigators. These centers will support basic research and long-term cohort studies, serve as loci for studies of efficacy of biomedical and behavioral prevention interventions (including Phase I, II, and III vaccine trials), function as training centers for investigators from throughout the region, and serve as bridges with programs that provide services.**

RESEARCH APPROACHES:

- Involve foreign scientists in all stages of the research, including conceptualization of the research question, study design, development of protocols, study implementation and collection of data, data analysis, publication and presentation of research results, and interaction with the media.
- Improve and sustain laboratory capacity; transfer sustainable technologies.
- Improve clinical capabilities.
- Enhance the capability of foreign institutions to conduct independent ethical and scientific review.
- Enlist the participation of local communities, nongovernmental organizations, and governments in the development of research protocols.
- Consider the need for study participants and their communities in host countries to have maximum possible access to any preventive or therapeutic products developed during the research.
- Enhance the critical mass of trained in-country investigators.

PRIORITY FOR FUTURE RESEARCH

- **Conduct studies relevant to the geographic areas of the world and specific populations hardest hit by the epidemic.**

RESEARCH APPROACHES:

- Characterize OIs prevalent in diverse geographic settings and develop diagnostic methods, prophylaxis, and clinical management approaches appropriate to each setting.
- Develop strategies to prevent blood-borne transmission in health care settings, including blood screening strategies and technologies, and the role (i.e., use/misuse) of transfusion and injections.
- Develop biomedical strategies to prevent heterosexual transmission of HIV, such as microbicides, barrier methods, and syndromic management of STDs, with particular emphasis on women.
- Identify the biological determinants of infectiousness and susceptibility.
- Further identify cost-effective drug and non-drug regimens for preventing MCT.
- Identify effective palliative care approaches.
- Investigate low-cost alternatives to highly active antiretroviral therapy (HAART) that are feasible in resource-poor settings, including intermittent-treatment regimens, lower-cost antivirals and combinations, and the use of a therapeutic vaccine.
- Conduct research in areas important for vaccine development, including molecular epidemiology and behavioral issues.
- Develop the best sustainable, behavioral, economic, and environmental interventions for selected populations at risk, including adolescents, IDUs, and heterosexual men.
- Develop interventions to mitigate the negative consequences of HIV infection, particularly among AIDS orphans, including AIDS stigma.
- Conduct research on ethical issues.

PRIORITY FOR FUTURE RESEARCH:

- **Enhance the translation of research results into action that will improve patient management, develop prevention programs appropriate to the setting, and effect policy changes.**

RESEARCH APPROACHES:

- Conduct translational research in areas such as syndromic management of STDs, implementation of nevirapine for MCT, and breast-feeding practices.
- Provide improved access to information through enhanced information technology.
- Expand the role of the mass media.
- Consider ethical issues in planning for the implementation of research results.

PRIORITY FOR FUTURE RESEARCH:

- **Continue to enhance training for research needs, clinical capability and for technology transfer, building bridges with programs providing services, where possible.**

RESEARCH APPROACHES:

- Develop in-country training partnerships.
- Encourage south-to-south training.
- Support training in ethical issues related to the conduct of research.

Training,
Infrastructure, and
Capacity Building

AREA OF SPECIAL INTEREST:

Training, Infrastructure, and Capacity Building

SCIENTIFIC ISSUES

For high-quality HIV-related research, it is vital that an adequate infrastructure be in place, both in the United States and abroad. Also critical is a cadre of well-trained basic, clinical, and behavioral AIDS scientists: newly recruited and trained young scientists, as well as established scientists recruited from other fields. It is equally critical that research institutions have adequate facilities for supporting the research, including appropriately equipped laboratories, computer and data management capabilities, inpatient and outpatient space for clinical research, and allied health and laboratory personnel. Because animal model research is necessary for HIV/AIDS, expanded animal facilities are needed, to house primates and other species, as well as to breed the primates themselves. Repositories also play an essential role in providing resources for basic science research.

NIH supports several intramural and extramural research resource programs. Included in these programs are grants for training scientists in AIDS research, support of animal facilities for animal model research, and construction or improvement of existing facilities and equipment for AIDS-related research.

TRAINING PROGRAMS

Numerous NIH-funded programs have served to increase the number of training positions in AIDS-related research. In addition, much of the predoctoral and postdoctoral training supported by NIH from non-AIDS funds provides broad interdisciplinary training that prepares

investigators to undertake AIDS-related research. NIH supports training through both intramural and extramural programs.

The NIH Loan Repayment Program (LRP) was mandated by Congress under Public Law 100-607 in 1988, authorized under 42 USC 288-1, and reauthorized under Public Law 103-43, to encourage health professionals to engage in AIDS-related research at NIH. Since the program enrolled the first participants in 1989, 121 professionals have been attracted to the NIH intramural research program consequent to NIH's loan repayment benefits, with more than half continuing on longer than their contractually obligated period. This program continues to attract qualified researchers to NIH.

For the past 11 years, the Fogarty International Center (FIC) has supported the AIDS International Training and Research Program (AITRP), a multidisciplinary program designed to strengthen research capacity in the epidemiology, prevention, diagnosis, and treatment of HIV/AIDS in developing countries; to facilitate the evaluation of AIDS drugs and vaccines internationally; and to provide global scientific leadership in HIV/AIDS. The program emphasizes collaborative prevention research, with the goals of (1) assisting developing countries to achieve independent capacity to conduct research and training and to devise feasible programs for translating efficacious outcomes into clinical and public health practice; (2) encouraging independent local research on HIV prevention; (3) ensuring compliance with international ethical standards; (4) assisting NIH Institutes in the conduct of their research missions internationally; and (5) stimulating multidisciplinary cooperation in research.

AITRP is active in 100 developing countries; its activities are focused in the dozen countries that have the most serious current or emerging HIV/AIDS epidemics. AITRP has provided both long-term and short-term training for more than 1,600 foreign health scientists in the United States. To facilitate their return to their home countries, the program includes an in-country research component, which provides support in the form of "reentry grants" for scientists returning home after completion of their training. An estimated 73 percent of foreign health scientists have returned to their home countries to work in positions of research or public health, predominantly in the field of HIV/AIDS.

Another component of the program, the Fogarty International Research Collaboration Award for AIDS (FIRCA), provides support for collaboration between U.S. and foreign scientists, in the foreign partner's laboratory, through a grant to a U.S. investigator who is already funded to conduct

HIV-related research. The FIC investment in research training has facilitated the conduct of many research studies supported by various Institutes and Centers (ICs) in a wide range of research disciplines. In this regard, FIC partners with the Institutes that have international HIV/AIDS portfolios, which provide support for aspects of the AITRP.

Future training needs in building international research capacity include (1) further enhancing the research capacity in those regions of the world anticipated to be most affected by HIV/AIDS, (2) strengthening developing countries' capacity in such related areas as biomedical research ethics and medical informatics, and (3) providing opportunities for U.S. investigators to obtain the benefits of research experiences in developing countries early in their research careers.

To address the need for clinicians and clinical researchers with the highly specialized skills necessary to address the clinical and research problems associated with AIDS-related malignancies, the National Cancer Institute (NCI) issued a Request for Application (RFA) in 1997 for the AIDS Oncology Clinical Scientist Development Program. Awards were made to five institutions for up to 5 years each. Through the program, institutions developed 2-year interdisciplinary training programs for candidates. These programs include didactic, clinical, and research components, and they integrate knowledge and skills across the various disciplines relevant for clinical research and care for AIDS patients with malignancies. Training provided under this program prepares clinicians to (1) address the clinical complexities of patients with HIV/AIDS and malignancies and (2) translate research results into clinical experiments, procedures, and trials directly involving patients with HIV/AIDS and malignancies. In addition, NCI supports a broad spectrum of training programs for basic and clinical researchers, at all career levels, that may include training in AIDS oncology. NCI also supports training programs directly targeted to minority scientists and/or institutions that may include training in AIDS oncology. These programs are described on the NCI Web site at <http://cancer.gov>.

The National Institute of Mental Health (NIMH) supported 35 research training programs focused on issues related to HIV infection and AIDS; as a result, 142 training positions were funded in 1999. The research foci of these programs include basic behavioral and social science, biopsychosocial and neuropsychological science, prevention and intervention science, and health services research. NIMH held a technical assistance workshop in 1999 for investigators from Historically Black Colleges and Universities (HBCUs), to help them develop HIV/AIDS research applications. Investigators from 12 HBCUs received information on the NIH grant

development and funding process, and collaborative relationships were established between these investigators and NIMH-funded investigators, to sustain the mentoring process. In addition, the NIMH Center for AIDS Prevention Studies (CAPS) in San Francisco supports two model training programs: a minority investigators training program, to provide mentoring and technical assistance to minority visiting professors who plan and conduct research on HIV risk behavior in minority populations; and an international scholars program, which provides research training for international scholars and builds partnerships to promote productive international research with these scholars.

