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National Institutes
of Health
Fiscal Year 2000
Plan for HIV-Related
Research

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

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OFFICE OF AIDS RESEARCH, NATIONAL INSTITUTES OF HEALTH**

Foreword

As the new Director of the Office of AIDS Research (OAR), I am pleased to present the National Institutes of Health Fiscal Year 2000 Plan for HIV-Related Research, our plan for the millennium. The development of this comprehensive plan represents a collaborative effort among hundreds of individuals: NIH Institute Directors; NIH scientists and program staff, non-Government experts, including scientists from academia, foundations, and industry; and AIDS community representatives. I am grateful for their participation and contributions to this important effort. I particularly thank my predecessor, Dr. William Paul, who conceived and initiated the OAR's planning process, which is a true model of inclusiveness and partnership between the Government and the public in setting research priorities. My thanks as well to Dr. Jack Whitescarver, my Deputy Director, who served as the Acting Director of OAR during the development of this FY 2000 Plan.

The Plan serves as the framework on which the development of the budget is based, as the basis for the determination of the use of AIDS-designated dollars, and as a tracking and monitoring mechanism for those expenditures. As such, the Plan defines those research areas for which AIDS-designated funds may be allocated.

The legislative authorities provided to OAR for planning and budgeting AIDS research make it possible to set new scientific priorities and to reshape and restructure the research enterprise in response to new scientific opportunities and needs. The Nation has invested major resources in the NIH AIDS research program. I believe that the steps taken by OAR over the past few years, and the priorities established in this Plan, demonstrate that the Nation's investment in AIDS research is indeed well spent and leading us toward our goal of preventing and curing AIDS.



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

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Legislative Mandate

The National Institutes of Health Revitalization Act of 1993 (Public Law 103-43) strengthened the Office of AIDS Research (OAR) and provided that the Director of OAR “shall plan, coordinate and evaluate research and other activities conducted or supported” by the 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 conducted by the agencies; provides for research that is supported 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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The Exploding Global HIV/AIDS Pandemic

The World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) recently released new data demonstrating that the deadly march of the pandemic had been underestimated. It is now estimated that 2.5 million people worldwide died of AIDS in 1998. Nearly half of the adult deaths were among women. The new report estimates that the number of people now living with HIV has grown to 33.4 million, an increase of 10 percent in just one year. More than 95 percent of cases occur in the poorest areas of the world that are

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 <i>Women</i>	5.2 Million <i>2.1 Million</i>	32.2 Million <i>13.8 Million</i>	2.0 Million <i>900,000</i>	10.7 Million <i>4.7 Million</i>
Children	590,000	1.2 Million	510,000	3.2 Million
Total	5.8 Million	33.4 Million	2.5 Million	13.9 Million

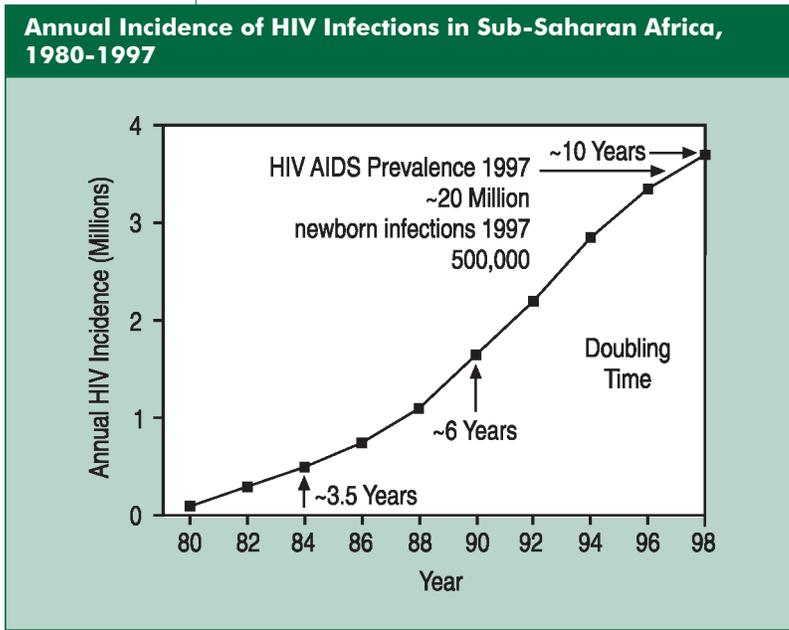
UNAIDS, December 1998.

the least equipped to control or treat a rampant new infectious and fatal disease, and more than 95 percent of deaths have occurred in those developing countries. The report states, “Whether measured against the yardstick of deteriorating child survival, crumbling life expectancy, overburdened health care systems, increasing orphanhood, or bottom-line

losses to business, AIDS has never posed a bigger threat to development.” A recent United Nations study estimates that in some African countries, HIV infection rates are as high as 20-25 percent of adults. In other parts of the world as well, including the Indian subcontinent and southeast Asia,

the epidemic continues to rage. New epidemics are emerging and rates of HIV and AIDS are increasing in other parts of the world, such as Eastern Europe and China.

The reality of the pandemic is that it consists of a number of quite distinct subepidemics. In the United States, while the *overall* death rate due to AIDS has declined, HIV incidence rates have not changed. Moreover, new HIV infections and AIDS-



UNAIDS, December 1998.

related deaths continue to increase dramatically in many subpopulations, particularly women and minorities. AIDS continues to affect those most disenfranchised in our society—the poor, the homeless, and those with addictive or mental disorders. AIDS cases are rising among women, racial/ethnic minorities, heterosexuals, adolescents, and drug users. AIDS remains a leading cause of death among Americans 18 to 45 years old. The Centers for Disease Control and Prevention (CDC) recently announced that AIDS is increasing in another group in our nation—people over 50 years of age. While the epidemic has stabilized among white gay men overall, it is increasing among younger homosexuals. These changes in the epidemic demand careful consideration in planning our research agenda, since different prevention and intervention strategies must be applied to each subepidemic.

By any criteria, AIDS must be considered the great plague of the 20th century. The transmissible nature of HIV makes it radically different from nontransmissible diseases such as heart disease and cancer. The epidemic’s spread around the globe has been rapid. The disease has already caused nearly 14 million deaths worldwide since its appearance in the late 1970s. With a cumulative total of 47 million infections and new infections occurring at the rate of more than 250,000 monthly, the actual magnitude of the

pandemic is truly profound. The transmissibility of HIV—between individuals and across borders and populations—is what most defines the global pandemic and makes it imperative that the United States help address prevention and treatment needs worldwide. The transmissibility of the infection means that there is the potential for unlimited spread. But it also means that there is the possibility for dramatic reductions in new infections—and ultimate control of the pandemic—in a way that will never be possible for noninfectious diseases. In response to this pandemic, the National Institutes of Health (NIH) has developed a comprehensive biomedical and behavioral research program to better understand the basic biology of HIV, develop effective therapies to treat it, and design interventions to prevent new infections from occurring.

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Overview of Research Priorities

The legislative mandate of the Office of AIDS Research (OAR) requires the OAR to set the scientific agenda for AIDS research at the NIH and to determine the relative distribution of effort across a wide variety of research goals. The priorities of the FY 2000 plan and budget reflect a slightly different perspective from years past, a perspective framed on the epidemic itself, or more specifically, on the many subepidemics that underlie it. As the epidemic has shifted over the past several years, with dramatic increases in infections among women and minorities, it is clear that the research plan and budget priorities must be directed to address these emerging subepidemics. These needs were clearly articulated throughout the year's planning process. The new Director of OAR, Dr. Neal Nathanson, arrived after the formal FY 2000 planning process had been completed, but at the beginning of the budget development process. Dr. Nathanson proposed that the NIH frame our research agenda and budget with a particular focus on the demographics of the epidemic and to "intervention research" strategies for these populations, determining where and how research can intervene, providing the tools needed to reduce transmission and the burden of disease.

TREATMENT

Ground-breaking research in basic biology has led to a revolution in drug design and diagnostic methodologies that are benefiting the fight not only against AIDS, but also against other diseases. In the case of AIDS, this basic research has been the foundation for the development of medications that are extending the quantity and quality of life for many HIV-infected individuals. The most dramatic development in the last 2 years has been the introduction of highly active antiretroviral treatment (HAART),

combinations of therapy that include protease inhibitors. This treatment has reduced viral burdens to minimal levels, arrested the progression to AIDS, sharply diminished the incidence of opportunistic infections and malignancies, and significantly reduced death rates.

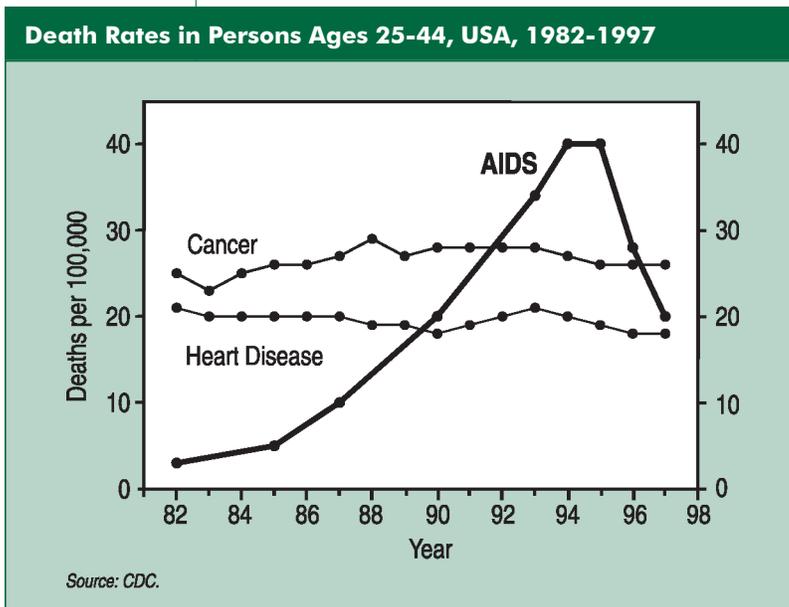
Nevertheless, many problems remain. Chief among these is that even when viral burden is greatly reduced, the virus has not been eliminated and may still be transmissible. However, evidence now exists from places as diverse

as urban London and rural Alabama that some individuals on HAART have lapsed into unsafe sexual behavior believing they are less infectious. The implications of this for increased HIV transmission are serious. In addition, we do not know how long the benefit of HAART will last or whether immune function of treated individuals can be restored without additional interventions.

There are many for whom

the new drug regimens have not been effective or for whom the side effects are not tolerable. A substantial proportion of patients cannot maintain long-term drug adherence in spite of effective therapeutic responses, and drug-resistant viral mutants are beginning to emerge in some instances. Complications of long-term therapy are now being identified. Many patients, particularly in minority communities, simply do not have the means to access these life-extending therapies.

It is critical to develop simpler, less toxic, cheaper drug regimens, new generations of antiviral drugs directed against different viral components, and therapies to reconstitute immune function in treated patients. It is also critical to develop more effective interventions to enhance access and adherence to complex therapeutic regimens. Each of these problems poses an urgent challenge for ongoing research, and NIH is poised to meet these challenges.



STORY OF DISCOVERY

Studies of Latent HIV Infection Lead to Development of Promising New Therapeutic Strategy

Major advances in basic research on HIV have led to the development of highly sophisticated research tools that allow investigators to identify the presence of minute amounts of HIV in the cells of infected individuals. The application of these tools enabled National Institute of Allergy and Infectious Diseases (NIAID) intramural investigators and two other groups last year to simultaneously report the discovery that HIV establishes a latent infection in resting or nonactivated immune cells in individuals on HAART. Furthermore, they found that these cells, when activated to proliferate in cell culture, were able to produce infectious virus. Further studies by the same investigators found that the pool of latently infected immune system cells is established during the acute phase of HIV infection, within weeks of exposure. Latent infection occurs even if a patient is treated expeditiously with HAART. The investigators analyzed blood samples from 10 patients who were treated with potent combination therapy between 10 days and 4.4 months following the initial onset of acute symptoms of HIV infection. All of the patients responded positively to therapy, including 5 individuals whose viral load dropped to undetectable levels. Nevertheless, the researchers found evidence of latent HIV infection in the blood samples of all 10 patients. Interestingly, the researchers found that neither the duration of therapy nor the speed with which therapy was initiated correlated with the number of latently infected immune cells in a patient's blood. The discovery of latent HIV infection presented a daunting challenge to investigators aiming to eliminate HIV from a person's body, but further research on this latent reservoir led to the development of innovative strategies to overcome this obstacle.

In another study by the same intramural team, latently infected "resting" immune cells were found to produce virus when exposed in cell culture to interleukin 6 (IL-6), tumor necrosis factor-alpha, and interleukin 2 (IL-2), three stimulatory molecules or "cytokines" found in the normal environment of the lymph node. Subsequent addition of the drugs that comprise HAART inhibited viral reproduction. This effect was seen in latently infected cells purified from patients on HAART as well as HAART-naive patients. This finding helped explain the resurgence of HIV viral load in individuals who discontinue HAART because of toxicity or for other reasons. The researchers hypothesized that administering these stimulatory cytokines to HIV-infected individuals could induce the latently infected cells to actively produce virus, ultimately killing these cells directly or targeting them for clearance by the immune system. Simultaneously treating the patients with HAART would keep HIV replication to a minimum. Ideally, immune activation combined with HAART would eliminate the latent HIV reservoir or at least reduce it to a level that could be controlled by the immune system. If such a strategy proved effective, preventing progression to AIDS by keeping HIV levels extremely low would again be a reasonable goal.

Recent, as yet unpublished results of a clinical study by the same NIAID team indeed suggest that combining immune activation strategies with HAART has a potent effect on latent HIV infection. In a study of 26 patients, 12 receiving HAART and 14 receiving HAART plus the cytokine IL-2 as an immune stimulator, researchers analyzed the patients' blood samples for the presence of latently infected resting immune cells. After searching millions of cells with sensitive laboratory procedures, the researchers thus far have been unable to find HIV capable of replicating in blood samples from patients on HAART plus IL-2. Furthermore, in one patient, replication-competent HIV could not be isolated from lymph node tissue, which is known to be a key site of sequestered HIV infection. Studies are ongoing to expand on these findings and determine the precise mechanisms involved.

PREVENTION

Important advances have also been made in diagnosis and prevention of perinatal HIV infection. An NIH-funded clinical trial (ACTG 076) showed that therapeutic intervention protocols can reduce perinatal transmission by approximately 70 percent in countries where AZT (azidothymidine; generic name zidovudine) is affordable. In addition, a recent trial of a modified, much less expensive protocol for potential use in developing countries demonstrated the ability to reduce transmission by 50 percent. To reduce transmission further, additional research is necessary, including studies to better understand the timing, mechanisms, and risk factors of perinatal transmission; whether specific strains are more likely transmitted; the potential benefit of cesarean section; and development of newer therapeutic regimens and immunotherapy. The virtual elimination of perinatal transmission in our nation and the world is a goal that must be vigorously pursued.

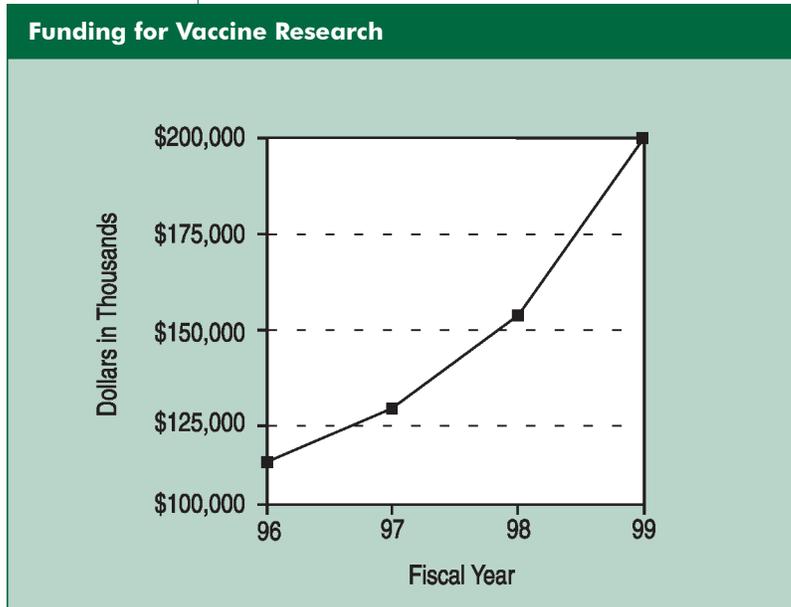
While the AIDS epidemic in the United States has stabilized among white gay men overall, it is increasing among younger men who have sex with men, including men of color. It is crucial to develop interventions to address the specific behavioral and psychosocial risk factors prevalent among communities of young gay men.

Drug users and their sex partners are the fastest growing segment of AIDS cases in the United States and many other countries. High priority must be given to research to understand the phenomenon of addiction itself, as well as the complex interaction of alcohol, drug use, and poor impulse control. Scientifically based interventions have been demonstrated to alter sexual and drug-using behavior and reduce the risk of transmission among a number of population groups. But we are still far from realizing the full potential of such prevention research on a global scale.

VACCINES

Vaccine research remains one of the highest research priorities. The toll of the epidemic in poorer countries where therapeutic and prevention interventions are unavailable or unaffordable, as well as in industrialized parts of the world, dictates the important emphasis on vaccine development. A safe and effective vaccine is the critical missing element in our armamentarium for the prevention of HIV and ultimate control of the pandemic. The changes that have been implemented in this area over the past few years have enormous potential significance, not only for AIDS but for other diseases as well, as progress made in the development of an AIDS vaccine will certainly have implications for vaccines against other life-threatening illnesses. The President also has made the discovery of an AIDS vaccine a national research priority.

To address the scientific obstacles and facilitate AIDS vaccine development, NIH continues to increase support for a broad program encompassing basic, preclinical, and clinical vaccine research on candidate vaccine products.



With a second year of targeted funding from the OAR, NIAID, in collaboration with the AIDS Vaccine Research Committee (AVRC), headed by Dr. David Baltimore, identified several new topic areas for the Innovative Vaccine Grants Program. This program provides 1- or 2-year funding to investigators to explore new concepts in basic research related to AIDS vaccines. It is anticipated

that some of these projects will continue and expand into larger competitive vaccine projects. In addition, a cross-Institute NIH Vaccine Research Center (VRC) has been initiated by focused staff discussions, and joint vaccine research will be funded through NIAID and National Cancer Institute (NCI) intramural programs. Plans for the building to house the VRC have moved forward rapidly, and construction now is under way, with occupancy projected by the year 2000.

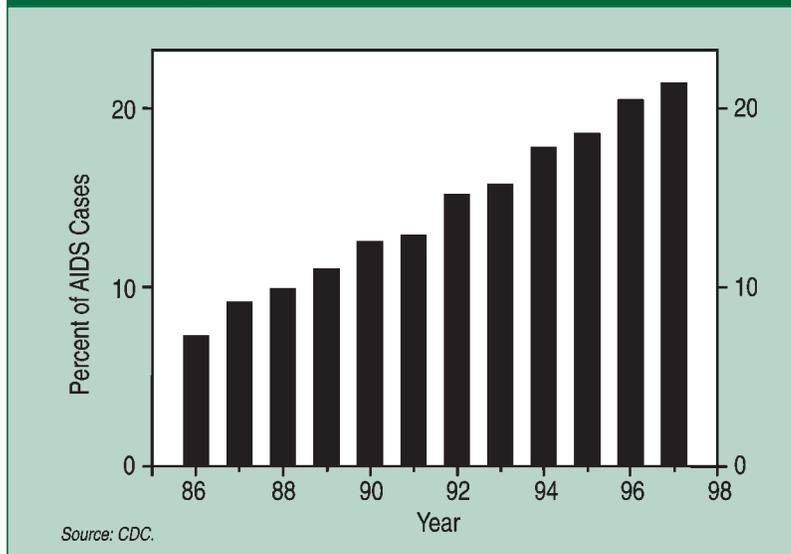
Recent experience has shown that development of an AIDS vaccine is a complex research challenge because HIV is unusually well-equipped to elude immune defenses, as exemplified by its ability to persist in almost all instances and eventually overcome the immune system. Many successful vaccines depend upon their ability to induce neutralizing antibodies, but neutralization of HIV is peculiarly difficult, perhaps because domains on the envelope protein that bind to receptors are shielded by carbohydrate side chains or are only transiently accessible during viral binding to host cells. Unfortunately, the initial attempts to formulate a vaccine, using recombinant technology to express envelope glycoproteins, have yielded products that elicit antibody with little neutralizing capacity and do not stimulate significant cytolytic T lymphocyte (CTL) activity. More promising from an efficacy viewpoint are potential vaccines using attenuated deletion mutants of SIV, the simian counterpart of HIV. However, the first generation

of attenuated mutants that replicate vigorously enough to provide impressive protection also retain residual virulence so that they cannot be considered safe for human trials.

Clearly, it will be more difficult to formulate an AIDS vaccine than was the case for prior vaccines directed against acute viral diseases. The scientific

community must be mustered to make a broad and diverse attack upon this daunting challenge. Vaccine research is needed to attempt to unravel a wide variety of questions about the structure of the virus, its immunogenicity, the protective role of different components of the immune response, the mechanism of viral escape from immune surveillance, and the like. In addition, fundamental work must be done to

AIDS Incidence in Women, USA, 1986-1997



develop and refine a number of potentially effective methods for presentation of HIV antigens, including vectors engineered from a wide variety of viruses, and naked DNA itself. Building on this base, it will probably be important to utilize primate models to elucidate the mechanisms of protective immunity and to screen a multitude of candidate immunogens for the most promising products for clinical trials in humans.

WOMEN AND AIDS

NIH is placing high priority on research to address the dramatic increases in HIV transmission to women, including basic biomedical research related to the etiology and pathogenesis of HIV disease in women. While many of the clinical manifestations of HIV infection in women and men are similar, HIV-infected women also experience some complications that are unique or more prevalent for them, such as vaginal and esophageal candidiasis, chronic herpes simplex infections, and cervical dysplasia. Examples of studies in this area include those characterizing the cells susceptible to infection in the female reproductive tract and studies assessing the influence of hormonal modulation on viral infectivity and vaginal immunity.

AIDS IN MINORITY POPULATIONS

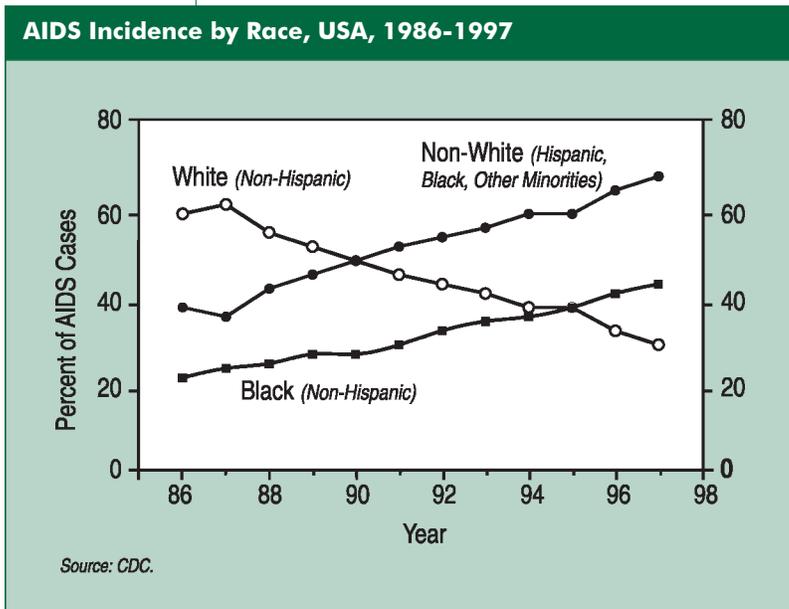
On October 27, 1998, the President announced a major initiative to address the disproportionate increases in HIV infection and AIDS cases in minority

populations. NIH supports a comprehensive portfolio of biomedical and behavioral research aimed at preventing, treating, and controlling HIV infection and its sequelae in minority communities. This Plan reflects and highlights these issues. NIH has for many years taken strong steps to assure minority participation in clinical trials, natural history and epidemiologic

studies, and prevention studies and to assure that the overall research agenda is responsive to the needs of minority communities.

NIH also supports a broad array of behavioral intervention studies with specific focus on African-American populations. These studies are characterizing the disease process in drug users, factors influencing disease progression, consequences

of multiple coinfections, effectiveness of therapeutic regimens, and impact of health care access and adherence to therapeutic regimens on disease outcomes. The development of topical microbicides is a high priority of NIH research, and recruitment for these studies is focusing on minority communities.



Minority Participation in NIH AIDS Clinical Trials: Cumulative Through 1997
 Compared with U.S. Distribution of New AIDS Cases (FY 97)

Group	1996 U.S. Population (256 Million)	FY 97 New AIDS Cases (64,900 Cases)	Clinical Trials (22,600 Subjects)
Black	12.6%	43.3%	39.4%
Hispanic	11.3%	19.6%	22.1%
White	72.0%	35.6%	36.3%
Other	4.1%	1.5%	2.2%

Other: Asian/Pacific Islanders, Native Americans/Alaska Natives.

NIH has established programs and policies specifically designed to recruit individuals from underrepresented racial and ethnic groups into research careers and to build research infrastructure in minority institutions. These programs provide training and research opportunities across the continuum

BASIC SCIENCE

from high school students to independent investigators. NIH also supports activities with the goal of disseminating research information to health care providers serving minority communities as well as directly to individuals at risk. A fact sheet on the NIH projects is included in the appendices.

To ensure the continued growth of a powerful arsenal against HIV, it is imperative that scientists continue to study the pathogenesis of HIV and identify new targets for the design of drugs and vaccines. Design and development of new drugs is based on the study of the fundamental structural properties of the relevant viral targets. The foundation of rational drug design emerged, in large part, from basic research supported by NIH and the pharmaceutical industry over a number of years. Although the potential benefits of this approach to drug development have yet to be fully realized, it will have applications to all aspects of human health and disease. Efforts to develop effective therapies to treat HIV infection and its associated conditions are providing a critical proving ground for the concept of rational drug design and for the refinement and advancement of its methods.

Basic research plays a vital role in the development of interventions to block transmission and slow disease progression in all populations at risk. The research programs of the NIH will continue to support a broad and vigorous program to study life processes, using cutting-edge methods. This area of investigation, driven by investigator-initiated research, has provided the constantly advancing knowledge base that permits the development of new applications for the prevention and treatment of disease.

The challenge of understanding HIV infection and disease also represents an extraordinary example of how the biology of other infectious diseases may be studied in the future. Never before has the behavior of an infectious microorganism within an infected human been examined in such detail. For this type of investigation, new research tools are required to facilitate sensitive, high-resolution analyses. The amount of virus present in an infected person must be determined and its level of replication and consequent damage measured. The need to understand HIV infection has driven technological developments in this area, and much of this effort has been fueled by support provided by NIH.

