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THE COURSE OF THE EPIDEMIC OF ACQUIRED IMMUNODEFICIENCY SYNDROME IN THE UNITED STATES HEMOPHILIA POPULATION[1]

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McGrady, G. A., J. M. Jason, and B. L. Evatt (CDC, Atlanta, GA 30333). The course of the epidemic of acquired immunodeficiency syndrome in the United States hemophilia population. *Am J Epidemiol* 1987;126:25-30.

The time course of the epidemic of acquired immunodeficiency syndrome (AIDS) as it has occurred in the US hemophilia population is examined using surveillance data collected by the Centers for Disease Control (CDC). These data indicate that the epidemic course in hemophiliacs is distinguishable from that in the homosexual/bisexual and intravenous drug-using populations in at least one respect—the epidemic in the hemophilia population is characterized by a lack of consistent increase in the number of new AIDS cases in successive time intervals. This difference is interpreted as being attributable to the mechanisms by which AIDS virus is spread among hemophiliacs. In addition, the short survival following diagnosis of AIDS in hemophiliacs and the magnitude of yearly incidence rates for this group in 1984 and 1985 show the hemophilia population to have been severely affected by the epidemic.

acquired immunodeficiency syndrome; hemophilia

Since the recognition of acquired immunodeficiency syndrome (AIDS) in 1981, the number of confirmed cases reported to the Centers for Disease Control has increased steadily (1). Through the end of 1985 each group at high risk for AIDS—except for hemophiliacs—showed the same pattern of increasing numbers of cases in successive three-month intervals. The pattern appeared different for hemophiliacs. In particular, for a period of several months in 1984 and early 1985 there appeared to be a peak of cases of hemophilia-associated AIDS diagnosed in the first three months of 1984 with fewer cases diagnosed subsequently. This difference raised the specific question of whether the epidemic in hemophiliacs was leveling off—a question answered in the negative by reporting after March 1985—and the more general question of whether the temporal course of the epidemic might be different for the US hemophilia population compared with other groups at high risk for AIDS.

METHODS

Surveillance data on cases of AIDS occurring in the United States have been collected by the Centers for Disease Control since 1981 (2). Presently, reporting of newly diagnosed AIDS cases is mandatory in 46 states.

The size of the US hemophilia population in the period 1981-1985 was estimated from US census data (3) using results and assumptions from a national survey of the hemophilia population completed in 1975 (4).

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Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

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Kaplan-Meier estimates of survival (5) following diagnosis of AIDS were calculated using data on 173 hemophilia-associated AIDS cases reported by March 30, 1986. For each case, survival was calculated from the exact or earliest possible date of diagnosis to the date of death (uncensored endpoint) or the date of the last contact with the case as indicated by the reporting source (censored endpoint). The exact diagnosis date was ascertainable in 52 of 173 cases; the earliest possible date was ascertainable in all cases. The endpoint of survival was incompletely specified for 22 of 173 cases—the month and year but not the day being reported. For these 22 cases the 15th day was assigned in performing the calculations.

Surveillance data for AIDS are incomplete in the sense that current data are subject to change due to reporting delays—the time from diagnosis to reporting. For example, the number and time-distribution of AIDS cases diagnosed in 1985 are subject to change with reporting in 1986. This incompleteness was analyzed by computer simulation of future reporting under a variety of assumptions, and using an empirical distribution of reporting delays (delays from all cases reported by November 30, 1985). The simulation computed report dates, diagnosis dates, and the frequencies with which cases reported in 1986 would have diagnosis dates in each quarter of 1985. Details of the simulation are not presented.

Results

Epidemic course

The number of AIDS cases occurring in the US hemophilia population in successive three-month intervals, beginning in 1981, defines a variable pattern with marked increases, plateaus, and definite declines (figure 1). No prolonged periods of constant increase or decrease of cases have occurred. Considered by year of diagnosis, the number of hemophilia-associated AIDS cases has increased constantly and this is reflected in yearly incidence rates (table 1); the marked increases in 1982, 1984, and 1985 are to be noted.

