

Special Article

AIDS — THE FIRST 20 YEARS

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THE disease now known as the acquired immunodeficiency syndrome, or AIDS, was first reported 20 years ago this week in the *Morbidity and Mortality Weekly Report* under the quiet title “*Pneumocystis pneumonia* — Los Angeles.”¹ The description was not the lead article; that distinction went to a report of dengue infections in vacationers returning to the United States from the Caribbean.

Not even the most pessimistic reader could have anticipated the scope and scale the epidemic would assume two decades later. By December 2000, 21.8 million people worldwide had died of the disease, including more Americans (438,795) than died in World War I and World War II combined.² This article reviews the many important developments in the first 20 years of AIDS.

EARLY YEARS: FREE FALL

The initial report described five young homosexual men in whom a rare disease, *Pneumocystis carinii* pneumonia, and other unusual infections had developed. Each had abnormal ratios of lymphocyte subgroups and was actively shedding cytomegalovirus. This report was followed quickly by more series, and within a few months, the basic outline of the epidemic was established (Table 1). Although the disease was first encountered in homosexual men and injection-drug users, the risk groups soon included Haitians,⁵ transfusion recipients, including those with hemophilia,^{6,10} infants,¹¹ female sexual contacts of infected men,^{8,12} prisoners,¹³ and Africans.¹⁵

Additional opportunistic complications were soon described, including mycobacterial infections, toxoplasmosis, invasive fungal infections, Kaposi's sarcoma, and non-Hodgkin's lymphoma. The working definition for AIDS, developed by the Centers for Disease Control,²¹ has required just a single revision in the past decade.²²

Causation

In the early years, there were numerous theories regarding the cause of AIDS, many of which now seem eccentric. The evidence that the disease was caused by cytomegalovirus, as posited in the early reports,^{1,23} was straightforward: groups with the new immunodeficiency had extremely high rates of infection with cytomegalovirus, a potentially immunosuppressive virus.

Some hypothesized that the virus had inexplicably become more virulent. Yet this theory failed to account for all cases, and attention turned elsewhere.

A case was made for attributing causality to amyl nitrite, a prescription drug, and to isobutyl nitrite, a closely related chemical marketed as a room deodorizer.²⁴ Both were used as sexual stimulants but were also known immunosuppressive agents. This theory had scientific plausibility and suggested a simple solution. But soon cases were reported among nonusers.

A sophisticated theory developed around the notion that repeated exposure to another's sperm could trigger an immune response, resulting in a condition resembling chronic graft-versus-host disease and, ultimately, opportunistic infections.²⁵ Another hypothesis invoked a general overloading of the immune system — a sort of physiological battle fatigue in which the immune system simply wore out.^{26,27} Outside the scientific community, there were suggestions that the disease was a punishment for homosexual men and injection-drug users.²⁸

A novel viral cause of the disease was only one of many plausible theories in the early years. It was favored by those familiar with the epidemiology of hepatitis B infection,^{8,29,30} which affected the same groups, and by those who worked with animal retroviruses. Feline leukemia virus had been described in the 1970s as a cause of general immunodeficiency (the “fading-kitten syndrome”) and was associated with lymphoma and leukemia as well.^{31,32} For the researchers in this field, the notion that a human retrovirus might cause a similar syndrome was a simple intellectual leap.

Nonetheless, doubt about a viral cause persisted until the actual virus was detected,¹⁶ confirmatory studies were performed,¹⁸ and the reports of transmission through blood and blood products became too numerous to ignore.^{6,9} The complicated and rivalrous story that culminated in the isolation of the virus has been well described. High-stakes scientific inquiry has seldom been placed in a less attractive light.

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TABLE 1. IMPORTANT DATES IN THE FIRST DECADE OF THE AIDS EPIDEMIC.*

DATE	REPORTED EVENT	COMMENT
June 5, 1981	5 Cases of <i>Pneumocystis carinii</i> pneumonia in homosexual men ¹	Initial report
July 3, 1981	26 Additional cases of new immunodeficiency syndrome ³	Cases in New York and California
June 18, 1982	Cluster in southern California ⁴	First report that “infectious agents [may be] sexually transmitted”
July 9, 1982	Initial cases in 34 Haitians ⁵	Mode of transmission unclear
July 16, 1982	Initial cases in 3 persons with hemophilia ⁶	Possibility of tainted blood supply
September 24, 1982	Term “acquired immune deficiency syndrome” (AIDS) used for first time ⁷	Term coined at July 1982 meeting, replacing “gay-related immune deficiency” (GRID)
October 1982	5 Cases in women reported, including 1 with only heterosexual exposure ⁸	First possibly heterosexually transmitted case
November 5, 1982	Precautions published for clinical and laboratory staff ⁹	“Patterns resemble the distribution and modes of spread of hepatitis B”
December 10, 1982	Initial transfusion-related case, in an infant ¹⁰	Further evidence of tainted blood supply
December 17, 1982	Initial vertically transmitted cases reported in 4 infants ¹¹	Reported as “Possible that these infants had AIDS”
January 7, 1983	Report of heterosexual transmission to 2 female partners of injection-drug users ¹²	“Supports infectious agent hypothesis”
January 7, 1983	Initial cases in 16 prisoners ¹³	Given known risk groups, occurrence in prisoners “might have been anticipated”
March 4, 1983	CDC releases prevention recommendations ¹⁴	Groups at risk advised not to donate blood
March 19, 1983	Initial cases in 5 persons from Central Africa ¹⁵	“Black Africans may be another group predisposed to AIDS”
May 20, 1983	Isolation of a virus from a patient with AIDS ¹⁶	Retrovirus belongs to HTLV group, but is “clearly distinct from each previous isolate”
July 15, 1983	Report of 4 possibly occupational cases among health care workers ¹⁷	Occupational transmission suspected but not proven
September 22, 1983	Infection-control guidelines published for care of patients with AIDS ¹⁸	“Measures consistent with those suggested for prevention of hepatitis B should be followed”
January 13, 1984	AIDS tabulated as “notifiable disease” for first time ¹⁹	25 Cases reported in first week
May 4, 1984	Frequent detection of HTLV-III in patients at risk ²⁰	“HTLV-III may be the primary cause of AIDS”
March 1985	FDA approves commercial test to detect HIV	Tremendous impact on patients at risk and blood supply
1986	CDC provides working definition of AIDS ²¹	Updated in 1993 ²²
1986	AIDS Clinical Trials Group established by NIH	Now largest clinical trials group in the United States
March 1987	FDA approves AZT (zidovudine)	First drug active against HIV

