

Comparative Risk of Liver-Related Mortality From Chronic Hepatitis B Versus Chronic Hepatitis C Virus Infection

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Background. It is not known whether chronic hepatitis B (CH-B) or chronic hepatitis C (CH-C) carries a greater risk of liver-related mortality. This study compared rates of liver-related mortality between these 2 groups in the Multicenter AIDS Cohort Study (MACS).

Methods. Six hundred eighty men with CH-B (n = 337) or CH-C (n = 343) at study entry into the MACS were prospectively followed to death, last follow-up visit, or 30 March 2010, whichever came first. Four hundred seventy-two (69.4%) of these men were infected with human immunodeficiency virus type 1 (HIV-1). Causes of death were obtained from death registry matching and death certificates. Liver-related and all-cause mortality rates (MRs) were compared between groups using Poisson regression and adjusted for potential confounders and competing risks.

Results. In 6728 person-years (PYs) of follow-up, there were 293 deaths from all causes (43.5 per 1000 PYs), of which 51 were liver-related (7.6 per 1000 PYs). The all-cause MR was similar between those with CH-B and CH-C; however, the liver-related MR was significantly higher in those with CH-B (9.6 per 1000 PYs; 95% confidence interval [CI], 6.9–13.2) than those with CH-C (5.0 per 1000 PYs; 95% CI, 3.0–8.4). In the HIV-infected subgroup, which had 46 (90.2%) of the liver-related deaths, the liver-related MR remained higher from CH-B after adjusting for potential confounders (incidence rate ratio, 2.2; *P* = .03) and competing risks (subhazard rate ratio, 2.4; *P* = .02). Furthermore, among HIV-infected subjects, CD4 cell counts <200 cells/mm³ were associated with a 16.2-fold (95% CI, 6.1–42.8) increased risk of liver-related death compared with CD4 cell counts >350 cell/mm³.

Conclusions. Chronic hepatitis B carries a higher risk of death from liver disease than does CH-C, especially in HIV-infected men with greater immunosuppression.

Both hepatitis B virus (HBV) and hepatitis C virus (HCV) infect the liver, resulting in chronic infection and increasing the risk for end-stage liver disease and death. Chronic HBV infection (CH-B) affects approximately 375 million individuals worldwide, whereas chronic HCV infection (CH-C) is less prevalent, affecting approximately 175 million individuals [1].

Chronic HBV is the leading cause of end-stage liver disease and hepatocellular carcinoma worldwide, which could be a consequence of its higher prevalence compared with CH-C. Alternatively, CH-B may lead to faster liver disease progression and death.

The host factors that affect liver disease progression in both CH-B and CH-C are similar and include age, human immunodeficiency virus (HIV) disease, alcohol use, and genetic variation [2–9]. Human immunodeficiency virus infection accelerates liver disease progression and increases the risk for liver-related mortality from both CH-B and CH-C [2, 4, 10, 11]. However, to date, neither liver disease progression nor liver-related mortality between CH-B and CH-C has been compared.

Received 30 December 2011; accepted 2 April 2012; electronically published 20 April 2012.

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Clinical Infectious Diseases 2012;55(4):507–13

Published by Oxford University Press on behalf of the Infectious Diseases Society of America 2012.

DOI: 10.1093/cid/cis432

A significant barrier to comparing liver-related mortality between these 2 chronic hepatitis infections is the challenge of findings cohorts with similar host characteristics in which subjects are infected with either HBV or HCV but not both. The Multicenter AIDS Cohort Study (MACS), a large, prospectively followed cohort of men who have sex with men, has equivalent numbers of men chronically infected with either HBV or HCV. Thus, in this study, liver-related mortality rates were compared between MACS men who had either CH-B or CH-C.

METHODS

Study Participants and Laboratory Testing

The MACS has prospectively followed men who have sex with men from 4 metropolitan areas in the United States (Baltimore, Maryland; Chicago, Illinois; Pittsburgh, Pennsylvania; and Los Angeles, California) since 1984. The MACS subjects were initially recruited April 1984–March 1985 and subsequently 1987–1991 and 2001–2003. The men are assessed semi-annually with repeat interviews and laboratory testing [12]. Participants who were HIV type 1 (HIV) seronegative at study entry have HIV-1 enzyme-linked immunosorbent assay testing at semiannual visits, with positive tests confirmed by Western blot [12]. Mortality data were obtained from death certificates retrieved from periodic death registry searches.

