FY2001

National Institutes of Health Fiscal Year 2001 Plan for HIV-Related Research

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

Foreword

As the Director of the Office of AIDS Research (OAR), I am pleased to present the National Institutes of Health (NIH) Fiscal Year 2001 Plan for HIV-Related Research. This Plan represents the contribution of many individuals: Directors of the NIH Institutes and their staff; scientists from academia, industry, foundations, NIH, and other Governmental agencies; and AIDS community representatives. It is our intent that the Plan be responsive to the changing face of the epidemic, to emerging scientific opportunities, and to the needs of the affected community. The participation of this diverse group of individuals is therefore crucial to the success of the planning process, and I greatly appreciate the time and careful consideration that they gave to the Plan's development.

The past months have witnessed a number of scientific advances, as well as changes in public perception about HIV/AIDS. In particular, the Nation as a whole is becoming increasingly aware of the epidemic in minority communities in the United States and of the rampant nature of the global pandemic.

The development of a vaccine for HIV continues to be a priority for NIH. In dedicating the Dale and Betty Bumpers Vaccine Research Center in May 1999, President Clinton reaffirmed his challenge to the Nation to develop a vaccine. Advances in basic science provide optimism that substantial progress is being made. In February 1999, the opening of the first vaccine

trial in Africa was announced. Supported by NIH, the study is an important step in the attempt to develop HIV vaccines for countries hardest hit by the AIDS pandemic.

Several advances have been reported in prevention of transmission of HIV from infected mother to infant, including a regimen of the drug nevirapine, a non-nucleoside reverse transcriptase inhibitor that is highly effective and more affordable and practical than other methods; increased documentation of the role of viral load of the mother in risk of transmission; and the potential of cesarean section in reducing transmission. These studies are relevant to further reducing the risk of transmission in the United States and abroad.

Other significant advances have been reported. New evidence has been reported concerning the primate origin of HIV. Another study has demonstrated gender differences in viral dynamics, suggesting that viral load may differ in men and women over the course of infection, and may not predict disease progression in women as it does in men. This information may have implications for initiation of treatment in women. In the field of behavioral and social science research, a study has demonstrated that culturally relevant behavioral interventions have dramatically decreased the incidence of several sexually transmitted diseases among populations of Mexican American and African American women. This study has implications for decreasing the risk of acquiring HIV infection in racial and ethnic minorities throughout the United States.

We will continue to assess and revise the planning process to ensure that our research program is on target. The most important change in the development of the FY 2001 Plan was the identification of a few narrowly defined priorities for each area of emphasis. These priorities identify the most important targets for new or expanded funding. Each year, our experts will be asked to identify several immediate and specific priorities. These priorities will not only guide the development of the budget, but will be used in making mid-course changes in direction to be responsive to the epidemic and take advantage of scientific opportunities.

Another change was implemented to highlight minority-related AIDS research by creating a new Area of Special Interest in the Plan for this topic. This will initiate an ongoing review of the participation of minorities in clinical trials, and of research that addresses disparities in the treatment or prevention of HIV/AIDS. In addition, the involvement of minority investigators and minority institutions in AIDS research will be scrutinized.

It is my hope that the research agenda described in the Plan will provide the necessary steps for further developing our ability to control this pandemic and treat those who have been infected.

Neal Nathanson, M.D.
Director
Office of AIDS Research
September 1999

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 sciences research."

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Executive Summary

Executive Summary

The AIDS pandemic continues to rage throughout the world. There are an estimated 33.4 million current infections, and new infections occur at the rate of more than 250,000 monthly. AIDS has already killed nearly 14 million people and has surpassed tuberculosis and malaria as the leading infectious cause of death worldwide, according to recent data released by the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS). The largest burden is carried by the poorest areas of the world—the very nations least equipped to control and treat the disease.

Global Estimate of Adults and Children Living with HIV/AIDS at the end of 1998

Source: UNAIDS, 1998.

In the United States, regimens of antiretroviral drugs resulting from National Institutes of Health (NIH)-supported research have dramatically reduced transmission from infected mother to infant. Advances in treatment also have brought about a decline in AIDS-related deaths. Nonetheless, the

incidence of new infections has not declined in the United States, and the number of people living with HIV/AIDS has actually increased. Further, surveillance indicates increased spread of HIV among young adults, women, and minority populations. In addition, treatment failures, as well as new adverse effects, are increasing among patients on highly active antiretroviral treatment (HAART).

It is critical to carefully plan HIV-related research efforts to address the changing nature of the epidemic and its subepidemics, to respond to issues and successes in treatment of infected persons, and to take advantage of scientific opportunities and advances.

VACCINES: A KEY PRIORITY

A key priority is the development of an effective vaccine to stem the global pandemic. In 1997, President Clinton challenged the Nation to develop a vaccine within 10 years. Another high priority is to develop and implement behavioral and biomedical interventions to prevent transmission in specific populations and settings. NIH also will continue to develop new treatments and regimens that are effective and safe. These efforts must be informed by basic science, clinical investigation, and population-based studies that help to elucidate progression of HIV disease, pathogenic mechanisms, and risk factors and behaviors, as well as identify populations at risk of infection and describe long-term outcomes of therapies.

THE NIH PLAN FOR HIV-RELATED RESEARCH

The Office of AIDS Research (OAR) is legally mandated by the NIH Revitalization Act of 1993 (Public Law 103-43) to establish a comprehensive plan for the conduct and support of all AIDS activities of the components of NIH and to update the plan annually. The NIH Plan for HIV-Related Research serves as the framework for developing the NIH AIDS budget and for determining the use of AIDS-designated dollars.

THE PLANNING PROCESS

OAR has established a unique model for developing a consensus on scientific priorities for a trans-NIH comprehensive research plan utilizing the expertise of both Government and non-Government scientists as well as representatives of the AIDS-affected community. To develop the FY 2001 Plan, NIH program staff prepared the first draft by updating the FY 2000 Plan, with review and comment provided by Institute and Center (IC) Directors and IC AIDS Coordinators.

To achieve the broadest possible consensus regarding the Plan, OAR sponsored a series of workshops to seek the input of non-NIH experts, including scientists from academia, foundations, and industry as well as community representatives. These experts participated in Planning Groups for Natural History and Epidemiology; Etiology and Pathogenesis;

Therapeutics; Vaccines; Behavioral and Social Science; and Research Related to Racial and Ethnic Minorities. Participants in each Planning Group were asked to review and revise the draft Plan based on the state of the science and to identify priorities for their research area. The Plan was then reviewed by the OAR Advisory Council.

STRUCTURE OF THE PLAN

The Plan is divided into categories representing the NIH AIDS *Scientific Areas of Emphasis:* Natural History and Epidemiology, Etiology and Pathogenesis, Therapeutics, Vaccines, and Behavioral and Social Science.

Areas of Special Interest cross all of the Scientific Areas of Emphasis. These include Training, Infrastructure, and Capacity Building, and Information Dissemination. This year, a new section was added on Racial and Ethnic Minorities.

OBJECTIVES AND STRATEGIES

The format of the Plan is intended to provide a comprehensive framework that defines the scope of NIH-supported HIV-related research. Objectives are described in order of importance for each Scientific Area of Emphasis, with each Objective having a number of Strategies to address the Objective. The NIH AIDS budget is tracked by Objective, but not at the level of Strategies.

PRIORITIES

For the FY 2001 cycle, OAR added another component to the Plan. Each Planning Group was asked to identify a set of specific priorities. In contrast to the comprehensive Objectives, this process was meant to more narrowly define a few high-priority areas based on the current scientific knowledge of opportunities and needs. Priorities reflect those programs most worthy of new or expanded funding. They will be used as a guide to the development of the FY 2001 AIDS budget and in adjusting the FY 2000 AIDS budget as needed. It is expected that these priorities will change from year to year, and expenditures in these areas will not be tracked over time. Priorities are described in the Scientific Issues sections for each of the Areas.

Selected priorities are listed below.

Natural History and Epidemiology

- Conduct studies on primary early infection and its impact on HIV transmission.
- Develop and maintain the domestic and international infrastructure for epidemiology cohorts and prevention studies, including communities and trust-building.

- Conduct prevalence and natural history studies on HIV-1 clades and HIV-2 to provide a better understanding of how the host controls the virus—including studies of viral acquisition, pathogenesis, and disease progression—and determine the correlates of immunity associated with long-term survival.

- Investigate through epidemiology studies the short-term, intermediate, and long-term effects of antiretroviral therapy usage during pregnancy and the postpartum period on the mother, fetus, and newborn.

Etiology and Pathogenesis

- Capitalize on new insights into HIV biology and HIV host interactions to identify new viral and cellular targets for therapeutics, microbicides, and vaccine development.

- Investigate the mechanisms of HIV persistence in the setting of effective antiretroviral therapies.

- Elucidate direct and indirect mechanisms of T-cell depletion and reconstitution in HIV infection and in response to therapy.

- Improve our understanding of the mechanisms underlying metabolic abnormalities and body composition changes during HIV infection and following effective antiretroviral therapies, and determine the risk of atherosclerotic cardiovascular disease in these settings.

Therapeutics

- Develop agents or treatment strategies to destroy or inhibit the expression of HIV in latently infected cells and anatomical and organ reservoirs, therapies for individuals who no longer respond to existing treatments, and new therapeutic regimens that allow for improved compliance and adherence.

- Evaluate the ability of the immune system to maintain or repair itself after viral suppression has been achieved through HAART; evaluate cytokines, modulators, and other immunoactive agents to prevent further immune deterioration and to reconstitute deficient immune systems in HIV-infected individuals; and evaluate immunotherapeutic approaches to increase immune responses following antiretroviral therapy.

- Develop agents targeted at drug-resistant virus.
- Support the discovery and development of improved, acceptable, effective, and safe physical and chemical barrier methods—including topical microbicides and other methods—to reduce sexual transmission of HIV and STDs in developed and developing nations.

Vaccines

- Perform essential prevention and trial design research and support clinical vaccine trials in collaboration with populations at high risk for HIV transmission, especially U.S. minority populations and international populations with high HIV incidence.
- Develop and test new vaccine strategies, alone or in combination, to induce broad functional immune responses—both humoral and cellular, mucosal and systemic—against primary NSI, R5-using HIV isolates from all genetic clades.
- Continue to improve animal models and to improve availability of nonhuman primate models for systematic, comparative efficacy testing of vaccine concepts and understanding of the mechanisms of protection that might be translated to HIV vaccine studies in humans.
    - Develop MHC-defined and/or histocompatible rhesus macaques, and define the associated epitopes of HIV/SIV proteins for vaccine studies.
    - Continue to develop and exploit SHIV chimeric viruses with different degrees of virulence to more closely reflect disease progression observed in HIV-infected people and the genetic variation observed in worldwide HIV epidemics.
- Enable rapid movement of vaccine concepts into clinical testing, including the development or procurement of GLP/GMP products or direct funding for production of candidate vaccines to stimulate industry partnerships for human and nonhuman primate trials.

Behavioral and Social Science

- Better understand and address through interventions the psychological, social, economic, and cultural dynamics of gender and sexual identity that operate in HIV risk, protection, and care.

- Develop and test interventions among individuals living with HIV/AIDS and other comorbid conditions (e.g., substance abuse, mental illness, hepatitis, tuberculosis, homelessness).
- Identify and address issues in the initiation, maintenance, sustainability, and durability of effective HIV prevention and care efforts among individuals (including HIV-infected individuals) and communities over time.
- Improve translation and transportability of effective HIV prevention and care interventions, both domestically and internationally.

Racial and Ethnic Minorities

- Develop, test, evaluate, and disseminate culturally sensitive and appropriate prevention interventions in racial and ethnic minority communities to reduce HIV transmission and acquisition in at-risk social networks. To the maximum extent possible, these interventions should intersect at multiple levels and reflect the role of socioeconomic status and language.
- Identify and address gaps in care, treatment, and research manifested by the differentials in access to care and HIV-associated morbidity and mortality in majority and minority HIV-infected communities.
- Identify, define, and address the infrastructural, technical, methodological, and sociocultural needs of communities of color for clinical trial participation.
- Support and expand programs that train racial and ethnic minority investigators in the areas of behavioral and social science, clinical research, and basic science to increase the number of investigators trained and funded to successfully complete such research.

Introduction

Introduction

THE AIDS PANDEMIC

Global Impact

Over the past decade the HIV epidemic has progressed virtually unimpeded, affecting nearly every country on every continent. There are an estimated 33.4 million current infections, and new infections occur at the rate of more than 250,000 monthly. With a predicted doubling time of 10 years, the potential enormity of the HIV/AIDS pandemic is truly profound. AIDS, which already has killed nearly 14 million people, has now surpassed

The Exploding Global HIV/AIDS Pandemic

Group	People Newly Infected in 1998	Number of People Living with HIV/AIDS	AIDS Deaths in 1998	Total AIDS Deaths Since Beginning of Epidemic
Adults *Women*	5.2 Million *2.1 Million*	32.2 Million *13.8 Million*	2.0 Million *900,000*	10.7 Million *4.7 Million*
Children	590,000	1.2 Million	510,000	3.2 Million
Total	**5.8 Million**	**33.4 Million**	**2.5 Million**	**13.9 Million**

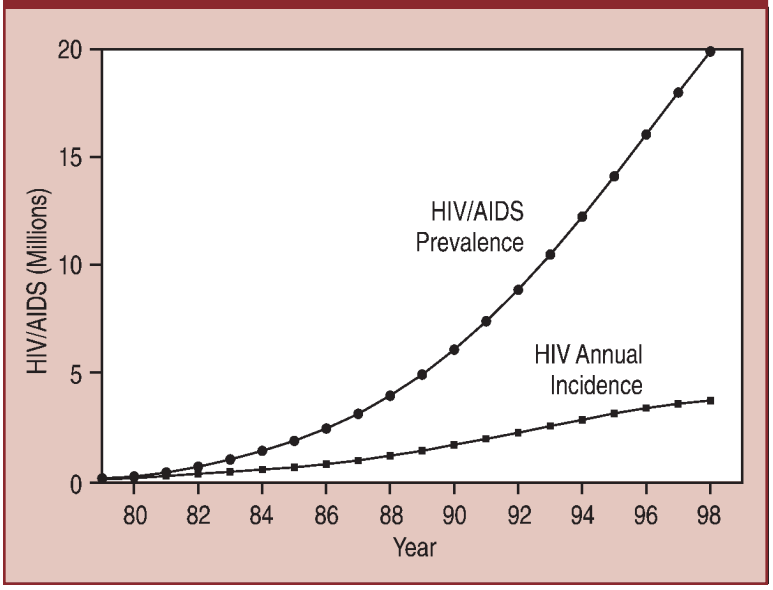
Source: UNAIDS, 1998.

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). Although there have been successes in stabilizing the epidemics in Brazil

and Senegal and in actually decreasing the incidence of new cases in Thailand and Uganda, epidemics continue in many countries in sub-Saharan Africa and Southeast Asia and are escalating in countries such as South Africa and on the Indian subcontinent.

