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*The
FY 1995
National
Institutes
of Health
Plan for
HIV-Related
Research*

*Office of AIDS Research
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The NIH HIV-Related Research Program

Since the onset of the AIDS pandemic, the National Institutes of Health (NIH) has played a key role in characterizing the virus and combating the disease. In accordance with the mission of the NIH to conduct and support biomedical and behavioral research on the causes, diagnosis, prevention, and cure of diseases, the NIH has established a comprehensive program of basic and clinical research on HIV infection, its sequelae, and AIDS. In support of such research, the NIH provides for the training of personnel and the development of other research resources, such as animal models for HIV-related research, and construction of research facilities. Finally, as part of its mandate to direct programs for the collection, dissemination, and exchange of scientific information, the NIH has developed systems for the dissemination of information on AIDS-related biomedical and behavioral research, particularly that relating to AIDS clinical trials.

The NIH continues to emphasize basic research at the cellular, chemical, and molecular levels. The scientific insight and expertise gained from HIV/AIDS research will be utilized to resolve a wide spectrum of other basic scientific issues in the fields of virology, immunology, microbiology, molecular biology, oncology, and animal models. Similarly, many of these important advances can be

directly applied to clinical medicine.

HIV/AIDS research has helped establish new approaches for the design and conduct of clinical studies addressing the special recruitment requirements of women, minorities, and other underserved populations. Thus, the Nation's investment in HIV-related research is providing major benefits in understanding and treating other diseases.

New strategies being developed for targeted drug and vaccine development are benefiting research on other diseases. The use of sophisticated computer imaging and crystallography permits the structural description of key proteins and enzymes that can be identified as targets for therapeutic agents. The delineation of the structural biology of infectious agents also can be used to design and develop potential vaccine candidates for the treatment and prevention of different diseases. Similarly, new and innovative technologies resulting from such investigations can be used to detect the presence of specific infectious agents for diagnostic purposes and for monitoring purposes during therapy. An example of these new technologies is the polymerase chain reaction (PCR) technique.

New animal models of viral diseases are being developed that allow for studies to better understand the stages of viral infection and disease progression. Animal

models are also used in testing potential therapeutic agents and vaccine candidates for safety and efficacy in preclinical studies before the initiation of clinical studies involving humans.

Basic scientific understanding is being advanced in the following areas: the function of the immune system, which has implications for diseases such as hepatitis, herpes, certain lymphomas and sarcomas, and autoimmune diseases including systemic lupus erythematosus; the mechanisms of gene expression, which will advance research on mechanisms of cellular transformation that in turn result in malignancy; the pathology of neurological disorders, which will advance research on dementia, Alzheimer's disease, mental retardation, neuropsychological disorders, and multiple sclerosis; the transmission of sexually transmitted diseases, including hepatitis, herpes, syphilis, chlamydia, and gonorrhea, and associated behavioral factors; the blood-brain barrier, which will advance research on the mechanisms involved in passage of infectious agents across this barrier as well as passage of therapeutic agents across this barrier for treatment of various diseases such as encephalitis and meningitis; the development of cardiovascular diseases, which will advance research on pulmonary, cardiac, and rheumatic disorders resulting from various infections; the development of nutritional disorders, which will advance research in such areas as wasting syndromes, metabolic abnormalities, and

gastrointestinal dysfunctions; the development of nervous and immune systems in children, which will advance research on neurological and neuropsychological disorders and immunological disorders including certain autoimmune disorders and cancers; and retroviral-associated malignancies, such as Kaposi's sarcoma, cervical dysplasia, anogenital cancers, and non-Hodgkin's lymphoma.

AIDS research has fostered cooperation of Federal, university, and pharmaceutical industry efforts in the identification, development, and preclinical evaluation of potential therapeutic agents and vaccine candidates. In addition, new approaches for conducting clinical trials have been developed, including community-based trials, which capture the expertise of community physicians. Similarly, AIDS clinical trials have demonstrated the importance of providing ancillary services to recruit and ensure the continued participation of underserved populations such as women, children, minorities, and injecting drug users (IDUs) in clinical trials for other diseases. These services provide for general health care, transportation, obstetrical care, day care for children, and other related services. Community advisory boards assist clinical trials sites in ensuring close cooperation with community constituency groups.

Other innovations brought about by AIDS-related research include the identification of surrogate markers that reliably provide valid information for determining the

outcome of clinical studies. AIDS clinical trials have provided access to experimental therapeutics through the parallel-track mechanism. This mechanism permits access to therapeutic regimens for individuals who would not otherwise qualify for participation in specific clinical studies. New strategies have been developed for drug administration, taking into account drug dosing, toxicity, resistance, and routes of administration. The NIH has played a unique role in conducting clinical studies directly comparing therapeutic agents from different pharmaceutical manufacturers, particularly in the area of testing new regimens for the prevention, treatment, and control of opportunistic infections (OIs). Because of the need to ensure that there are sufficient numbers of appropriately trained researchers available to conduct biomedical and behavioral studies, the NIH has developed and implemented innovative recruitment and training programs for NIH researchers.

In addition, NIH AIDS research has fostered the development of international collaborations for tracking the natural history and epidemiology of infectious diseases, for obtaining and identifying variants of infectious agents from different geographic regions, and for developing the infrastructure necessary to conduct therapeutic and vaccine efficacy trials in international sites that have populations with high risk of infection.

In the United States, recent advances in the identification of effective antiretroviral

therapies, such as zidovudine (AZT), dideoxyinosine (ddI), dideoxycytidine (ddC), and therapies for the treatment and prophylaxis of HIV-associated OIs, have resulted in delay of the onset of AIDS, an increased life expectancy, and improved quality of life for HIV-infected individuals. Although progress is encouraging, no definitive cure or vaccine for HIV infection and AIDS is yet available. More than 137,000 agents have been tested for activity against HIV in the AIDS Drug Screen, and more than 80 agents are currently being evaluated in 70 ongoing clinical trials.

