

## End-stage liver disease in persons with hemophilia and transfusion-associated infections

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Many persons with hemophilia were infected with hepatitis C and B viruses (HCV, HBV) and HIV, but the consequences of these transfusion-acquired infections are poorly defined. We estimated the risk of HCV-related end-stage liver disease (ESLD) and the associations of age, HBV, and HIV with that risk. All 1816 HCV-seropositive hemophilic patients at 16 centers were followed for up to 16 years. Of these, 624 were HIV<sup>-</sup> and 1192 were HIV-coinfected; 135 had persistent HBV surface antigenemia, 1374 had resolved HBV infection, and 287 were HBV-uninfected. ESLD was defined as bleeding esophageal varices, hepatic encephalopathy, persistent ascites, or death excluding nonhepatic causes of these conditions. Competing risk models were used to estimate the annual hazard rate and cumulative incidence of ESLD. Proportional hazards models were used to estimate relative hazards of ESLD with covariates. ESLD developed in 127 of the HCV/HIV-coinfected participants, with an estimated 16-year cumulative incidence of 14.0% (95% confidence interval [CI], 11.6%-16.4%). Without HIV, 10 HCV-infected participants developed ESLD, for a significantly lower cumulative incidence of 2.6% (95% CI, 1.0%-4.3%,  $P < .0001$ ). ESLD risk increased steeply with

age in both groups. With HIV, ESLD risk was increased 8.1-fold (95% CI, 1.9-35.2) with HBV surface antigenemia, 2.1-fold (95% CI, 1.3-3.3) with fewer than  $0.2 \times 10^9/L$  ( $200/\mu L$ ) CD4<sup>+</sup> lymphocytes, and 1.04-fold (95% CI, 1.03-1.06) per year of age. Thus, HIV is associated with a markedly increased risk of HCV-related ESLD for persons with hemophilia, particularly with HBV infection, low CD4<sup>+</sup> lymphocytes, or older age. (Blood. 2002;100:1584-1589)

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### Introduction

Hepatitis C virus (HCV), a single-stranded RNA virus of the Flaviviridae family, was discovered in 1989 and subsequently shown to account for most cases of non-A, non-B posttransfusion hepatitis.<sup>1,2</sup> Approximately 80% of patients with acute disease develop persistent HCV infection, manifested as detectable viremia.<sup>3</sup> With chronic hepatitis C for 20 years, up to 20% develop cirrhosis.<sup>4,5</sup> Once cirrhosis is established, hepatocellular carcinoma develops at a rate of 1% to 4% per year.<sup>6-8</sup>

Most persons with hemophilia acquired HCV infection from intravenous infusions of contaminated clotting factor concentrates that were widely available from the early 1970s to the mid 1980s.<sup>9-13</sup> HCV seroprevalence rates approach 100% among those who received frequent infusions of plasma-derived factor VIII or factor IX concentrates. Virally inactivated concentrates were phased in during the mid 1980s and completely by 1987. Between 1978 and 1986, two thirds of the HCV-infected patients in the United States were also infected with HIV.<sup>10-12</sup>

Thus, the likelihood of liver disease is high among persons with hemophilia. Liver biopsies, however, are not performed routinely, because of the risk of hemorrhage and the expense of prophylaxis with large doses of clotting factors. More than 15 years ago, of 115 hemophiliacs who underwent liver biopsy for clinical indications, 18 (16%) were found to have cirrhosis and an additional 10 (9%) had severe chronic active hepatitis.<sup>14</sup> Now, supported by liver histology in nonhemophilic coinfecting patients,<sup>15</sup> hemophilic patients who are coinfecting with HCV and HIV are developing a clinical picture of end-stage liver disease (ESLD) manifested by persistent ascites, bleeding esophageal varices, or hepatic encephalopathy.<sup>11,16-19</sup> Because the natural history of HCV/HIV coinfection is still uncertain, we sought to quantify the effects of immunodeficiency, age, and hepatitis B virus (HBV) on ESLD among participants in the Multicenter Hemophilia Cohort Study (MHCS) using data collected before the widespread use of highly active antiretroviral therapy.