The National Institute on Drug Abuse (NIDA) continues to advance training opportunities that provide research skills necessary for addressing the joint epidemics of drug abuse and HIV/AIDS. NIDA has integrated the study of HIV/AIDS into all of the 40 research training programs it supports, and 10 of these are now targeted specifically to the study of HIV/AIDS. The NIDA Center on AIDS and Other Medical Consequences of Drug Abuse (CAMCODA) has worked to diversify the expertise of drug abuse researchers in the field of AIDS and to attract investigators from other fields to the study of the drug abuse-related aspects of HIV/AIDS. The number of training opportunities has also been expanded through research supplements to existing AIDS and non-AIDS grants. The HIV/AIDS research program at NIDA spans the gamut of basic, clinical, behavioral, and epidemiological research, and it offers a broad range of instruction. Trainees are commonly found in community-based prevention and treatment settings, as well as in academic molecular biology or basic neuroscience facilities.

NIH Institutes are adopting innovative approaches to expand the cadre of new investigators in critically needed research areas, including HIV/AIDS. For example, NIMH and NIDA have a small-grants program, the Behavioral Science Track Award for Rapid Transition (B/START). The B/START program is designed specifically to assist new behavioral scientists in entering the research environment, through expedited application and review procedures. While these programs are not limited to HIV/AIDS research, they have provided new behavioral scientists with an opportunity to conduct HIV/AIDS studies and collect the pilot data needed to compete for regular research grants at NIH. Other Institutes are also exploring various small-grant mechanisms to facilitate new scientists' research efforts.

National Institute of Allergy and Infectious Diseases (NIAID)-sponsored programs included over 120 trainee slots for AIDS training in FY 1999, as well as a large number of training grants in infectious diseases. Mentored career development awards also provide support for young investigators

in clinical and basic research. This training effort has been very successful in assisting young scientists to establish independent research programs. In addition, the Adult AIDS Clinical Trials Group (ACTG) has initiated a Minority AIDS Training Program to recruit and train minority health professionals. The program provides fellowships for four minority researchers each year. In another new NIAID training effort, the University of Washington Center for AIDS Research (CFAR) provides assistance to 20 percent of the students who are enrolled in the Minority International Research Training Program at the University of Washington. To further increase the number of available opportunities, this CFAR has established an institutional and intellectual linkage with the AIDS Research Program at the University of Hawaii at Manoa, which in turn is linked with the Research Center in Minority Institutions (RCMI) program. This linkage provides direct support for collaborative studies between CFAR investigators in Washington and minority investigators at the University of Hawaii. RCMI investigators from Hawaii can use the core facilities at the University of Washington and collaborate with investigators at Washington, thereby maximizing their current productivity and ability to compete for their own independent NIH funding.

SUPPORT OF ANIMAL FACILITIES

The National Center for Research Resources (NCRR) and NCI have several successful programs in place that are designed to produce primate models for use in the evaluation of potential simian immunodeficiency virus (SIV)/HIV vaccines and to ensure adequate supplies of these animals. These programs include the specific-pathogen-free rhesus macaque colonies for the SIV/macaque model system and the Chimpanzee Biomedical Research Colonies for AIDS studies. NCI produces in large scale, and maintains, the viral stocks used in AIDS vaccine trials in chimpanzees. In addition, the Regional Primate Research Centers (RPRCs) program provides specialized facilities, scientific and technical personnel, animal models research and breeding, and a wide variety of nonhuman primate species to support diverse requirements for AIDS-related research. NCRR continues to sponsor an initiative to provide non-RPRC investigators with greater access to RPRC resources. Development of the severe combined immunodeficiency (SCID) mouse model is ongoing, for analysis of vaccine candidates and for use in screening potential therapeutics. The National Heart, Lung, and Blood Institute (NHLBI) currently supports studies on transfusion-associated HIV infection and AIDS and on the development and evaluation of blood products for the prevention or treatment of HIV/AIDS. The NHLBI Chimpanzee Colony at the Southwest Foundation for Biomedical Research, San Antonio, Texas, has been used to conduct this

**INTRAMURAL AND
EXTRAMURAL
RESEARCH SITE
INFRASTRUCTURE**

type of research. Future plans include the use of this primate colony to evaluate the efficacy of HIV-specific monoclonal antibody preparations.

Special facilities and equipment are required for performing AIDS-related research. NIH has provided funding for the improvement of biomedical research facilities and instrumentation. As part of the plan for improving the physical infrastructure at NIH, numerous projects are now being designed, improved, or constructed for AIDS-related research on the NIH campus.

NCRR, through the General Clinical Research Centers (GCRCs), provides the research infrastructure required for multidisciplinary studies on both children and adults. Specifically, the GCRCs provide the patient research facilities, computerized data management and analysis, and specialized laboratories—as well as research nurses, dietitians, and biostatisticians—needed for translating basic and clinical research into medical practice. These facilities support a variety of studies focused on the area of HIV infection and therapy. The NIH-sponsored RCMI program provides for the development of biomedical research infrastructure at minority institutions. As a result of awards previously provided through this program, the infrastructure has been enhanced at three minority institutions; this has enabled them to compete successfully for funding as ACTG clinical trial sites.

NIH supports CFARs that provide infrastructure and promote a comprehensive program of basic, clinical, behavioral, and translational research for investigators in AIDS and AIDS-related research at institutions that receive significant NIH AIDS funds. In addition, CFARs foster industry collaborations, support minority scientists, provide AIDS research communications and community outreach, and encourage international collaboration. For FY 1999, six NIH Institutes are participating in the CFAR program—NIAID, NCI, NIDA, NIMH, the National Institute of Child Health and Human Development (NICHD), and NHLBI.

Computers and high-speed computer networks play an increasingly important role in (1) gaining a better understanding of HIV-related pathophysiology at a molecular level and (2) providing rapid communication among basic and clinical investigators. The NCI Biomedical Supercomputer Center facility was a key resource for the prediction of the secondary structure of the entire 9,433 bases of HIV ribonucleic acid (RNA). NCRR-supported supercomputing centers at Pittsburgh, Illinois, Cornell, and Columbia universities provide similar facilities for investigators

nationwide. In addition, NCRR supports several synchrotron and nuclear magnetic resonance (NMR) facilities that provide the technology needed to determine the structure of candidate HIV-related proteins, and the National Institute of General Medical Sciences (NIGMS) supports a Protein Data Bank located at the Brookhaven National Laboratory, which is a repository for the three-dimensional coordinates of all proteins whose structures have been determined. Understanding of molecular structures has allowed new drugs to be developed that are targeted to block virus infection and reproduction. These new drugs will provide new therapies for HIV/AIDS and its complications.

The use of the Internet has bestowed extraordinary benefits on biomedical research, including AIDS-related research. Over the last 2 years, Internet use by the biomedical research community has increased exponentially. The National Library of Medicine (NLM)'s transition to a system of free Web-based access to MEDLINE and other NLM databases has contributed to and reflected this trend. However, full realization of the benefits of the Internet requires that AIDS and other biomedical researchers have the requisite Internet infrastructure and training so that they can easily access relevant research information and also contribute new information to the ever-expanding AIDS-related databases. This can still be a considerable challenge for researchers in remote, rural, or underserved communities. For researchers in major urban biomedical facilities, Internet access can be problematic because of peak-hour congestion and the increasing size and complexity of the information being transmitted.

NLM is working to improve the Internet infrastructure and training for AIDS-related research on several fronts. NLM is the leading participant on behalf of NIH in the development of the Next Generation Internet (NGI). NGI will connect Government and university research laboratories with high-speed networks that are 100 to 1,000 times faster than today's Internet. Also, NGI is promoting experimentation with new technologies and applications in areas such as biomedical research. In October 1998, NLM announced the award of 24 contracts to biomedical institutions and companies to develop innovative medical projects that demonstrate the application and use of NGI in a variety of areas.

In addition to research on the development of advanced technology, NLM is encouraging the deployment of the current Internet infrastructure, to promote the rapid exchange of biomedical information nationally and throughout the world. To accelerate the pace at which health-related institutions become part of the electronic information web, NLM is offering grants to support institution-wide Internet connections.

NLM also supports the implementation of current Internet technology in geographic areas that lack these capabilities and where there are significant at-risk populations. This effort includes a series of small purchase orders to improve Internet infrastructure and training for researchers, health care providers, patients, and others within the AIDS community, as discussed in the section on Information Dissemination. Also, through a contract from NLM, the Regional Medical Library (RML) at the University of Washington is providing assistance with Internet connections to 16 tribes and Native American villages in Alaska, Idaho, Montana, Oregon, and Washington. Native Americans are at high risk for HIV/AIDS. The aim of this connectivity is to provide easy access to biomedical research and health care information, including AIDS-related information, thus minimizing the isolation of these villages and improving access to remote social, health, and research resources. NLM supports training and outreach along with the improved connectivity to help ensure that the participating tribal communities take full advantage of Internet-based health information. This initiative includes the development of AIDS-related information resources on the Web that are sensitive to the cultural and health needs of tribal communities. NLM expects to include additional tribal communities in other parts of the country in the future.