In all of these efforts, an integral role is played by AIDS activists and advocates for HIV-infected individuals. AIDS-community representatives serve on all AIDS-related advisory committees and on protocol design teams of clinical trials in an unprecedented collaboration between researchers and those affected and infected by HIV.

The NIH HIV-related research effort can be divided into five major scientific categories: (1) natural history and epidemiology, (2) etiology and pathogenesis, (3) therapeutics, (4) vaccines, and (5) behavioral research. These scientific areas, while defined separately, are linked together and form stepping stones to each other. The basic scientific foundation of etiology and pathogenesis is necessary for defining the natural history of the disease as well as for the development and evaluation of drugs and vaccine candidates.

In addition, resources for research are divided into two areas of emphasis: training and infrastructure and information dissemination. An explanation of these areas follows.

Areas of Emphasis

Natural History and Epidemiology

The NIH performs epidemiologic research that is complementary to that of the CDC in prospectively studying cohorts of HIV-infected individuals and healthy individuals who are at risk of infection. The NIH is conducting a number of epidemiologic studies to examine the natural history of HIV infection and the effects of viral factors, host factors, cofactors, and therapeutic and prophylactic interventions on the risk of infection and disease progression. This research is performed in the United States as well as in other countries that may exhibit different patterns of the epidemic. Such studies therefore provide unique opportunities to identify risk factors, to understand the natural history of HIV infection, and to identify populations suitable for participation in future domestic and international HIV vaccine efficacy trials. Examples of such research include the study of sexual transmission in specific populations; the study of the natural history of HIV-related disease in women, men, adolescents, and children; the study of perinatal transmission; and the study of behavior relative to the risk of transmission of HIV.

Etiology and Pathogenesis

Efforts to combat HIV infection and AIDS are based on developing an understanding of the HIV life cycle through elucidation of the mechanisms of infection, viral activation and expression, and immunosuppression. Examples of such research include the isolation and cloning of HIV and the sequencing and delineation of the function of HIV genes. Also included in the category of pathogenesis are basic and clinical research on the progression of HIV infection, HIV-related malignancies, HIV-associated OIs, neuropsychological and neuropsychiatric sequelae, and other sequelae such as wasting and endocrine disorders as well as research on the mechanisms by which cofactors may exert their effects. The NIH also focuses efforts on improving the understanding of the progression of disease and clinical manifestations in women, children, and adolescents. The development of improved diagnostics for HIV infection and its associated OIs and the development of appropriate animal models are crucial to research in this category.

Therapeutics

NIH-sponsored studies are actively pursuing the discovery and development of potential therapies for the prophylaxis, early intervention, and treatment of HIV infection and its sequelae. Two approaches are being taken for the identification of potential antiretroviral agents, including targeted drug

development that utilizes structural biology techniques specifically to design drugs that interfere at various stages of the HIV life cycle, and drug screening of synthetic and natural products for anti-HIV activity. The NIH sponsors intramural and extramural clinical trials of these potential therapeutic agents in single or multidrug regimens to demonstrate drug safety and efficacy for the control and treatment of HIV infection and its accompanying OIs and malignancies in individuals of all ages.

Vaccines

The discovery and development of safe and effective AIDS vaccines are based on basic biomedical research on HIV. Vaccine candidates are being evaluated for prevention of HIV transmission, including transmission via the maternal-fetal route of infection, and for treatment of HIV-infected individuals as immune modulators and immune enhancers. Preclinical evaluation of vaccine candidates involves testing in primate and nonprimate animal models for demonstration of safety and efficacy. Current vaccine candidates under development include whole killed virus, purified viral products, synthetic viral peptides, recombinant products, genetic recombinant viruses, and anti-idiotypic antibodies. Vaccine discovery and development are closely coordinated with international epidemiology studies to identify genetic variations of HIV that may affect the development of potential AIDS vaccines and to identify populations suitable for future vaccine efficacy clinical

trials. In addition, strategies are being developed to increase adherence to study protocols in future clinical trials.

Behavioral Research

The NIH conducts basic research on behavior and the means of motivating and sustaining behavior change, providing information on the influence of behavior associated with the transmission of HIV, by elucidating the nature and extent of high-risk behavior. These efforts provide information that is relevant to the design of intervention programs aimed at reducing HIV transmission through identifying effective approaches to modifying behavior and sustaining behavior change, identifying cultural barriers and enhancers to behavior change, and identifying populations resistant to behavior intervention. The NIH supports a multisite, multipopulation intervention study to evaluate prevention strategies. Some studies are international in scope, including a collaborative effort between the NIH and the U.S. Agency for International Development with the goal of collecting information in support of the development of behavioral intervention strategies. Studies in other areas of behavioral research are determining how HIV-infected individuals are perceived and how individuals and their families respond to and cope with the disease and its manifestations. Behavioral research is also critical for the HIV vaccine research effort and for strategies to provide HIV vaccines once they are shown to be safe and effective.

Training and Infrastructure

The NIH supports a number of intramural and extramural research resource programs. Included in these programs are grants for training AIDS researchers, developing animal models, and constructing or improving existing facilities and equipment for AIDS research.

Information Dissemination

The NIH has addressed the important need for information dissemination in a number of arenas. Standards-of-care information requires coordination among various agencies of the Public Health Service (PHS) as well as outside organizations. The NIH supports a number of computerized databases as well as mechanisms such as the "Clinical Alerts" to rapidly disseminate critical clinical trials results to health professionals.