From the beginning, Africa has been the epicenter of HIV/AIDS globally and continues to carry the largest disease burden, with 70 percent of people living with AIDS worldwide, 83 percent of global AIDS deaths, and 95 percent of global AIDS orphans. In many southern African countries, HIV/AIDS has become an unprecedented emergency, with 20 to 26 percent of people between the ages of 15 and 49 infected. In Botswana, Malawi, Kenya, Mozambique, Namibia, Rwanda, South Africa, Zambia, and Zimbabwe, life expectancy will be reduced from 64 to 47 years by 2015 as a result of HIV/AIDS. HIV/AIDS has negated the progress of decades of public health work immunizing children, controlling diseases, and improving nutrition.

HIV Incidence and HIV/AIDS Prevalence in Sub-Saharan Africa, 1980-1998



Source: UNAIDS, 1998.

If the global spread of HIV/AIDS continues unchecked, South Asia, Southeast Asia, and perhaps China will follow the disastrous course of sub-Saharan Africa. Currently, there are an estimated 6.7 million HIV-infected people in South and Southeast Asia. In India alone, it is estimated that between 3 and 5 million of its nearly 1 billion population are infected, and the number of new infections will double every 14 months. Rapid increases also are occurring in Eastern Europe and Central Asia, and HIV remains a serious threat in Latin America and the Caribbean.

Social and economic conditions in many parts of the world have promoted the rapid spread of the HIV/AIDS epidemic. Limited resources for health care, diagnostics, therapies, and prevention programs are primarily responsible for the continuing rise in morbidity and mortality associated with HIV infection in developing countries. A combined high prevalence of risk behaviors and sexually transmitted diseases (STDs) act synergistically

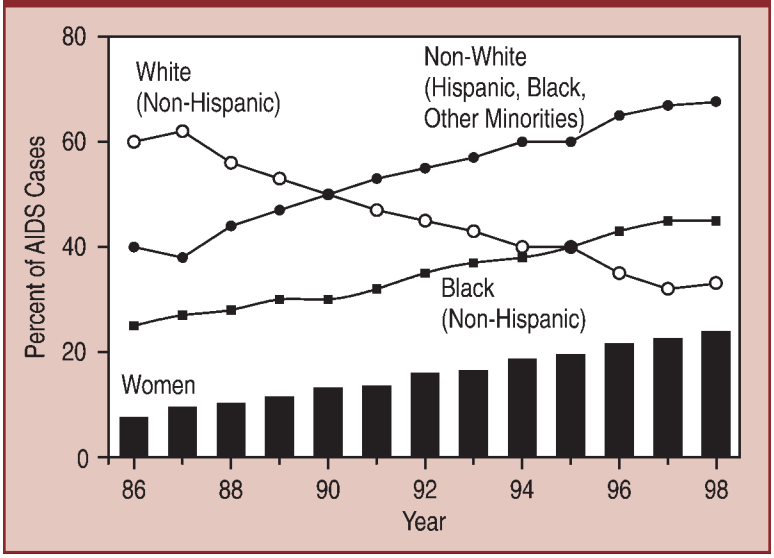
to further propel the epidemic. The coexistence of other endemic diseases widely prevalent in developing countries, such as respiratory and gastrointestinal infections, complicate treatment and pose additional problems for medical personnel caring for HIV-infected individuals. Of particular note is the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

The contrast in the impact of HIV/AIDS between developed and developing countries is striking, and the factors responsible for this discrepancy, in terms of the diagnosis and care of HIV-infected individuals and the magnitude of the HIV pandemic, are multifactorial. Surveys have demonstrated that nearly 70 percent of HIV-infected individuals are aware of their serostatus in the United States and Europe, whereas 80 to 90 percent of infected individuals in developing countries have never been tested for HIV and remain unaware of their infection status. There is growing recognition that many individuals who become HIV infected also have, or are vulnerable to, a host of coinfections (e.g., hepatitis, STDs, tuberculosis), which enhance the transmission of HIV and complicate its treatment. But access to even basic treatment for these coinfections remains a problem for many in less developed countries. Recent treatment advances in antiretroviral therapy have dramatically improved the ability to slow the progression of HIV to AIDS and prolong life in North America, Western Europe, and Australia. However, the high cost for this therapy puts it beyond the reach of all but a privileged few in the majority of the world.

AIDS in the United States

In the United States, the nature of the epidemic continues to evolve. In general, the incidence of AIDS cases has declined overall by an average of 15 percent in the United States, which can be attributed largely to new antiretroviral therapies. In October 1998, the National Center for Health Statistics announced that the age-adjusted death rate from AIDS in the United States declined by an unprecedented 47 percent from 1996 to 1997, causing AIDS cases to fall from 8th to 14th place among leading causes of death for that same period. However, the rate of decline in the progression of HIV to AIDS is disparate among subgroups of the U.S. population, with the decrease smaller among women (8 percent) and blacks (9 percent). Furthermore, even as the death rate from AIDS is declining, HIV infection rates continue to climb in a number of subpopulation groups, such as women, racial and ethnic minorities, people over 50 years of age, and

AIDS Incidence by Race and Sex in the United States, 1986-1998



Source: CDC, 1998.

those with addictive disorders. Although the incidence of HIV infection has stabilized among white gay men overall, it is increasing among younger homosexual men.

As a result of these dynamics, more Americans are living with HIV infection than before. The Centers for Disease Control and Prevention (CDC) estimate that between 700,000 and 900,000 Americans are currently infected with HIV. Once again, the demographics show that racial and ethnic minorities are more heavily affected. Prevalence of AIDS is higher among African Americans and Hispanics, who account for 45 percent and 20 percent, respectively, of all persons diagnosed with AIDS during 1998. This disparity is even more striking among women, with minorities accounting for 82 percent of cases.

IMPLICATIONS FOR THE AIDS RESEARCH AGENDA: INTERVENTION RESEARCH

The demographics of the AIDS epidemic provide a useful basis on which to develop a research agenda. In particular, it is essential that NIH focus increased attention on strategies to address the escalating subepidemics in racial and ethnic minorities, women, adolescents, injecting drug users, and heterosexuals. In addition, by considering the nature of events associated with transmission of HIV and progression of HIV disease, it is possible to identify points of intervention where research can provide the tools needed to reduce transmission and ameliorate the burden of disease. Thus, our intervention research agenda focuses both on prevention of new infections and on treatment of existing HIV infections and clinical AIDS.

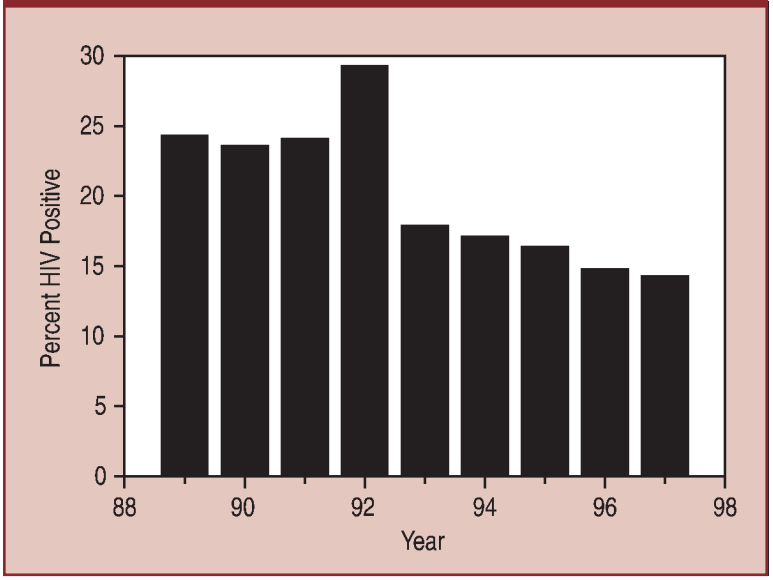
It should be noted that although the primary responsibility of NIH is to plan and fund the U.S. AIDS research program, our plans recognize the global status of AIDS, since the dynamics of the epidemic are dramatically distinct in different countries. The exploding nature of the epidemic in those countries most severely affected has escalated the urgency of improved intervention strategies. For this reason, we fund 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. In addition, NIH supports an active program for training of researchers and health professionals from many countries.

Prevention of Transmission

NIH continues to place a high priority on primary prevention of new HIV infections as the most effective means of controlling the spread of the epidemic, both in the United States and globally. Both behavioral and biomedical efforts are critical to this effort. The multifaceted nature of the epidemic, specifically within racial and ethnic minority communities, requires a range of research on interventions that target those components of the epidemic that facilitate, as well as limit, transmission. The Office of AIDS Research (OAR) is focusing the NIH AIDS research enterprise on intervention research that targets both short- and long-term opportunities to prevent HIV transmission, recognizing that different prevention and intervention strategies must be applied to each subepidemic, in the United States and around the world.

Prevalence of HIV Infection, Antenatal Clinic Attendees, Uganda, 1989-1997 (Median of 3 Clinics)



Source: Uganda Ministry of Health, 1998.

Studies have demonstrated that behavioral change can successfully prevent or reduce the spread of HIV/AIDS. Programs resulting from such studies have altered sexual and drug-using behaviors and have reduced the risk of transmission. For example, heterosexual transmission has been significantly reduced in some developing countries. In Uganda, prevalence of HIV infection among pregnant women has declined from 25 to 30 percent to approximately 15 percent. In the United States, transmission in gay men has declined from an annual incidence of new infections of more than 15 percent to approximately 2 percent in selected cities such as New York and San Francisco. A comparison of rates of new infections among injecting drug users demonstrates lower incidence in cities with needle exchange programs than in cities without such programs.

Nonetheless, more culturally appropriate behavioral interventions aimed at reducing transmission rates through unsafe sex and injecting drug use practices are needed. Extensive research is needed to understand addiction and the complex interaction of alcohol use, drug use, and poor impulse control. Further exploration is needed of the role of culture, family dynamics, and other social factors, as well as mental illness, in the transmission and prevention of HIV, especially in minority communities. Most importantly, a greater understanding is needed 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.

Needle Exchange Programs (NEPs) and the Reduction of HIV Transmission

	Cities With NEPs	Cities Without NEPs
Number of Cities	29	52
Number of Injecting Drug Users Surveyed	~192,000	~130,000
Annual Change in Seroprevalence	Decrease -5.8%	Increase +5.9%

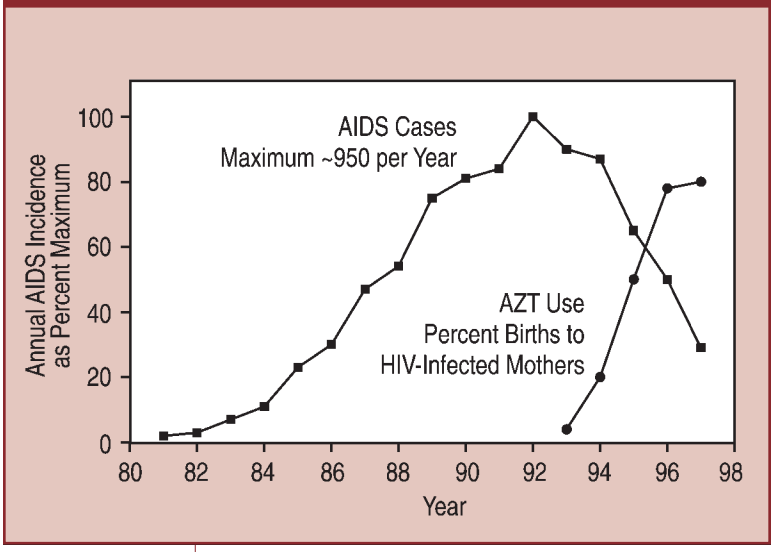
Source: Hurley, et al., Lancet *1997, 349(9068):1797.*

Biomedical interventions are an important component of a comprehensive primary prevention strategy. The relationship between STDs and increased incidence of HIV infection is well known. Further research into interventions that address this relationship is needed. The vulnerability of women globally to acquiring HIV infection demands the development of effective and acceptable female-controlled barrier methods to reduce HIV transmission. Microbicides are chief among these.

Transmission from Mother to Child

In the United States, regimens of antiretroviral drugs resulting from NIH-supported research have dramatically reduced transmission from infected mother to infant. However, the high cost and complexity of administration make this option impractical for much of the developing world. NIH-supported clinical trials in Uganda recently demonstrated that a single dose of the non-nucleoside reverse transcriptase inhibitor 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

Pediatric AIDS (<13 Years) and Perinatal Treatment with Zidovudine (AZT), United States, 1981-1997



Source: CDC, 1998.

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 HIV transmission. However, lack of 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 needed.

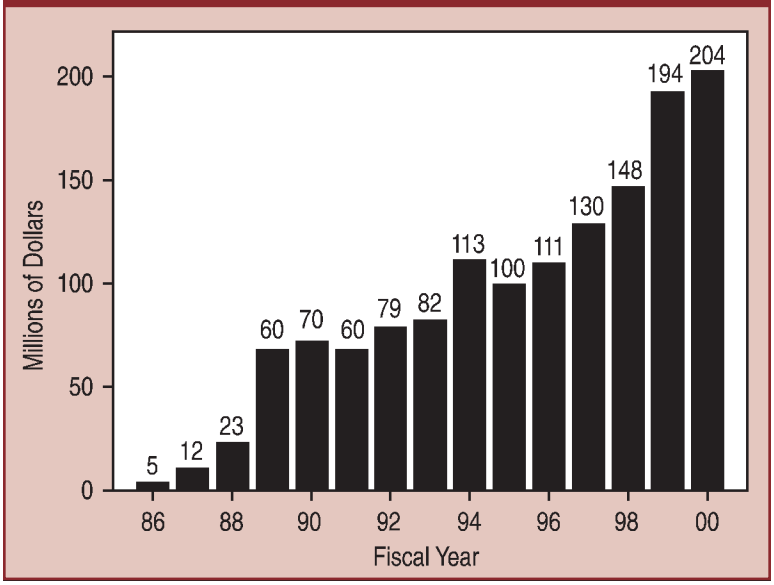
Vaccines

There is no question that 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 a vaccine. Consistent with this challenge, NIH funding for HIV vaccine research increased by nearly 80 percent between FY 1995 and FY 1999, resulting in the award of several grants to foster innovative research on HIV vaccines and the invigoration and reorganization of the NIH vaccine clinical trials effort. To implement its integrated vaccine development program, the National Institute of Allergy and Infectious Diseases (NIAID) appointed Dr. Margaret Johnson in September 1998 as Assistant Director for HIV/AIDS Vaccines and Associate Director of the Vaccine and Prevention Research Program in the Division of AIDS. Construction of the new Vaccine Research Center began in August 1998 and is expected to be completed by mid-2000. Its new director, Dr. Gary Nabel, was appointed in May 1999. In February 1999, NIH-supported investigators initiated the first AIDS vaccine trial in Africa. Meanwhile, the AIDS Vaccine Research Committee, chaired by Nobel laureate Dr. David Baltimore, continues to advise on all aspects of the NIH AIDS vaccine development program.

