Survival Analysis of Hemophilia-Associated AIDS Cases in the US

JEANETTE K. STEHR-GREEN, MD, ROBERT C. HOLMAN, MS, AND MAUREEN A. MAHONEY, MT*

Abstract: Using national hemophilia-associated AIDS (acquired immunodeficiency syndrome) surveillance data and the life table method of survival analysis, the median length of survival of hemophilic patients in the United States after the diagnosis of AIDS was 11.7 months; the cumulative probability of survival at one year was 49.2 ± 2.0 percent; at two years, 28.9 ± 2.3 percent. Patients 13–29 years of age at the time of diagnosis had the longest survival and those 60 years and older had the shortest. Patients diagnosed since 1986 survived longer than those diagnosed before 1986. Length of survival did not differ significantly by race, coagulation disorder, AIDS manifestation at the time of diagnosis, or region of residence. Seven patients survived more than 36 months after AIDS was diagnosed. These patients were similar to those surviving for a shorter duration except that they were more likely to have met only the 1987 revision of the Centers for Disease Control AIDS surveillance case definition (as opposed to the 1985 case definition). Results of this study suggest that survival among hemophilic patients after the diagnosis of AIDS is similar to that reported by other investigators for other AIDS risk groups, excluding patients with Kaposi's sarcoma. (*Am J Public Health* 1989; 79:832–835.)

Introduction

The natural history of human immunodeficiency virus (HIV) infection in persons with hemophilia and other coagulation disorders is not well established and may differ from that in other acquired immunodeficiency syndrome (AIDS) risk groups.[1–3] Differences in the route and frequency of exposure to HIV, differences in the prevalence of potential cofactors for the development of AIDS (e.g., coexistent infections), and differences in routine medical care could lead to a variation in disease progression and ultimate outcome, such as survival. Using national surveillance data for hemophilia-associated AIDS, we examined the survival of hemophilic patients in the United States following the diagnosis of AIDS.

Methods

National surveillance of AIDS in persons with hemophilia and other coagulation disorders is maintained through the receipt of standardized AIDS case report forms submitted by individual state health departments to the Centers for Disease Control (CDC).[4] CDC personnel obtain supplemental information, including update of living status, through routine telephone interviews with the treating physician, nurse, or public health worker.

Only patients with illnesses that meet the CDC surveillance case definitions for AIDS, as revised in 1985 and 1987,[5,6] are included in the analyses. 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. Patients with multiple risk factors for HIV infection (i.e., risk factors in addition to a coagulation disorder, such as a history of male to male sexual contact or intravenous drug use) were excluded from the analyses (n = 24). Only patients reported before August 31, 1988 are included in the analyses.

The date of AIDS diagnosis was defined as the date the first AIDS-indicator disease (i.e., opportunistic infection or cancer meeting the CDC AIDS case definition)[5,6] was diagnosed. Survival time in months for each individual was calculated from the month of AIDS diagnosis to the month of death, if the patient had died, or from the month of AIDS diagnosis to August 1988, if the patient was still alive. Because length of survival was expressed in month intervals, the life table method of survival analysis was used to estimate the survivorship function from censored data.[7] The version of the Kruskal Wallis or generalized Wilcoxon test proposed by Breslow was used to compare the distribution of survival among patient subgroups.[8] CDC personnel obtained additional information on patients surviving longer than 36 months after the diagnosis of AIDS, including development of subsequent disease, other reasons for immunosuppression, and use of anti-HIV therapies, through telephone interview of the patient's physician, nurse, or associated public health worker in June 1988. Median ages at diagnosis of these patients and those surviving shorter periods were compared using Wilcoxon rank-sum test.[9] The method of Thomas and Gart was used to calculate odds ratios and 95% confidence intervals for dichotomous variables.[10]

Results

Between January 1, 1981 and August 31, 1988, 716 cases of hemophilia-associated AIDS (with no other risk factors for HIV infection) were reported to CDC. Six hundred and twenty-eight (88 percent) patients had hemophilia A (factor VIII deficiency); 61 (9 percent) had hemophilia B (factor IX deficiency); 16 (2 percent), von Willebrand's disease; five (<1 percent), acquired inhibitor to factor VIII; two (<1 percent), factor VII deficiency; two (<1 percent), factor X deficiency; and one each factor V and factor XI deficiency. All except 18 (3 percent) patients were male. The median age at the time of AIDS diagnosis was 31 years; however, patients diagnosed before 1986 were significantly older than those diagnosed in 1986 or later (median age of 34 years vs 30 years, $p < 0.001$). Of the 716 patients, 611 (86 percent) were White; 46 (6 percent), Black; 47 (7 percent), Hispanic; nine (1 percent), Asian/Pacific Islander; and three (<1 percent), American Indian/Alaskan Native.