The powerful tools developed to monitor the location and extent of HIV replication within infected persons have elucidated critically important details of how HIV infection leads to AIDS. Application of these new tools has revolutionized our understanding of the extent of HIV replication that takes place in infected people and how virus replication is directly linked to the destruction of T cells and the resultant compromise of the immune

system. The broad outlines of the pathogenic mechanisms of HIV disease are now known, but the precise details of the process await definition. An improved understanding of these issues is necessary to permit definition of the optimal ways to use therapies to treat the primary HIV infection and its associated opportunistic complications.

Impact of AIDS Research

The Nation's investment in HIV-related research also is providing major benefits in our ability to understand and treat a wide spectrum of other infectious, malignant, neurologic, autoimmune, and metabolic diseases. Basic knowledge of the biology of HIV infection and the processes by which it causes AIDS benefits other areas of basic research including immunology, virology, microbiology, molecular biology, and genetics. Knowledge gained from the study of drugs to treat HIV infection and its complications also has helped establish new approaches for the design and conduct of more rapid clinical studies, as well as those that address the special recruitment requirements of women, minorities, and other underserved populations.

Effective drugs to treat other infectious diseases

The successful development of two classes of drugs that limit the replication of HIV, reverse transcriptase (RT) inhibitors and protease inhibitors, represents a landmark in drug development for the control of viral diseases. As a result, AIDS research has provided a new paradigm for confronting viral diseases in general. Prior to the development of these potent drugs, virtually all efforts to deal with viral diseases involved prevention (using vaccines) or palliation (treating symptoms). Few effective treatments were available for most common viral infections. The impact of the AIDS drug development experience not only benefits development of treatments for other viral diseases, but also will hasten drug development efforts for bacterial, mycobacterial, and fungal diseases.

The drug lamivudine (also known as 3TC), initially developed to treat HIV infection, now has been shown to be the most effective therapy for chronic hepatitis B infection. Prior to its availability, no effective therapies existed, and many infected persons would proceed inexorably to cirrhosis, liver failure, and liver cancer. Lamivudine represents a "lead compound" that should expedite the development of even more effective agents to treat, and perhaps even cure, chronic hepatitis B infections. Experience gained in the course of HIV drug development is being applied to potential therapies for hepatitis C, influenza, and cytomegalovirus (CMV) infection.

New animal models developed in the course of AIDS research will facilitate studies of other infectious diseases.

Advances in methods for drug design

AIDS therapeutic research has demonstrated the importance of rational drug design and has resulted in a new generation of powerful inhibitors of HIV replication. Progress in this area depends on the identification of a promising molecular target for drug therapy, determination of the three-dimensional structure of the target molecule using sophisticated X-ray crystallographic methods, and structure-based drug design aided by the techniques of structural biology and computer-based molecular modeling. HIV research has benefited from the availability of these individual methods and has fostered significant improvements in each of these critical technologies, including X-ray crystallographic methodologies, nuclear magnetic resonance techniques, and computational approaches to chemical processes. These advances will continue to benefit efforts to develop new drugs for other diseases.

Treatments for opportunistic infections

Individuals who receive drugs that intentionally or unintentionally suppress the function of the immune system are, like AIDS patients, at significantly increased risk of opportunistic infections (OIs). Many forms of modern treatment for cancer involve the use of drugs that suppress the immune system. Transplantation of solid organs as treatment for organ failure (e.g., heart, liver, or kidney failure) and bone marrow transplants to treat malignant (e.g., leukemia) or hematologic diseases (e.g., immunodeficiency syndromes or genetic disorders of hemoglobin production such as sickle cell anemia) necessarily involve the use of drugs that suppress the immune system to prevent rejection of the transplanted organs or tissues. The development of effective drugs to prevent and treat many of the microorganisms that cause OIs promise real benefit to those undergoing cancer chemotherapy or receiving antitransplant rejection therapy.

Clinical research to delay or prevent life-threatening AIDS-related opportunistic diseases has stimulated the development of effective drugs to treat these pathogens in immunosuppressed persons, such as *Pneumocystis carinii*, CMV (a cause of blindness in people with AIDS and life-threatening pneumonias and serious gastrointestinal infections in bone marrow and organ transplant recipients), and a variety of serious fungal infections that cause meningitis or disseminated infections.

AIDS research has helped establish the concept of “prophylaxis” of certain infections in immunosuppressed persons. Providing regular, low doses of drugs that are intended to prevent development of disease decreases the risk of OI. This approach is now standard practice to prevent infections caused by a variety of viruses (such as CMV), fungi, and mycobacteria in immunosuppressed patients.

Understanding the origins and manifestations of malignancies

One of the cardinal manifestations of AIDS is the predisposition to develop specific types of cancer, including Kaposi’s sarcoma (KS) and non-Hodgkin’s lymphomas. That these cancers arise in the setting of host immunodeficiency provides strong support for the notion that the immune system can play an important role in suppressing the development of cancers. HIV infection provides a unique model to study the role of the immune system in the emergence of cancers and to test novel approaches by which immune responses can be modified to help treat established malignancies.

The discovery of the likely cause of KS, human herpes virus type 8 (HHV-8), provides a model for using novel techniques of molecular biology to search for infectious cancer-causing agents in any type of cancer. Studies involving HIV-infected persons are now serving as the model to identify potential infectious etiologies for a wide variety of common malignancies.

HIV-infected women who are also infected with human papillomavirus (HPV) are at increased risk of developing cervical cancer, suggesting that the immune system also plays an important role in controlling this disease. A link between HPV infection and cervical cancer is also seen in women not infected with HIV. Study of HIV-associated cervical cancer has stimulated new areas of research and therapeutic strategies to treat this disease.

Wasting, the intractable loss of weight, is a common clinical manifestation of both cancer and advanced HIV disease. New therapies developed to treat HIV-associated wasting, such as growth hormone treatment, may prove to be of benefit to persons with cancer. New anti-HIV treatments that effectively inhibit HIV replication seem to reverse the process of AIDS-associated wasting, providing an opportunity to understand how this disease manifestation arises. The results of these studies may also be relevant to understanding the process of cancer-associated wasting.

Advances in the ability to diagnose infection and monitor the efficacy of therapy

HIV research has provided new paradigms for the diagnosis of infectious diseases and for monitoring the efficacy of therapy. Molecular diagnostic

methods use sensitive techniques to detect and quantify the pathogen in an infected patient. These methods now permit more rapid diagnosis of infectious diseases; facilitate earlier introduction of effective, potentially life-saving therapies; permit the design of faster, more informative clinical trials; and allow the individualization of optimal therapies.

Among these new technologies is the polymerase chain reaction (PCR) test used to diagnose HIV infection or the so-called viral load assays used to assess disease progression and the efficacy of anti-HIV therapies. The development of these approaches and their validation in the course of AIDS investigations have helped speed the process of clinical evaluation of candidate AIDS therapies, and similar approaches are now being employed to study treatments for other infectious diseases. PCR-based tests are now routinely used to rapidly diagnose a number of important infectious diseases, including tuberculosis (TB), chlamydia, Lyme disease, and a variety of fungal infections.

The development of tests to screen blood donations for the presence of HIV infection has stimulated advances in technologies that could be used to screen blood for the presence of other important infectious diseases, such as hepatitis C virus and the human T lymphotropic virus type 1 (HTLV-1) and type 2 (HTLV-2) that are associated with the development of leukemia and serious neurologic diseases. As a result, the safety of the blood supply has been substantially improved.

Insight into the function of the human immune system in health and disease

The investment in AIDS research has enormously accelerated the development of our understanding of the human immune system. Research on AIDS has led to major advances in our understanding of and ability to manipulate human immune responses. This should allow more effective approaches to treat diseases in which dysregulated immune responses are either the actual cause of, or substantial contributing factors to, the fundamental disease process, including allergies, multiple sclerosis, juvenile diabetes, rheumatoid arthritis, and systemic lupus erythematosus.

Promising immunologic approaches currently being investigated to control cancer include the use of cytokine therapy to boost antitumor immune responses, the use of genetically modified tumor cells that express cytokines or other gene products intended to redirect host immune responses to more effectively fight the resident tumor cell burden, and the expansion (in tissue culture) and transfer of immune cells that can recognize and kill tumor cells. Similar approaches have been actively pursued in the course

of research on HIV therapies, and experience from studies in HIV-infected persons has helped accelerate the development and testing of these treatments in the context of cancer therapy.

New approaches to the design and conduct of drug trials

The national HIV research effort has brought about unprecedented cooperation among Federal, university, and pharmaceutical industry scientists in the development of potential therapeutic agents and vaccines. HIV research has resulted in new approaches for designing and conducting clinical trials and for recruiting and enrolling patients, especially women, children, and minorities in these studies. These models are now being applied to test treatments for other diseases in faster, more efficient, and more inclusive ways.

New approaches for conducting clinical trials have been developed, including community-based trials, which capture the expertise of community physicians. AIDS clinical trials have demonstrated the importance of providing ancillary services, such as general health care, transportation, obstetrical care, day care for children, and other related services, to recruit and ensure the continued participation of women, children, adolescents, and minorities in clinical trials.

AIDS clinical trials pioneered the development of community advisory boards (CABs) to assist clinical trial sites in assuring close cooperation with community constituency groups (CCGs). Such strategies will be applied in the study of treatments for other diseases in the future.

The “parallel-track” mechanism has been shown to be consistent with the conduct of effective clinical studies of candidate therapies and will benefit persons suffering from all types of life-threatening diseases. This mechanism permits access to promising drug treatments prior to their formal approval by the Food and Drug Administration (FDA) for individuals who would not otherwise qualify for participation in specific clinical studies.

Advances in the study of neurologic manifestations

Research aimed at understanding how HIV enters the central nervous system (CNS) and how it results in neurologic disease has yielded important knowledge regarding the role that inflammatory processes within the CNS can have in neuronal degeneration and impairment of cognitive and motor functions. Studies on the mechanisms involved when HIV crosses the blood-brain barrier to infect cells within the brain and how drug therapies can be delivered more effectively to the brain have led to a better understanding

of the mechanisms through which this barrier functions and how it may be circumvented. The results of this research have important implications for research on Alzheimer's disease, dementia, multiple sclerosis, neuropsychological disorders, encephalitis, and meningitis.

Expansion of basic science knowledge base

The investment in AIDS and HIV research has enormously sped our progress in many areas of basic science, including those directly impinging upon the biotechnology industry. Indeed, this effort has been a major contributor to the knowledge base upon which the biotechnology industry has been built. Biotechnology companies are capitalizing on the new basic biomedical information provided by HIV research, most notably new findings regarding chemokines and novel proteins as targets for drug and vaccine development.

Insights into the impact of human behavior on public health

Behavioral and social sciences research on HIV infection and AIDS has demonstrated the important interaction of biological, psychological, and social factors as contributors to disease prevention, transmission, and progression among individuals and population groups. Lessons learned from these studies have improved our ability to study human behaviors that affect disease risk and to develop effective methods to encourage behavior change.

Progress in understanding "emerging" and reemerging infectious diseases

The emergence of HIV infection, Ebola virus infection, and hantavirus infection within the past 15 years has demonstrated not only that new diseases can appear in human populations, but that they will likely continue to "emerge" in the future. Diseases once deemed "under control" also have reemerged as important health problems in this country and around the world. Studies of the origin of HIV infection and the processes that contributed to its worldwide spread have significant implications for preventing or limiting similar epidemics in the future.

HIV infection in humans appears to have originated from a virus present in certain nonhuman primates. Inadvertent transmission of the virus across species (so-called zoonotic infection) allowed the virus to enter human populations. Study of the origins and spread of HIV infection will provide a better understanding of how this process occurs and how it can be prevented.

Studies of HIV-infected individuals with clinical syndromes of previously unknown etiology have led to the discovery of a number of important new infectious agents including human herpes virus 6 (HHV-6), the cause of a number of clinical illnesses including exanthema subitum in children; human herpes virus 7 (HHV-7), not yet associated with a specific clinical illness; HHV-8 (or KSHV), the likely causative agent of KS; bacteria of the genus *Rochalimaea*, also known as Bartonella, the causative agent of bacillary angiomatosis and “cat scratch fever”; and a variety of previously uncharacterized fungi. The discovery of these agents and diagnostic methods to detect them also led to their identification in persons not infected with HIV. HHV-6, for example, causes serious clinical complications in persons not infected with HIV.

Using molecular diagnostic techniques developed in the study of the AIDS epidemic, CDC researchers rapidly identified hantavirus as the causative virus infection of an outbreak of cases of fatal pneumonia in the southwestern United States a few years ago. These techniques allowed the researchers to determine the origin of the virus in local populations of mice and to limit the spread of infection.

The development of international collaborations for tracking the natural history and epidemiology of infectious diseases and for obtaining and identifying variants of infectious agents from different geographic regions helped expedite research on AIDS. This experience, and the collaborations established, will be of great value should new epidemic diseases emerge in the future.

Computational methods and mathematical modeling developed to study HIV transmission now are being applied to track the parameters of transmission and dissemination of the bovine spongiform encephalopathy agent, and will certainly benefit the study of other infectious agents as well.

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. The primary responsibility of the OAR was to coordinate the AIDS research effort across NIH and serve as a focal point for AIDS policy and budget development within the Office of the Director, NIH. The NIH Reauthorization Act of 1993 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 Institutes and Centers (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 supports the efforts of six trans-NIH Coordinating Committees in the following areas: Natural History and Epidemiology, Etiology and Pathogenesis, Therapeutics, Vaccines, Behavioral and Social Sciences, 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 its Advisory Council (OARAC), composed of non-Government experts from a broad array of disciplines as well as AIDS community representatives. The Advisory Council reviews the annual plan, budget requests, and discretionary fund disbursements. A list of members is included in the Appendices. OAR has also established the Prevention Science Working Group and the Therapeutics Working Group to provide advice in these critical scientific areas. OAR supports the Intramural AIDS Targeted Antiviral Program (IATAP) and the NIH AIDS Research Loan Repayment Program (LRP). The OAR supports a number of initiatives to promote the distribution of research information to researchers, physicians, institutions, and communities. The 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.

NIH Institute and Center Support of HIV/AIDS Research

Each NIH IC is involved in some HIV/AIDS-related research activity, consistent with its individual mission. The ICs whose research programs are most heavily concerned with HIV, AIDS, and their sequelae are NIAID, 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). The Warren Grant Magnuson Clinical Center provides the infrastructure for intramural clinical studies sponsored by the ICs.

OAR Priority Setting and Development of the FY 2000 Plan

OAR has established a 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. The NIH Reauthorization Act of 1993 mandates OAR to develop an annual comprehensive plan and budget for all NIH AIDS research.

The planning process instituted by the OAR involves the participation of NIH and non-Government experts and community representatives to develop a consensus on the direction and priorities for AIDS research. The six OAR Coordinating Committees prepare the first draft of the Plan for their specific areas of AIDS/HIV research, as well as for training and infrastructure needs in those areas. The draft plan is 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 sponsors 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 are asked to review and prioritize the objectives and strategies of the draft plan in a series of Planning Groups: Natural History and Epidemiology; Etiology and Pathogenesis; Vaccines; Therapeutics; and Behavioral and Social Sciences. Each Planning Group includes non-NIH scientists, community representatives, and the members of the OAR Coordinating Committee for that area. These groups also include the members of OAR's Prevention Science Working Group; the AIDS Vaccine Research Committee, chaired by Dr. David Baltimore; and the Therapeutics Working Group. Each of these groups was established to seek outside advice of non-Government experts, including community representatives, on an ongoing basis around these critical areas of the AIDS research agenda. The Plan is also reviewed by the OAR Advisory Council.

The Plan serves as the framework not only for the development of the budget, but also for the determination of 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. OAR distributes the annual comprehensive plan to a wide audience, and it also appears on the OAR web site.

OAR plans to reassess the planning process this year and will make refinements to better capture the broadest range of expertise and community participation, particularly women and minorities.

The research objectives and priorities of this NIH FY 2000 Plan for HIV-Related Research thus reflect a broad scientific consensus including Government and non-Government experts as well as community representatives.

Structure of the Plan

The Plan is divided into categories representing the NIH AIDS research areas of emphasis: Natural History and Epidemiology, Etiology and Pathogenesis, Therapeutics, Vaccines, Behavioral and Social Sciences, Training, Infrastructure, and Capacity Building, and Information Dissemination. The format of the Plan is as follows:

AREA OF EMPHASIS: The seven major areas listed above.

STATUS: A brief review of current research activities and the state of knowledge within that scientific area.

SCIENTIFIC ISSUES: The gaps in knowledge that must be addressed are listed in priority order.

OBJECTIVES: The scientific question to address each of the prioritized Scientific Issues.

STRATEGIES: Specific scientific strategies to be addressed are not prioritized, but serve to define those avenues and approaches that may be pursued within the scope of AIDS and AIDS-related research.

AREA OF EMPHASIS:

Natural History and
Epidemiology

AREA OF EMPHASIS:

Natural History and Epidemiology

STATUS:

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 overlapping epidemics: AIDS, STDs, TB, and drug use. NIH conducts studies to examine the transmission of HIV, the progression of HIV-related disease (including the occurrence of OIs), the development of malignancies, the incidence of neurological and neurobehavioral dysfunction, the occurrence of oral manifestations, and the development of other sequelae. Such studies examine the effects of viral factors, host factors, and other factors on the risk of infection and disease progression, which will provide useful insights into the prevention, as well as management of HIV infection.

Ethnic and racially diverse cohorts of HIV-infected individuals and HIV-uninfected individuals at risk of infection are followed in clinical epidemiology studies at domestic and international sites. By maintaining this diversity, data obtained from such studies will have validity for all communities impacted by HIV infection.

NIAID supports the HIV Network for Prevention Trials (HIVNET) in preparation for vaccine and other prevention trials of biomedical and behavioral interventions. Working in collaboration with other ICs, this network has already begun to evaluate STD treatments, microbicides, and perinatal interventions with antiretrovirals and immunotherapy, as well as

other behavioral and biomedical interventions. Project EXPLORE, an example of a HIVNET pilot project, has been conducted in six urban high-seroprevalence cities, with wide community acceptance. Its community advisory boards provide an avenue for ongoing community feedback and cultural awareness.

International epidemiologic studies supported by NIH 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 preventive behavioral 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, as a means of primary HIV prevention. Another area of primary prevention research focuses 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. The NIH-sponsored international collaborative research activities include numerous studies supported by the NCI, National Institute of Dental and Craniofacial Research (NIDCR), and Fogarty International Center (FIC). FIC training programs foster the development of research skills and infrastructure in countries where HIV infection and AIDS are epidemic, in order to facilitate biomedical and behavioral intervention trials, including future international HIV vaccine efficacy trials.

NIH maintains repositories and databases from cohort-based studies and clinical trials. The specimens and data are made available to all qualified investigators to test specific scientific hypotheses. To ensure that repositories and databases are more widely available, NIAID, NHLBI, and NCI have recently established review mechanisms for collaborators seeking access to specimen and specific data collected from NIH-funded natural history and epidemiology, clinical trial, and behavioral AIDS-related studies. Repositories maintained by NIH include the NIAID National AIDS Specimen Repository, which contains more than 1 million biological specimens linked to a database from fully characterized and longitudinally followed cohorts; the NCI Tissue and Biological Fluids Bank of HIV-Related Malignancies, which contains specimens from subjects enrolled in cross-sectional and prospective studies; the NHLBI Biological Specimen Repository, which contains more than 2 million specimens from volunteer blood donors and recipients of blood components or plasma derivatives; and the NIMH National Neurological Research Specimen Bank, which collects and distributes CNS specimens from HIV-infected donors.

INCREASES IN HIV-RELATED MALIGNANCIES AND TUBERCULOSIS

The NIH investment in establishing and maintaining these unique domestic and international cohorts, repositories, and databases provides 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 understand the dynamics of the epidemic in a population-based context. Population-based cohorts of at-risk HIV-uninfected individuals remain critical to the elucidation of the natural history of primary HIV infection.

NIH is actively supporting studies on the occurrence, natural history, and molecular epidemiology of HIV-associated preneoplastic conditions and cancers. These efforts are designed to address the significantly increased incidence and aggressiveness of cancers and preneoplastic conditions in immunodeficient individuals; e.g., increases in cancers associated with oncogenic human viruses such as non-Hodgkin's lymphoma, Hodgkin's lymphomas, KS, and HPV.

Recent data continue to implicate HHV-8 in the development of KS, some non-Hodgkin's lymphomas, and multiple myeloma. Ongoing efforts are being focused to better understand the natural history and epidemiology of HHV-8. The importance of this and related research will increase further since the incidence of AIDS-associated malignancies is expected to increase with the extended life expectancy of HIV-infected patients through triple-drug therapies and prophylaxis for HIV-related OIs.

Marked increases in the incidence of TB and multidrug-resistant TB in the setting of HIV infection, both globally and in minority, urban, and drug-using populations in the United States, make this an important public health problem. NIH has responded in part to this problem by supporting programs to address the spread of TB among injecting drug users (IDUs). Research efforts focus 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, such as Directly Observed Therapy (DOT), in order to reduce infectivity and transmission.

NIH will continue to emphasize studies on the possible impact of OIs on the natural history of HIV disease, including the potential influence of such infections on HIV concentration in body fluids and tissues. The findings from these studies may be useful in identifying future opportunities to prevent disease progression and HIV transmission.

HIV INFECTION IN WOMEN

AIDS is the leading cause of death among African-American women between 25 and 44 years of age in the United States. Between January 1994 and June 1997, the majority of HIV infections reported in this time period were among African-American women between 15 and 24 years of age. While many of the clinical manifestations of HIV infection in women and men are similar, HIV-infected women also experience some complications that are unique to or more prevalent in them, such as vaginal and esophageal candidiasis, chronic herpes simplex infections, and cervical dysplasia. The Women's Interagency HIV Study (WIHS) is a major study cofunded by the National Institute of Child Health and Human Development (NICHD), National Institute of Allergy and Infectious Diseases (NIAID), and National Institute of Dental and Craniofacial Research (NIDCR) in collaboration with other DHHS agencies. WIHS investigates the nature and rate of disease progression in women to better characterize the clinical manifestations of HIV infection as well as to determine the effects of therapeutic regimens in women. WIHS will also identify the sociocultural and health care access factors that affect disease outcomes in women. With 82 percent of WIHS participants being women of color, these studies will yield information pertinent to a wide range of vulnerable subpopulations.

An important area of concern is the impact of HIV on cervical cancer. Case reports suggest that HIV-associated cervical cancers progress more rapidly than those in HIV-negative women and are refractory to therapy. The NCI Surveillance, Epidemiology, and End Result (SEER) program maintains a Special Surveillance Study to define more closely the incidence and spectrum of the histopathology of cervical cancer in HIV-infected women. The Multistate AIDS Cancer Match Registry also collects information relevant to this and other HIV-associated cancers. Coinfection with HPV is common in HIV-infected women, and HPV has been shown to act synergistically with HIV to increase expression of individual viral genes. The enhanced expression of viral proteins has been shown to increase viral replication, abrogate host tumor suppressor functions, and further exacerbate cellular immunodeficiency. Recent findings indicate that the risk of developing cervical neoplasia is not the same with all variants of HPV, with certain variants conferring greater risk than others. Continued emphasis on this research area is needed.

MOTHER-TO-CHILD TRANSMISSION

NIH continues to study the progression of HIV-related disease in infants and pregnant women. This research includes efforts to further characterize the timing, mechanisms, and risk factors of maternal-fetal transmission. Specific efforts of importance include those to develop improved diagnostic assays for the early detection of HIV infection among infants, as well as assays to identify markers for predicting rapid versus slow disease

progression. Another ongoing effort involves the development of quantitative methods to assess viral concentration in body fluids and tissues and to determine how viral concentrations affect vertical transmission and disease outcome.

In the United States, NIH is funding a large epidemiologic study to evaluate factors associated with risk of perinatal transmission, as well as factors associated with maternal and infant disease progression. This study, the Women and Infants Transmission Study (WITS), cofunded by several ICs, includes extensive laboratory studies and supports a specimen repository. Participants from the United States and Puerto Rico reflect the diverse populations impacted by HIV in women and children. More than 75 percent of the women and children with HIV disease in the United States are racial/ethnic minorities. Another pediatric epidemiologic study is under way to assess cardiac and pulmonary complications among HIV-infected children. Perinatal prevention trials in the United States are conducted within the Pediatric AIDS Clinical Trials Group (PACTG).

Internationally, a wide variety of perinatal HIV prevention and transmission studies are under way. These include NIAID- and NICHD-funded antiretroviral and immunotherapy trials in Africa, the Caribbean, and Thailand. In addition, NICHD, NIAID, and FIC are collaborating on several studies in Africa to determine whether micronutrient supplementation can reduce mother-to-child transmission or ameliorate disease progression in HIV-infected children. Similarly, NCI, NIAID, and FIC are collaborating on studies in Africa to determine whether vaginal and neonatal cleansing with microbicides or providing Vitamin A to pregnant women can reduce the risk of perinatal HIV transmission and to clarify the role of breastfeeding in HIV transmission.

DISEASE PROGRESSION

NIDA supports research on characterization of the disease process in drug users, including host and virologic factors influencing progression, clinical sequelae, consequences of multiple coinfections, effectiveness of therapeutic regimens, and the impact of health care access and adherence on disease outcomes. Two of these studies, ALIVE I and ALIVE II, are cohort studies of HIV-positive IDUs and high-risk IDUs. More than 90 percent of the participants of these studies are African American. The third project, HERO, is conducted with IDUs in New York City. Of the participants, 65 percent are Hispanic and 18 percent African American. The diverse populations represented in these three studies will provide an opportunity to further study the impact of HIV disease in several vulnerable subpopulations. The characterization of the virologic and immunologic parameters of rapid and slow disease progression is currently under way in

subsets of adult and pediatric patients in cohort studies funded by several ICs. Data have shown that the amount of HIV circulating in the bloodstream is predictive of the rate of disease progression. NIAID and NCI are supporting research on 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 that now are known to serve as coreceptors for HIV and on characteristics of the viral strain. Information from these cohort studies will be crucial in designing and evaluating new therapeutic approaches and vaccines. Reverse transcriptase PCR technology has made quantification of HIV in plasma or serum highly reproducible, sensitive, and predictive of HIV infection. This technology likely will facilitate the elucidation of the *in vivo* natural history of HIV infection and also of sexual and mother-to-child transmission.

Scientific Issues and Objectives

SCIENTIFIC ISSUE:

Despite substantial insights concerning the risk factors and modes of transmission, sizable numbers of new HIV infections are occurring, especially among minorities, adolescents, and young adults, in the United States and worldwide. There is a continued need to identify the populations of HIV-infected individuals and at-risk populations inclusive of ethnic minorities, adolescents, and substance abusers in this country and abroad. Thus, the development of biologically and behaviorally based interventions to interrupt transmission is an essential component of a comprehensive HIV prevention strategy including efforts to develop a vaccine(s). Epidemiologic studies, including those related to vaccine preparedness research, provide opportunities for intervention research in defined cohorts of well-characterized populations. Strategies that employ therapies, devices, and other approaches (e.g., STD control, topical microbicides, and access to needle/syringe exchange programs) using HIV seroconversion endpoints are useful approaches for proving epidemiologic causation and evaluating effectiveness in preventing or reducing HIV transmission. As has been the case in AIDS clinical research, representatives of the HIV-affected community can make valuable contributions to the planning and implementation of intervention research studies.