Development of an HIV vaccine presents a formidable scientific challenge with a number of significant obstacles, including the geographic variability of HIV subtypes, the lack of clear understanding of the correlates of protective immunity in HIV infection, the limitations of available animal

models of HIV infection, and the challenges of inducing mucosal immunity to prevent sexual transmission. Over the last 10 years, more than 25 HIV vaccine candidates have been tried in humans with disappointing results due to limited immune responses or lack of protection against infection. In an effort to develop new vaccine candidates, it is necessary to analyze the underlying biological issues that make it so difficult to design and construct a vaccine, such as lifelong persistence of HIV infection due to the evasion of immune surveillance, HIV-specific immune "exhaustion," and viral immunobiology. A number of recent basic scientific findings have yielded insights defining new targets for vaccine development and raising the expectation that new vaccines could be developed and prepared for testing in large-scale efficacy trials in the forseeable future.

NIH AIDS Vaccine Funding, FY 1986-FY 2000



Source: NIH, 1999.

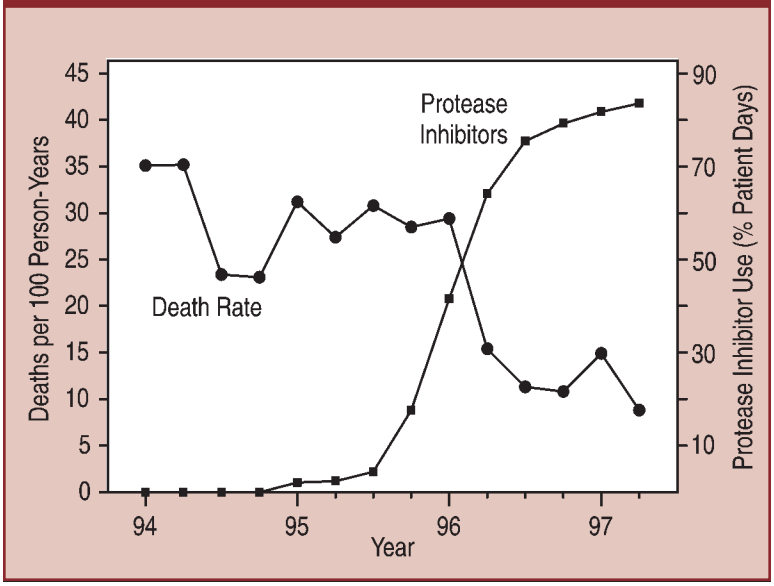
Treatment of HIV Infection and AIDS

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 protease inhibitors has been extremely successful in extending the length and quality of life for many HIV-infected people in the United States and Western Europe. These agents, along with the ongoing introduction of other novel antiretroviral chemotherapeutic agents, have provided a wider array of drugs that can be used to overcome viral resistance and can be combined into multiple regimens capable of achieving near full suppression of viral replication and amelioration of HIV-related symptoms. Long-term followup of HIV-1 infected individuals on near fully suppressive regimens reveals ongoing improvement in immunologic parameters associated with HIV-1-induced immune dysfunction.

However, while combination antiretroviral therapy has produced tremendous benefits for many HIV patients, treatment failure now affects

a growing proportion of patients receiving therapy. Some patients find it difficult or impossible to comply with arduous treatment regimens or cannot afford their high cost of approximately $15,000 per year, while others fail to obtain a satisfactory reduction in viral load even while complying with treatment regimens. In addition, metabolic complications—such as lipodystrophy, hypercholesterolemia, hypertriglyceridemia, hyperinsulinemia, and deforming deposits of visceral abdominal adipose tissue—are beginning to emerge in individuals who have been on long-term antiretroviral regimens that include protease inhibitors. Finally, an increasing number of treatment failures are linked to the increasing emergence of drug-resistant HIV subtypes, which are caused by the virus' extremely rapid rate of replication and mutation. The need for simpler, less toxic, and cheaper drugs and drug regimens to treat HIV infection, including new generations of antiviral drugs directed against new targets, continues to be a high priority.

Death Rate Among Patients with CD4 <100/ml Use of Protease Inhibitors, 1994-1997



Source: Palella, et al., New England Journal of Medicine *1998, 338:853.*

Basic and Clinical Science

The development of preventive and therapeutic interventions must be informed by basic biomedical research on the nature of the virus, how it establishes infection, and its mechanisms of pathogenesis, as well as clinical investigations and population-based studies that help to elucidate transmission, disease progression, and the development of sequelae. Studies also need to be conducted to provide further information on risk factors and behaviors, identify populations at risk of infection, and describe long-term outcomes of therapies. These studies will provide powerful insights into the prevention and clinical management of HIV disease. NIH has historically provided sound support for such research. Before the identification of HIV, basic research on retroviruses was actively supported. This body of research enabled the rapid identification and characterization of HIV, and the study of HIV itself has led to the discovery of groups of antiviral drugs that have so dramatically changed the outlook for people living with HIV/AIDS. Consistent with this research vision, a substantial

portion of AIDS-related research will continue to be devoted to fundamental biomedical and behavioral research.

THE NIH AIDS RESEARCH PROGRAM

The Role of the Institutes

Each NIH Institute supports HIV/AIDS-related research activities, consistent with its individual mission. The Institutes and Centers (ICs) whose research programs are most heavily concerned with HIV, AIDS, and their sequelae are 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 of this Plan. 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 development of 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 funds between Institutes.

OAR has established and supported the efforts of six trans-NIH Coordinating Committees in the following areas: Natural History and Epidemiology, Etiology and Pathogenesis, Therapeutics, Vaccines, Behavioral and Social Science, and Information Dissemination. The Committees represent those Institutes with the most significant research portfolios in these areas; members were nominated by the ICs. The Committees foster collaboration and coordination and assist in the development of the NIH Plan and budget for AIDS research.

To carry out its activities, OAR depends upon the expert advice of several committees. One of these is the OAR Advisory Council (OARAC), which is composed of non-Government experts from a broad array of disciplines, as well as AIDS community representatives. OARAC reviews the annual Plan, budget requests, and discretionary fund disbursements. A list of members is included as Appendix D. OAR also has established the Prevention Science Working Group and the Therapeutics Working Group to provide advice in these critical scientific areas. One of OAR's areas of specific focus is the impact of HIV/AIDS on racial and ethnic minorities. To address this issue, OAR established the *ad hoc* Minority Working Group in 1999. Composed of NIH staff and non-NIH scientists and experts, this group advises the Director of OAR on needed research and research-related efforts specifically targeted to these populations.

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). Other initiatives are supported on an as-needed basis, based on specific scientific gaps or other needs. In addition, OAR supports a number of initiatives to promote the distribution of research information to researchers, physicians, institutions, and communities. OAR also monitors and fosters plans for NIH involvement in international AIDS research activities and provides financial assistance to allow participants from developing countries to attend AIDS conferences.

OVERVIEW OF THE PLAN

The Planning Process

OAR has established an effective model for developing a consensus on scientific priorities for a trans-NIH comprehensive research plan utilizing the expertise of both Government and non-Government scientists and representatives of the AIDS-affected community. To develop the FY 2001 Plan, the OAR Coordinating Committees prepared a first draft by reviewing and updating the FY 2000 Plan for their specific areas of HIV/AIDS research, as well as for training and infrastructure and information dissemination needs in those areas. The draft Plan was then provided to each IC Director and IC AIDS Coordinator for their recommendations and suggestions.

To achieve the broadest possible consensus regarding the Plan, OAR sponsored a series of workshops to seek the input of non-NIH experts, including scientists from academia, foundations, and industry, and community representatives. These experts participated in Planning Groups for Natural History and Epidemiology; Etiology and Pathogenesis; Therapeutics; Vaccines; Behavioral and Social Science; and Research Related

to Racial and Ethnic Minorities. 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. The Plan was then reviewed by OARAC.

OAR continues to reassess the planning process and will make refinements to better capture the broadest range of expertise and community participation, particularly among women and minorities, and to facilitate the identification of specific scientific priorities. This year, a new section on Racial and Ethnic Minorities was added.

Structure and Use of the Plan

The Plan is divided into categories representing five Scientific Areas of Emphasis and three Areas of Special Interest. *Scientific Areas of Emphasis* include: Natural History and Epidemiology, Etiology and Pathogenesis, Therapeutics, Vaccines, and Behavioral and Social Science.

Areas of Special Interest cross all of the Scientific Areas of Emphasis. These include: Racial and Ethnic Minorities; Training, Infrastructure, and Capacity Building; and Information Dissemination.

The format of the Plan is intended to provide a comprehensive framework that defines the scope of NIH-supported HIV-related research. All components of the Plan are structured around the Scientific Areas of Emphasis and the Areas of Special Interest listed above.

Comprehensive Plan

Objectives consist of a comprehensive list, in order of importance, of the scientific questions to be addressed for each Scientific Area of Emphasis or Area of Special Interest. Under each Objective are a set of Strategies to be addressed that serve to define those avenues and approaches that may be pursued within the scope of AIDS and AIDS-related research.

Priorities

For the FY 2001 cycle, OAR added another component to the Plan. Each Planning Group was asked to identify a set of specific priorities. In contrast to the comprehensive Objectives, this process was meant to more narrowly define a few high-priority areas based on the current scientific knowledge of opportunities and needs. Priorities reflect those programs most worthy of new or expanded funding. They will be used as a guide to the development

of the FY 2001 AIDS budget and in adjusting the FY 2000 AIDS budget as needed. It is expected that these priorities will change from year to year, and expenditures in these areas will not be tracked over time. Priorities are described in the Scientific Issues sections for each of the Scientific Areas of Emphasis and Areas of Special Interest.

Uses of the Plan

The Plan serves several purposes:

- As the framework for developing the NIH AIDS budget.
- For determining the use of 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 and becomes the definition of "AIDS research" at NIH.
- As a document that provides information to the public, the scientific community, AIDS advocates, and other interested parties. OAR distributes the annual comprehensive Plan to a wide audience, and it appears on the OAR Web site.

Scientific Areas of Emphasis

SCIENTIFIC AREA OF EMPHASIS:

Natural History and Epidemiology

SCIENTIFIC AREA OF EMPHASIS:

Natural History and Epidemiology

SCIENTIFIC ISSUES

Epidemiologic research continues to show the demographics of HIV infection and AIDS in the United States shifting from an illness primarily affecting homosexual and bisexual men to an epidemic with increasing and disproportionate rates of infection in minorities, women, adolescents, drug users, and heterosexuals. This shift has placed urban, minority, and disenfranchised communities at the intersection of several epidemics: AIDS, sexually transmitted diseases (STDs), tuberculosis (TB), and drug use. HIV/AIDS continues to spread globally, with the most dramatic increases seen throughout Africa and Asia. Additional research is critical to better understand the transmission of HIV, the progression of HIV-related disease, the development of malignancies, the incidence of metabolic complications and neurological and neurobehavioral dysfunction, and the development of other sequelae. Future studies will continue to examine the effects of viral, host, and other factors on the risk of infection and disease progression. Results from this research will provide useful insights into the prevention and clinical management of HIV infection.

Ethnic and racially diverse cohorts of HIV-infected and -uninfected individuals at risk will continue to be followed in natural history and epidemiology studies at domestic and international sites. Maintaining this diversity will ensure that findings obtained from such studies will have validity for all communities impacted by the AIDS epidemic.

COHORT STUDIES OF VIROLOGIC AND IMMUNOLOGIC FACTORS OF TRANSMISSION AND DISEASE PROGRESSION

International epidemiologic studies contribute significantly to the understanding of the cellular and molecular mechanisms of HIV transmission, the progression of HIV-related disease, and the risk factors associated with HIV infection. These studies also contribute to the development of new biomedical and behavioral preventive intervention strategies. NIH-sponsored natural history and epidemiology studies are investigating the transmissibility of non-B HIV clades and the reduction of HIV transmission through prevention and treatment of coexisting STDs. Recent findings have shown virulent HIV in the vagina, vaginal secretions, semen, and seminal fluids from individuals with no detectable virus in the plasma as a result of highly active antiretroviral therapy (HAART). Additional research is needed to determine if these virulent viruses could serve as a potential source of infection during sexual and perinatal transmission of HIV. Another area of primary prevention research will continue to focus on developing new or improved means of reducing perinatal transmission in the United States and worldwide, with particular emphasis on methods appropriate to the developing world.

PRIORITIES FOR FUTURE RESEARCH:

- **Investigate host, extrinsic, and virologic factors and cofactors, including viral heterogeneity, that mediate viral transmission and disease progression and assess the effects of interventions that effectively slow viral transmission and disease progression in domestic and international populations.**
- **Characterize and monitor the determinants of risk, incidence, and mechanisms of transmission with the goal of preventing HIV transmission in domestic and international populations.**
  - **Determine the impact of improved therapies on behavior, HIV infectiousness, and transmission, including studies on residual reservoirs of virus.**
  - **Further define the timing, mechanisms, and risk factors associated with mother-to-infant transmission and postnatal (breast-feeding) transmission.**

Domestic and international cohorts, repositories, and databases provide opportunities for epidemiologists and basic researchers to study unique populations, cooperatively pursue fundamental research on critical aspects of HIV transmission and disease described by intensive laboratory-based studies, and better understand the dynamics of the epidemic in a population-based context. Cohorts of individuals at risk of HIV infection and those recently infected remain critical to the elucidation of the natural history of primary HIV infection.

PRIORITIES FOR FUTURE RESEARCH:

- **Conduct studies on primary early infection and its impact on HIV transmission.**
- **Develop and maintain the domestic and international infrastructure for epidemiology cohorts and prevention studies, including communities and trust-building.**

DISEASE PROGRESSION

Further characterization of the virologic and immunologic parameters of rapid and slow disease progression in cohort studies are crucial to designing and evaluating new therapeutic approaches and vaccine candidates. Recent findings have shown that the amount of HIV circulating in the bloodstream is predictive of the rate of disease progression. Further studies are needed to answer scientific questions about disease progression in individuals who (1) do not become infected despite repeated exposure to HIV, (2) appear to show clearing of the virus after initial documented infection, (3) manifest infection without immunologic progression (long-term nonprogressors), and (4) maintain stable clinical states even with prolonged immunosuppression (long-term survivors). Special focus is being placed on host genetics, such as allelic heterogeneity in chemokine receptors, which serve as coreceptors for HIV, and on characteristics of the viral strain. Recent studies have shown genetic restriction in a CCR5 structural gene of HIV infection and progression to AIDS.

PRIORITIES FOR FUTURE RESEARCH:

- **Conduct prevalence and natural history studies on HIV-1 clades and HIV-2 to provide a better understanding of how the host controls the virus—including studies of viral acquisition, pathogenesis, and disease progression—and determine the correlates of immunity associated with long-term survival.**
- **Conduct natural history studies on the effects of HAART on virologic and immunologic markers or predictors of disease progression.**

NIH will continue to place a priority on natural history studies on the unique clinical manifestations and nature and rate of disease progression in women, the impact of HIV on cervical cancer, the effects of HIV and human papillomavirus (HPV) coinfection, and the development of an HPV vaccine for control of cervical cancers.