Databases and computer programs provide another type of infrastructural resource for HIV researchers. The National Center for Biotechnology Information (NCBI) at NLM serves as a national resource for molecular biology information and has developed a set of resources specifically designed to support research on retroviruses. These resources include the Genotyping tool, which uses the BLAST algorithm to identify the genotype of a query sequence; the Alignment tool, which provides global alignment of multiple sequences; HIV-1 automatic sequence annotation, which generates a report in GenBank format for one or more query sequences; and Genome maps, annotated maps of 16 retroviruses, which are viewable in GenBank, FASTA, and graphic formats, with links to associated sequence records.

NIH supports numerous repositories that provide resources for HIV/AIDS researchers. NHLBI maintains a repository of blood specimens from individuals with transfusion-associated HIV infection and from AIDS patients who have pulmonary disease. NIAID supports the AIDS Research and Reference Reagent Program, which provides a wide range of reagents, such as antibodies, cell lines, recombinant deoxyribonucleic acid (DNA) clones, peptides, viruses, and chemicals to investigators worldwide and is one of the World Health Organization AIDS Collaborating Centres. NHLBI

and NIAID have established a series of procedural guidelines to increase access to specimens from their patient cohort and subjects in clinical trials by qualified investigators not collaborating in the specific studies supported by these ICs. In addition, NIAID maintains a centralized repository for specimens from clinical trials and epidemiologic cohort studies. NCI has established and maintains the AIDS and Cancer Specimen Bank, to provide specimens to qualified investigators studying the pathogenesis of malignancies in HIV-infected individuals.

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE:

Provide both domestic and international training in biomedical and behavioral research on HIV, with an emphasis on multidisciplinary research in culturally diverse settings.

6.A

STRATEGIES:

- Increase predoctoral, doctoral, and postdoctoral training, as well as advanced research training, in a range of AIDS-related disciplines, to a level comparable with that of other training programs within NIH.
- Develop and expand programs for AIDS-related research training tailored and targeted to minority researchers, primarily at the pre- and postdoctoral levels.
- Provide incentives to attract researchers from other fields to pursue HIV/AIDS research.
- Provide incentives to AIDS-related basic, clinical, epidemiologic, statistical, and behavioral investigators to foster better linkages across scientific disciplines.
- Increase training to strengthen global capacity to conduct multidisciplinary AIDS-related prevention research in developing countries.
- Support the training of biomedical and behavioral scientists in both developed and developing countries in the use of advanced computer and information technologies for HIV-related research.
- Expand the NIH AIDS LRP to bring scientists and physicians to NIH, to increase the cadre of trained HIV/AIDS researchers.
- Taking advantage of existing AIDS clinical trials infrastructures, develop specific training programs in clinical trials methodology, including issues related to the design and analysis of observational studies.
- Develop integrated training opportunities that focus on the ethical issues of trial design and implementation of vaccine and other prevention modalities in at-risk populations, in both domestic and international settings.

- Support training opportunities for HIV prevention researchers interested in adding specific methodological skills to their research expertise (e.g., methods to conduct cost-effectiveness analyses, measurement of biologic outcomes in behavioral intervention studies, ethnographic and other qualitative methods, and network analysis).
- Support multidisciplinary training, with particular emphasis on AIDS-related intervention research such as research on vaccines, interventions to interrupt mother-to-child transmission, behavioral interventions, opportunistic infections (OIs), sexually transmitted diseases (STDs), microbicides, nutritional interventions, and substance abuse prevention and treatment, as well as clinical trials methods.
- Expand international AIDS training and research programs, coupling the training of scientists from developing countries with increased opportunities to conduct AIDS research when they return to their home countries (e.g., reentry grants).
- Develop new grant mechanisms, and expand existing grant mechanisms, to link U.S. AIDS research scientists and institutions with each other and with investigators and institutions in both developed and developing countries.
- Support the training of affected community members, so as to make it easier for them to participate in biomedical and behavioral science research.
- Collaborate with other PHS agencies in the development of training regarding HIV prevention, treatment, research, and education for health care providers, AIDS service providers, and health educators.

OBJECTIVE:

Establish the appropriate infrastructure needed to conduct HIV research domestically and internationally.

6.B

STRATEGIES:

- Enhance and improve research capacity and infrastructure, with particular emphasis on AIDS-related intervention research, such as research on vaccines, interventions to prevent mother-to-child transmission, behavioral interventions, OIs, AIDS-associated malignancies, STDs, microbicides, and nutrition, as well as clinical trials methodologies.
- Develop the infrastructure for the conduct of vaccine trials in domestic and foreign sites, including laboratory capacity, trained scientists and other personnel, appropriate participant cohorts, and mechanisms to address ethical issues.
- Ensure an adequate infrastructure for producing the optimal vectors for vaccines and therapy.
- Ensure adequate facilities and resources as well as the appropriate ethical and procedural training needed to investigate HIV animal models.
- Expand the production of genetically defined, specific-pathogen-free nonhuman primates.
- Develop and characterize appropriate reagents for use in nonhuman primates.
- Provide expanded funding for pilot animal model studies at primate centers and other facilities.
- Support programs that enhance the current research infrastructure, particularly the trans-NIH infrastructure, such as the CFARs, the Research Facilities Infrastructure Program (RFIP), and the GCRC Program.
- Increase support for, and awareness of, the Biomedical Technology Resources Program for structural studies of viral and host proteins.

- Provide for the long-term support of advanced in-country research and research infrastructure in developing countries participating in priority AIDS-related intervention research, such as methods to interrupt mother-to-child, sexual, or parenteral transmission, and trials of candidate HIV vaccines.
- Increase collaboration between community-based organizations and other service providers (such as those funded by the Ryan White CARE Act) and academic researchers, to improve the quality and capacity of research endeavors in service settings.
- Establish and support quality-controlled repositories for, and ensure access by, qualified scientists to samples (i.e., serum, peripheral blood mononuclear cell [PBMC], plasma, derived cell lines, cerebrospinal fluid [CSF], tissues, and other key patient samples) and HIV strains from clinical trials and natural history and epidemiological studies, especially in complex study settings (e.g., mother-to-child transmission studies).
- Maintain the present AIDS-related tumor registries, and ensure linkages between AIDS and cancer registries, for both domestic and international studies.
- Improve (and adequately disseminate) the process of requesting, prioritizing, and receiving laboratory samples, so that access is as timely and equitable as possible.
- Promote Internet connections and availability of pertinent information at health sciences centers, hospitals, outpatient clinics, community-based organizations, and other access points, both domestically and internationally, for HIV-related research and patient care.
- Promote research in, and application of, medical informatics (e.g., high-performance computing), both domestically and internationally, for HIV/AIDS research and clinical practice.
- Develop statistical sampling methodologies, data collection protocols, and statistical analysis tools that are easy to use and adaptable to different settings, facilitate efficient statistical analysis and report generation, and enhance standardization, when appropriate.

Information Dissemination

AREA OF SPECIAL INTEREST:

Information Dissemination

SCIENTIFIC ISSUES

Effective and efficient information dissemination and exchange are important tools in the effort to control and end the AIDS epidemic. NIH has responsibility for disseminating information to support research, treatment, and prevention related to HIV and AIDS. Progress in these areas depends on the transfer of information to researchers, health care and service providers, and HIV-infected individuals and their advocates. These audiences have varying needs for information that is critical in the fight against HIV/AIDS. The changing demographics of the epidemic provide challenges to disseminating HIV research results to communities at risk in the United States, including women and minorities, as well as those at risk in developing countries. An additional challenge is providing information in formats that are useful to both health care providers and patients. The flow of information among researchers, health care providers, and the affected communities represents new opportunities to rapidly translate research into practice and to shape future research directions.

A *Guide to NIH HIV/AIDS Information Services* is updated annually and made available in both printed and electronic form through the National Library of Medicine (NLM) AIDS Home Page (<http://sis.nlm.nih.gov>). This pamphlet provides a comprehensive listing of NIH-supported information services that assist care and service providers, patients, and the public. The electronic version provides links to NIH and Public Health Service (PHS) sites and resources.

CLINICAL ALERTS

A Clinical Alert service, maintained on the NLM Web site, includes links to Clinical Alerts issued by the NIH Institutes and Centers (ICs). Clinical Alerts are notifications to health professionals and the public of new research information critical to patient care. These notifications are frequently issued before they are published in a peer-reviewed scientific journal.