This study included men who had either CH-B or CH-C at entry into the MACS. Tests to determine viral hepatitis status were performed on serum stored at -70°C from all MACS men. Hepatitis B surface antigen (HBsAg) was determined by an enzyme immunoassay (Abbott Laboratories). Hepatitis C virus antibody testing was performed with an enzyme immunoassay (ADVIA Centura HCV assay), and HCV RNA was determined with the COBAS AmpliPrep TaqMan HCV Assay. A participant had CH-B if the HBsAg was positive and had CH-C if the HCV antibody and HCV RNA were positive at study entry. Men who were coinfecting with both HBV and HCV or who did not have follow-up were excluded.

Study Design

Men with CH-B or CH-C were followed from study entry to death, last follow-up visit, or 30 March 2010, whichever came first. The primary outcome was liver-related mortality rate (MR). Causes of death were ascertained from death registry matching and death certificates coded per the *International Classification of Diseases, Ninth Revision*. Any cause of death recorded as hepatitis B, hepatitis C, viral hepatitis, chronic hepatitis, chronic liver disease, portal hypertension, liver cirrhosis, liver failure, hepatic coma, hepatorenal syndrome, or liver cancer was included as liver related.

Data on age, race, injection drug use, alcohol use, HIV status, CD4 cell count, highly active antiretroviral therapy (HAART)

use, anti-HBV agent (lamivudine/emtricitabine/tenofovir) use, and anti-HCV therapy (ribavirin and pegylated interferon) use were abstracted for each participant at every visit. Alcohol use was quantified in grams of alcohol consumed per week based on participant response to a questionnaire at each visit. Given the low levels of alcohol use in this cohort, 210 grams per week was defined as heavy alcohol use.

The institutional review boards at each MACS site approved the study, and all participants provided written informed consent for participation in the MACS.

Statistical Analyses

All analyses were performed with Stata version 11.0 (Stata-Corp). The number of person-years (PYs) of follow-up was calculated for each individual. For participants who became HIV-positive during follow-up, the PYs of time accrued before or after HIV seroconversion were classified among the seronegative or seropositive group, respectively. All-cause MRs were calculated for the CH-B and CH-C groups by dividing the number of observed deaths by the PYs of follow-up. Liver-related MRs were calculated similarly. The MRs between the CH-B and CH-C groups were compared based on the Poisson distribution. A multivariable analysis was performed to adjust the incidence rate ratios (IRR) for covariates, including age, race, cumulative alcohol use, CD4 T-cell count, and use of HAART, HBV-active agents, or anti-HCV therapy. All covariates except race were examined as time-varying covariates by partitioning follow-up time into intervals defined according to when these covariates were assessed. Because study participants occasionally missed study visits, time intervals >2 years were censored to ensure validity of the covariates. We also applied this censoring algorithm to follow-up time accrued after a subject's final MACS study visit, which resulted in 5 deaths (1 HCV, 4 HBV) being excluded from the multivariable analysis. A P value $< .05$ was considered significant.

Prior to 1996, few individuals in MACS were on HAART, but by December 1996 and December 1997, 50% and 65% of HIV-infected individuals, respectively, had initiated HAART [13]. Tenofovir disoproxil fumarate (TDF) was approved for use by the US Food and Drug Administration on 26 October 2001. On the basis of these data, the study period was divided into 3 periods in order to assess the effect of HAART and TDF on liver-related mortality: (1) study entry up to 31 December 1996, the pre-HAART era; (2) 1 January 1997 to 31 December 2001, the pre-TDF/early HAART era; and (3) 1 January 2002 to 30 March 2010, the TDF/current HAART era.

Another consideration is the concept of competing risk of death. The idea is that individuals may die of a cause (competing risk) other than the cause of interest. For this study, subjects may die of a non-liver disease death before they have the chance to develop liver disease severe enough to cause a

Table 1. Characteristics of Participants by Hepatitis Status

Variable	Chronic HBV (n = 337)	Chronic HCV (n = 343)
Age in years, mean (SD) ^{a,*}	32.7 (7.4)	38.7 (8.8)
White, No. (%) [*]	260 (77%)	152 (44%)
HIV-1 positive, No. (%) ^b	229 (68%)	243 (71%)
Ever used injection drugs, No. (%) ^{c,*}	36 (11%)	206 (60%)
Alcohol per week, median (IQR) (g) ^d	22 (2–74)	11 (0–74)
Nadir CD4 count in cells/μL, median (IQR) ^e	294 (86–571)	310 (98–612)
Recruited after 2001, No. (%) [*]	37 (11%)	163 (48%)

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; SD, standard deviation.