HIV-RELATED OPPORTUNISTIC INFECTIONS AND MALIGNANCIES

Studies on the occurrence, natural history, and molecular epidemiology of HIV-associated preneoplastic conditions and cancers are critical for the development of better treatment regimens. Research in this area is particularly important as the incidence and aggressiveness of AIDS-

associated malignancies and preneoplastic conditions are expected to increase with the extended life expectancy of HIV-infected patients as a result of HAART and prophylaxis for HIV-related opportunistic infections (OIs). Recent findings continue to implicate human herpesvirus-8 (HHV-8) in the development of Kaposi's sarcoma (KS) and some non-Hodgkin's lymphomas. A better understanding of the natural history and epidemiology of HHV-8 is necessary for the development of appropriate treatments.

Marked increases in the incidence of TB and multidrug-resistant TB in the setting of HIV infection—both globally and in U.S. minority, urban, and drug-using populations—make this an important public health problem. Additional research is needed on the incidence and progression of TB in HIV-infected and -uninfected active drug users, as well as on the development of improved screening and adherence strategies in order to reduce infectivity and transmission.

Studies on the possible impact of OIs on the natural history of HIV disease may be useful in identifying future opportunities to prevent disease progression and HIV transmission.

PRIORITY FOR FUTURE RESEARCH:

- **Identify and prevent the occurrence of adverse consequences and sequelae in HIV-infected individuals, including drug-resistant TB, new and emerging OIs, coinfections, comorbidities of aging, malignancies, metabolic complications, and body composition disorders that may accompany extended survival resulting from HAART.**

HIV INFECTION IN DRUG USERS

The increasing incidence of HIV transmission through risk behaviors associated with drug use underscores the need to better characterize HIV disease in this population. Studies of drug-using populations need to focus on host and virologic factors affecting disease progression, clinical sequelae, consequences of multiple coinfections, effectiveness of therapeutic regimens, and the impact of health care access and treatment adherence on disease outcomes.

PRIORITY FOR FUTURE RESEARCH:

- **Further investigate the biological consequences of illicit drug use on HIV transmission and disease progression, and the impact of illicit drugs and the consequences of illicit drug use on the effects of antiretroviral therapy and disease progression.**

MOTHER-TO-CHILD TRANSMISSION

Cohort-based studies of affected populations are essential to evaluate the factors associated with the risk of perinatal transmission and maternal and infant disease progression. Findings from these studies will be directly applicable to the development of appropriate treatments for infected women and children. Domestic and international perinatal HIV prevention and transmission studies are critical in identifying antiretroviral and immunotherapy trials for reducing mother-to-child transmission or ameliorating disease progression in HIV-infected children.

PRIORITY FOR FUTURE RESEARCH:

- **Investigate through epidemiology studies the short-term, intermediate, and long-term effects of antiretroviral therapy usage during pregnancy and the postpartum period on the mother, fetus, and newborn.**

ASSAYS

Reverse transcription-polymerase chain reaction (RT-PCR) technology has made quantification of HIV in plasma or serum highly reproducible, sensitive, and predictive of HIV infection. This technology may facilitate the elucidation of the *in vivo* natural history of HIV infection and also of sexual and mother-to-child transmission. Improved diagnostic assays are needed for the early detection of HIV infection among infants, the identification of markers for predicting rapid versus slow disease progression, and the development of quantitative methods to assess viral concentration in body fluids and tissues to determine how viral concentrations affect vertical transmission and disease outcome. While the recent development of two new sensitive assays may permit the individualization of therapies, further research will be needed to determine whether these techniques can be clinically validated and routinely used to determine the most effective drug regimens for each patient.

PRIORITY FOR FUTURE RESEARCH:

- **Develop and evaluate accurate, reproducible, and inexpensive virologic, immunologic, genetic, and bacteriologic assays suitable for large-scale natural history studies, clinical trials, and community interventions in developed and developing nations.**

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE:

Develop and evaluate independent and integrated biomedical and behavioral prevention strategies in 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, and women 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 (e.g., STD treatment, multidrug therapy, nutritional supplementation, and behavioral interventions such as condom distribution and group prevention sessions—singly or in combination).
- Develop and maintain the infrastructure in HIV epicenters to conduct vaccine, behavioral, and other intervention trials.
- Develop and evaluate methods to access, recruit, and retain at-risk populations, including minorities, adolescents, and drug users, 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 such as short-course antivirals; cesarean section; vaginal cleansing; STD prophylaxis and treatment; altered breast-feeding practices; nutritional interventions; and community-based, behavioral, and other approaches that may prevent perinatal transmission.
- Develop and assess the effectiveness of various strategies, such as early weaning and vitamin A supplementation, to reduce HIV transmission via breast-feeding.
- Develop and assess the effectiveness of multiple approaches that may decrease HIV transmission among adolescents and drug users, such as needle/syringe exchange, treatment of drug abuse, and decontamination of injection equipment.
- Develop and evaluate biomedical and independent and integrated behavioral interventions to control STDs as a means of preventing HIV transmission.
- Evaluate potential risks and benefits of providing prophylaxis against infection following 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 therapy used to reduce HIV transmission on the development of chromosomal damage, mutagenesis, or carcinogenesis.
- Examine the ability of vaccines, antivirals, STD therapy, and nutritional supplementation to decrease infectiousness among persons who subsequently become HIV-infected despite the administration of vaccines.

OBJECTIVE:

Use epidemiologic studies in international and domestic settings to identify virologic, immunologic, host, and other biological and behavioral factors that influence disease progression and to assess how interventions alter disease progression.

1.B

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, including other retroviruses and other microbiological agents; hormonal factors such as pubertal development, pregnancy, contraceptives, menopause, and hormonal replacement; drug use; reexposure to HIV; and interventions such as nutritional supplementation, exercise, and health-enhancing behaviors.
- Develop approaches for identification of 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 interventions in minority, adolescent, drug-using, 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) 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 above.

- Evaluate the rate of progression with the effects of feasible interventions to delay or prevent progression in international settings or populations with different viral clades and possible cofactors such as nutrition and 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 natural infections on disease progression in HIV-infected populations.

OBJECTIVE:

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

1.C

STRATEGIES:

- Evaluate the impact of antiretroviral therapies on HIV infectiousness and transmission.
- Evaluate HIV transmission and acquisition in relation to
  - 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, hormonal replacement, 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 such that these studies are more directly relevant to HIV transmission in humans.

OBJECTIVE:

Undertake epidemiologic research to identify, reduce morbidity from, and prevent the occurrence of adverse health outcomes—including OIs, malignancies, adverse effects associated with treatment regimens, comorbidity with other infections, and other serious health outcomes—in HIV-infected persons in domestic and international populations.

1.D

STRATEGIES:

- Develop new and continue long-term followup of cohorts, including observational cohorts and intervention populations, 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 access to health care, compliance/adherence to therapy regimens, and health outcomes in HIV-infected populations; consider the effects of HAART and drug use treatment and other infections (e.g., hepatitis C virus [HCV]) on each other and on the changing nature of the treatment of HIV disease.
- Explore low-cost, low-technology interventions to prevent 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
  - Infectious diseases;
  - Malignancies and associated oncogenic infections;
  - Consequences of treatment interventions; and
  - Other HIV-associated diseases, including central and peripheral nervous system diseases, cardiovascular manifestations, and wasting and other metabolic disorders.

OBJECTIVE:

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

1.E

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.
- Develop 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.

SCIENTIFIC AREA OF EMPHASIS:

Etiology and Pathogenesis

SCIENTIFIC AREA OF EMPHASIS:

Etiology and Pathogenesis

SCIENTIFIC ISSUES

In the quest for vaccines to prevent HIV infection and 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 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.

TRANSMISSION, ESTABLISHMENT, AND SPREAD OF HIV INFECTION

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, 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 provided the foundation for all efforts to develop effective 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 basic research insights into mechanisms of viral entry and the mechanisms by which the infection becomes established and spreads are crucial for vaccine development efforts.

The challenge remains to develop cheaper, easier to take, more potent drugs with fewer adverse effects for the treatment of HIV infection, along with new 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.

PRIORITY FOR FUTURE RESEARCH:

- **Capitalize on new insights into HIV biology and HIV host interactions to identify new viral and cellular targets for therapeutics, microbicides, and vaccine development.**

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 the molecular interaction between the virally encoded regulatory proteins and host cell factors, and the identification of "fusion competent" structures able to elicit a strong and cross-reactive neutralizing response are affording us the opportunity to identify these new viral and cellular targets.

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. This basic knowledge is crucial for our efforts to develop effective vaccines and microbicides.

PRIORITY FOR FUTURE RESEARCH:

- **Elucidate determinants of HIV transmission between individuals and facilitate basic epidemiologic and multidisciplinary research in this area.**

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); the cells or tissue types that represent the first target of infection; and the role of viral genotypes/phenotypes and dose on HIV entry and establishment of infection.

The recent findings on the 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. These findings also suggest that the early interaction of HIV with target cells at the portal of entry is critical for the subsequent establishment of infection. 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 immunity, viral and host genetic factors, and other infectious agents and sexually transmitted diseases (STDs) on HIV-1 susceptibility and 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 is also 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.

Recently, 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 to progression to disease. This new 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 has raised the intriguing possibility that prolonged therapy may lead to virus eradication. However, recent data have demonstrated that the virus can persist in the body of HIV-infected patients almost for a lifetime. A better understanding of the different mechanisms of viral persistence is needed in order 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 HIV persistence in the setting of effective antiretroviral therapies.**

Research efforts should focus on identifying the cells and tissue reservoirs of virus infection, the mechanisms of latent virus reactivation, the impact of low-level viral replication on virus transmissibility, the timing of initiation of treatment on establishment and maintenance of HIV persistence, and the ability of natural and induced immunity to control and eliminate persistent infection.

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 during HIV infection and disease, and following the introduction of effective antiretroviral therapies, will provide valuable insights into this pathogenic process.

PRIORITY FOR FUTURE RESEARCH:

- **Elucidate direct and indirect mechanisms of T-cell depletion and reconstitution in HIV infection and 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.

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 to identifying the characteristics of the immune response 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 this experimental system, 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 on human immunology to guide immune reconstitution and vaccine development efforts.**

A great emphasis should be placed on *in vivo* studies, and recent technological breakthroughs are affording us this opportunity. 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, 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 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, analyzing humoral and cellular immunity at mucosal sites, and better understanding of mechanisms leading to maintenance of immunological memory will greatly benefit research aimed at developing effective HIV vaccines.

Continued support of *in vivo* research is a high priority at NIH in order to further understand the interaction between the virus and host immune system response. NIH-sponsored longitudinal cohort studies constitute a major resource for this type of 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 provide 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.

HIV PATHOGENESIS AFFECTING WOMEN AND MATERNAL-FETAL TRANSMISSION

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 data generated by these cohorts is providing critical information about 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 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 afterwards. Further studies are warranted to elucidate the biological underpinnings for these findings.

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 RNA levels in plasma or vaginal secretions and an increased risk of neonatal infection; the delineation

of the role of maternal immunity in prevention of transmission 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, 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.

METABOLIC ABNORMALITIES 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 of 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 long-term cardiovascular complications.

PRIORITY FOR FUTURE RESEARCH:

- **Improve our understanding of the mechanisms underlying metabolic abnormalities and body composition changes during HIV infection and following effective antiretroviral therapies, and determine the risk of atherosclerotic cardiovascular disease in these settings.**

Elucidation of the factors contributing to metabolic abnormalities and body composition changes 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, wasting 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. Weight loss in AIDS results in a significant reduction in survival, independent of other factors influencing survival, 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 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 in 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.

NEURO-PATHOGENESIS

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 and resides in the brain parenchyma for many years prior to manifestation of neurologic impairment. Very intense research efforts have focused on elucidating how HIV persists in the CNS and how it causes such devastating multifocal disease. 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 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, establishes infection, and persists 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 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.

Since 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 simian immunodeficiency virus (SIV) model. NIH-supported researchers are investigating the contribution of OIs, acquired deficiencies in intestinal enzymes, malignancies, and 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 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 load on transmission of cell-free and cell-associated virus.
- 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 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 biologic, environmental, social, gender-related, and host factors determining 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 and 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 approached in human subjects.

- Promote augmented access to and sharing of key patient samples, animal model resources, laboratory reagents, 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 HIV-related immune dysfunction in 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 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 approached in human subjects.

- Promote programs to facilitate augmented access to and sharing of key patient samples, animal model resources, laboratory reagents, 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 abnormalities 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 abnormalities and body composition changes (including studies performed on appropriate animal models) that may be operative at various stages of disease.
- Elucidate the virologic and host consequences of HIV infection that result in metabolic abnormalities, 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 abnormalities, 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 abnormalities, body composition changes, and impaired growth and development; evaluate how HIV-associated metabolic abnormalities, 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 abnormalities, 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, 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.
- 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.
- 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 and patient specimens for HIV-associated malignancies.

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;
  - Determining the relationship of virologic, host, 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-1 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.
- 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.
- 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 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 they 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.

SCIENTIFIC AREA OF EMPHASIS:

Therapeutics

SCIENTIFIC AREA OF EMPHASIS:

Therapeutics

SCIENTIFIC ISSUES

Significant scientific findings from basic research have had a direct impact in advancing AIDS drug discovery, drug development, and clinical research efforts. Most important of these advances has been the demonstration that multidrug combinations of antiretroviral drugs significantly reduce the viral load in many patients to undetectable levels. The effects of highly active antiretroviral therapy (HAART) can be dramatic in some patients, including those with advanced HIV-related disease and/or opportunistic infections (OIs), as a profound reduction in viral load may be accompanied by an increase in CD4 cell count and, in many cases, amelioration of HIV-related symptoms.

Additional research, however, is needed to maximize the likelihood of continued success in treating HIV-infected individuals with these multidrug combinations. The most compelling questions in this area include the following:

- How long can the virologic, cellular, and clinical responses be maintained on an initially successful regimen?
- What are the earliest detectable signs of failure that indicate that the drug regimen should be changed?
- What are the most common reasons for failure of these regimens?

- Can treatment strategies aimed at minimizing the risk of clinical progression be developed?

The synergy of regimens that combine one or more reverse transcriptase inhibitors with one or more protease inhibitors demonstrates that inhibition of more than one critical viral enzyme offers a promising approach to treatment. Therefore, the development of new agents designed to inhibit one or more of the other known enzymatic or regulatory proteins of HIV is a high priority.

The advances in therapeutics research over the past few years highlight the need for continued and improved collaborative efforts between Government- and industry-sponsored drug development and clinical trials, with the goal of providing patients with improved quality of life and extended lifespans.

DRUG DISCOVERY AND PRECLINICAL DEVELOPMENT

NIH supports an active and comprehensive drug discovery and drug development program that may permit the design and identification of new and more effective drugs with the goals of (1) entering host compartments serving as viral reservoirs, (2) producing less toxicity and fewer side effects, (3) eliminating viral mutation, which results in drug resistance, and (4) permitting increased compliance to treatment regimens.