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## Materials and methods

### Study design and participants

The MHCS was established in the mid 1980s as a prospective cohort study of risk factors for AIDS and related conditions among all registered patients with hemophilia and other coagulation disorders at 12 comprehensive hemophilia centers in the United States and 4 in Europe.<sup>20</sup> The study was reviewed and approved by the appropriate institutional review boards. Signed informed consent was obtained from each participant, parent, or guardian, and signed assent was obtained from competent minor participants. As soon as the study was approved and implemented at a center, and at approximately annual routine clinic visits, each participant underwent a standardized physical examination, medical record review, and phlebotomy. Median enrollment date was March 1, 1985 (interquartile range [IQR] October 21, 1981–April 30, 1987), for participants later found to have HCV infection.

### Laboratory methods

HIV status was defined by antibody testing in a central laboratory.<sup>20</sup> HCV antibody status was determined with a commercially available second- or third-generation enzyme immunoassay, with most of the reactive samples confirmed by recombinant immunoblot assay (HCV RIBA2.0 or 3.0, Chiron, Emeryville, CA). CD4<sup>+</sup> and CD8<sup>+</sup> lymphocyte counts were determined centrally or locally by standard methods.<sup>20</sup> Hepatitis B status was defined by vaccination history and by serology using commercially available kits. “Chronic” was defined as persistent hepatitis B surface antigenemia for at least 6 months. “Resolved” was defined as detectable hepatitis B antisurface antibodies (with no antecedent hepatitis B vaccination) or anticore antibodies. “Uninfected” was defined as undetectable hepatitis B anticore antibodies or hepatitis B vaccination with negative antecedent hepatitis B serology.

### Outcome measure

ESLD was defined as persistent ascites (n = 97), bleeding esophageal varices (n = 33), hepatic encephalopathy (n = 33), or death (n = 85) excluding nonhepatic causes; 2 or more of these conditions were recorded for 118 of the 137 ESLD cases.

### Statistical methods

The annual hazard rate and cumulative incidence of developing ESLD and of having a nonhepatic death were estimated with follow-up starting from the median MHCS HIV seroconversion date (May 29, 1982) or the participant’s birth date, if later. For those with HIV, starting follow-up on May 29, 1982, versus on each individual’s HIV seroconversion date (imputed by statistical modeling of HIV antibody results on stored sera, type and severity of coagulopathy, and geography<sup>21</sup>), yielded essentially identical results (data not presented).

Smoothed annual cause-specific hazard rates were estimated using spline functions.<sup>22</sup> The cumulative incidence rates of ESLD and nonhepatic death were estimated using competing risk survival methods.<sup>23</sup> Cause-specific hazard rates measure the annual incidence of a condition (ESLD or nonhepatic death) among persons who are still susceptible. The units in this analysis are cases per 100 person years (py). By definition, anyone who is susceptible as of a given time did not have the condition of interest or the competing condition up to that time. In contrast, the cumulative incidence of a condition at a given year (year 16 of follow-up) is the probability that that condition has occurred at any time up to the given year despite the competing risk. Cumulative incidence measures the net impact of a specific condition in a specific population at risk for other conditions.

Gray’s method<sup>24</sup> was used to test for heterogeneity in the cumulative incidence curves by HIV status, HBV status, age, and CD4<sup>+</sup> and CD8<sup>+</sup> lymphocyte counts closest to the start of follow-up. Proportional hazards modeling (PHREG procedure, SAS Institute, Cary, NC) was used to estimate the relative hazard (and 95% confidence interval [CI]) of ESLD by

forced entry of age and other variables; late entry at the date of the CD4<sup>+</sup> count (median of 5.5 years [IQR, 4.2–7.0 years] after HIV seroconversion) was used for models including this variable. Data were censored at the date of last follow-up (median July 10, 1994, IQR March 12, 1991–October 20, 1997) and no later than May 28, 1998 (16 years of follow-up).