*CDC denotes Centers for Disease Control, FDA Food and Drug Administration, HIV human immunodeficiency virus, HTLV human T-cell lymphotropic virus, and NIH National Institutes of Health.

†Each quoted statement is from the reference cited under the corresponding Reported Event.

The delay on the part of some in accepting a novel viral cause may appear puzzling now, but investigators may have been intimidated by the enormous implications that a new virus would carry for blood banking, the safety of health care workers, and the overall public health. There was also a hesitancy, particularly among those outside the medical community, to acknowledge that the infection could be spread through heterosexual contact. Indeed, many preferred to invoke any but the obvious cause. The spread of the disease in Haiti, for example, was postulated to be a result of voodoo practices rather than heterosexual sex.³³ Today, most human immunodeficiency virus (HIV) in-

fections in the world derive from heterosexual transmission — a fact that is still overlooked by many.

In some quarters, doubt persists that HIV causes AIDS. One prominent dissident has theorized that the disease occurs because of long-term use of recreational drugs and is exacerbated by nucleoside analogues given as treatment.³⁴ The improvements that have been made in antiviral therapies for HIV disease have, paradoxically, only intensified the debate.^{35,36}

Treatment

Recent advances in therapy have obscured the difficult and often demoralizing character of the early

years of therapies for HIV. As the 1980s wore on, a hard-boiled fatalism settled in. Although patients and physicians did their best, they were all just playing out the same grim script.

Many of the agents that were studied in the first years of the epidemic are shown in Table 2. The list is incomplete; dozens and possibly hundreds of other concoctions were tried. The story for most was remarkably similar: a few patients in San Francisco, Los Angeles, or New York took a certain medication; some felt better; a few had improvements in CD4 cell counts. With the first whisper of encouragement, others joined in, a clinical trial was organized, and another great hope was born.

After the intense excitement came tempered optimism, then fading expectations, and finally an unsentimental assignment of the treatment to the scrap heap. Two agents, compound Q (Chinese cucumber plant root)³⁷ and peptide T,³⁸ are particularly representative. Each was briefly the darling of the emerging community of patients and activists seeking an effective therapy, but each moved slowly into formal clinical trials, prompting patients to criticize the medical-industrial complex as uncaring and uncooperative.⁴⁶ When studied, neither drug proved to be effective.

The growing sense of despair and frustration opened the door for charlatans. A typical fraudulent therapy was MM-1, promoted by an Egyptian rectal surgeon with “unbelievable claims of cure,” but support for the claims was never presented.⁴⁷ The cost of the therapy, however, was presented: \$75,000, including the trip to Zaire, where the treatment was administered.

THE LATE 1980s: SLOW PROGRESS

Once a retrovirus had been identified, the search began for agents that might act on reverse transcriptase, the enzyme necessary for transcribing HIV RNA to DNA. To study potential therapies, the National Institutes of Health (NIH) organized the AIDS Clinical Trials Group (ACTG) in 1986. Since its inception, the ACTG has systematically studied dozens of candidate therapies in adults and children. This research, along with trials sponsored by pharmaceutical companies, has led to the current guidelines that advocate triple-drug therapy.⁴⁸

Zidovudine (earlier known as azidothymidine, or AZT) was among the earliest compounds tested⁴⁹ and, in 1987, became the first drug approved for the treatment of AIDS. After initial exuberance, many in the community of AIDS patients turned against the drug.⁴⁶ They came to see its promotion as an almost hostile act on the part of the NIH, Burroughs Wellcome, and treating physicians. Accusations abounded that cheap and simple treatments had been overlooked in favor of a mediocre, costly, and toxic agent. Patients soon claimed that everyone they knew who took zidovudine was dead — still a familiar lament.

This was the time of greatest tension between the community of patients and the medical establishment.⁵⁰ There was discord about access to study drugs, protocol selection, design, and interpretation, and perhaps most of all, the overall pace and sincerity of scientific investigation. Even the bedrock concept of the placebo-controlled trial became a point of contention, because it struck many as unethical.