Drug discovery and therapeutics research efforts may benefit from recent advances in understanding the molecular dimensions of HIV entry into the cell. Several new viral and host/cellular targets have been identified, and aggressive efforts are under way to develop agents to block or compete with their function. Examples include the host-cell chemokine coreceptors CCR5 and CXCR4, which are necessary for HIV infection; a zinc-binding domain in the HIV nucleocapsid protein involved in viral packaging; a nuclear localization signal in the HIV matrix protein, which is critical for transport of proviral DNA into the host genome; HIV accessory proteins, all of which are involved in HIV infectivity, replication, and/or pathogenesis; and other host factors required for HIV replication, such as cellular kinases, cytoskeleton components, and nuclear components, which may provide novel molecular targets for new agents that are less likely to result in drug-resistant strains of HIV.

PRIORITY FOR FUTURE RESEARCH:

- **Identify and characterize new or understudied viral and host targets for anti-HIV therapy; define the cell-specific factors leading to viral fusion, integration, transcription, assembly, budding, replication, and infectivity; define molecular and cellular determinants affecting HIV virulence and pathogenicity; and develop predictive test models that include the use of appropriate lentivirus systems to aid in the identification of agents and strategies active against these targets.**

The discovery and development of safe, effective, and acceptable physical and chemical barrier methods—such as topical microbicides—to reduce sexual transmission of HIV and sexually transmitted diseases (STDs) is critical to halting the further global spread of AIDS. These efforts require 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:

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

DEVELOPMENT AND EVALUATION OF AGENTS TO TREAT HIV AND RESTORE IMMUNE FUNCTION

Significant progress in understanding HIV pathogenesis has led to the development of a potent class of anti-HIV drugs—protease inhibitors—as well as to the development of more sensitive assays for measuring the concentration of HIV RNA in different body tissues. The recently developed genotypic and phenotypic assays will permit further characterization of the unique drug-sensitive/drug-resistant strains of HIV. These assays therefore will allow the development of more effective and individualized therapeutic regimens to increase patient longevity, delay disease progression, and improve the patient's quality of life. These assays also will permit researchers to better study and monitor emerging strains of drug-resistant HIV. In addition, studies on the molecular determinants of HIV drug resistance may provide a better understanding of the mechanisms involved in the development of resistance to a variety of AIDS drugs.

Protease inhibitors target a viral enzyme different from that inhibited by reverse transcriptase (RT) inhibitors. The use of a two-pronged approach (i.e., the combination of one or more protease inhibitors with one or more RT inhibitors) can result in improved antiviral activity and a delay in the

development of drug resistance. Currently available antiretroviral drugs, however, are not able to achieve complete viral suppression. HIV continues to replicate at low levels in various reservoirs or sanctuary sites, making it possible for drug-resistant strains to emerge. Recent research has demonstrated the existence of a reservoir of latently infected cells that persists for prolonged periods of time, even in patients whose plasma viral load decreases to undetectable levels. These cells are infected during the acute phase of primary infection and form a source for HIV replication following drug withdrawal or HIV gene activation. There is a need to develop new drugs that are safe and effective, can penetrate all compartments of the body, can be easily adhered to, and possess few toxic or complicating side effects, such as metabolic complications and body composition alterations, which have been associated with protease inhibitors.

PRIORITIES FOR FUTURE RESEARCH:

- **Develop agents or treatment strategies to destroy or inhibit the expression of HIV in latently infected cells and anatomical and organ reservoirs.**
- **Develop agents targeted at drug-resistant virus.**
- **Determine the regional and global patterns of resistance to antiretroviral therapies and how this could reduce the long-term effectiveness of antiretrovirals.**

The development of HAART has provided researchers with new opportunities to study HIV pathogenesis. The demonstration of high levels of viral replication in untreated patients throughout the long period of clinical latency has resulted in a new focus of therapeutics research on individuals with acute infection. Studies are needed to determine whether HAART should be initiated shortly after an individual is newly infected in order to eradicate the infection. If viral eradication or a cure cannot be accomplished with currently available therapies, early treatment still may reduce permanently the "steady state" rate of viral replication observed between 6 and 12 months following initial infection, and result in delaying disease progression. Given the limits of antiretroviral therapies, immune-based and immune restorative therapies are needed, especially for individuals at more advanced stages of disease and immune depletion.

PRIORITY FOR FUTURE RESEARCH:

- **Evaluate the ability of the immune system to maintain or repair itself after viral suppression has been achieved through HAART; evaluate cytokines, modulators, and other immunoactive agents to prevent further immune deterioration and to reconstitute deficient immune systems in HIV-infected individuals; and evaluate immunotherapeutic approaches to increase immune responses following antiretroviral therapy.**

Systematic studies are needed to improve our understanding of the interaction between the biomedical and behavioral factors that affect compliance/adherence to drug treatment regimens; to optimize the dosing regimen based on the individual's metabolism, virologic response, and tolerance; and to develop new compounds and drug regimens that are easier to comply with and are active against drug-resistant viral strains. There also is an important scientific need to identify regimens for treatment-exposed individuals who have not responded to standard therapies.

PRIORITIES FOR FUTURE RESEARCH:

- **Develop treatment regimens that allow for improved compliance and adherence.**
- **Develop and evaluate therapies for individuals who no longer respond to existing therapies.**

CLINICAL TRIALS

The evaluation of potential therapies for the treatment of HIV infection and its associated OIs, malignancies, and other complications is one of the highest priorities. 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 and development of HIV-related manifestations, including metabolic complications and body composition transformations.

PRIORITIES FOR FUTURE RESEARCH:

- **Conduct clinical trials of potential therapeutic agents and combinations of agents in adults, the elderly, and children to determine pharmacokinetics and tissue bioavailability, antiviral activity, effects on the immune system, safety, and clinical efficacy.**
- **Evaluate potential delayed or late toxic effects of antiretroviral therapy (e.g., hepatotoxicity, carcinogenicity, and metabolic/endocrine abnormalities) following short-term administration of prophylaxis regimens as well as during chronic treatment.**

PEDIATRICS

The prevention of perinatal HIV transmission, which is the predominant source of HIV acquisition in children, is critical. While the use of an antepartum, intrapartum, and neonatal zidovudine (ZDV) regimen has significantly reduced perinatal HIV transmission in the United States and Europe, further research is needed to develop a prophylactic regimen(s) capable of lowering perinatal transmission in developed and developing nations. Combination therapy that includes protease inhibitors has become the standard of care in some developed nations for treatment of HIV-infected individuals, including pregnant women. Perinatal and pediatric clinical trials to determine the pharmacokinetics and safety of combination therapy with ZDV/3TC and more potent antiretrovirals are needed.

PRIORITY FOR FUTURE RESEARCH:

- **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.**

Long-term followup of infants with *in utero* exposure to antiretroviral drugs for possible adverse consequences is important because drug exposure occurs during periods of organ system development. While followup data from NIH-sponsored clinical trials have shown no differences in neurodevelopment, immunologic parameters, and growth between those uninfected infants with *in utero* ZDV exposure and those in a placebo group who were followed for as long as 5.6 years, the exposed children will continue to be monitored through 21 years of age.

PRIORITY FOR FUTURE RESEARCH:

- **Evaluate the safety of antiviral agents in pregnant women, including transplacental passage of the agents and safety of the fetus; evaluate pharmacokinetics, metabolism, tissue absorption, and drug elimination in the newborn.**

NIH will continue to support the development and evaluation of agents against OIs and other complications of HIV infection, including AIDS-related malignancies. As the demographics of HIV infection and AIDS have changed, the diversity of groups affected by the disease has increased among women, children, adolescents, injecting drug users (IDUs), minorities, the urban poor, and individuals residing in rural areas. NIH will continue to place a high priority on the recruitment and accrual of individuals representative of these affected groups into clinical trials.

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE:

Increase the understanding of viral and cellular functions required for replication of HIV and identify 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, integration, transcription, assembly, budding, replication, and infectivity; define molecular and cellular determinants affecting HIV virulence and pathogenicity; develop predictive test models, including the use of 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, which 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.
- Develop analytical methods and chemical formulations of new compounds and combinations of compounds, including those derived from 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—when they cannot appropriately 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 toxicity/efficacy.

- Develop agents with desirable biopharmaceutical characteristics, such as improved bioavailability and tissue penetration, including 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 early markers and genotypic mutations leading toward 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 investigating new 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 simulation for the purpose of predicting *in vivo* efficacy, toxicity, and outcomes of clinical trials.

- Investigate host cell effects of antiretroviral drugs.

- Investigate therapies to control 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 great; assume full responsibility, when necessary, for the development of potential therapies with high public health relevance and need.

OBJECTIVE:

Conduct clinical trials and develop new methodologies to evaluate the 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-naive and in pretreated 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.

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.
- 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 a variety of prior antiretroviral drug experience, including pretreated individuals with advanced disease.
- Support long-term clinical trials to study the timing, selection, and sequencing of antiretroviral agents to optimize clinical outcomes.
- 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 abnormalities) following short-term administration of prophylaxis regimens as well as 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 trials and individual patient management (therapeutic drug monitoring).
- Develop approaches to prevent or reverse potential metabolic abnormalities (e.g., changes in body composition, increased risk of atherogenecity, and endocrine disorders) based on an understanding of the mechanisms by which antiviral therapies and/or suppression of HIV replication may affect metabolic processes.
- 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.
- 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 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 the potential for fewer drug-drug interactions.
- Determine the factors influencing adherence to multidrug regimens in injecting drug users 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 on subsequent clinical disease course and on 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 safety of antiviral agents in pregnant women, including transplacental passage of the agents and safety for the fetus; evaluate the 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.
- Evaluate the impact of potent antiretroviral therapy on the reactivation of hepatitis viruses, the potential need for treatment of viral hepatitis in coinfected patients, and the development of late-stage complications of viral hepatitis.
- Design methods to improve 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 this 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 therapeutic approaches that will enhance, restore, and/or maintain the immune systems of HIV-infected individuals and extend our understanding of immunopathogenesis.

3.C

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 in 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, evaluate, and implement strategies for interrupting vertical transmission of HIV from mother to child in developed and developing countries, and extend our understanding of the pathogenesis of perinatal transmission and early infection.

3.D

STRATEGIES:

- Use 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), vitamin supplementation, HIV vaccines, adjuvants, and virucides, alone or in combination.
- Evaluate the short- and long-term toxicities, pharmacokinetics, and antiretroviral activity of anti-HIV 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 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, including evaluating the risk of postpartum morbidity in infected women with elective cesarean delivery and 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, statistical methodologies, and 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.
- 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:

Discover and delineate the structure and function of potential molecular targets and agents for prevention and treatment of HIV-associated OIs 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.

3.E

STRATEGIES:

- Improve our understanding of the interplay between HIV-associated immune deficits and the onset of infectious complications.
- Support discovery and preclinical drug development programs to identify targets and to develop therapies against opportunistic pathogens, especially *Cryptosporidium*, *Mycobacterium avium complex* (MAC), multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB), microsporida, 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 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 to treat OIs; provide support for medicinal chemistry, structural databases, resynthesis, and toxicity testing.
- Determine the high-resolution molecular structures for proteins from OI microorganisms; apply these structures to 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—when they cannot be done appropriately by industry—to assess immunologic effects, pharmacokinetics and pharmacodynamics, toxicity, teratogenicity, transplacental carcinogenicity, and effects on fertility of anti-OI drugs.

- Conduct clinical trials to evaluate agents for the prophylaxis and treatment of HIV-associated OIs; target OIs that have proven to cause significant morbidity based on 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 immunosuppression.

- Support clinical trials that assess the impact of new antiretroviral regimens on the risks for and manifestations of opportunistic infections associated with HIV/AIDS in adults and children.

- Develop better strategies for simultaneous prevention of multiple OIs in the context of antiretroviral treatment; determine optimal time to initiate/discontinue 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 opportunistic infections 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 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 design, 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 the 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 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 great; assume full responsibility, when necessary, for the development of potential therapies with high public health relevance and need.

OBJECTIVE:

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

3.F

STRATEGIES:

- Support the discovery and development of improved, acceptable, effective, and safe physical and chemical barrier methods, including topical microbicides and other methods, 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 physical and chemical barriers, including topical microbicides, for prevention of mucosal HIV transmission.
- Develop sensitive, specific, and reproducible methods for quantitation of 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 microbicidal agents and other 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 microbicidal agents, especially in areas where public health needs are great; assume full responsibility, when necessary, for the development of potential microbicides with high public health relevance and need.

OBJECTIVE: (The scientific objectives 3.G through 3.I are of equal weight.)

Discover, develop, and evaluate improved strategies for the assessment, treatment, and prevention of HIV-associated malignancies.

3.G

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 on the basis of 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 immunodeficiency-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 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 3.G through 3.I are of equal weight.)

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, 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 knowledge of pathogenesis.
- Characterize the CNS pharmacokinetics and pharmacodynamics of antiretroviral drugs; determine the importance of CNS drug penetration in reducing CNS infection in neurologically symptomatic and asymptomatic subjects.
- 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 cerebrospinal fluid (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 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 3.G through 3.I 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.I

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 HIV-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 that are potentially clinically significant for patients with HIV infection, and in particular the interactions between antiretroviral agents and psychotropic medications; develop strategies to avoid or minimize the clinical impact of these interactions.

SCIENTIFIC AREA OF EMPHASIS:

Vaccines

SCIENTIFIC AREA OF EMPHASIS:

Vaccines

SCIENTIFIC ISSUES

CLINICAL HIV/AIDS VACCINE RESEARCH

New HIV infections continue to increase unabated in some populations, and HIV has become established in new populations both in the United States and in international settings. AIDS surveillance data continue to indicate that women and minority populations in the United States are becoming infected at an increasing rate and that sexually active individuals worldwide, particularly adolescents and young people of all races, are at risk of acquiring HIV. Inadequate education about the risks of exposure and acquisition of HIV and other sexually transmitted diseases (STDs) through early and unprotected sexual intercourse contributes to fuel the epidemic both in the United States and abroad. Inadequate access to health care and to effective modes of prevention exacerbate the problem both on an individual basis and in countrywide scenarios. The development of vaccines that are safe and effective is a national and international public health priority. Recent insights from basic research have raised the expectation that improved vaccine candidates can be developed.

As promising vaccines move further in the vaccine pipeline, expanded trials with populations at higher risk for HIV infection will become increasingly important. In the changing epidemic in the United States, it has become disturbingly clear that minority populations bear a disproportionate burden of HIV infection and AIDS. AIDS has even more directly impacted populations in many developing countries. HIV/AIDS vaccine research requires trained health care, medical research, and prevention specialists

from the populations at risk who will be integrally involved in development of vaccine candidates and clinical vaccine and prevention trials. Trial-related research must develop outreach and incorporate education to include at-risk populations from disadvantaged settings. International and domestic trial sites also need to develop a cadre of trained indigenous or minority personnel for the interdisciplinary research needed for the conduct of vaccine trials so that there is direct involvement of communities in vaccine trials at all levels and that trials are conducted in a collaborative manner.