OBJECTIVE:

Develop and evaluate new and expand current successful biomedical and behavioral integrated prevention intervention strategies in all age-group risk cohorts to further reduce HIV acquisition or prevent HIV transmission in both domestic and international settings.

1.A

STRATEGIES:

- Identify subpopulations, especially among 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., trials of microbicides, barriers, STD treatment, multidrug therapy, nutritional supplementation, and behavioral interventions—singly or in combination);

- Develop and maintain the infrastructure in 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 abusers, for preventive intervention studies;
- Support development and evaluation of improved, acceptable, effective, and safe physical and chemical barrier methods including topical microbicides and other noncontraceptive methods to prevent sexual transmission of HIV and STDs;
- 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 sections; 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 to reduce HIV transmission via breast-feeding, such as early weaning and Vitamin A supplementation;
- 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 integrated behavioral interventions to control STDs as a means of preventing HIV transmission;
- Evaluate differences in compliance with prophylaxis as a function of type of exposure;
- Evaluate potential risks and benefits of providing prophylaxis against infection following occupational and nonoccupational exposures to HIV;
- Evaluate the effects of contraception choices and practices on STD/HIV transmission through sexual and perinatal routes;

- 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 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 transmission on the development of chromosomal damage, mutagenesis, or carcinogenesis; and
- 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.

SCIENTIFIC ISSUE:

Epidemiologic studies provide a critical knowledge and resource base for more basic investigations of HIV pathogenesis. A better understanding of (1) human immunodeficiency virus characteristics; (2) host factors that mediate disease progression; (3) infectious, genetic, immunologic, environmental, hormonal, nutritional, pharmacologic compliance, and behavioral factors that influence progression; and (4) predictors of disease progression will be important in furthering attempts to develop anti-HIV vaccines and more effective therapeutic interventions against HIV and its sequelae. Epidemiology-based studies also will provide essential information on the effectiveness of treatment, such as information on (1) when to begin treatment; (2) which combinations are effective; (3) the prevalence and causes of treatment failure; (4) the identification, causes, and prevalence of side effects associated with treatment; (5) health care resource utilization; and (6) the effects of antiviral treatment on behaviors that can affect HIV treatment. Continuation and replenishment of established clinical-epidemiological cohort studies are important because these are valuable resources for formulating and testing hypotheses relating to progression and pathogenesis and for facilitating intercohort comparative studies.

OBJECTIVE:

Elucidate through epidemiologically based domestic and international studies the progression of HIV infection, from its earliest stages through long-term sequelae, in order to identify virologic, naturally occurring, and host factors and to assess how interventions (e.g., antiretroviral therapy) that effectively slow disease progression affect patients, public health outcomes, and health care utilization.

1.B**STRATEGIES:**

- Elucidate the pathogenic mechanisms mediating HIV disease progression in well-defined subsets of individuals;
- Investigate the role of potential cofactors and mediators of disease progression, including host genetic factors; immunological factors; infectious agents, including other retroviruses; 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 levels of compliance with and adherence to drug regimens affect HIV drug resistance;
- Study the effectiveness of compliance interventions in minority, adolescent, drug-abusing, and international populations;
- Study the effect of nutritional deficiencies, oxidative stress, and body composition on HIV disease progression;
- Elucidate through long-term seronegative cohorts the behavioral dynamics of risk-taking and risk-reducing behaviors;
- Develop and evaluate counseling procedures;
- Investigate the influence of HIV viral factors including genotype, phenotype, and 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; and
- Assess the effectiveness and impact of immunizations and natural infections on disease progression in HIV-infected populations.

SCIENTIFIC ISSUE:

Understanding the determinants of risk and the mechanisms of HIV transmission is critical to the development of biologically and behaviorally based strategies to interrupt transmission of HIV. Of particular importance is a better understanding of the effect of antiretroviral therapy on infectivity and transmission of HIV. Epidemiologic studies, including population-based surveys, provide important biological and behavioral information, including information on the role of other factors (e.g., contextual and environmental factors) that may reduce or enhance transmissibility, and information on the ways in which biological interventions may be enhanced or attenuated by behavioral responses and/or targeted interventions.

OBJECTIVE:

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

1.C**STRATEGIES:**

- Evaluate the impact of improved therapies on HIV infectiousness and transmission;
- Evaluate HIV transmission and acquisition in relation to the following:
 - *Viral factors such as viral concentration in blood, genital and oral secretions, and at mucosal sites; characteristics of HIV (genotype, phenotype, and drug resistance); and HIV infection stage;*
 - *Host intrinsic factors such as menstrual cycle, cervical ectopy, pregnancy, menopause, hormone replacement, circumcision, mucosal immunity, and immunologic and genetic determinants;*
 - *Environmental factors including intercurrent STDs, exogenous irritants, other causes of oral and anogenital inflammation contraceptive use, hormonal replacement, drug abuse, 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 factors such as socioeconomic status, race, ethnicity,*

age, community and neighborhood variables, physician expertise, and access to health care;

- Investigate the impact of intensive combination or new antiretroviral regimens during all phases of HIV infection on disease progression, quality of life, and survival and renewed risk behavior;
- Further define the timing, mechanisms, and risk factors in perinatal and postnatal transmission, including concurrent STDs, bacterial vaginosis, chorioamnionitis, nutritional deficiencies, and breast-feeding;
- Evaluate the occurrence of transient HIV infection and the mechanisms by which it may occur; and
- 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.

SCIENTIFIC ISSUE:

Most morbidity and mortality in HIV-infected persons results from the occurrence of OIs and malignancies. Strategies to prevent these illnesses include prevention of exposure to the etiologic agents, prevention of disease in those who are exposed, and prevention of disease recurrence. With the profound effects of combination antiviral therapies on the course and complications of HIV infection, additional epidemiologic strategies are needed to assess the impact of intervention(s) on these adverse consequences, including recognized and new HIV-related OIs and malignancies, and to develop treatments for them. The impact will differ substantially across populations (according to availability of therapies). Studies also are needed to assess the potential long-term morbidity of newer, highly active antiretroviral therapy.

OBJECTIVE:

Undertake epidemiologic research to identify, reduce, and prevent the occurrence of adverse health outcomes, including new OIs, malignancies, 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 at-risk populations such as minorities, adolescents, and drug-abusing groups, to determine the changing spectrum of disease in HIV-infected populations, 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;
- Explore low-cost, low-technologic interventions to prevent HIV disease progression in developing countries, including better prophylaxis and treatment of OIs and nutritional interventions; and
- Evaluate risk factors and develop and assess interventions in HIV-infected populations that reduce or prevent the following:

- *Infectious diseases;*
- *Malignancies and associated oncogenic infections; and*
- *Other HIV-associated diseases, including central and peripheral nervous system diseases and wasting syndrome.*

SCIENTIFIC ISSUE:

As the epidemic continues to evolve, there is a critical need to build on recent laboratory breakthroughs, such as PCR assays and viral load assays, to develop and evaluate new methodologies for epidemiology-based studies. Epidemiologically defined populations provide insights into HIV transmission, including resistance and susceptibility to infection and infectiousness, and progression of HIV-related disease from early infection through long-term sequelae. The development of innovative biomedical, behavioral, and analytical methodologies that can be applied to epidemiologic studies will greatly increase understanding at the biological level and will help scientists identify strategies for preventing HIV transmission and disease progression.

OBJECTIVE:

Develop and evaluate new laboratory assays, information technologies, sampling methodologies, statistical techniques, and age and culturally relevant recruitment and retention methods for epidemiologic studies.

1.E

STRATEGIES:

- Develop and evaluate accurate, reproducible, and inexpensive virologic, immunologic, bacteriologic, and genetic assays suitable to large-scale epidemiologic research;
- Develop telephone and face-to-face survey and sampling methodologies 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 modern information technologies to facilitate the conduct of HIV research in managed care settings as well as in developing countries;

- Develop rapid and inexpensive diagnostic assays for STDs;
- Develop and evaluate mechanisms for effective dissemination of HIV information to researchers, community-based organizations, health care providers, and the general public that affects prevention and disease progression in developed and developing countries; and
- Support a comprehensive program of interdisciplinary methodologic 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.

AREA OF EMPHASIS:

Etiology and Pathogenesis

AREA OF EMPHASIS:

Etiology and Pathogenesis

STATUS:

In the quest for vaccines to prevent HIV infection and more effective drugs to contain the infection and treat the 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 and OIs that characterize AIDS? These outstanding questions define the central contemporary issues encompassed within the area of etiology and pathogenesis research. The ability of new antiviral therapies to lower HIV replication to undetectable levels and halt disease progression is changing the natural history of HIV infection and focusing investigators' attention to key questions within this area. What is the nature of the tissue reservoirs for HIV which allow viral persistence in HIV-infected persons on effective antiretroviral therapy? What is the regenerative capacity of the host immune system during HIV infection and in the period following effective antiretroviral therapy? Definition of these scientific issues will likely drive the NIH-sponsored research effort in the coming years.

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. 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. Progress in these areas, much of it fueled by support provided by NIH, continues at a rapid pace. Indeed, it is likely that more is now known about the fundamental biology of HIV than any other virus that causes disease in humans; yet much still remains unknown.

While the fundamental principles of the HIV life cycle have been defined in an expeditious fashion, insights into how HIV establishes infection, replicates, persists, and causes disease in infected people have been more difficult to obtain. However, the concerted efforts by numerous NIH-sponsored investigators are now yielding impressive discoveries that are advancing our understanding of the disease process. The development and functioning of the human immune system have been the foci of significant interest and scrutiny about which great discoveries have emerged. The fundamental complexity of the immune system operates in both health and disease. Better understanding of the normal functioning of the immune system will be necessary if we are to understand the pathogenesis of AIDS. Likewise, a better understanding of the pathogenesis of AIDS will yield important insights into the normal immune system and how it also may fail in conditions such as autoimmune disease or common infections and malignancies that are seen in persons not infected with HIV.

The challenge of understanding HIV infection and disease also represents an extraordinary example of how the biology of other infectious diseases may be studied in the future. Never before has the behavior of an infectious organism within an infected human been examined in such detail. For this type of investigation, new research tools are required to facilitate sensitive, high-resolution analyses. The amount of virus present in an infected person must be determined and its level of replication and consequent damage measured. The need to understand HIV infection has driven technological developments in this area, and much of this effort has been fueled by support provided by NIH.

The powerful tools recently developed to monitor the location and extent of HIV replication within infected persons have elucidated critically important details of how HIV infection leads to AIDS. Application of these new tools has revolutionized our understanding of the extent of HIV replication that takes place in infected people and how virus replication is

directly linked to the destruction of T cells and the resultant compromise of the immune system. The broad outlines of the pathogenic mechanisms of HIV disease are now known, but the precise details of the process await definition. An improved understanding of these issues is necessary to permit definition of the optimal ways to use therapies to treat the primary HIV infection and its associated opportunistic complications.

The process of developing new drugs is based on the study of the fundamental structural properties of the relevant target of drug design. The foundation of the concept of rational drug design emerged, in large part, from basic research supported by NIH and the pharmaceutical industry over a number of years. Although the potential benefits of this approach to drug development have yet to be fully realized, it will have applications within all aspects of human health and disease. It is likely that the effort to develop effective therapies to treat HIV infection and its associated conditions will provide a critical proving ground for the concept of rational drug design and a source of great experience for the refinement and advancement of its methods. Already, new and extremely potent antiviral drugs have been developed using basic research results concerning the HIV life cycle. The derivation of these drugs would not have been possible without the elucidation of the structure and function of two of the critical viral enzymes, reverse transcriptase and protease.

The challenge remains to develop even more effective treatments for HIV infection. The inherent ability of HIV to develop resistance to antiviral drugs must be overcome. This will require a continued effort to delineate the structure of HIV gene products and the molecular and structural basis for drug resistance. In addition, continued progress in understanding the intricate details of the virus life cycle, both within individual cells and within infected people, will permit identification of new targets for antiviral drug development and determination of the most effective ways to use these drugs. As in the past, it is likely that continued progress in the development of new and more effective treatments for HIV infection will benefit from the productivity and creativity of NIH-supported investigators.

While significant progress has been made in understanding HIV disease and developing more effective treatments, a vaccine to prevent HIV infection remains an elusive goal. Because of the unique features of HIV infection, it is considered unlikely that an effective HIV vaccine will emerge from the same type of empirical developmental efforts that have produced many of the available, effective vaccines such as those that prevent polio virus and measles virus infections. A much better understanding is essential

HIV TRANSMISSION

of the mechanisms of transmission of HIV between individuals and the process by which the infection becomes established and persists. Likewise, improved understanding is necessary of the nature of the immune response that contains, albeit temporarily, the replication of HIV and its resultant damage in infected persons. NIH continues to be the major sponsor of basic research in these critical areas.

HIV-1 is transmitted through various routes: sexual, parenteral, and perinatal. Worldwide, sexual contact, primarily heterosexual intercourse, is the dominant mode of HIV-1 transmission, accounting for more than 80 percent of all incident infections. Examples of the responsive efforts supported by NIH in this area include the prior and current investigations of transmission in cohorts and collections of blood and sexual fluids for the genotypic and phenotypic characterization of viruses. The factors that determine the ability of an HIV-infected person to transmit the virus are not completely understood and, therefore, are also under active investigation by NIH-supported researchers. Studies are directed at understanding the contribution of cell-free versus cell-associated virus; the influence of high viral loads in blood, semen, urine, cervical/vaginal secretions, and oral fluids of the transmitter; and the effect of the transmitted viral strain phenotype on HIV transmission.

The variables that may influence a person's susceptibility to HIV-1 infection following exposure have yet to be clearly defined. 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, therefore, 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 STDs on HIV-1 susceptibility and transmission.

PATHOGENIC MECHANISMS OF HIV INFECTION FROM ACUTE-STAGE INFECTION THROUGH CLINICAL LATENCY TO ADVANCED DISEASE

Ongoing research at the molecular, cellular, and organ-system levels is elucidating the pathogenic mechanisms of HIV infection. Recent studies have shown that newly infected patients experience a high rate of viral replication and that, in an as-yet unpredictable manner, their immune systems undergo changes that continue until the development of AIDS. Research at the cellular and molecular levels includes studies of the mechanisms by which HIV enters and infects various cell types; the

interaction between the viral regulatory elements and infected cells that appears to be directed at maintaining a persistent infection; the mechanisms of inappropriate immune activation; the net balance among various types of immune cells and the immunomodulatory growth factors expressed by those cell types; and the viral- and host-mediated mechanisms that influence the level of viral expression seen in successive stages of HIV disease.

NIH-supported investigators 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 destruction of T-cell populations in infected individuals. This new understanding of the magnitude and kinetics of HIV replication *in vivo* has great implications for understanding and potentially overcoming the obstacle to effective antiviral therapy that is posed by the development of viral variants that are resistant to the inhibitory effects of antiviral drugs. The quantitation of HIV in plasma provides a new, direct virologic endpoint for monitoring virtually all infected people and is of particular utility in assessing antiviral efficacy in clinical studies, especially in early-stage disease, where conventional virologic markers are often negative. In addition to measuring viral burden, NIH-sponsored investigators are characterizing the breadth and specificity of the anti-HIV immune response as a possible factor in a longer period of clinical latency.

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. 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 in HIV-infected persons.

To further understand the interaction between the virus and host immune system response, NIH is placing particular importance on the study of the *in vivo* effects of HIV infection. 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.

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

In vivo research into mechanisms of viral immunopathogenesis also utilizes animal models. All the available animal models contribute to our understanding of disease mechanisms. Continued support of *in vivo* research is a high priority at NIH.

Genetic or environmental factors or other infectious agents, in addition to HIV infection, may promote specific disease manifestations. For example, a novel herpesvirus identified in KS tissues and primary effusion lymphoma cells may prove to be the causative agent of these malignancies. Other such factors, often referred to as cofactors, may enhance or retard HIV transmission and/or alter the rate of progression from HIV infection to the development of symptomatic disease.

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 and the course of disease progression in these populations.

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 tract, the influence of hormonal modulation on viral infectivity and vaginal immunity, and the gynecological manifestations attending HIV infection. These studies will contribute to a greater understanding of the biology of HIV infection and disease progression in women.

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. A large NIH clinical trial has determined that administration of zidovudine during gestation and labor and to the infant after birth significantly reduces the rate of HIV transmission. A subsequent trial has proven the effectiveness of a short-course regimen of orally administered zidovudine in reducing perinatal transmission, offering a real hope of extending perinatal prevention to the developing world. Ongoing clinical trials will help in further defining the optimal timing for delivery of antiviral therapy to limit maternal-fetal transmission, the mechanism of

**DISEASE
MANIFESTATIONS**

the protective effect, and whether new antiviral agents and treatment modalities may be even more effective.

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.

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 also 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 might alter its manifestations. The influence of new antiretroviral therapies, able to lower viral load to undetectable levels, on the natural history of AIDS is also providing an unprecedented opportunity to gain insights into the pathogenic mechanisms underlying the disease manifestations associated with HIV infection and AIDS.

AIDS-Related Malignancies

AIDS is associated with a broad spectrum of neoplasms, including KS, lymphomas, cervical and anogenital carcinomas, Castleman's disease, leiomyomas, leiomyosarcomas, and hepatitis B-related hepatocellular carcinomas. The proportion of malignancies and their incidence rates might increase as the development of effective antiretroviral therapies and prophylaxes against OIs leads to prolonged survival of HIV-infected patients with compromised immune systems. Immune deficiency is clearly linked with development of some types of lymphomas in HIV-1- and HIV-2-infected subjects and SIV-infected macaques. 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 role of a newly discovered human herpesvirus, 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 disease prevention and treatment.

Neuropathogenesis

Neurological disease and neurobehavioral dysfunction associated with HIV infection cause considerable morbidity and mortality in afflicted children and adults. These manifestations include diseases associated with opportunistic infection of the brain resulting from the underlying immunodeficiency and the AIDS dementia complex, a disorder that is unique to HIV infection. 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. OIs will clearly remain a major manifestation as long as immunodeficiency is the inevitable result of progressive HIV infection. 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' genome; 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.

NIH-funded researchers are studying viral infections by HSV-1 (herpes simplex virus-1) and -2, VZV (varicella zoster virus), CMV, HHV-6, HHV-7, and JCV (JC virus); fungal infections by candida, cryptococcus, and histoplasma; bacterial infection by *Mycobacterium avium* (*M. avium*) and *Mycobacterium tuberculosis* (*M. TB*); and protozoal infection by *Cryptosporidium*, *Microsporidium*, *P. carinii*, and *Toxoplasma gondii* (*T. gondii*). Since OIs remain the most important complication of HIV infection and the principal cause of death in HIV-infected individuals, understanding the fundamental biology and pathogenesis of these organisms will translate into new or more rational approaches to the prevention and treatment of their associated diseases.

Wasting

Wasting is one of the most devastating aspects and one of the major causes of morbidity and mortality in AIDS. 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. The etiology of wasting associated with AIDS is complex and multifactorial. Critical loss of lean body mass is the hallmark of wasting in AIDS. AIDS patients with wasting illness escape a homeostatic control system and fail to generate normal responses to weight loss.

Alterations in energy expenditure, metabolic and endocrine abnormalities, and cytokine dysregulation have all been implicated in the pathogenic mechanisms underlying the wasting syndrome. Wasting occurs episodically and is a manifestation of secondary diseases such as infections and gastrointestinal disease. OIs are associated with episodes of rapid weight loss, as cytokine-mediated inflammatory and immune responses occurring during these infections induce metabolic disturbances and have a profound effect on food intake inducing anorexia, which may be a major contributor to weight loss.

Available interventions for the wasting syndrome in adults and related failure to thrive and growth retardation in children are either poorly effective or very expensive. Elucidation of the factors contributing to wasting will allow effective therapies to be tailored to the specific mechanism by which wasting occurs, with the potential for prolonging life and enhancing its quality in AIDS patients.

Organ-System-Specific Complications of HIV Infection

Organ-system-specific manifestations also attend HIV infection and disease. Gastrointestinal dysfunction and malabsorption are commonly observed in HIV-infected subjects. The gastrointestinal tract is one of the most important routes of transmission of HIV and appears to be a major site of viral replication and the major site of CD4+ T-cell depletion in early stages of infection in the SIV model. NIH-supported researchers are investigating the contribution of OIs, 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 system. 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 Issues and Objectives

SCIENTIFIC ISSUE:

The mechanisms of HIV transmission and the early events in the establishment and spread of infection in the host need to be better understood.

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 portal of entry and support subsequent spread of HIV;
- Investigate transmission, establishment, and spread of HIV upon re-exposure in previously infected individuals;
- 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;
- Identify biologic, environmental, social, gender-related, and host factors determining relative efficiency of HIV transmission in various populations, especially developing versus developed world populations; and
- 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; and
- Promote augmented access to and sharing of key patient samples, animal model resources, laboratory reagents, information databases, and quantitative virologic and immunologic assays.

SCIENTIFIC ISSUE: Basic scientific information regarding mechanisms that underlie HIV-related immune dysfunction and viral pathogenesis is critical to all areas of AIDS research.

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;
 - Determine the impact of reinfection by HIV on the clinical course of the disease;
 - 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 individual CD4+ T lymphocytes;*
 - *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 lifespan 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;
- Define the reservoirs of virus infection that permit HIV persistence in the setting of effective antiretroviral therapies; and
- 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; and

- 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.

SCIENTIFIC ISSUE: Knowledge about the origins and pathogenesis of HIV-related cancers is urgently needed.

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.C

- 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 in the development of HIV-associated malignancies;
 - Identify the mechanisms by which immune dysregulation, oncogenes, suppressor genes, carcinogens, and non-HIV viral and other microbial genes and proteins contribute to the development of HIV-associated malignancies; correlate these molecular factors with epidemiologic studies;
 - Identify the characteristics of the host that predispose to development of HIV-associated malignant disease;
 - 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;
 - Identify novel pathogens that may contribute to the development of AIDS-related malignancies; develop new methodologies for novel pathogen identification; and
 - 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.

SCIENTIFIC ISSUE:

It is critical to understand the neuropathogenesis of HIV-1 infection in both the central and peripheral nervous systems and the relationship of nervous system infection to disease progression.

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.D**STRATEGIES:**

- Determine the cellular and molecular bases and pathogenic mechanisms involved in HIV-associated neurobehavioral and neurological dysfunction, including:
 - *Identify how HIV enters, establishes infection, spreads, and persists in the central nervous system (CNS);*
 - *Identify the specific cells and regions of the brain involved;*
 - *Determine the relationship of virologic, host, pharmacologic, and environmental factors to HIV-associated CNS dysfunction;*
 - *Determine the consequences of the biologic activity of cytokines, other mediators, and their receptors on the CNS in the context of HIV-1 infection; and*
 - *Develop 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; and
- Determine factors associated with clinical response and lack of response to therapeutic interventions for neurologic and neurobehavioral complications of HIV disease.

To facilitate the research goals listed above:

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

SCIENTIFIC ISSUE: It is critical to understand the processes of establishment of infection and development of disease for the HIV-associated OIs.

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.E

- 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 the 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; and
- 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.

SCIENTIFIC ISSUE: It is critical to understand the etiologic and pathogenic mechanisms of HIV-related wasting and growth retardation.

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

Elucidate the etiology and pathophysiology of HIV-related wasting, metabolic abnormalities, and impaired growth and development, as relates to adults and children.

2.F

- STRATEGIES:**
- Define the etiologic and pathogenic mechanisms of HIV-related wasting (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 wasting, alterations in body composition and nutritional status, impaired growth and development, metabolic abnormalities, malabsorption, and anorexia;
 - Elucidate the pathogenic mechanisms by which OIs, hormonal dysregulation, and other consequences of HIV infection lead to wasting, impaired growth and development, metabolic abnormalities, malabsorption, and anorexia;
 - Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms of HIV-associated wasting and impaired growth and development; evaluate how HIV-associated wasting and impaired growth and development are altered by such therapies;
 - Investigate the mechanisms by which antiviral therapies and/or suppression of HIV replication may affect metabolism and body composition; and
 - Determine factors associated with clinical response and lack of response to therapeutic interventions against AIDS-associated Wasting Syndrome (AWS) and impaired growth and development.

SCIENTIFIC ISSUE: It is important to understand various other organ/tissue-specific complications of HIV infection.

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 (HIVAN), 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; and

- Employ animal models to investigate the etiology and pathogenesis of lentivirus-associated disorders in the above systems.

AREA OF EMPHASIS:

Therapeutics

AREA OF EMPHASIS:

Therapeutics

STATUS:

Important scientific advances in recent years have had a direct impact on HIV preclinical and clinical therapeutics research. Most significant of these advances has been the demonstration that potent new combinations of antiretroviral drugs (usually including an HIV protease inhibitor) reduce the viral load in many patients to levels below the current limits of detection. While individuals who have not previously taken antiretroviral drugs typically experience the best responses to these new three-drug combinations, a substantial proportion of patients who have previously taken some of these agents still respond well to combinations containing at least two drugs that they have not previously taken.

Additional research 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: (1) How long can the virologic, cellular, and clinical responses be maintained on an initially successful regimen? (2) What are the earliest detectable signs of failure that indicate that the drug regimen should be changed? (3) What are the most common reasons for failure of these regimens? and (4) 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 confirms the finding 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.

If viral replication is not completely suppressed by antiviral treatment, drug-resistant strains of HIV emerge, viral load increases, and disease progression may occur. Available drugs are difficult to take, are accompanied by significant side effects (toxicities), and have the potential for drug interactions that may alter potency and tolerance, thus providing an opportunity for incomplete suppression of the virus. Adding to these challenges is one highlighted by recent research that confirmed the existence of a reservoir of latently infected cells (resting memory CD4 cells) that persists for prolonged periods of time, even in patients whose 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.

Systematic studies are needed to improve our understanding of the interaction between the biomedical and behavioral factors that affect 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 that are active against drug-resistant viral strains. The FDA (<http://www.fda.gov/>) recently approved the first drug that combines two antiretroviral drugs (lamivudine and zidovudine) in one tablet formulation. This drug is the result of efforts to improve adherence to complex multidrug regimens by reducing the number of pills taken each day.

