Hemophilia-Associated AIDS in the United States, 1981 to September 1987

JEANETTE K. STEHR-GREEN, MD, ROBERT C. HOLMAN, MS, JANINE M. JASON, MD AND BRUCE L. EVATT, MD

Abstract: Between January 1, 1981 and September 4, 1987, 407 cases of hemophilia-associated acquired immunodeficiency syndrome (AIDS) had been reported to the Centers for Disease Control. The number of cases diagnosed each year nearly doubled, except in 1986, when cases increased only 50 per cent. Demographic characteristics of the patients did not change over time. The majority (74 per cent) had severe hemophilia and 97 per cent received commercially produced concentrated clotting factors. The cumulative incidence of AIDS between 1981 and September 1987 for persons with severe hemophilia A was substantially greater than that for persons with severe hemophilia B (4.2 cases vs 1.9 cases per 100 persons). (*Am J Public Health* 1988; 78:439–442.)

Introduction

Persons with hemophilia or a disorder in the coagulation process are at an increased risk for infection with many blood-borne diseases, including the acquired immunodeficiency syndrome (AIDS). The first AIDS patient with an underlying coagulation disorder was diagnosed as having *Pneumocystis carinii* pneumonia in 1981.[1] By December 1983, 20 additional cases of hemophilia-associated AIDS had been reported.[2] Following the identification in 1984 of the human immunodeficiency virus (HIV) as the causative agent of AIDS, investigators discovered that heat treatment (60°C for more than two hours) of concentrated clotting factors inactivated HIV.[3] This, with the development of serologic methods to screen blood for HIV and the self-deferral of high-risk blood donors, minimized further risk of infection in persons with hemophilia. However, many hemophilics had already been infected; 33 per cent–92 per cent of persons with hemophilia A and 14 per cent–52 per cent of persons with hemophilia B in hemophilia treatment center-based studies have been shown to have antibody to HIV.[4-9] As a result, although effective interventions have been undertaken to minimize further HIV infection in persons with hemophilia, the number of hemophilia-associated AIDS cases continues to grow. This report presents data on the epidemiology of AIDS in persons with hemophilia and other coagulation disorders in the United States since 1981.

Methods

National surveillance of AIDS in persons with coagulation disorders is maintained through the receipt of standardized AIDS case report forms submitted by the individual state health departments to the Centers for Disease Control (CDC). Supplemental information pertaining to the status of the patient's coagulation disorder is obtained through telephone interview with the treating physician, nurse, or public health worker by CDC personnel. A 1986 survey of hemophilia treatment centers suggests that approximately 97 per cent of hemophilia-associated AIDS cases are reported through this system.[10]

Only patients meeting the CDC AIDS surveillance case definition, as revised in June 1985, are included in the analyses.[11] To be classified as having hemophilia-associated AIDS, the patient must have received blood or blood components since 1978 as treatment for a dysfunction in the normal coagulation system. The method of Thomas and Gart was used to calculate odds ratios and 95 per cent confidence intervals for dichotomous variables.[12,13] The Wilcoxon rank-sum test and the Kruskal-Wallis test were used to compare age at diagnosis among various patient subgroups.[14] Age-specific incidence rates by race were calculated using 1980 US census estimates[15] and were compared using the chi-square test for goodness of fit.[16] Population estimates of persons with hemophilia A, hemophilia B, severe hemophilia A (as determined by clotting factor activity), and severe hemophilia B were set at 11,572, 2,895, 6,365, and 724, respectively.[17] Cumulative incidence rates refer to the five year, eight month incidence between January 1, 1981 and September 4, 1987. Results of analyses did not differ when cases with multiple risk factors were excluded; therefore the analyses presented include all cases.

