

The AIDS Research Model

Implications for Other Infectious Diseases of Global Health Importance

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THE EVOLUTION OF THE ACQUIRED IMMUNODEFICIENCY syndrome (AIDS) as a global pandemic has heightened awareness of the persistent threat posed by established, emerging, and re-emerging infectious diseases of global health importance.¹ Examples of such diseases include resurgent endemic diseases such as malaria and tuberculosis, newly recognized conditions such as liver disease due to hepatitis C virus, and diseases such as West Nile fever and dengue, which have appeared in previously uninvolved geographical settings. In addition, endemic conditions such as acute respiratory infections, diarrheal diseases, and measles remain leading causes of illness and death worldwide.²

Each of these global health threats requires a multifaceted response involving a variety of public health measures, such as surveillance; public education and other prevention efforts; vector control; sanitation; programs to improve nutritional status; and the efficient provision of health services, including available treatments and vaccines.³ More broadly, alleviation of poverty and economic development are central to improving health since higher income is strongly associated with access to many of the goods and services that promote health.^{2,3}

In addition to these classic public health considerations, critical (but sometimes overlooked) components of any strategic approach to the control of infectious diseases are basic and clinical research efforts to improve the diagnosis, prevention, and treatment of the disease(s) in question.⁴ In this regard, on the occasion of the 20th anniversary of the recognition of the first cases of AIDS,⁵ it is appropriate to reflect on the fact that the research effort in AIDS over the past 2 decades serves as a model or paradigm of what can be accomplished when a robust commitment of financial and human resources is applied to a rapidly escalating public health problem of enormous magnitude.

AIDS Research: Investment and Returns

US government funding for biomedical research related to the human immunodeficiency virus (HIV) and AIDS has been unprecedented in magnitude, dwarfing that of any other in-

fectious disease in history. Budget figures of the US National Institutes of Health (NIH) are illustrative of the extraordinary financial commitment to AIDS research (FIGURE 1). Total NIH funding for HIV/AIDS research since the recognition of AIDS in 1981 exceeds \$20 billion (NIH Office of Financial Management, written communication, May 15, 2001); spending on AIDS research by other government agencies, pharmaceutical companies, philanthropies, and other funders also has been substantial.

The returns on these investments have been extraordinary and built rapidly on the explosion of knowledge in disciplines such as immunology and virology that occurred in the 1960s and 1970s.⁶ Within 3 years of the recognition of the first AIDS cases in 1981, the etiologic agent of the syndrome was discovered and causality proven.⁷ In 1984, a sensitive and specific diagnostic test for antibodies to HIV was developed and subsequently used in numerous seroprevalence surveys and other epidemiological studies to illuminate the scope of the epidemic.⁸ Using this test, the blood supplies in the United States and other developed countries were screened for HIV and rendered extremely safe by 1985.⁹ Extensive molecular analysis of HIV has delineated the novel genetic organization of the virus and its complex mechanisms for regulation of replication.¹⁰

This information, together with remarkable advances in the understanding of the pathogenesis and natural history of HIV disease, facilitated the rapid development of antiretroviral drugs that can limit HIV replication and immune system damage and the formulation of strategies and guidelines for the use of these medications.^{11,12} Combination therapy with potent antiretroviral drugs, referred to as highly active antiretroviral therapy (HAART), has played a major role in the dramatic decrease in morbidity and mortality due to HIV disease in the United States and other developed countries¹³ (FIGURE 2). The possibility of greatly increased access to these medications in poor countries may soon be realized because of recent commitments to reduce the price of antiretroviral drugs in developing nations and to establish the infrastructure to deliver them.¹⁴

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In addition to their role in the treatment of HIV-infected individuals, certain antiretroviral drug regimens also have been shown to dramatically reduce the risk of HIV transmission from mother to child, in both developed and developing countries.¹⁵ The risk factors associated with HIV transmission have been well defined, providing the foundation for prevention efforts.¹⁶ In virtually all developed nations and in certain developing countries (eg, Uganda, Senegal, Brazil, and Thailand), education and behavioral modification programs have proven effective in slowing the spread of HIV.¹⁷ A safe and effective HIV vaccine has not yet been developed. The reasons for this relate to a number of formidable obstacles faced by vaccine developers, including HIV clade and strain diversity and a lack of a clear understanding of the correlates of protective immunity in HIV infection.¹⁸ Nonetheless, a considerable effort is being mounted and promising candidate vaccines are in various stages of preclinical and clinical development in the United States and abroad.¹⁸