Progress was very slow in the years after the ap-

TABLE 2. EARLY THERAPIES FOR THE MANAGEMENT OF HIV INFECTION.

DRUG	SOURCE	POSSIBLE MECHANISM	FINDINGS	COMMENT
Putative antiviral drugs				
Compound Q	Chinese cucumber root	Enters macrophage to eradicate virus	Ineffective ³⁷	Increase of 1 CD4 cell per cubic millimeter per month
Peptide T	Synthetic	Competitive receptor blockade ³⁸	Never published	Trials continue for HIV-related cognitive impairment
AL 721 (active lipids at 7-2-1 ratio)	Hen's-egg yolks	Destabilizes cell membrane	Ineffective ³⁹	Transient weight gain
Soluble CD4	Synthetic	Competitive receptor blockade	Ineffective ⁴⁰	No oral form
Dextran sulfate	Synthetic	Anticoagulant, blocks attachment	Ineffective ⁴¹	Not absorbed orally
Putative immune modulators				
Isoprinosine	Synthetic	Immune stimulation, possible antiviral activity	Minimally effective ⁴²	Prolonged controversy regarding efficacy
Imuthiol	Metal chelator similar to disulfiram	Modulates T-cell differentiation	Ineffective ⁴³	Investigators reported, “Use of [drug] should be discontinued”
Ampligen	Antisense RNA	Enhancement of killer cells	Ineffective ⁴⁴	Prolonged controversy regarding efficacy
Imreg-1	Synthetic	Enhanced production of interferon, interleukin-2	Minimally effective ⁴⁵	Prolonged controversy regarding efficacy; slower CD4 cell decrease with drug

proval of zidovudine, further fraying the relationship between physicians and the community. Additional nucleosides were identified and compared in numerous trials, and incremental differences were noted. Real advances were made in the area of prophylaxis against opportunistic infections, especially *P. carinii* pneumonia and *Mycobacterium avium* complex infection.^{51,52}

THE MID-1990s: HIGH HOPES

In the 1990s, highly active antiretroviral therapy (HAART) first became available, and it fundamentally altered the epidemic in the United States (Fig. 1). By this time, the community of patients and the medical community had begun a productive collaboration that remains the hallmark of AIDS care today.

The potential effectiveness of the new drugs was evident long before the confirmatory clinical trials had been performed (Table 3). First came a new understanding of the dynamics and pathophysiology of HIV infection.⁵⁴ Patients with chronic infection who were treated with the protease inhibitor ritonavir had a precipitous drop in HIV RNA level, reflecting an abrupt interruption of high-grade replication of HIV (billions of copies daily). They also had an increase in the CD4 cell count, which revealed the regenerative capacity of the CD4 cell population. The establishment of these two principles profoundly influenced clinicians' subsequent approach to antiviral therapy.⁵⁴

A crucial study examined the fate of 180 homosexual men from whom serial plasma specimens had been collected for more than 10 years.⁵⁸ In this group, the viral load proved to be a significantly more powerful predictor of long-term survival than the CD4 cell count, which had been used since the start of the epidemic. Thus, the viral load became a central new piece of information for decisions about beginning and modifying treatments.

Armed with these new insights, investigators confidently initiated a series of landmark clinical trials.^{56,60} Most studies have shown dramatic and durable responses for at least two thirds of patients with minimal previous antiviral exposure who adhere to a regimen of triple-drug therapy. In the United States, 15 agents have been approved in three classes of drugs: nucleoside analogue reverse-transcriptase inhibitors, nonnucleoside reverse-transcriptase inhibitors, and protease inhibitors. With the use of these potent medications, there have been sharp and sustained declines in the incidence of AIDS and in AIDS-related mortality (Fig. 1).⁶⁴ Although this type of treatment is expensive, the cost is offset by savings in other areas, particularly hospital and home care charges.⁶⁵

Current efforts focus on simplifying the drug regimens to improve adherence, developing alternatives for those in whom the current medications have failed, and managing the wide range of side effects, particularly the metabolic disorders, including lipodystrophy.⁵⁹ The optimal time at which to initiate therapy

remains controversial, as it has been throughout the epidemic. Most recently, experts have suggested that the risk of long-term side effects from the current regimens argues against routine early therapy, in contrast to the "hit early, hit hard" strategy that had been favored since the introduction of the protease inhibitors.⁴⁸ The complete eradication of the infection, particularly latent virus, remains the focus of intense investigation.⁶⁶

THE LATE 1990s: GLOBAL CRISIS

Despite these advances, there is a gathering sense of doom in the face of the scale of the global epidemic. The numbers are familiar but bear repeating: 36.1 million persons worldwide are infected with HIV; an additional 21.8 million have died; and 13.2 million children have become "AIDS orphans," having lost their mother or both parents to the disease.² More than 14,000 new infections occur daily — 5.3 million in 2000 alone, including 600,000 in children younger than 15 years old. Approximately 70 percent of cases occur in sub-Saharan Africa, where, in some regions, the seroprevalence of HIV among adults exceeds 25 percent.² The Caribbean, Southeast Asia, and eastern Europe are also struggling with substantial rates of new infection.

