HIV/AIDS Research: Successes Bring New Challenges

THE KAISER FAMILY FOUNDATION

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This issue brief was developed for the Kaiser Family Foundation Capitol Hill Briefing Series on HIV/AIDS. It provides an overview of key HIV/AIDS research issues and activities.

WHY FOCUS ON HIV/AIDS RESEARCH?

Even as we approach the third decade of the HIV/AIDS epidemic, HIV is still considered a new and complex disease for which there is no cure. As such, it presents unique challenges for research. In recent testimony before Congress, the Director of the Office of AIDS Research at the National Institutes of Health called HIV the "great plague of the 20th century – an epidemic of biblical proportions."[1]

According to the World Health Organization, 16.3 million men, women, and children with AIDS have died since the AIDS pandemic began in the early 1980s – including more than 420,000 American men, women, and children. AIDS has now surpassed tuberculosis and malaria as the leading infectious cause of death worldwide. In 1999 alone, a record 2.6 million people died from AIDS.[2,3] Given the continuing impact of the epidemic in the U.S. and around the world, there remains a critical need for HIV research to continue to identify ways to prevent and treat HIV infection.

WHO CONDUCTS HIV/AIDS RESEARCH?

HIV/AIDS research is conducted by government research agencies, private industry, including pharmaceutical companies, and academic research centers and other institutions and organizations. In the U.S., most HIV/AIDS research is sponsored by the Federal government, primarily by the

What is the Focus of HIV/AIDS Research?

HIV/AIDS research consists of a multitude of activities that focus on basic and clinical science to understand and treat HIV infection and its related conditions; prevention science to track and prevent the spread of HIV, understand the behaviors that put people at risk for HIV infection, and develop interventions to change these behaviors; and health services research to address the nexus between scientific research and the application of that research into health care services.

Basic research	Explores the body's immune system, the molecular structure of the human immunodeficiency virus (HIV) that causes AIDS, and the ways in which the virus attacks the human body.
Clinical research	Examines the impact of HIV on the human body and helps to identify the various medical conditions that affect people living with HIV/AIDS. Clinical research includes research conducted through clinical trials.
Epidemiologic research	Studies the distribution and control of HIV/AIDS within populations, population subgroups and communities. Epidemiologic research includes the study of HIV and AIDS incidence (current rate or number of new cases) and prevalence (proportion or number of people living with HIV or AIDS at a particular point in time).
Behavioral and social science research	Investigates ways to understand and change behaviors that may lead to HIV infection (e.g., unprotected sexual intercourse and the use of HIV-contaminated injection drug equipment) as well as the factors that may lead to such behaviors (e.g., low self-esteem, poverty, and complacency).
Health Services Research	Addresses such issues as cost, access, quality, and outcomes of services and care, including disparities in access across different population groups.

WHAT IS HIV?

The human immunodeficiency virus (HIV) is the virus that causes AIDS by invading human immune cells and multiplying. HIV is a retrovirus, a subgroup of virus whose genes are composed of ribonucleic acid (RNA) molecules. RNA can create a DNA copy that can enter into the genes of the host cell. Among retroviruses, HIV is classified as a lentivirus, or "slow" virus, resulting in a long interval between initial infection and the onset of serious symptoms. Lentiviruses have a complex genetic structure, making it easy for them to change or mutate. HIV was first identified by researchers in 1984.[5]

WHAT ARE THE TYPES OF HIV?

In the United States, the most typical form of HIV is known as HIV-1. A different but related form of the virus – known as HIV 2 – is primarily found in West African countries. Since the beginning of the HIV pandemic, more than 50 million people worldwide have been infected with HIV, of whom more than 16.3 million have died. In the United States, approximately 800,000-900,000[6] people are living with HIV/AIDS; an additional 420,201 people with AIDS had died as of June 30, 1999.[3]

National Institutes of Health (NIH). Federal HIV/AIDS research also is conducted and supported by the Department of Veterans Affairs (the largest direct provider of HIV care services), the Department of Defense, the Food and Drug Administration, the Centers for Disease Control and Prevention (which focuses primarily on prevention and epidemiological research), and the Agency for Healthcare Research and Quality (which focuses on health services research). Other Department of Health and Human Services agencies also conduct some health services research on HIV/AIDS.