Much remains to be accomplished in AIDS research, both in terms of the scientific and medical challenges of HIV disease and with regard to the logistical and operational challenges of making HIV therapies, prevention services, and other interventions available to poor countries. However, the extraordinary research effort devoted to AIDS during the first 2 decades of the pandemic and the rapidity with which advances have been realized surpass those associated with any other life-threatening infectious disease in history and certainly any newly recognized disease. The successes of the research effort in AIDS over just 2 decades suggest that similar outcomes, ie, rapid advances in understanding “new” or resurgent diseases and the development of new interventions with direct relevance to public health, could be achieved for other diseases that exact an enormous toll but receive comparatively few research resources.

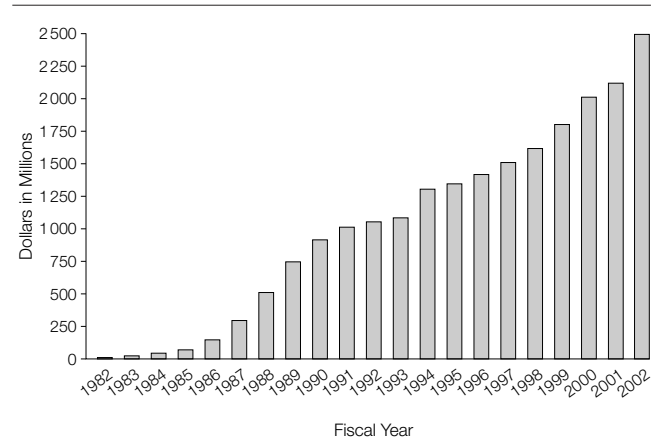
In this regard, the opportunities for productive research in tuberculosis, malaria, and other infectious diseases are unprecedented, particularly in light of the availability and application of genomic sequence information for *Mycobacterium tuberculosis*, *Plasmodium falciparum*, and scores of other pathogenic microbes,¹⁹ as well as information regarding host immunity that the Human Genome Project and related efforts surely will provide.^{20,21} Recently, a global health research agenda delineated the many opportunities in tuberculosis, malaria, and HIV/AIDS research that could be pursued with robust funding.²² Operational research also is needed to illuminate how best to deliver proven control strategies (eg, insecticide-treated bed nets for malaria; directly observed therapy for tuberculosis), as is the training of scientists and the development of research infrastructure, in both rich and poor countries. In addition, the development of vaccines, new drugs and diagnostics, and (in the case of malaria) improved tools of vector control are fertile research areas.

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Driving Forces in the AIDS Research Effort

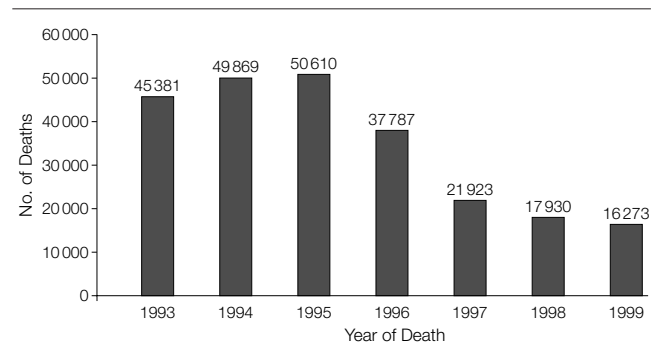
Although the need to devote substantial research resources to AIDS was clear to many US public health officials from the early days of the epidemic, a major impetus for the rapidity and magnitude of the allocation of AIDS research funding was the highly effective pressure applied by AIDS activists.²³ Activist groups were comprised largely of homosexual men, the US constituency predominantly afflicted by HIV early in the epidemic. Their successes were achieved through classic organized lobbying efforts as well as theatrical demonstrations, the likes and extent of which had never been as effectively applied by any other patient or disease advocacy groups. Despite early skepticism regarding the magnitude of the threat posed by AIDS, the efforts of well-informed and politically astute activists, together with those of committed local and federal public health officials, resulted in the allocation of large sums of money

Figure 1. History of Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome Research Funding at the US National Institutes of Health



Funding from fiscal year 1982 through fiscal year 2002. The years 2001 and 2002 are estimated funding levels. Source: Office of Financial Management, National Institutes of Health, Bethesda, Md.

