

Mortality rates and causes of death among all HIV-positive individuals with hemophilia in Canada over 21 years of follow-up

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Many individuals with hemophilia were infected with human immunodeficiency virus (HIV) in the early 1980s through contaminated blood products. Most also were co-infected with hepatitis C virus (HCV). Deaths among the entire cohort of HIV-positive hemophiliacs in Canada up to 2003 are described. Using registry data, we analyzed Kaplan-Meier survival curves, determined the effect of age at HIV seroconversion on mortality, and described cause-specific proportional mortality patterns over time. Of 2427 Canadians with

hemophilia, 660 (27.2%) were HIV-positive, of whom 406 (61.5%) died. In contrast, 114 (6.5%) deaths occurred in HIV-negative controls. Median age at HIV seroconversion was 20 (range, < 1-67 years), and median survival was 15.0 years (95% confidence interval, 13.6-16.4 years). Younger age at HIV seroconversion was associated with improved survival; however, this finding was not explained by differences in causes of death across age groups. Following the introduction of highly active antiretroviral

therapy, the proportion of deaths due to acquired immune deficiency syndrome has decreased, while the proportion of deaths due to liver disease has increased. There were 1134 HCV-positive individuals, of whom only 444 (39.2%) were also HIV-positive. Liver disease is a growing health concern among many hemophiliacs, not only those who are HIV-positive. (Blood. 2006;108:460-464)

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Introduction

During the early 1980s, many patients with severe hemophilia became infected with human immunodeficiency virus (HIV) through contaminated plasma-derived clotting factors. Soon thereafter, acquired immune deficiency syndrome (AIDS) became the dominant cause of death in this population, increasing multifold the overall death rate. In the mid-1980s, transfusion-transmitted HIV ceased with the introduction of virally inactivated factor concentrates. Thus, individuals who were infected during this time period, mostly between 1982 and 1985, form a unique cohort of HIV-infected patients with a well-defined time of seroconversion.

The rates and causes of death in HIV-infected individuals with hemophilia have been previously documented from other national registries,¹⁻⁷ and data from Canada have been reported up to 1995.^{8,9} The death rate increased steadily during the late 1980s before the introduction of antiretroviral therapy, reached a peak from 1991 to 1993, and then appeared to decrease thereafter.⁹ The major causes of death have been due to AIDS and HIV-related complications, and liver failure and hepatoma as a result of co-infection with hepatitis C (HCV).

The objectives of the current study were to update survival trends among HIV-positive individuals with hemophilia in Canada up to December 2003 and to describe the causes of death among this cohort. We examined the relative contribution of liver disease

to the overall mortality and the relationship between age at time of HIV seroconversion and death.

Patients, materials, and methods

The Canadian Hemophilia Registry

The Canadian Hemophilia Registry (CHR)¹⁰ is a registry of all individuals with hereditary bleeding disorders in Canada and, with permission from the Association of Hemophilia Clinic Directors of Canada, was used as the source of data for this study. Every individual with hemophilia is registered in 1 of the 24 Canadian Hemophilia Treatment Centres (HTCs), which coordinates the care and provision of factor concentrates for these individuals. Health status and demographic data obtained by the HTC on all individuals with hemophilia are recorded and maintained in the CHR. Data are both anonymous and confidential. The registry data are kept on a secure server at McMaster University in Hamilton, ON, and approval for this study and for all registry procedures was obtained from the institutional research ethics board of Hamilton Health Sciences. Access to the data is available only with permission from the director of the registry and the developer. HTCs have been providing data prospectively to the CHR since the formation of the registry in 1989, and at that time HTCs also provided retrospective data back to 1980. Data are updated regularly and reconciled annually against current HTC census and demographic data. The registry has been validated and has been shown to represent the entire Canadian hemophilia population.¹¹ Individuals with severe hemophilia had factor

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A complete list of the members of the Association of Hemophilia Clinic Directors of Canada (AHCDC) appears in "Appendix."

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levels less than 1% of normal; moderate, between 1% and 5%; and mild, between 5% and 35%.