Mechanisms and Responsibilities

NIH-supported HIV-related research is conducted through intramural and extramural studies. Most of the NIH AIDS budget is expended extramurally to fund investigator-initiated research conducted at academic institutions and other organizations throughout the country and the world. Investigator-initiated basic research provides the foundation upon which applied research, such as therapeutics and vaccine research, is built.

Overall coordination of the NIH effort is provided by the Office of AIDS Research. Whereas all the Institutes, Centers, and Divisions (ICDs) are involved in some HIV-related activities, as defined by their respective missions, the effort is led by the National Institute of Allergy and Infectious Diseases (NIAID), with major contributions by the National Cancer Institute (NCI), the National Institute on Drug Abuse (NIDA), the National Center for Research Resources (NCRR), the National Institute of Mental Health (NIMH), 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 ICDs.

Office of AIDS Research, Office of the Director (OAR, OD)

The Office of AIDS Research, in the Office of the Director, NIH, is responsible for coordination of the scientific, budgetary, legislative, and policy elements of the NIH AIDS research program. Through participation on the PHS Executive Task Force on AIDS and management of the NIH AIDS Executive Committee, the OAR has increased its efforts to improve cross-PHS and cross-NIH coordination and collaboration. Special attention has been given to improving the dissemination of AIDS-related information to ensure that research

findings are rapidly incorporated into treatment guidelines used by health care providers.

To foster cross-NIH collaboration and participation, the OAR provides financial support to the ICDs for important scientific opportunities as well as for scientific meetings and other necessary research-related expenses. When it was discovered that the *Macaca nemestrina* monkey could be used as a model for HIV pathogenesis and vaccine development, OAR funds were transferred to NCRR to begin development of breeding colonies. The OAR also provided support to extramural researchers in the NCI Cancer Centers Program to increase research on HIV-associated malignancies, especially cervical cancer. In addition to supporting such research opportunities, the OAR sponsored numerous workshops and conferences to address pressing scientific issues, such as tuberculosis (TB), drug and vaccine development and evaluation, and the oral manifestations of HIV infection. In collaboration with the Inter-Agency Animal Model Committee, the OAR also convened a primate viral challenge stock workshop, which met to further the development of vaccine candidates in nonhuman primates.

To facilitate the development of the NIH AIDS programs, the OAR supports the AIDS Program Advisory Committee (APAC), a committee of experts from academia and industry who provide guidance to the NIH Director and the OAR Director. During FY 1992, the

APAC reviewed this Plan for HIV-Related Research and also focused on a number of scientific issues: the impact of AZT on HIV disease progression and survival; the inclusion of HIV-infected women and children in clinical trials; early diagnosis and treatment of HIV-infected infants; the emergence of TB among HIV-infected individuals and health care workers; and legal and ethical issues relating to vaccine trials. In addition, OAR program staff are assigned to the NIH Division of Legislative Analysis and the NIH Budget Office to provide analysis for the OAR and to respond to numerous congressional requests regarding NIH AIDS research.

The OAR supports the Intramural AIDS Targeted Antiviral Program (IATAP) and the Protein Expression Laboratory. Using state-of-the-art techniques of structural biology, molecular biology, and biochemistry, IATAP is assisting in the development of a new therapeutic agent that selectively kills CD4 cells with replicating HIV; developing approaches to design HIV inhibitors aimed at interfering with transcription; and increasing understanding of HIV mutation. Using recombinant DNA techniques, the Protein Expression Laboratory continues to produce HIV proteins for NIH scientists conducting structural, biochemical, and pharmacologic studies.

The OAR supports the NIH AIDS Research Loan Repayment Program (LRP), which was established by Congress to counter the growing economic disincentives for embarking on research

careers and to spur AIDS research. This program reduces the educational debts of researchers at Federal Government laboratories in exchange for a minimum 2-year service period.

The OAR monitors and fosters plans for NIH involvement in international AIDS research activities and provides financial assistance to allow participants from developing countries to attend international AIDS conferences. These efforts promote collaborative research activities in an international setting.

The Missions of the ICDs Relative to HIV/AIDS Research

National Cancer Institute (NCI)

The NCI conducts research that contributes to the basic understanding and therapeutic management of all stages and manifestations of HIV infection. Investigative efforts encompass the broad areas of biomedical research, natural history, vaccine development, and treatment, with special emphasis on AIDS drug discovery and preclinical and clinical drug development programs. Targeted initiatives are also conducted by the NCI to address the biologic changes within organ systems associated with the spread of HIV infection. These initiatives focus on disparate and aggressive HIV-related cancers, such as Kaposi's sarcoma, non-Hodgkin's lymphoma, and cervical

neoplasia, and on the growing HIV-infection rates in women and children.

National Heart, Lung, and Blood Institute (NHLBI)

The NHLBI supports research to ensure the safety and adequacy of the Nation's blood supply and to investigate the pulmonary, hematologic, and cardiac complications of HIV infection. Areas of research include pretransfusion testing, inactivation of viruses in blood products, the natural history of transfusion-transmitted HIV infection, heart and lung disorders associated with HIV infection, and educational efforts to ensure that physicians use blood and blood products appropriately.

National Institute of Dental Research (NIDR)

The NIDR conducts research to identify and treat oral pathologies associated with HIV infection and progression to AIDS in all patient groups. Research includes the search for oral diagnostic markers and studies to determine the mechanisms of action of salivary components that can inhibit HIV. The NIDR also studies the structure of HIV proteins; the role of monocytes and their potential as targets for antiviral therapy; the development of synthetic vaccines and drug delivery systems; and the use of transgenic mice and other methods to elucidate the effects of HIV genes on selected tissues.

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

The NIDDK conducts and supports research on the basic mechanisms of HIV infection; the structure of HIV and the development of antiviral agents; the physiologic mechanisms of wasting associated with HIV infection and AIDS; and the endocrine, metabolic, gastrointestinal, renal, urologic, and hematologic complications of HIV infection and AIDS.