PRIORITY FOR FUTURE RESEARCH:

- **Conduct domestic and international vaccine trials; include populations at high risk for HIV transmission from different routes of transmission; and perform prevention and trial design research necessary to conduct clinical vaccine trials, especially in U.S. minority populations and in developing countries. To do this, it is also essential to ensure continued and expanded participation of minorities at all levels in vaccine trials.**

BASIC VACCINE RESEARCH

One of the major stumbling blocks in the development of HIV vaccines has been the inability to develop vaccine candidates that induce broadly reactive antibodies capable of neutralizing non-syncytia-inducing (NSI) isolates of HIV. NSI viruses are commonly isolated early in HIV infection, utilize the CCR5 (R5) chemokine receptor, and are primarily macrophage-tropic. The first generation of candidate vaccines that were tested in human volunteers induced antibodies capable of neutralizing syncytia-inducing (SI), or laboratory-adapted, T-cell-tropic virus isolates. Structural studies of the gp41 and gp120 components of the HIV envelope protein and preliminary immunogenicity studies indicate that there are several conserved sites that might be used as targets of neutralizing antibodies, particularly if sugar moieties are removed.

Vaccine studies in nonhuman primate models have shown that it is possible to protect from infection or reduce viral load and delay disease development with a variety of vectors or vaccine approaches that induce cytotoxic T lymphocytes (CTLs). Furthermore, studies in different HIV-infected populations have demonstrated that CTLs can recognize and lyse targets with epitopes derived from highly divergent HIV-1 strains. However, we do not know the limits of this immunity, nor do we know how effective immunity induced by these vaccines will be. Because HIV transmission from sexual contacts or from mothers to breast-feeding infants occurs at mucosal sites, vaccines that can induce effective, long-lasting immunity against HIV at mucosal sites of viral entry need to be developed and tested.

New insights into the structure and function of the HIV envelope, plus new studies of immunogenicity with deglycosylated envelope, exposure of transient or induced epitopes, complex immunogens, and mimetopes that present conserved domains, offer opportunities that should be explored in HIV vaccine development. For a highly effective vaccine, it may be important to develop methods to improve the breadth and the duration of the humoral response to HIV envelope in new vaccine approaches. At the same time, important progress in the induction of CTL responses and immune responses at mucosal surfaces must be sustained.

PRIORITY FOR FUTURE RESEARCH:

- **Develop and test new vaccine strategies, alone or in combination, to induce broad functional immune responses—both humoral and cellular, mucosal and systemic—against primary NSI, R5-using HIV isolates from all genetic clades.**

PRECLINICAL VACCINE RESEARCH

The evaluation of vaccine approaches in nonhuman primates has evolved from early testing of candidates in chimpanzees to a variety of species of macaques or baboons. Rhesus macaques have presented particular opportunities for assessment of HIV/simian immunodeficiency virus (SIV) vaccine strategies because of the development of disease from SIV in this model and the adaptation of several pathogenic SHIV chimeric isolates. Reproducibility of testing has been of great concern because monkeys, like humans, are highly variable in their major histocompatibility complex (MHC) genes, which control the immune response. Differences in experimental outcome can often be attributed to the immune responses that are generated by particular animals. The ability to control variables in groups of animals would greatly facilitate interpretation of vaccine experiments. The generation of additional SHIV chimeric isolates for vaccine applications permits the direct evaluation of vaccine candidates with HIV envelope components for different types or clades of HIV-1 isolates.

Proof-of-concept testing in animal models and definition of potential correlates of immune protection in nonhuman primates would accelerate development of vaccine candidates. With the expansion of research on new vaccine concepts, multiple new vaccine products will need to be tested for immunogenicity and the ability to protect against infection or disease development. Further exploration of alternative animal models for HIV infection and optimization of the use of existing or modified nonhuman primate models will aid in vaccine development.

PRIORITIES FOR FUTURE RESEARCH:

- **Continue to improve animal models and to improve availability of nonhuman primate models for systematic, comparative efficacy testing of vaccine concepts and understanding of the mechanisms of protection that might be translated to HIV vaccine studies in humans.**
  - **Develop MHC-defined and/or histocompatible rhesus macaques, and define the associated epitopes of HIV/SIV proteins for vaccine studies.**
  - **Continue to develop and exploit SHIV chimeric viruses with different degrees of virulence to more closely reflect disease progression observed in HIV-infected people and the genetic variation observed in worldwide HIV epidemics.**

With accumulating evidence in nonhuman primate studies and clinical studies that polyvalent antibodies can be effective for preventing transmission or altering disease course, it is timely to pursue the development of this strategy where prolonged or sustained intervention might be appropriate. In addition, understanding of antibody-based passive immune prophylaxis has often played an important conceptual role in vaccine development. The use of polyvalent antibodies to HIV in conjunction with active vaccination and/or short-term antiretroviral drug intervention may optimize prophylaxis.

PRIORITY FOR FUTURE RESEARCH:

- **Utilize new information about functional antibodies to identify and develop broadly effective, polyvalent anti-HIV cocktails of antibodies or other products for prophylaxis of HIV transmission, alone or in combination with vaccination and/or short-term antiretroviral prophylaxis. These approaches should be targeted for use in studies of mother-to-infant transmission, including transmission due to breast-feeding, and be used to inform vaccine design for antibody responses.**

One of the roadblocks for vaccine development that has been identified, particularly by academic and Government AIDS vaccine investigators, is the ability to produce products under Good Laboratory Practices or Good Manufacturing Practices (GLP/GMP) that could meet Food and Drug Administration (FDA) expectations for products suitable for initial testing in human volunteers. In addition to the expense of producing such products, research investigators outside private industry often do not have the experience or dedicated laboratory facilities needed to prepare vaccine candidates for testing in human volunteers.

PRIORITY FOR FUTURE RESEARCH:

- **Enable rapid movement of vaccine concepts into clinical testing, including the development or procurement of GLP/GMP products or direct funding for production of candidate vaccines to stimulate industry partnerships for human and nonhuman primate trials.**

The mechanisms of protection were never established for many highly effective non-HIV viral vaccines. Further exploration or reassessment of several vaccine strategies has revealed immune responses to core proteins after apparent vaccine protection following immunization with vaccines composed of surface antigens. In other antiviral systems, the complexity of several components of the immune system—CTL, T-helper responses, as well as antibodies—all appear to be contributing to a protective immune response. Lessons learned in this broad area of vaccine research could contribute to the effective development of new HIV vaccines. This research should be of sufficient merit that it should not require redirecting AIDS resources for this effort. Crossover benefit, however, would be substantial and justify timely funding of key projects.

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.
- Determine how HIV or other lentiviral proteins, particularly glycosylated proteins, are synthesized and how epitopes are selected and presented 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 responses; carry out translational research in non-human 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).

- 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, and nonprogressors to define early immune responses to HIV-1 and HIV-2 and 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 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 scientific analyses; and acquire appropriate epidemiological information to enable interpretation of these analyses.

- Monitor the effects on immune activation with intercurrent 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 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 high throughput assays with specificity for primary virus isolates.
- Develop or improve sensitive quantitative measures of HIV (and SIV) concentration in body fluids, 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 with 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;
  - 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 and industry sponsors 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 with, industry and other agencies in the research, development, production, and clinical testing of candidate vaccines.

- Foster the development of multivalent and combination HIV vaccines to optimize characteristics appropriate for broad international use, including designs possessing stability and ease of administration; this may include
  - Combined use of two or more vaccine candidates (indicated above) 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 presentation 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 that might have an impact on vaccine responses.

- Evaluate the efficacy of vaccine and other 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 biologic characteristics of breakthrough virus including transmissibility;
- Determining the impact of genetic factors 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, studying potential concomitant effects on the genital tract immune system and inflammatory activity that might compromise integrity of the genital tract or inductive ability of vaccines.

- Support development of reagents and 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 serological and cellular responses due to immunization versus those due to virus infection; and
  - Characterizing and evaluating the potential negative side effects of candidate vaccine designs, including the potential to increase the frequency of infection or the rate of disease progression in animal models.

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 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 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 prevent transmission of HIV or establishment of infection in infants, and control viral replication in either the mother and/or the infant.

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 to block interaction of HIV with its receptors and coreceptors and/or to target infected cells.
- Characterize the transmitted viral subtypes and changes that are occurring in proposed trial sites; evaluate the impact that genetic polymorphisms in different racial or ethnic backgrounds might have on receptor usage or immune responsiveness.
- Select and evaluate, in Phase I/II studies, the safety and immunogenicity of various HIV vaccines, adjuvants, vaccine administration regimens, or the pharmacokinetics of passive antibody preparations among both HIV-infected pregnant women and newborns with HIV exposure (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 and modification of criteria for advancement of candidate vaccines, adjuvants, and passive antibody preparations from Phase I/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 HIV-exposed children.

- 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.

4.D

STRATEGIES:

Support the conduct of Phase I, II, and III clinical trials that will determine long-term and short-term safety as well as 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:

- Develop a mechanism to evaluate the suitability of vaccine candidates and facilitate entry into Phase I and Phase II trials—animal model data related to concept and safety should be included in the evaluation criteria.

- Design and conduct Phase I and Phase II trials using promising HIV vaccine candidates that are genetically or immunologically related to HIV isolates circulating in a proposed trial population. Trials should address questions that test vaccine concepts, 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 initiation of vaccine trials, vaccination, and followup of vaccinees to defined endpoints, as follows:

- Prepare for adequate long-term followup of volunteers in HIV vaccine clinical trials to determine the longevity 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. 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; and
- Including strategies that will promote prevention of HIV infection.

- Isolate and characterize virus and follow clinical course and immune responses of vaccinees who become HIV-infected; study 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 that would facilitate broader participation.
- 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 and test interventions to prevent relapse to high-risk behaviors as a result of participation in a vaccine trial; conduct behavioral research with specific emphasis on individuals who become infected during trials to identify interventions that may prevent reversion to 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, communities, and industry necessary for ensuring 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 genetic 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:

- Carry out appropriate epidemiologic studies that determine and 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 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 recent seroconverters representative of potential efficacy trial populations, so that genetic and antigenic information about virus circulating in the population can be obtained.
- Develop and maintain the necessary immunology and virology laboratory infrastructure, including education and training, at designated sites for conducting domestic and foreign vaccine efficacy trials.

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 domestic 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.

- For all vaccine trials, 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, non-Governmental organizations, and communities being targeted, 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, and retention strategies pertinent to the design and execution of a successful efficacy trial, especially for populations that have been historically underrepresented in clinical trials.

- 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 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 (TB) and STDs; integrate research on vaccines against opportunistic infections (OIs) as appropriate.

SCIENTIFIC AREA OF EMPHASIS:

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 in the United States and globally result from two activities: unprotected sexual intercourse with an HIV-infected person and the use of HIV-contaminated injection drug equipment. The primary goal of National Institutes of Health (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, their families, the health care system, and society.

UNDERSTANDING AND INTERVENING IN HIV TRANSMISSION

Current research priorities in behavioral and social science 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. A growing proportion of new HIV and AIDS diagnoses are 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, and the relative effectiveness of individual behavioral change interventions and community-based prevention strategies.

PRIORITIES FOR FUTURE RESEARCH:

- **Better understand and address through interventions the social, economic, and cultural dynamics that underlie racial and ethnic disparities in access to and use of HIV prevention and care services.**
- **Better understand and address through interventions the psychological, social, economic, and cultural dynamics of gender and sexual identity that operate in HIV risk, protection, and care.**
- **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.**

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 to ensure societal commitment to HIV prevention for the duration of the epidemic.

PRIORITIES FOR FUTURE RESEARCH:

- **Better understand the changing perceptions of risk of acquisition and transmission of HIV infection related to developments such as improved HIV/AIDS treatment and/or participation in HIV prevention studies, including vaccine trials.**
- **Identify and address issues in the initiation, maintenance, sustainability, and durability of effective HIV prevention and care efforts among individuals (including HIV-infected individuals) and communities over time.**

A third important development is the recognition that large-scale HIV prevention strategies adopted by national and local governments have been effective in reducing transmission in a number of 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 need to study further the impact of 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 greater public health impact. In doing so, it is important to identify and address cultural, ethical, and logistical (e.g., infrastructure-building, cost, and training) issues that arise in replicating and/or adapting interventions with different populations and in different settings.

PRIORITY FOR FUTURE RESEARCH:

- **Improve translation and transportability of effective HIV prevention and care interventions, both domestically and internationally.**

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 comorbid conditions, including other infectious diseases (e.g., hepatitis, sexually transmitted diseases [STDs], tuberculosis), substance abuse, mental illness, and homelessness. Both the risks and consequences of HIV infection for these individuals must be evaluated and addressed in the context of these other conditions. Studies are needed to 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:

- **Develop and test interventions among individuals living with HIV/AIDS and other comorbid conditions (e.g., substance abuse, mental illness, hepatitis, tuberculosis, homelessness).**

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 behavioral and social science 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.

PRIORITY FOR FUTURE RESEARCH:

- **Further develop research methods to improve HIV prevention and intervention science.**

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 the 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 behavioral and social science 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 social and behavioral interventions at the societal, community, organizational, social network, dyadic, and individual levels to prevent HIV transmission and acquisition by reducing HIV-related risk behaviors and increasing protective behaviors. In addition, interventions should address the social and cultural contexts within which risks occur (e.g., social class, gender, race, age, and ethnicity), both domestically and internationally. Multisite, cross-national, and international studies are encouraged.

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 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 research to prevent and treat HIV.

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

AREA OF SPECIAL INTEREST:

Racial and Ethnic Minorities

AREA OF SPECIAL INTEREST:

Racial and Ethnic Minorities

SCIENTIFIC ISSUES

The disproportionate impact of the ongoing HIV/AIDS epidemic upon communities of color has presented significant challenges to biomedical, behavioral, social, and clinical research. The multifaceted nature of the epidemic in general, and specifically within racial and ethnic minority communities, requires a range of research interventions that target those components of the epidemic that facilitate, as well as limit, transmission. Within these communities, the impact of the main routes of HIV transmission in the United States—unprotected sexual intercourse and injecting drug use—are further confounded by other societal and community factors. These factors include poverty, homelessness, immigration, racism, and homophobia. The goal of National Institutes of Health (NIH)-sponsored research in racial and ethnic minority communities is to discover not only the cultural, racial, and social contexts within which HIV transmission is prevented (or is not prevented), but also to determine the impact of interventions at multiple levels within these communities. Finally, NIH seeks, through infrastructural and technical support, to address the paucity of appropriate investigators to address these issues.

THE IMPACT OF THE CULTURAL CONTEXT

Central to the epidemic in racial and ethnic minorities is the influence of social forces, including gender roles and sexual orientation, in risk behavior. These forces are often superimposed upon a context that includes poverty, racism, violence, religion, social stigma, homophobia, the sociocultural roles of women, and the impact of acculturation.

PRIORITY FOR FUTURE RESEARCH:

- **Identify the macrostructural forces—including social, economic, and cultural—that create contexts of powerlessness and HIV risk behavior for racial and ethnic minorities.**

Knowledge gained from behavioral interventions in these communities continues to underscore the importance of understanding culture and its impact upon interventions that are not only acceptable, but successful. The rising numbers of minority AIDS cases provide a powerful reminder that behavioral research must continue to define and utilize cultural, social, and contextual factors that affect HIV risk behavior. The role of alcohol and drug use in facilitating HIV transmission through social networks in all communities must also be explored within these social frameworks.