## Results

### Patient characteristics and viral prevalence

Typical of the hemophilia population, most of the 2056 MHCS participants were male, white, and had hemophilia A with or without an inhibitor (anti-factor VIII antibody), especially those with HIV infection (Table 1). Overall, 1194 (58%) were seropositive for HCV and HIV (“coinfected”), 624 (30%) were seropositive for HCV but not HIV, 20 (1%) were seropositive for HIV but not HCV, and 218 (11%) were negative for both viruses. Of the 1194 HCV/HIV-coinfected participants, 104 (9%) had chronic HBV surface antigenemia, 987 (83%) had resolved HBV infection, and 91 (8%) were HBV-uninfected (Table 1). Of the 624 with HCV but not HIV, 31 (5%) had chronic HBV surface antigenemia, 389 (62%) had resolved HBV infection, and 196 (31%) were HBV-uninfected. Fewer of the HCV/HIV-coinfected participants had hemophilia B or mild coagulopathy (8% and 10%) than did the participants with HCV but not HIV (20% and 26%, respectively; Table 1).

**Table 1. Characteristics of 2056 participants in the MHCS**

Variable	No. of participants by HCV, HIV status*			
	HCV <sup>+</sup> , HIV <sup>+</sup>	HCV <sup>+</sup> , HIV <sup>-</sup>	HCV <sup>-</sup> , HIV <sup>+</sup>	HCV <sup>-</sup> , HIV <sup>-</sup>
Age, y, median (IQR)	21 (13-30)	18 (4-30)	13 (5-27)	4 (0-21)
Sex (%)				
Male	1185 (99)	600 (96)	20 (100)	189 (87)
Female	9 (1)	24 (4)	0	29 (13)
Race/ethnicity (%)				
White	1006 (84)	488 (78)	15 (75)	188 (86)
Black	108 (9)	87 (14)	5 (25)	15 (7)
Other/missing data	80 (7)	49 (8)	0	15 (7)
Coagulopathy type (%)				
Hemophilia A	916 (77)	340 (54)	12 (60)	111 (51)
Hemophilia A, inhibitor	152 (13)	100 (16)	4 (20)	9 (4)
Hemophilia B	96 (8)	124 (20)	2 (10)	40 (18)
Hemophilia B, inhibitor	5 (< 1)	2 (< 1)	0	2 (1)
Von Willebrand	9 (1)	30 (5)	2 (10)	30 (14)
Von Willebrand, inhibitor	1 (< 1)	2 (< 1)	0	0
Other	6 (1)	13 (2)	0	23 (11)
Missing data	9 (1)	11 (2)	0	2 (1)
Coagulopathy severity (%)				
Severe	979 (82)	344 (55)	14 (70)	57 (26)
Moderate	92 (7)	108 (17)	1 (5)	48 (22)
Mild	114 (10)	161 (26)	5 (25)	111 (51)
Missing data	9 (1)	11 (2)	0	2 (1)
Hepatitis B status (%)				
Chronic (HBs antigenemia)	104 (9)	31 (5)	3 (15)	2 (1)
Resolved	987 (83)	389 (62)	11 (55)	50 (23)
Uninfected/vaccinated	91 (8)†	196 (31)†	6 (30)	165 (76)
Missing data	12 (1)	8 (1)	0	1 (< 1)

HBs antigenemia indicates hepatitis B surface antigenemia.

\*HCV<sup>+</sup> and HIV<sup>+</sup> indicate infection based on detection of specific antibody, as described in “Materials and methods.” HCV<sup>-</sup> and HIV<sup>-</sup> indicate noninfection.

†Includes 7 HCV<sup>+</sup>, HIV<sup>+</sup> participants and 15 HCV<sup>+</sup>, HIV<sup>-</sup> participants who were vaccinated against hepatitis B.

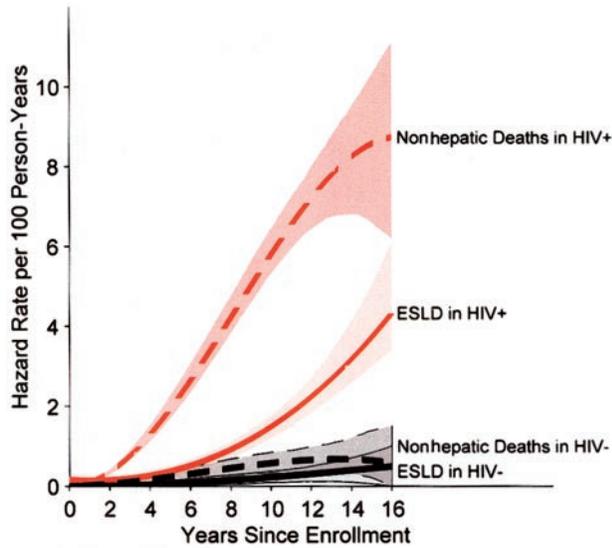


Figure 1. Annual hazard rates of end-stage liver disease (ESLD) and nonhepatic deaths among hepatitis C virus (HCV)-seropositive participants in the MHCS. By HIV status (positive [HIV+] or negative [HIV-]).