Another recent scientific advance with major implications for drug discovery and therapeutics research was the identification of several coreceptor molecules critical for HIV entry into the cell. HIV infection of a human cell requires that the target cell express two or more membrane receptors: the primary receptor or binding site for HIV (e.g., CD4) and a coreceptor (e.g., CCR5). The discovery of different chemokine coreceptors necessary for HIV entry has opened research opportunities that focus on initial virus-host interactions, including opportunities for research on receptor biology and the role of chemokine receptors in an individual's genetic susceptibility to HIV infection. (A small proportion of individuals who have a mutated gene that codes for one of the chemokines appears much less susceptible to HIV infection and/or disease progression.) Research is ongoing to design novel therapeutic agents that block the coreceptors—preventing spread of infection—and to develop better strategies to restore the immune systems of HIV-infected individuals, particularly those with more advanced disease.

Important advances have been made in the medical management of OIs. Improved understanding of the use of therapeutic and prophylactic agents

**DRUG DISCOVERY
AND PRECLINICAL
DEVELOPMENT**

has advanced the options available to people living with HIV/AIDS. Significant challenges remain, including the need to develop new therapeutics for OIs for which no therapies are currently available, stimulate drug discovery of more effective and less toxic agents, and improve the understanding of the pathogenesis of OIs in HIV-infected individuals.

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.

The development of new therapies to reduce the adverse outcomes of HIV infection and its associated OIs, malignancies, and CNS complications requires active drug discovery and development programs, including specialized drug activity screening and rational drug design. Screening involves the testing of compounds that inhibit HIV replication and activity while rational (targeted) drug development characterizes the structural biology of HIV and its associated components for the purpose of developing agents that inhibit specific steps in the HIV life cycle.

NIH-sponsored, investigator-initiated research grants (R01s) support comprehensive drug discovery and development efforts. Basic biomedical research on HIV pathogenesis provides important information that serves as the foundation for successful drug discovery and development. NIAID (<http://www.niaid.nih.gov/>) complements these efforts with more specialized programs that augment, enhance, and accelerate the discovery and translational processes. The National Cooperative Drug Discovery Groups for HIV (NCDDG-HIV) (<http://www.nih.gov/grants/guide/1995/95.04.14/pa-national-cooperat011.html>) and the National Cooperative Drug Discovery Groups for the Treatment of the Opportunistic Infections Associated with AIDS (NCDDG-OIs) (<http://www.nih.gov/grants/guide/1994/94.03.25/rfp-rfa-national-coo011.html>) are designed specifically to expand collaborative efforts among academia, industry, and Government researchers interested in undertaking comprehensive therapeutic discovery and development efforts. A similar program has been established for NIH intramural scientists through IATAP.

Program projects organized to support structure-based targeted drug design and investigator-initiated grants have resulted in the identification of the structural determinants of several HIV components, including integrase, RNaseH, p24, RT, the zinc (Zn) fingers of the nucleocapsid, and most recently, gp41. Potential inhibitors of these compounds currently

are being tested. The NIAID-supported Strategic Program for Innovative Research on AIDS Treatment (SPIRAT) is designed to accelerate the translation of novel therapeutic strategies from bench to bedside.

Together, these and other investigator-initiated programs have resulted in the discovery and development of several FDA-approved drugs with activity against HIV RT and protease enzymes. These drugs include the nucleoside analog RT inhibitors zidovudine (ZDV), didanosine (ddI), zalcitabine (ddC), stavudine (d4T), and lamivudine (3TC); the protease inhibitors saquinavir, indinavir, ritonavir, and nelfinavir; and two nonnucleoside RT inhibitors, nevirapine and delavirdine. New drugs under development include an inhibitor of HIV fusion with the cell membrane, an inhibitor of integrase, inhibitors of RT (both nucleoside and nonnucleoside), and others.

In addition, 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 recently identified host cell chemokine coreceptors CCR5 and CXCR4 that are necessary for HIV infection; a Zn-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, including Nef, Vpu, Vpr, and Vif, 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.

Scientists also are exploring novel molecular and genetic strategies to slow or halt HIV replication. Such strategies include developing molecular approaches to presenting HIV antigens to the immune system with the objective of stimulating immune reactivity against HIV; enhancing the ability of cytotoxic T cells to recognize and destroy HIV-infected target cells; improving DNA-based therapeutic vaccines to augment and/or enhance cell-mediated and humoral (antibody-based) immune responses in infected patients; and developing gene-based therapies that modify natural target cells (e.g., CD4 cells) with anti-HIV genes to prevent viral replication.

NIH collaborates with the pharmaceutical industry via contract resources to promote drug formulation research of promising therapeutic agents to enhance drug solubility, improve bioavailability, enhance drug stability, and target drug distribution to specific tissues or organs.

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

During the past several years, remarkable progress has been made in understanding HIV pathogenesis. This information has been instrumental to advancing drug discovery and development. A new class of potent antiretroviral drugs—the protease inhibitors—and more sensitive assays for measuring the concentration of HIV RNA in different body tissues have been developed, significantly improving the therapeutic armamentarium of the physician caring for infected individuals.

The protease inhibitors target a viral enzyme different from that inhibited by 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) results in better antiviral activity and a longer time prior to the development of drug resistance. A large proportion of patients treated with these new triple-drug combinations, referred to as “highly active antiretroviral therapy” or HAART, experience a significant decrease in plasma viral load, often to levels below the current limits of detection. In patients with more advanced HIV-related symptoms and/or OIs, the profound reduction in viral load may be accompanied by a rise in CD4 cell count and, in many cases, amelioration of these symptoms.

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 newly infected individuals. One research question under study in these patients is whether aggressive HAART that is begun shortly after infection can eradicate the infection. If viral eradication or a cure cannot be accomplished with currently available therapies, early potent treatment still may reduce permanently the “steady state” rate of viral replication observed between 6 and 12 months following the initial infection, resulting in an improved clinical prognosis.

For the majority of HIV-infected persons who are beyond the acute phase of infection, lifelong antiretroviral treatment with potent drug combinations represents the best option for delaying disease progression. If the drugs completely suppress viral replication throughout the body, drug resistance should not develop. Currently available antiretroviral drugs are not able to achieve complete suppression, and even if the plasma viral load falls below the current limits of detection, HIV may continue to replicate at very low levels or in the various “sanctuary sites,” permitting drug-resistant strains to emerge. The immediate challenge, therefore, is to develop new drugs and treatments that are potent, penetrate into all parts of the body, are well-tolerated with minimal risk of therapeutic failure, and can be easily adhered to.

**DEVELOPMENT
AND EVALUATION
OF AGENTS FOR
OIs AND OTHER
COMPLICATIONS
OF HIV INFECTION**

Even with the availability of safe and effective antiretroviral therapy, it is likely that immune-based therapies, particularly those having the capacity to restore immune function, will still be needed, especially for individuals at more advanced stages of immune depletion. IL-2, which has been studied by NIAID intramural scientists, is an immune-based therapy that has the potential to provide clinical benefit. Research plans are under way to design and implement a large controlled study to determine if the typical rise in CD4 counts following this treatment yields a significant clinical benefit.

Future therapeutic research will focus on developing easier-to-use and less toxic protease inhibitors, more potent RT inhibitors, and drugs targeted against other enzymes critical for viral replication. The recent identification of cofactors necessary for HIV entry into cells will foster an intensive effort to identify and develop pharmaceutical agents that block the passage of HIV through the cell surface, which is the earliest event in the viral replication cycle.

OIs are the most common cause of morbidity and mortality of HIV-infected individuals. Discovery and development of drugs against AIDS-related OIs have resulted in the approval of three new agents for clinical use: azithromycin for prevention of bacterial infections in patients with advanced HIV disease; cidofovir for treatment of CMV retinitis; and an intravitreal implant containing ganciclovir for treatment of CMV retinitis.

NIH, through both its intramural and extramural programs, has developed a multifaceted approach to the discovery, development, and clinical evaluation of anti-OI agents. Priority has been placed on identifying therapies where effective strategies do not currently exist and on the evaluation of new agents that have shown the potential of improving the efficacy or reducing the toxic effects of existing treatments or prophylactic regimens.

Biomedical research on OIs faces significant challenges: the limited understanding of the basic biology and natural history of the causative microorganisms; the lack of *in vitro* culture systems for susceptibility testing and biochemical studies; the lack of targeted screens and rational design of new agents; the need for better animal models; the need for improved mechanisms by which drug combinations can be evaluated for efficacy and safety, drug interactions, pharmacology, and immunotoxicology; and the limited level of pharmaceutical involvement in the development of agents directed against HIV-associated OIs.

Preclinical and clinical therapeutics research is targeted on the most prevalent and medically challenging opportunistic pathogens. These include CMV, *M. avium* complex (MAC), infectious causes of diarrhea (*Cryptosporidium*, Microsporida), pathogenic fungi (including candida and cryptococcus), *P. carinii*, *T. gondii*, *M. tuberculosis*, and other opportunistic pathogens (JCV and herpes viruses), bacteria, and endemic mycoses.

CMV retinitis is common in late-stage AIDS. It leads to a substantial loss of vision, a decreased quality of life, and a high cost of treatment. The Studies of the Ocular Complications of AIDS (SOCA), supported by the National Eye Institute (NEI) (<http://www.nei.nih.gov/neitrials/socaintro.htm>), is a network of resource centers and sites that conduct clinical trials to evaluate treatments for CMV retinitis and other studies to assess the epidemiology of this disease. Treatment options for patients with CMV retinitis have been better defined and improved as a result of SOCA trials.

Scientific areas of emphasis include strategies for prevention and suppression of infection, understanding of the pathogenesis of each disease and its interaction with HIV, discovery and development of novel therapeutic agents, development of improved methods to quantify the infectious load and to monitor response to therapy, improving the understanding of the pathogenesis of HIV-related neurologic disorders and developing therapeutic agents that penetrate the CNS or other viral sanctuary sites, development of strategies to control drug resistance, and development of appropriate animal models to evaluate the efficacy and safety of novel therapeutic agents.

DEVELOPMENT OF APPROACHES FOR AIDS-RELATED MALIGNANCIES

NCI (<http://www.nci.nih.gov/>) and NIAID, and their sponsored investigators, have collaborated since 1992 in the development of the AIDS Malignancy Program, which consists of the following components:

- The NCI-funded AIDS Malignancy Bank (AMB) (<http://cancernet.nci.nih.gov/amb/amb.html>) provides the research community access to a large bank of well-characterized tumor tissue, biological fluids, and demographic and clinical data from HIV-infected patients with malignancies. The specimens and clinical data are available for research studies, particularly those that translate basic research findings to clinical application.

- The NCI-funded AIDS Malignancy Consortium (AMC) (<http://www.ccc.uab.edu/amc>) conducts early-phase clinical trials that utilize the expertise of both NCI- and NIAID-sponsored scientists. The following approaches are being tested: immune therapy directed against tumor-associated antigens, biologic therapy to alter the cytokine milieu, tumor differentiation therapy, antiangiogenesis, immune restoration, and HAART. In addition to assessing potential antitumor activity and drug-drug interactions, these clinical trials also evaluate the impact of therapy on viral load and underlying immune function. The AMC is being reconfigured in FY 1999 to support innovative, early-phase clinical trials and conduct large, randomized trials for treatment and prevention. International collaboration in these larger trials is being pursued.
- The NCI-funded Clinical Trials Cooperative Groups are an established clinical trials network engaged in the evaluation of new cancer treatments. They have received set-aside funding since 1994 to conduct clinical trials in men, women, and children with AIDS-related malignancies, including non-Hodgkin's lymphoma, primary CNS lymphoma, KS, and HPV-related malignancies, such as cervical cancer. Investigators from both the AMC and Cooperative Groups are working together in developing complementary research agendas and are donating specimens to the AMB.
- The AIDS Malignancies Working Group (AMWG) consists of extramural and NIH scientists who represent a spectrum of disciplines working on AIDS-related malignancies. The AMWG has been instrumental in forging alliances between investigators at cancer centers and centers for AIDS research and in AIDS Clinical Trials Units (ACTUs); formulating user-friendly mechanisms for dissemination of research information on AIDS-associated malignancies; devising a forum for the exchange of scientific information and the facilitation of multidisciplinary collaboration through the annual NCI-sponsored AIDS Malignancy Conference; and providing insight on new training opportunities for clinicians to gain a better understanding of this field.

The NCI intramural clinical trials efforts are conducted in the HIV and AIDS Malignancy Branch.

CLINICAL TRIALS

NIH has the primary responsibility for the federally supported clinical trials efforts in the evaluation of potential therapies for the treatment of HIV infection and its sequelae. NIH supports several clinical trials networks

including the Adult AIDS Clinical Trials Group (AACTG) (<http://aactg.s-3.com/>), the Pediatric AIDS Clinical Trials Group (PACTG) (<http://pactg.s-3.com/>), the Terry Bein Community Programs for Clinical Research on AIDS (CPCRA) (<http://www.cpcra.org/>), SOCA, and the AMC. More than 50,000 patients have been enrolled to date in NIH-sponsored clinical studies, which have involved the evaluation of more than 200 agents.

Past accomplishments of NIH-sponsored clinical trials include demonstration of the efficacy and clinical benefits of ZDV for both adults and children with early and asymptomatic infection; the safety and efficacy of ddI and ddC for HIV-infected adults and children; the benefits of ddI and ddC in patients who are intolerant of, or who have failed, ZDV treatment; the antiviral activity of interferon and its benefits for reducing KS lesions; the utility of paclitaxel in advanced KS; the benefits of nimodipine for the treatment of AIDS dementia complex; and the therapeutic benefits of ddC plus ZDV combination therapy.

Recent accomplishments of NIH-sponsored clinical trials include the completion of two combination nucleoside trials in adult and one trial in pediatric HIV-infected populations that demonstrated the clinical superiority of ddI monotherapy and ddI/ZDV combination therapy over ZDV monotherapy; another pediatric trial demonstrating that combination ZDV/3TC and ZDV/ddI are superior to monotherapy with either ZDV or ddI with regard to disease progression or death; and other NIH-sponsored trials that have shown clinical benefit of thalidomide in the treatment of oral aphthous ulcers, recombinant human growth hormone for treatment of AIDS-associated Wasting Syndrome (AWS), and megestrol acetate for AWS.

Additional NIH trials have contributed to the understanding of the combination of protease inhibitors, such as saquinavir, indinavir, ritonavir, and nelfinavir; with nucleoside analog RT inhibitors, such as stavudine and lamivudine; or with nonnucleoside RT inhibitors, such as nevirapine and delavirdine, including the impact of these agents on viral load and clinical outcomes. To further the understanding of HIV pathogenesis, small clinical studies have been conducted using new combinations of three or more antiretroviral agents to explore the viral life cycle, viral turnover, and CD4 turnover and to investigate the development of mutations predictive of drug resistance.

Accomplishments in combating HIV-associated OIs include demonstration of the efficacy of atovaquone, dapson, and aerosolized pentamidine for prevention of *P. carinii* pneumonia (PCP) in patients intolerant to

trimethoprim-sulfamethoxazole (TMP-SMX); TMP-SMX for prophylaxis of recurrent PCP; aerosolized pentamidine for prophylaxis and treatment of PCP; fluconazole for the treatment of cryptococcal meningitis and prevention of fungal infections; intravenous (IV) gamma globulin for reducing OIs in HIV-infected children; the combination of pyrimethamine and clindamycin for toxoplasmic encephalitis; and itraconazole for disseminated histoplasmosis.

Antiretroviral and OI prophylaxis regimens are becoming increasingly complex with respect to drug-drug interactions and adherence. The 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 (including utilizing some beneficial drug-drug interactions, e.g., between ritonavir and saquinavir) with the goal of minimizing viral replication and delaying the development of HIV-related disease manifestations.

Over the past few years, the development and commercialization of quantitative viral load assays, which measure the level of HIV replication in the body, have revolutionized the development and evaluation of new antiretroviral drugs and combination regimens and enabled a more rational approach to monitoring patients for therapeutic efficacy and individualization of therapy. As additional research results in more sensitive assays, it becomes increasingly possible to determine whether the goal of completely suppressing viral replication has been achieved. Clinical research aimed at identifying the most potent antiretroviral drugs and combination regimens can be evaluated more easily and quickly with these assays, and viral “escape” (replication) can be identified much earlier.

PEDIATRICS

A priority for NIH is the prevention of perinatal HIV transmission, which is the predominant source of HIV acquisition in children. Since the important results of the PACTG 076 study in 1994 showing that an antepartum, intrapartum, and neonatal ZDV regimen decreases transmission by approximately 66 percent, epidemiologic data from multiple geographic areas in the United States and Europe indicate that incorporation of this regimen into clinical practice results in significant declines in perinatal transmission. Recent data from another perinatal trial, PACTG 185, demonstrated that ZDV prophylaxis is also effective in decreasing perinatal HIV transmission in HIV-infected pregnant women with advanced disease, low CD4 counts, and prior ZDV therapy. The transmission rate in this study, in which all patients received ZDV, was 4.8 percent. The development of a prophylactic regimen(s) capable of lowering perinatal transmission to less than 2 percent is an ongoing goal of the

PACTG. Another priority is the development of simpler and less expensive interventions to interrupt perinatal transmission, particularly regimens that will also be effective in breast-feeding populations in the developing world, where the largest proportion of HIV infection in women and children occurs.

In the United States, combination therapy that includes protease inhibitors has become the standard of care for treatment of HIV-infected individuals, including pregnant women. Pediatric and perinatal clinical trials to determine the pharmacokinetics and safety of combination therapy, including one of the four currently available protease inhibitors in HIV-infected pregnant women and their infants, will be completed shortly. While higher maternal viral load is associated with an increased risk of transmission, data from PACTG 076 indicated that lowering maternal viral load accounted for only a small portion of the observed efficacy of the ZDV prophylaxis regimen. Additional research is needed to determine whether the use of more potent antiretroviral drugs in the clinical management of HIV-infected pregnant women will decrease further the rates of perinatal transmission.

The PACTG, supported jointly by NICHD and NIAID, includes 42 clinical trials sites. The PACTG supports clinical trials in HIV-exposed and -infected infants and in HIV-infected children, adolescents, and pregnant women. The mission of the PACTG encompasses the evaluation of antiretroviral drugs, immune-based therapies, prophylaxis and treatment of OIs, and other complications of HIV infection.

The PACTG has established a collaboration with European sites to conduct perinatal studies (PACTG 076 and 316) and Ryan White CARE Act Title IV-funded sites in the United States to conduct a nutritional intervention protocol. Perinatal trials in the developing world are also conducted through investigator-initiated research grants.

Progress was made recently in establishing the antiretroviral efficacy of various combination regimens in NIH-supported clinical trials. PACTG 152 demonstrated that initial therapy with combination ZDV/ddI or ddI is clinically superior to initial therapy with ZDV in symptomatic infected children, and combination ZDV/ddI is virologically superior to monotherapy with either ddI or ZDV. Building on these results, PACTG 300 demonstrated that initial therapy with ZDV/3TC or ZDV/ddI is clinically, virologically, and immunologically superior to initial therapy with ddI alone. PACTG 338 showed that, for infected children on antiretroviral therapy, the change to combination therapy that includes ritonavir is virologically and immunologically superior to ZDV/3TC combination therapy.

Long-term followup of infants with *in utero* exposure to antiretroviral drugs for possible adverse consequences of such exposure is an important component of PACTG perinatal trials, because drug exposure occurs during periods of organ-system development. Three-year followup data from infants enrolled in PACTG 076 showed no differences in neurodevelopment, immunologic parameters, and growth between those uninfected infants with *in utero* ZDV exposure compared with those in the placebo group. There were no malignancies observed in the ZDV-treated group.

Ongoing pediatric trials are evaluating the pharmacokinetics, safety, and virologic efficacy of additional protease combinations and newer antiretroviral drugs, such as abacavir (1592U89), efavirenz (DMP-266), amprinavir (141W94), and a new formulation of saquinavir. Data obtained from these clinical trials provided the basis for updating the guidelines for antiretroviral use in pregnant HIV-infected women and children that were recently published (<http://www.hivatis.org/revpedgu.html>).

The natural history of virologic parameters in infected children differs from infected adults in that high plasma HIV RNA levels persist in perinatally infected children following initial infection and slowly decline over the first several years of life. These findings have formed the rationale for early intervention trials evaluating the virologic and immunologic efficacy of triple and quadruple antiretroviral combination therapy in young infants. Promising virologic responses to such therapies have been observed in several small trials, and further data from these and additional studies will be available soon. Pathogenesis-based research conducted as a component of these early intervention trials includes evaluation of the kinetics of HIV replication and CD4 turnover in early perinatal infection. In addition, evaluation of the potential for immune reconstitution with potent antiretroviral therapies is an important component of NIH-sponsored AIDS clinical trials.

PARTICIPATION OF UNDERREPRESENTED POPULATIONS

It is important that participation of specific populations in NIH-funded clinical trials reflect the changing demographics of HIV infection and AIDS. These groups include women, children, adolescents, IDUs, minorities, the urban poor, and individuals residing in rural areas. Recruitment and enrollment of aforementioned groups are a high priority in NIH-sponsored studies as reflected in new and strengthened guidelines for the inclusion of women and minorities in clinical trials. Whenever possible, interagency collaboration is fostered to enhance participation of these populations, including the provision of ancillary services as needed.

NIH-supported clinical trials programs strive to ensure that a sufficient proportion of minority participants are enrolled in clinical trials so that the results of the research may be generalizable to the entire HIV-affected population. NIH collaborates with researchers in these programs to identify the need for and/or assist in the development of culturally sensitive education materials, to identify real or potential barriers to recruitment and retention in clinical research for these groups, and to identify mechanisms to overcome these barriers.

Pediatric clinical trials enroll principally minority populations. The PACTG has the option to adjust the location of trial sites to accommodate the changing epidemiology of HIV in women and children, as well as to establish advanced technology sites investigating HIV pathogenesis in the context of clinical trials.

In addition, NIAID supports the AIDS Clinical Trials Infrastructures in Minority Institutions program to enhance clinical research on AIDS performed in these unique facilities. Four institutions received 4-year awards in 1995 for adult ACTUs: Howard University (Washington, D.C.), Meharry Medical College (Nashville, Tennessee), University of Puerto Rico (San Juan), and University of Hawaii (Honolulu). This program increases the number of minority staff involved in ACTG research and the number of minority participants enrolled in the studies.

Drug-abusing and other at-risk populations may tend not to adhere to their therapy. This risk should be considered in the development of therapeutics in terms of (1) developing delivery systems that minimize adherence demands, (2) assessing the implications of each therapeutic regimen that is developed, (3) developing strategies to minimize the undesirable effects of interrupted treatment, and (4) studying interactions between drugs of abuse and new anti-HIV and/or anti-OI therapies in terms of alterations in pharmacokinetics, development of adverse consequences, or progression of disease.

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Scientific Issues and Objectives

SCIENTIFIC ISSUE:

The complex nature of HIV infection—including the rapid rate of genetic mutation of HIV and development of drug resistance, changes in viral tropism, and persistence of viral reservoirs—requires the discovery and development of novel therapeutics to suppress HIV replication at multiple critical stages of the viral life cycle.

OBJECTIVE:

Increase understanding of viral and cellular functions required for reproduction of HIV and identify new targets for their inhibition; design and develop *in vitro* and *in vivo* test systems that predict antiretroviral activity and clinical efficacy; discover and develop novel agents and therapeutic strategies directed against viral and/or host factors involved in HIV reproduction; identify new compounds to prevent and/or treat drug-resistant strains of HIV.

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, and budding; define molecular and cellular determinants affecting HIV virulence and pathogenicity; develop predictive test models 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;
- 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; correlate intracellular pharmacokinetic parameters with drug toxicity/efficacy;
- Develop agents with desirable biopharmaceutical characteristics, such as improved bioavailability and tissue penetration, including the 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;
- 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 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 formulations of existing and experimental agents that facilitate adherence;
- Support the development and evaluation of new compounds to inhibit sexual transmission of HIV, including systemic agents, topical microbicides, HIV-specific virucides, and biologic approaches;
- 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; and

- 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.

SCIENTIFIC ISSUE:

Sustained HIV replication is a major factor in the pathogenesis of HIV/AIDS, and antiretroviral agents constitute an integral component of treatment of the disease. Clinical studies are necessary to determine agents and strategies that will prolong a disease-free state and survival in HIV-infected individuals.

OBJECTIVE:

Conduct clinical trials and develop new trial methodologies to evaluate the safety and efficacy of new 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 heavily pretreated HIV-infected individuals; define and evaluate factors that adversely affect the success of therapeutic strategies against HIV infection (including adherence and resistance); advance our understanding of disease pathogenesis and progression as part of the design and conduct of clinical trials.

**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, toxicity-sparing, and non-cross-resistant in individuals with a variety of prior antiretroviral drug experience, including heavily 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;
- 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-1 in different tissue compartments during HAART; investigate the possible role of HIV-1 compartmentalization in the development of HIV-1 drug resistance, transmission, and establishment of long-term reservoirs;
- Develop more accurate and simpler approaches to quantification of HIV-1 RNA 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 drug addicts 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, its complications, and 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, including sexual, injection-related, mother-to-infant (e.g., breast-feeding), mucosal, broken skin, etc.;
- Evaluate the impact of potent antiretroviral therapy on the reactivation of hepatitis viruses, the potential need for treatment of viral hepatitis in coinfecting patients, and the development of late-stage complications of viral hepatitis;
- Support clinical trials to evaluate the safety and efficacy of gene therapy;

- 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;
- Enhance the development of international collaborations that will assist in addressing important therapeutic research questions by including populations of HIV-1 infected individuals outside the United States; and
- Assist developing nations, as appropriate, in technology transfer to facilitate the evaluation of antiretroviral agents in local settings.

SCIENTIFIC ISSUE:

Progressive deterioration of immune function is an underlying cause of morbidity and premature mortality in HIV disease. Maintaining or restoring the integrity of the immune system is an important component of improving clinical outcomes for HIV-infected individuals.

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 hematopoietic stem cells and stromal elements 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 storage of lymphocytes and/or stem cells of 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; and
- Develop, incorporate, and validate appropriate quality-of-life parameters in clinical trials of immunoactive agents.

SCIENTIFIC ISSUE:

Opportunistic infections (OIs) are the most common immediate causes of morbidity and mortality in HIV-infected individuals; better therapeutic approaches to their prevention and treatment are important to improving clinical outcome.

OBJECTIVE:

Discover and delineate the structure and function of potential molecular targets and agents for prevention and treatment of HIV-associated OIs, while improving understanding of the biology and pathogenesis of HIV-associated opportunistic microorganisms; develop and evaluate new agents and strategies for preventing and treating OIs.

