Risk of Developing AIDS in HIV-Infected Cohorts of Hemophilic and Homosexual Men

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The latency period and/or incidence of the acquired immunodeficiency syndrome (AIDS) may differ in persons infected with the human immunodeficiency virus by different routes or having different "cofactors." We compared 79 hemophilic men in Pennsylvania and 117 homosexual and bisexual men in California, all having known dates of infection and long postinfection observation periods, to examine these hypotheses. By 1987, twenty-one percent of the hemophilic and 27% of the homosexual men had developed AIDS. However, seroconversion patterns differed for the two groups, and when this was taken into account, the conditional odds ratio for AIDS was 1.20. Kaplan-Meier survival analysis showed no significant difference in the cumulative proportion with AIDS, from time of infection. These results are limited by the small size and geographically localized nature of our study populations, but they suggest that currently the relative length of human immunodeficiency virus infection is of primary importance in comparing disease outcome for different populations.

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IT HAS been suggested that the incidence of the acquired immunodeficiency syndrome (AIDS) may differ among human immunodeficiency virus (HIV)–infected populations and/or among AIDS risk groups,[1-5] for at least three reasons. First, populations might differ in terms of important cofactors, such as HLA type[6-8]; the allelic form of group-specific component[9]; and the presence, absence, nature, or timing of other infections or antigenic exposures that might lead to T-helper cell activation.[2,5,10-14] Second, HIV strain type may differ between persons and between populations. Strain type may be related to HIV disease course and clinical outcome.[5,15-20] Third, exposure characteristics, such as route of exposure; frequency of exposure; presence or absence of noninfective, disrupted virus in the inoculum (inocula); or size of inoculum (inocula), may be related to disease outcome.[1,5,21]

It has also been suggested that the median latency period to AIDS, defined as the time between infection with HIV and date of AIDS diagnosis, may differ from one risk group to another.[22-24] (Latency period to AIDS is often referred to as an "incubation period"; estimates to date have been based largely on transfusion recipients.[25-27]) If latency periods are prolonged and differ among risk groups, it becomes difficult to assess differences in AIDS incidence this early in the HIV epidemic.[5,21-23] Even if latency periods do not differ, a comparison of AIDS incidence must consider the length of time each population has been infected with HIV. Furthermore, the populations in question must have been infected for a number of years, given the years-long AIDS latency period.[5,25-27] Cohorts with information concerning individuals' dates of seroconversion have rarely been followed up for more than a few years.

In this report we compare data from two cohorts exposed to HIV by different routes: hemophilic patients in Pennsylvania and homosexual men in San Francisco. We examine two questions, taking into account length of infection: (1) Does the cumulative incidence of AIDS differ between the two cohorts? (2) What is the quantitative magnitude of the relative incidence of AIDS between these two specific cohorts? To examine these important questions, we make three assumptions about HIV infection in both hemophilic and homosexual men; these assumptions are all strongly supported by HIV literature and research. First, we assume that seroconversion for both hemophilic and homosexual men usually occurs within weeks (rarely up to months but certainly not years) following infection.[28-31] Second, we assume that the latency period for AIDS (the time between HIV infection and the development of AIDS) is long relative to the time between infection and seroconversion.[5,25-27] Thus, any hypothetical differences in times between infection and seroconversion between these groups are not pertinent to our analyses. Third, virtually all individuals with antibody to HIV are infected with this virus.[32]

PATIENTS AND METHODS

Cohorts

These cohorts have been described in detail elsewhere; information concerning them is current as of December 1988.[33-35] Briefly, the hemophilic cohort included 79 of 82 HIV-seropositive men from a hemophilia treatment center in western Pennsylvania from whom serum samples were available annually or biannually between 1977 and 1987. Seroconversion date was considered to be the midpoint between last HIV-seronegative and first HIV-seropositive sample date. One hemophilic man seroconverting in 1983 committed suicide in 1985, permitting only a two-year observation time. These individuals were clinically assessed at least yearly, both prior to HIV seroconversion and thereafter; many showed immune test abnormalities prior to seroconversion.[35]

The homosexual cohort included 117 homosexual or bisexual men from a group of 6702, examined for sexually transmitted diseases at the San Francisco City Clinic between 1978 and 1980 and voluntarily enrolled in studies to assess the prevalence, incidence, and prevention of hepatitis B virus infections.[36,37] None of these individuals were assessed clinically or with immune tests at enrollment. The only criterion for en-