**Annual hazard and cumulative incidence of ESLD with HCV, by age and HIV and HBV status**

During a median follow-up of 12.1 years, 137 HCV+ participants developed ESLD, including 10 (1.6%) of the 624 HIV- participants and 127 (10.6%) of the 1194 HIV-positive participants. The ESLD cases included 2 with hepatocellular carcinoma (1 confirmed, 1 suspected). Median ages at the starting date were 28 years (IQR 19-36 years) for the HIV+ ESLD cases and 40.5 years (IQR 29-51 years) for the HIV- ESLD cases, which were substantially older than their respective cohorts (median ages 21 and 18 years, respectively; Table 1). Two of the HIV+ ESLD cases occurred prior to the starting date and were excluded, leaving 1192 HIV+ participants for prospective analysis. Seventeen participants (14 HIV+, 3 HIV-) were treated with interferon- $\alpha$  before ESLD, as were 14 participants (13 HIV+) who did not develop ESLD. No participant had received ribavirin. Among HIV+ participants, 91 (73%) had received zidovudine before ESLD, as had 661 (62%) of those who did not develop ESLD. Other nucleoside reverse transcriptase inhibitors and cotrimoxazole were used less often, and use of these medications did not readily distinguish ESLD risk from preferential treatment of patients at highest risk for AIDS (data not presented).<sup>25</sup>

As shown in Figure 1, the annual hazard of ESLD among the 1192 HIV+ participants increased over time to a rate of 4 per 100 py. The cumulative incidence of ESLD at year 16 in this group was 14.0% (95% CI, 11.6%-16.4%). The annual hazard of ESLD among the 624 HIV- participants increased more slowly, to a peak rate of 0.5 per 100 py. The cumulative incidence of ESLD for HIV-negatives was 2.6% (95% CI, 1.0%-4.3%) at year 16 ( $P < .0001$ ). To put these rates in context, ESLD among the HIV+ participants was overshadowed by nonhepatic deaths (predominantly due to AIDS), which reached an annual hazard of 9 per 100 py and cumulative incidence of 45.0% (95% CI, 41.6%-48.3%). Nonhepatic deaths (predominantly hemorrhage) among HIV- participants had an annual hazard of approximately 0.5 per 100 py and cumulative incidence of 6.2% (95% CI, 3.6%-8.7%).

The annual hazard rate of ESLD was very high and increased over time for the oldest participants, as shown in Figure 2A for the HIV+ participants. The cumulative incidence was 23.3% (95% CI,

17.2%-29.5%) among the HIV+ participants who enrolled after age 32, compared with 9.7% to 15.9% in the middle-age quintiles and 5% in the youngest quintile ( $P_{\text{trend}} < .0001$ ). Among the HIV- participants, 7 of the 10 ESLD cases occurred in the oldest quintile (cumulative incidence 7.8% vs 1.2% among all younger participants,  $P = .0003$ ). Available data were insufficient to distinguish whether the association was related to older age at HCV infection, longer duration of infection, or both.

By proportional hazards modeling (Table 2), ESLD risk was greatly increased with HIV coinfection (relative hazard 7.9 [95% CI, 4.2-15.2]) and older age (relative hazard 1.6 [95% CI, 1.0-2.5] for ages 17 to 32; relative hazard 5.0 [95% CI, 3.2-7.9] after