Figure 2. Estimated Deaths of Persons With Acquired Immunodeficiency Syndrome, 1993 Through 1999 in the United States



Source: US Centers for Disease Control and Prevention, Atlanta, Ga.¹³

for AIDS research. Ultimately, the success of AIDS activists and other advocates for AIDS research funding demonstrated that decisions regarding the allocation of biomedical research resources can be influenced by aggressive and creative lobbying by individuals within and outside of the public health community.²³ This lesson has been heeded by advocates for other diseases such as breast cancer, diabetes, and Parkinson disease, and, increasingly by advocates of research for other infectious diseases of global health importance, notably malaria and tuberculosis.

An important element in the sustained commitment to the support of AIDS research has been the growing realization by political leaders, in both the executive and legislative branches, of the importance of global health to the interests of the government and people of the United States. In recent years, the concept that infectious diseases pose broad threats to our national interests has been brought into sharp focus by the HIV/AIDS pandemic. A number of observers, including the US National Intelligence Council,²⁴ have concluded that the expansion of the AIDS epidemic has the potential to greatly exacerbate social, economic, and political instability in nations and regions of the world in which the United States has significant economic and political interests.

Summarizing such concerns, the US Institute of Medicine has concluded that “America has a vital and direct stake in the health of people around the globe, and that this interest derives from both America’s long and enduring tradition of humanitarian concern and compelling reasons of enlightened self-interest.”¹ It is clear that the notion of “enlightened self-interest” has helped sustain funding for HIV/AIDS research; increasingly, world leaders are realizing that this concept has relevance to other diseases with a huge global impact, notably tuberculosis and malaria. Similar to HIV/AIDS, these diseases have the potential to provoke social fragmentation, economic decay, and political polarization in countries where they are endemic and as such should be considered to be security as well as humanitarian issues deserving of robust research support.

Global Health and Foreign Policy: The AIDS Paradigm

In January 2000, the Security Council of the United Nations made history when it devoted an entire session to HIV/AIDS, the first time that body, normally concerned with issues of war and peace, had focused specifically on a health issue.²⁵ Subsequently, AIDS has become a core issue of the Security Council, and in June 2001 the United Nations convened a special session of the General Assembly to discuss HIV/AIDS and formulate a global response to the pandemic.²⁶ In the United States, the White House formally designated HIV/AIDS as a threat to the national security of the United States, indicating that it could potentially contribute to the fall of governments, incite ethnic wars, and undermine decades of efforts to build free-market economies abroad.²⁷

Clearly, the AIDS pandemic in recent years has captured the attention and interest of western leaders to an extent that

far exceeds the attention paid to malaria, tuberculosis and other infectious diseases that have devastated populations in developing countries for centuries. This is not surprising: AIDS was first recognized in the United States and other developed nations and unlike many “tropical diseases” has significantly impacted most developed nations. However, within the past 2 years, the sheer magnitude of the global pandemic has reached the public consciousness, including an unprecedented focus on global health issues discussed at the 13th International AIDS Conference in 2000, held for the first time in a developing country—South Africa. Discussion at the conference focused public attention on global health realities that had been little appreciated outside the public health community: life expectancy for several sub-Saharan African nations have taken a sharp turn downward, with projections for continued decline, and the gross domestic product for many nations in this region had decreased substantially as a result of the impact of HIV/AIDS on the youngest and most productive segment of those societies.^{17,28} When the burden of AIDS is added to the toll exacted by other major diseases, the collapse of poor nations becomes a sobering possibility.

The recent recognition of the global threat of AIDS, superimposed on almost 2 decades of domestic focus on HIV/AIDS by the United States and other developed nations, has led to a truly unprecedented galvanization of resources and commitment on the part of governments, private foundations, the World Bank, other international organizations, and private industry toward curtailing this pandemic.^{14,29} The building of infrastructure necessary for the delivery of the fruits of AIDS research to developing nations has often been considered beyond the realm of feasibility in the poorest countries of the world. However, the intensity of the interest and the diversity of commitments among public and private enterprises have now brought such considerations to the forefront.