Period of follow-up: 1982 to 2003

The beginning of the observation period was pragmatically set to 1982 to represent the start of HIV infection in all patients, although the exact date of HIV transmission was not known in all cases. This time period is consistent with the first descriptions of AIDS in individuals with hemophilia in both the United States and Canada¹²⁻¹⁵ and with the rapid rise in the prevalence of HIV seropositivity among individuals with severe hemophilia.¹⁶ In 1985, viral inactivation of blood products was introduced, marking the end of the period during which individuals were infected by blood products. This study was conducted in 2004 after all 24 HTCs had reconciled data to December 2003, the end of the follow-up period.

HIV-negative controls

A cohort of HIV-seronegative individuals with hemophilia also was examined, consisting of all patients in the database with dates of birth in the same range as the HIV-infected patients (between October 1915 and May 1985).

Case definitions

The cause of death was attributable to AIDS when opportunistic infection or other AIDS-defining illness was present. Deaths due to infections excluded opportunistic or other AIDS-defining infections.

Statistical analysis

Overall survival was estimated and summarized using Kaplan-Meier methods. Tests comparing survival between groups defined by their age at the time of seroconversion (ie, < 16, 16-24, 25-34, > 34) were conducted using a log-rank test. The latest of either January 1, 1980 or the date of birth was used as each patient's entry date. The exit date was either the date of death or the end of the follow-up period (December 31, 2003), whichever occurred first. All deaths occurring between 1982 and 2003 were included. Since only the year of death was collected in the CHR, the month and day were imputed as June 30. For categorical data, exact permutation tests for association were used, and for trends over age groups, the Kruskal-Wallis test was used. For cause-specific proportional mortality patterns over calendar time, logistic regression was employed. All tests were 2-sided, and the significance level was set at 1%. SAS version 9.1 (SAS Institute; Cary, NC) and StatXact version 6.3 (Cytel Software; Boston, MA) were used for the statistical analysis.

Results

Characteristics of individuals with hemophilia in Canada

The CHR received data on 3307 males with hemophilia, including 2721 (82.3%) with hemophilia A and 586 (17.7%) with hemophilia B. Of all subjects, 1111 (33.6%) had severe, 546 (16.5%) had moderate, and 1635 (49.4%) had mild factor deficiency. In 15 cases (0.5%), hemophilia severity was unknown. Of the 3307 subjects, 540 (16.3%) had died and 172 (5.2%), mostly with mild hemophilia, were lost to follow-up. At the time of analysis, inhibitors to factor VIII or factor IX were present in 114 (prevalence, 3.4%), representing 7.7% of all individuals with severe hemophilia and 9.0% of individuals with severe factor VIII deficiency. There were 663 subjects (20.0%), living and deceased, infected with HIV, most (70.9%) of whom had severe hemophilia. Three HIV-seropositive individuals were excluded because they were infected before immigrating to Canada. Of 660 HIV-positive subjects, 622 (94.2%) had hemophilia A, and 38 (5.8%) had hemophilia B. Of the 458 HIV-positive subjects tested for HCV,

442 (96.5%) were positive. Overall, the follow-up of the HIV-positive cohort was 99.5%.

Comparison of HIV-negative and HIV-positive cohorts

A number of important characteristics of HIV-positive individuals (n = 660) differed significantly from those in the HIV-negative comparison group (n = 1767) as shown in Table 1. Only median age and the proportion with inhibitors were similar. Compared with HIV-negative controls, a higher proportion of HIV-positive individuals died during the follow-up period (61.5% vs 6.5%, $P < .001$); had hemophilia A (94.2% vs 78.3%, $P < .001$); had severe hemophilia (71.2% vs 15.6%, $P < .001$) and were co-infected with HCV (67.3% vs 36.1%, $P < .001$). Overall, 1801 (74.2%) HIV-positive and HIV-negative individuals were tested for HCV.