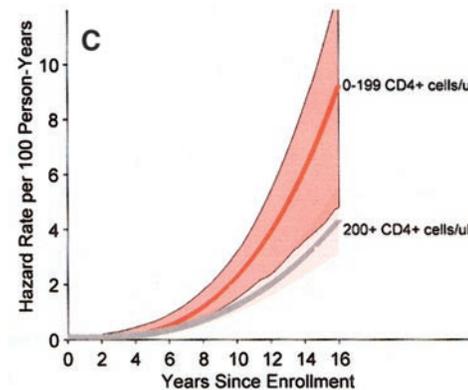
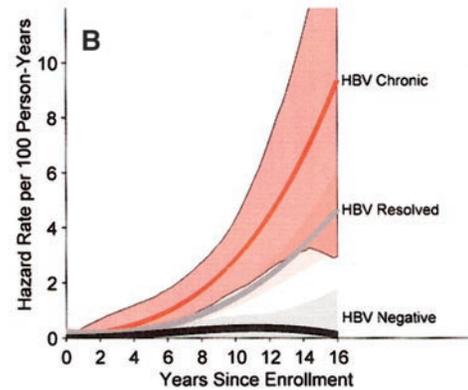
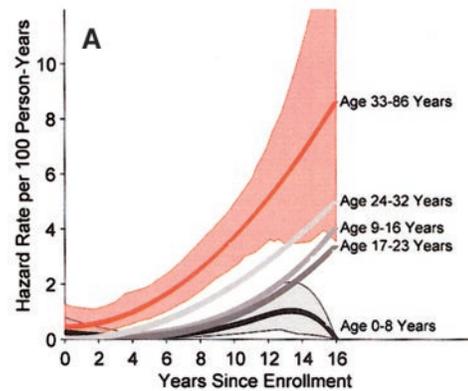


Figure 2. Annual hazard rates of end-stage liver disease (ESLD) among hepatitis C virus (HCV)- and HIV-seropositive participants with complete data in the MHCS. By age group ([A] n = 1192), hepatitis B virus (HBV) status ([B] n = 1180), and CD4+ lymphocyte count ([C] n = 1049).

age 32). Risk increased with older age in both HIV<sup>-</sup> and HIV<sup>+</sup> participants (Table 2).

With HIV coinfection, the annual hazard of ESLD increased over time for participants with chronic HBV surface antigenemia or with resolved HBV infection but not for the HBV<sup>-</sup> participants (Figure 2B). With HIV, cumulative incidence rates of ESLD were 30.1% (95% CI, 15.3%-44.8%) with chronic HBV antigenemia, 13.8% (95% CI, 11.1%-16.4%) with resolved HBV infection, and 2.7% (95% CI, 0-6.5%) with no HBV infection. Without HIV, cumulative incidence of ESLD was increased, but not significantly, with chronic HBV antigenemia (6.3% vs 2.3%, *P* = .58).

**Markers of ESLD with HCV and HIV coinfection**

Participants whose CD4<sup>+</sup> lymphocyte counts obtained closest to enrollment were 0.2 × 10<sup>9</sup>/L to 0.499 × 10<sup>9</sup>/L (200-499/μL) and more than 0.5 × 10<sup>9</sup>/L (500 × 10<sup>9</sup>/L) had overlapping ESLD hazard rates (data not shown). Combining these 2 groups, ESLD hazard rates increased steadily during follow-up, especially for those with CD4<sup>+</sup> lymphocyte counts below 0.2 × 10<sup>9</sup>/L (200/μL) (Figure 2C). Although hazard rates differed between these 2 CD4 count groups, they both had an ESLD cumulative incidence rate of 13% (*P* = .76). CD8<sup>+</sup> lymphocyte count was not associated with the rate of ESLD (*P* = .60, data not presented).

Multivariate proportional hazards modeling was used to determine the independent relationships of age, HBV status, and baseline CD4<sup>+</sup> lymphocyte count to ESLD risk among coinfecting participants. In the final model (Table 3), ESLD risk was increased 1.04-fold (95% CI, 1.03-1.06) per year of age, 8.1-fold (95% CI, 1.9-35.2) with chronic HBV, 3.4-fold (95% CI, 0.8-14.0) with resolved HBV, and 2.1-fold (95% CI, 1.3-3.3) with fewer than 0.2 × 10<sup>9</sup>/L (200/μL) CD4<sup>+</sup> lymphocytes. With the same variables but changing the HBV referent group, ESLD risk was 2.4-fold (95% CI, 1.50-3.94) higher with chronic compared with resolved HBV.