PRIORITY FOR FUTURE RESEARCH:

- **Develop, test, evaluate, and disseminate culturally sensitive and appropriate prevention interventions in racial and ethnic minority communities to reduce HIV transmission and acquisition in at-risk social networks. To the maximum extent possible, these interventions should intersect at multiple levels and reflect the role of socioeconomic status and language.**

UNDERSTANDING AND INTERVENING IN HIV TRANSMISSION

Through better understanding of social networks and transmission through these networks in minority communities, interventions can be designed, tested, and ultimately tailored to specific population needs. Additional anthropological, behavioral, and social science research is needed to identify those institutions that may serve as entry points into these communities, such as church and community groups. Social marketing research is needed to identify ways to reach more hidden and/or marginalized populations, such as high-risk core transmitters, lesbians of color, gay and bisexual men, drug users, and heterosexual men.

PRIORITY FOR FUTURE RESEARCH:

- **Design and conduct research to specifically address vulnerable subgroups within minority communities that are particularly affected by HIV due to a confluence of social, economic, and other factors. Such groups, for whom culturally and contextually appropriate interventions are especially needed, include, but are not limited to, gay men of color, commercial sex workers, the transgendered, women, adolescents, the homeless, the chronically mentally ill, and drug users.**

Ongoing research on the role of stigma within communities of color is needed not only to identify determinants of high-risk drug and sexual behavior, but also to determine the infrastructure necessary to maintain such research. The impact of community-level homophobia, as well as the impact of disenfranchisement on risk behavior and the impact of drug addiction, are areas that have been identified for additional study. Such factors influence not only the effectiveness of interventions but their durability within social networks as well.

HIV TREATMENT AND CARE RESEARCH FOR RACIAL AND ETHNIC MINORITIES

Significant changes in HIV therapy occurred at the end of the past decade, including the advent of protease inhibitor therapy, followed in rapid succession by a growing number of novel and potent therapies. The benefits achieved from these therapies were not uniformly distributed across the diverse communities impacted by HIV infection. Further, the continued and ongoing impact of inadequate drug treatment and the impact of comorbidities—such as sexually transmitted diseases (STDs) and hepatitis C—on racial and ethnic minorities raises a number of clinical research questions.

PRIORITY FOR FUTURE RESEARCH:

- **Identify and address gaps in care, treatment, and research manifested by the differentials in access to care and HIV-associated morbidity and mortality in majority and minority HIV-infected communities.**

Minority participation in clinical trials must continue to keep pace with minority representation in the epidemic. For such participation to occur, research to identify the barriers to participation in clinical trials, as well as provider- and client-related barriers and needs, is essential. Identifying underlying community, provider, and individual impediments to clinical trials will help inform the treatment protocols for ethnic and racial minorities.

INFRASTRUCTURE AND SUPPORT

Research on the impact of the clinical setting upon study enrollment, as well as community acceptance, is of great importance. Incarceration, as well as community perceptions of clinical trials not designed to address their needs, are potential barriers.

PRIORITY FOR FUTURE RESEARCH:

- **Identify, define, and address the infrastructural, technical, methodological, and sociocultural needs of communities of color for clinical trial participation.**

Research areas include the impact of community perceptions on individual participation in clinical research, as well as research on novel methodologies for clinical trial recruitment and participation. Trust is the foundation upon which minority participation in clinical, behavioral, and social science research must be built. Despite a legacy of mistrust, racial and ethnic minority participation in clinical research can be, and has been, achieved through a number of creative and diverse mechanisms. These cannot and should not supersede the need for a greater number of racial and ethnic minority scientists to participate in all areas of research.

PRIORITY FOR FUTURE RESEARCH:

- **Support and expand programs that train racial and ethnic minority investigators in the areas of behavioral and social science, clinical research, and basic science to increase the number of investigators trained and funded to successfully complete such research.**

SCIENTIFIC PRIORITIES AND RESEARCH APPROACHES

PRIORITY FOR FUTURE RESEARCH:

- **Identify the macrostructural forces—including social, economic, and cultural—that create contexts of powerlessness and HIV risk behavior for racial and ethnic minorities.**

RESEARCH APPROACHES:

- Encourage novel and innovative research designed to explore how social forces affect individuals, groups, and communities and their ability to protect against HIV infection.
- Support innovative and culturally appropriate research designs that explore gender norms in sexual decision making.
- Support intervention research targeting alcohol- and substance-abusing women that is developed within the community and the cultural contexts of the women's lives.
- Support research that explores and evaluates the impact of physical and sexual abuse upon subsequent HIV-risk behavior.
- Encourage and support research that explores, evaluates, and addresses the role of emotional, social, and financial dependence in HIV-risk behavior.
- Support research on culturally focused outreach-based prevention interventions that address risk behavior and misconceptions, especially among adolescent gay men of color.
- Encourage and support research that explores, evaluates, and addresses the impact of perceptions of risk and hierarchy of risk in individual decision making.

PRIORITY FOR FUTURE RESEARCH:

- **Develop, test, evaluate, and disseminate culturally sensitive and appropriate prevention interventions in racial and ethnic minority communities to reduce HIV transmission and acquisition in at-risk social networks. To the maximum extent possible, these interventions should intersect at multiple levels and reflect the role of socioeconomic status and language.**

RESEARCH APPROACHES:

- Encourage innovative community-level intervention research that addresses unique sociocultural needs, e.g., in gay and bisexual men of color.
- Support studies that examine the normative patterns of sexual behavior among different ethnic or cultural groups.
- Support behavioral intervention research to address psychosocial vulnerabilities among women of color, especially lesbian women.
- Encourage and support innovative research on interventions designed for effecting long-term change in AIDS-related attitudes, beliefs, and behaviors, especially in heterosexual men.
- Encourage and support research on interventions that assess the relative effectiveness of a variety of change agents, including nontraditional community institutions such as the church, the social network, or the community group.
- Support innovative early intervention research for women who seek STD treatment.
- Encourage and support innovative behavior research in heterosexual men, specifically designed to explore gender, cultural, and community influences on adopting and maintaining safe sexual practices.

PRIORITY FOR FUTURE RESEARCH:

- **Design and conduct research to specifically address vulnerable subgroups within minority communities that are particularly affected by HIV due to a confluence of social, economic, and other factors. Such groups, for whom culturally and contextually appropriate interventions are especially needed, include, but are not limited to, gay men of color, commercial sex workers, the transgendered, women, adolescents, the homeless, the chronically mentally ill, and drug users.**

RESEARCH APPROACHES:

- Support research to develop behavioral interventions for gay and bisexual men of color who combine drugs as well as alcohol with sexual behavior.
- Support research to develop culturally focused outreach-based prevention activities for young ethnic minority transgender individuals.
- Encourage and support innovative research on interventions for homeless and chronically mentally ill persons.
- Encourage and support research to identify and address community perceptions of drug abuse and the role of these perceptions in enhancing or limiting community-based interventions.
- Encourage studies designed to establish the efficacy of culturally specific AIDS prevention strategies in drug treatment and community settings.
- Develop approaches that are culturally sensitive and linguistically appropriate to reach persons in different racial and ethnic minority groups.
- Encourage and support studies that assess and address the impact of comorbid conditions upon treatment readiness, long-term recovery, and adoption of safe behaviors.
- Encourage innovative research that utilizes peer-driven interventions to promote behavioral change among drug and alcohol abusers.

PRIORITY FOR FUTURE RESEARCH:

- **Identify and address gaps in care, treatment, and research manifested by the differentials in access to care and in HIV-associated morbidity and mortality in majority and minority HIV-infected communities.**

RESEARCH APPROACHES:

- Encourage community-based outreach projects that target medically underserved ethnic and minority populations and that provide avenues for ongoing community input.
- Encourage and support research that tests and evaluates the combination of drug treatment and primary health care onsite for alcohol- and drug-abusing populations.
- Encourage and support research that elucidates factors such as alcoholism that result in progression of comorbidities such as hepatitis C, and that modify response to therapy.
- Investigate alternative support structures designed to increase adherence and improved health outcomes, especially for the homeless and the chronically mentally ill.
- Encourage multidisciplinary research to explore, identify, and define the cultural, socioeconomic, racial, and other barriers for providers and patients in the therapeutic relationship.
- Conduct research to develop community-level interventions designed to identify and address the macrostructural forces that undermine or enhance participation in care.

PRIORITY FOR FUTURE RESEARCH:

- **Identify, define, and address the infrastructural, technical, methodological, and sociocultural needs of communities of color for clinical trial participation.**

RESEARCH APPROACHES:

- Support innovative and culturally sensitive research that focuses upon increased minority participation and retention in clinical trials.
- Encourage ongoing multidisciplinary research that identifies and addresses the cultural, economic, and individual barriers to participation in clinical research.
- Support research to develop novel methodologies that utilize community-based agencies or centers for research information dissemination, recruitment, and participation.
- Encourage and support programs that train research scientists in the sociocultural, anthropological, and economic issues that potentially confound clinical trials for racial and ethnic minority populations.

PRIORITY FOR FUTURE RESEARCH:

- **Support and expand programs that train racial and ethnic minority investigators in the areas of behavioral and social science, clinical research, and basic science to increase the number of investigators trained and funded to successfully complete such research.**

RESEARCH APPROACHES:

- Develop culturally competent training programs for minority HIV specialists, to include an awareness of cultural issues, as well as responsiveness to specific cultural needs in all aspects of organizational behavior, staff composition and training, and culturally appropriate language in the development of training materials and manuals.
- Develop and expand existing infrastructure within minority communities to disseminate AIDS prevention, treatment, and research information.
- Focus on development of a collaborative relationship between the Historically Black Colleges and Universities (HBCUs), as well as other established centers of higher education for racial and ethnic minorities, for the recuitment of minority investigators and physicians to address minority-specific research and therapeutic considerations.
- Provide widespread dissemination of information on existing opportunities for minorities in biomedical research to ethnic minority communities and organizations and HBCUs, as well as monitor the effectiveness of the techniques used to disseminate such information.
- Strengthen and enhance collaborations with other Department of Health and Human Services agencies to expand existing infrastructures within minority communities to disseminate AIDS treatment and research information efficiently and rapidly to the large numbers of special populations at risk.

AREA OF SPECIAL INTEREST:

Training, Infrastructure, and Capacity Building

AREA OF SPECIAL INTEREST:

Training, Infrastructure, and Capacity Building

SCIENTIFIC ISSUES

The National Institutes of Health (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 increased 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. 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, 115 professionals have been attracted to NIH as a result of loan repayment benefits, with more than half remaining longer than their contractually obligated period. This program continues to attract qualified researchers to NIH.

For the past 10 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 realistically translate 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 research cooperation.

AITRP is active in 100 developing countries, with activities 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 1,500 foreign health scientists in the United States. To facilitate return to their home countries, the program includes an in-country research component, which provides support for "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 collaborator'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.

Future needs in building research capacity include (1) ensuring that every major NIH research effort in a developing country also has the capability to provide in-country research support; (2) further enhancing research capacity in those parts of the world anticipated to be most affected by HIV/AIDS in the future; (3) strengthening developing country capacity in such related areas as biomedical research ethics and medical informatics; and (4) providing opportunities for U.S. investigators to obtain the benefits of research experiences in developing countries early in their research careers.

The National Institute of Mental Health (NIMH) currently fully supports 32 research training programs that are focused exclusively on issues of HIV infection and AIDS and partially supports 11 other research training programs to allow components of the programs to focus on HIV infection

and AIDS. The research emphasis of these programs includes basic behavioral and social science, biopsychosocial and neuropsychological science, prevention and intervention science, and health services research. In addition, the NIMH AIDS Research Center in San Francisco supports an international scholar training program.

To address the relationship between drug abuse and the spread of HIV, the National Institute on Drug Abuse (NIDA) has taken steps to diversify the expertise of researchers in this area so that future researchers will possess a broad array of biological and behavioral research skills. NIDA's research training program supported 399 predoctoral and postdoctoral investigators through individual and institutional awards in 1999. Spanning basic, clinical, behavioral, and epidemiological research areas, 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 increase the cadre of new investigators in needed research areas, including HIV/AIDS. For example, NIMH and NIDA have a small-grants program known as 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 the opportunity to conduct HIV/AIDS studies and collect pilot data that are needed to compete for regular research grants at NIH. Other Institutes are also exploring different 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.

SUPPORT OF ANIMAL FACILITIES

The National Center for Research Resources (NCRR) and the National Cancer Institute (NCI) have several successful programs designed to produce primate models for use in the evaluation of potential SIV/HIV vaccines and to ensure adequate supplies of these animals. These programs include the Specific Pathogen Free Rhesus Biomedical Research Colonies Program for the SIV/macaque model system and the successful Chimpanzee Biomedical Research Colonies Program for AIDS studies. NCI produces in large scale and maintains the viral stocks for 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 continues 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 type of research. Future plans include the use of this primate colony to evaluate the efficacy of HIV-specific monoclonal antibody preparations.

INTRAMURAL AND EXTRAMURAL RESEARCH SITE INFRASTRUCTURE

NCRR, through the General Clinical Research Centers (GCRCs), provides research infrastructure for multidisciplinary studies on both children and adults. Specifically, the GCRCs provide patient research facilities, computerized data management and analysis, and specialized laboratories—as well as research nurses, dietitians, and biostatisticians—for the translation of 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 Research Centers in Minority Institutions (RCMI) program provides for the development of biomedical research infrastructure at minority institutions. Awards previously provided through this program have resulted in infrastructure development at three minority institutions, which enabled them to compete successfully for funding as AIDS Clinical Trials Group (ACTG) clinical trial sites.

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

NIH supports Centers for AIDS Research (CFARs) for the purposes of providing infrastructure and promoting 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 collaborations. 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 facilitating the understanding of HIV-related pathophysiology at a molecular level and 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 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 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 Brookhaven National Laboratory, which is a repository for the three-dimensional coordinates of all proteins whose structures have been determined. Specific drugs are being developed on the basis of known molecular structures to block virus infection and reproduction and provide new therapies for HIV/AIDS and its complications.

The use of the Internet has brought many extraordinary benefits to biomedical research, including AIDS-related research. Over the last 2 years, Internet use by the biomedical research community has increased exponentially. NLM's transition to 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 Internet infrastructure and training to easily access relevant research information, and to contribute new information to the growing AIDS-related databases. This still can be a considerable challenge for researchers in remote, rural, or underserved communities. And even for researchers in major urban biomedical facilities, Internet access can be problematic due to 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 development of the Next Generation Internet (NGI). The NGI is intended to 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 interchange of biomedical information nationally and throughout the world. To accelerate the pace with which health-related institutions become part of the electronic information web, NLM is offering grants to support institution-wide Internet connections.

NLM also is supporting the implementation of current Internet technology in areas that lack these capabilities and where there are significant at-risk populations. This 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 to 16 tribes and Native villages in Alaska, Idaho, Montana, Oregon, and Washington in connecting to the Internet. Native Americans are considered to be at high risk for HIV/AIDS. The aim of this connectivity is to provide access to biomedical research and health care information, including AIDS-related information, thus minimizing isolation and improving access to remote social, health, and research resources. NLM is supporting 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 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.