Overall survival and causes of death

Median survival of the HIV-positive group was 15.0 years (95% confidence interval, CI: 13.6-16.4), while the median survival for the HIV-negative group has not been reached (> 20 years), as shown in Figure 1. Total deaths and deaths due to liver disease (per 100 person-years) among HIV-positive individuals are shown in Figure 2. The overall death rate increased steadily from 0 (95% CI: 0-0.5) in 1982 to 12.4 (95% CI: 9.8-15.6) in 1993, and then declined, reaching a plateau of 3 to 4 deaths per 100 person-years from 1998 on. In a logistic regression model, the proportional odds of hepatic deaths increased by 13% per year ($P < .001$). Causes of death among HIV-positive individuals are summarized in Table 2. The most common primary cause of death was AIDS (283; 69.7%), followed by liver failure (47; 11.6%), bleeding (18; 4.4%), and non-AIDS-defining infections (17; 4.2%). There were 10 suicides (2.4%) in this cohort. Twenty-seven additional patients had liver disease listed as a secondary or contributing cause of death; thus, liver disease was the primary or contributory cause of death in 74 (18.2%) individuals. When separated into 2 follow-up periods, before (1982-1997) and after (1998-2003) the adoption of highly

Table 1. Characteristics of all HIV-positive individuals and HIV-negative controls from the Canadian Hemophilia Registry (1982-2003)

Characteristic	HIV-positive	HIV-negative	P
No.	660	1767	
Median age, y (range)	18 (< 1-64)	17 (< 1-64)	.9
Patient status, no. (%)			< .001
Active	249 (37.3)	1513 (85.6)	
Deceased	406 (61.5)	114 (6.5)	
Left Canada	2 (0.3)	28 (1.6)	
Lost to follow-up	3 (0.5)	112 (6.3)	
Factor deficiency, no. (%)			< .001
Hemophilia type			
Hemophilia A	622 (94.2)	1384 (78.3)	
Hemophilia B	38 (5.8)	383 (21.7)	
Severity			< .001
Mild (5%-35%)	84 (12.7)	1195 (67.6)	
Moderate (1%-5%)	105 (15.9)	287 (16.3)	
Severe (< 1%)	470 (71.2)	276 (15.6)	
Unknown	1 (0.2)	9 (0.5)	
Inhibitors			.7
Without inhibitors	644 (97.6)	1717 (97.2)	
With inhibitors	16 (2.4)	50 (2.8)	
HCV serostatus, no. (%)			< .001
HCV-positive	444 (67.3)	690 (36.1)	
HCV-negative	16 (2.4)	651 (36.8)	
HCV-unknown	200 (30.3)	426 (24.1)	

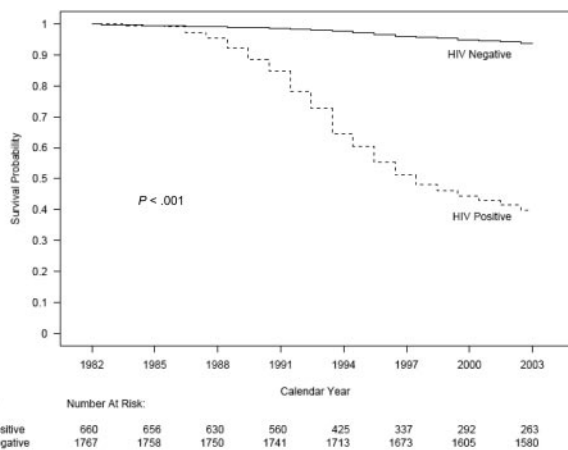


Figure 1. Kaplan-Meier survival curves of HIV-positive (n = 660) and HIV-negative (n = 1767) individuals with hemophilia in Canada (1982-2003).

active antiretroviral therapy (HAART), the distribution of cause-specific deaths were significantly different ($P < .001$). In the post-HAART period, deaths due to liver disease increased, while deaths due to AIDS decreased.