3.D**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*, MAC, multidrug-resistant *M. tuberculosis* (MDR-TB), microsporidia, JCV (the etiologic agent of progressive multifocal leukoencephalopathy[PML]), CMV, HPV, and azole-resistant fungi, with emphasis on innovative approaches and agents with favorable bioavailability and pharmacokinetics;
- Develop *in vitro* culture systems for opportunistic organisms such as *P. 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 natural products and novel synthetic compounds 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 organisms; apply these structures to the design of inhibitors; make coordinates for resolved structures available 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 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, PCP, acyclovir-resistant herpes simplex and VZV 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 OIs associated with HIV/AIDS in adults and children;
- Develop better strategies for simultaneous prevention of multiple OIs in the context of antiretroviral treatment; determine optimal time to initiate/discontinue prophylaxis for different OIs; develop improved OI strategies to minimize toxicities and the development of resistant organisms;
- Develop more precise tools to identify those patients at high risk for development of specific OIs in order to improve the efficiency of clinical trial design and to improve the risk-benefit ratio of the drugs in clinical use for prophylaxis and for treatment;
- Support research on the effectiveness of pharmacologic and other approaches to facilitate better adherence to anti-OI regimens;
- Support clinical research in the context of drug abuse treatment to reduce OIs among HIV-infected drug abusers; 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 organisms 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 with 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; and
- 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.

SCIENTIFIC ISSUE: Vertical transmission of HIV from the infected mother to child is the predominant mode of transmission of pediatric HIV infection worldwide.

OBJECTIVE: (The scientific objectives 3.E through 3.H are of equal weight.)

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

3.E

- 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 to facilitate development of 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 the treatment of the pregnant women; such strategies may include antiviral agents, anti-HIV immunoglobulin, monoclonal antibodies, vitamin supplementation (e.g., Vitamin A), 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 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 antiaddiction therapy in pregnant women; evaluate the impact of such interactions on the maintenance of antiaddiction 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;
- 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; and
- Develop, incorporate, and validate appropriate quality-of-life parameters in clinical trials of HIV-infected pregnant women.

SCIENTIFIC ISSUE:

HIV-associated malignancies have a significant adverse impact on morbidity and mortality, and some are expected to become increasingly common as survival with severe immune dysfunction is prolonged and as the demographics of HIV infection change. Recent advances in pathogenesis (e.g., KSHV/HHV-8) offer new potential areas for therapeutic intervention.

OBJECTIVE: (The scientific objectives 3.E through 3.H are of equal weight.)

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

3.F**STRATEGIES:**

- Identify novel mechanisms and targets (e.g., cytokines, angiogenesis factors, hormones) for treatment and prevention of HIV-associated tumors such as KS, non-Hodgkin's lymphoma, 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) in their pathogenesis;
- Use structural biologic and biochemical information to design rationally 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 to the treatment of AIDS 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; and
- Support research on the effectiveness of pharmacologic and other approaches to facilitate better adherence to complex therapeutic regimens in individuals with HIV-associated malignancies.

SCIENTIFIC ISSUE:

HIV infection of the nervous system is a component of the biology of HIV that may require special therapeutic targeting. Both central and peripheral nervous system disorders are common and important causes of morbidity.

OBJECTIVE: (The scientific objectives 3.E through 3.H 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-1-associated neurologic complications.

3.G**STRATEGIES:**

- Develop and evaluate novel strategies and 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-resistant strains and other mutants;
- Design and conduct clinical trials addressing nervous system complications of HIV infection in adults and in children;
- Develop objective quantitative assessments (e.g., surrogate markers in cerebrospinal fluid [CSF], neuroimaging) of treatment effects;
- Develop therapeutic agents to block HIV entry into the CNS and treat HIV in the CNS; evaluate their safety and efficacy in clinical trials;
- Develop better strategies to prevent, diagnose, and treat peripheral neuropathies in HIV-infected persons while improving 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 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; and
- Selectively incorporate neurologic and neuropsychological assessments into other HIV-related clinical trials.

SCIENTIFIC ISSUE: HIV affects many organ systems, causing significant morbidity for which effective therapeutic management strategies are limited.

OBJECTIVE: (The scientific objectives 3.E through 3. H 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.H

- 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 abuse illicit drugs;
 - Support research and development of new, more relevant clinical trial designs 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 to the treatment of wasting syndrome, growth failure, and other complications of HIV infection;
 - 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; and
 - 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.

AREA OF EMPHASIS:

Vaccines

AREA OF EMPHASIS:

Vaccines

STATUS:

Developing vaccines against HIV that are safe and effective increasingly has been recognized as a national and international public health priority. HIV vaccines that could prevent HIV infection, reduce disease progression to AIDS, or decrease the likelihood of transmission would all be valuable in stemming the tide of this devastating pandemic. The relentless spread of HIV infection and AIDS now has been projected to increase well beyond the year 2000.

Even with the reduced number of AIDS deaths in the United States in the past several years with the introduction of combination antiretroviral therapies in some populations, it is estimated that 40,000 new infections still are occurring annually. A revolving door of drug use and incarceration with increased risk of sexual abuse may be fueling a subepidemic, particularly in young minority populations. From vaccine preparedness studies, concern has been raised that the trends for reduced risk in populations of men who have sex with men may have been reversed, particularly in young men who may have increased risk-taking behaviors in the unsubstantiated belief that new drug combinations will provide a cure.

Delivery of effective drug therapy will continue to reduce the number of AIDS deaths in the near term in the United States and Western Europe, and behavioral interventions remain a critical component in preventing the spread of HIV worldwide. But these activities alone will not be sufficient to contain the epidemic. Transmission of HIV that is resistant to multiple frontline drugs has already been documented. Thus, HIV vaccines may be the only cost-effective way to prevent HIV infection worldwide. Affordable,

safe, and effective vaccines that are also easily delivered and acceptable to various populations at risk are urgently needed.

To address the scientific obstacles and facilitate HIV vaccine development, NIH continues to increase support for a broad program encompassing basic, preclinical, and clinical vaccine research on candidate vaccine products. With targeted funding through the OAR, NIAID in collaboration with the AIDS Vaccine Research Committee (AVRC), headed by Dr. David Baltimore, has continued to identify additional topic areas for the Innovative Vaccine Grants Program. This program provides 1- or 2-year funding to investigators to explore new concepts in basic research related to HIV vaccines. It is anticipated that some of these projects will continue and expand into larger competitive vaccine projects. In addition, a cross-Institute NIH Vaccine Research Center (VRC) has been initiated by focused staff discussions, and joint vaccine research will be funded through NIAID and NCI intramural programs. Plans for the building to house the VRC have moved forward rapidly, and construction now is under way with occupancy projected in the year 2000.

In parallel, NIH supports epidemiological and behavioral research on risk factors and preventive interventions that will form an essential foundation for vaccine trials. Many of these studies are conducted in collaboration with other Federal agencies, local communities, industry, and international organizations.

GOALS FOR A PREVENTIVE VACCINE

The goal of preventive vaccines is to slow and eventually halt the HIV pandemic and to protect the individual from HIV infection and/or disease. Protective efficacy against HIV infection can be measured by a range of clinical and virological endpoints. The prime objectives are to induce immune responses that block and/or rapidly clear incoming virus or infected cells, that control viral replication and spread if an initial infection is established, and that maintain a low viral load, thereby preventing disease progression and HIV transmission. Optimally, these vaccine-induced immune responses would be capable of clearing both virus and virus-infected cells. Thus, even if viral replication occurred at the site of viral entry, disseminated HIV infection could be prevented.

Early immunological control of HIV replication, by itself, could reduce viral load and/or reduce viral shedding, thereby preventing secondary transmission of HIV to sexual partners and from mother to infants. In the public health arena, this would be a highly effective vaccine approach and may be the underlying mechanism for many other efficacious viral vaccines. Vaccine-induced diminution in viral load also might be correlated with

prevention or delay in disease progression in an individual; a correlation between low viral load and long-term nonprogression has been observed in both epidemiologic investigations of HIV and animal studies of vaccines and passive administration of immunoglobulin. Efficacy of vaccines in preventing disseminated HIV infection can be determined relatively easily in the conduct of a vaccine trial by culture of viruses from peripheral blood mononuclear cells (PBMCs) or PCR of plasma or cells. However, assessment of long-term control of viral replication, immunosuppression, and disease progression, which may be critical for assessing efficacy, may be feasible but will make conduct of efficacy trials more complex. This may be particularly true in populations with access to highly effective, multiple-drug antiretroviral regimens for early HIV therapy.

Vaccine efficacy also may be influenced by the dose of infecting virus and by the site or route of exposure. There are substantial differences in the risk between different routes of transmission. For example, animal experiments with SIV suggest that a vaccine or immunoglobulin may protect against a high dose of HIV at vaginal, oral, or rectal sites of exposure but not protect against an equivalent or even lower intravenous inoculum. Alternatively, a vaccine may protect against exposure to virus intravenously but not protect against spread of HIV infection from an established mucosal site. It has been known for some time that the risk of vaginal transmission to women is higher per contact than sexual transmission from females to males. Thus, combination vaccine strategies eliciting broadly effective immune responses may be needed to optimize protection against biologically different routes of exposure.

Various strategies for stimulating a protective immune response against HIV infection are being explored through basic research, evaluation in animal models, and clinical trials. There are many inherent uncertainties, not only in the identification of the immune responses required for protection against HIV infection or disease but also in the vaccine designs and strategies needed to induce such protective responses. More intensive use of the SIV and SHIV chimeric viruses in macaque models for concept testing and comparative studies of different vaccines is warranted. This will permit multiple conceptual and practical approaches for development of candidate vaccines to be pursued at the preclinical level. Parallel advancement of vaccine candidates to small Phase I trials should be encouraged when product development and appropriate protocols to evaluate safety and immunogenicity in human volunteers are developed. Conducting small clinical trials early in product development affords the opportunity to rapidly return to the laboratory and incorporate

**BASIC RESEARCH
RELEVANT TO
VACCINE
DEVELOPMENT**

improvements or refine promising vaccine candidates that induce less than optimal immune responses.

Vaccines also may serve as immunomodulators to diminish HIV disease progression by improving immune function or stimulating newly generated T cells. Combining HIV vaccines with early antiretroviral therapy may be particularly advantageous in recently infected infants, adolescents, and young adults, where long-term adherence to complex drug regimens might be the most difficult to achieve and successful reconstitution of immune cell subsets may be highly feasible. One of the most vulnerable populations for HIV infection worldwide, women of childbearing age, also would benefit greatly from immunotherapeutic vaccine regimens both for themselves and for interruption of HIV transmission to their infants.

Genetic Variation

Basic research on HIV and on other lentiviruses and the ability of the immune system to respond to these viruses provides information required for the design and development of vaccine candidates. Vaccine design efforts continue to be complicated by the many unique aspects of HIV infection, including an unprecedented degree of genetic variation. Genetic variation has been shown to affect recognition by and escape from both humoral and cellular immune responses, particularly where strong immune responses are generated to a single dominant HIV-1 variant. Generally, extensive variation is observed within a single subtype (clade) and even in a single infected individual. At least two major groups of HIV-1 (M and O) exist with major genotypic clades within the M group that is dispersed worldwide. Virus from one clade (B) still predominates in the United States. However, recent isolates from geographic sites with evolving or newly emerging epidemics have revealed recombinant HIV-1 variants between B and C, A and B, as well as A/G, A/E, and B/F recombinants that were previously identified. Epidemiological studies of viral variants in women have indicated that vaginal transmission, possibly enhanced by endogenous or exogenous hormonal factors, permits entry of multiple variants from their infected partners, providing a plausible scenario for generation of diverse recombinants. Intravenous injection of several strains of virus into individual chimpanzees has resulted in at least one incident of recombination between strains and generation of a more pathogenic variant. Thus, multiple modes of transmission could permit generation of recombinant strains and further add to the identification of what types of virus must be incorporated in any vaccine.

Despite the high degree of variation in HIV, serum and monoclonal antibodies derived from some infected individuals are able to effect broad,

cross-clade neutralization of HIV-1 subtypes. This suggests the existence of common or conserved sites on the HIV-1 envelope, possibly related to the requirement of these sites, expressed on divergent HIV isolates, to interact with the cellular receptors and coreceptors. Vaccine strategies that have been tested in clinical trials have been unable to induce this type of broad cross-reactivity. Substantial data now exist which indicate that cytotoxic T cells, both from infected individuals and from HIV vaccine recipients, can recognize epitopes from widely divergent HIV subtypes. It is not yet clear how major histocompatibility (MHC) differences in persons from vastly different ethnic and racial backgrounds will affect their ability to make cytolytic T-lymphocyte (CTL) responses to candidate vaccines. A Phase I vaccine trial planned in Uganda will be the first to address this important basic vaccine research issue.

Immunity to Viral Proteins

The nature of the immune response needed to protect against HIV infection or to ameliorate established HIV infection is poorly understood in part because of the limited information about how existing vaccines provide immune protection in general. Furthermore, only one vaccine, the varicella zoster vaccine, has been licensed for an attenuated virus with the potential to establish latent infection. In this context, a great deal of immunologic information may be necessary to create effective vaccines against HIV which infects and lyses infected T helper lymphocytes, replicates within macrophages/dendritic cells impairing antigen-presenting function essential for an effective immune response, integrates into the host cellular genome, and can spread by cell-to-cell contact. Fundamental knowledge is still needed about (1) the factors that establish and maintain virus-specific immunologic memory, (2) the factors and signaling events that determine whether the effector immune responses to key antigens are amplified rather than tolerized or deleted, (3) the identity, source, regulation, and mechanism of action of cytokines and chemokines that affect, directly or indirectly, the induction of CTLs capable of curbing viral replication and eliminating virus-infected cells, (4) the role and mechanism of action of antibodies in neutralizing virus, reducing viral load, or controlling the spread of viral infection through antibody-dependent, cell-mediated lysis, and (5) the induction and interaction of humoral and cellular immune responses at mucosal sites to block the spread of viral infection.

In the last few years, reports about the structure and glycosylation of HIV (and SIV) envelope proteins have revealed critical information about both the surface (SU) component gp120 and the transmembrane (TM) component gp41, and their interaction. Use of these data to expose sites

of the virus envelope to immune responses and to design new immunogens is now under way in several laboratories. Similarly, the identification of the chemokine receptors, CXCR4 (X4) and CCR5 (R5), as major coreceptors for HIV has led to studies to develop new vaccines and drugs that might attack this new target of virus and host cell interaction. Cell lines designed to express specific coreceptors are being used as tools to evaluate the ability of immune sera from vaccinees to neutralize primary HIV isolates with specific coreceptor use, and genetically engineered small animal models with human coreceptors are being explored for future vaccine studies.

Recently, the technology has been developed to detect individual T cells with specific T-cell receptors (TCR) by dimeric or tetrameric MHC molecules associated with specific peptide epitopes. It is now possible to study, in selected human subjects as well as animals, the magnitude and duration of immune T-cell responses to viral infections and vaccines. As additional reagents to study diverse human MHC types become available, this new technology may make it possible to study the peak and diversity of the CTL responses generated in addition to the number of long-term memory cells in vaccinees receiving candidate HIV vaccines. Detection of T cells expressing interferon gamma is being used also to measure the subset of cells activated for lytic function. Studies to crosswalk these two technologies are being conducted in animals and human vaccinees.

Animal Models

With the development of methods to measure viral load for lentiviruses in animals as well as HIV human subjects, it has been possible to compare the *in vivo* replicative capacity of stocks of different virus isolates and the impact of prior vaccination. Key developments for various vaccine approaches have resulted from studies using pathogenic SIV in macaque models. With plasma viral loads comparable to HIV in human subjects, an AIDS-like syndrome that develops in several species of macaques, disease endpoints, and the different degrees of pathogenicity that reflect the spectrum of HIV infections that occur in humans, SIV has become the primary model for AIDS vaccine studies. The SIV/macaque models have provided a framework to evaluate not only sterilizing immunity capable of preventing any infection, but also vaccine-induced modulation of viral replication and protection against disease.

Chimeric viruses (SHIVs) that contain HIV *env* and other selected genes of HIV inserted into SIV have been developed and provide additional tools to evaluate vaccines. SHIV isolates infect and persist in macaques, and

several animal-adapted isolates have induced rapid CD4 T-cell depletion, AIDS, and death. Thus the adapted chimeric SHIV isolates with inserted HIV-1 *env* genes permit the direct evaluation of HIV-1 envelope-based vaccines in a disease model. The SHIV constructs currently available for vaccine testing have incorporated both T-cell-tropic, X4-using and macrophage-tropic, R5-using HIV-1 *env* genes. SHIV isolates with non-clade B HIV *env* are being developed to evaluate vaccines against divergent isolates. However, there is clearly a preference for replication and growth in macaques of the X4 or dual-tropic variants, and it appears that SIV macrophage-tropic isolates may be using a different constellation of chemokine receptors for infection.

The ability of HIV-1 to infect chimpanzees was established soon after HIV-1 was first isolated, and the chimpanzee provided an early model for vaccine and passive immunity studies. However, HIV-1 replication was limited in most animals, and nearly all of the isolates that have infected chimpanzees have been of the X4 type. The recent description of AIDS in chimpanzees that were injected with several HIV-1 isolates demonstrates that HIV-1 can recombine and adapt to cause slow pathogenesis in these animals. Chimpanzees also are being used to explore the level of protection induced by attenuated viruses and evidence of superinfection. Stocks for more pathogenic variants and isolates derived from different clades are being investigated for future vaccine studies.

Other lentivirus animal models continue to be explored because of their unique characteristics that make them relevant to AIDS vaccines. Baboons and pigtailed macaques can be infected with HIV-2 to study HIV-2 vaccines that utilize a human pathogen and not a surrogate such as SIV or SHIV. Feline immunodeficiency virus (FIV) presents opportunities to evaluate vaccine concepts with diverse variants and pathogenic clones, where cross-strain protection has been observed. FIV vaccine studies, at the same time, provide opportunities to test vaccines relevant for household pets. Equine infectious anemia virus (EIAV) in horses permits the *in vivo* evaluation of enhancement of a highly macrophage-tropic viral infection and pathogenesis that is induced with EIAV envelope protein vaccines.

Correlates of Immune Protection

Assessment of individuals who appear to be protected from high-risk exposure to HIV-1 or who have remained asymptomatic for long periods of time continues to provide evidence of HIV-specific immune responses that only occasionally may be linked to genetic impairment of the virus or to defective host coreceptors. Studies of virus-specific immune responses

**VACCINE
STRATEGIES AND
DEVELOPMENT**

to vaccines in macaques have advanced with the improving ability to measure CTL and cytokine expression in vaccinated animals. Studies of both systemic responses and vaginal or rectal mucosal responses to vaccines have been performed. Attempts to dissect the correlates of immunity for different vaccine approaches and different animal models have generated data that indicate that there is no single correlate of immune protection. For some vaccines, particularly in the SHIV and chimpanzee models, there is evidence that neutralizing antibody to the challenge virus is important for complete protection against infection. However, in animals infected with attenuated SHIV viruses and challenged with pathogenic SIV, protection or control of viral load that does not appear to be linked to neutralization via envelope epitopes is observed. Several studies indicate that cellular immunity to the internal, core proteins may be important for this protection. The ability to dissect the components of cellular protection would be greatly enhanced by the availability of genetically characterized, inbred, or genetically cloned macaques, which are being developed at several Regional Primate Research Centers (RPRCs).

NIH-supported researchers are pursuing multiple approaches for the development of HIV vaccines, including traditional approaches such as the incorporation of killed viruses in defined adjuvants and the development of attenuated viruses. Serious concerns about the safety of these two approaches remain unresolved, but studies in animal models on killed and attenuated virus vaccines may reveal correlates of immune protection and the requirements for a safe and effective attenuated vaccine. Data presented within the past year indicate that singular deletion of the *nef* gene, which has a profound effect on the ability of the virus to replicate *in vivo*, is not adequate to attenuate the pathogenicity of SIV and possibly HIV-1. Several safety studies in animals have indicated that the permissible level for continued viral replication in animals infected with attenuated virus is vanishingly low. However, variants produced by genetic changes in other regions of the SIV genome have revealed sites in genes of other regulatory proteins, *env*, *gag*, and the integrase region of the *pol* gene which may provide additional or alternative targets for attenuation of AIDS viruses.

Studies with a new pseudovirion vaccine candidate, incorporating the *env* of a non-syncytia-inducing (NSI) R5 HIV-1 isolate, is scheduled to enter Phase I studies. This “genetically killed” candidate vaccine contains multiple genetic deletions for improved safety, is noninfectious, and is somewhat comparable to a chemically killed virus. Currently it is designed for incorporation as a boost in “prime-boost” strategies that first vaccinate with avipox-HIV-1 candidate vaccines.

Additional complex HIV-recombinant vector vaccine candidates, capable of producing multiple HIV antigens, have been designed. Live infectious vectors also have the advantage of delivering an increased antigen dose to the host via pathways that are capable of inducing CTLs and priming T-cell help for antibody production. A number of live, attenuated viral and bacterial vectors incorporating copies of HIV genes are being explored in animal testing, and several are being studied in clinical trials. Increasingly complex poxvirus constructs, with genes for SIV or HIV in vaccinia, avipox, or modified vaccinia Ankara (MVA), continue to be evaluated in animal models. Both avipox and vaccinia vectors with copies of several HIV protein genes are being tested in clinical trials. SIV studies suggest that protection from infection is difficult to achieve with these vectors alone, but protection from development of high viral loads and disease is very often observed despite differences in the relative pathogenicity of the viral challenge. The different poxvirus vectors have variable, but generally poor, ability to induce antibodies. However, there is ample evidence from both animal studies and clinical trials that these vectors prime the T-helper memory immunity so that high levels of antibody are induced rapidly after a single protein boost. Vaccine strategies that employ two or more vaccine approaches where the host is primed with one vaccine candidate and boosted with a second vaccine candidate have many advantages, both in terms of inducing different immune mechanisms and in terms of providing different components of the viral genome.

Viral vectors for delivery of genetic material, e.g., polio and Venezuelan equine encephalitis virus (VEE), are being explored for production of viral antigens in the vaccine host in the form of replication-incompetent viruses, called replicons. Several viral or bacterial vectors that have particular advantages as vectors to target induction of immune responses in the mucosal immune system have shown promise in animal models. Mucosal vector approaches, such as adenovirus or attenuated *Salmonella typhi*, which may be extremely important to induce immunity to prevent transmission at mucosal sites of exposure, have made modest headway in development and testing. Protection against an intravenous challenge of heterologous HIV in chimpanzees vaccinated via mucosal routes with adenovirus vectors has been reported. In general, data from several different vaccine strategies have indicated that it may be easier than previously anticipated to protect against vaginal or rectal routes of mucosal exposure with SIV or SHIV isolates. This may be, in part, because transmission in the animal models usually is not complicated by abrasion or other STDs that often accompany HIV transmission. Alternatively, complex pathogenesis patterns in the mucosa with different HIV isolates may provide a window of time for the host to initiate an immune response.

DNA vaccines or genetic immunization vaccine strategies for HIV are particularly appealing for international applications, because they provide potential flexibility for incorporating new variants into the vaccine. In small animals, DNA vaccines have demonstrated the potential of inducing both cell-mediated and humoral immune responses. Studies of DNA vaccines in nonhuman primate models have met with mixed results. HIV or SIV DNA vaccine candidates containing only *env* genes have been able to protect from infection only when boosted with a protein product and/or challenged with HIV in chimpanzees or nonpathogenic SHIV in macaques, whereas reduced viral load has been observed in several studies. Evaluation of DNA vaccines derived from genetically attenuated, nonreplicating, “killed” viruses, e.g., SIV with deletions in nucleocapsid sites, has resulted in partial protection or reduced viral load in animals challenged with pathogenic SIV. While DNA vaccines must be further refined to improve their level of expression in mammalian hosts, this approach appears to induce CTL relatively easily because DNA is taken up and expressed by dendritic cells which then present processed antigens in the MHC class I pathway to the host immune system. Several companies as well as a number of academic investigators are exploring DNA HIV vaccine candidates.

A major current focus of HIV vaccine research is the attempt to improve envelope proteins so that vaccinees can produce neutralizing antibodies to conserved neutralization domains of primary, R5-using isolates of HIV. The previously tested monomeric gp120 envelope proteins induce relatively high titers of antibody that neutralize X4, syncytia-inducing (SI) isolates of HIV. However, they have failed to induce antibodies that will neutralize R5, NSI, macrophage-tropic isolates. Investigators have hypothesized that this is due to the monomeric nature of the gp120 envelope protein used in the candidate vaccines. Because monomeric gp120 is only part of the envelope protein complex at the surface of the virus, new strategies to produce trimeric gp120 attached to the outer part of the gp41 molecule, as oligomeric gp140, are now being attempted. The envelope protein of HIV-1 is a highly glycosylated protein that may mask critical neutralization sites; therefore, some investigators are attempting to remove glycosylation sites to provide a “nude” gp120 core to the immune system. The envelope protein vaccine candidates first tested in human volunteers were derived from X4, SI isolates of HIV-1; therefore, new vaccine candidates are utilizing envelope protein derived from R5, NSI isolates, alone or in combination with other envelope proteins and other vectors. Finally, investigators are attempting to identify and formulate conformational epitopes derived from the envelope protein or mimetopes that might induce antibodies to conserved domains.

**VACCINES AND
PASSIVE IMMUNE
INTERVENTIONS
AGAINST
PERINATAL
HIV TRANSMISSION**

The ACTG 076 trial demonstrated that a complex regimen of ZDV treatment of mother and infant to prevent perinatal transmission of HIV was highly effective despite a minimal effect on the maternal plasma viral load. For most of the developing world, where the majority of HIV infection of women and children is occurring, a more useful prevention regimen would be given once or for a limited time, easily administered, nontoxic to both mother and child, inexpensive, and have the potential to prevent postpartum transmission via colostrum or breast milk. Passive administration of HIV immune globulin (with or without added monoclonal antibodies) and active vaccination to prevent infection might be equally effective, if delivered in the interpartum period and to the infant to prevent breast-milk transmission. Several passive immunity studies in animal models have shown that transmission can be blocked or the clinical progression greatly altered by virus-specific antibody. The clinical study ACTG 185 provided pooled immunoglobulin from asymptomatic HIV-infected subjects (HIVIG) or a standard preparation of intravenous immunoglobulin (IVIG) to pregnant women and their infants who also received the 076 regimen of ZDV. Completed analyses of this passive immunity study indicate that infection was not prevented in all infants, and there were somewhat fewer infections in the HIVIG arm of the trial. However, none of the infants who became infected in the HIVIG arm of the study had detectable viruses by culture at birth, whereas about one-third of the infected infants in the IVIG arm of the study had a culturable virus. Analysis of the transmission, by maternal CD4 count and/or prior ZDV use, indicated a strong trend for reduction of transmission with HIVIG in women who were more immune compromised. These results reflect the range of outcomes that has been observed in animal studies. Some infections appear to have been averted; others may have been delayed in virus replication and detection. Improved products for passive immunity continue to be developed. With evidence of antibody synergy for virus neutralization, future development of effective cocktails to prevent viral escape from a monovalent product is highly desirable.