National Institute of Neurological Disorders and Stroke (NINDS)

The NINDS conducts and supports basic and clinical research on the neurologic complications of HIV infection itself as well as research on OIs of the nervous system of immunocompromised HIV-infected individuals.

National Institute of Allergy and Infectious Diseases (NIAID)

The NIAID conducts a comprehensive program of basic and clinical research on HIV infection, its sequelae, and AIDS. Basic research is focused on increasing the understanding of the etiology and pathogenesis of HIV infection as well as the immune response to the virus. Epidemiologic studies, based on various populations in the United States and internationally, are amassing information on the natural history of the disease, its

transmission, and the impact of treatment on disease progression. The NIAID supports extensive programs on the development of strategies for the early diagnosis, treatment, control, and prevention of HIV infection and its manifestations, including the development and testing of vaccine candidates and therapeutic agents.

National Institute of General Medical Sciences (NIGMS)

The NIGMS program of HIV-related research focuses on efforts to design drugs for the treatment of HIV infection on the basis of knowledge of the three-dimensional structure of various viral proteins. This approach relies on the field of structural biology, in which the relationship between the form and function of biologic materials is studied by use of sophisticated techniques, such as x-ray crystallography, and by applying theoretical chemistry as directed toward molecular modeling. Additionally, the NIGMS supports training programs in structural biology.

National Institute of Child Health and Human Development (NICHD)

The NICHD focuses its HIV-related research on investigating the unique features of HIV infection and AIDS in women, infants, children, and adolescents by studying the transmission of HIV from mother to child; studying the natural history of HIV infection in perinatally infected children; examining

the impact of HIV infection on the developing nervous systems of vertically infected children; studying the impact of HIV infection on physical growth and development, immune systems, and neurodevelopmental outcomes of hemophilic children; developing appropriate methodologies to assess the impact of HIV and of anti-HIV therapies on the neurologic and neurodevelopmental status of HIV-infected children; sponsoring trials of therapeutics in HIV-infected children and pregnant women; developing methods to prevent the sexual transmission of HIV; and increasing the understanding of behaviors and attitudes that contribute to the spread of HIV infection.

National Eye Institute (NEI)

Blindness is one of the many complications of HIV infection and AIDS. The NEI supports research on HIV-associated ophthalmic disorders, such as retinitis caused by infection with cytomegalovirus (CMV), and potential therapies for these disorders. The NEI also monitors patients for the possible development of ocular toxic effects related to treatment of HIV infection.

National Institute of Environmental Health Sciences (NIEHS)

HIV-related research of the NIEHS focuses on evaluating the toxicologic properties of promising antiretroviral

agents, immunomodulators, therapeutics for OIs, and possible vaccines and on studying the molecular properties of HIV-related enzymes (e.g., HIV-1 reverse transcriptase and protease), contributing to the development of therapeutic strategies to inhibit their function.

National Institute on Aging (NIA)

NIA-sponsored studies are directed toward understanding the biomedical, clinical, and behavioral aspects of HIV infection and AIDS in an aging society. The NIA is concerned with how aging and the associated dysfunction of the immune system affect the course of the disease and treatment in middle-aged and older individuals. Of special interest is research focused on AIDS-related behaviors and behavioral change in the middle and later years, the impact of a diagnosis of HIV infection on families and social networks, and the impact of HIV infection and AIDS on the health care of middle-aged and older individuals.

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

The NIAMS supports research on the natural history and pathogenesis of rheumatic and cutaneous manifestations of HIV infection. The Institute also conducts studies on the relationship between the structure of HIV and its infectivity.

National Institute on Deafness and Other Communication Disorders (NIDCD)

The NIDCD-sponsored studies are directed toward understanding aspects of HIV infection in relation to impairment of hearing, balance, taste, smell, speech, voice, and language. One of the complications of AIDS is deafness. The NIDCD supports research on HIV-associated OIs, such as CMV, which can cause loss of hearing.

National Center for Research Resources (NCRR)

The NCRR develops and supports critical research technologies that underpin health-related research to maintain and improve the health of our Nation's citizens. The NCRR supports shared resources, sophisticated instrumentation and technology, animal models for studies of human disease, clinical research environments, and research capacity building for underrepresented groups. These critical research technologies are contributing to HIV-related research discoveries.

National Institute for Nursing Research (NINR)

HIV research supported by the NINR focuses on physiologic/psychosocial factors related to the care of HIV-infected individuals and on the prevention of infection. Investigations are being

conducted to assess compliance with investigational drug regimens and nutritional and quality-of-life issues related to HIV-infected individuals. The NINR research program also encourages studies of the needs of HIV-infected individuals and members of their social support system as well as ethical issues. International research includes transmission prevention studies as well as behavioral education and intervention programs.

Fogarty International Center (FIC)

The FIC is the NIH focal point for international cooperation in biomedical research, facilitating the global exchange of ideas and collaborative research. The FIC has established two international training programs to increase the expertise of both U.S. and foreign scientists in epidemiology related to HIV infection and AIDS research. These programs strengthen the capabilities of scientists or governments of developing countries to design and conduct research, care for HIV-infected individuals, develop collaborative relationships between American and foreign scientists, and facilitate the international testing of anti-HIV drugs and vaccines.

National Library of Medicine (NLM)

The NLM collection of more than 4 million items, its MEDLARS computerized databases, and its Regional Medical Library program are the foundation of a national health information

network designed to ensure timely dissemination of scientific and medical information concerning this important disease to the biomedical community. The MEDLARS online databases include AIDSLINE, a file of more than 40,000 references to published literature; DIRLINE, a database of health-related resource information that includes more than 1,500 AIDS-related organizations and other resources; and AIDSDRUGS and AIDSTRIALS, which provide information on clinical trials of vaccines and drugs against HIV and its associated illnesses. In addition, a monthly publication, *AIDS Bibliography*, is distributed worldwide.