Table 3 compares the causes of death in the HIV-positive and HIV-negative cohorts. The proportion of deaths due to AIDS, liver disease, and infection were higher among HIV-positive individuals; however, deaths from bleeding, cancer, and cardiovascular causes were proportionally higher in the HIV-negative cohort, most likely a result of their low risk of dying from AIDS. Of patients with inhibitors, 27 (41.0%) died, including 16 who were HIV-positive; the causes of death were bleeding (n = 10), AIDS (n = 6), liver failure (n = 3), cardiovascular disease (n = 2), and other (n = 6). Of the 43 patients with bleeding as the primary cause of death, 10 had inhibitors, including one who was HIV-positive.

HCV-positive individuals

There were 1134 HCV-positive individuals, of whom 444 (39.2%) were co-infected with HIV. There were 267 HCV-positive individuals who died, of whom 207 (77.5%) were HIV-positive and 58 (21.7%) were HIV-negative. In 2 (0.8%) patients, HIV status was unknown. Thus, 207 of 444 (46.6%) co-infected individuals died compared with 58 of 712 (8.1%) HCV-positive/HIV-negative individuals. Liver disease was the cause of death in 39 (8.8%) co-infected patients and 8 (1.1%) HCV-positive/HIV-negative patients.

Age at HIV seroconversion

Younger age at the time of HIV seroconversion was a strong predictor of overall survival ($P < .001$, log-rank test) as shown in

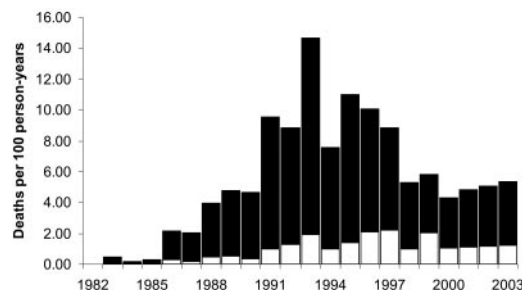


Figure 2. Total deaths and deaths due to liver disease per 100 person-years among all HIV-positive individuals with hemophilia in Canada (1982-2003). Most individuals (96.5% of those tested) were co-infected with hepatitis C. Unshaded areas represent deaths due to liver disease.

Table 2. Frequency (percent) of primary causes of death among all HIV-positive individuals with hemophilia in Canada by year of death before (1982-1997) and after (1998-2003) the adoption of highly active antiretroviral therapy

Cause of death*	Year of death, no. (%)*		
	1982-1997	1998-2003	All
AIDS	256 (74.6)	27 (42.9)	283 (69.7)
Liver disease	30 (8.7)	17 (27.0)	47 (11.6)
Bleeding	12 (3.5)	6 (9.5)	18 (4.4)
Infection	14 (4.1)	3 (4.8)	17 (4.2)
Unknown	5 (1.5)	6 (9.5)	11 (2.7)
Suicide	7 (2.0)	3 (4.8)	10 (2.5)
Accidental	10 (2.9)	0 (0.0)	10 (2.5)
Cancer	4 (1.2)	0 (0.0)	4 (1.0)
Cardiovascular	2 (0.6)	1 (1.6)	3 (0.7)
Other	3 (0.9)	0 (0.0)	3 (0.7)
All causes	343 (100)	63 (100)	406 (100)

*Exact 2-sided test of association, $P < .001$.

Figure 3. Median age at seroconversion was 20 years (range, < 1-67 years). There were 238 subjects (36.1%) under the age of 16; 192 (29.1%) between 16 and 24 years of age; 135 (20.5%) between 25 and 34 years of age; and 95 (14.4%) older than 34 years of age at the time of seroconversion. Causes of death for the entire cohort and by age at seroconversion are summarized in Table 4. The distribution of cause-specific deaths differed marginally over the age groups but was not statistically significant ($P = .038$). While the proportion of deaths due to liver disease seemed to increase with age, this trend also was not statistically significant ($P = .22$).

Discussion

This cohort, with a well-defined time of seroconversion, offers a unique opportunity to study survival trends among HIV and HCV co-infected individuals through a period of time when treatment for HIV infection evolved from observation, to single-agent therapy, to treatment combinations with HAART.