In these areas, AIDS has evolved into two distinct epidemics: a horizontal epidemic in adults, spread by sexual contact or shared needles, and a vertical epidemic in which infected mothers give birth to infected children. Each requires a different approach to control and management, and each raises different sets of complex issues. For example, women are advised to abstain from breast-feeding to prevent transmission through breast milk, but a mother who does not breast-feed is immediately assumed to be HIV-infected and may be shunned by neighbors.

The high seroprevalence of HIV in some countries has raised concern that AIDS may represent a threat to the political stability of entire nations.⁶¹ In 2000, the Security Council of the United Nations began to address the possibility that, by devastating a country's entire population of young adults, AIDS now threatens the world's security. This marked the first time that a medical illness had received the attention of this important deliberative body.

Recent events in Africa appear to herald a profound change in the way antiretroviral drugs are distributed in the developing world. In response to local and international pressure, some pharmaceutical companies will offer expensive agents to African patients at a fraction of their cost in the United States.⁶² In addition, there are efforts to allow generic-medication companies to produce antiretroviral agents for local sale,⁶³ as is done in Brazil.⁶⁷ The sharply reduced price will still be too high for most infected persons.

Despite recent developments, control of AIDS still awaits a vaccine. In 1997, President Bill Clinton chal-

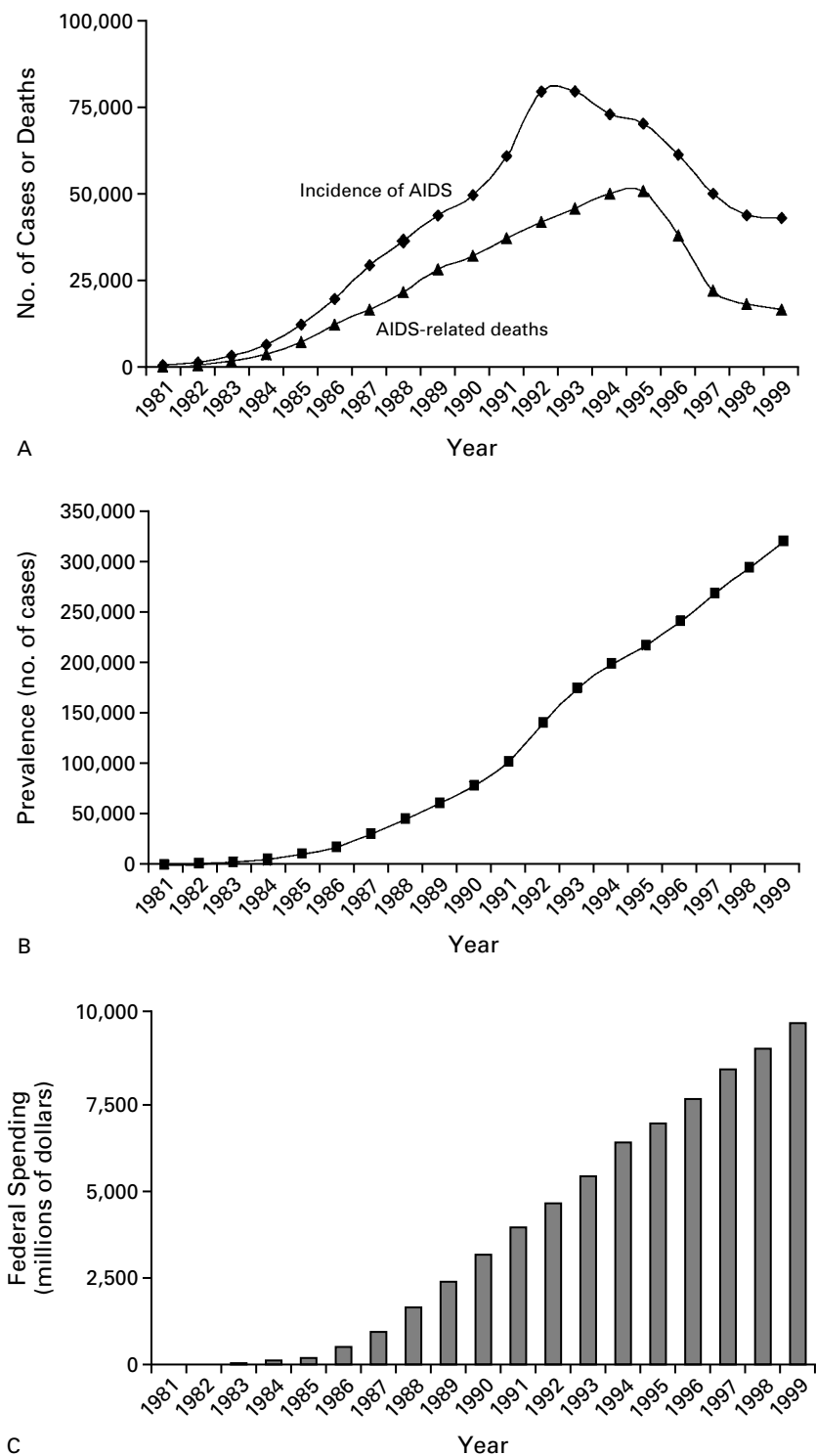


Figure 1. U.S. Trends in New AIDS Cases (Incidence) and AIDS-Related Deaths (Panel A), People Alive with AIDS (Prevalence, Panel B), and Federal Spending for AIDS Care, Prevention, and Research (Panel C), 1981 to 1999.