**Table 2. Relative hazard of ESLD during 16 years of follow-up of all participants with hepatitis C virus (HCV) infection in the MHCs**

Variable	No. of participants	ESLD cases (%)	Relative hazard (95% CI)*
All HCV <sup>+</sup> (n = 1816, with 135 ESLD cases)			
HIV <sup>-</sup>	624	10 (1.6)	1.0 (Referent)
HIV <sup>+</sup>	1192	125 (10.5)	7.9 (4.2-15.2)
Age 0-16 y	718	29 (4.0)	1.0 (Referent)
Age 17-32 y	728	52 (7.1)	1.6 (1.0-2.5)
Age 33-86 y	370	54 (14.6)	5.0 (3.2-7.9)
HCV <sup>+</sup> , HIV <sup>-</sup> (n = 624, with 10 ESLD cases)			
Age 0-16 y	297	1 (0.3)	1.0 (Referent)
Age 17-32 y	194	2 (1.0)	3.5 (0.3-38.7)
Age 33-86 y	133	7 (5.3)	17.7 (2.2-143.6)
HCV <sup>+</sup> , HIV <sup>+</sup> (n = 1192, with 125 ESLD cases)			
Age 0-16 y	421	28 (6.7)	1.0 (Referent)
Age 17-32 y	534	50 (9.4)	1.5 (0.96-2.4)
Age 33-86 y	237	47 (19.8)	4.6 (2.9-7.3)

All of the age categories refer to age at the start of analysis (time = 0 at May 29, 1982, or birth date [age 0], if later).

\*Relative hazards for HIV and age are adjusted for each other in the "all HCV<sup>+</sup>" model. The lower 2 models ("HIV<sup>-</sup>" and "HIV<sup>+</sup>") included only the age categories.

**Table 3. Relative hazard of ESLD during 16 years of follow-up of hemophilia patients infected with HIV and HCV and with known CD4<sup>+</sup> lymphocyte counts and hepatitis B status**

Variable	No. of participants	ESLD cases (%)	Relative hazard (95% CI)*
Age at CD4 testing			
1045			
105 (10.0)			
1.04 (1.03-1.06)			
Hepatitis B status			
Chronic antigenemia†			
92			
19 (20.7)			
8.1 (1.9-35.2)			
Resolved infection†			
883			
84 (9.5)			
3.4 (0.8-14.0)			
Uninfected/vaccinated†			
70			
2 (2.9)			
1.0 (Referent)			
CD4 <sup>+</sup> lymphocyte count			
0 to 0.199 × 10 <sup>9</sup> /L			
207			
23 (11.1)			
2.1 (1.3-3.3)			
0.2 to 0.499 × 10 <sup>9</sup> /L			
460			
50 (10.9)			
1.0 (Referent)			
0.5 to 2.195 × 10 <sup>9</sup> /L			
378			
32 (8.5)			
1.0 (Referent)			
CD8 <sup>+</sup> lymphocyte count			
0.012 to 0.499 × 10 <sup>9</sup> /L			
346			
38 (11.0)			
Not included			
0.5 to 0.899 × 10 <sup>9</sup> /L			
419			
36 (8.5)			
Not included			
0.9 to 5.403 × 10 <sup>9</sup> /L			
280			
31 (11.1)			
Not included			

\*Relative hazard and 95% CI from proportional hazards model, adjusted for age, hepatitis B status, and CD4<sup>+</sup> lymphocyte count. Each participant entered the model at the date of the CD4<sup>+</sup> lymphocyte count.

†Hepatitis B status defined by serology and vaccination history: Chronic participants had persistent hepatitis B surface antigenemia for at least 6 months; resolved had detectable hepatitis B anticore antibodies or antisurface antibodies with no antecedent hepatitis B vaccination; uninfected had undetectable hepatitis B anticore antibodies or hepatitis B vaccination with negative antecedent hepatitis B serology.

**Discussion**

Fifty-eight percent of our participants were HCV/HIV-coinfecting, and an additional 30% were infected with HCV without HIV. We used competing risk survival methods to estimate the instantaneous rate and the cumulative incidence, which is the net effect, of ESLD and nonhepatic deaths. Primarily because of AIDS, the coinfecting participants had a high risk of nonhepatic death. Cumulative incidence rates of nonhepatic death and ESLD were 45.0% and 14.0%, respectively, with coinfection; and they were 6.2% and 2.6%, respectively, without HIV.