Living status and date of death were known for 714 patients. As determined by the life table method, median survival from the time of AIDS diagnosis was 11.7 months. The cumulative probability of survival at one year was 49.2 ± 2.0 percent and at two years was 28.9 ± 2.3 percent.

From the Division of Host Factors, Center for Infectious Diseases, CDC, USPHS. Address reprint requests to Dr. Jeanette K. Stehr-Green, Medical Epidemiologist, Surveillance Branch, AIDS Program, Center for Infectious Diseases, Centers for Disease Control, Atlanta, GA 30333. Mr. Holman is statistician, and Ms. Mahoney is medical technologist, both with the Division of Host Factors, CID, CDC.

*Ms. Mahoney is Medical Technologist (American Society of Clinical Pathology) Specialist in Blood Banking.

This paper, submitted to the Journal August 26, 1988, was revised and accepted for publication February 6, 1989.

Survival did not differ by race, coagulation disorder, or region of residence (Table 1). Patients 13–29 years of age at the time of AIDS diagnosis had a significantly longer survival than the older patients 30–59 years of age and ≥60 years of age (Table 1 and Figure 1). Patients <13 years of age and 30–59 years of age also had a significantly longer survival than patients 60 years and older.

Patients diagnosed with AIDS before 1986 had a shorter survival than those diagnosed in 1986 or later (Table 2). Because the number of patients in our study diagnosed with only one AIDS-indicator disease other than *Pneumocystis carinii* pneumonia or esophageal candidiasis was small, survival by AIDS-indicator disease was limited to these two diagnoses. No difference in survival was observed (Table 2). Survival did not differ by case definition used to diagnose AIDS (1985 vs 1987 revision of the CDC AIDS case definition) (Table 2). Because the median age at diagnosis was younger among patients diagnosed in 1986 or later, analysis of survival time by year of diagnosis was stratified by age group (Table 3). In each age group, patients diagnosed since 1986 had a longer survival.

Seven patients survived longer than 36 months after the diagnosis of AIDS (Table 4). All were male; six had hemophilia A. These patients were similar to the patients surviving for shorter periods with respect to age at AIDS diagnosis, sex, race, and coagulation disorder. They were more likely to have met only the 1987 case definition (diagnosed retrospectively) as opposed to the 1985 case definition (4/7 [57 percent] vs 122/709 [17 percent], odds ratio = 6.4, 95% CI = 1.1, 44.2). All seven had antibody to HIV. Only one had been cultured for HIV and was found to be positive. No strain typing had been attempted on any of the patients. Five of the seven had been treated with some form of anti-HIV therapy; unfortunately, similar data were not available for patients living for a shorter duration.

Discussion

Our study, including patients with hemophilia and other coagulation disorders exclusively, expands upon studies of the natural history of HIV infection among different groups

TABLE 1—Length of Survival after Diagnosis of AIDS among Hemophilic Patients by Patient Characteristics, United States, January 1981–August 1988

Characteristics	Number	Median Survival Estimate (in months)	Cumulative Probability of Survival at: One Year	Two Years
Total	714	11.7	49.2 ± 2.0%	28.9 ± 2.3%
Age Group* (years)				
<13	60	12.0	50.1 ± 6.6%	34.8 ± 7.0%
13–29	255	16.4	60.2 ± 3.3%	40.3 ± 4.1%
30–59	333	9.8	44.5 ± 2.9%	23.3 ± 3.2%
≥60	66	3.0	28.7 ± 6.3%	5.4 ± 4.9%
Race				
White	611	11.9	49.5 ± 2.1%	28.7 ± 2.5%
Black or Hispanic	92	10.5	45.3 ± 5.9%	26.2 ± 6.4%
Coagulation Disorder				
Hemophilia A	626	11.4	48.1 ± 2.1%	27.5 ± 2.5%
Hemophilia B	61	14.9	60.7 ± 6.5%	42.7 ± 7.8%
Region of Residence				
Northeast	174	13.8	53.0 ± 4.0%	31.1 ± 4.7%
Northcentral	158	9.7	45.2 ± 4.1%	30.8 ± 4.3%
South	188	11.4	47.6 ± 3.9%	25.5 ± 4.8%
West	189	12.1	50.3 ± 4.0%	24.7 ± 5.3%