**CLINICAL VACCINE
TRIALS**

The NIH now has conducted or initiated a total of 49 Phase I and II trials with 23 vaccine candidates and 10 different adjuvant substances. Most of these trials have been conducted in the AIDS Vaccine Evaluation Group (AVEG), but also include trials conducted by the NIAID-sponsored HIVNET and intramural laboratories as well as the Pediatric AIDS Clinical Trials Group (PACTG). More than 3,300 volunteers have participated in these safety and immunogenicity trials. Within the past year, several new Phase I trials were initiated with new recombinant vectors, including an attenuated *Salmonella typhi*-HIV envelope vaccine candidate and additional poxvirus vectors or protocols with combined vaccine candidates. Canarypox

vectors of HIV are being used in mucosal applications, and the vaccinia vector currently in trials is being evaluated in a variety of delivery applications including intradermal. These studies will determine whether it is possible to induce immune responses more frequently or at the mucosal sites of entry with the recombinant vectors delivered to these sites.

Of great importance to future HIV vaccine trials in the international setting is the fact that CTLs have been detected in response to the poxvirus-based vaccine candidates that recognize proteins from isolates of different HIV clades. Of serious concern, however, is the unresolved issue about the genetic variability of the vaccinees with regard to major histocompatibility backgrounds and whether individuals of different genetic backgrounds will respond at the same level as vaccinees currently being tested in domestic sites. Responses to *gag* and *env* genes are detected in vaccinees receiving poxvirus vaccine candidates containing both gene products. The frequency of responses varies from 20 to 60 percent, dependent on the amount of HIV genetic material incorporated into the vector, the number of times the volunteers receive the vaccine candidates, and the number of times individuals are tested. Responses to additional HIV gene products incorporated in the vectors do not appear to be detected at the same frequency in the same time frame. As studies of poxvirus vaccinees have been extended, it appears that CTLs detected at late post-vaccine time points are at higher frequency in volunteers who have received up to four vaccinations with the recombinant vectors.

The NIH currently is conducting a Phase II trial in a collaboration between the AVEG and HIVNET sites and the pharmaceutical sponsors. This trial will evaluate a canarypox vector containing copies of the genes for HIV gp120 envelope protein anchored with the TM region of gp41, *gag*, and protease (VCP 205). Vaccinees are being vaccinated with this vector and boosted with gp120 protein from SF2. In earlier trials it was demonstrated that the immunization with the protein product substantially increases the antibody response in vaccinees and appears to also increase the lymphocyte proliferative responses to the product in the boost. New Phase I trials have begun to evaluate alternative recombinant vectors and protein products for the boost that include gp120 derived from primary NSI isolates to determine whether improved neutralizing antibody responses to primary NSI isolates can be generated in these protocols.

Additional vaccine candidates are expected to move into expanded Phase II and possibly Phase III testing based on current immunogenicity studies. NIH-sponsored research required to prepare for clinical evaluations of potential vaccine candidates in efficacy trials is being performed in more

than 20 domestic and international sites where populations have been identified at increased risk of HIV infection. Interdigitation of biomedical and behavioral research is perceived as essential to the expanded testing of HIV vaccines. Domestic trials are being linked with parallel trials in international settings where site preparation and cohort studies have indicated feasibility of vaccine testing. Education and training to conduct vaccine studies in additional domestic sites need to be expanded with an increased presence in and recruitment of minority populations who have borne disproportionate hardships in the HIV epidemic.

SUMMARY

The NIH has made clear its commitment and intent to expand and accelerate AIDS vaccine research, development, and testing at multiple levels. New programs for funding basic vaccine research, animal resources to conduct tests of concepts, resources for development and production of new candidate vaccines, development and provision of products for vaccine evaluation, expanded grant programs for development of collaborative investigator groups, and clinical trials groups to conduct HIV vaccine trials are already in place. A new study section to review vaccine research applications has been formed to recognize the essential role of vaccines in the public health arena and to ensure competent and fair review of the often pragmatic issues in testing vaccines for infectious diseases. Research cohorts for expanded testing of vaccines and biomedical and behavioral modes of prevention of HIV infection have been identified and utilized for vaccine preparedness studies and for participation in a Phase II vaccine trial as well as other HIV prevention studies.

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Scientific Issues and Objectives

SCIENTIFIC ISSUE:

More basic knowledge is needed to define protective immune responses to HIV in order to facilitate the development of vaccines and other biomedical intervention strategies to prevent and control HIV infection.

OBJECTIVE:

Increase scientific knowledge of host defense mechanisms leading to protection against HIV infection and disease.

4.A

Basic research on the topics of immune responses to HIV viral antigens and on the mechanisms underlying protective immunity is an essential first step to the development of successful vaccines against HIV. Recent information about the HIV envelope structure and coreceptor usage as well as information about the control of viral load in HIV-infected, long-term nonprogressors and acute infections provides new keys for definition of immune control of HIV. Several strategies to address these and other areas are outlined.

STRATEGIES:

Define the mechanisms underlying protective systemic and mucosal immunity to HIV and other lentiviruses by pursuing research that will:

- Determine the mechanisms of immunologically mediated control of infection with HIV and other related retroviruses, 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 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; 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; 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; define factors that favor establishment and maintenance of memory cells able to generate effective recall to vaccine antigens and development of long-term protective immunity, particularly in human subjects;
- Study the mechanism of action of vaccine adjuvants and enhanced modes of antigen presentation to induce different cytokine responses; carry out translational research in nonhuman primates and human vaccinees; and
- 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 the immune system that are responsible for lack of disease induction and protection from challenge with wild-type virus; determine the protective mechanism, duration, and extent of cross-protection.

Seek new clues from HIV-infected or highly exposed but uninfected individuals, both adults and infants, and lentivirus models that will provide the basis for further design of candidate vaccines:

- Study acutely infected individuals, exposed/uninfected, or possibly transiently infected humans (and other nonhuman primates), and nonprogressors to define early immune responses to lentiviruses and potential vaccine-inducible host immune responses and viral factors (or viral attenuations) that reduce the amounts of circulating virus and impact 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;
- 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; and
- 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; acquire appropriate epidemiological information to enable interpretation of these analyses.

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:

- Develop reagents, improved *in vitro* 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 and viral suppression responses and develop high-throughput assays with specificity for primary virus isolates;
- Define the heterogeneity of specific responses to an immunogen within diverse tissue compartments and identify factors that confer protection from infection by various routes, including vaginal, rectal, oral, and parenteral;
- Develop methods to determine which factors promote development of particular 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 biotypes);

- 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*;
- Develop or improve sensitive quantitative measures of HIV (and SIV) concentration in body fluids, including genital secretions, to assess the effectiveness of vaccines designed to lower viral load and interrupt transmission or prevent disease progression;
- Develop and improve animal models of lentivirus infection that are practical and representative of the spectrum of HIV infections, including use of appropriate HIV cellular receptors, and different modes of transmission and development of AIDS; make models amenable to use in evaluating protection by vaccines or other biomedical interventions; and
- 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.

SCIENTIFIC ISSUE: The identification of viral antigens and vaccine delivery methods that elicit long-lasting protective immune responses against a broad range of HIV isolates will facilitate development of effective vaccines.

OBJECTIVE:

Apply findings from basic, epidemiologic, and clinical research to the design and preclinical evaluation of vaccine strategies in laboratory studies and animal models, and foster collaboration with industry in the research and development of candidate vaccines.

4.B

Because of the uncertainty of the success of any single approach for an HIV vaccine, experiments must be designed to test a broad array of vaccine concepts for development of potential novel HIV vaccine products, including vaccines with combinations of different approaches. Findings from research on immune responses to lentiviruses and on mechanisms to induce effective immune control of viral replication should be incorporated into new vaccine designs. Methods to enhance the breadth and duration of the immune response should be incorporated into preclinical testing. Testing should include both immunogenicity and early, preclinical safety/toxicology testing as well as evaluation of protection against infectious or pathogenic viral challenge, if appropriate. Research should be integrated with industry partners as soon as reasonably possible to ensure timely production and preclinical evaluation of products for human testing.

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

- 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 the following:
 - *Virus-like particles or pseudovirions containing one or more virus proteins, peptides, or antigens;*
 - *Whole-killed HIV and safer, genetically engineered, noninfectious HIV mutant virions;*

- *Naturally occurring and genetically engineered, live-attenuated strains of HIV;*
- *DNA 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 of critical nonlinear structural epitopes for induction of effective antibody responses;*
- *Structurally constrained viral protein fragments, peptides, or complex peptides capable of inducing and boosting cellular or humoral immunity to HIV; and*
- *Cell surface components carried on the viral surface;*
- 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 the 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;*
 - *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, especially for both humoral and cellular aspects of systemic and mucosal immunity, by:

- *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; and*
- Foster collaboration between academic investigators and industry sponsors on research and development of novel vaccine design concepts:
 - *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; 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.*

SCIENTIFIC ISSUE:

Distinct study designs and vaccine or intervention strategies are needed to achieve protection of newborns and infants because of the unique nature of their immune responses and modes of exposure to HIV.

OBJECTIVE:

Identify mechanisms of protective immunity to HIV in newborns and infants, and support the development of safe and effective active and passive vaccine strategies for preventing or controlling HIV infection in this population.

4.C

Transplacental maternal transmission of antibody *in utero* and via breast milk to an infant provides powerful strategies to prevent some viral and bacterial diseases. Active vaccination of a mother to prevent HIV transmission and/or direct administration of antibody at the time of birth to prevent interpartum HIV transmission are conceptual modes of immune-based protection that should be explored in parallel with other vaccine studies. In addition, vaccines, sometimes modified to improve induction of T-cell immunity, are administered to infants to induce effective immune responses and to provide protection from pathogenic organisms. In breast-fed infants in the developing world where HIV is widespread, immune intervention strategies, particularly combined with the benefits derived from short-course antiviral drugs (such as AZT), might provide prolonged protection. Because of the relatively long half-life of antibody, additional clinical benefit might be observed that cannot be achieved with transient effects of antiviral drugs.

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:

- 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;*

- *Evaluate efficacy of vaccines and passive immunotherapy for prevention of perinatal 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:
 - *Determine the importance of viral load and viral phenotypes (or biotypes) and genotypes in perinatal HIV transmission and what viral factors are associated with differences in perinatal transmissibility;*
 - *Develop standardized methods to detect, characterize, and quantify HIV in cervicovaginal secretions to determine their potential relevance in perinatal transmission; and*
 - *Determine if virus in maternal genital secretions is distinguishable from virus found in blood and which type is transmitted from mother to fetus and mother to infant; and*
- Identify maternal and infant immune responses that might prevent transmission of HIV or establishment of infection in infants, and control viral replication in 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 the safety in human subjects:

- 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; and

- 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).

Develop the capacity to test the efficacy of active and passive HIV vaccine interventions particularly in the international setting where sustained administration of effective antiretroviral therapy would be unlikely:

- 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 and maintain 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; and
- Study the impact of early antiviral therapy on the antiviral immune responses of HIV-infected infants.

SCIENTIFIC ISSUE: Suitable candidate vaccines need to be selected, developed, and evaluated in Phase I and Phase II trials to determine safety and immunogenicity.

OBJECTIVE:

Select candidate vaccines or concepts suitable for Phase I and Phase II trials, and conduct these trials.

4.D

STRATEGIES:

Many HIV vaccine candidates have shown exciting promise in immunogenicity in small rodents and sometimes even in macaque models without parallel immunogenicity in human trials. Thus, it is imperative to conduct Phase I/II trials in human volunteers. Several of the safety issues that have been raised with envelope proteins, adjuvants, live vectors, and/or attenuated virus must be addressed both in preclinical studies in nonhuman primate models and in human volunteers.

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

- 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 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 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; and
- 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.

Develop and coordinate educational and information programs about HIV and HIV vaccines for the individual participants and the communities that will be involved in trials; include mechanisms that will address social harm and provide protection messages:

- 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 and II trials that would facilitate broader participation;
- Conduct behavioral research during vaccine trials, particularly on Phase II trial participants, to identify changes in risk behavior 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; and
- Closely coordinate the evaluation of research findings on prophylactic AIDS vaccines with preclinical research and immunotherapeutic interventions.

SCIENTIFIC ISSUE:

Preparation for HIV vaccine efficacy trials requires characterization of the biological and behavioral factors in affected populations, including seroincidence, and development of trial site infrastructure, including a series of studies and planning activities to ensure trial feasibility.

OBJECTIVE:

Identify domestic and foreign populations, and maintain appropriate cohorts; develop strategies, infrastructure, and collaborations with governments, communities, and industry necessary for ensuring adequate performance of efficacy trials, while balancing the prevention needs of the at-risk populations.

4.E

Preparation for HIV vaccine efficacy studies requires identification of populations with a high seroincidence, identification of the types of HIV present in the population, and development of sites that will be capable of acquiring samples and conducting trials with multiyear followup. The communities and individuals participating need to be informed and knowledgeable about HIV vaccine issues. Laboratory infrastructure must be acquired, and personnel must be trained to conduct sample processing and some evaluations during the trial.

STRATEGIES:

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

- 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 compliant participants in vaccine trials;
- 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; and
- Develop and maintain the necessary immunology and virology laboratory infrastructure at designated sites for conducting domestic and foreign vaccine efficacy trials.

Establish linkages with communities or community organizations where efficacy trials might be conducted to optimize education, recruitment, and followup activities and to help address community concerns, resolve social issues, and ensure ethical conduct of AIDS vaccine efficacy trials:

- For domestic trials, educate and inform communities participating in the trials through community action boards (CABs) on a continuing basis so that social as well as medical concerns are addressed; work to establish trust through open discussions of fears and concerns; and
- For international trials, work closely with national (host) governmental and regulatory authorities, collaborating institutions or agencies, vaccine manufacturer(s), and UNAIDS to prepare for, plan, and conduct vaccine efficacy trials adhering to the highest ethical and scientific standards.

Explore behavioral and social issues and prevention activities that might have a substantial impact on either the design or the conduct of a trial:

- 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; assess 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; and
- 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:

- Consider the impact of early antiretroviral therapy on HIV infections in complex trial designs; and
- Encourage linkage between vaccine preparedness studies in high-risk populations and other research activities including research on TB and STDs; integrate research on vaccines against OIs as appropriate.

SCIENTIFIC ISSUE:

Conduct HIV vaccine efficacy trials of the most promising candidate vaccines in well-characterized, high-risk populations to identify effective vaccines for the control of HIV infection.

OBJECTIVE:

Select suitable vaccine candidates and support efficacy trials when appropriate criteria are met.

4.F**STRATEGIES:**

Vaccine development is a reiterative process incorporating vaccine design changes and testing in different populations of people at risk for infection. The test of vaccine efficacy is ultimately decided by an efficacy trial. The selection of candidates to move into large-scale “proof of concept” or efficacy trials will be made based on multiple factors.

Develop a comprehensive plan for initiation of vaccine trials, vaccination, and followup of vaccinees to defined endpoints:

- Establish criteria with concurrence of an advisory group that has the requisite scientific, public health, Government, and community expertise;
- 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; and
- 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:
 - *Evaluate HIV vaccine candidate efficacy against infection, disease, and/or transmission;*
 - *Evaluate additional virologic, immunologic, and behavioral outcomes, particularly potential correlates of protective immunity; and*
 - *Ensure that trials are conducted with the highest regard for social and ethical standards.*

AREA OF EMPHASIS:

Behavioral and Social
Sciences

AREA OF EMPHASIS:

Behavioral and Social Sciences

STATUS:

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 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.

Current research priorities in the behavioral and social sciences reflect 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 rising 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.

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.

A third major 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 high-seroprevalence countries, such as Thailand and Uganda. This suggests the need to study further the impact of legal and policy changes on stemming the AIDS epidemic through behavioral change, both domestically and internationally.

With these recent developments in mind, NIH sponsors 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 the behavioral and social sciences is a continued

**INTERVENTIONS TO
PREVENT HIV
TRANSMISSION**

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.

Rapid advancement of meaningful and effective HIV-related behavioral and social science research requires further development of methodological tools. As with other areas of HIV research, methodology represents the essential building blocks of HIV-related behavioral and social science research, and, therefore, it must be given special attention at NIH to facilitate rapid advancement of both basic and intervention research.

Since the advent of the HIV/AIDS epidemic, much has been learned and accomplished in the area of HIV/AIDS prevention through behavioral change interventions. Theory-driven intervention models have been developed and employed by researchers supported by NIH and have demonstrated that preventive interventions work even among “hard-to-reach” and socially disenfranchised populations. These interventions have resulted in marked changes in the sexual and drug-using behaviors most implicated in HIV transmission (i.e., engaging in unprotected sexual intercourse and sharing unsterile drug injection equipment) among such groups as rural gay men, out-of-treatment IDUs, homeless and runaway youth, women in public housing units, and the seriously mentally ill.

For example, NIH-supported research has demonstrated that multifaceted risk-reduction programs (including drug treatment, outreach and education on HIV risk, and provision of sterile injection equipment) can produce significant and sustained decreases in HIV risk behavior among IDUs, even among those who continue their drug abuse. Numerous studies have documented that drug abuse treatment, particularly methadone maintenance programs, significantly reduces needle-related risk behaviors, such as frequency of drug injection. These behavioral changes are consistent with seroprevalence and seroincidence data, indicating reduced risk of HIV transmission. Studies of outreach strategies for out-of-treatment IDUs also have demonstrated significant levels of behavioral change. A recent summary of NIH-supported studies in 12 cities documents the effectiveness of HIV risk-reduction education in reducing drug injecting and multiperson use of syringes and other drug injection equipment. Other studies have shown a relationship between the use of sterile syringes obtained through needle exchange programs or pharmacy sales and reductions in needle sharing.

Delaying the initiation of sexual intercourse and dissuading youth from engaging in drug use also have been important HIV prevention strategies developed and tested by NIH-supported researchers. In one study, 89 percent of abstinent youth who received HIV information and a skills-training intervention delayed initiation of sexual activity for 1 year postintervention, compared with 68 percent of those who received only the HIV information.

To date, most behavioral change interventions have been tested in small groups, in a limited number of communities, and over relatively short periods of time (6- to 12-month followup periods). It is now important to replicate and refine the most successful of these interventions to test their effectiveness on a broader scale and over longer periods of time, and to develop new interventions to address behaviors that have proven most resistant to change. More data should be collected on high-risk behaviors and seroconversions in cohort studies to permit better modeling of HIV. Where appropriate, interventions should be tested in randomized, controlled trials, and, when possible, HIV seroincidence should be an additional outcome measure. NIH-supported researchers are engaged in multisite investigations to identify the most effective components of behavioral interventions for different populations, including IDUs, crack cocaine users, and primary health care and STD clinic patients, and to assess their effect on both behavioral change and STD and HIV seroincidence in those populations. In addition, determining the cost-effectiveness and cost-utility of such interventions is an area of current exploration by NIH-supported researchers.

Research has demonstrated that, in order to be successful, preventive interventions should be tailored to specific populations and must take into account the cultural and social contexts of different people's lives. NIH-supported projects utilizing theoretical models from the behavioral and social sciences are uncovering the specific elements of social and cultural life that contribute to HIV risk and protective behaviors and that must be addressed in interventions. For example, one study investigated how different personal and social resources, threat appraisal processes, and coping styles affected the differential use of condoms among homeless African-American and Latina women and concluded that culture-specific strategies that attend to these differences are necessary to effect positive behavioral change among these women.

Community-level interventions may be an important way to effect behavioral change on a broad scale. NIH-supported researchers have investigated

**UNDERSTANDING
HIV TRANSMISSION**

the impact of community-level approaches both in the United States and abroad. For example, in a study of five cities in which HIV had entered a heterosexual IDU community but where HIV seroprevalence remained low and stable, three common prevention components were identified: beginning prevention early; community outreach; and access to sterile injection equipment. The researchers concluded that in low-seroprevalence areas, such community-level approaches may limit transmission of HIV among populations of IDUs despite continuing risk behavior among a substantial proportion of the population.

Other important areas of intervention research at NIH include the following: the acceptability of both biomedical and behavioral interventions among different individuals and communities; the behavioral aspects of the adoption of new HIV prevention technologies, such as the female condom, microbicides, or the use of ZDV by pregnant women to prevent vertical transmission of HIV; and social and psychological factors influencing participation in study trials and adherence to medical regimens for the treatment of HIV- and AIDS-associated disorders.

Ensuring the relevance and effectiveness of behavioral change interventions for HIV prevention requires understanding the psychological, social, and cultural factors that contribute to HIV risk and protective behavior. Specifically, NIH-supported researchers are investigating the mechanisms that influence risk behaviors—from neurobiological factors related to sexual drive and drug addiction, to psychological factors related to self-esteem and the ability to negotiate safe sex, to social and cultural factors related to laws, norms, and values about sexuality, drug and alcohol use, and HIV/AIDS itself. This basic research, including the development and testing of theories of behavioral change and maintenance in the context of HIV risk, is the essential underpinning of primary prevention and early intervention efforts.

Studies of decision-making processes have identified psychological factors, knowledge, attitudes, and behavioral intentions as important in leading to behavioral change among individuals. Most of these approaches focus on the individual at one point in time or stage of life. However, HIV risk and behavioral change may be experienced differently by people at different stages of development and different points in their lives. This suggests the importance of including a developmental and a life-course perspective in HIV prevention and intervention research.

Moreover, it has become apparent that the social nature of HIV risk behavior requires a broader focus than merely on the individual. NIH-

supported research has demonstrated the significance of partners, social networks, families, and peer groups in influencing an individual's engagement in or avoidance of risk behavior. For adolescents, research has determined the important role both parents and peers play in decisions to initiate or postpone sexual activity. For example, in a study of inner-city youth, simply having the parents monitor the adolescents' activities was associated with a delay in sexual initiation. The dynamics of relationships play a central role in influencing protective behaviors. Studies show that adolescent males' use of condoms declines the longer they remain with a given partner. One study demonstrated that an intervention that helped women develop negotiation skills was very effective with new partners, but was less so with ongoing partners.

Personal networks have been determined to be both sources of HIV transmission and potential targets of HIV preventive interventions. In one study among IDUs, for example, researchers found that higher total personal network density and larger drug network size were positively associated with needle sharing. Another study of sexual networks demonstrated that individuals who had partnerships that overlapped in time had five times the risk for HIV infection than those who practiced serial monogamy. Understanding the characteristics and dynamics of networks has led to interventions that interrupt such risky practices.

Another area of particular importance for understanding HIV transmission is the overlap in HIV-related risk behaviors. NIH-supported researchers are investigating the complex interplay of alcohol use, drug use, and poor impulse control and their impact on risky sexual behavior, including the situational factors that contribute to their mix. For example, one study determined that partner characteristics (steady, long-term versus casual) moderated the relationship between alcohol use and high-risk sexual behavior among gay men. Individuals without steady partners were four times more likely to engage in risky sex (unprotected intercourse) under the influence of alcohol than those with steady partners.

Despite progress in prevention and treatment of HIV disease, AIDS will continue to have a significant impact on individuals and communities both domestically and globally. NIH-supported researchers have been studying the consequences of HIV and AIDS on individuals, their loved ones, and caregivers for some time now. These investigations span the sciences from neuroimmunology to social psychology, as they address such issues as the bidirectional relationship between stress, depression, and immune functioning in individuals, the psychological costs and benefits of caregiving, and the impact of bereavement on individuals' mental health.

CONSEQUENCES OF HIV INFECTION AND AIDS

**RESEARCH AND
EVALUATION
METHODOLOGIES**

Because the AIDS epidemic has a devastating impact on families and communities, it has become increasingly important to investigate its social and cultural consequences. For example, NIH-supported researchers are examining the implications of the “stigma” of HIV/AIDS—that is, as a disease that is generally fatal and whose transmission is characterized primarily by socially marginalized activities—on the care and treatment of infected persons; the social and psychological status of orphaned children whose parents have died from AIDS; and the impact of HIV/AIDS on health care systems and economies of communities that have been most affected by the epidemic.

As advances in the range and type of research questions being addressed are made, so are advances in the methods being employed to answer them. Since the advent of the HIV/AIDS epidemic, significant improvements have been made in enhancing data collection. Advances and refinements of qualitative and quantitative methods for gathering information, e.g., computer-assisted survey instruments, have improved both the collection and the confidentiality of data, including self-reported data. Some NIH-supported studies are collecting microbiological and disease outcome data (e.g., STD and HIV serological test results) as an additional measure to use in conjunction with self-reports. Laboratory tests for detecting STDs and HIV have improved and the collection of specimens in the field has improved (e.g., through saliva tests for HIV and improved urine collection bottles). These developments were recently applied for the first time in a nationally representative study of sexual risk and protective behaviors among adolescent and young adult men.

Some behavioral change interventions have been developed to the point where they now can be tested in quasi-experimental or randomized, controlled trial designs to better ascertain their effectiveness. One such NIH-supported multisite, randomized, controlled study demonstrated the efficacy of a cognitive-behavioral intervention using both self-reported behavioral change and STD incidence as outcome measures. In addition to behavioral change and STD outcomes, HIV seroincidence data are also being collected as an intervention outcome measure in a number of studies, including a large-scale randomized trial among gay men.

Additionally, new techniques for improving our ability to quantitatively estimate the success of behavioral interventions in preventing the spread of HIV are being developed by researchers with expertise in mathematical modeling and biostatistics. For example, NIH-supported researchers have developed models to estimate the number of HIV infections averted

through the implementation of a one-for-one sterile needle exchange program and to estimate how effective a vaccine program would be in stemming the rate of HIV transmission in one city given various scenarios related to the level of vaccine efficacy, use of the vaccine, and behavioral change. Continued support over the next few years should see further refinement in such methodologies, which will produce better estimates for projecting the course of the AIDS epidemic in different regions and populations and the possibilities for stemming it through specific interventions. In turn, this will improve our ability to determine which interventions are successful and which are not and to apply resources accordingly.

The evaluation of HIV prevention strategies and programs is a vital part of the behavioral and social science agenda at NIH. Conducting successful evaluation—both program evaluation and cost-effectiveness/cost-utility evaluation—requires sophisticated methods, including the identification and operationalization of appropriate outcome measures. Further development of methods in this area will allow us to determine not only which interventions are most successful, but also whether particular components of interventions are more effective than others.

Scientific Issues and Objectives

SCIENTIFIC ISSUE:

HIV prevention interventions have demonstrated that HIV-related risk behaviors can be measured and modified. As the epidemic evolves, effective strategies are required for reducing or preventing HIV transmission in many at-risk populations not yet reached by these interventions or for whom effective interventions have not yet been developed. To be most effective, prevention interventions need to take into account both the salient characteristics of the at-risk population and the sociocultural context in which people live. Integrated interventions have been shown to be effective, but also need continued development. For example, research has demonstrated that drug and alcohol abuse treatment, outreach and counseling, and syringe availability programs reduce risk of HIV infection among IDUs. Further development of comprehensive interventions are needed to address the varying profiles of risk factors, including combinations of alcohol and drug use, mental health issues, and sexual risk-taking behaviors, that are related to HIV infection and transmission in diverse populations. Efforts must be expanded to integrate interventions at multiple levels of impact and intensity and to use multiple methodologies and outcomes to validate their effects. In addition, feasibility, maintenance, and replication of intervention effects, including the demonstration of their impact on HIV seroincidence, need to be tested with results disseminated to affected communities.