Results

Between January 1, 1981 and September 4, 1987, 407 cases of hemophilia-associated AIDS had been reported to CDC. The number of hemophilia-associated AIDS cases diagnosed each year nearly doubled, except in 1986 when cases increased only 50 per cent (Figure 1); however, reporting during that period may not have been complete in September 1987. Patients resided in 42 states and Puerto Rico; 38 per cent were from California, New Jersey, New York, and Pennsylvania. No cases were reported from Alaska, Arkansas, Delaware, Idaho, Montana, Nevada, Oklahoma, and Utah. All but 10 patients (2 per cent) were male. The median age at the time of diagnosis of AIDS was 31 years (range: 3–86). There was no decline in the median age of patients diagnosed each year (1982–87). Sixteen patients were known to have had risk factors for AIDS in addition to a coagulation disorder: six were reported to be homosexual/bisexual, nine had a history of intravenous drug abuse, and one had a sex partner who used intravenous drugs.

Of the 407 patients, 344 (85 per cent) were White, 26 (6 per cent) Black, 30 (7 per cent) Hispanic, five (1 per cent) Asian/Pacific Islander, and two (< 1 per cent) American Indian/Alaskan Native. No racial trends were seen over time; however, the number of patients other than White with AIDS was small. The median age at the time of diagnosis for Whites was 34 years (range: 4–86); for Blacks, 24.5 years (range: 3–60); and for Hispanics, 24.5 years (range 7–74). A comparison of age-specific incidence rates using selected age groups showed little difference between Whites and others. Blacks and Hispanics were more likely than Whites to have had other risk factors for AIDS in addition to their coagulation disorder (7/56 [13 per cent] vs 9/344 [3 per cent], OR = 5.3, 95% CI = 1.6–16.8).

From the Center for Infectious Diseases, Centers for Disease Control. Address reprint requests to Jeanette K. Stehr-Green, MD, Medical Epidemiologist, Division of Host Factors, Center for Infectious Diseases, Centers for Disease Control, 1600 Clifton Road, Bldg. 1, Room 1407, Atlanta, GA 30333. This article, submitted to the Journal July 6, 1987, was revised and accepted for publication November 25, 1987.