*$p < 0.005$ using the Breslow test.[8]

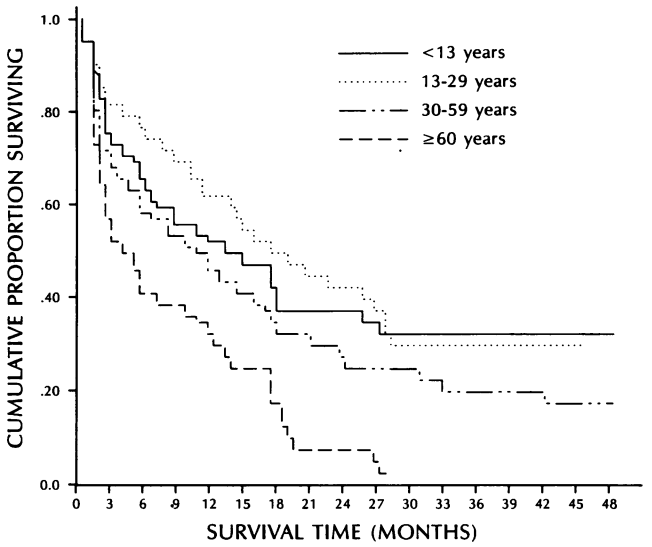

FIGURE 1—Survival after the Diagnosis of AIDS among Hemophilic Patients by Age at Diagnosis, United States, January 1981–August 1988.

TABLE 2—Length of Survival after Diagnosis of AIDS among Hemophilic Patients by Patient Characteristic, United States, January 1981–August 1988

Characteristics	Number	Median Survival Estimate (in months)	Cumulative Probability of Survival at: One Year	Two Years
Year of Diagnosis*				
Before 1986	185	6.4	36.2 ± 3.5%	14.6 ± 2.6%
1986 and after	529	15.0	54.6 ± 2.3%	39.4 ± 3.2%
AIDS Diagnosis				
P. carinii pneumonia only	302	14.2	54.2 ± 3.0%	29.9 ± 4.0%
Esophageal candidiasis only	57	16.0	55.7 ± 7.2%	37.6 ± 9.0%
Case Definition				
1985/1987	593	11.5	48.4 ± 2.2%	27.3 ± 2.4%
1987 only	121	13.7	54.8 ± 4.9%	44.9 ± 6.2%

*$p < 0.005$ using the Breslow test.[8]

TABLE 3—Median Length of Survival by Year of Diagnosis and Age Group

Age Group (years)	Year of Diagnosis: Before 1986 N	Before 1986 Median Survival Time (in months)	1986 and after N	1986 and after Median Survival Time (in months)
<13	14	—	46	10.9
13–29*	50	11.0	205	>29.0
30–59*	103	6.3	230	11.9
60+	18	1.7	48	4.9

*$p < 0.005$ using the Breslow test.[8]

at risk for AIDS. Rothenberg, *et al*, analyzed data from 5,833 AIDS patients in New York City.[11] Median length of survival ranged from 9.4 months in patients with a history of intravenous drug use to 13.1 months in patients with a history of homosexual activity. Patients with both risk factors had a median survival of 10.1 months and those with other risk

TABLE 4—Seven Patients with Hemophilia-Associated AIDS Surviving Longer than 36 Months after AIDS Diagnosis

Patient	Age at Diagnosis	Date of AIDS Diagnosis	AIDS Indicator Disease	Comment
A	35	1/84	cryptococcal meningitis*	on prednisone for thrombocytopenia at time of meningitis; treated with AZT and acyclovir; still living**
B	48	1/85	presumptive esophageal* candidiasis	treated with AZT; subsequently developed HIV encephalopathy; still living
C	10	9/83	recurrent bacterial infections*	treated with AZT; subsequently developed a lymphoma; still living
D	36	11/84	presumptive esophageal candidiasis*	treated with AZT; eventually died with severe liver disease
E	31	3/84	Kaposi's sarcoma	treated with radiation therapy; still living
F	37	3/84	*P. carinii* pneumonia	treated with gamma interferon and ribavirin; still living
G	13	12/84	*P. carinii* pneumonia	subsequently developed esophageal candidiasis, cryptosporidiosis, and *Mycobacterium avium-intracellulare;* treated with AZT; still living