TREATMENT GUIDELINES

Access to clinical care guidelines, standards of care, and results of state-of-the-art meetings is critical for physicians and patients. Treatment guidelines for the use of new and complex antiretroviral regimens are continually updated. The guidelines are available in print form and on the Internet Web site of the HIV/AIDS Treatment Information Service (ATIS) (<http://hivatis.org>) (see below). Titles available include the following:

- *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents.*
- *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection.*
- *Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant Women Infected with HIV-1 for Maternal Health and for Reducing Perinatal HIV-1 Transmission in the United States.*
- *Public Health Service Guidelines for the Management of Health-Care Worker Exposures to HIV and Recommendations for Postexposure Prophylaxis.*
- *Management of Possible Sexual, Injecting-Drug-Use or Other Nonoccupational Exposure to HIV, Including Considerations Related to Antiretroviral Therapy.*
- *1999 USPHS/IDSA Guidelines for the Prevention of Opportunistic Infection in Persons Infected with HIV.*
- *Updated Guidelines for the Use of Rifabutin or Rifampin for the Treatment and Prevention of Tuberculosis Among HIV-Infected Patients Taking Protease Inhibitors or Nonnucleoside Reverse Transcriptase Inhibitors.*
- *Prevention and Treatment of Tuberculosis Among Patients Infected with HIV: Principles of Therapy and Revised Recommendations.*

**ELECTRONIC
INFORMATION
RESOURCES**

To ensure the widest possible dissemination of the guidelines through the most effective mechanisms, NIH supports and participates in the Department of Health and Human Services (DHHS) Working Group on Information Dissemination.

Computerized databases are a vital component of NIH AIDS information dissemination, allowing global access to information concerning basic research, clinical trials availability and results, standards of care, and other information of interest to HIV-infected individuals, their care providers, and their advocates. Examples of these critical resources follow.

MEDLARS Databases

Internet: <http://www.ncbi.nlm.nih.gov/PubMed>

These databases are available free of charge to users worldwide. The AIDS subset of PubMed includes citations (with abstracts when available) to AIDS-related journal articles and newsletters. Relevant abstracts from meetings and conferences are included in the new Gateway, which also provides access to other NLM information resources. Descriptions of clinical trials and the agents studied in those trials (AIDSTRIALS and AIDSDRUGS) are accessed through the AIDS Clinical Trials Information Service (ACTIS) Web site, where users may also find supporting materials such as fact sheets and links to published trial results. International, national and state organizations involved in AIDS are found in DIRLINE: (<http://sis.nlm.nih.gov/dirline>).

AIDS Clinical Trials Information Service (ACTIS)

Internet: <http://www.actis.org>

Phone: 1-800-TRIALS-A

E-mail: actis@actis.org

Initiated in 1989, ACTIS is a centralized resource providing information on federally and privately funded HIV/AIDS clinical trials for adults and children at all stages of HIV/AIDS. This free service is jointly sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), NLM, and the Food and Drug Administration (FDA) in collaboration with the Centers for Disease Control and Prevention (CDC). Callers can speak to trained multilingual health specialists who access an AIDS clinical trials database. The ACTIS Web site includes databases that provide information about new and ongoing clinical trials that evaluate experimental drug treatments and candidate vaccines, including descriptions of clinical trials and the agents studied in those trials (AIDSTRIALS and AIDSDRUGS).

The Web site also provides HIV vaccine information, supporting materials such as factsheets, and links to published trial results and to other databases. ACTIS collaborates with the NIH Clinical Trials Information Program (<http://clinicaltrials.gov>) by supplying data and providing links for additional information.

HIV/AIDS Treatment Information Service (ATIS)

Internet: <http://www.hivatis.org>

Phone: 1-800-HIV-0440

E-mail: atis@hivatis.org

NIH collaborated with other PHS agencies to develop ATIS—a toll-free telephone and Web-based reference service for people with HIV disease, their families and friends, and health care providers—to provide information about federally approved treatment guidelines. ATIS is staffed by multilingual health information specialists who answer questions on HIV treatment options using a broad network of Federal, national, and community-based information resources. ATIS is sponsored by NIH, CDC, the Health Resources and Services Administration (HRSA), the Substance Abuse and Mental Health Services Administration (SAMHSA), the Indian Health Service (IHS), and the Health Care Financing Administration (HCFA).

NIH Web Pages

NIH continues to expand and improve its use of the Internet as an important medium for HIV/AIDS information dissemination efforts. NIH Home Pages such as those for NIH overall (<http://www.nih.gov>), Office of AIDS Research (OAR) (<http://www.nih.gov/od/oar>), and all of the NIH ICs and Office of the Director (OD) offices provide extensive HIV/AIDS research and programmatic information for the public, patients, health care providers, scientific investigators, and policymakers. NLM has created a Web site specifically for HIV/AIDS-related information (<http://sis.nlm.nih.gov/aidswww.htm>). This site serves as an entry point to many of the HIV/AIDS-related resources available from NIH and serves as a guide to selected resources worldwide.

COMMUNITY OUTREACH PROGRAMS

Providing accurate and up-to-date HIV/AIDS prevention and treatment information to communities at risk, including women and minorities, is a critical challenge. NIH has initiated a number of new projects, in addition to its ongoing programs, in response to the initiative of DHHS, the White House, and the Congressional Black Caucus (CBC) to address AIDS in minority communities.

Since FY 1994, NIH, through NLM, has made awards of up to \$40,000 each on an annual basis to enable community-based organizations and public and health science libraries to design their own programs for improving access to AIDS information for targeted groups, including people living with HIV/AIDS, their caregivers, communities at risk, and the general public. These awards support activities such as purchasing equipment and telecommunications services, implementing Internet access, training in the use of sophisticated information tools, and developing language- and culture-specific materials. NLM has also supported three innovative efforts for improving HIV/AIDS information access, which (1) examined the functioning of a consortium of academic, public, and hospital libraries along with community organizations to disseminate information to the affected community; (2) developed and field-tested a training curriculum on accessing HIV/AIDS information by non-health professionals; and (3) provided access through dedicated centers in public libraries.

Training in the use of electronic HIV/AIDS resources, including the use of online databases, is included in NIH information dissemination programs. Curriculum-based AIDS information programs and modules are made available nationwide, including through the Historically Black Colleges and Universities (HBCUs) and other groups of minority health professionals, such as the National Association for Equal Opportunity in Higher Education (NAFEO).

NIH HIV/AIDS public education materials include specifically targeted television, radio, and print materials aimed at audiences at high risk for contracting or transmitting HIV infection. Along with six other Federal agencies, NIH has sponsored a series of DHHS satellite broadcasts on HIV/AIDS-related issues. The goal of this series is to make the latest guidelines, data, and information on HIV/AIDS topics available to a wide audience of people interested in HIV/AIDS prevention and care.

Regional Technology Transfer Meetings

OAR sponsors a series of regional information dissemination programs to bring current research information to community health care professionals, particularly in minority communities and to communities with the least access to information. Meetings have been targeted to Hispanic, Native American, and African American communities. Future efforts are anticipated that focus on Asian and Pacific Islanders and with a group representing health care providers serving prison populations. Other conferences have focused on issues relating to women, children, and injecting drug users.

Caribbean-wide Technology Transfer Meeting

Congressional appropriations language identified the need for HIV/AIDS information in the U.S. Virgin Islands. After consultation with Representative Donna Christian-Christensen, and in collaboration with the U.S. Virgin Islands Department of Health, NIH's OAR expanded this initiative to other communities throughout the Caribbean. An International Planning Committee was convened, including groups from the U.S. Virgin Islands, Bahamas, Barbados, Jamaica, and Trinidad and Tobago. On February 24-25, 2000, a major conference, "Heightening Awareness of HIV/AIDS in the Caribbean Region: Bridging the Gap from Denial to Acceptance to Prevention—Preparing for the Next Millennium" took place. St. Thomas, U.S. Virgin Islands, was the host site for the conference. Morning plenary sessions were broadcast by satellite to Barbados, Bahamas, Jamaica, and Trinidad and Tobago. Each island then held its own afternoon sessions on topics specific to its interests and needs. Each island's events were audio-and-video recorded and placed on the Internet for online viewing after the conference.

Community Forums

OAR sponsored a community forum program designed to bring research information to the public and to communities at risk. A series of scientific meetings, featuring nationally recognized researchers, was held around the United States in collaboration with national and local HIV/AIDS community organizations. OAR has folded this program, along with the Regional Technology Transfer Meetings, into support for the National Minority AIDS Council (NMAC) Regional Training Programs.

Collaboration with the National Minority AIDS Council

OAR and NMAC are collaborating on information dissemination projects that include Internet access to AIDS conferences and presentations, AIDS treatment publications targeted to minority communities, and exhibits of NIH AIDS research information at local and national minority AIDS meetings. Examples of the collaborative projects include:

- **Epidemiological Video Series Initiative:** OAR and NMAC are co-sponsoring a video initiative to create awareness of the health care crisis that AIDS poses in minority communities. Videos targeted to African American and Latino communities have been developed, and they include data and statistics demonstrating the dramatic rise in infection rates in those communities.

- **Equal Access Initiative—Computer Grants Program:** This initiative provides computers, Internet access, and computer training for minority communities to facilitate learning, collaboration, and dissemination of patient and provider information.
- **Meet the Expert Session:** This program, which, along with NIH, is sponsored by HRSA, provides access via the Internet to presentations by experts followed by interactive question-and-answer periods. Sessions have included “HIV-Related Anemia,” “AIDS Treatment Guidelines,” “HAART 101,” and updates from the annual Retrovirus Conference.
- **Video Streaming:** In a continued effort to reach broad audiences, this program brings conference information to the Internet so that individuals unable to attend the meetings have access to the information.