The Office of AIDS Research (OAR), created in 1988, directs the scientific, budgetary, legislative, and policy elements of the NIH AIDS research program. In 1993, Congress enacted the NIH Revitalization Act (P.L.103-43), which created a permanent OAR, an OAR Advisory Council (composed of 18 non-government experts), and a full-time OAR Director. Under the statute, OAR is required to develop an annual comprehensive plan and budget for all NIH-supported HIV/AIDS research.

HIV/AIDS research at the NIH is conducted both through the NIH's intramural research program and through its extramural grants programs to researchers in academic settings around the country.[4] While all of NIH's 25 Institutes and Centers (ICs) conduct or support HIV/AIDS research, most of the work is led by 7 IC's (see box on right).

Private industry, including pharmaceutical and biotechnology companies, have also played an important role in converting scientific advances into the development of effective treatments for HIV infection and the various conditions that affect people living with HIV/AIDS. A total of 75 pharmaceutical and biotechnology companies are involved in HIV/AIDS research and, as of December 1999, 61 AIDS-related medicines had been approved for sale in the U.S. A 1999 drug industry survey indicated that 102 medicines were in development for

ROLES AND RESPONSIBILITIES WITHIN THE NIH INSTITUTES

- ***The National Institute of Allergy and Infectious Diseases (NIAID)*** *has the lead responsibility within the NIH for the discovery and development of interventions to treat or prevent HIV infection.*
- ***The National Cancer Institute (NCI)*** *focuses its research on AIDS-related malignancies (about 30% of people with AIDS develop some form of malignancy). NCI houses the HIV Drug Resistance Program, the HIV and Malignancies Branch, and the NIH Vaccine Research Center, a joint project with NIAID.*
- ***The National Institute on Drug Abuse (NIDA)*** *focuses on developing strategies to reduce drug related behaviors that are linked to the transmission of HIV.*
- ***The National Institute of Mental Health (NIMH)*** *focuses on the impact of HIV on the central nervous system (CNS), mechanisms to motivate behavior change, behavioral prevention strategies in at-risk populations and therapeutics for CNS complications of HIV.*
- ***The National Center for Research Resources (NCRR)*** *provides critical research technologies and shared resources across all NIH Institutes and Centers.*
- ***The National Heart, Lung and Blood Institute (NHLBI)*** *supports research on the pulmonary, hematologic, and cardiac complications of HIV infection and research designed to maximize the safety and adequacy of the nation's blood supply.*
- ***The National Institute of Child Health and Human Development (NICHD)*** *supports research focused on maternal, pediatric, and adolescent HIV infection and AIDS.*

WHAT ARE OPPORTUNISTIC INFECTIONS?

Because of their compromised immune systems, people with HIV are susceptible to a range of infections and medical conditions – known as opportunistic infections or OIs. These conditions often are the cause of death among persons living with HIV/AIDS. Research conducted in the early and mid-1980s led to the development of effective preventive therapies for several OIs including Pneumocystis carinii pneumonia (PCP), toxoplasmosis, Mycobacterium avium complex disease, and bacterial infections. Research also has led to the use of these therapies to prevent the onset of many OIs in people with HIV and other patients with suppressed immune function including cancer patients. The U.S. Public Health Service and the Infectious Diseases Society of America issue guidelines for the prevention of opportunistic infections in persons with HIV (see www.hivatis.org for the most recent version).