The trends were affected by the change in 1993 to a more inclusive definition of AIDS. Annual funding does not include state, city, philanthropic, and pharmaceutical-industry spending on AIDS care, prevention, and research. Data on annual incidence, death, and prevalence are from the Centers for Disease Control and Prevention. The annual federal spending figures are from the records of the U.S. Senate.

TABLE 3. IMPORTANT DATES IN THE SECOND DECADE OF THE AIDS EPIDEMIC.*

DATE	REPORTED EVENT	COMMENT†
1991	Approval of didanosine and zalcitabine	Second and third approved drugs; combination therapy used increasingly
1993	AIDS becomes leading cause of death of Americans 25–44 years old ⁵³	AIDS surpasses unintentional injuries as cause of death in this group
January 12, 1995	Dynamics of HIV replication redefined ⁵⁴	“Primary [therapeutic] strategy ought to be to target virally mediated destruction”
May 4, 1995	Identification of viral cause of Kaposi’s sarcoma ⁵⁵	Human herpesvirus 8 isolated
July 15, 1995	First Public Health Service guidelines to prevent opportunistic infections ⁵¹	Two subsequent revisions
August 1995	First protease inhibitor, saquinavir, approved ⁵⁶	Within 18 months, 3 additional protease inhibitors approved
1996	U.S. AIDS death rate decreases ⁵⁷	“For the first time, deaths among persons with AIDS have decreased substantially”
May 24, 1996	Prognostic power of viral-load determination established ⁵⁸	Important laboratory determination for routine management
1997	President Bill Clinton seeks AIDS vaccine in 10 years	HIV Vaccine Trials Network established
May 7, 1998	First published report of lipodystrophy syndrome ⁵⁹	Lipodystrophy, hyperlipidemia, diabetes, and other metabolic abnormalities described with increasing frequency in patients with AIDS
June 1998	Efavirenz approved ⁶⁰	“Protease-sparing” regimens introduced
January 10, 2000	UN Security Council discusses AIDS ⁶¹	“AIDS threatens our security”
December 2000	WHO estimates 36.1 million have HIV–AIDS, with an additional 21.8 million already dead ²	5.3 million new infections in 2000; 14,500 new infections per day
March 2001	U.S. pharmaceutical companies substantially reduce prices and may allow generic drugs for Africa ^{62,63}	Cost will be 1–10% of U.S. price

*UN denotes United Nations, and WHO World Health Organization.

†Each quoted statement is from the reference cited under the corresponding Reported Event.

lenged scientists to provide an effective vaccine within 10 years. Toward this end, a national HIV Vaccine Trials Network has been established to develop and test possible compounds. Among the difficulties confronting researchers are viral heterogeneity, uncertainty about how to achieve optimal immunogenicity, the lack of a practical animal model, and the ethical dilemmas involved in conducting primary prevention trials in the United States and abroad.

THE BLOOD SUPPLY AND AIDS ACTIVISM

AIDS has had lasting effects on several areas separate from HIV-infected patients and those who care for them. These include the changes the epidemic has brought to blood banking and activism by patients.

Blood Banking

The first alarm about the safety of the blood supply was sounded in July 1982, when the newly described immunodeficiency syndrome developed in three persons with hemophilia.⁶ Those with hemophilia are at particular risk for transfusion-related infections, since a single dose of cryoprecipitate contains products from between 1000 and 20,000 donors.

Disagreement arose because of the competing priorities of the professional groups that were involved. On the basis of the three reported cases of the disease, the public health community sensed an impending disaster. Hemophilia specialists, on the other hand, had witnessed the enormous benefit cryoprecipitate had provided their patients and thought that this gain dwarfed the theoretical concern that the blood supply might contain a possibly transmissible virus that would take years to cause disease. And the blood-banking community, wrestling then as now with a barely adequate blood supply, was concerned about scaring off donors.

The debate intensified, and various solutions were rejected as either too costly (testing for surrogate markers) or too stigmatizing (the exclusion of members of various risk groups from donation). Finally, the virus was isolated, and in March 1985, a screening test became available. By then, HIV had been transmitted to at least 50 percent of the 16,000 persons with hemophilia in the United States and to an additional 12,000 recipients of blood transfusions.⁶⁸

In its investigation, the Institute of Medicine criticized the blood-banking community.⁶⁸ It found that

the safety measures that had been adopted were “limited in scope” and that opportunities for more effective interventions had been lost. Screening to rule out the presence of infectious agents that would require rejection of blood products now requires 10 tests on each donated unit of blood, as compared with the 2 (for syphilis and hepatitis B surface antigen) that were required in 1981.