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, and ethnicity). 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 high-risk populations (e.g., IDUs, other drug users, partners of drug users, men who have sex with men) focusing on drug use and sex-related risks;
- Support 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; 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 should also identify which public health applications most effectively attend to cultural contexts;
- Investigate the interaction of behavioral and pharmacologic therapies for drug 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 within prison and returning to society from the prison system—strategies include increasing access to education, information, therapeutic care, prevention services, and clinical trials; and

- Support the capacity to develop rapid-response 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 HIV-related drug abuse, mental health, alcoholism treatment, and family planning interventions 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; and
- 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 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; and
- 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 HIV preventive intervention research; and
- Support behavioral intervention studies that include HIV seroincidence data and other biologic markers as outcome measures.

SCIENTIFIC ISSUE:

The HIV/AIDS epidemic continues to spread, now affecting the most severely underserved populations. At the same time, recent years have witnessed important improvements in HIV treatment and care. Understanding the implications of these two developments requires basic behavioral and social science research focused on HIV-infected individuals and on populations likely to become infected with HIV. Research is needed to understand the antecedents and consequences of risk and protective behaviors at the societal, community, organizational, network, dyadic, familial, and individual levels. Additional basic research is needed to identify the behavioral, psychological, cognitive, cultural, contextual, and social factors that affect HIV treatment and disease management. Models based on this understanding should be developed for guiding interventions to prevent the transmission of HIV and to reduce its adverse consequences. Further research on the improvement of methodologies to address fundamental issues in the prevention and the consequences of HIV is also needed.

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 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;
- 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; support theory-building studies developed in the context of HIV prevention research,

including studies that adopt a developmental and life-course perspective; and

- 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 of health care workers regarding the offering of HIV counseling and testing and other prevention services and 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; and
- 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); and
- Support basic and preintervention research on behavior modification and maintenance of new behavioral patterns for developing prevention and intervention strategies.

SCIENTIFIC ISSUE:

Research is needed on interventions to improve treatment adherence and to ameliorate negative physical, behavioral, psychological, cognitive, and social consequences of HIV infection. Advances in therapy for HIV mean that infected individuals need access to treatment strategies, as well as strategies for coping with HIV disease and for enhancing quality of life. Research also is needed to facilitate improved identification and treatment of people with HIV infection, including early and acute infections, to improve delivery of care and access to therapeutics among diverse population groups. Qualitative and quantitative research methodologies should be further developed to address these adherence, quality-of-life, and health care delivery issues.

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.

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

- Support research on adherence to treatment regimens, including communication techniques to improve shared decision making between health care providers and HIV-infected individuals, 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; and
- 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; and
- 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.

SCIENTIFIC ISSUE:

Behavioral and social science methods have greatly enhanced understanding of HIV transmission, consequences of HIV infection, and health maintenance among at-risk and HIV-infected individuals. However, advances in prevention and treatment require further development of behavioral and social science methods that are standardized, rigorous, and culturally sensitive. These methods are essential to answer critical questions about HIV-related behavior and behavior change; the linkage between HIV-related risk behaviors, HIV transmission, and disease progression; and evaluation of interventions.

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; and
- Develop and refine research techniques for measuring responses to HIV by organizations 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; and
- 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, 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 nonnormal distributions; and
- 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; and
- Develop and evaluate mechanisms for dissemination of behavioral research findings to the HIV/AIDS research and service communities.

AREA OF EMPHASIS:

Training, Infrastructure,
and Capacity Building

AREA OF EMPHASIS:

Training, Infrastructure, and Capacity Building

STATUS:

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 and was authorized under 42 USC 288-1 to encourage health professionals to engage in AIDS-related research at NIH. Twenty-five professionals are currently enrolled. This program continues to attract qualified researchers to NIH.

FIC sponsors the AIDS International Training and Research Program (AITRP), a program established in 1988 at the request of Congress for training scientists in developing countries to undertake epidemiologic and postdoctoral research. Goals of the Program include expanding scientific capabilities in the epidemiology, prevention, diagnosis, and treatment of HIV/AIDS throughout the world and of facilitating the evaluation of AIDS drugs and vaccines internationally. As a result of a 1996 scientific review of the AITRP, the Program continues to have an increased emphasis on multidisciplinary prevention research, with the goals of encouraging

development of international collaboration; assisting developing countries to achieve independent capacity to conduct research and training; encouraging independent local research on HIV prevention; assisting NIH Institutes in the conduct of their research missions internationally; and stimulating multidisciplinary cooperation. Since its inception, the Program has provided training in the United States for approximately 1,300 health scientists from 85 countries and supported over 600 in-country training courses in 60 countries. The Program includes an in-country research component, which provides support for reentry grants for scientists returning home after completion of their training, and a Fogarty International Research Collaboration Award (FIRCA) for AIDS. The 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. OAR discretionary funds were provided in FY 1997 to support new and minority investigators through the AITRP. This program is designed to provide overseas research training experiences for U.S. investigators with a special emphasis on new and minority investigators. The FIC investment in research training has facilitated the conduct of many research studies supported by various ICs.

The NIMH research training program currently fully supports 16 programs that are focused exclusively on issues of HIV infection and AIDS and partially supports 10 other research training programs to allow components of the program 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, 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 398 predoctoral and postdoctoral investigators through individual and institutional awards in 1997. 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.

NIAID-sponsored programs increased the number of trainee slots for AIDS training to approximately 150 for FY 1998. In addition, another 20 postdoctoral fellows receive funds from individual training fellowship awards (F32s). Mentored career development awards also provide support for young investigators in clinical and basic research. This program has been very successful in assisting young scientists to establish independent research programs.

SUPPORT OF ANIMAL FACILITIES

NCRR and 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 Breeding and Research Program for the SIV/maaque model system and the successful Chimpanzee Breeding and Research 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 (RPRC) 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. In FY 1997, NCRR sponsored a special initiative to support non-RPRC investigators 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. (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 was necessary for them to compete successfully and receive funding as 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 1998, there are six NIH Institutes participating in the CFAR program—NIAID, NCI, NIDA, NIMH, 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.

A multiagency High Performance Computing and Communications (HPCC) initiative includes the National Library of Medicine (NLM), NCRR, Center for Information Technology (CIT), and NCI. This initiative permits the development of faster computers and better algorithms for predicting molecular structure and function from genetic sequences, which is an important area of research.

The HPCC initiative will create a National Information Infrastructure (NII) linking academic and commercial research centers. Nearly 10 million users worldwide are connected to the Internet at this time. NLM provides support for connecting medical centers and community hospitals to the Internet and for developing prototype biomedical digital image libraries that use the Internet as a high-speed distribution channel. The NII will provide an increasingly faster communication line for sharing data among laboratories on an international scale.

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 WHO 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 Issues and Objectives

SCIENTIFIC ISSUE:

The HIV epidemic is expanding into traditionally underserved communities in the United States and abroad. Meeting the needs of research on HIV/AIDS requires recruiting and training biomedical and behavioral scientists in the United States and abroad in the many disciplines necessary to carry out this diverse scientific agenda. This requirement includes attracting researchers from other scientific disciplines and from diverse cultural backgrounds to pursue HIV/AIDS research.

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;
- Provide incentives to attract researchers from other fields to pursue HIV/AIDS research;
- Provide incentives to AIDS-related basic, clinical, 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 ethical issues related to clinical research and other issues related to the design and analysis of observational studies;

- 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, mother-to-child interventions, behavioral interventions, OIs, STDs, microbicides, nutritional interventions, and clinical trials methodologies;
- Develop and expand programs for AIDS-related research training tailored and targeted to minority researchers, primarily at the postdoctoral level;
- 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 to link U.S. AIDS research scientists and institutions with each other and with investigators and institutions in both developed and developing countries; and
- Support the training of affected community members that will increase their capacity to participate in biomedical and behavioral science research.

SCIENTIFIC ISSUE:

The conduct of HIV research in the United States and abroad requires establishment and maintenance of infrastructure to carry out this research program, including facilities and instrumentation, computers, databases, data communications, laboratories, repositories, and animal models. Reaching HIV-affected communities requires the development of facilities and communication networks among diverse groups of community participants and organizations, and researchers from multiple disciplines.

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, mother-to-child interventions, behavioral interventions, OIs, STDs, microbicides, nutrition, and clinical trials methodologies;
- Ensure adequate facilities and resources 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 General Clinical Research Centers Program (GCRC);
- 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 vertical, sexual, or parenteral transmission, and efficacy trials of candidate HIV vaccines;

- Increase collaboration between community-based organizations and other service providers (such as those funded by the Ryan White Comprehensive AIDS Resources Emergency 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, PBMC, plasma, derived cell line, CSF, tissue, and other key patient samples) and HIV strains from clinical trials and natural history and epidemiological studies, especially in complex study settings (e.g., maternal-infant transmission studies);
- Continue AIDS-related tumor 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; and
- Promote research in and application of medical informatics (i.e., high-performance computing) both domestically and internationally for HIV/AIDS research and clinical practice.

AREA OF EMPHASIS:

Information Dissemination

AREA OF EMPHASIS:

Information Dissemination

STATUS:

As we enter the new millennium, the need for effective information dissemination approaches will continue to be integral to HIV prevention and treatment efforts. While the need for innovative and effective information approaches, especially theory-based, testable approaches, has existed throughout the AIDS epidemic, it has been underscored in recent years. The continuing development of new and complex antiretroviral therapeutics, the adherence issues related to HIV/AIDS treatment, the need for research communities to be working and communicating globally, and the need to translate behavioral and social prevention approaches into practice exemplify this need. The changing pandemic and the increasing number of HIV infections in specific population groups, such as women and adolescents, also underscore the need to disseminate HIV research findings and other related information efficiently and effectively.

The rapidly expanding field of information technology, coupled with communications and information science research, provides unprecedented opportunities to enhance the capabilities of individuals, organizations, and communities to address HIV and AIDS in the diverse ethnic, racial, age, and cultural groups they serve. 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.

Consistent with this philosophy, the NIH AIDS Information Dissemination Coordinating Committee, under the auspices of OAR, provides planning direction and assists OAR and NIH in identifying and facilitating

**ASSESSING AND
RESPONDING TO
INFORMATION
NEEDS**

HIV/AIDS-related information dissemination activities, especially those that are trans-NIH.

The NIH AIDS Research Plan describes the breadth and depth of the comprehensive AIDS research program, serves as the definition of AIDS research at NIH, drives the NIH AIDS budget formulation and serves to inform others about current scientific and programmatic objectives and strategies that are considered a priority under each of the Plan's areas of emphasis. With the input of the Information Dissemination Coordinating Committee and the NIH ICs, this section of the NIH FY 2000 Plan for HIV-Related Research reports on key activities and provides planning priorities and direction for the area of information dissemination. (The NIH FY 2000 Plan for HIV-Related Research and other HIV-related information may be found on the NIH Office of AIDS Research Home Page at <http://www.nih.gov/od/oar>).

NIH recognizes that it is critical to establish relationships with target audiences that encourage and foster bidirectional communication. In this regard, NIH works with members of these audiences to understand their information needs, involve them in developing strategies for information access and dissemination, and involve them with the development of treatment and prevention guidelines as well as specific informational materials.

To enhance understanding of information needs, resources, and services, NIH sponsors activities (e.g., conferences, workshops, technical assistance sessions) that bring together users of NIH information resources, including health care providers, scientists, information specialists, journalists, and members of the community affected by HIV/AIDS. Other purposes of these and related activities are to review the various HIV/AIDS information services, assess current efforts with respect to needs, identify additional needs, provide insights about barriers to effective communication, and recommend solutions. Results and recommendations are widely circulated and are utilized for planning and informational purposes.

Since FY 1994, NIH, through NLM, has made awards of up to \$35,000 each on an annual basis to enable community-based organizations and public and health science libraries to design their own programs for improving AIDS information access to targeted groups within their communities. Such groups include people with HIV/AIDS and the affected community as well as their caregivers and the general public. Supported activities include purchasing equipment and telecommunications services, implementing Internet access, training in the use of sophisticated

information tools, and developing language and culturally specific materials. NLM has also funded three major innovative efforts for improving HIV/AIDS information access: (1) examined the functioning of a multitype consortium of academic, public, and hospital libraries along with community organizations to get 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 a dedicated center in a public library.

An important challenge to NIH is to provide accurate and up-to-date HIV/AIDS prevention and treatment information to people, including people from underserved communities and communities of color. NIH has taken significant steps in disseminating timely and accurate information on prevention and treatment issues such as AZT treatment to prevent perinatal HIV transmission and the principles and guidelines concerning combination antiretroviral therapies.

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

NIH is also working to increase understanding of clinical research and the differences between clinical trials and patient care, particularly by those in underserved communities. This communication effort is essential to NIH's longstanding goal of recruiting hard-to-reach populations into clinical trials. A key part of this effort is building trust and strengthening outreach to local and national community organizations. Toward this end, NIH has developed and disseminated information kits and materials in English and Spanish to assist health care providers, particularly in community clinics, in educating their patients about HIV and the diseases associated with AIDS and how to find out about clinical trials. Most of these materials are available through the National AIDS Clearinghouse.

NIH has a history of HIV/AIDS public education program activities through specifically targeted television, radio, and print materials aimed at audiences at high risk for contracting or transmitting HIV infection. HIV/AIDS-related web pages and transportable exhibits are also utilized to inform and converse with the public, including the scientific, advocacy, and patient communities.

NIH also supports other channels of information dissemination. For example, NIH community-based HIV prevention and treatment research programs provide mechanisms whereby information can be rapidly shared among research staff, research participants, and their respective communities. NIH also 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.

NIH has also increased efforts in the area of technology translation and transfer. NIH groups and consortia develop and test different models of transferring HIV prevention technology from research settings to service settings and from service settings to researchers. These efforts also include assessing the benefits of translating research findings on effective strategies for HIV prevention for community-based providers, funding agencies, health planners, and policymakers. Areas of focus have included (1) increased use of methods of behavior change whose effectiveness has been empirically demonstrated; (2) increased capacity to identify and provide outreach to hard-to-reach populations; (3) increased use of more sophisticated and rigorous evaluation designs and methods; and (4) increased coordination of individual prevention methods in comprehensive community-wide strategies to change norms. Ultimately, technology translation/transfer studies such as these are summarized and provided to service providers and policymakers as guidelines for HIV prevention dissemination.

In addition, NIH holds consensus development conferences to review areas of NIH-supported research where there may be a gap between research accomplishments and clinical care. After careful review of the research, a statement is developed and circulated widely to policy and health-related communities to inform them of the panel's consensus recommendations. HIV/AIDS scientific issues such as the effectiveness of AIDS prevention programs have been addressed through this mechanism.

CLINICAL AND COMMUNITY ALERTS

Since 1991, NIH has used a dedicated system of electronic and print notification, collectively known as Clinical Alerts, to rapidly disseminate to health care professionals, the news media, and the general public information that critically affects the care of patients, such as results of HIV-related clinical trials. This mechanism was recommended by participants, including researchers, medical journal editors, and others, in a workshop convened by NIH to discuss expedited information

dissemination. While affirming that traditional systems of reporting research results should be maintained, the group recognized that, in some exceptional circumstances, information with immediate clinical relevancy should be expeditiously reviewed and widely distributed prior to publication in a peer-reviewed medical journal. Clinical Alerts are available on-line on the MEDLARS system and provided for dissemination in academic health science centers and more than 3,000 hospitals; they are also transmitted via Internet to all requestors. The National Network of Libraries of Medicine has developed methods to ensure the wide dissemination of the Clinical Alerts. Physicians and patients must have access not only to Clinical Alerts and the results of clinical trials but also to clinical care guidelines, standards of care, and results of state-of-the-art meetings that redefine clinical care guidelines. Established dissemination efforts have included the availability and distribution of the guidelines on OI prophylaxis, PCP prophylaxis for children with HIV, and recommendations for the use of AZT to prevent perinatal HIV transmission, which have been developed by NIH and other agencies of the Public Health Service (PHS). This clinical practice information, the Report of the NIH Panel to Define Principles of Therapy of HIV Infection, and the DHHS Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents are available on-line in their complete versions as well as through an NIH-supported toll-free service (1-800-448-0440).

It is also critical to ensure that treatment and prevention information is effectively disseminated to health care and other community service providers as well as the affected communities themselves. NIH has a history of supporting and developing new approaches to address this need. NIH was a key architect and sponsor of the first in 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 the largest possible audience of people interested in HIV/AIDS prevention and care. In addition to NIH, there are six other Federal agencies cosponsoring this innovative satellite broadcast series. The first 2-hour live broadcast of this series aired in February 1998. This broadcast, an interactive forum on the recently developed Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents, was beamed to downlink sites across the country and has been reaired again since in its tape form by satellite health networks, effectively reaching increasing numbers of HIV/AIDS health care providers and others concerned with this critically important topic. The second of this series focused on the Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

**ELECTRONIC
INFORMATION
RESOURCES**

and aired in July 1998. The third broadcast “Adherence to HIV Therapies: HIV Treatment and Prevention Issues” is planned for February 1999.

Existing computerized databases including those on the MEDLARS system (AIDSLINE, AIDSTRIALS, AIDSDRUGS, and DIRLINE), as well as the AIDS Clinical Trials Information Service (ACTIS) and the HIV/AIDS Treatment Information Service (ATIS), are vital to information dissemination. They provide the foundation for the global dissemination of information concerning basic research, clinical trials availability and results, and standards of care as well as information of interest to HIV-infected individuals and their advocates.

Information available from the MEDLARS databases includes citations (with abstracts when available) to journal articles, books, and audiovisuals as well as abstracts from many major AIDS-related meetings and conferences (AIDSLINE); descriptions of clinical trials related to HIV, AIDS, and AIDS-related opportunistic diseases and the agents that are being studied in those trials (AIDSTRIALS/AIDSDRUGS); and international, national, and State organizations working in the AIDS area (DIRLINE). The databases are available free of charge to users worldwide through a simple-to-use interface (<http://igm.nlm.nih.gov>). 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. In addition, citations, with brief summaries, to substantive articles from more than 20 newsletters are being added to the database.

Initiated in 1989, ACTIS is a centralized resource providing information on NIH- and industry-sponsored clinical trials for HIV/AIDS. This is a free service to users and is jointly sponsored by NIAID, NLM, and FDA in collaboration with CDC. By dialing a toll-free number, 1-800-TRIALS-A, callers can speak to trained health specialists who access a database featuring information on AIDS clinical trials. Spanish-speaking specialists are available. The ACTIS Internet e-mail address is actis@actis.org, and its web site address is <http://www.actis.org>. The information can also be accessed directly through NLM’s AIDSTRIALS and AIDSDRUGS databases. This information is also available electronically from NLM as part of the Health Services and Technology Assessment Text (HSTAT) database, which includes clinical practice guidelines and recommendations on many health concerns.

To complement the ACTIS project, NIH collaborated with other agencies of PHS in the development of ATIS, which provides timely, accurate

treatment information on HIV and AIDS through the CDC National AIDS Clearinghouse. Available since November 1, 1994, ATIS is a toll-free (1-800-HIV-0440), bilingual, telephone reference service for people with HIV disease, their families and friends, and health care providers, providing answers to questions about treatment of HIV infection as well as copies of federally approved HIV/AIDS treatment guidelines and information. The ATIS Internet e-mail address is atis@hivatis.org and its web site address is <http://www.hivatis.org>.

NIH is expanding its use of the Internet as an important medium for its HIV/AIDS information dissemination efforts, often in tandem with its other information dissemination avenues. For example, NIH Home Pages such as for the NIH overall (<http://www.nih.gov>), OAR (<http://www.nih.gov/od/oar>), and NIH ICs are on-line, providing extensive HIV/AIDS research and programmatic information for the public, patients, health care providers, scientific investigators, and policymakers. ACTIS (<http://www.actis.org/>) and ATIS (<http://www.hivatis.org/>) both have World Wide Web sites that increase their usefulness and global access. NLM has created a World Wide Web home page specifically for HIV/AIDS-related information (<http://sis.nlm.nih.gov/aidswww.htm>). This serves as an entry point to many of the HIV/AIDS-related resources available from NIH as well as those from NLM. It also serves as a guide to selected resources worldwide.

A number of NIH ICs continue to establish and improve telephone- and fax-based information systems to provide the public with critical information on all aspects of HIV/AIDS. Information on these information services will be available through the ICs (listed on the NIH Home Page and/or through the NLM at <http://sis.nlm.nih.gov/aids/index.html>).

IMPROVED COORDINATION

NIH strives to identify and develop new avenues and opportunities to facilitate HIV/AIDS information dissemination efforts. This often includes coordinated efforts within NIH as well as collaborative efforts with groups, agencies, and others outside NIH. For example, NIH worked in collaboration with the National Minority AIDS Council and the Forum for Collaborative HIV Research to hold a national conference, "Adherence to New HIV Therapies: A Research Conference." This conference brought together representatives from research, clinical practice, the pharmaceutical industry, health care providers, and HIV-affected communities in a focused scientific discussion of the medical and behavioral issues in adherence to HIV treatment regimens. The resulting conference report is available upon request through any one of the three cosponsors.

A “Guide to NIH HIV/AIDS Information Services,” which is updated annually, is made available in both printed and electronic form through NLM’s 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 in their quest for knowledge about HIV/AIDS. This pamphlet describes these services as well as selected information services sponsored by other agencies of the PHS. The electronic version provides links to all the NIH and PHS sites and resources that are described in the pamphlet.

NIH strives to disseminate information in a manner that is useful to health care providers, service providers, people with HIV/AIDS and their advocates, at-risk populations, and basic and applied researchers in diverse geographic regions and varied resource settings. It is, therefore, important to further understand and improve all aspects of information dissemination and communication processes. NIH strives to better understand and improve the information exchange process, especially with respect to identifying and overcoming barriers to effective communication. Important to this process is research that evaluates and improves the effectiveness of information and behavior change communication campaigns.

NIH recognizes the critical importance of disseminating internationally 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. One example of NIH’s increased effort to enhance research information dissemination and communication involves the establishment of a global research network of researchers conducting HIV and substance abuse research, which may serve as a model for other HIV research areas.

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 providers, those who provide HIV-related services, and HIV-infected individuals and their advocates. These audiences have varying needs for information that is critical in the fight against HIV/AIDS. Three scientific issues are presented below, each relating to the others, each an NIH priority in FY 2000.

Scientific Issues and Objectives

SCIENTIFIC ISSUE:

Effective Communication: Exchange of information about basic, clinical, and behavioral HIV/AIDS research findings is essential to progress in research and ultimately to improved care and treatment for HIV-infected people. The traditional methods of reporting ongoing studies and research results in peer-reviewed journals and at scientific meetings reach only a limited audience. Health educators, health care providers, patients, and other constituents of NIH need to know the results of clinical and prevention intervention studies, state-of-the-art recommendations, and the most up-to-date standards of health care. As the epidemic has spread to new and hard-to-reach populations, special information outreach efforts need to be made to provide critical information to affected populations and their service providers. This information should be timely, should include discussion of the potential implications of research findings for patient care, and should be in a form that audiences can use. The latest computer and information technologies should be exploited whenever appropriate. The findings resulting from communications research should be incorporated into the strategies to carry out this objective.

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 on prevention, care, and treatment of HIV-infected individuals;
- Utilize cutting-edge 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, on-line access (AIDSTRIALS and AIDS DRUGS databases and HSTAT) 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;
- 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 by developing and disseminating educational information;
- Develop mechanisms for rapidly disseminating information on research in progress to the research community in order to increase collaboration, reduce duplication of effort, and enhance the discovery process;
- Develop 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 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 on-line (in advance when possible) the full text of abstracts and other information (e.g., slides, plenary presentations) from scientific meetings;
- Collect, archive, and promote use of existing data from NIH-supported basic and applied research for secondary data analysis;
- Disseminate widely information concerning specimen repositories, including existing repositories, specimens available, and relevant information concerning cohorts, contact people, and the process for obtaining access to samples;
- Evaluate the effectiveness of communication efforts by appropriate means, including obtaining feedback from target audience members and information dissemination intermediaries; and
- Disseminate widely the annual update of the NIH Plan for HIV-Related Research and other HIV-related reports as they become available.

SCIENTIFIC ISSUE:

Research: In light of the changing HIV/AIDS epidemic, assessments are needed to identify the important information needs of and barriers for relevant target audiences such as health care providers, service providers, people with HIV and their advocates, at-risk populations, basic and applied researchers, and the general public. Although significant communications efforts have been initiated, some communities still may not be (1) receiving needed information, (2) receiving information in a context appropriate for the audience, (3) comprehending the information, or (4) translating the information into action. New approaches are needed to ensure that the communication of information resulting from HIV/AIDS research is optimally effective.

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 of, and sources of information 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., adolescents, drug users, and other hard-to-reach populations) 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; and
- Evaluate the effectiveness of new technologies for disseminating basic and applied research findings.

SCIENTIFIC ISSUE:

Coordination: The scientific and lay communities look to NIH as a central source of information on HIV/AIDS. Since multiple NIH ICs disseminate HIV/AIDS information to these communities, coordination of efforts is essential. For more effective use of limited Federal dollars, increased efficiency, better use of new technologies, and continued credibility with the scientific and lay communities, there must be ongoing collaboration and coordination of communication activities within NIH and between NIH and other Federal agencies, public health departments, private companies, libraries, AIDS education and training centers, international groups, other granting agencies, community groups, and universities.

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 ongoing partnerships between community-based organizations and basic, clinical, and behavioral researchers to encourage exchange of information and experience;
- Enhance research, treatment, and prevention efforts through requirements in appropriate funding proposals to establish communication and coordination;
- Support the NIH OAR Information Dissemination Coordinating Committee to promote and foster information dissemination, research, and programmatic efforts across the ICs and between U.S. Government agencies;
- 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 UNAIDS, the Pan American Health Organization (PAHO), and 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 within DHHS, including the Health Care Financing Administration (HCFA), and with the private sector in the development of medical 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; and
- Expand the inclusion of academic, medical, and other communities, as appropriate, in the dissemination of NIH HIV-related reports.

Appendices

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
NIHES	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

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NIH Fact Sheet on
AIDS Research in
Minority Populations

NATIONAL INSTITUTES OF HEALTH FACT SHEET ON AIDS RESEARCH AND MINORITY POPULATIONS

The National Institutes of Health (NIH) supports a comprehensive portfolio of biomedical and behavioral research aimed at preventing, treating, and controlling HIV infection and its sequelae in minority communities. Half of the total NIH AIDS research budget is devoted to basic research that benefits HIV-infected adults and children of all racial and ethnic populations. The remaining portion of the budget is invested in more clinically oriented research. Of that portion, NIH invested an additional \$266 million in FY 1996 for research focusing specifically on AIDS in minority populations. In FY 1997 that sum increased to approximately \$278 million. In FY 1998, more than \$300 million was devoted to research targeting minorities; and in FY 1999, NIH plans to spend more than \$323 million.