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE:

Support the effective dissemination, communication, and utilization of HIV/AIDS information to all constituent communities of NIH.

7.A

STRATEGIES:

- Rapidly disseminate new research findings with information on their potential implications for prevention, care, and treatment of HIV-infected individuals, using existing and innovative methods.
- Facilitate the development of HIV treatment guidelines based on the latest clinical research findings.
- Utilize computer and other information dissemination technology (including the Internet) to disseminate up-to-date HIV/AIDS information; information about HIV therapeutic, vaccine, and prevention trials; and information about HIV training programs.
- Expand access to and education about current state-of-the-art treatment and patient management guidelines, including information on clinical trials, using multiple technologies such as online access (AIDSTRIALS and AIDSDRUGS databases) and voice access (ATIS and ACTIS).
- Improve current techniques and develop and evaluate new techniques for the two-way communication of information to scientific and lay audiences, particularly to hard-to-reach populations, including information about clinical trials.
- Improve outreach and support access to HIV/AIDS information resources (including computers) by community groups, health care providers, and community-based HIV/AIDS service organizations, including those serving minority communities.
- Work with community-based organizations to develop and promote effective methods of information dissemination in target populations.
- Develop and disseminate educational information to enhance understanding of HIV and basic and clinical research processes by health care providers, community-based HIV/AIDS service organizations, social service organizations, policymakers, and persons with HIV/AIDS.

- Evaluate the effectiveness of communication efforts by appropriate means, including obtaining feedback from target audience members and information dissemination intermediaries.
- Promote wide dissemination of the annual NIH Plan for HIV-Related Research and other HIV-related reports as they become available.
- Maintain a database of AIDS-related researchers, AIDS research organizations, and associated groups to facilitate and increase collaborations and cross-sharing of research ideas, data, and results.
- Promote and enhance the exchange of scientific information and communication between public and private research enterprises, such as enhancing communication with the pharmaceutical industry concerning research on the development of therapeutics and vaccines, and working with industrial scientists to make information concerning basic science and HIV protein structures available to the general scientific community.
- Communicate and exchange information internationally on topics such as prevention and treatment, patient management guidelines, and research results that improve the care of HIV-infected individuals, including those in developing countries.
- Support the exchange of basic and applied research information at community, regional, national, and international conferences and workshops.
- Support the cross-collaborations of HIV/AIDS information providers to develop more integrated and comprehensive information dissemination approaches.
- Provide online access to presentation materials, including full text of abstracts and other information (e.g., slides, graphics, plenary presentations) from scientific meetings.
- Collect, archive, and promote use of existing data from NIH-supported basic and applied research for secondary data analysis, including rapid development of public use data sets that can be used for secondary data analysis in NIH-supported studies, especially baseline survey and HIV/STD (sexually transmitted disease) incidence data.

- Widely disseminate information concerning specimen repositories, including existing repositories, specimens available, and relevant information concerning cohorts, contact information, and the process for obtaining access to samples.

OBJECTIVE:

Support research to identify existing gaps in communication approaches, identify and evaluate existing strategies, and develop and test new and innovative communication strategies that will improve access to and use of state-of-the-art HIV information by all relevant target audiences.

7.B

STRATEGIES:

- Assess the information needs and resources used by various audiences, including biomedical and behavioral research communities, health care providers, service providers, people with HIV and their advocates, at-risk populations, scientific and lay media, and the general public.
- Identify obstacles to information dissemination and develop and test possible ways to overcome these obstacles.
- Develop, test, and evaluate innovative strategies for effectively reaching specific audiences (e.g., minority communities, adolescents, drug users, other hard-to-reach populations, and health care providers) with relevant HIV information.
- Investigate how and under what circumstances different communication and dissemination strategies influence the adoption of scientifically based HIV behavior-change interventions and clinical practices in specific audiences.
- Promote use of new technologies and evaluate their effectiveness for disseminating basic and applied research findings.

OBJECTIVE:

Develop, implement, and evaluate methods of coordination and collaboration on HIV/AIDS communications activities among NIH ICs and with other Federal and non-Federal groups.

7.C**STRATEGIES:**

- Build and enhance partnerships among community-based organizations and basic, clinical, and behavioral researchers to encourage exchange of information and experience.
- Promote and foster information dissemination regarding research and programmatic efforts across the ICs, among U.S. Government agencies, and with international partners.
- Promote collaboration among all ICs in providing information about their HIV/AIDS clinical trials to ACTIS and clinicaltrials.gov.
- Maintain an interface with data sources such as the Cancer Information Service and Physician Data Query (PDQ) to provide information on clinical trials for AIDS-related malignancies.
- Expand the development of HIV/AIDS resources on the Internet to facilitate national and international research collaboration and data sharing.
- Continue collaborations with the Joint United Nations Programme on HIV/AIDS (UNAIDS), the Pan American Health Organization (PAHO), and other international AIDS agencies or societies on information/communications efforts, including information about international clinical trials.
- Collaborate with public and health sciences libraries, health care providers, AIDS education and training centers, and community-based HIV/AIDS service organizations to facilitate access to needed information.
- Expand collaboration to include academic, medical, and other communities, as appropriate, in the dissemination of NIH HIV-related reports.

Appendices

APPENDIX A:

NIH Institutes
and Centers

NIH INSTITUTES AND CENTERS

NCI	National Cancer Institute
NEI	National Eye Institute
NHLBI	National Heart, Lung, and Blood Institute
NHGRI	National Human Genome Research Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NICHD	National Institute of Child Health and Human Development
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIDA	National Institute on Drug Abuse
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIMH	National Institute of Mental Health
NINDS	National Institute of Neurological Disorders and Stroke
NINR	National Institute of Nursing Research
NLM	National Library of Medicine
NCCAM	National Center for Complementary and Alternative Medicine
NCRR	National Center for Research Resources
FIC	John E. Fogarty International Center
CC	Warren Grant Magnuson Clinical Center
CIT	Center for Information Technology
CSR	Center for Scientific Review

APPENDIX B:

Summary of
HIV/AIDS Funding

HIV/AIDS FUNDING BY NIH INSTITUTE, CENTER, AND OFFICE
(dollars in thousands)

Institute/Center	FY 1999 Actual	FY 2000 Estimate	FY 2001 Request
NCI	\$234,653	\$244,494	\$255,342
NHLBI	64,511	65,527	67,175
NIDCR	17,959	20,193	21,100
NIDDK	17,846	21,983	22,907
NINDS	29,335	33,658	34,416
NIAID	802,658	915,484	971,047
NIGMS	31,850	37,128	38,696
NICHD	75,745	89,540	94,204
NEI	10,351	10,890	11,176
NIEHS	7,023	7,541	7,678
NIA	2,068	4,143	4,298
NIAMS	4,683	5,022	5,233
NIDCD	1,690	1,590	1,591
NIMH	114,105	128,697	135,294
NIDA	188,919	218,227	229,173
NIAAA	16,187	19,243	20,083
NINR	6,229	7,497	7,810
NHGRI	3,989	4,188	4,313
NCRR	95,957	105,915	111,464
NCCAM	1,030	1,030	1,030
FIC	12,448	14,416	15,479
NLM	4,114	5,063	5,193
OD	43,289	44,714	46,522
B&F	6,100	—	—
TOTAL	\$1,792,739	\$2,006,183	\$2,111,224

HIV/AIDS FUNDING BY AREA OF EMPHASIS
(dollars in thousands)

Area of Emphasis	FY 1999 Actual	FY 2000 Estimate	FY 2001 Request
Natural History and Epidemiology	\$225,965	\$252,752	\$266,565
Etiology and Pathogenesis	556,921	602,925	631,364
Therapeutics	483,631	514,291	528,120
Vaccines	182,256	238,711	267,519
Behavioral & Social Sciences	242,388	290,194	305,577
Training and Infrastructure	75,858	79,923	83,668
Information Dissemination	25,720	27,387	28,411
TOTAL	\$1,792,739	\$2,006,183	\$2,111,224

APPENDIX C:

Office of AIDS Research
Advisory Council

OFFICE OF AIDS RESEARCH ADVISORY COUNCIL

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FY 2002 OAR
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FY 2002 OAR PLANNING GROUPS

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APPENDIX E:

Fiscal Year 2002
Plan and Budget
Timeline

OAR ANNUAL PLAN AND BUDGET PROCESS FY 2002 Timeline

PLAN	
February 2000	Draft 1 External Consultants NIH Program Staff IC AIDS Coordinators IC Directors
March 2000	Draft 2 OAR Advisory Council Comments
July 2000	Final Plan Published
BUDGET	
May 2000	ICs Prepare Budget Using Draft Plan
June 2000	Draft Budget Developed Based on IC Request
August 2000	AIDS Budget Submitted to Director, NIH
August-December 2000	NIH Budget to Secretary, DHHS DHHS Budget to OMB
February 2001	FY 2002 President's Budget to Congress
March 2001	Appropriations Subcommittee Hearings
April-September 2001	House, Senate, Conference Action
October 2001	FY 2002 Begins

APPENDIX F:

NIH AIDS Research Program
Evaluation Working Group
Report: Implementation of
Recommendations

NIH AIDS RESEARCH PROGRAM EVALUATION WORKING GROUP REPORT: IMPLEMENTATION OF RECOMMENDATIONS

In late 1994, the Office of AIDS Research (OAR) Advisory Council, chaired by Dr. Charles Carpenter of Brown University, established the AIDS Research Program Evaluation Working Group. Dr. Arnold Levine of Princeton University was recruited to lead this group of outstanding scientists and community advocates. The Working Group subsequently established six Area Review Panels to review AIDS research on Etiology and Pathogenesis; Drug Discovery; Clinical Trials; Vaccine Research and Development; Behavioral, Social Sciences and Prevention Research; and Natural History, Epidemiology, and Prevention Research. Over 100 scientists from academia and industry as well as community advocates participated in these panels.