AIDS and AIDS-related conditions including an anti-HIV fusion inhibitor, 11 preventive vaccines, a new protease inhibitor designed to overcome resistance, and a gene therapy that infuses healthy CD4 cells into a person with AIDS.[7]

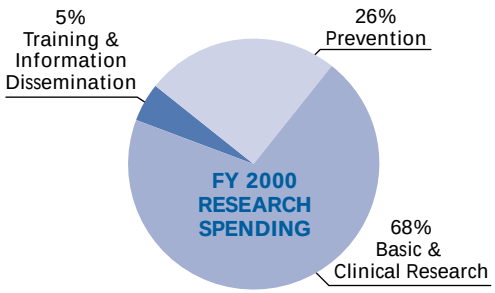
Finally, academic institutions are a major source of HIV/AIDS research and treatment. Medical schools and their affiliated teaching hospitals perform more than 50% of all NIH-supported research in the U.S.[8] and provide a disproportionate share of AIDS care in the U.S. Because of their expertise, NIH has entered into agreements with numerous academic health centers to house and conduct ongoing HIV-related basic, clinical, and prevention research around the country, including some of the major national and international clinical trial networks.

HOW MUCH IS SPENT ON FEDERAL HIV/AIDS RESEARCH?

In FY 1999, federal spending on HIV/AIDS research totaled $1.9 billion across the federal agencies. Research comprised 19% of the $9.7 billion in total federal spending on AIDS-related programs in that year. Most federal HIV/AIDS research spending is for activities conducted and sponsored by the NIH, which totaled $1.8 billion in FY 1999 and $2 billion in FY 2000.[4, 9] Approximately 68% of HIV/AIDS research funding at NIH is spent on basic and clinical research; 26% is spent on prevention research, including vaccine research (12%). The remainder is spent on training and information dissemination.[10]

In the early years of the epidemic, increases in HIV/AIDS research funding were larger in size as the research enterprise ramped up to confront a new, emerging infectious disease. More recently, however, increases in NIH spending on HIV/AIDS research have lagged slightly behind the overall increases in the NIH budget. For example, between FY 1999 and FY 2000, spending on HIV/AIDS research increased 11% compared with a 14% increase in the overall NIH budget.[4,11]

Total NIH Research Spending on HIV/AIDS, FY2000



Total: $2 Billion

Note: May not total 100% due to rounding.

WHAT IS THE ROLE OF CLINICAL TRIALS?

A major component of clinical research is the process of testing and evaluating the safety and effectiveness of potential treatments. Such trials are funded by NIH, FDA, pharmaceutical companies, and others. They are conducted in a variety of settings including universities, clinics, and individual physicians' offices. While the primary aim of clinical trials is to determine which treatments work for which people, these trials are also a source of free or low-cost care for patients who are enrolled in them. In fact, in some cases, patients are paid for their participation. Generally speaking, before being approved by the FDA for sale in the U.S., medications must go through three stages of clinical trials[12]:

- *Phase I trials seek to determine the safe dosage levels for a treatment being tested. Such trials usually have 10 to 20 patients enrolled.*

- *Phase II trials seek to determine the safety and effectiveness of the treatment with as many as several hundred patients enrolled.*

- *Phase III trials seek to determine the long-term benefits of the treatment with as many as several thousand patients enrolled.*

NIH sponsors a series of extramural AIDS clinical trials networks including the Adult AIDS Clinical Trials Group, the Pediatric AIDS Clinical Trials Group, the Strategic Program for Innovative Research on AIDS, and the Terry Beirn Community Programs for Clinical Research on AIDS, which is based in primary care settings.

WHAT ROLE DO COMMUNITY-BASED GROUPS AND PEOPLE WITH HIV/AIDS PLAY IN HIV/AIDS RESEARCH?