Table 1.—Proportion of HIV-Infected Men Developing AIDS as of 1987, by Risk Group and Year of Infection*

Year of Infection	No. With AIDS/No. Infected (%)	
	Hemophilic	Homosexual
1978	1/3 (33)	2/6 (33)
1979	3/3 (100)	1/11 (9)
1980	0/2 (0)	5/20 (25)
1981	5/24 (21)	17/44 (39)
1982	3/20 (15)	6/25 (24)
1983	3/17 (18)	0/15 (0)
1984	2/8 (25)	1/4 (25)
1985	0/1 (0)	0/0 (. . .)
1986	0/1 (0)	0/2 (0)
1987	0/0 (. . .)	0/0 (. . .)
Total	**17/79 (21)**	**32/117 (27)**

*HIV indicates human immunodeficiency virus; and AIDS, the acquired immunodeficiency syndrome.

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Table 2.—Distribution of Latency Periods for Hemophilic and Homosexual Cohorts Infected With HIV*

Cohort	Latency Period, y†										
	<1	1-<2	2-<3	3-<4	4-<5	5-<6	6-<7	7-<8	8-<9	9-<10	10-<11
Hemophilic											
AIDS (n=17)	0	0	1	6	2	3	4	1	0	0	0
Censored‡ (n=62)	0	0	2	1	5	15	17	18	2	1	1
Homosexual											
AIDS (n=32)	0	2	5	8	5	8	3	1	0	0	0
Censored‡ (n=85)	0	2	0	3	5	19	27	15	10	4	0

*HIV indicates human immunodeficiency virus; and AIDS, the acquired immunodeficiency syndrome.
†$P = .19$ by generalized Wilcoxon rank-sum test.
‡Censored consists of infected men who had not developed AIDS as of 1987 or, for one man, who died of other causes.

Table 3.—Cumulative Proportion With AIDS, by Maximum Number of Months Infected With HIV, for Hemophilic and Homosexual Cohorts*

No. of Months†	% With AIDS (95% CI)	
	Hemophilic	Homosexual
18	0 . . .	0 (. . .)
30	1.0 (0-4)	5.0 (1-9)
42	10.0 (3.5-16.5)	11.0 (5-17)
54	12.0 (5-19)	16.0 (9-23)
66	16.0 (7.5-24.5)	24.0 (16-32)
78	24.0 (13.5-34.5)	30.0 (21-29)
90	27.0 (15-39)	33.0 (23-43)

*AIDS indicates the acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; and CI, confidence interval.
†Based on data from Table 2.

rollment was that hepatitis B virus vaccine trial participants have normal alanine aminotransferase blood levels. These 117 men included (1) 13 selected at random from the entire group; (2) 83 who were hepatitis B virus antibody–negative and were vaccine-trial participants, returned to City Clinic after October 1983, and agreed to be studied for AIDS; and (3) 21 men falling into both groups (1) and (2). These 117 men represented persons who (1) could be located, were contacted, and gave written consent for their samples to be tested for HIV antibody or were known to be dead and (2) had serum samples available to document the date of seroconversion within 12 months. Ninety percent of these San Francisco cohort members were clinically assessed following their AIDS diagnosis or in 1987 or 1988, by San Francisco Department of Health personnel. For the remaining 12 individuals, AIDS cases were identified through (1) name-identified reports to the San Francisco Department of Health, for individuals known to reside in the San Francisco area, and (2) periodic comparisons of all AIDS cases reported to the Centers for Disease Control, matched by soundex codes of surname and dates of birth. Possible matches were confirmed by contacting the cohort member identified as a possible case or, if the patient was dead, by contacting the source of the report.

Laboratory Methods

For both cohorts, IgG antibody to HIV was measured by an enzyme-linked immunosorbent assay technique; positive samples were confirmed by Western blot assay.

Statistical Methods

We compared seroconversion patterns with the χ^2 test of goodness of fit.[38] We compared the overall incidences of AIDS using a one-tailed Fisher's exact test, since postulations published to date have been that hemophilic patients have a lower incidence of or longer latency period for AIDS than do homosexual men (eg, references 4, 5, 22, 23, and 24). We used the generalized Wilcoxon rank-sum test to compare the cumulative incidence of AIDS for the hemophilic and homosexual cohorts.[39,40] To remove the confounding effect of observation time by conditioning on observation time while the participant was infected with HIV, we calculated the conditional maximum likelihood estimate of the odds ratio for developing AIDS through 1987 for the homosexual cohort compared with the hemophilic cohort.[41,42] We also used a Kaplan-Meier survival analysis to compare the cumulative incidence of AIDS.[43]

RESULTS

Seroconversion patterns differed significantly for the two cohorts ($P<.001$). Before 1981, only 10% of the hemophilic cohort, but 32% of the homosexual cohort, were HIV seropositive. Between 1981 and 1983, seventy-seven percent of the hemophilic group and 63% of the homosexual group seroconverted. Between 1984 and 1987, thirteen percent of the hemophilic cohort and 5% of the homosexual cohort seroconverted.