The lessons from the AIDS epidemic influence decisions regarding blood-banking procedures today. A recent example is the scramble to develop guidelines to prevent the possible introduction into the blood supply of the agent of bovine spongiform encephalopathy, a prion disease that has not yet been demonstrated to be transmissible through blood.⁶⁹

New Drugs and Disease-Related Activism

AIDS has radically altered the development of drugs. Before the AIDS epidemic, the Food and Drug Administration (FDA) was often viewed as a remote bureaucracy. With the advent of AIDS and the community that formed around it, numerous innovative approaches were developed to expedite the development of new drugs and patients’ access to investigational drugs.⁴⁶ The FDA became substantially more efficient: in 1986, the average interval between a drug application and the granting of FDA approval was 34.1 months; by 1999, it had decreased to 12.6 months.⁷⁰

Activism related to diseases has also evolved remarkably.⁴⁶ In the 1970s, Washington-based, organized advocacy groups that focused on particular diseases were few; now, at least 150 such organizations exist (Trull FL, National Association for Biomedical Research: personal communication). Activism by patients with AIDS has influenced advocates for patients with other diseases, including breast cancer, Parkinson’s disease, Alzheimer’s disease, and juvenile diabetes.⁴⁶ Using creative approaches rather than following the established rules of lobbying, AIDS activists created a new model. Their techniques ranged from drug buyers’ clubs and red ribbons pinned to the lapel to aggressive civil disobedience and telephone “zaps,” wherein the telephone switchboard of a specific company was jammed by a coordinated barrage of incoming calls. Today, patients are routinely consulted regarding the design of studies, and community-based research is conducted across the country.

The success of AIDS activists led to criticism by the public and Congress alike that federal dollars were not being apportioned according to the burden of disease, but according to a more political set of criteria. The Institute of Medicine has recommended broader public input into decisions about the allotment of funds.⁷¹

CONCLUSIONS

In 20 years, the AIDS epidemic has grown from a series of small outbreaks in several risk groups scat-

tered throughout the United States and western Europe into a global public health calamity. Tremendous strides have been made in understanding the disease, from the molecular level to the broadest perspective of public health. In addition, important advances in antiretroviral therapy and blood-supply safety have been achieved. During the 1990s, the disease was transformed for many patients in industrialized nations from a predictably fatal infection to a chronic condition requiring daily medication and occasional visits to the doctor’s office.

Despite these gains, however, the epidemic threatens to spin completely out of control in many of the world’s poorest nations. Until a vaccine is available, two humble but effective interventions have been shown to limit the horizontal spread of HIV: sex education and the use of condoms that results from it,^{72,73} and drug-abuse treatment, including the provision of clean needles.⁷⁴ Widespread implementation of these interventions, however, continues to be hampered by personal, social, and political barriers in almost all countries and governments.⁷⁵ To some extent, the disease has continued to spread horizontally because of an unwillingness to use effective control measures, rather than because of the lack of a vaccine or other remedy.

Given these difficulties, improved control of HIV infection in the next decade looms as a daunting task. An effective vaccine is not imminent, and most governments are unlikely to initiate frank public discussions about sexual intercourse and injection-drug use, despite the glaring need. Nonetheless, patients and health care workers alike should find solace and inspiration in the remarkable achievements of the past 20 years. Not so long ago, the hope that a cause of AIDS would be found and that effective therapies for the disease would be developed seemed as unlikely as global control of the disease seems today.

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REFERENCES

1. *Pneumocystis pneumonia* — Los Angeles. MMWR Morb Mortal Wkly Rep 1981;30:250-2.
2. UNAIDS, WHO. AIDS epidemic update: December 2000. Geneva: Joint United Nations Programme on HIV/AIDS, 2000.
3. Kaposi’s sarcoma and *Pneumocystis pneumonia* among homosexual men — New York City and California. MMWR Morb Mortal Wkly Rep 1981; 30:305-8.
4. A cluster of Kaposi’s sarcoma and *Pneumocystis carinii* pneumonia among homosexual male residents of Los Angeles and Orange Counties, California. MMWR Morb Mortal Wkly Rep 1982;31:305-7.
5. Opportunistic infections and Kaposi’s sarcoma among Haitians in the United States. MMWR Morb Mortal Wkly Rep 1982;31:353-4, 360-1.
6. *Pneumocystis carinii* pneumonia among persons with hemophilia A. MMWR Morb Mortal Wkly Rep 1982;31:365-7.
7. Update on acquired immune deficiency syndrome (AIDS) — United States. MMWR Morb Mortal Wkly Rep 1982;31:507-8, 513-4.
8. Masur H, Michelis MA, Wormser GP, et al. Opportunistic infection in previously healthy women: initial manifestations of a community-acquired cellular immunodeficiency. Ann Intern Med 1982;97:533-9.
9. Acquired immune deficiency syndrome (AIDS): precautions for clinical and laboratory staffs. MMWR Morb Mortal Wkly Rep 1982;31:577-80.