The six panels and the Working Group met regularly throughout 1995 and early 1996 to review information provided by the NIH Institutes, Centers and Divisions (ICDs) that conduct and support AIDS research and to review budget and program information retrieved from databases maintained by the OAR and the Division of Research Grants (DRG). In addition, reviewers met with ICD Directors, key program staff, intramural and extramural scientists, and a wide variety of experts from inside and outside the field of AIDS research. Special *ad hoc* subpanels were convened to examine cross-cutting issues, such as animal models, opportunistic infections (OIs), AIDS centers, complementary and alternative medicine treatments, methods to increase the number of AIDS researchers, and the optimization of community involvement in the NIH AIDS research program.

Each Area Review Panel identified the scientific priorities within its area, evaluated the current research portfolio, and developed recommendations to improve, enhance, and streamline AIDS research. The individual Area Review Panels documented their specific evaluations and detailed recommendations. The Working Group took a broader view, identifying key issues and developing major recommendations that span scientific areas and underpin the overall NIH AIDS effort. In some cases, the Working Group recommendations reflect a consensus position that reconciles somewhat divergent conclusions found by an individual Area Review Panel.

Status of recommendations follows.

NIH AIDS Research Program Evaluation Working Group Report: Implementation of Recommendations

I. INVESTIGATOR-INITIATED RESEARCH				
Recommendation	Completed	Ongoing	Planned	Comment (see note)
I.1 The proportion of the NIH AIDS research budget allocated to support unsolicited investigator-initiated research should be approximately doubled.		✓		*
I.2 Selected members of AIDS-related IRGs should participate in OAR's process for setting research priorities. As an integral part of the IRG process, these individuals, in concert with DRG ¹ and OAR staff, should familiarize their IRG members with OAR- and ICD ² -defined AIDS research priorities.	✓			*
I.3 Scientific Review Administrators of AIDS-related IRGs should be included as members of the OAR Coordinating Committees corresponding to their area of expertise.	✓			
I.4 OAR, in concert with the ICDs, should inform the ICD advisory bodies and councils of the NIH AIDS research priorities as outlined in the NIH Plan for HIV-Related Research.		✓		
I.5 OAR should develop a strategy to distribute the NIH Plan for HIV-Related Research to the scientific community and other interested parties.	✓			
I.6 AIDS-related grant proposals should include a discussion of how the proposed investigation relates to the research priorities detailed in the NIH Plan for HIV-Related Research.	✓			*
I.7 It is critical that the DRG work with OAR and the ICDs to provide IRGs with high-caliber, mature, and diverse scientists and clinicians. DRG should investigate possible mechanisms to ensure high-quality reviews responsive to the changing scientific issues. Such mechanisms might include working with learned societies to identify distinguished scientists with a broad range of expertise to serve on IRGs, making greater use of voting <i>ad hoc</i> members, and exercising flexibility on the term limits for IRG participation.		✓		

NIH AIDS Research Program Evaluation Working Group Report: Implementation of Recommendations

I. INVESTIGATOR-INITIATED RESEARCH (CONT'D)				
Recommendation	Completed	Ongoing	Planned	Comment (see note)
I.8 DRG should be responsive to the evolving character of AIDS research and modify IRG composition or define new IRGs as needed. The Working Group believes that the existing AIDS-related IRGs should be redefined and reconfigured to reflect the current scientific priorities for AIDS research, particularly as they relate to vaccine and prevention science research needs.	✓			
I.9 Given the crucial importance of training for the research enterprise, OAR should establish a Coordinating Committee on Training and Infrastructure, with the same responsibilities as other OAR Coordinating Committees.				*
I.10 OAR Coordinating Committee on Training and Infrastructure should review the NIH Plan for HIV-Related Research and address a wider range of NIH training mechanisms (such as the K awards, supplements, and predoctoral research opportunities). The Plan should include strategies for the systematic outcome evaluation of training awards.				*
I.11 Innovative mechanisms to provide short-term (2-3 year) support for young investigators at levels sufficient to initiate quality research programs should be developed.				*
1.12 Many investigator-initiated research grants in areas unrelated to HIV/AIDS objectives, held by distinguished senior scientists, generate findings that may be relevant to questions in AIDS research. To encourage these laboratories to explore AIDS-related avenues of research, a program should be established that offers supplemental funding to support postdoctoral fellows or graduate students to carry out AIDS-related research.				*
I.13 NIH should develop programs for AIDS-related research training explicitly tailored and targeted to ethnic minority individuals, primarily at the postdoctoral level. Rather than simply supplementing existing grants, these programs should involve collaborative mentoring activities in research projects defined by the minority scientists. Programs should include intense and long-term mentoring and support in the NIH grant application process. A criterion of evaluation of these programs should be the number of new NIH-funded principal investigators (PIs) of ethnic minority background.		✓		*

NIH AIDS Research Program Evaluation Working Group Report: Implementation of Recommendations

I. INVESTIGATOR-INITIATED RESEARCH (CONT'D)				
Recommendation	Completed	Ongoing	Planned	Comment (see note)
I.14 OAR should investigate the possibility of extending the AIDS Loan Repayment Program (LRP) to forgive student loan debts for postdoctoral fellows working in AIDS research outside of the NIH intramural program.				*
II. AIDS VACCINE RESEARCH				
II.1 The entire NIH AIDS vaccine research effort should be restructured. A trans-NIH vaccine program should be established with leadership and oversight provided by distinguished, non-Government scientists.	✓			
II.2 A National AIDS Vaccine Task Force (NAVTF), chaired by the Director of OAR, should be established in the White House Office of National AIDS Policy, with responsibility for coordinating all Government-sponsored vaccine programs.	✓			*
II.3 NIAID, in partnership with other ICDs with complementary expertise, should promptly develop a comprehensive plan for HIVNET's organization, governance, research, and funding. This plan should be reviewed in 1996 by a joint OAR/ICD-convened panel of extramural experts in behavioral, social, epidemiological, prevention, pathogenesis, and treatment research as well as vaccine research. If reviewers determine that there are significant deficiencies in the plan, funds could be released for retargeting to other essential areas of AIDS research.	✓			
III. RESEARCH ON THE HUMAN IMMUNE SYSTEM				
III.1 OAR should convene a series of workshops of expert immunologists to develop a plan to accelerate progress in understanding the following:		✓		
<ul style="list-style-type: none"> • The basic biology and development of human immunocompetent cells and of the unique aspects of the physiology of the human immune system. 	✓			
<ul style="list-style-type: none"> • How HIV or SIV perturbs the human or primate immune system to impair the function of and destroy immunocompetent cells. 		✓		

NIH AIDS Research Program Evaluation Working Group Report: Implementation of Recommendations

III. RESEARCH ON THE HUMAN IMMUNE SYSTEM (CONT'D)				
Recommendation	Completed	Ongoing	Planned	Comment (see note)
<ul style="list-style-type: none"> Why normal replacement mechanisms are unable to restore a functional immune system in infected individuals. 	✓			
<ul style="list-style-type: none"> Why normal host defenses are unable to ultimately contain HIV infection. 		✓		
III.2 NIH should increase support for research on the human immune system by traditional mechanisms of investigator-initiated research and intramural projects.		✓		
III.3 NIH should facilitate interactions between basic immunologists and AIDS researchers through consortial approaches. Anticipated benefits of the consortial mechanism include overcoming basic immunologists' unfamiliarity with AIDS research and concerns about working with infectious agents; facilitating the exchange of ideas, techniques, reagents, and personnel; and increasing the likelihood that postdoctoral fellows enter AIDS research.		✓		
IV. HIV PREVENTION SCIENCE RESEARCH				
IV.1 NIH, acting through OAR, should develop a coordinated and comprehensive Prevention Science Agenda that includes and combines biomedical, behavioral, and social interventions. This agenda should begin with an NIH-wide plan that then is integrated where possible with similar plans at the Centers for Disease Control and Prevention (CDC) and other relevant Federal agencies.		✓		
IV.2 NIH should convene an HIV Prevention Science Advisory Committee reporting to the Director of OAR.	✓			
IV.3 OAR should appoint an HIV Prevention Science Coordinator charged with coordinating the implementation of the Prevention Science Agenda.	✓			
IV.4 NIH IRGs for the review of AIDS research grants should be reconfigured to include one with appropriate expertise in and responsibility for HIV prevention science proposals (including cross-disciplinary studies).				*