The overall incidence of AIDS did not differ for the two groups (21% for the hemophilic vs 27% for the homosexual, $P=.22$) (Table 1). The overall estimate of the odds ratio as of 1987 was 1.37 (homosexual cohort compared with hemophilic cohort). The cumulative incidence of AIDS did not differ for the two cohorts ($P=.19$) (Table 2). When year of infection and observation time were taken into account, we derived the conditional maximum likelihood estimate of the odds ratios for developing AIDS as of 1987 to be 1.2 (95% confidence interval, 0.5 to 2.6). A Kaplan-Meier survival analysis also revealed no difference in the cumulative incidence of AIDS for the hemophilic and homosexual cohorts, through 90 months of infection (Table 3).

COMMENT

Whether different risk groups are at different risk for developing AIDS is of scientific interest and important for counseling infected persons. Its resolution has implications for our understanding of the natural history of HIV infection and for devising ways to modulate or prevent the disease spectrum it produces. However, it is difficult to compare disease outcomes this early in the AIDS epidemic because of (1) the long latency period for AIDS,[5,25-27] (2) the differing HIV epidemic patterns for various risk groups and for various subpopulations within risk groups,[1,5,23,44,45] (3) the generally unknown or short observation times of infected cohorts that are now being followed up prospectively,[5,46] and (4) the geographically localized or single-risk nature of most cohorts now being followed up. We were fortunate to have data from two cohorts with relatively long observation periods and known times of HIV infection and could thus compare the development of AIDS in these two groups, taking into account the cohort members' observation times since HIV infection. When this important factor was taken into account, we could find no evidence of significant differences in the cumulative incidence of AIDS between the two risk groups, as of 1987. This is not meant to suggest that differences may not be found in the future, but rather that current data do not support assumptions that differences exist.

By May 1988, the cumulative incidence of AIDS for the total (HIV-infected and noninfected) US hemophilic population was four per 100 (Jeannette K. Stehr-Green, MD, oral communication, May 1988), compared with 8% to more than 30% for various cohorts of HIV-infected homosexual men.[5,33] These differences have often been quoted and attributed to the relative absence of sexually transmitted diseases and of ongoing exposure to HIV in hemophilic men, who now receive only donor-screened, virus-inactivated factor concentrate products. However,

this assumption does not take into account that (1) not all hemophilic men are infected with HIV and (2) there are striking differences in the timing and pattern of the US hemophilic population's HIV epidemic, compared with these characteristics for other risk groups.[1,5,33,44]

Our findings must be interpreted cautiously and not extended to all infected hemophilic and homosexual men. Our study populations may have been limited in a number of respects, although recent studies suggest these limitations may be minimal. First, these cohorts were from distinct geographic locations, and their criteria for and techniques of enrollment were entirely different. Second, the homosexual cohort analyzed herein represents only a very small subset of the San Francisco homosexual population. However, this cohort's HIV seroprevalence and sexual practices are similar to those reported from a San Francisco homosexual/bisexual household survey.[47] Also, a recent study using 84 of our study's 117 homosexual men concluded that an estimated 99% of these individuals will eventually develop AIDS.[48] Thus, it is unlikely that our homosexual cohort represents a group of homosexual individuals who are at an exceptionally low risk of AIDS. Third, the incidence of HIV-related disease in the Pennsylvania hemophilic population may currently be greater than that of other US hemophilic populations.[2] However, a recently completed study suggests that this is not the case (Jeannette K. Stehr-Green, MD, J.J. Bruce L. Evatt, MD, et al, unpublished data, 1987).

We cannot determine how these potential limitations might affect the generalizability of these cohorts in regard to their risk groups and thus encourage other researchers who may have similar data to duplicate and expand these analyses. However, these results support that the relative length of HIV infection is of primary importance in determining disease outcome and should be taken into account before conclusions are made or hypotheses raised with the HIV-infected public.

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