Increasingly, the lessons of AIDS—including an appreciation of the need for sustained research efforts in addition to classical public health measures—are being applied to other important health threats. Initiatives aimed at enhancing the development and delivery of vaccines not only for HIV/AIDS but also for malaria and tuberculosis have been proposed.^{22,29,30} In the US Congress, numerous legislative proposals are being pursued to support the discovery and to facilitate the delivery of therapeutics, vaccines, and other tools of prevention for these 3 major killers (Senate bills: S 463, 895, 1032, 1120, 1115, and 1116; House bills: HR 684, 933, 1167, 1168, 1185, 1269, 1504, 1567, 1771, 2069, 2104, and 2209).³⁰ Philanthropic foundations, particularly the Bill and Melinda Gates Foundation, have contributed billions of dollars, and pledged even more for global health initiatives, most involving a variety of infectious diseases.^{29,31}

The commitment of other nations to global health has likewise been catalyzed by the recognition of the real and potentially catastrophic nature of the AIDS pandemic. At a meet-

ing of the G8 nations in Okinawa in July 2000, a communiqué was issued stating that “infectious and parasitic diseases, most notably HIV/AIDS, tuberculosis and malaria, as well as childhood diseases and common infections threaten to reverse decades of development and to rob an entire generation of hope for a better future . . .”³² The communiqué articulated goals of reducing the number of infections due to HIV/AIDS, malaria, and tuberculosis by 25% to 50% by the year 2010, and these global health issues will be revisited during the 2001 G8 summit in Italy.

The Future

The biomedical research and public health response to the AIDS pandemic has clearly demonstrated that extraordinary results can emanate relatively rapidly from large infusions of resources. In addition, the brief history of the AIDS epidemic has demonstrated that the galvanization of a broad-based interest in global health can be accomplished by considering not only humanitarian aspects of these problems, but also their relevance to issues of domestic health and national security. In the 20th century, the “enlightened self-interest” that allowed the physical sciences to play an important role in foreign policy was related to fear engendered by the cold war and the perceived need to develop nuclear weapons, as well as by the race for space exploration. In the 21st century, the global nature of societies and the recognition of the importance of global health will likely be a factor in the formulation of US foreign policy.

In this regard, the potential for biomedical research to provide the tools for lasting solutions to the major infectious disease killers and indeed all diseases that afflict mankind is enormous. It remains critical that the medical and public health communities continue to argue cogently for adequate attention and sustained research support for all diseases of global health importance. The biomedical research experience with the AIDS epidemic should serve as an important paradigm in the pursuit of this goal.