The death rate among HIV-infected individuals with hemophilia in Canada reached a peak in 1993 and then subsequently declined

Table 3. Comparison of primary causes of death among HIV-positive and HIV-negative individuals with hemophilia in Canada (1982-2003)

Cause of death	HIV-positive, no. (%)	HIV-negative, no. (%)
AIDS	283 (69.7)	2 (1.8)*
Liver disease†	47 (11.6)	13 (11.4)
Bleeding‡	18 (4.4)	25 (21.9)
Infection	17 (4.2)	4 (3.5)
Unknown	11 (2.7)	13 (11.4)
Suicide	10 (2.5)	4 (3.5)
Accidental	10 (2.5)	10 (8.8)
Cancer	4 (1.0)	14 (12.3)
Cardiovascular	3 (0.7)	20 (17.5)
Other	3 (0.7)	9 (7.9)
All causes	406 (100)	114 (100)

There were 660 HIV-positive and 1767 HIV-negative individuals, exact 2-sided test of association, $P < .001$.

*Two patients died with AIDS-defining illness before the availability of HIV testing.
 †Four patients in the HIV-positive group, and 3 in the HIV-negative group had hepatoma.

‡Ten bleeding deaths were in patients with inhibitors.

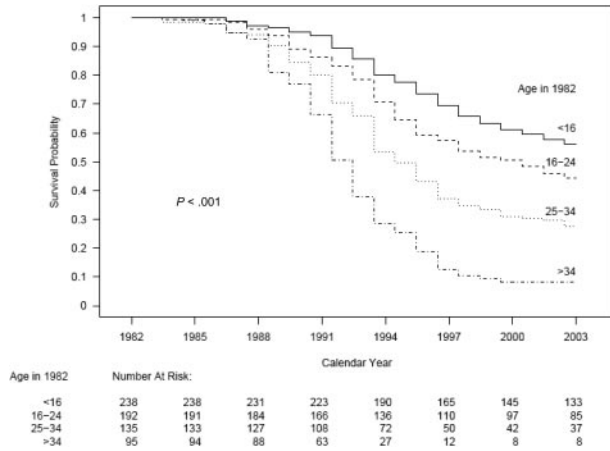


Figure 3. Kaplan-Meier survival curves of all HIV-positive individuals (n = 660) with hemophilia in Canada (1982-2003). Shown is the probability of survival over time by age at time of seroconversion (in 1982).

following the introduction of effective antiretroviral therapy. The death rate began to plateau as of 1999, albeit at a rate higher than in the pre-HIV era. This excess mortality was due largely to the relative increase in the number of non-AIDS-related deaths, in particular, deaths due to liver disease.

Recent data from other national hemophilia registries have shown a similar increase in the proportion of deaths due to liver disease and other non-AIDS-related deaths.^{4,6} Our cohort, with more than 21 years of follow-up, lends support to the importance of liver disease as an ongoing cause of morbidity and mortality in this cohort of HIV and HCV co-infected individuals with hemophilia. With the introduction of HAART in Canada between 1995 and 1997,¹⁷ overall mortality and deaths due to AIDS has decreased,^{18,19} while deaths due to liver disease have increased. Liver disease may soon dominate as the most important cause of death among HIV-positive patients with hemophilia. Moreover, HCV-induced liver disease has been shown to progress more rapidly in HIV-infected individuals, even with effective antiretroviral therapy.²⁰⁻²³ The reasons for this synergy remain poorly understood; however, the impact of social barriers to effective treatments, toxicities of therapies, and delayed immune reconstitution²⁴ require further investigation. The relative increase in deaths due to

liver disease, and the likelihood that this trend will be maintained or even increase over time, makes it imperative that treatment of HCV be considered in all cases. Our data suggest that liver disease is becoming a health priority for all hemophiliacs with HCV, not only those who are HIV-positive. This is mainly because the proportion of patients with HCV infection who are HIV-negative has increased (since many HIV-positive individuals have died) to 72%, and they have survived long enough for liver disease to progress, even if at a slower pace than in HIV-positive individuals.