NIH AIDS Research Program Evaluation Working Group Report: Implementation of Recommendations

V. CLINICAL TRIALS				
Recommendation	Completed	Ongoing	Planned	Comment (see note)
V.1 A single integrated adult clinical trials network should be created with primary sponsorship from NIAID and ancillary funding from other Institutes involved in clinical trials.		✓		*
V.2 A uniform standard for clinical trials databases should be developed to ensure that data can be shared between studies both within and across trials programs.		✓		
V.3 The Working Group recommends an early reexamination of the optimal approach to future pediatric AIDS clinical trials. Furthermore, significant reductions in allocations to the PACTG are recommended. These should be implemented in such a manner so that the essential clinical trials function of the PACTG is not impaired.		✓		*
V.4 An oversight committee for all NIH-sponsored AIDS clinical trials should be created and based in OAR, and should include broad scientific and community representation.	✓			
VI. DRUG DISCOVERY RESEARCH				
VI.1 An external scientific advisory board, including a representative from OAR, should be constituted to provide guidance regarding appropriate goals for future DTP AIDS research activities. Future assessment of the DTP AIDS drug discovery program should include its ability to support the overall NIH drug discovery effort for HIV and for the anti-OI discovery efforts of other ICDs. NCI bears a particular responsibility for the development of novel treatments for AIDS-associated malignancies. To accomplish these goals, DTP management and structure require careful review, both to determine what can be eliminated from the AIDS drug discovery effort and to appropriately assign the funds allotted to AIDS-directed research. A substantial decrease in the size and funding of the DTP's current AIDS-related drug discovery effort is appropriate.		✓		*
VII.1 Reinvigorate the basic science research effort on AIDS-associated OIs, emphasizing				

NIH AIDS Research Program Evaluation Working Group Report: Implementation of Recommendations

VII. RESEARCH ON OPPORTUNISTIC INFECTIONS				
Recommendation	Completed	Ongoing	Planned	Comment (see note)
studies of fundamental aspects of the biology of the responsible microorganisms and the mechanisms of disease pathogenesis.		✓		
VII.2 NIH should pursue innovative approaches, such as enhancing the quality and AIDS focus of the Small Business Innovative Research (SBIR) grant program, to foster the transfer of new laboratory findings to early “proof of concept” clinical evaluation.		✓		
VIII. COMPLEMENTARY AND ALTERNATIVE MEDICINE RESEARCH				
VIII.1 OAR should establish an <i>ad hoc</i> advisory group to communicate community interest in the area of CAM therapies for HIV disease and to help identify therapies with apparent promise or potential danger for persons with HIV infection. This advisory group should consist of scientists experienced in clinical and laboratory evaluation of candidate therapies for HIV infection or its complications, and community representatives, including individuals who use CAM therapies.				*
VIII.2 A catalog should be prepared of all research relating to HIV-related CAM therapies currently being supported by NIH. OAR and its <i>ad hoc</i> advisory group should work with OAM ³ to establish an operational definition of CAM therapy as it relates to HIV disease and to construct a taxonomy to categorize CAM therapies in this area.				*
VIII.3 OAR and its <i>ad hoc</i> advisory group should work with OAM to sponsor a workshop on the research methodology for the evaluation of the efficacy of CAM therapies for HIV disease. OAR also should work with OAM to sponsor workshops to educate individuals interested in the evaluation of candidate CAM therapies for HIV disease about the preparation of NIH grant applications and the processes by which such applications are evaluated.				*

NIH AIDS Research Program Evaluation Working Group Report: Implementation of Recommendations

VIII. COMPLEMENTARY AND ALTERNATIVE MEDICINE RESEARCH (CONT'D)				
Recommendation	Completed	Ongoing	Planned	Comment (see note)
VIII.4 OAR should work with OAM and DRG to suggest individuals to serve as <i>ad hoc</i> members of IRGs that are reviewing HIV CAM therapy research proposals. Criteria for the selection of such members should include those currently utilized by DRG to select IRG members, as well as experience in the scientific evaluation of novel therapeutic approaches and knowledge of the concepts and practices of CAM therapies.				*
IX. REGIONAL PRIMATE RESEARCH CENTERS				
IX.1 OAR should commission a panel to define optimal mechanisms to support AIDS research at the RPRCs and to devise strategies that permit the most promising research ideas to be tested.		✓		*
IX.2 The process for competition of NCRR AIDS supplemental funding should be opened up to all extramural investigators.	✓			
IX.3 To optimize the quality and productivity of AIDS research conducted at the RPRCs, the NCRR IRGs that review the Centers should be strengthened by the addition of scientists with expertise in AIDS and AIDS-related research.	✓			
IX.4 Open competition for funds to support relevant animal costs included in DRG-reviewed grants might be accomplished through a regularly recurring RFA.				*
X. AIDS RESEARCH CENTERS				
X.1 The Working Group recommends that funding for the CFAR program as a whole be increased by approximately 50 percent. This would allow annual funding in the range of \$750,000 to \$1.5 million per year, to be allocated in proportion to a Center's research capacity and its ability to build an interdisciplinary research program and attract R01s.	✓			
X.2 The comprehensive research centers program, funded by NIMH, has been found to be productive and should be maintained.		✓		

NIH AIDS Research Program Evaluation Working Group Report: Implementation of Recommendations

XI. REPOSITORIES AND DATABASES				
Recommendation	Completed	Ongoing	Planned	Comment (see note)
XI.1 Improvements should be made in repositories and databases in accordance with three principles: repositories and databases should be investigator-designed and hypothesis-driven, accessible to all qualified investigators, and coordinated under a new user-friendly central tracking system maintained under the auspices of OAR. Support should be provided for collection of specimens, as dictated by scientific needs, and for these repositories and databases.	✓			*
XII. AIDS RESEARCH INFORMATION SYSTEM				
XII.1 A new information database system should be developed containing grant, contract, or intramural project titles and numbers; names of principal investigator and institutional affiliations; budget amounts; funding ICDs; and an abstract for each proposal. In addition, the Working Group recommends that a yearly summary abstract of ongoing activities and list of publications resulting from each award be prepared by the principal investigator and included in the database. The database should contain this information for every project coded by the ICDs as AIDS or AIDS-related.		✓		*
XIII. DEFINITIONS OF AIDS AND AIDS-RELATED RESEARCH				
XIII.1 The Working Group has determined that a substantial proportion of NIH AIDS funds has been previously and is presently inappropriately classified as AIDS or AIDS-related by many ICDs. Such funds should be redirected to research programs appropriately classified as AIDS and AIDS-related. It is recognized that an orderly plan for redirection is needed and that its implementation may require a period of time.	✓			
XIII.2 The Working Group strongly recommends that OAR, in cooperation with the ICDs, develop guidelines/criteria for the classification and coding of projects as AIDS and AIDS-related. Such a coding system should be implemented immediately to permit multiyear analyses of projects by these categories. The Working Group recognizes that these guidelines may evolve as AIDS research priorities change. It is crucial that this coding system be developed to ensure that AIDS research funds are effectively, efficiently, and optimally utilized.	✓			*

NIH AIDS Research Program Evaluation Working Group Report: Implementation of Recommendations

XIII. DEFINITIONS OF AIDS AND AIDS-RELATED RESEARCH (CONT'D)				
Recommendation	Completed	Ongoing	Planned	Comment (see note)
XIII.3 AIDS funds should continue to support excellent work in selected underdeveloped areas of basic research judged to be likely to make substantial contributions to progress against this disease and its sequelae. The research areas for potential investment should be clearly identified in the annual NIH Plan for HIV-Related Research so that they can be targeted for NIH-wide additional support.		✓		
XIV. OFFICE OF AIDS RESEARCH				
XIV.1 OAR should immediately develop a plan to implement the recommendations in this evaluation report.	✓			

- ¹ Division of Research and Grants (ORG) is now Center for Scientific Research (CSR).
- ² NIH Institutes, Centers, and Divisions; now Institutes and Centers (ICs).
- ³ Office of Alternative Medicine (OAM); now the National Center for Complementary and Alternative Medicine (NCCAM).

NIH AIDS RESEARCH PROGRAM EVALUATION WORKING GROUP REPORT: OAR COMMENTS

1.1

Between 1994 and 1999, the proportion of funds allocated to unsolicited investigator-initiated research increased by 105 percent. OAR continues to stress the importance of investigator-initiated research.

1.2

NIH continues to support the principle of separation of scientific review from program prioritization, which has traditionally been the role of IC program staff and advisory councils. However, in recognition of the relevance of scientific review to program priority, DRG (now CSR), OAR, and the ICs have begun to work together to improve communication and encourage mutual awareness. The Scientific Review Administrator (SRA) participates in the planning process.

1.6

The instructions for preparing applications for Public Health Service (PHS) research grants (PHS 398) state that “applicants are urged to take note of the yearly NIH Plan for HIV-Related Research, and indicate how their application addresses the NIH priorities set forth in that Plan.”