^a Age at study entry.

^b Includes 43 men who acquired HIV-1 infection during follow up (25 with chronic HBV and 18 with chronic HCV).

^c Before or during study.

^d Median of each person's median weekly alcohol use over course of study (a median of 210 grams per week was defined as heavy alcohol use).

^e CD4 measured in both HIV-1 infected and uninfected individuals.

* $P < .05$.

liver-related death. If, by chance, there are more competing causes in 1 group than the other, the risk of liver-related death can be underestimated in the group with more competing causes of death. This is particularly important for data from the pre-HAART era, during which AIDS deaths precluded the occurrence of many liver-related deaths. To account for competing causes of death, a standard method was used in which parallel competing risk models were fit using the method of Fine and Gray, as implemented in Stata 11 [14].

RESULTS

Of the 6972 men enrolled in the MACS, 757 (10.8%) had CH-B and/or CH-C at study entry. Of these, 77 were excluded

from this study—15 because they were coinfecting with both HBV and HCV and 62 because they did not have any follow-up. Of the remaining 680 men, the distribution of CH-B and CH-C was similar, with 337 in the CH-B group and 343 in the CH-C group. Approximately 70% in both groups were infected with HIV. The CH-B and CH-C groups were similar with respect to alcohol use and nadir and baseline CD4 T-cell count (Table 1). However, HCV-infected individuals were older and more likely to have used injection drugs, and a larger proportion of this group was recruited after 2001. The median follow-up time was 8.5 years (interquartile range (IQR), 5.4–15.9) for the CH-B group and 6.9 years (IQR, 5.1–9.8) for the CH-C group.

These 680 men had 6728 PYs of follow-up during which there were 293 deaths, yielding an all-cause MR of 43.5 per 1000 PYs (Table 2). As expected, the all-cause MRs were significantly higher in individuals infected with HIV (63.1 per 1000 PYs) than in individuals not infected with HIV (8.7 per 1000 PYs) ($P < .001$). There was, however, no significant difference in all-cause MRs between those with CH-B and those with CH-C (41.2 per 1000 PYs and 46.4 per 1000 PYs, respectively; $P = .5$).

Of the 293 deaths, 51 (17%) were attributable to liver-related causes, yielding an overall liver-related MR of 7.6 per 1000 PYs. Interestingly, 46 (90.2%) of these 51 liver-related deaths occurred in individuals coinfecting with HIV (liver-related MR, 10.7 per 1000 PYs vs 2.1 per 1000 PYs in infected and HIV-uninfected individuals, respectively; $P < .001$). In HIV-infected men, the liver-related MR rose from the pre-HAART era to the early HAART era, but it has dropped since 2002 (Figure 1).

The liver-related MR was significantly higher in men with CH-B than in men with CH-C (9.6 per 1000 PYs vs 5.0 per 1000 PYs, respectively; IRR, 1.9; $P = .027$). This finding remained true when stratified by HIV status with IRRs of 2.0 (95% CI, 1.1–3.7) and 3.0 (95% CI, .3–26.5) in HIV-infected and HIV-uninfected men, respectively.

Table 2. Mortality Rates by Cause, Hepatitis Status, and HIV-1 Status

Participant Category	PYs	Liver-Related			All-Cause		
		Deaths	Mortality Rate (per 1000 PYs)	IRR (<i>P</i>)	Deaths	Mortality Rate (per 1000 PYs)	IRR (<i>P</i>)
All	6728	51	7.6		293	43.5	
HIV negative							
HBV	1378	4	2.9	2.9 (.33)	11	8.0	0.8 (.6)
HCV	1039	1	1.0	1	10	9.6	1
HIV positive							
HBV	2379	32	13.4	2.0 (.03)	144	60.5	1.0 (.9)
HCV	1932	14	7.2	1	128	66.3	1

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PY, person-year.