When the time course of the AIDS epidemic among hemophiliacs is compared with that in homosexual/bisexual men and intravenous drug-users (figure 2), one difference is apparent. For the latter two groups, diagnosed AIDS cases have increased each quarter, except for the second quarter of 1982 and the final quarter of 1985. Cases diagnosed in the second quarter

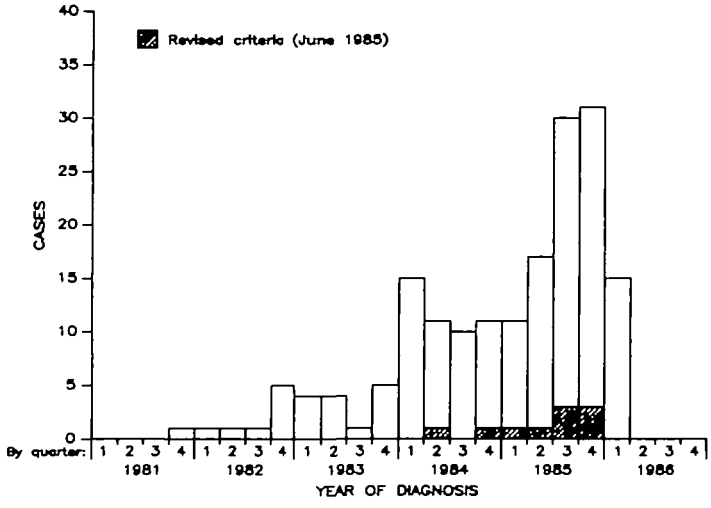

FIGURE 1. Hemophilia-associated AIDS cases, United States, October 1981–March 1986.

approximately equaled those diagnosed in the previous quarter for both groups. The decline in cases diagnosed in the final quarter of 1985 is a manifestation of the reporting delay problem. Thus, consistently increasing numbers of cases characterize the epidemic in these groups, but not in hemophiliacs.

Survival of hemophilia patients following AIDS diagnosis is discouraging. Median survival for the 173 hemophilia-associated AIDS cases reported by March 30, 1986 is 167 days. The estimated one-year survival is 34.6 per cent; survival at 720 days is 7.9 per cent (figure 3).

Simulation

Of all hemophilia-associated AIDS cases reported by December 31, 1985, 27.4 per cent were reported within one week of diagnosis, and 66.4 per cent were reported within four weeks; delays as long as 31–38 weeks did occur, however (table 2).

Results of the computer simulation of reporting of hemophilia-associated AIDS cases for 1986 indicate that the probability that the number of cases diagnosed in 1985 will be increased by nine or more after the reporting for 1986 is complete (making the number of cases double that of 1984) is less than 0.003. Recent quarters of 1985 are more likely to be affected than more remote quarters. Thus, with high probability, the temporal course of hemophilia-associated AIDS as depicted (figure 1) is more than 90 per cent complete and undistorted.

TABLE 1

Incidence rates of acquired immunodeficiency syndrome, US hemophilia population, 1981–1985

Year	No. of cases diagnosed	Estimated population	Incidence (per 10,000)
1981	1	13,989	0.72
1982	8	14,121	5.67
1983	13	14,151	9.19
1984	46	14,181	32.44
1985	83*	14,211	58.41

* Based on reporting as of March 30, 1986.

DISCUSSION

The course of the AIDS epidemic in the hemophilia population is distinguishable from that in other high risk groups in that uninterrupted increase in the number of new cases in successive time intervals is not characteristic of the epidemic in this population. Thus, the experience in hemophilia-associated AIDS is not well described by epidemic models which predict increasing numbers of cases in successive time intervals through the peak of the epidemic—exponentially increasing when the population is large relative to the number

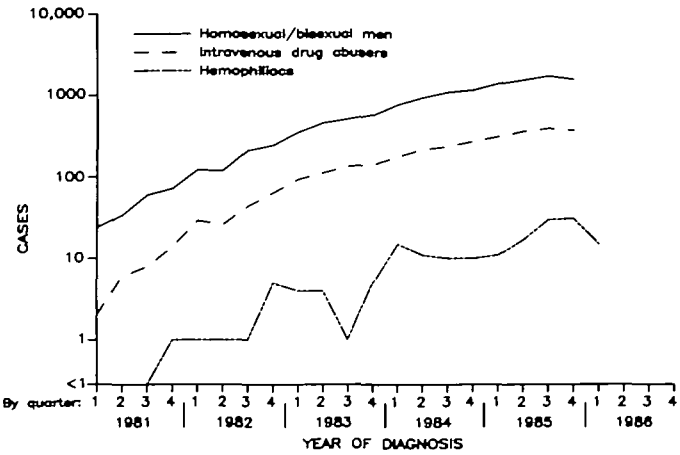

FIGURE 2. Acquired immunodeficiency syndrome, United States, January 1981–March 1986.