10. Possible transfusion-associated acquired immune deficiency syndrome (AIDS) — California. MMWR Morb Mortal Wkly Rep 1982;31:652-4.
11. Unexplained immunodeficiency and opportunistic infections in infants — New York, New Jersey, California. MMWR Morb Mortal Wkly Rep 1982;31:665-7.
12. Immunodeficiency among female sexual partners of males with acquired immune deficiency syndrome (AIDS) — New York. MMWR Morb Mortal Wkly Rep 1983;31:697-8.
13. Acquired immune deficiency syndrome (AIDS) in prison inmates — New York, New Jersey. MMWR Morb Mortal Wkly Rep 1983;31:700-1.
14. Prevention of acquired immune deficiency syndrome (AIDS): report of inter-agency recommendations. MMWR Morb Mortal Wkly Rep 1983;32:101-3.
15. Clumeck N, Mascart-Lemone F, de Maubeuge J, Brenze D, Marcelis L. Acquired immune deficiency in black Africans. Lancet 1983;1:642.
16. Barre-Sinoussi F, Chermann JC, Rey F, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science 1983;220:868-71.
17. An evaluation of acquired immune deficiency syndrome (AIDS) reported in health-care personnel — United States. MMWR Morb Mortal Wkly Rep 1983;32:358-60.
18. Conte JE Jr, Hadley WK, Sande M. Infection-control guidelines for patients with the acquired immunodeficiency syndrome (AIDS). N Engl J Med 1983;309:740-4.
19. Summary — cases specified notifiable diseases, United States. MMWR Morb Mortal Wkly Rep 1984;33:4-5.
20. Gallo RC, Salahuddin SZ, Popovic M, et al. Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. Science 1984;224:500-3.
21. Classification system for human T-lymphotropic virus type III/lymphadenopathy-associated virus infections. MMWR Morb Mortal Wkly Rep 1986;35:334-9.
22. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Morb Mortal Wkly Rep 1992;41(RR-17):1-19.
23. Gottlieb MS, Schroff R, Schanker HM, et al. *Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. N Engl J Med 1981;305:1425-31.
24. Goedert JJ, Neuland CY, Wallen WC. Amyl nitrite may alter T lymphocytes in homosexual men. Lancet 1982;1:412-6.
25. Mavligit GM, Talpaz M, Hsia FT, et al. Chronic immune stimulation by sperm alloantigens: support for the hypothesis that spermatozoa induce immune dysregulation in homosexual males. JAMA 1984;251:237-41.
26. Sonnabend J, Witkin SS, Purtilo DT. Acquired immunodeficiency syndrome, opportunistic infections, and malignancies in male homosexuals: a hypothesis of etiologic factors in pathogenesis. JAMA 1983;249:2370-4.
27. Levy JA, Ziegler JL. Acquired immunodeficiency syndrome is an opportunistic infection and Kaposi's sarcoma results from secondary immune stimulation. Lancet 1983;2:78-81.
28. Shilts R. And the band played on: politics, people, and the AIDS epidemic. New York: St. Martin's Press, 1987.
29. Waterson AP. Acquired immune deficiency syndrome. BMJ 1983;286:743-6.
30. Francis DP, Curran JW, Essex M. Epidemic acquired immune deficiency syndrome: epidemiologic evidence for a transmissible agent. J Natl Cancer Inst 1983;71:1-4.
31. Hardy WD Jr, Old LJ, Hess PW, Essex M, Cotter S. Horizontal transmission of feline leukaemia virus. Nature 1973;244:266-9.
32. Cotter SM, Hardy WD Jr, Essex M. Association of feline leukemia virus with lymphosarcoma and other disorders in the cat. J Am Vet Med Assoc 1975;166:449-54.
33. Leonidas J-R, Hyppolite N. Haiti and the acquired immunodeficiency syndrome. Ann Intern Med 1983;98:1020-1.
34. Duesberg P, Rasnick D. The AIDS dilemma: drug diseases blamed on a passenger virus. Genetica 1998;104:85-132.
35. The Durban Declaration. Nature 2000;406:15-6.
36. Stewart GT, Mhlongo S, de Harven E, et al. The Durban Declaration is not accepted by all. Nature 2000;407:286.
37. Byers VS, Levin AS, Malvino A, Waites L, Robins RA, Baldwin RW. A phase II study of effect of addition of trichosanthin to zidovudine in patients with HIV disease and failing antiretroviral agents. AIDS Res Hum Retroviruses 1994;10:413-20.
38. Pert CB, Hill JM, Ruff MR, et al. Octapeptides deduced from the neuropeptide receptor-like pattern of antigen T4 in brain potentially inhibit human immunodeficiency virus receptor binding and T-cell infectivity. Proc Natl Acad Sci U S A 1986;83:9254-8.
39. Mildvan D, Buzas J, Armstrong D, et al. An open-label, dose-ranging trial of AL 721 in patients with persistent generalized lymphadenopathy and AIDS-related complex. J Acquir Immune Defic Syndr 1991;4:945-51.
40. Schooley RT, Merigan TC, Gaut P, et al. Recombinant soluble CD4 therapy in patients with the acquired immunodeficiency syndrome (AIDS) and AIDS-related complex: a phase I-II escalating dosage trial. Ann Intern Med 1990;112:247-53.
41. Abrams DI, Kuno S, Wong R, et al. Oral dextran sulfate (UA001) in the treatment of the acquired immune deficiency syndrome (AIDS) and AIDS-related complex. Ann Intern Med 1989;110:183-8.
42. Pederson C, Sandström E, Petersen CS, et al. The efficacy of inosine pranobex in preventing the acquired immune deficiency syndrome in patients with human immunodeficiency virus infection. N Engl J Med 1990;322:1757-63. [Erratum, N Engl J Med 1990;323:1360.]
43. The HIV87 Study Group. Multicenter, randomized, placebo-controlled study of ditiocarb (Imuthiol) in human immunodeficiency virus-infected asymptomatic and minimally symptomatic patients. AIDS Res Hum Retroviruses 1993;9:83-9.
44. Thompson KA, Strayer DR, Salvato PD, et al. Results of a double-blind placebo-controlled study of the double-stranded RNA drug polyI:polyC12U in the treatment of HIV infection. Eur J Clin Microbiol Infect Dis 1996;15:580-7.
45. Gottlieb MS, Zackin RA, Fiala M, et al. Response to treatment with the leukocyte-derived immunomodulator IMREG-1 in immunocompromised patients with AIDS-related complex: a multicenter, double-blind, placebo-controlled trial. Ann Intern Med 1991;115:84-91.
46. Arno PS, Feiden KL. Against the odds: the story of AIDS drug development, politics and profits. New York: HarperCollins, 1992.
47. Treatment issues. In: Gingell B, ed. The GMHC newsletter of experimental AIDS therapies. Vol. 2. No. 7. New York: Gay Men's Health Crisis, 1988:11-2.
48. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. MMWR Morb Mortal Wkly Rep 1998;47(RR-5):43-82. (Updated as a living document February 2001.) (See <http://hivatis.org/trtgdlns.html#adultadolescent>.)
49. Fischl MA, Richman DD, Grieco MH, et al. The efficacy of zidovudine (AZT) in the treatment of patients with AIDS and AIDS-related complex: a double-blind, placebo-controlled trial. N Engl J Med 1987;317:185-91.
50. Kolata G. After 5 years of use, doubt still clouds leading AIDS drug. New York Times. June 2, 1992:C3.
51. USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: a summary. MMWR Morb Mortal Wkly Rep 1995;44(RR-8):1-34.
52. Shafer RW, Seitzman PA, Tapper ML. Successful prophylaxis of *Pneumocystis carinii* pneumonia with trimethoprim-sulfamethoxazole in AIDS patients with previous allergic reactions. J Acquir Immune Defic Syndr 1989;2:389-93.
53. Update: mortality attributable to HIV infection among persons aged 25-44 years — United States, 1994. MMWR Morb Mortal Wkly Rep 1996;45:121-5.
54. Ho DD, Neumann AU, Perelson AS, Chen W, Leonard JM, Markowitz M. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. Nature 1995;373:123-6.
55. Moore PS, Chang Y. Detection of herpesvirus-like DNA sequences in Kaposi's sarcoma in patients with and without HIV infection. N Engl J Med 1995;332:1181-5.
56. Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus zidovudine in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. N Engl J Med 1997;337:725-33.
57. Update: trends in AIDS incidence, deaths, and prevalence — United States, 1996. MMWR Morb Mortal Wkly Rep 1997;46:165-73.
58. Mellors JW, Rinaldo CR Jr, Gupta P, White RM, Todd JA, Kingsley LA. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. Science 1996;272:1167-70. [Erratum, Science 1997;275:14.]
59. Carr A, Samaras K, Burton S, et al. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. AIDS 1998;12:F51-F58.
60. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. N Engl J Med 1999;341:1865-73.
61. Birmingham K. UN acknowledges HIV/AIDS as a threat to world peace. Nat Med 2000;6:117.
62. Stolberg SG. Africa's AIDS war: pressure for affordable medicine: 'if' becomes 'when' for patients. New York Times. March 10, 2001:A1, A4.
63. Petersen M, McNeil DG Jr. Maker yielding patent in Africa for AIDS drug. New York Times. March 15, 2001:A1, A14.
64. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med 1998;338:853-60.
65. Gebo KA, Chaisson RE, Folkemer JG, Bartlett JG, Moore RD. Costs