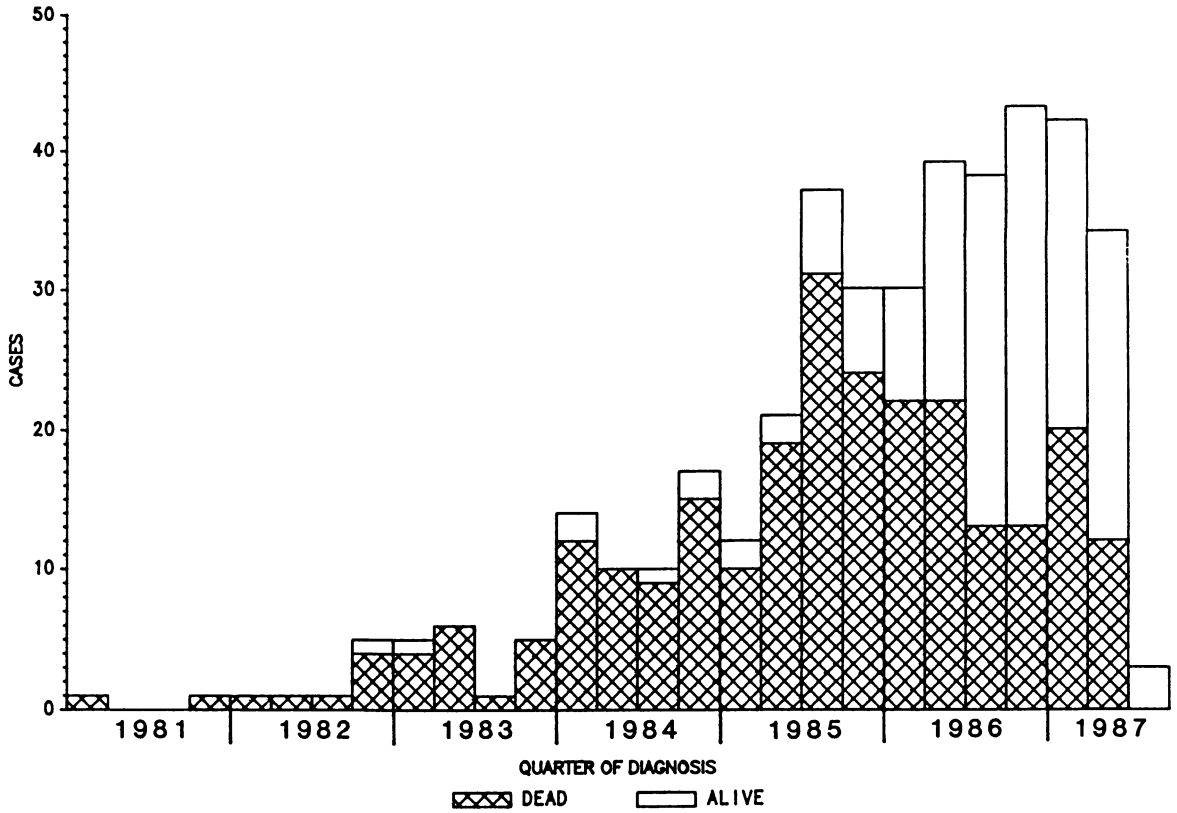

FIGURE 1—U.S. Hemophilia-associated AIDS, by Quarter of Diagnosis, January 1, 1981 to September 4, 1987

Hemophilia Status

Three hundred and sixty-four (89 per cent) AIDS patients had hemophilia A (deficiency of clotting factor VIII); 26 (6 per cent), hemophilia B (deficiency of clotting factor IX); 10 (3 per cent), von Willebrand's Disease; three (< 1 per cent), acquired antibody to factor VIII; two (< 1 per cent), factor X deficiency; and one each, factor V deficiency and factor VII deficiency. The severity of hemophilia was known for 385 (99 per cent) of the 390 patients with hemophilia A and hemophilia B: 284 (74 per cent) were considered to have severe hemophilia (≤ 1 per cent of the normal clotting factor activity in the blood); 51 (13 per cent), moderate (2–5 per cent of normal clotting factor activity); and 50 (13 per cent), mild (>5 per cent of normal clotting factor activity). The cumulative incidence of AIDS for persons with severe hemophilia A was substantially greater than for persons with severe hemophilia B (4.2 cases per 100 persons [270/6365] vs 1.9 per 100 persons [14/724], OR = 2.2, 95% CI = 1.3–4.2). Thirty-two (10 per cent) of the 326 patients whose status was known had inhibitor to factor VIII or IX.

Information on the types of blood products received by the patient was known for 371 (91 per cent): 195 (53 per cent) received factor VIII concentrate exclusively, 18 (5 per cent) received factor IX concentrate exclusively, 147 (40 per cent) received either factor VIII or factor IX concentrate and single donor blood products (cryoprecipitate, plasma, or red blood cells), and 11 (3 per cent) received only single donor blood products. Blacks and Hispanics were more likely than Whites to have received single donor blood products (32/53 [60 per cent] vs 116/312 [37 per cent], OR = 2.6, 95% CI = 1.4–4.9).

Diagnoses

All diseases at least moderately indicative of cellular immunodeficiency and AIDS as listed in the CDC case definition[11] (except strongyloidiasis and isosporiasis) were reported among the hemophilia-associated AIDS cases (Table 1). Of the 407 patients, 315 (77 per cent) were reported to

TABLE 1—Comparison of Diseases Indicative of AIDS in Hemophilia-, Homosexual/Bisexual-, and Intravenous Drug Abuse-associated AIDS Cases, United States, 1981–87*

Indicative Diseases	Hemophilia No.	Hemophilia (%)**	Homosexual %	IVDA %
Pneumocystis carinii pneumonia	265	(65)	63	67
Esophageal candidiasis	75	(18)	9	15
Cryptococcosis, extrapulmonary	47	(12)	6	12
Chronic cryptosporidiosis	27	(7)	4	2
Mycobacterium avium complex, disseminated	32	(8)	4	4
Cytomegalovirus infection, internal organ	19	(5)	5	2
Lymphoma***	16	(4)	NA	NA
Toxoplasmosis, internal organ	12	(3)	2	3
Chronic mucocutaneous *Herpes simplex* infection	11	(3)	4	3
Histoplasmosis, disseminated	10	(3)	NA	NA
Kaposi's sarcoma	5	(1)	27	3
Chronic interstitial pneumonitis	3	(1)	NA	NA
Progressive multifocal leukoencephalopathy	2	(<1)	NA	NA