New NIH Institutes

On October 1, 1992, the reorganization of the Alcohol, Drug Abuse, and Mental Health Administration became effective. The reorganization brought three new research institutes to the NIH: the National Institute on Drug Abuse, the National Institute of Mental Health, and the National Institute on Alcohol Abuse and Alcoholism. These three Institutes bring large AIDS research portfolios and will increase the magnitude and breadth of AIDS research at the NIH.

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

The NIAAA conducts and supports HIV-related alcohol research in the areas of basic science, epidemiology, and prevention. On the biological level, areas of research include alcohol-induced

alterations of the immune system that compromise host defense against HIV. In the social-psychological area, research is focused on the causal and correlational relationships between alcohol use/abuse and unsafe sexual practices, relevant decision-making processes, and behavioral interventions to reduce the alcohol-related risk of HIV exposure.

National Institute on Drug Abuse (NIDA)

The NIDA supports a comprehensive research program to address the AIDS pandemic among drug users, including studies to assess prevention and treatment strategies to reduce behaviors that are linked to HIV transmission and progression to AIDS and its associated diseases; epidemiologic studies of seroincidence, seroprevalence, and progression to disease among drug users (in and out of treatment), their sexual partners, and their children; and studies of the effects of drugs of abuse on the immune system.

National Institute of Mental Health (NIMH)

The NIMH supports HIV prevention research on behavior change strategies as well as research to understand, assess, and treat the neurobehavioral, neuropsychiatric, and psychosocial sequelae of HIV infection and AIDS. The NIMH conducts studies to identify the determinants of high-risk sexual and drug-using behaviors; elucidate the effect of

HIV on the central nervous system (CNS) and on the brain-immune interaction and endocrine system; understand neuropsychiatric syndromes and cognitive functioning, developing pharmacological and psychosocial treatments; develop more accurate methods to assess and treat HIV-related mental disorders; and improve delivery and access to mental health services for HIV-infected persons.

Cross-Cutting Research Issues

The complexity of the AIDS pandemic, and the populations it affects, presents many cross-cutting biomedical and behavioral issues, which the NIH is addressing. These issues cross Institutes, PHS agencies, and areas of science as well. Examples of such issues are pediatric AIDS, women and AIDS, issues relevant to adolescents and AIDS, and AIDS in minority populations. NIH research targets the epidemiology, natural history, and clinical and behavioral issues for each of these populations, reflecting the changing and dynamic demographics of the pandemic itself.

Pediatric AIDS

AIDS is now clearly recognized as one of the leading causes of death in some populations of children and adolescents in the United States. At the beginning of the HIV epidemic, children with AIDS were predominantly those who had hemophilia or who had received transfusions of blood products. As the epidemic progressed, the

number of HIV-infected infants and newborns also increased. Minority children have been specifically affected, with African American children comprising 51 percent and Hispanic children comprising 23 percent of pediatric AIDS cases. Pediatric AIDS (children under the age of 19 years) represents 2 percent of the total number of cases reported to date to the CDC.

However, as the number of women with HIV continues to increase, the rate of HIV infection in the pediatric population is likely to increase as well. With approximately 6,000 HIV-infected women giving birth each year in the United States, the number of children at risk for HIV infection and the number of children whose family life will be disrupted by the illness and premature death of one or both parents will remain substantial in the foreseeable future.

Reflective of these demographics, the NIH has developed a multifaceted approach to gaining insight into and understanding of the complex scientific nature of HIV infection and AIDS in children and adolescents. High priority has been placed on the diagnosis, treatment, prevention, and control of pediatric AIDS. Natural history studies have shown that disease caused by HIV in children follows a course different from that in adults. In very young children, HIV progresses more rapidly, and the range of OIs differs. There is an increased incidence of bacterial infections in HIV-infected children compared with adults. Furthermore, the immunosuppressive

effects of HIV infection are superimposed on immature immune and nervous systems, leading to a wide range of developmental problems affecting many vital organs. Almost 50 percent of the children born with the disease develop AIDS during the first year of life, and nearly 70 percent of the remainder in the second year.

The majority of the ICDs of the NIH are actively supporting research in the area of pediatric AIDS. The major research activities are cooperatively developed and conducted by the NIAID, the NICHD, and the NCI. Basic research sponsored through the NIH has provided and will continue to provide a better understanding of the origins, pathogenesis, and early diagnosis of HIV infection and HIV-associated OIs and malignancies in children and infants. Current NIH research in this area seeks to define the means for early diagnosis, timing of transmission of the virus, pathogenic mechanisms involved in the pediatric population, and the role of immune response in protection or delay of clinical progression.

The NIH also supports drug and vaccine development efforts designed to identify and develop new therapeutic and prophylactic agents. The coordination of ICD activities results in an efficient approach for obtaining the scientific base necessary for developing safe and efficacious therapies for the treatment, control, and prevention of pediatric HIV infection and AIDS. Significant advances

in the treatment of pediatric AIDS resulting from cross-NIH-sponsored clinical studies include the approval of ddI, the extension of AZT therapy for children as young as 3 months, the demonstration of the capacity of intravenous immunoglobulin (IVIG) for reducing the number of OIs, the approval of ganciclovir and foscarnet for the treatment of CMV retinitis, and the establishment of pediatric guidelines for *Pneumocystis carinii* pneumonia (PCP) prophylaxis. Ongoing and planned pediatric AIDS clinical trials are designed to evaluate new antiretroviral agents, immune-enhancing agents, multidrug or combination drug therapy, agents targeted against OIs, and agents for the prevention of HIV transmission from infected mothers to infants.