Irrespective of HIV status, the risk of ESLD increased markedly with older age. For those with coinfection and over age 32, 23.3% developed ESLD during 16 years of follow-up. It is unknown whether this will apply to current patients whose HIV infection is treated with highly active antiretroviral therapy, because most of our participants received no specific therapy or only zidovudine during the first 14 years of follow-up.<sup>26,27</sup> With age adjustment, ESLD risk for the coinfecting participants was increased significantly by 2.4-fold with a CD4<sup>+</sup> lymphocyte count below 0.2 × 10<sup>9</sup>/L (200/μL) and 8-fold with chronic HBV infection. Their risk was increased nonsignificantly by 3.4-fold with resolved HBV infection.

Two cross-sectional studies found increased prevalence rates of resolved or occult HBV infection with cirrhosis or hepatocellular carcinoma,<sup>28,29</sup> supporting the concept that HBV's contribution to the risk of ESLD may be underestimated, especially with subsequent or concurrent HCV infection. Our estimate of the contribution of HBV is imprecise, because we had so few HBV<sup>-</sup> participants for comparison. Nonetheless, the approximately 3- to 8-fold increased risk of ESLD with chronic or resolved HBV infection should be studied further, in younger persons with hemophilia who had the opportunity to be vaccinated against HBV in the early 1980s.

Our study had several limitations. First, because our population is predominantly white and almost entirely male, we could not

study differences by race or sex. Second, because we could not accurately estimate the date of HCV infection for each participant, we could not corroborate the finding of Telfer et al that older age and duration of HCV infection were independently associated with an increased risk of ESLD.<sup>16</sup> Third, we had limited data (not presented) on alcohol use. Reported alcohol use was directly correlated with age. However, because it was substantially less than the 50 g per day reported to increase liver fibrosis,<sup>30</sup> alcohol use is unlikely to account for most of our observed associations with ESLD. Fourth, although we found no consistent association of ESLD with any particular medication (data not presented), our study was poorly suited to assess medication complications.<sup>25</sup> The hepatotoxic potential of medications commonly used in the care of people with HIV and HCV should be investigated further. And, fifth, because routine liver biopsy is seldom performed in patients with hemophilia because of the risk of hemorrhage, we could not estimate the prevalence of compensated cirrhosis or less severe liver pathologies, much less their incidence. The prevalence is certain to be high; 20 years ago, liver biopsy of 115 hemophilic patients revealed that one quarter of the population had cirrhosis or severe chronic active hepatitis.<sup>14</sup> In the current study, during 16 years of follow-up of participants with HCV but not HIV, we observed a 3% cumulative incidence of ESLD, similar to that seen among Irish women and U.S. veterans<sup>31,32</sup> but lower than the cirrhosis rate reported in biopsy studies.<sup>30</sup>

The extraordinary incidence of ESLD among our HCV/HIV-coinfected participants corroborates the mortality experience of

hemophilic men in the United Kingdom.<sup>18,19</sup> These findings point to a profound effect of impaired immunity on the development of HCV-related ESLD. The mechanisms that underlie this relationship are not clear. In studies performed elsewhere, detection of intrahepatic cytotoxic T lymphocytes (CTLs) has been associated with severe liver pathology but relatively low HCV viral load.<sup>33-35</sup> The CD4<sup>+</sup> and CD8<sup>+</sup> lymphocytes that we could measure in peripheral blood may not accurately reflect those that home to the liver.

In summary, in a prospective study that is highly representative of the hemophilia population in the United States,<sup>36</sup> 88% were infected with HCV and two thirds of these were coinfecting with HIV. With 16 years of active follow-up, ESLD developed in 14.0% of the coinfecting participants compared with 2.6% of those with only HCV. With coinfection, ESLD incidence was substantially increased with older age, chronic HBV, or a low CD4<sup>+</sup> lymphocyte count. These observations suggest that HCV-related ESLD is a major cause of morbidity and mortality among people also infected with and untreated for HIV and HBV.

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## Appendix

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