*AIDS cases as of September 4, 1987 for hemophilia-associated cases and as of February 9, 1987 for homosexual/bisexual- and intravenous drug abuse-associated cases.[18]

**Cases may have more than one diagnosis.

***Non-Hodgkin's lymphoma of high-grade pathologic type and of B-cell or unknown immunologic subtype.

have one disease indicative of AIDS; 70 (17 per cent), two such diseases; 16 (4 per cent), three; and six (2 per cent), four or more. The presence of any specific disease was not correlated with the presence of another. Except for Kaposi's sarcoma, the distribution of specific diseases was similar to that seen in other risk groups.[18] Blacks and Hispanics were less likely than Whites to have been diagnosed as having *Pneumocystis carinii* pneumonia (28/56 [50 per cent] vs 235/344 [68 per cent], OR = 0.5, 95% CI = 0.3–0.9) and were more likely to have had cryptosporidiosis (9/56 [16 per cent] vs 17/344 [5 per cent], OR = 3.7, 95% CI = 1.4–9.3). The incidence of cryptosporidiosis was similar in White children and children who were not White (5/43 [12 per cent] vs 3/20 [15 per cent], respectively); however, in adults, the incidence in Whites was 12/301 [4 per cent], in others (6/36 [17 per cent], OR = 4.8, 95% CI = 1.4–15.0).

Living Status

As of September 4, 1987, 257 (63 per cent) of the 407 patients were known to have died, an AIDS mortality rate similar to that seen in other risk groups.[19] Of those who died, 84 per cent died within one year of the diagnosis of AIDS. There were no racial differences in mortality rates.

Discussion

Hemophilia-associated AIDS cases comprise only 1 per cent of all AIDS cases reported in the United States. Nevertheless, continued surveillance of AIDS in this population is important:

- Fifteen to 18,000 persons in the United States have a coagulation disorder. The high HIV seroprevalence rate in this group indicates that more cases will occur.
- The route and frequency of exposure to HIV among hemophilics (through commercially produced concentrated clotting factors) differed from that of homosexual/bisexual men, intravenous drug users, and transfusion recipients. The natural history of HIV infection in the hemophilic population may, therefore, differ from other risk groups.
- Sexual partners and offspring of hemophilics are also at risk for HIV infection. In a recent survey, US hemophilia treatment centers reported that, of the sexual partners of seropositive hemophilics who had been tested for antibody to HIV, 10 per cent were seropositive.[20] Counseling and public health interventions need to be directed toward these persons to prevent further spread of the infection.

Surveillance findings parallel serologic studies of hemophilia treatment center-based populations.[4-9,21,22] The majority of AIDS patients had hemophilia A, were severely affected by their coagulation disorder, and received concentrated clotting factors. Concentrated clotting factors are composed of blood components from hundreds to thousands of donors. Due to the large number of donors, the potential risk of contamination of the concentrated factor with HIV is high, even if the prevalence of infection in the donor population is low. Therefore, patients receiving concentrated clotting factors are at risk for HIV infection. Those with severe hemophilia, who receive larger and more frequent doses of concentrated clotting factor, would be expected to be at a higher risk of HIV infection that those with less severe hemophilia. The larger number of AIDS cases among persons with severe hemophilia A compared to severe hemophilia B reflects, in part, more frequent and larger doses of concentrated clotting factor used to treat hemophilia A. Factor IX (used to treat hemophilia B) has a longer half-life than factor VIII (used to treat hemophilia A) and therefore does not need to be given as frequently.[17] However, fractionation processes for factor IX concentrate differ from factor VIII and may result in a differential degree of inactivation of HIV in the two products. One purification process for factor IX includes the use of ethanol,[23] a substance found to be an effective inactivator of HIV.[24] Researchers have demonstrated a $10^{3.5}$-fold decrease in HIV infectivity in plasma (seeded with HIV) following exposure to 20 per cent ethanol in a common manufacturing process.[25] This and surveillance data suggest some factor IX products may have been associated with a lower degree of contamination with HIV and, as a result, a lower risk of HIV infection and AIDS in recipients.