Adolescents and HIV

Increasing numbers of HIV-infected adolescents have been infected through sexual transmission or injecting drug use. While all young people under the age of 18 years are generally considered in pediatric AIDS research mentioned above and all NIH pediatric clinical trials include the participation of children and adolescents under the age of 18 years, a number of special initiatives have been undertaken specifically to address HIV-infected adolescents.

The NIAID has awarded supplements to clinical trials sites to provide ancillary services, establish linkages with community-based organizations, and

increase enrollment and retention of HIV-infected adolescents in clinical trials. A clinical HIV database has been developed to help characterize sociodemographic, immunologic, risk behavior, and clinical status of HIV-infected adolescents receiving services from these funded centers. This will provide needed baseline information to characterize the eligible population for clinical trials.

A number of epidemiologic and natural history studies are under way. For example, in collaboration with the CDC, new cohorts are being developed focusing on adolescents and young adults for seroincidence studies that are being initiated in a dozen sites nationwide to assess the feasibility of vaccine efficacy trials and other prevention-oriented intervention research in the United States. In collaboration with the CDC, a high-risk young men's cohort is being assembled to assess seroincidence, effects of counseling, and feasibility of intervention research among gay and bisexual men from 18 to 29 years of age. In the NIAID-funded Heterosexual AIDS Transmission Study in Brooklyn, young women were recruited for a study of sexually transmitted diseases (STDs), HIV, and behavior, designed to assess HIV risk and biologic correlates of seroconversion. Adolescent and young-adult IDUs are being recruited into NIH studies of seroincidence, effects of counseling, and feasibility of intervention research. NIH-sponsored programs on adolescent risk behavior and HIV infection include the identification and development

of potential intervention strategies for decreasing the high-risk behaviors of this population, including an NIMH-supported study of teenage runaways in New York City.

Women and HIV

Manifestations of HIV infection and the range of OIs and malignancies differ in women compared with men. HIV infection and its sequelae are frequently diagnosed at a later stage of the disease in women. This, however, appears to be due to poor access to health care by women, especially those from minority populations, and hardships associated with serving as heads of households and/or providing care to HIV-infected spouses, partners, or children. The majority of the ICDs are actively supporting research in the area of women and AIDS. The major research activities are cooperatively developed and conducted by the NIAID, the NICHD, and the NCI. Basic research sponsored by the NIH has provided and will continue to provide a better understanding of the origins, pathogenesis, and early diagnosis of HIV infection and HIV-associated OIs and malignancies in women. The NIH also supports drug and vaccine development efforts designed to identify and develop new therapeutic agents targeted for this population as well as behavioral studies related to the development and use of barrier contraceptive methods.

The NIH has developed a concerted effort to identify and determine how HIV disease

is manifested in women compared with men. To understand, prevent, control, and treat the disease in women, research has been targeted to address a number of issues regarding the transmission of HIV infection to women and maternal-fetal transmission; factors that affect progression to AIDS; the natural history of HIV infection; behavioral factors associated with transmission; and clinical, virologic, and immunologic markers of disease progression.

In 1990, the NIH, in collaboration with several PHS agencies, sponsored the first National Conference on Women and HIV Infection. This Conference developed a series of recommendations (Appendix A) addressing many of the biomedical, psychosocial, and behavioral needs of HIV-infected women. These recommendations emphasized the collection and analysis of existing clinical trials data and supported plans to initiate a collaborative large-scale natural history cohort study between the NIH and the CDC using information from existing studies as a base. Other recommendations concerned the need for primary care and ancillary services related to research; linking funding to performance standards relative to enrollment and retention of women and minorities; developing studies of OIs and malignancies in women; and increasing behavioral research relative to women.

The Institute of Medicine (IOM) report, *The AIDS Research Program of the National Institutes of Health*, similarly

addressed the NIH's programs on natural history studies and clinical trials and recommended a high priority be placed on the enrollment of HIV-infected women and minorities in these studies. Many of the plans proposed in these recommendations had already been implemented by the NIH before publication of the IOM report.

A large number of NIH-sponsored natural history and epidemiology studies provide crucial information concerning heterosexual transmission of HIV and transmission of HIV infection from infected mothers to their children. In addition, these studies provide important baseline data that can be used in determining the efficacy of therapies and vaccines for the treatment of HIV infection and its sequelae. Some examples of these studies include the Heterosexual AIDS Transmission Study (HATS), which is addressing reproductive outcomes, STDs, and crack cocaine use in women; strategies for recruitment of women into HIV research studies; and a study of risk behavior associated with HIV infection among inner-city women in a high-prevalence area. The NCI Hemophilia Cohort, a large multicenter study, is evaluating the natural history of HIV and associated cancers in female spouses and sexual partners of hemophilic men. An ongoing series of NCI-sponsored longitudinal studies have defined the incidence of human papillomavirus (HPV)-associated cervical cancer in HIV-infected women. Approximately 60 percent of HIV-infected women have

cervical dysplasia, suggesting that HIV and HPV act synergistically. These studies will provide significant insight into HIV-associated neoplasia.

Planned NIH-sponsored natural history studies will continue research on perinatal transmission issues; basic research into biologic factors associated with HIV transmission; tracking transmission in other countries where seroconversion rates among discordant heterosexual couples are much higher than in the United States; and research on the biologic and behavioral and psychosocial aspects of HIV infection and its treatment in women in all subpopulations including minorities and IDUs.

The NIH has placed a high priority on the evaluation of therapeutic regimens for the prevention, treatment, and control of HIV infection and its sequelae in women and has provided resources for ancillary services to enhance the enrollment of women in clinical studies. Three ICDs of the NIH have the primary responsibility for the clinical trials programs in this population: NIAID, NICHD, and NCI.