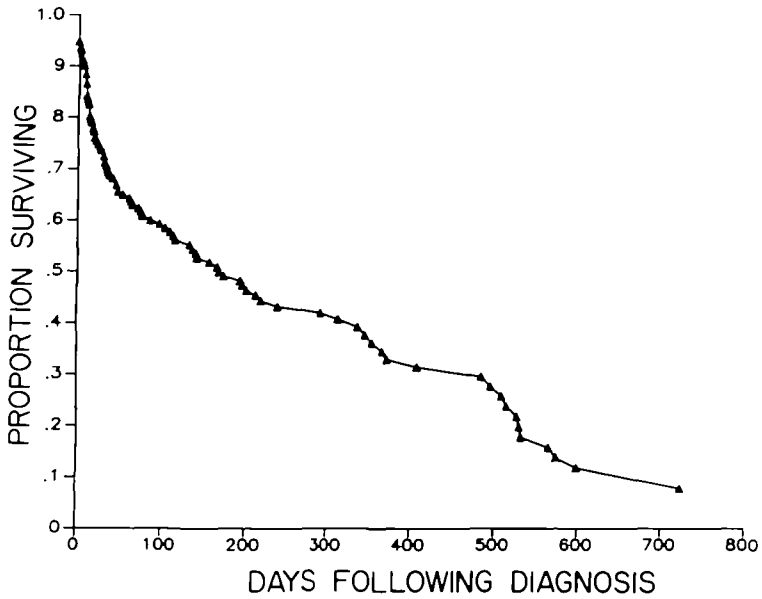

FIGURE 3. Survival time of hemophilia-associated AIDS cases following diagnosis, United States, October 1981–March 1986.

TABLE 2

Frequency of delay times (diagnosis to reporting), hemophilia-associated AIDS, October 1981–December 1985

Delay times (days)	No. of cases
7	31
8–14	15
15–21	14
22–28	15
29–35	7
36–42	2
43–49	2
50–56	7
57–63	7
64–70	3
71–140	6
141–210	2
211–266	2

of individuals capable of transmitting disease. Mathematical models of epidemics assume new cases arise from contact with infected individuals capable of transmitting disease, and additionally that the number of new cases occurring in an interval of time will be proportional to the number of such contacts. The course of the AIDS epidemic is consistent with predictions from such models for all high risk groups except hemophiliacs. This difference is probably a result of the route of transmission of AIDS virus in hemophiliacs—use of commercially prepared factor concentrates rather than some mode of person-to-person spread (6–12). Difference in mode of transmission may not completely explain the disparate characteristics of the AIDS epidemic in hemophiliacs since transfusion-associated AIDS cases also arise outside of person-to-person spread. Still, transmission of human immunodeficiency virus (HIV) by concentrates does allow a more uneven pattern of exposure and development of AIDS than person-to-person transmission. In particular, large increases in new cases is possible, as in 1984.

Surveillance data are limited in describing the epidemic process, and it is important to examine these limitations of the data.

One description of the epidemic process divides a population into three classes—susceptibles (persons without immunity or infection), infectives (infected persons capable of transmitting the infectious agent), and removed (persons who have passed

through the first two classes). The manner in which these three classes change with time constitutes a description of the epidemic process. Since person-to-person spread is not characteristic of hemophilia-associated AIDS (15), only susceptibles and removed individuals need be considered in describing the epidemic.

Consider susceptibles. Evidence from several studies indicates that exposure to HIV began in 1978 for the US hemophilia population, and that 70–85 per cent of this population had been infected with the virus by the end of 1984 (13–15); susceptible hemophiliacs, as categorized by absence of antibody to HIV, decreased from 100 per cent to approximately 21 per cent of the total US hemophilia population over six years. This change, relatively rapid with respect to estimated changes in other high risk groups (8, 16, 17), is not apparent in the surveillance data since neither susceptibles nor the total number in the removed class are available from surveillance data.

The removed class is represented in surveillance data by confirmed cases, but confirmed cases constitute only a small proportion of all those infected (1.5 per cent, approximately). Characteristics of this class are important from a public health perspective. In March of 1985, mass screening of donated blood and plasma was made possible with the marketing of commercial kits for detecting antibody to HIV (18). In October 1984, heat-treated factor concentrates were officially recommended as products of choice for most hemophilia patients requiring therapy (19). These measures are expected to reduce and possibly eliminate the risk of exposure to AIDS virus for hemophiliacs. If effective, the remainder of the epidemic process in this population will be defined by the natural history of HIV infection among those already infected, the removed class. What will be the cost of the epidemic in morbidity and mortality from AIDS? This is an extremely important question, and while surveillance data can provide a look at the costs, it may be a biased one.