ACKNOWLEDGMENTS

For their contributions to the surveillance of AIDS in persons with hemophilia, the authors thank Maureen Mahoney, Gloria Dixon, Sharon Richardson, and Mitzi Mays, Division of Host Factors, CID, CDC; Tom Starcher, Marie Blair, and Mary Catherine Noa, AIDS Program, CID, CDC; and the National Hemophilia Foundation. This paper was presented in part as a poster at the III International AIDS Conference in Washington, DC, June 1987.

REFERENCES

1. Centers for Disease Control: *Pneumocystis carinii* pneumonia among persons with hemophilia A. MMWR 1982; 31:365–367.
2. Centers for Disease Control: Update: Acquired immunodeficiency syndrome among patients with hemophilia—United States. MMWR 1983; 32:613–615.
3. McDougal JS, Martin LS, Cort, SP, *et al:* Thermal inactivation of acquired immunodeficiency syndrome virus, human T-lymphotropic virus-III/lymphadenopathy-associated virus with special reference to antihemophilic factor, J Clin Invest 1985; 76:875–877.
4. Jason J, Holman RC, Kennedy MS, Evatt BL: Longitudinal assessment of hemophiliacs exposed to HTLV-III/LAV. *In:* Program and abstracts of the 26th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, Louisiana, 1986; 97.
5. Waskin H, Smith KJ, Simon TL, Gribble TJ, Mertz GJ: Prevalence of HTLV-III antibody among New Mexico residents with hemophilia. West J Med 1986; 145:477–480.
6. Ragni MV, Tegtmeier GE, Levy JA, *et al:* AIDS retrovirus antibodies in hemophiliacs treated with factor VIII or factor IX concentrates, cryoprecipitate, or fresh frozen plasma: prevalence, seroconversion rate, and clinical correlations. Blood 1986; 67:592–595.
7. Goedert JJ, Sarngadharan MG, Eyster ME, *et al:* Antibodies reactive with human T cell leukemia viruses in the serum of hemophiliacs receiving factor VIII concentrate. Blood 1985; 65:492–495.
8. Gjerset GF, McGrady G, Counts RB, *et al:* Lymphadenopathy-associated virus antibodies and T cells in hemophiliacs treated with cryoprecipitate or concentrate. Blood 1985; 66:718–720.
9. Kreiss JK, Kitchen LW, Prince HE, *et al:* Human T cell leukemia virus type III antibody, lymphadenopathy, and acquired immune deficiency syndrome in hemophiliac subjects. Am J Med 1986; 80:345–350.
10. Centers for Disease Control: Surveillance of hemophilia-associated acquired immunodeficiency syndrome. MMWR 1986; 35:669–671.
11. Centers for Disease Control: Revision of the case definition of acquired immunodeficiency syndrome for national reporting—United States. MMWR 1985; 34:373–375.
12. Thomas DG: Exact and asymptotic methods for the combination of 2 X 2 tables. Comput Biomed Res 1975; 8:423–446.
13. Thomas DG, Gart JJ: A table of exact confidence limits for differences and ratios of two proportions and their odds ratios. J Am Stat Assoc 1977; 72:73–76.
14. Lehman EL: Nonparametrics—statistical methods based on ranks. San Francisco: Holden-Day, 1975.
15. US Bureau of the Census. State and Metropolitan area data book, 1982. Washington, DC: Govt Printing Office, 1982.
16. Snedecor GW, Cochran WG: Statistical Methods. Ames, Iowa: Iowa State University Press, 1980.
17. US Department of Health, Education, and Welfare: Study to evaluate the supply-demand relationship for AHF and PTC through 1980. DHEW Pub. No. 77–1274. Washington, DC: Govt Printing Office, 1977.
18. Selik RM, Starcher ET, Curran JW: Opportunistic diseases reported in AIDS patients: Frequencies, associations, and trends. AIDS 1987; 1:175–182.