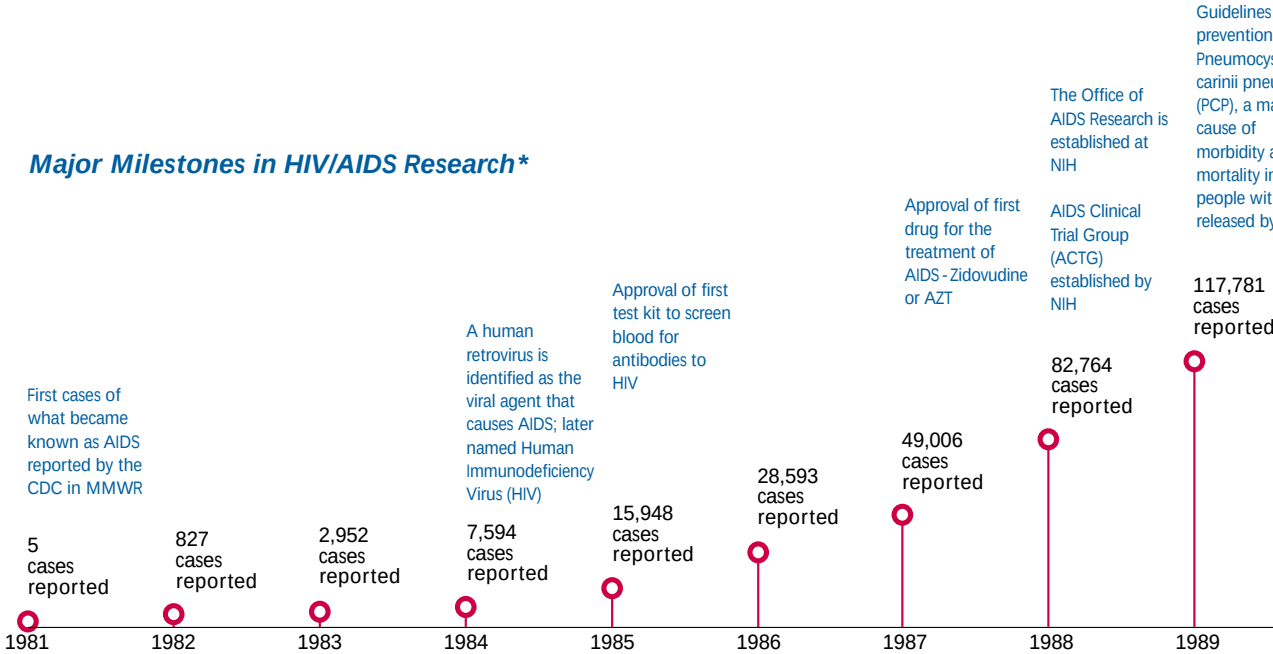
People with HIV/AIDS and the community-based organizations that serve them have played an essential role in research. Community-based trial groups provided some of the early tests of AIDS drugs. AIDS activism has led to dramatic changes in public and private responses to AIDS, including speeding up the drug review and approval process at the Food and Drug Administration, increasing participation of women and minorities in clinical trials, and greater accountability among research institutions. People with HIV now are incorporated into the research and drug development process and provide valuable input into the design of clinical studies, the implementation of research programs, and the setting of research priorities.

HOW ARE WOMEN AND MINORITY AMERICANS INVOLVED IN HIV/AIDS RESEARCH?

Because women and minority Americans represent a significant portion of people living with HIV/AIDS, new AIDS cases, and new HIV infections, their involvement in HIV/AIDS research is critical. Yet, in the earlier years of the epidemic, women and minorities often were left out of many research trials and protocols, resulting in a lack of clinical data about the impact of HIV and HIV-related treatments on these populations.