Repositories play an important role in providing resources for basic science research. 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 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 cohort and 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 Tissue and Biological Fluids Bank of HIV-Related Malignancies 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 level.
- 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 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 upon 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 that will increase their capacity to participate in biomedical and behavioral science research.

OBJECTIVE:

Establish appropriate infrastructure for the conduct of 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.
- Ensure adequate facilities and resources as well as appropriate ethical and procedural training to study HIV animal models.
- Expand the production of genetically defined 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.
- Continue the Research Facilities Infrastructure Program (RFIP) and the General Clinical Research Centers (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).

- Continue AIDS-related tumor registries and linkages of AIDS and cancer registries for 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 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, data collection protocols, and statistical analysis tools that are easy to use, are adaptable to different settings, facilitate efficient statistical analysis and report generation, and enhance standardization when appropriate.

AREA OF SPECIAL INTEREST:

Information Dissemination

AREA OF SPECIAL INTEREST:

Information Dissemination

SCIENTIFIC ISSUES

Effective information dissemination approaches are integral to HIV prevention and treatment efforts. The changing demographics of the epidemic provide challenges to disseminating HIV research results to communities at risk, including women and minorities. An additional challenge is to provide the information in formats that are useful to both health care providers and patients. Treatment guidelines for the use of new and complex antiretroviral regimens are being continually updated. Understanding of these guidelines and adherence to the regimens are critical. 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*, which is updated annually, is 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 National Institutes of Health (NIH) and Public Health Service (PHS) sites and resources.

CLINICAL ALERTS

Since 1991, NIH has used a dedicated system of electronic and print notification, collectively known as Clinical Alerts, to rapidly disseminate information critical to patient care—such as results of HIV-related clinical trials—to health care professionals, the news media, and the public. This

mechanism allows information with immediate clinical relevancy to be expeditiously reviewed and widely distributed prior to publication in a peer-reviewed medical journal. Clinical Alerts are available online on the MEDLARS system; provided for dissemination in academic health science centers and more than 3,000 hospitals; and available via Internet. The National Network of Libraries of Medicine helps ensure wide dissemination of the Clinical Alerts.

TREATMENT GUIDELINES

Access to clinical care guidelines, standards of care, and results of state-of-the-art meetings is critical for physicians and patients. For example, NIH disseminates guidelines on opportunistic infection (OI) prophylaxis, guidelines on *Pneumocystis carinii* pneumonia (PCP) prophylaxis for children with HIV, recommendations for the use of AZT to prevent perinatal HIV transmission, the *Report of the NIH Panel to Define Principles of Therapy of HIV Infection*, and the Department of Health and Human Services (DHHS) *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents*. To ensure the widest possible dissemination of the guidelines through the most effective mechanisms, NIH supports and participates in the DHHS Working Group on Information Dissemination. The guidelines are available in print form and on the Internet Web site of the HIV/AIDS Treatment Information Service (ATIS) (see page 149).

ELECTRONIC INFORMATION RESOURCES

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://igm.nlm.nih.gov**

These databases are available free of charge to users worldwide and include citations (with abstracts when available) to journal articles, books, and audiovisuals; abstracts from many major AIDS-related meetings and conferences (AIDSLINE); descriptions of clinical trials and the agents studied in those trials (AIDSTRIALS/AIDSDRUGS); and international, national, and State organizations involved in AIDS (DIRLINE). NIH has expanded the AIDSLINE database with the addition of abstracts from many scientific meetings—including the Conference on Retroviruses and Opportunistic Infections and the International Conference on AIDS—and citations, with brief summaries, to substantive articles from more than 20 newsletters.

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. The Web site also provides links to other databases and includes a page of HIV vaccine 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), 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

A critical challenge is to provide accurate and up-to-date HIV/AIDS prevention and treatment information to communities at risk, including underserved communities, women, and communities of color. NIH supports a number of ongoing projects and has initiated a number of new projects 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 Program

OAR established the Regional Technology Transfer Program in 1990 to deliver new research information to underserved and disadvantaged communities. For example, workshops for HIV-infected individuals and health care providers have been sponsored by OAR in collaboration with regional organizations in Puerto Rico and with organizations serving Native Americans. Upcoming workshops will focus on minority communities in the Virgin Islands, on Asian/Pacific Islander communities in the United States, and on issues for individuals providing health care to prison populations.

Community Regional Training and Research Forum Program

OAR initiated this program in 1998 to provide information to individuals working on a community level, such as counselors, case workers, and health care providers, as well as patients and their families. The program is now combined with a project of the National Minority AIDS Council (NMAC) that also provides technical assistance and care information. Forums have been held in more than 15 cities in collaboration with local community organizations, and a dozen more are planned over the next year, focusing on minority communities.

Collaboration with Other Agencies and Organizations

OAR and many of the NIH Institutes have initiated collaborative programs with other agencies and organizations. For example, OAR and NMAC are collaborating on a project to provide Internet access to minority communities by providing computers to community sites and through Webcasts of various meetings, including the U.S. Conference on AIDS. A video entitled *HIV/AIDS and African Americans* was developed in collaboration with NMAC, and more than 6,000 copies have already been distributed. NIH provides support to the U.S. Conference on AIDS, the largest national meeting focusing on AIDS in minority communities. OAR developed a computer kiosk that provides easy access to AIDS information. In collaboration with HRSA, these kiosks will be provided to HBCUs through the HRSA AIDS Education and Training Center (AETC) program. In conjunction with the DHHS HIV Prevention Conference this year, OAR is sponsoring a Training and Career Development Workshop on HIV Prevention Research For and By Racial and Ethnic Minorities. This

workshop is aimed at increasing the number of minority scientists engaged in community-based HIV prevention research.

INTERNATIONAL ISSUES

NIH recognizes the critical importance of disseminating research and treatment information, patient management guidelines, and research results that impact on the care of HIV-infected individuals in diverse international settings. The existing computerized databases from NLM, as well as from ATIS and ACTIS, are available worldwide. However, a number of special issues remain, including the lack of computer capabilities and access to journals in many countries, language barriers between the United States and other countries (as well as dialect and cultural barriers within countries), and the lack of resources to provide a standard of care comparable to that available in the United States.

To address this issue, future NIH-supported international research and training efforts will include mechanisms to facilitate access of foreign collaborators to current published literature and specific plans for in-country dissemination of research results through exchange of newsletters among grantees, in-country meetings for scientists and trainees, and advanced electronic technology for dissemination of new information as well as less formal exchange and dialogue among sites.

NIH convenes and/or cosponsors forums for U.S. and international agencies to present and discuss emerging HIV/AIDS trends and correlates, develop research agendas, and discuss implications of research results. This information is then distributed to prevention, treatment, and public health agency representatives, researchers, and policymakers.

CONCLUSION

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 upon 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.

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.
- Utilize computer and other information dissemination technology (including the World Wide Web) to disseminate up-to-date HIV/AIDS information.
- Expand access to and education about current treatment and patient management guidelines, including state-of-the-art care and information on clinical trials using multiple technologies such as, but not limited to, 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.
- Improve outreach and support access to HIV/AIDS information resources 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.
- Develop mechanisms to rapidly disseminate information on research in progress to the research community in order to increase collaboration, reduce duplication of effort, and enhance the discovery and development process.
- 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 incidence data.

- Widely disseminate information concerning specimen repositories, including existing repositories, specimens available, and relevant information concerning cohorts, contact people, 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, 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 between 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.
- Coordinate collaboration among all ICs in the provision of information about their clinical trials for HIV/AIDS to ACTIS.
- 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 and use 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.
- Work with other DHHS agencies, including HCFA, and with the private sector in the development of clinical standards of care for determining guidelines for reimbursement.
- 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.

- Expand collaboration to include academic, medical, and other communities, as appropriate, in the dissemination of NIH HIV-related reports.
- Enhance research, treatment, and prevention efforts through requirements in appropriate funding proposals to establish communication and coordination.

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:

HIV/AIDS Funding By NIH Institute and Center

HIV/AIDS Funding By NIH Institute and Center
(dollars in thousands)

Institute/Center	FY 1998 Actual	FY 1999 Estimate	FY 2000 Estimate
NCI	$221,473	$235,669	$240,124
NHLBI	63,487	64,511	66,043
NIDCR	13,493	17,959	18,397
NIDDK	15,353	17,884	18,322
NINDS	26,294	29,433	30,154
NIAID	703,204	805,943	825,294
NIGMS	28,694	31,850	32,630
NICHD	67,485	75,745	77,599
NEI	9,655	10,351	10,604
NIEHS	6,552	7,023	7,194
NIA	1,910	2,068	2,118
NIAMS	4,391	4,683	4,797
NIDCD	1,838	1,942	1,874
NIMH	100,690	114,359	117,101
NIDA	167,093	189,176	193,505
NIAAA	14,368	16,195	16,581
NINR	5,543	6,244	6,395
NHGRI	3,047	3,989	4,086
NCRR	82,223	96,182	98,435
NCCAM	—	1,030	1,030
FIC	10,591	12,481	12,776
NLM	3,371	4,114	4,211
OD	40,459	43,493	44,556
B&F	11,600	6,100	—
TOTAL	**$1,602,814**	**$1,798,424**	**$1,833,826**

APPENDIX C:

FY 2001 OAR Planning Groups

FY 2001 OAR PLANNING GROUPS

FY 2001 NATURAL HISTORY AND EPIDEMIOLOGY PLANNING GROUP

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APPENDIX E:

NIH AIDS Research Program Evaluation Working Group Report: Implementation

NIH AIDS Research Program Evaluation Working Group Report: Implementation

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 and OAR staff, should familiarize their IRG members with OAR- and ICD[1]-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 *ad hoc* members, and exercising flexibility on the term limits for IRG participation.		✓		

NIH AIDS Research Program Evaluation Working Group Report: Implementation

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

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:		✓		
	• The basic biology and development of human immunocompetent cells and of the unique aspects of the physiology of the human immune system.	✓			
	• 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

III. RESEARCH ON THE HUMAN IMMUNE SYSTEM (CONT'D)				
Recommendation	Completed	Ongoing	Planned	Comment (see note)
• Why normal replacement mechanisms are unable to restore a functional immune system in infected individuals.	✓			
• 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

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.		✓		

NIH AIDS Research Program Evaluation Working Group Report: Implementation

VII. RESEARCH ON OPPORTUNISTIC INFECTIONS				
Recommendation	Completed	Ongoing	Planned	Comment (see note)
VII.1 Reinvigorate the basic science research effort on AIDS-associated OIs, emphasizing 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 *ad hoc* 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 *ad hoc* advisory group should work with OAM[2] 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 *ad hoc* 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.				*

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 *ad hoc* 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.		✓		

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Recommendation	Completed	Ongoing	Planned	Comment (see note)
XI. REPOSITORIES AND DATABASES				
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.	✓			*

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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] NIH Institutes, Centers, and Divisions; now Institutes and Centers (ICs).

[2] Office of Alternative Medicine; now the National Center for Complementary and Alternative Medicine (NCCAM).

NIH AIDS RESEARCH PROGRAM EVALUATION WORKING GROUP REPORT: OAR COMMENTS

I.1

Between 1994 and 1998, the proportion of funds allocated to unsolicited investigator-initiated research increased by 77 percent. OAR continues to stress the importance of investigator-initiated research.

I.2

NIH continues to support the principle of separation of scientific review from program prioritization, which has traditionally been the role of ICD program staff and advisory councils. However, in recognition of the relevance of scientific review to program priority, DRG, OAR, and the ICs have begun to work together to improve communication and encourage mutual awareness.

I.6

The instructions for preparing applications for 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."

I.9, I.10, I.11, I.12, and I.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.

I.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 BSSR Study Sections as part of integrating NIMH and NIDA 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 and V.4

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. The Program Announcement (PA) that was developed using this approach was issued, and applications have been reviewed. Funding will be awarded through a cooperative agreement later this year.

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.

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 F:

List of Acronyms

LIST OF ACRONYMS

ACTG	AIDS Clinical Trials Group
ACTIS	AIDS Clinical Trials Information Service
AETC	AIDS Education and Training Center, HRSA
AIDS	acquired immunodeficiency syndrome
AITRP	AIDS International Training and Research Program, FIC
ATIS	HIV/AIDS Treatment Information Service
AZT	azidothymidine (zidovudine)
B/START	Behavioral Science Track Award for Rapid Transition, NIMH & NIDA
B&F	Buildings and Facilities, NIH
BSSR	Behavioral, Social Science, and Prevention Research
CAB	community advisory board
CAM	Complementary and Alternative Medicine
CBC	Congressional Black Caucus
CDC	Centers for Disease Control and Prevention
CFAR	Center for AIDS Research
CMV	cytomegalovirus
CNS	central nervous system
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)
DTP	Developmental Therapeutics Program, NCI
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
FIRCA	Fogarty International Research Collaboration Award

FY	fiscal year
GCRC	General Clinical Research Center
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HAART	highly active antiretroviral therapy
HBCU	Historically Black Colleges and Universities
HCFA	Health Care Financing Administration
HCV	hepatitis C virus
HHV-8	human herpesvirus-8
HIV	human immunodeficiency virus
HIVNET	HIV Vaccine Efficacy Trials Network, NIAID
HPV	human papillomavirus
HRSA	Health Resources and Services Administration
IATAP	Intramural AIDS Targeted Antiviral Program
IC	Institute and Center
IDU	injecting drug user
IHS	Indian Health Service
IRG	Initial Review Group (review unit within CSR)
JCV	JC virus
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma herpesvirus
LRP	Loan Repayment Program, NIH
MAC	*Mycobacterium avium complex*
MDR-TB	multiple drug-resistant TB
MHC	major histocompatibility complex
NAFEO	National Association for Equal Opportunity in Higher Education
NAVTF	National AIDS Vaccine Task Force
NEP	needle exchange program

NGI	Next Generation Internet
NHL	non-Hodgkin's lymphoma
NLM	National Library of Medicine, NIH
NMAC	National Minority AIDS Council
NMR	nuclear magnetic resonance
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
PA	Program Announcement
PACTG	Pediatric AIDS Clinical Trials Group
PAHO	Pan American Health Organization
PBMC	peripheral blood mononuclear cell
PCP	*Pneumocystis carinii* pneumonia
PDQ	Physician Data Query
PHS	Public Health Service
PI	principal investigator
PML	progressive multifocal leukoencephalopathy
R01	investigator-initiated award (R01 grant)
RCMI	Research Centers in Minority Institutions
RFA	Request for Applications
RFIP	Research Facilities Infrastructure Program
RML	Regional Medical Library
RNA	ribonucleic acid
RPRC	Regional Primate Research Center
RT	reverse transcriptase
RT-PCR	reverse transcription-polymerase chain reaction

SAMHSA	Substance Abuse and Mental Health Services Administration
SBIR	Small Business Innovative Research
SCID	severe combined immunodeficiency
SHIV	simian HIV
SI	synctia-inducing
SIV	simian immunodeficiency virus
STD	sexually transmitted disease
TB	tuberculosis
3TC	lamivudine
TRWG	Therapeutics Research Working Group
UNAIDS	United Nations Joint Programme on AIDS
WHO	World Health Organization
ZDV	zidovudine

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