REFERENCES

- Institute of Medicine. *America's Vital Interest in Global Health: Protecting our People, Enhancing Our Economy, and Advancing Our International Interests*. Washington, DC: National Academy Press; 1997.
- The World Health Report 2000*. Geneva, Switzerland: World Health Organization; 2000.
- World Health Organization Report on Infectious Diseases: Removing Obstacles to Health Development*. Available at: <http://www.who.int/infectious-disease-report/index-rpt99.html>. Accessibility verified June 28, 2001.
- Fauci AS. New and reemerging diseases: the importance of biomedical research. *Emerg Infect Dis*. 1998;4:374-378.
- Centers for Disease Control and Prevention. *Pneumocystis pneumonia*, Los Angeles. *MMWR Morb Mortal Wkly Rep*. 1981;30:250-252.
- Shorter E. *The Health Century*. New York, NY: Doubleday; 1987.
- Gallo RC, Montagnier L. The chronology of AIDS research. *Nature*. 1987;326:435-436.
- Sarnagadharan MG, Popovic M, Bruch L, Schupbach J, Gallo RC. Antibodies reactive with human T-lymphotropic retroviruses (HTLV-III) in the serum of patients with AIDS. *Science*. 1984;224:506-508.
- Selik RM, Ward JW, Buehler JW. Trends in transfusion-associated acquired immune deficiency syndrome in the United States, 1982 through 1991. *Transfusion*. 1993;33:890-893.
- Greene WC. The molecular biology of human immunodeficiency virus type 1 infection. *N Engl J Med*. 1991;324:308-317.
- Fauci AS. Multifactorial nature of human immunodeficiency virus disease: implications for therapy. *Science*. 1993;262:1011-1018.
- Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. *MMWR Morb Mortal Wkly Rep*. 1998;47:43-82. Update available at: <http://www.hivatis.org>. Accessibility verified June 28, 2001.
- US HIV and AIDS cases reported through June 2000 Midyear edition. *HIV/AIDS Surveillance Report*. 2000;12:1-44. Available at: <http://www.cdc.gov/hiv/stats/hasrlink.htm>. Accessibility verified July 2, 2001.
- Binswanger HP. Public health: HIV/AIDS treatment for millions. *Science*. 2001;292:221-223.
- Mofenson LM, McIntyre JA. Advances and research directions in the prevention of mother-to-child HIV-1 transmission. *Lancet*. 2000;355:2237-2244.
- Auerbach JD, Coates TJ. HIV prevention research: accomplishments and challenges for the third decade of AIDS. *Am J Public Health*. 2000;90:1029-1032.
- UNAIDS. *Report on the Global HIV/AIDS Epidemic: December 2000*. UNAIDS Web site. Available at: <http://www.unaids.org/publications/index.html>. Accessibility verified June 28, 2001.
- Nabel GJ. Challenges and opportunities for development of an AIDS vaccine. *Nature*. 2001;410:1002-1007.
- The Institute for Genomic Research. TIGR microbial database. Available at: <http://www.tigr.org/tdb/mdb/mdbcomplete.html>, accessed April 20, 2001. Accessibility verified June 28, 2001.
- Lander ES, Linton LM, Birren B, et al. Initial sequencing and analysis of the human genome. *Nature*. 2001;409:860-921.
- Venter JC, Adams MD, Myers EW, et al. The sequence of the human genome. *Science*. 2001;291:1304-1351.
- National Institute of Allergy and Infectious Diseases. *NIAID Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis*. Bethesda, Md: National Institutes of Health; 2001. Available at: <http://www.niaid.nih.gov>. Accessibility verified June 28, 2001.
- Wachter RM. AIDS, activism, and the politics of health. *N Engl J Med*. 1992;326:128-133.
- National Intelligence Council. *The Global Infectious Disease Threat and Its Implications for the United States*. Washington, DC: National Intelligence Council; 2000. <http://www.odci.gov/cia/publications/nie/report/nie99-17d.html>. Accessed April 30, 2001. Accessibility verified June 28, 2001.
- AIDS now core issue at UN Security Council [news release]. Geneva, Switzerland: UNAIDS; January 19, 2001. Available at: http://www.unaids.org/whatsnew/press/eng/pressarc01/newyork_190101.html. Accessed April 30, 2001. Accessibility verified June 28, 2001.
- United Nations General Assembly Special Session on HIV/AIDS. Declaration of Commitment on HIV/AIDS: “Global Crisis - Global Action.” New York, NY: United Nations; June 27, 2001. Available at: <http://www.un.org/ga/aids/coverage/FinalDeclarationHIVAIDS.html>. Accessibility verified July 2, 2001.
- Gellman B. AIDS is declared threat to security: White House fears epidemic could destabilize world. *Washington Post*. April 30, 2000:A1.
- Plot P, Bartos M, Ghys PD, Walker N, Schwartlander B. The global impact of HIV/AIDS. *Nature*. 2001;410:968-973.
- Institute for Global Health. *Creating Global Markets for Neglected Drugs and Vaccines: A Challenge for Public Private Partnership*. *Global Health Forum I: Consensus Statement*. San Francisco, Calif: Institute for Global Health; 2000. Available at: <http://www.epibiostat.ucsf.edu/igh/programs/GlobalForum.pdf>. Accessed April 30, 2001. Accessibility verified June 28, 2001.
- Legislative information available at: <http://thomas.loc.gov/>. Accessibility verified July 2, 2001.
- Lawrence C. Health Funding Update. New York, NY: Foundation Center; 2001. Available at http://www.fdncenter.org/research/trends_analysis/pdf/health_update.pdf. Accessibility verified July 2, 2001.
- G8 Communiqué Okinawa 2000. Washington, DC: US Department of State, International Information Programs; July 23, 2000. Available at <http://usinfo.state.gov/topical/econ/group8/summit00/wwwwhfirstcome.html>. Accessibility verified July 2, 2001.