The NIH Revitalization Act (P.L.103-43) required NIH and other research agencies to expand the involvement of women and minority Americans in all research. In 1994, NIH implemented Guidelines requiring applicants for NIH grants to address "the appropriate inclusion of women and minorities in clinical research."[13] The amount of NIH AIDS research funds spent on research focused on

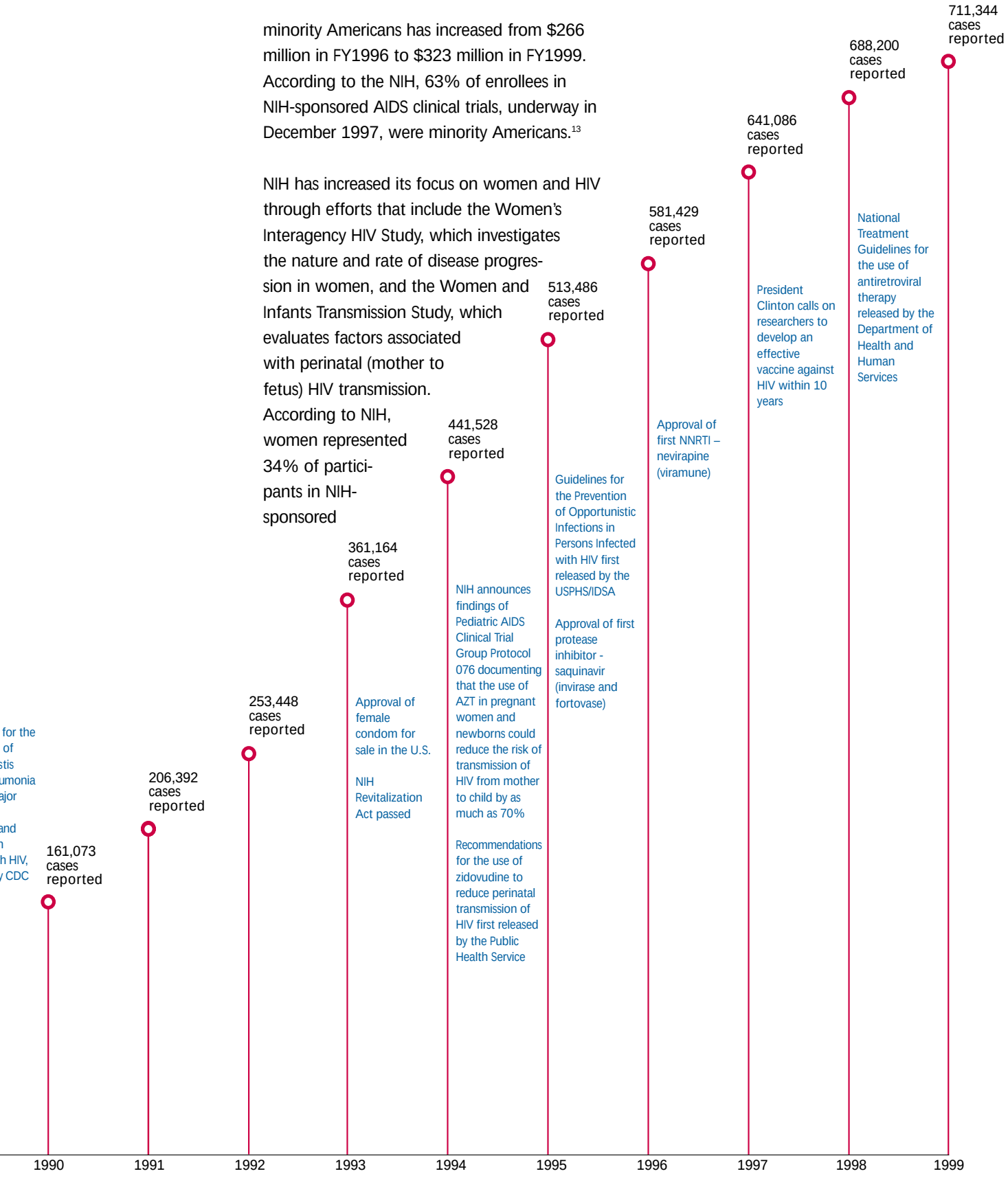
Major Milestones in HIV/AIDS Research*



*AIDS cases are cumulative reported cases at the end of each year, except for 1999 which represents cases reported through June 1999.
Sources: Centers for Disease Control and Prevention, Food and Drug Administration, National Institutes of Health, and the American Foundation for AIDS Research.