Special committees have been developed within the NIAID-funded clinical trials networks to address the unique issues associated with women and HIV. The major goals of these committees are to enhance participation of women in clinical trials and review entry criteria to ensure that the trials do not exclude women; to ensure that clinical trials contain gynecologic recommendations to meet the

medical needs of HIV-infected women; to participate in the design and development of clinical trials testing treatments for HIV-associated conditions that specifically affect both pregnant and nonpregnant women; and to participate in the development and design of clinical trials to interrupt maternal-fetal HIV transmission.

Ongoing NIH-sponsored clinical trials include a gender-specific OI protocol studying the efficacy of fluconazole prophylaxis for mucosal candida infections in HIV-infected women; the safety of AZT during the third trimester of pregnancy; and the safety, efficacy, and tolerance of oral AZT versus placebo in pregnant HIV-infected women and their infants. NIH-sponsored clinical studies are also being conducted to identify effective regimens for preventing HIV transmission from mothers to infants. Current studies are evaluating AZT treatment in the second and third trimesters of pregnancy and treatment during the first 6 weeks of the infant's life; recombinant CD4; and a Phase I study of CD4-IgG. An NHLBI/NIAID/NICHD collaborative Phase III study is planned to evaluate hyperimmune anti-HIV intravenous immunoglobulin (HIVIG) as a means of reducing vertical transmission. This study is currently awaiting supply of the agent from the new manufacturer.

Planned AIDS clinical trials sponsored by the NIH will investigate combination drug therapies; cytotoxic chemotherapy; the

neurodevelopmental and neurologic manifestations of HIV infection; anti-TB and multidrug-resistant TB agents; the possible role of high-dose steroids for treating PCP; two dose regimens of dapsone for PCP prophylaxis; fluconazole for prophylaxis of oral candidiasis; parenteral pentamidine for PCP prophylaxis; the rheumatic and cutaneous manifestations of HIV infection and AIDS; and psychotropic medications for treatment of HIV-associated psychiatric and emotional disorders.

Minority Populations and HIV

Epidemiologic studies indicate that HIV infection and AIDS are steadily increasing among several populations that include minorities, IDUs, adolescents, and women and their offspring. African Americans account for 53 percent and Hispanics for 21 percent of AIDS cases in women, while in children, 51 percent of the cases are in African American children and 23 percent are in Hispanic children. In comparison, African Americans comprise 12 percent and Hispanics less than 8 percent of the total U.S. population. Among the total number of AIDS cases in the United States, 52 percent are Caucasian, 30 percent are African American, and 17 percent are Hispanic. Minority populations are disproportionately represented among cases of HIV transmission associated with injecting drug use. African Americans and Hispanics account for 79 percent of IDUs with AIDS (female and heterosexual male) and 79 percent of AIDS cases

among heterosexual partners of IDUs. Among HIV-infected children of IDU mothers or mothers with IDU sexual partners, 84 percent are African American or Hispanic while only 15 percent are Caucasian.

The NIH has strived to increase the enrollment of minority populations in its AIDS clinical trials. The recent recompetition of the adult AIDS Clinical Trials Units (ACTUs) provided a means to enhance the accountability of the AIDS Clinical Trials Group (ACTG) system and link performance with incremental funding. Patient accrual to ACTG trials is detailed in Table 1. Sites funded under the recompetition are expected to perform scientifically based studies, resulting in quality data, accrue patients into high-priority protocols, and recruit members of underrepresented populations.

The Terry Bein Community Programs for Clinical Research on AIDS (CPCRA) enables community-based physicians to be involved in setting research priorities and conducting clinical trials, thereby successfully enhancing participation of underrepresented populations, specifically minorities, women, and IDUs. Of the 6,375 patients entered into CPCRA clinical trials as of March 1993, more than 57 percent are minorities, approximately 19 percent are women, and 38 percent identify injecting drug use as an HIV transmission category (Table 2). Both the ACTG and CPCRA programs have required their sites to develop community advisory boards to ensure

Table 1. Patient Accrual to ACTG Trials Demographic Information

Population Group	% of Total Population	% of AIDS Cases	% in Clinical Trials 1987	% in Clinical Trials 3/93
Sex				
Male	48.7	88.6	95	85.3
Female	51.3	11.4	5	14.7
Race				
Caucasian	80.9	52.8	82	66.5
African American	11.7	29.5	7	17.3
Hispanic	7.4	16.5	11	14.8
Other		< 1		1.4
IDU		28.6		
Never			88	87.9
Previous/ Current			12	12.1
Number of People in Trials			2,503	22,489

participation of underrepresented populations and to increase awareness of specific community requirements for participation in protocols.

The NIH has focused efforts on building infrastructure in institutions and geographic areas serving minority populations in order to better treat people in need and to increase access to clinical studies for minority populations. In collaboration with the NCRR, the NIAID began a program to provide funds to

minority institutions for the development of the infrastructure required to compete as an ACTU. Among those receiving awards are Howard University, the University of Hawaii, and the University of Puerto Rico. The NCRR manages the Research Centers for Minority Institutions (RCMIs) program. One of the objectives is to provide for the development of research infrastructure for AIDS clinical and basic research. The recipients include Meharry Medical School, Morehouse School of Medicine, University of Puerto

Table 2. Patient Accrual to CPCRA Trials Demographic Information

Population Group	% of Total Population	% of AIDS Cases	% in Clinical Trials 3/93
Sex			
Male	48.7	88.6	80.4
Female	51.3	11.4	19.6
Race			
Caucasian	80.9	52.8	42.5
African American	11.7	29.5	39.9
Hispanic	7.4	16.5	15.8
Asian/Pacific Islander		<1	0.6
Aleut Eskimo/Native American		<1	0.5
Other		<1	0.8
IDU		28.6	38.4
Number of People in Trials			6,339

Rico, Universidad Central del Caribe, Ponce School of Medicine, Charles R. Drew University of Medicine and Science, University of Hawaii, City College of the City University of New York, Clark Atlanta University, Florida A&M University, Tennessee State University, Hunter College, Tuskegee University, and Texas Southern University.