19. Centers for Disease Control: Update: acquired immunodeficiency syndrome—United States. MMWR 1986; 35:17–21.
20. Centers for Disease Control: HIV infection and pregnancies in sexual partners of HIV-seropositive hemophilic men—United States. MMWR 1987; 36:593–595.
21. Jason J, McDougal S, Holman RC, *et al:* Human T-lymphotropic retrovirus type III/lymphadenopathy-associated virus antibody. JAMA 1985; 253:3409–3415.
22. Evatt BL, Gomperts ED, McDougal JS, Ramsey RB: Coincidental appearance of LAV/HTLV-III antibodies in hemophiliacs and the onset of the AIDS epidemic. N Engl J Med 1985; 312:483–486.
23. Aronson DL: Factor IX complex. Seminars in thrombosis and hemostasis 1979; 6:28–43.
24. Martin LS, McDougal JS, Loskoski SL: Disinfection and inactivation of the human T lymphotropic virus type III/lymphadenopathy-associated virus. J Infect Dis 1985; 152:400–403.
25. Piszkiewicz D, Kingdom H, Apfelzweig R, *et al:* Inactivation of HTLV-III/LAV during plasma fractionation. Lancet 1985; 2:1188.

The Health Worker's Declaration on the Arms Race and the Threat of Nuclear war

DECLARATION

The arms race threatens all life on our planet; it must be stopped for the sake of human survival.

The arms race is the great enemy of humankind, rather than our competing economic and social systems, our differing political beliefs, or our varied religious creeds.

The arms race has erupted into wars which have killed more than 20 million people since the end of World War II.

The arms race has created nuclear arsenals equal to more than 1,000,000 Hiroshimas, enough to destroy every man, woman and child, every city, town and village, every tree, every flower, every form of life on planet earth.

The arms race has caused a decline in productivity, has aggravated unemployment, has created a staggering burden of debt, and has seriously hampered economic and social development throughout the world.

The arms race has fostered military domination of national policies, as well as the growth of military dictatorships with their attendant denial of democratic rights, brutality, torture, disappearances, and political murders.

The arms race has resulted in severe cutbacks in health services, in education, in nutrition, in every aspect of human services. Deadly diseases continue to destroy and maim our children, our men and women, because safe water supplies and basic sanitation facilities are not available, because people have no access to medical services, because they are hungry and undernourished, because they are poor and illiterate and know little of personal hygiene.

We pledge our unremitting effort to arouse the peoples of the world to stop the arms race, to save humanity from nuclear annihilation, to reverse our perverted priorities, and to help bring social well-being, health, and peaceful development to all the nations of the earth.

We stand unequivocally for:

- A total ban on nuclear testing.
- Reduction and then elimination of nuclear weapons.
- A total ban on chemical and bacteriological weapons.
- Disarmament and Development: we fully endorse the United Nation's General Assembly recommendation for a 10% reduction in the military budgets of the permanent members of the Security Council and allotment of 10% of the fund so released for assistance to the developing countries.
- Dialogue and Negotiation, no War, Aggression, and Destruction, as the human norm for conflict resolution among the nations of our single, indivisible world community.

ACTION PROGRAM

1. Marking the day of October 1 as Health Workers for Peace Day, a suitable focal point for mobilization and action in all countries, including meetings, demonstration, or other activities appropriate to the situation in each country.

2. Wide distribution and collection of signatures on the "Appeal from Hiroshima and Nagasaki for a Total Ban and Elimination of Nuclear Weapons."

3. Use of mass media—television, radio, posters and buttons, press conferences, meetings with heads of state and prominent religious, cultural and industrial leaders—to inform the people and mobilize public opinion.

4. Extending and strengthening international coordination and joint action by all health workers' organizations, including trade unions, public health associations, professional societies, and voluntary health organizations, working in close collaboration with the International Physicians for the Prevention of Nuclear War (IPPNW).

5. Participation in an information network on the arms race, disarmament and development, in cooperation with relevant international organizations devoted to peace, disarmament, health, social well-being, and economic development.

—Adopted unanimously at the World Conference of Health Workers on Social Well-Being, Health and Peace, Moscow, May 29–June 1 1987. The 121 conference participants represented 53 health workers' trade unions, 12 public health associations (including APHA), 13 professional organizations, four other national health organizations, and 12 international and regional organizations. There were 50 countries represented: 13 in Africa, nine in Asia, and the Near East, 16 in Europe, 10 in Central and South America, and two in North America.