minority Americans has increased from $266 million in FY1996 to $323 million in FY1999. According to the NIH, 63% of enrollees in NIH-sponsored AIDS clinical trials, underway in December 1997, were minority Americans.[13]

NIH has increased its focus on women and HIV through efforts that include the Women's Interagency HIV Study, which investigates the nature and rate of disease progression in women, and the Women and Infants Transmission Study, which evaluates factors associated with perinatal (mother to fetus) HIV transmission. According to NIH, women represented 34% of participants in NIH-sponsored



WHAT ARE ANTI-RETROVIRAL DRUGS?
Antiretroviral drugs are designed to prevent HIV from replicating in the human body. There are three classes of antiretroviral drugs currently on the market: nucleoside analog reverse transcriptase inhibitors (NRTIs), such as AZT, that interrupt an early stage of virus replication; non-nucleoside reverse transcriptase inhibitors (NNRTIs) that also target early stages of replication; and protease inhibitors (PI's) that interrupt viral replication at a later stage, preventing new strains of viruses from emerging.

Because HIV can rapidly become resistant to individual drugs, physicians typically prescribe a combination of antiretroviral drugs also known as "highly active retroviral therapy" or HAART. National treatment guidelines have been developed by the Department of Health and Human Services (see www.hivatis.org for the most recent version).

clinical trials enrolled in December 1997,[13] but criticism about the inclusion of minorities and women in clinical trials still remains.[14]

WHAT HAS HIV/AIDS RESEARCH PRODUCED?

After nearly 18 years of effort, the nation's investment in HIV/AIDS research has resulted in numerous advances including[15,16,17,18]:

- *The identification of HIV, the viral agent causing AIDS;*
- *The development of a test to detect the presence of antibodies to HIV in blood and other tissues;*
- *A doubling of the average survival time for a person living with HIV/AIDS;*
- *The development of drugs to treat HIV infection that reduce the impact of the virus on the human body;*
- *Advances in the treatment and prevention of several HIV-related diseases and infections including pneumocystis pneumonia, CMV retinitis, and toxoplasmosis;*
- *The identification of barriers to access to care for people with HIV and disparities in access and outcomes for some populations;*
- *A dramatic reduction in the number of new HIV infections in the U.S. due to successful community and individual level prevention interventions; and*
- *The discovery that the use of antiretroviral drugs can dramatically reduce the risk of transmission of HIV from a pregnant woman to a fetus.*

Still, there is no cure for HIV, and the potential for the development of an effective vaccine is many years away.

HOW HAS HIV/AIDS RESEARCH HELPED IN OTHER AREAS?

Beyond its direct impact on the treatment and prevention of AIDS-related conditions, HIV/AIDS research has also led to major advances in other areas of science and medicine. HIV/AIDS research is helping to unravel the mysteries surrounding many other infectious, malignant, neurologic, autoimmune and metabolic diseases. Most importantly, HIV research has significantly enhanced our understanding of the immune system and the ways in which our bodies fight against disease and infection. HIV/AIDS research has provided an entirely new paradigm for drug design and development to treat viral infections. For example, the recent development of the new flu drug, Relenza directly benefited from AIDS research. The drug known as 3TC, developed to treat AIDS, is now the most effective therapy for chronic hepatitis B infection. Drugs developed to prevent and treat AIDS-related opportunistic infections also provide benefit to patients undergoing cancer chemotherapy or receiving anti-transplant rejection therapy. AIDS is also providing new understanding of the relationship between viruses and cancer.[15, 16] Additionally, HIV/AIDS research has contributed to:

- *Accelerated research into viruses in general and retroviruses in particular;*
- *Provided insight into treatment with protease inhibitors of other conditions including bone loss and heart muscle damage;*
- *Enhanced understanding of the spread of infectious agents through the blood/brain barrier (which has implications for research on Alzheimer's disease, dementia, encephalitis, and meningitis);*
- *Improved treatment and prevention of infections among people with advanced breast cancer, organ transplants, or autoimmune conditions; and*

- *Improved diagnostic tests to detect cancer cells and tuberculosis.*

WHAT ARE CURRENT CHALLENGES FOR HIV/AIDS RESEARCH?