Coordination of Efforts

The NIH, through the OAR, coordinates its HIV-related research efforts in several arenas: among the ICDs of the NIH; with

other agencies of the PHS and other components of the Department of Health and Human Services (DHHS); with other Federal Government agencies; with governments of other nations; with international organizations; with private philanthropic organizations; with academia; and with private industry. Some of the formal mechanisms employed in this coordination are described below.

- The NIH AIDS Executive Committee functions as the NIH coordinating body among the ICDs. It is composed of the Directors and the AIDS Coordinators of

the ICDs and staff from the Office of the Director. The OAR provides staff support for the Committee.

- The NIH interacts with coordinating bodies at the level of the Assistant Secretary for Health, DHHS, such as the National AIDS Program Office (NAPO), the PHS AIDS Leadership Group, and the PHS Executive Task Force on AIDS. The NIH also coordinates with other PHS agencies through participation in meetings of the agencies' advisory committees.
- The NIH AIDS Program Advisory Committee is composed of outside experts, including advocates for HIV-infected individuals. The APAC includes several subcommittees that provide advice and guidance in the coordination of the NIH HIV-related research program.
- The NIH serves on the Federal Coordinating Committee on AIDS Information, Education and Risk Reduction (FCC), which coordinates government-wide activities.
- The Federal Coordinating Council on Science, Engineering, and Technology (FCCSET) Working Group on HIV Vaccine Development in International Field Trials has been established to address factors involved in vaccine development, production and testing of potential candidates, coordination of Federal Government activities and consensus development, identification of

funding resources for trials, and collaboration with foreign governments.

- The NIH has established bilateral agreements with foreign governments and institutions for cooperation and collaborative efforts in HIV-related research.
- The NIH coordinates activities with the Global Programme on AIDS (GPA) of the World Health Organization (WHO) through participation on the GPA Steering Committees for scientific areas, participation in GPA programmatic activities, and participation in the United States delegation to the meetings of the Management Committee of the GPA.

In addition, the NIH supports and participates in a variety of activities designed for coordination in specific scientific arenas, including working groups of PHS staff targeted to designated research or policy areas; groups developed to foster collaboration among government, academia, and industry, such as the National Cooperative Drug Discovery Groups (NCDDG) and the National Cooperative Vaccine Development Groups (NCVDG); the International Network for AIDS Research and Training; the International Subcommittee of the Federal Coordinating Committee on AIDS, which provides a mechanism for sharing of information among Government agencies concerning international AIDS efforts; and the PHS Panel on Women, Adolescents, and Children with HIV Infection.

Development of the Plan

The Public Health Service recently developed a Strategic Plan to Combat HIV and AIDS in the United States. The NIH Plan for HIV-Related Research complements and further elucidates the NIH responsibilities within the overall PHS plan.

In addition, as research on HIV is integrated into the overall research agenda of the NIH, the NIH Plan for HIV-Related Research will complement the other planning efforts of the NIH. These efforts include the current NIH Strategic Plan; the current effort to develop a 10-year plan for increasing NIH behavioral research (Appendix B); and the strategic plans of the individual ICDs.

During the preparation of this document, advice was sought and considered from various sources. The APAC was chartered to advise the Director, NIH, and the Director, OAR, on HIV/AIDS research priorities and policy issues. Since its first meeting in February 1988, the APAC has provided advice and guidance in these areas. At the April 1991 meeting of the APAC, the development of the NIH Plan for HIV-Related Research was discussed as part of a review conducted by the Institute of Medicine (IOM) on *The AIDS Research Program of the National Institutes of Health*. The IOM study and the ensuing report resulted from a request by the OAR for an unbiased, objective review of NIH

HIV-related research activities. The findings and recommendations contained in the report have been seriously considered in the development of the objectives and strategies contained in this plan. Other sources of recommendations and advice considered in the development of this plan included scientists and researchers both within and outside the NIH, representatives of AIDS advocacy groups, the recommendations of the PHS-sponsored National Conference on Women and HIV Infection, the National Commission on AIDS, and numerous other extramural expert advisory groups.

The plan identifies the major areas of emphasis for biomedical and behavioral research on HIV infection and AIDS. A brief update on current knowledge or the status of research has been prepared for each area of emphasis. For each area of emphasis, objectives and research strategies specific to these objectives are described. The plan thus presents where we are now, where we hope to be, and what we need to accomplish in the next 5 years to address the pandemic of HIV infection and AIDS.

The content of each section is described below.

- **AREA OF EMPHASIS:** The broad area of research.
- **STATUS:** A brief review of current research activities and knowledge in the area of emphasis.

- Budget table of funding for the area of emphasis by ICD.
- SCIENTIFIC ISSUES: In priority order, the gaps in knowledge that must be addressed.
- OBJECTIVES: Scientific questions to be addressed.
- STRATEGIES: Specific scientific strategies that the NIH will pursue in order to answer the scientific questions.

After each strategy, the superscript initials indicate those ICDs that conduct or support research related to that strategy or plan to conduct or support such research.

- FY 1995 Planned Activities: Specific ongoing and proposed projects within each ICD supporting research in this area.
- Budget table of funding for the objective by ICD.
- Budget summary table of funding for the area of emphasis by objectives.

This plan is a working document and will be updated annually to reflect emerging scientific priorities and opportunities as well as the changing demographics and manifestations of the pandemic.