1.9, 1.10, 1.11, 1.12, AND 1.14

Because of the implications for all of the Scientific Areas of Emphasis included in the Plan, OAR has asked the Planning Groups for each area to review the Training, Infrastructure, and Capacity Building section of the Plan during the annual workshops convened to review and revise the Plan. Beginning with the development of the FY 2001 Plan for HIV-Related Research, OAR has begun to examine more closely the Areas of Special Interest. In the FY 2001 Plan, a new Area of Special Interest was included to focus on issues related to racial and ethnic minorities. In the coming year, OAR plans to utilize the expertise of the members of the Coordinating Committees for the scientific areas, appropriate NIH program staff, and outside experts by convening an *ad hoc* group to review the Training, Infrastructure, and Capacity Building section. This group will address a wide range of issues related to training, as well as infrastructure and capacity building.

1.13

Programs are funded by NIMH that provide experience for postdoctoral minority fellows in research grant writing and research design development. NIMH regularly holds a technical assistance workshop for HBCU faculty, most recently from June 14 to 17, 1999. The June workshop covered details on developing a research idea and how to apply research. Participants were given an opportunity to visit NIH labs and were provided with names of mentors. The OAR *ad hoc* Minority Working Group will look more closely at training and infrastructure issues as part of its mission. OAR also hosted a 2-day minority faculty HIV prevention science workshop prior to the CDC National HIV Prevention Conference in August 1999. Attendees primarily were postdoctoral minority fellows interested in performing behavioral research. The fellows had a chance to meet other successful and senior minority researchers.

II.2

An Interagency HIV Vaccine Collaborative Group has been established with representatives of each Federal agency involved in AIDS vaccine research, with representation from White House staff. Chaired by the Director, this group has met twice (the first time in conjunction with OARAC) and plans to meet twice per year. The first series of meetings will serve to inform participants of ongoing and planned AIDS vaccine-related activities in different agencies.

IV.4

This has been deferred while CSR completes reorganization of Study Sections and finalization of recommendations of the Panel on Scientific Boundaries for Review, which is examining the organization and function of the review process.

V.1

The Therapeutics Research Working Group (TRWG) has been established under the auspices of OARAC to provide advice and guidance to the OAR Director on all components of NIH-sponsored AIDS therapeutics research, including drug discovery, drug development, and clinical trials. The TRWG includes representatives from academia, industry, and community constituency groups. The TRWG has played a critical role in the development of the plan to establish a single NIAID Adult Clinical Trials Network as recommended. Funding was awarded through a cooperative agreement in late 1999 to the Adult AIDS Clinical Trials Group. NIAID is currently considering approaches to long-term clinical studies on HIV-1 infection.

V.3

The OAR in collaboration with NIAID and NICHD convened in June 1999 the Working Group to Review the NIH Perinatal, Pediatric, and Adolescent HIV Research Priorities. The Working Group, chaired by Dr. John Modlin, Dartmouth Medical School, released a report in January 2000 that outlines a broad scientific agenda including recommendations for the United States, developed nations, and developing nations. NIH is currently developing plans for the recompetition of the Pediatric AIDS Clinical Trials Group to ensure that it effectively and efficiently responds to both the scientific opportunities and recommendations identified in the report.

VI.1

The Trans-NIH Drug Discovery and Development Committee recently was established by NCI and NIAID to further coordinate the research resources available to screen, develop and pre-clinically evaluate potential agents against HIV infection and its associated malignancies and opportunistic infections. Senior scientific staff from the Institutes and Centers supporting drug discovery and development programs, as well as the OAR Therapeutics Research Coordinator, participate on this newly established committee. The Committee is facilitated by NIAID.

VIII.1 THROUGH VIII.4

The new National Center for Complementary and Alternative Medicine (NCCAM) at NIH was established by Congress in FY 1998. NCCAM is in the process of establishing its leadership and operationalizing its new, expanded functions. OAR sees NCCAM as having a central role in each of the four recommendations and looks forward to the opportunity to review them with the Director of NCCAM in light of NCCAM's newly reformulated mission. NCCAM has recently established a Trans-Agency CAM Coordinating Committee to better coordinate NIH Institutes and Centers as well as other Federal Government Agencies programs in this field. OAR participates on this Coordinating Committee to ensure AIDS-related research issues are addressed.

IX.1

NCRR has commissioned an external review of its entire program of Regional Primate Research Centers and the funding of these activities. The review is ongoing and will be discussed at an OARAC meeting upon completion.

IX.4

OAR reviewed this concern with input from ICs and investigators performing animal studies on vaccines. Serious concerns were raised about the timeliness of such support when warranted. With additional information and support from NIH staff, IRGs have been encouraged, at the time of review, to approve adequate funds to conduct studies of vaccines, particularly in nonhuman primates. Additional contract resources are available through NIAID to conduct experimental vaccine studies. Information on how to access these resources is available on the NIAID vaccine Web site.

XI.1

Improvements have been made in standardizing access to and providing samples and tissues from NIH-sponsored AIDS repositories for investigator-driven research. Because repositories are supported and maintained by the ICs, OAR has not established a tracking system of these repositories as proposed in this recommendation.

XII.1

A new information database system has been developed containing project titles, project numbers, names of principal investigator and institutional affiliations, budget amounts, and funding ICs. The summary abstract data are to be collected by the "COMMONS," which is a system being developed by the OD/Office of Extramural Research. When the database becomes available, the abstracts will be added to the ARIS.

XIII.2

Since 1998, NIH has used the annual Plan for HIV-Related Research to define what constitutes AIDS research.

APPENDIX G:

List of Acronyms

LIST OF ACRONYMS

ACTG	AIDS Clinical Trials Group
ACTIS	AIDS Clinical Trials Information Service
AIDS	acquired immunodeficiency syndrome
AITRP	AIDS International Training and Research Program, FIC
APA	American Psychological Association
ATIS	HIV/AIDS Treatment Information Service
B/START	Behavioral Science Track Award for Rapid Transition, NIMH & NIDA
CAB	community advisory board
CAMCODA	Center on AIDS and Other Medical Consequences of Drug Abuse
CAPS	Center for AIDS Prevention Studies
CBC	Congressional Black Caucus
CDC	Centers for Disease Control and Prevention
CFAR	Center for AIDS Research
CMV	cytomegalovirus
CNS	central nervous system
CPCRA	Community Program for Clinical Research on AIDS
CSF	cerebrospinal fluid
CTL	cytotoxic T lymphocyte
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DRG	Division of Research Grants, NIH (now the Center for Scientific Review)
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
FIRCA	Fogarty International Research Collaboration Award, FIC
FY	fiscal year
GCRC	General Clinical Research Center

HAART	highly active antiretroviral therapy
HBCU	Historically Black Colleges and Universities
HBV	hepatitis B virus
HCFA	Health Care Financing Administration
HCV	hepatitis C virus
HHV-8	human herpesvirus-8
HIV	human immunodeficiency virus
HIVIG	HIV immunoglobulin
HIVNET	HIV Network for Prevention Trials, NIAID
HPV	human papillomavirus
HRSA	Health Resources and Services Administration
IC	Institute and Center
IDU	injecting drug user
IHS	Indian Health Service
IVIG	intravenous immunoglobulin
JCV	JC virus
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma herpesvirus
LRP	Loan Repayment Program, NIH
MAC	Mycobacterium avium complex
MCT	mother-to-child transmission
MDR-TB	multiple drug-resistant TB
MHC	major histocompatibility complex
NAFEO	National Association for Equal Opportunity in Higher Education
NGI	Next Generation Internet
NHL	non-Hodgkin's lymphoma
NIH	National Institutes of Health
NMAC	National Minority AIDS Council

NRTIs	nucleoside reverse transcriptase inhibitors
NSI	non-synctia-inducing
OAR	Office of AIDS Research, NIH
OARAC	Office of AIDS Research Advisory Council
OD	Office of the Director, NIH
OI	opportunistic infection
OMB	Office of Management and Budget
PAHO	Pan American Health Organization
PBMC	peripheral blood mononuclear cell
PCP	<i>Pneumocystis carinii pneumonia</i>
PDQ	Physician Data Query
PHS	Public Health Service
PML	progressive multifocal leukoencephalopathy
RCMI	Research Center in Minority Institution
RFA	Request for Applications
RFIP	Research Facilities Infrastructure Program
RML	Regional Medical Library
RNA	ribonucleic acid
RPRC	Regional Primate Research Center
SAMHSA	Substance Abuse and Mental Health Services Administration
SCID	severe combined immunodeficiency
SHIV	chimeric simian/human immunodeficiency virus
SI	synctia-inducing
SIV	simian HIV
SPF	specific pathogen-free
STD	sexually transmitted disease
STI	Structured Treatment Interruption
SRA	Scientific Review Administration

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TB	tuberculosis
UNAIDS	United Nations Joint Programme on AIDS
VA	Veterans' Administration
VEE	Venezuelan equine encephalitis
WHO	World Health Organization
ZDV	zidovudine

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