*met 1987 CDC AIDS surveillance case definition only.
**as of June 1988

factors had a median survival of 8.5 months. In an analysis of 663 AIDS cases from the United Kingdom,[12] Reeves and Overton reported a median survival of 12.6 months in AIDS patients with a history of homosexual activity and 10.5 months in other transmission categories combined. Both studies found the most favorable survival among patients with Kaposi's sarcoma alone (25.0 and 15.0 months, respectively). Neither study was able to examine hemophilic patients separately. Our results suggest that survival among hemophilic patients with AIDS is comparable to that observed in other patient groups, excluding those with Kaposi's sarcoma. However, data from studies by Rothenberg and Reeves were collected in 1985 and 1987, respectively. Survival may have improved in these groups. In our study, survival improved over time. This improved survival could reflect changes in health care for AIDS patients including earlier diagnosis and institution of treatment of AIDS-indicator diseases, prophylactic treatment for some opportunistic infections (e.g., *Pneumocystis carinii* pneumonia),[13] and development of anti-HIV therapies such as azidothymidine.[14,15] To facilitate comparisons between patient groups, survival analyses should be repeated in other groups to determine the impact of more recent changes in health care.

Similar to studies by Rothenberg and Reeves, we found a decreasing length of survival after the diagnosis of AIDS with increasing patient age. It has been shown that antigenic stimulation causes increased replication of HIV which may lead to a more rapid development and progression of HIV-related disease.[16] Repeated exposure to factor concentrate (also a powerful antigenic stimulus),[17] exposure to environmental contaminants, and a higher prevalence of hepatitis B and sexually transmitted diseases (Stehr-Green JK: unpublished data) could lead to a more rapid progression of HIV infection among older hemophilic patients and a less favorable survival. A more rapid progression of infection could also explain the decrease in median age of hemophilia-associated AIDS cases over time, consistent with findings of Eyster, *et al,* which showed age to be a cofactor for AIDS independent of date of infection.[18]

The 1987 revision of the CDC AIDS surveillance case definition includes a broader range of AIDS-indicator diseases (including HIV dementia and HIV wasting syndrome), indicator diseases that are presumptively diagnosed, and elimination of exclusions due to other causes of immunodeficiency. The large proportion of long survivors with illnesses meeting only the 1987 revision seems to suggest that these illnesses may be associated with a more favorable survival than those included in the 1985 case definition. However, the illnesses included in the revision may allow the patient to be diagnosed with AIDS and reported to CDC at an earlier point in the progression of HIV-related disease. That is, the interval between infection and development of clinical manifestations of AIDS may be shortened, resulting in an apparent increase in the length of survival after the diagnosis of AIDS. Analyses of survival from date of infection to death could eliminate this potential confounder. Unfortunately, the date of seroconversion is not available for most hemophilic patients due to multiple exposures to potentially contaminated blood products.

ACKNOWLEDGMENTS

The authors thank Janine M. Jason, M.D., Division of Host Factors (DHF), Center for Infectious Diseases (CID), CDC, for her support and guidance; and Michael Zelasky, DHF, CID, CDC; Tom Starcher, Marie Blair, and Mary Catherine Noa, AIDS Program, CID, CDC; and the National Hemophilia Foundation; for their contributions to the surveillance of AIDS in persons with hemophilia.

REFERENCES

1. Goedert JJ, Biggar RJ, Weiss SH, *et al:* Three-year incidence of AIDS in five cohorts of HTLV-III-infected risk group members. Science 1986; 231: 992–995.
2. Ekert H: AIDS incubation period. Nature 1987; 329:494.