NIH has for many years taken strong steps to assure minority participation in clinical trials, in natural history and epidemiologic studies, and in prevention studies and to assure that the overall research agenda is responsive to the needs of minority communities. NIH supports a broad array of behavioral intervention studies with specific focus on African-American populations. Research focusing on HIV and drug use includes mostly African-American participants. These studies are characterizing the disease process in drug users, factors influencing disease progression, consequences of multiple coinfections, effectiveness of therapeutic regimens, and impact of health care access and adherence to therapeutic regimens on disease outcomes. The development of topical microbicides is a high priority of NIH research, and recruitment for these studies is focusing on minority communities.

NIH has established programs and policies specifically designed to recruit individuals from underrepresented racial and ethnic groups into research careers and to build research infrastructure in minority institutions. These programs provide training and research opportunities across the continuum from high school students to independent investigators. NIH also supports a number of activities with the goal of disseminating research information to health care providers serving minority communities as well as to individuals at risk.

Specific information about these initiatives is provided below.

INCLUSION OF MINORITIES IN AIDS RESEARCH

The NIH has implemented a series of guidelines, policies, and programs to ensure that HIV-infected individuals from the most at-risk populations for HIV/AIDS are enrolled and accrued into federally sponsored AIDS clinical trials. In 1994, NIH implemented revised Guidelines on the Inclusion of Women and Minorities in Clinical Research, requiring applicants to address the appropriate inclusion of women and minorities in clinical research. Applications that fail to meet these requirements, as evaluated by peer review, are barred from funding. In such cases, the NIH staff work with the applicants to resolve problems, e.g., by changing the composition of the study populations or identifying projects in the Institutes' portfolios that address similar research objectives and that include women and minorities with which data can be compared.

The NIH's commitment to enrolling HIV-infected individuals from at-risk populations into AIDS clinical trials is underscored in the NIH FY 1998 Plan for HIV-Related Research, which states the following: "It is critical that the participation of specific populations in NIH-funded clinical trials reflect the changing demographics of HIV infection and AIDS, including women, children, adolescents, drug abusers, injection drug users (IDUs), minorities, the urban poor, and individuals residing in rural areas. Recruitment and enrollment of these underrepresented populations is a high priority in NIH-sponsored studies. Whenever possible, interagency collaboration should be fostered to enhance participation of these populations, including provision of ancillary services."

Several examples of NIH efforts include:

Women's Natural History Studies: Minorities represent more than 82 percent of the participants in two major natural history and epidemiology studies, the Women and Infant Transmission Study and the Women's Interagency HIV Study, which focus on mother-to-infant transmission of HIV and manifestations of HIV infection and its sequelae among women.

Clinical Trials: As of December 1997, 63 percent of the participants in NIH-sponsored AIDS clinical trials were minorities, including 40 percent African American and 22 percent Hispanic. Minorities represent 54 percent of AIDS cases in the United States. In addition, while women represent 15 percent of all AIDS cases in the United States, they represent 34 percent of the participants in NIH-sponsored AIDS clinical trials. The AIDS Clinical Trials Group (ACTG) continues to recruit participants to reflect the changing demographics of the epidemic. The research focus in the clinical trials is to determine the best therapeutic interventions to limit HIV replication and disease progression. Research also focuses on the rapid development of agents that prevent or delay the complications of HIV-related disorders that are of high incidence in both the majority and minority communities, such as cardiovascular disease, diabetes, lipid disorders, and neoplasias.

Perinatal Intervention Trials: Most of the women participating in the ACTG 076 trial, which demonstrated the effectiveness of AZT therapy in preventing HIV transmission from mother to infant, as well as in the ongoing followup studies to determine more effective and less complicated regimens to prevent perinatal transmission, are minorities.

Minority Institutions: The NIH ACTG includes three sites in minority institutions at Howard University, University of Puerto Rico, and the University of Hawaii. The ACTG will recompile in FY 2000, and the Request for Applications (RFA) has been designed to ensure optimal participation in clinical trials of all subpopulations in which the epidemic is now raging, including women, minorities, adolescents, children, and IDUs.

Prevention Trials for Drug Users: NIH supports several programs targeting minorities who are IDUs, including the Community-Based Outreach Risk Reduction Strategy to Prevent HIV Risk Behaviors in Out-of-Treatment Injection Drug Users program. Twenty-three sites have participated in the HIV Prevention Trial supported through this program. Participants have included 56.2 percent African American, 11.4 percent Puerto Rican, 9.0 percent Hispanic, 2.7 percent Native American, 0.3 percent Asian/Pacific Islander, 1.4 percent other Latino, and 17.2 percent Caucasians.

AIDS Malignancy Programs: NIH awarded funds to clinical trial sites that demonstrated the ability to recruit minorities into studies on AIDS-related malignancies.

TRAINING OF MINORITIES IN AIDS RESEARCH

The NIH recognizes the value of the contributions made by African-American health professionals to the conduct of research and research training. A number of NIH programs and policies are specifically designed to recruit individuals from underrepresented racial and ethnic groups into research careers. These programs provide training and research opportunities across the continuum from high school students to independent investigators, with the goal of increasing the diversity of the labor pool in all segments of health-related research.

For example, for individuals at the high school, college, graduate, postdoctoral, and investigator levels, the NIH offers Research Supplements for Underrepresented Minorities. Using this program, the principal investigator on a currently funded research project can request an administrative supplement to support the salary of an individual from an underrepresented group who wishes to participate in the ongoing research.

Specific programs in AIDS research include:

The AIDS Clinical Trials Infrastructures in Minority Institutions: The AIDS Clinical Trials Infrastructures in Minority Institutions are supported by NIH to enhance HIV clinical research performed at minority institutions. This program enhances the training and number of minority investigators involved in ACTG research and the number of minority participants in clinical studies. NIH funds the Research Centers in Minority Institutions (RCMI) to support the infrastructure to conduct biomedical research at minority institutions.

HBCUs: NIH outreach programs provide training to health professionals affiliated with Historically Black Colleges and Universities (HBCUs) in the use of electronic information resources so that this information is readily available for health professionals working closely with HIV-affected communities.

Overseas Training: NIH began a new initiative in FY 1997 designed to provide high-quality overseas research training experience for U.S. pre- and postdoctoral research investigators, with a special emphasis on the participation of minority scientists. This program should result in an increase in the number of minority investigators in all areas of basic and clinical research including AIDS-related studies.

Loan Repayment Program: The AIDS Loan Repayment Program assists investigators who come to conduct research in the intramural AIDS research program of NIH. It has cumulatively supported 23 percent minorities and 30 percent women.

Bench-to-Bedside Information Dissemination Program: The NIH Office of AIDS Research (OAR) supports regional programs to bring current research information to community health care professionals, particularly in minority communities.

MINORITY PARTICIPATION IN RESEARCH PLANNING AND PRIORITY SETTING

OAR includes minority representatives in all AIDS research advisory groups, and the OAR Advisory Council, which provides overall guidance on the scientific direction of the NIH AIDS research program, includes 7 minority members out of the total 18 members. In addition, the OAR research planning groups, which develop the annual AIDS research plan and set scientific priorities, also include minority representatives. These groups have been specifically charged with ensuring that the plan appropriately addresses the needs in minority communities.

NEW NIH AIDS RESEARCH PRIORITIES

Under its newly appointed Director, Neal Nathanson, OAR has adopted a new vision that is directly focused on the epicenters of the AIDS epidemic, including the multiple epidemics in minority communities. This vision, which we have termed “intervention research,” gives priority to research that will generate the products and methods required to control the epidemic.

Specific priorities include vaccine development, microbicides and other female-controlled interventions, behavioral intervention, interruption of perinatal transmission, immune reconstitution, and simpler and less expensive antiretroviral treatment regimens. This strategy focuses on the salient problems confronting African-American and other minority populations, as well as the medically indigent, homeless, and drug-using groups. The key priorities are prevention of transmission, prevention of disease progression, and prevention of mortality.

RESEARCH ON ISSUES OF CONCERN TO COMMUNITIES OF COLOR

Population-Specific Interventions

A number of NIH Institutes, including National Institute of Mental Health (NIMH), National Institute on Drug Abuse (NIDA), National Institute of Child Health and Human Development (NICHD), National Institute of Nursing Research (NINR), and National Institute of Allergy and Infectious Diseases (NIAID), currently fund a broad array of basic and intervention studies with specific focus on African-American populations. Additional studies are in the planning stages. For example, NIMH supports intervention studies involving African-American women in public housing units, mothers and sons, adolescent males, gay men, and families. NIDA supports ethnographic and intervention studies focused on African-American male and female drug users, including IDUs and crack-cocaine users. NIAID is currently planning an intervention trial focusing on HIV prevention among crack-using African-American women. These studies generally are supported through usual NIH grant mechanisms, and some have received special OAR HIV Prevention Science Initiative funds or other supplements. Some specific examples of behavioral research programs targeted to minority populations include:

- Community Based Risk Reduction for IDUs
- AIDS Prevention Among Minority Adolescents
- Washington, DC, AIDS Outreach/Intervention Research Program

- HIV Prevention in African-American Drug-Dependent Women
- Living with HIV—Racial Differences
- HIV Prevention in African-American Adolescent Women
- African Americans with AIDS—Caregiving Experience
- Reducing AIDS in Black Mothers

HIV Prevention Trial: NIH supports several programs targeting minorities who are IDUs, including the Community-Based Outreach Risk Reduction Strategy to Prevent HIV Risk Behaviors in Out-of-Treatment Injection Drug Users program. This trial has involved 23 sites, with 56.2 percent of the participants African American, 11.4 percent Puerto Rican, 9.0 percent Hispanic, 2.7 percent Native American, 0.3 percent Asian/Pacific Islanders, 1.4 percent other Latino, and 17.2 percent Caucasian.

Natural History and Epidemiology Research: NIH conducts studies to examine the transmission of HIV, the progression of HIV-related disease (including the occurrence of opportunistic infections [OIs]), the development of malignancies, the incidence of neurological and neurobehavioral dysfunction, the occurrence of oral manifestations, and the development of other sequelae. Ethnic and racially diverse cohorts of HIV-infected individuals and HIV-uninfected individuals at risk of infection are followed in clinical epidemiology studies at domestic and international sites. By maintaining this diversity, data obtained from such studies will have validity for all communities impacted by HIV infection. Examples of studies include:

- **The Women’s Interagency HIV Study:** WIHS is a major study cofunded by NICHD, NIAID, and NIDCR in collaboration with other Department of Health and Human Services (DHHS) agencies to investigate the nature and rate of disease progression in women to better characterize the clinical manifestations of HIV infection in women, and to determine the effects of therapeutic regimens. WIHS will also identify the sociocultural and health care access factors that affect disease outcomes in women. **Women of color comprise 82 percent of WIHS participants.** These studies will yield information pertinent to a wide range of vulnerable subpopulations.
- **Women and Infants Transmission Study:** WITS is a large epidemiologic study evaluating factors associated with risk of perinatal transmission, as well as factors associated with maternal and infant disease progression. This study includes extensive laboratory studies and supports a specimen repository. Participants from the United States and Puerto Rico reflect the diverse populations impacted by HIV in women and children.
- **HIV and Drug Use:** NIDA supports research on characterization of the disease process in drug users, including host and virologic factors influencing progression, clinical sequelae, consequences of multiple coinfections, effectiveness of therapeutic regimens, and the impact of health care access and adherence on disease outcomes. Two of these studies, ALIVE I and ALIVE II, are cohort studies of HIV-infected IDUs and high-risk IDUs. **More than 90 percent of the participants of these studies are African American.** Another project, HERO, is conducted

with IDUs in New York City. Sixty-five percent of the participants are Hispanic and 18 percent African American. The diverse populations represented in these three studies will provide an opportunity to further study the impact of HIV disease in several vulnerable subpopulations.

- HIV Epidemiology Study Among African Americans
- Cocaine Use and HIV in African-American Women
- HIV Infection and Drug Use in Adolescents
- AIDS Prevention for Low-Income African-American Women

Topical Microbicides: The development of topical microbicides, chemical and physical barriers that can be used intravaginally or intrarectally to inactivate HIV and other sexually transmitted diseases (STDs), has been and will remain one of the highest priorities of the NIH intervention research agenda. NIH is supporting Phase I, Phase II, and Phase III trials of various topical microbicides that fall generally into four categories: broad-spectrum microbicides, such as nonoxynol-9; buffer gel, and lactobacilli products; inhibitors of viral entry, such as sulfated polymers; inhibitors of HIV replication, such as nucleoside/nucleotide reverse transcriptase (RT) inhibitors, including 9-(2-phosphonylmethoxypropyl)-adenine (PMPA); and combination products. Increased funds are included in the FY 1999 budget for this purpose.

Clinical Trials: As of December 1997, 63 percent of the participants in NIH-sponsored AIDS clinical trials were minorities, including 40 percent African American and 22 percent Hispanic. Minorities represent 54 percent of AIDS cases in the United States. In addition, while women represent 15 percent of all AIDS cases in the United States, they represent 34 percent of the participants in NIH-sponsored AIDS clinical trials. The Community Programs for Clinical Research on AIDS (CPCRA), the Pediatric AIDS Clinical Trials Group (PACTG), and the ACTG continue to recruit participants to reflect the changing demographics of the epidemic. The research focus in the clinical trials is to determine the best therapeutic interventions to limit HIV replication and disease progression. Research also focuses on the rapid development of agents that prevent or delay the complications of HIV-related disorders that are of high incidence in both the majority and minority communities such as cardiovascular disease, diabetes, lipid disorders, and neoplasias. These networks will recompile for funding in FY 2000, and the RFA requires sites to demonstrate their ability to recruit and retain minority participants in studies.

AIDS Clinical Trials Infrastructures in Minority Institutions: The AIDS Clinical Trials Infrastructures in Minority Institutions are supported by NIH to enhance HIV clinical research performed at minority institutions. This program enhances the training and number of minority investigators involved in ACTG research and the number of minority participants in clinical studies. NIH funds the Research Centers in Minority Institutions (RCMI) to support the infrastructure to conduct biomedical research at minority institutions.

HBCUs: NIH outreach programs provide training to health professionals affiliated with Historically Black Colleges and Universities (HBCUs) in the use of electronic information resources so that this information is readily available for health professionals working closely with HIV-affected communities.

PARTICIPATION OF PEOPLE OF COLOR IN NIH-SPONSORED RESEARCH

Minority Participation in Research Planning and Priority Setting

The OAR includes minority representatives in all AIDS research advisory groups, and the OAR Advisory Council, which provides overall guidance on the scientific direction of the NIH AIDS research program, includes 7 minority members out of the total 18 members. In addition, the OAR research planning groups, which develop the annual AIDS research plan and set scientific priorities, also include minority representatives. These groups have been specifically charged with ensuring that the plan appropriately addresses the needs in minority communities.

Inclusion of Minorities in AIDS Research

Research Guidelines: The NIH has implemented a series of guidelines, policies, and programs to ensure that HIV-infected individuals from the most at-risk populations for HIV/AIDS are enrolled and accrued into federally sponsored AIDS clinical trials. In 1994, NIH implemented revised Guidelines on the Inclusion of Women and Minorities in Clinical Research, requiring applicants to address the appropriate inclusion of women and minorities in clinical research. Applications that fail to meet these requirements, as evaluated by peer review, are barred from funding. In such cases, the NIH staff work with the applicants to resolve problems, e.g., by changing the composition of the study populations or identifying projects in the Institutes' portfolios that address similar research objectives and that include women and minorities with which data can be compared.

Annual AIDS Research Plan: The NIH's commitment and priority of enrolling HIV-infected individuals from at-risk populations into AIDS clinical trials is underscored in the NIH Plan for HIV-Related Research, which states the following: "It is critical that the participation of specific populations in NIH-funded clinical trials reflect the changing demographics of HIV infection and AIDS, including women, children, adolescents, drug abusers, injection drug users (IDUs), minorities, the urban poor, and individuals residing in rural areas. Recruitment and enrollment of these underrepresented populations is a high priority in NIH-sponsored studies. Whenever possible, interagency collaboration should be fostered to enhance participation of these populations, including provision of ancillary services."

Examples of NIH efforts include:

Women's Natural History Studies: Minorities represent more than 82 percent of the participants in two major natural history and epidemiology studies, the Women and Infant Transmission Study and the Women's Interagency HIV Study, which focus on mother-to-infant transmission of HIV and manifestations of HIV infection and its sequelae among women.

Clinical Trials: As of December 1997, 63 percent of the participants in NIH-sponsored AIDS clinical trials were minorities, including 40 percent African American and 22 percent Hispanic. Minorities represent 54 percent of AIDS cases in the United States. In addition, while women represent 15 percent of all AIDS cases in the United States, they represent 34 percent of the participants in NIH-sponsored AIDS clinical trials. The CPCRA, ACTG, and PACTG continue to recruit participants to reflect the changing demographics of the epidemic. The research focus in the clinical trials is to

determine the best therapeutic interventions to limit HIV replication and disease progression. Research also focuses on the rapid development of agents that prevent or delay the complications of HIV-related disorders that are of high incidence in both the majority and minority communities, such as cardiovascular disease, diabetes, lipid disorders and neoplasias.

Prevention Trials for Drug Users: NIH supports several programs targeting minorities who are IDUs, including the Community-Based Outreach Risk Reduction Strategy to Prevent HIV Risk Behaviors in Out-of-Treatment Injection Drug Users program. Twenty-three sites have participated in the HIV Prevention Trial supported through this program. Participants included 56.2 percent African American, 11.4 percent Puerto Rican, 9.0 percent Hispanic, 2.7 percent Native American, 0.3 percent Asian/Pacific Islander, 1.4 percent other Latino, and 17.2 percent Caucasian.

Perinatal Intervention Trials: Most of the women participating in the ACTG 076 trial, which demonstrated the effectiveness of AZT therapy in preventing HIV transmission from mother to infant, as well as in the ongoing followup studies to determine more effective and less complicated regimens to prevent perinatal transmission, are minorities.

Minority Institutions: The NIH AIDS ACTG includes three sites in minority institutions at Howard University, University of Puerto Rico, and the University of Hawaii. The ACTG will re compete in FY 2000, and the RFA has been designed to ensure optimal participation in clinical trials of all subpopulations in which the epidemic is now raging, including women, minorities, adolescents, children, and IDUs.

AIDS Malignancy Programs: NIH awarded funds to its clinical trial sites that demonstrated the ability to recruit minorities into studies on AIDS-related malignancies.

ADHERENCE/COMPLIANCE RESEARCH

NIH supports a significant portfolio of research on adherence/compliance with AIDS therapeutic regimens, including:

- A group of therapeutic studies within the Adult AIDS Clinical Trials Group using electronic compliance monitoring devices as a research tool for monitoring adherence to therapeutic regimens.
- A study addressing the relationship between HIV treatment adherence, risk behaviors, and HIV transmission. At 3-, 6-, and 9-month followup, this cohort will be assessed on adherence measures (behavioral, pharmacological, medical records, virological) to determine patterns and extent of adherence, predictors of adherence, and changes in sexual or drug risk behavior, serostatus disclosure, and perceived infectivity.
- A study to measure two aspects of adherence that can influence HIV transmission: adherence to effective drug treatment and adherence with recommended changes in risk-associated behaviors, combining biologic and behavioral data. The study will assess the validity of self-report data and assess changes over time in objective and subjective measures of well-being and their impact on changes in patterns of treatment adherence and sexual risk taking.

- A behavioral intervention designed to improve adherence to therapy for HIV infection among African-American and Latino men and women in South Central Los Angeles, including an 8-week psychoeducational group program emphasizing problem-solving skills building around adherence and reducing substance use, mental illness, high-risk behaviors, and other life stressors. Clinical and behavioral assessments will be used.
- A study of attitudes of an understudied population (late middle aged and older HIV-infected adults) toward compliance with combination therapies.
- A study of the effects of HIV treatment advances on the attitudes, beliefs, and sexual risk behavior and determinant of medical treatment adherence among men and women in HIV serodiscordant relationships.
- The NIH OAR Prevention Science Working Group identified adherence as one of the highest priorities for funding through the OAR Prevention Science funds. The OAR has provided supplemental funds to the NIH Institutes for peer-reviewed research in this area, including those mentioned above.
- NIH also supports a significant portfolio of research grants and projects supported with AIDS research funds focusing on adherence with tuberculosis (TB), drug abuse, AIDS-related malignancies, and other therapies.

TRAINING AND INFRASTRUCTURE

A number of NIH programs and policies are specifically designed to recruit individuals from underrepresented racial and ethnic groups into research careers. These programs provide training and research opportunities across the continuum from high school students to independent investigators, with the goal of increasing the diversity of the labor pool in all segments of health-related research.

For example, for individuals at the high school, college, graduate, postdoctoral, and investigator levels, the NIH offers Research Supplements for Underrepresented Minorities. Using this program, the principal investigator on a currently funded research project can request an administrative supplement to support the salary of an individual from an underrepresented group who wishes to participate in the ongoing research.

Specific programs in AIDS research include:

AIDS Clinical Trials Infrastructures in Minority Institutions. The AIDS Clinical Trials Infrastructures in Minority Institutions are supported by NIH to enhance HIV clinical research performed at minority institutions. This program enhances the training and number of minority investigators involved in ACTG research and the number of minority participants in clinical studies. NIH funds the RCMI to support the infrastructure to conduct biomedical research at minority institutions.

HBCUs. NIH outreach programs provide training to health professionals affiliated with HBCUs in the use of electronic information resources so that this information is readily available for health professionals working closely with HIV-affected communities.

AIDS Loan Repayment Program. The AIDS Loan Repayment Program assists investigators who come to conduct research in the intramural AIDS research program of NIH. It has cumulatively supported 23 percent minorities and 30 percent women.

Behavioral Research Training. NIMH supports a program at the Center for AIDS Prevention Studies (CAPS), University of California, San Francisco, titled “Collaborative HIV Prevention in Ethnic Minority Communities.” As part of that program, CAPS supports about eight minority scholars in behavioral and social research to spend two summers there to work with mentors and to further develop research, publication, and grant-writing skills. In 1998, four of the eight scholars were African American and focused on issues of HIV prevention and service delivery among African-American communities (including the development of Africentric models).

International Training. NIH began a new initiative in FY 1997 designed to provide high-quality overseas research training experience for U.S. pre- and postdoctoral research investigators with a special emphasis on the participation of minority scientists. This program should result in an increase in the number of minority investigators in all areas of basic and clinical research including AIDS-related studies.

Many NIH Institutes have additional training programs. One Institute, for example, NIDA, has implemented a number of programs to encourage African-American and other ethnic minority students and scholars to pursue careers in drug abuse research. The following initiatives have been established to increase the participation of African Americans and other ethnic minorities in NIDA’s research program. None of these initiatives are specifically focused on AIDS research; however, individuals interested in AIDS research may seek support through these programs.

Research Supplements for Underrepresented Minorities Program. This program has been utilized to train ethnic minorities to conduct drug abuse research. A number of grants have been supplemented to support training for African-American scholars, many of whom have been involved in NIDA’s AIDS research grant program. Funds awarded through this program may be used to support salaries, tuition, travel, and supplies for recipients.

The Minority Institutions’ Drug Abuse Research Development Program (MIDARP). This grant program replaced the Minority Institutions’ Research Development Program (MIRDP) and is designed to assist minority institutions to build a research infrastructure and provide support for individual research projects to be conducted by faculty with assistance from students. The announcement for this program was issued at the beginning of FY 1998. Minority institutions and HBCUs, in particular, are encouraged to apply for support through this program. Participation in this grant program continues to increase.

The Historically Black Colleges and Universities Research Scholars Award Program. This RFA was designed to assist HBCUs to develop a research infrastructure and program involving faculty and students. This grant program, funded at the end of FY 1998, allows HBCUs to recruit an experienced research scientist to carry out a drug abuse research program and to train faculty and students. Funds are available through this program to conduct research and enhance the research capacity of the university.

Technical Assistance to Historically Black Colleges and Universities Program. A contract was awarded to Howard University to provide technical assistance to faculty and staff at HBCUs to increase their research readiness and to encourage their pursuit of careers in drug abuse research. A number of drug abuse research applications have been developed under this program.

HBCU Drug Abuse Research Infrastructure Building Program. A contract was awarded to Howard University to strengthen its drug abuse research infrastructure and train faculty and students for careers in drug abuse research. AIDS research was one of several subject areas emphasized by the University. Several drug abuse research applications have been developed by Howard University faculty members under this program.

African-American Researchers and Scholars Work Group. NIDA has established an African-American Researcher and Scholars Work Group to advise the Special Populations Office on issues relating to NIDA's research programs and strategies for increasing the involvement of African Americans in drug abuse research.

The Intramural Minority Research Training Program. NIDA has established a summer training program for minority college students and university faculty members. This program is hosted by NIDA's Intramural Research Program located in Baltimore, Maryland, and provides training for individuals interested in drug abuse research. Participants in the program are mentored by NIDA intramural research staff and encouraged to establish a publication record based on their experience in the program.

Summer Intern Program for High School and Undergraduate Students. NIDA sponsors a summer program for ethnic minority high school and undergraduate students. Students are placed in NIDA-supported research projects across the country and are provided a structured research experience consistent with their background and training.

Special Events and Training Seminars for Ethnic Minorities. NIDA sponsors special events and workshops to encourage minority students and scholars to pursue drug abuse research careers. Poster sessions and workshops targeted at ethnic minorities have been sponsored as a part of national scientific meetings. Special efforts have been made to attract minority high school and college students to attend these sessions. Training seminars, lasting approximately 1 week, have been supported by NIDA to encourage students and minority faculty from universities to pursue drug abuse research careers.

DISSEMINATION OF RESEARCH INFORMATION TO MINORITY COMMUNITIES

The NIH Office of AIDS Research supports a number of activities with the goal of disseminating research information to health care providers serving minority communities as well as to individuals at risk. These programs are sponsored in collaboration with national and local community-based organizations serving minority communities:

Regional Meetings: OAR sponsors a series of regional information dissemination programs to bring current research information to community health care professionals, particularly in minority

communities and to communities with the least access to information. Meetings have been targeted to Hispanic, Native American, and African-American communities. Other conferences have focused on issues relating to women.

Community Forums: OAR sponsors a community forum program designed to bring research information to the public and communities at risk. A series of scientific meetings, featuring nationally recognized researchers, have been held around the country in collaboration with national and local HIV/AIDS community organizations.

Collaborations: OAR sponsors collaborative projects with national community organizations. For example, through an ongoing collaboration with the National Minority AIDS Council (NMAC), OAR is conducting an AIDS Research Institute at the U.S. Conference on AIDS, the largest meeting of minority health care providers and the AIDS-affected community. OAR also is planning to work with the National Medical Association to develop regional outreach activities in association with the Office of Research on Minority Health and the Office of Research on Women's Health.

National Minority AIDS Council: In collaboration with NMAC, OAR is collaborating on information dissemination projects that include Internet access to AIDS conferences and presentations, AIDS treatment publications targeted to minority communities, and exhibiting of NIH AIDS research information at local and national minority AIDS meetings and conferences.

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