of HIV medical care in the era of highly active antiretroviral therapy. *AIDS* 1999;13:963-9.

66. Chun TW, Justement JS, Moir S, et al. Suppression of HIV replication in the resting CD4+ T cell reservoir by autologous CD8+ T cells: implications for the development of therapeutic strategies. *Proc Natl Acad Sci U S A* 2001;98:253-8.

67. Rosenberg T. Look at Brazil. *New York Times Sunday Magazine*. January 28, 2001:26.

68. Leveton LB, Sox HC Jr, Stoto MA, eds. HIV and the blood supply: an analysis of crisis decisionmaking. Washington, D.C.: National Academy Press, 1995.

69. Food and Drug Administration. Revised precautionary measures to reduce the possible transmission of Creutzfeldt-Jakob disease (CJD) by blood and blood products: guidance document. *Fed Regist* 1997;62(184):49694-5.

70. New medicines in development: annual summaries 1988 and 1999. Washington, D.C.: Pharmaceutical Research and Manufacturers of America, 1989, 2000.

71. Committee on the NIH Research Priority-Setting Process. Scientific

opportunities and public needs: improving priority setting and public input at the National Institutes of Health. Washington, D.C.: National Academy Press, 1998.

72. Nelson KE, Celentano DD, Eiumtrakol S, et al. Changes in sexual behavior and a decline in HIV infection among young men in Thailand. *N Engl J Med* 1996;335:297-303.

73. Celentano DD, Nelson KE, Lyles CM, et al. Decreasing incidence of HIV and sexually transmitted diseases in young Thai men: evidence for success of the HIV/AIDS control and prevention program. *AIDS* 1998;12:F29-F36.

74. Monterroso ER, Hamburger ME, Vlahov D, et al. Prevention of HIV infection in street-recruited injection drug users: the Collaborative Injection Drug User Study (CIDUS). *J Acquir Immune Defic Syndr* 2000;25:63-70.

75. Ruiz MS, ed. No time to lose: getting more from HIV prevention. Washington, D.C.: National Academy Press, 2001.

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