3. Turner MJ, White JO, Soutter WP: AIDS incubation period in male hemophiliacs. Nature 1987; 330:702.
4. Stehr-Green JK, Holman RC, Jason JS, Evatt BL: Hemophilia-associated AIDS in the United States, 1981 to September 1987. Am J Public Health 1988; 78;439–442.
5. Centers for Disease Control: Revision of the case definition of acquired immunodeficiency syndrome for national reporting—United States. MMWR 1985; 34:373–375.
6. Centers for Disease Control: Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. MMWR 1987; 36(suppl):1S–15S.
7. Lee ET: Statistical Methods for Survival Data Analysis. Belmont, California: Lifetime Learning Publications, 1980.
8. Dixon WJ: BMDP Statistical Software. Berkley: University of California Press, 1983.
9. Lehmann EL: Nonparametrics—Statistical Methods Based on Ranks. San Francisco: Holden-Day, 1975.
10. Thomas DG, Gart JJ: Table of exact confidence limits for differences in ratios of two proportions and their odds ratios. J Am Stat Assoc 1977; 72: 73–76.
11. Rothenberg R, Woelfel M, Stoneburner R, Milberg J, Parker R, Truman B: Survival with acquired immunodeficiency syndrome: Experience with 5833 cases in New York City. N Engl J Med 1987; 317:1297–1302.
12. Reeves GK, Overton SE: Preliminary survival analysis of UK AIDS data. Lancet 1988; 1:880.
13. Fischl M, Dickenson GM, LaVoie L: Safety and efficacy of sulfamethoxazole and trimethoprim chemoprophylaxis for *Pneumocystis carinii* pneumonia in AIDS. JAMA 1988; 259:1185–1189.
14. Fischl MA, Richman DD, Grieco MH, *et al:* The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. N Engl J Med 1987; 317:185–191.
15. Kaplan LD, Wofsy CB, Volberding PA: Treatment of patients with acquired immunodeficiency syndrome and associated manifestations. JAMA 1987; 257:1367–1374.
16. Zagury D, Bernard J, Leonard R, *et al:* Long-term cultures of HTLV-III infected T-cells; a model of cytopathology of T-cell depletion in AIDS. Science 1986; 231:850–853.
17. Sullivan JL, Brewster FE, Brettler DB, *et al:* Hemophiliac immunodeficiency: Influence of exposure to factor VIII concentrate, Lav/HTLV-III, and herpesviruses. J Pediatr 1986; 108:504–510.
18. Eyster ME, Gail MH, Ballard JO, Al-Mondhiry H, Goedert JJ: Natural history of human immunodeficiency virus infection in hemophiliacs: Effects of T-cell subsets, platelet counts, and age. Ann Intern Med 1987; 107:1–6.

$5 Million Awarded to States to Help Low-Income AIDS Patients Purchase Medicines

An additional $5,075,490 in federal funds from the Health Resources and Services Administration (HRSA) of the US Public Health Service was recently awarded to 26 states to help low-income AIDS patients obtain drugs that would prolong their lives. The Food and Drug Administration (FDA) has determined that three drugs prolong the lives of AIDS patients—azidothymidine (AZT), alpha interferon, and aerosolized pentamidine.

The funds were distributed on March 31 just before the authorizing legislation, Public Law 100-471, expired. Those eligible for assistance are low-income individuals not covered by Medicaid or private insurance. Each state determines eligibility. The 26 states receiving the funds are: Alabama, Alaska, Arizona, California, Colorado, Florida, Georgia, Idaho, Illinois, Indiana, Kansas, Kentucky, Maine, Massachusetts, Mississippi, North Dakota, Ohio, Oklahoma, Oregon, Rhode Island, South Carolina, Tennessee, Texas, Utah, Vermont, and Wisconsin.

Of the total distributed, $5 million came from the transfer of fiscal 1989 funds appropriated for AIDS programs administered by the Office of the Assistant Secretary for Health and four Public Health Service agencies. The remaining $75,490 derived from jurisdictions that reported they would not be able to use by September 30, 1989 funds distributed last November under PL 100-471. At that time, HRSA distributed to the 50 states and other jurisdictions some $15 million including $5 million from a private pharmaceutical company. The drug reimbursement program began in fiscal 1987 when HRSA awarded $30 million to states. The latest distribution brings the total federal funds awarded under the AIDS Drug Program to $45 million.

For further information, contact Frank Sis, HRSA, PHS, USDHHS, 5600 Fishers Lane, Room 14-43, Rockville, MD 20857. Tel: (301) 443-3377.