There are several important challenges for HIV/AIDS research over the next decade that form the basis for current and future research priorities, both for the federal research effort and for those working in the private sector and in the community. These include[1]:

- **The global epidemic.** *With more than 90% of new infections occurring in developing countries where therapeutic interventions are unaffordable and hard to deliver, HIV/AIDS research efforts are addressing the need to develop treatments that can be implemented in these countries and are accessible to their populations.*

- **Health disparities in the U.S. and the impact of HIV on minorities, women, and young people.** *Despite recent positive trends, HIV remains a leading cause of death among minority Americans, and HIV increasingly impacts minorities, women, and young people. Research challenges include: increasing the number of minority researchers conducting behavioral and clinical research; educating minority physicians about HIV treatment approaches; including women and minorities in clinical research in proportion to their increasing representation in the epidemic; developing and evaluating prevention interventions designed to reduce HIV risk behaviors and transmission in communities disproportionately impacted by HIV; and reducing barriers to prevention and treatment.*

- **Improved therapies.** *Researchers are focusing on the development of new, simpler, less toxic, and less expensive drugs to address the issues of side effects and complicated regimens.*

- **Long-term clinical effectiveness research.** *Clinical studies are needed to identify strategies for the long-term use of HIV antiretroviral therapy and answer questions such as when to begin therapy, how to manage side effects, how to improve adherence to HIV therapy and avoid the development of drug resistance, and how to treat patients for whom therapy is failing.*

- **Prevention research.** *Without a cure for HIV, prevention efforts continue to be the most cost-effective way to address the epidemic. Prevention priorities include management of sexually transmitted diseases; perinatal prevention, including enhancing understanding of breast-feeding risk; and the development of topical microbicides (microbicides, a synthetic or natural substance that can kill or neutralize HIV during sexual intercourse, offer a promising new prevention intervention).[19, 20] In addition, understanding how to assist people in changing behaviors that place them at risk for HIV infection is a critical priority. This includes addressing the issue of complacency.[21]*

- **Vaccines.** *The NIH and many private and community organizations continue to make developing a vaccine against HIV a priority. Several AIDS vaccine trials are now underway.*

- **The link between public and private investments and research.** *The relationship between government-sponsored research, private industry research and research conducted by academic institutions is key to how scientific knowledge is produced and applied in the U.S., within and beyond the field of HIV research. Pharmaceutical companies, for example, frequently utilize the knowledge gained from NIH-supported HIV research to help them develop new drugs and other products. This has sometimes led to criticism of the high price of HIV-related drugs in the U.S. and around the world, and questions have*

been raised about whether drug makers should discount those prices to reflect the public investment and, more generally, how to make drugs and other new interventions more affordable to all people with HIV.

- **Translating research into practice.** *To be effective, research efforts must continue to identify ways to translate knowledge into programs and practices. For example, although national guidelines exist for HIV/AIDS-related drug treatment and prophylaxis, challenges remain to putting these guidelines into practice throughout different clinical settings and among different providers and payers in the U.S.*

CONCLUSION

As a new infectious disease that emerged at a time when many believed that the threat of infectious disease in the U.S. had largely been eliminated, HIV presented considerable challenges to scientific research. Overall, HIV/AIDS research has resulted in tremendous advances, including a dramatic reduction in AIDS-related mortality and the discovery of increasingly effective treatments for HIV disease and its related conditions. Despite these advances, however, the research community will be challenged with the need to continue to develop interventions to address an epidemic that increasingly affects racial and ethnic minorities, women, and young people throughout the U.S. and around the world.

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