We found that younger age at HIV seroconversion was associated with improved survival. The disease-attenuating effect of age has been demonstrated previously in a cohort study of HIV-positive subjects who were infected before the widespread use of HAART²⁵ and is consistent with findings from other studies of individuals with hemophilia and transfusion recipients.²⁶⁻²⁹ In fact, in a meta-analysis of individual patient data from 38 HIV cohort studies, the effect of age on disease progression was noted to be even more pronounced among individuals with hemophilia compared with other exposure categories.²⁵ The authors hypothesized that the age effect was likely the result of HCV co-infection and liver-related deaths; however, we were unable to show a significant difference in the distribution of deaths by cause (including liver disease) across age categories at the time of seroconversion. We speculate that poor immune reconstitution and attenuated response to HAART in older individuals may contribute to the disease modifying effect of age,³⁰ although the precise mechanism has not yet been fully explained.

A limitation of this study is that patients sometimes died at a distance from the clinic while under the care of another physician. Attempts to secure death certificates or hospital discharge summaries were unsuccessful in some cases, and the cause of death had to be determined from background clinical history together with verbal information obtained from the treating physician. Another limitation was the HIV-negative cohort used as a control group in this study. We compared the death rate and causes of death of HIV-positive hemophiliacs with a cohort of HIV-negative hemophiliacs born in the same era (before 1985); however, these groups were not matched for the type and severity of hemophilia and the frequency of HCV-positivity.

HIV-positive individuals with hemophilia in Canada have been followed through the entire period of the HIV epidemic, receiving

Table 4. Frequency (percent) of deaths and causes of death among all HIV-positive individuals with hemophilia in Canada (1982-2003) by age at time of HIV seroconversion (in 1982)

	Age at seroconversion				All	P
	Under 16 y	16-24 y	25-34 y	More than 34 y		
No.	238	192	135	95	660	
Alive, no. (%)	131 (55.0)	81 (42.2)	34 (25.2)	8 (8.4)	254 (38.5)	< .001*
Dead, no. (%)	107 (45.0)	111 (57.8)	101 (74.8)	87 (91.6)	406 (61.5)	
Primary cause of death, no. (% of all deaths)						.038†
AIDS	80 (74.8)	79 (71.2)	64 (63.4)	60 (69.0)	283 (69.7)	
Liver disease	8 (7.5)	10 (9.0)	17 (16.8)	12 (13.8)	47 (11.6)	
Bleeding	4 (3.7)	6 (5.4)	6 (5.9)	2 (2.3)	18 (4.4)	
Infection	4 (3.7)	1 (0.9)	7 (7.0)	5 (5.8)	17 (4.2)	
Unknown	4 (3.7)	5 (4.5)	2 (2.0)	0 (0.0)	11 (2.7)	
Suicide	5 (4.7)	4 (3.6)	1 (1.0)	0 (0.0)	10 (2.5)	
Accidental	1 (0.9)	5 (4.5)	1 (1.0)	3 (3.5)	10 (2.5)	
Cancer	0 (0.0)	0 (0.0)	1 (1.0)	3 (3.5)	4 (1.0)	
Cardiovascular	0 (0.0)	1 (0.9)	1 (1.0)	1 (1.2)	3 (0.7)	
Other	1 (0.9)	0 (0.0)	1 (1.0)	1 (1.2)	3 (0.7)	

*Exact 2-sided test for trend over age groups of the proportion who died.

†Exact 2-sided test of association.

whatever optimal therapy was available, from no specific therapy in the early 1980s, to single-agent therapy, to combination HAART. Despite the lack of modern therapy for much of the follow-up period, the high rate of HCV co-infection, and the fact that about 15% of subjects died of causes not directly related to HIV infection, 38.5% of subjects have survived more than 20 years. Continued documentation of survival trends and causes of death among this cohort will provide important natural history data on HIV infection in individuals with hemophilia and help guide the future care of survivors.

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Appendix

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