The problem lies with the estimated long incubation period of AIDS. Estimation of the incubation period for AIDS in hemophiliacs has not been possible because, with few exceptions, hemophiliacs have had multiple possibilities for infection over many years. However, if we assume that the pathogenesis of HIV infection is similar across all high risk groups, then the estimates of incubation period made from transfusion-associated AIDS cases can be applied to hemophiliacs. The mean time from exposure to diagnosis of AIDS for transfusion-associated AIDS cases was estimated to be 4.5 years; the range seen was one to 65 months (20). Confirmed hemophilia-associated AIDS cases are likely, then, to be more representative of those in the removed class for whom the time to development of AIDS is short compared with all those infected and destined to develop AIDS. This is an unavoidable, systematic bias in the data that may distort our view of the epidemic's cost in terms of full-blown AIDS cases.

Thus, because surveillance data describe only a portion of one of the two classes necessary for a full description, information is limited; the rapid spread of the AIDS virus through the US hemophilia population is not evidenced in surveillance information since changes in the susceptible population are not measured or deducible, and for the reason noted, the long-term costs of the epidemic among hemophiliacs are not apparent.

References

1. Centers for Disease Control. Update: acquired immunodeficiency syndrome, United States. MMWR 1986;35:17–21.
2. Centers for Disease Control. Follow-up on Kaposi's sarcoma and pneumocystis pneumonia among homosexual men—New York City and California. MMWR 1981;30:305–8.
3. US Bureau of the Census. Statistical abstracts, United States, 1984;104:31–3.
4. US Department of Health, Education, and Welfare. Study to evaluate the supply-demand relationships for AHF and PTC through 1980. DHEW, publication no. 77-1274.
5. Lee ET. Statistical methods for survival data analysis. Lifetime Learning Publications. Belmont, CA: 1980:75–154.

6. Popovic M, Sarngadharan MG, Read E, et al. Detection, isolation, and continuous production of cytopathic retroviruses (HTLV-III) from patients with AIDS and pre-AIDS. Science 1984;224:497–500.
7. Sarngadharan MG, Popovic M, Bruch L, et al. Antibodies reactive with human T-lymphotropic retrovirus (HTLV-III) in the serum of patients with AIDS. Science 1984;224:506–8.
8. Centers for Disease Control. Antibodies to a retrovirus etiologically associated with acquired immunodeficiency syndrome (AIDS) in populations with increased incidence of the syndrome. MMWR 1984;33:377–9.
9. CDC Task Force on Kaposi's sarcoma and opportunistic infections. Epidemiologic aspects of the current outbreak of Kaposi's sarcoma and opportunistic infections. N Engl J Med 1982;31:365–7.
10. Fauci AS. The syndrome of Kaposi's sarcoma and opportunistic infections: an epidemiologically restricted disorder of immunoregulation. Ann Intern Med 1982;96:777–9.
11. Centers for Disease Control. Pneumocystis carinii pneumonia among persons with hemophilia A. MMWR 1982;31:365–7.
12. Centers for Disease Control. A cluster of Kaposi's sarcoma and pneumocystis carinii pneumonia among homosexual male residents of Los Angeles and Orange counties, California. MMWR 1982;31:305–7.
13. Evatt BL, Gomperts ED, McDougal JS, et al. Coincidental appearance of LAV/HTLV-III antibodies in hemophiliacs and the onset of the AIDS epidemic. N Engl J Med 1985;312:493–6.
14. Eyster ME, Goedert JJ, Sarngadharan MG, et al. Development and early natural history of HTLV-III antibodies in persons with hemophilia. JAMA 1985;253:2219–23.
15. Ragni MV, Tegtmeier GE, Levy JA, et al. AIDS retrovirus in hemophiliacs treated with factor VIII or factor IX concentrates, cryoprecipitate, or fresh frozen plasma: prevalence, seroconversion rate, and clinical correlations. Blood 1986;67:592–5.
16. Curran JW. The epidemiology and prevention of the acquired immunodeficiency syndrome. Ann Intern Med 1985;103:657–62.
17. Blattner WA, Biggar RJ, Weiss SH, et al. Epidemiology of human T-lymphotropic virus type III and the risk of the acquired immunodeficiency syndrome. Ann Intern Med 1985;103:665–70.
18. Centers for Disease Control. Results of human T-lymphotropic virus type II test kits reported from blood collection centers, United States, April 22–May 19, 1985. MMWR 1985;34:375–6.
19. National Hemophilia Foundation Medical and Scientific Advisory Council recommendations concerning AIDS and therapy of hemophilia (revised October 13, 1984). New York: National Hemophilia Foundation, 1984.
20. Lui KJ, Lawrence DN, Morgan WM, et al. A model-based approach for estimating the mean incubation period of transfusion-associated acquired immunodeficiency syndrome. Proc Natl Acad Sci, USA. 1986;83:3051–5.