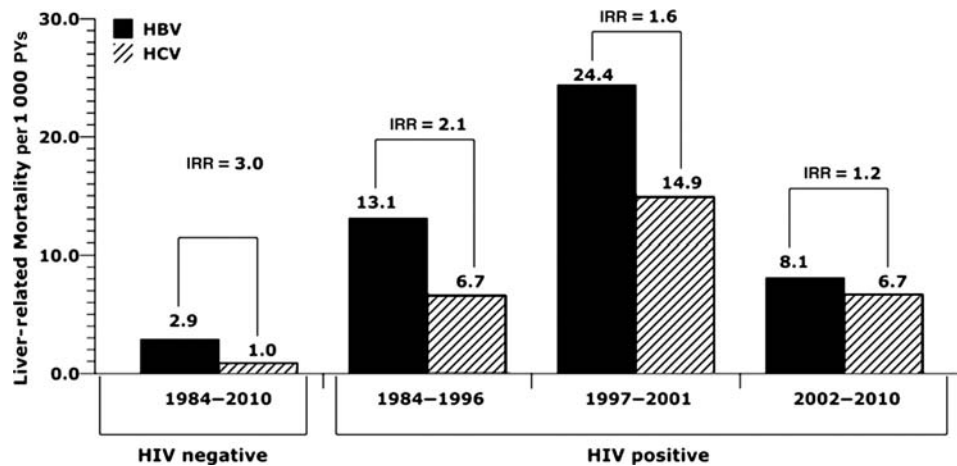


Figure 1. Time trend in liver-related mortality rates by hepatitis and human immunodeficiency virus type 1 status. Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IRR, incidence rate ratio; PY, person-year.

Because nearly all of the liver-related deaths occurred in HIV-infected individuals, the multivariable analyses were restricted to this group. In a multivariable analysis adjusting for factors associated with liver-related mortality, CH-B remained significantly associated with an increased risk (IRR, 2.2; $P = .03$) (Table 3). Notably, more severe immunodeficiency, as represented by lower CD4 cell counts, was

independently associated with an increased risk of liver-related mortality (adjusted IRR of 16.2 and 7.0 for those with CD4 cell counts of <200 and $200-350$ cells/mm³, respectively, compared with CD4 cell counts >350 cells/mm³). Older age was also independently associated with increased liver-related mortality (adjusted IRR per 10 years, 1.6; $P = .01$). When a competing risk model with the same covariates included in the above multivariable model was fit, CH-B remained associated with an increased risk of liver-related death (subhazard rate ratio, 2.4; 95% CI, 1.14–5.04; $P = .02$).

Table 3. Multivariable Analysis of Liver Death in HIV-Infected Individuals

Variable	IRR	95% CI	<i>P</i> Value
Hepatitis status			
HCV	1		
HBV	2.2	1.1–4.5	.03
Older age			
Per 10-year increase	1.6	1.1–2.3	.01
Latest CD 4 count			
>350 cells/mm ³	1		
$200-350$ cells/mm ³	7.0	2.4–20.1	$<.001$
<200 cells/mm ³	16.2	6.1–42.8	$<.001$
HAART			
Never	1		
Ever	0.7	.3–1.6	.43
Recruitment period			
Before 2001	1		
2001–2003	0.8	.2–2.3	.64

Adjusted for race and cumulative alcohol use. Age, CD4 cell count, cumulative alcohol use, and highly active antiretroviral therapy use included as time updated covariates.

Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IRR, incidence rate ratio.

Because some men were treated for HCV, it was possible that the increased risk of death in those with CH-B was due to men with CH-C clearing HCV with treatment. In the sensitivity analysis excluding the 6 men who had treatment-induced HCV clearance, the association of increased risk of liver-related death with CH-B remained (IRR, 2.3; $P = .02$).

To determine if HAART affected the relative liver-related MRs for CH-B vs CH-C, we compared the risk of liver-related mortality over various time periods. Although liver-related MRs were consistently higher in the HIV/HBV coinfecting group than in the HIV/HCV coinfecting group, the comparative risk of liver-related mortality associated with CH-B vs CH-C decreased from an IRR of 2.1 to 1.6 to 1.2 across the 3 consecutive time periods (Figure 1), but this trend was not statistically significant. The lower IRR in the most recent time period is due to a decrease in liver-related MRs in those with CH-B because the HCV-associated liver-related MR was identical in the pre-HAART and the current HAART periods at 6.7 per 1000 PYs. However, in those same periods, the HBV-associated liver-related MR dropped from 13.1 per 1000 PYs to 8.1 per 1000 PYs. Although this decline was not statistically significant, it did show a trend toward a reduction in

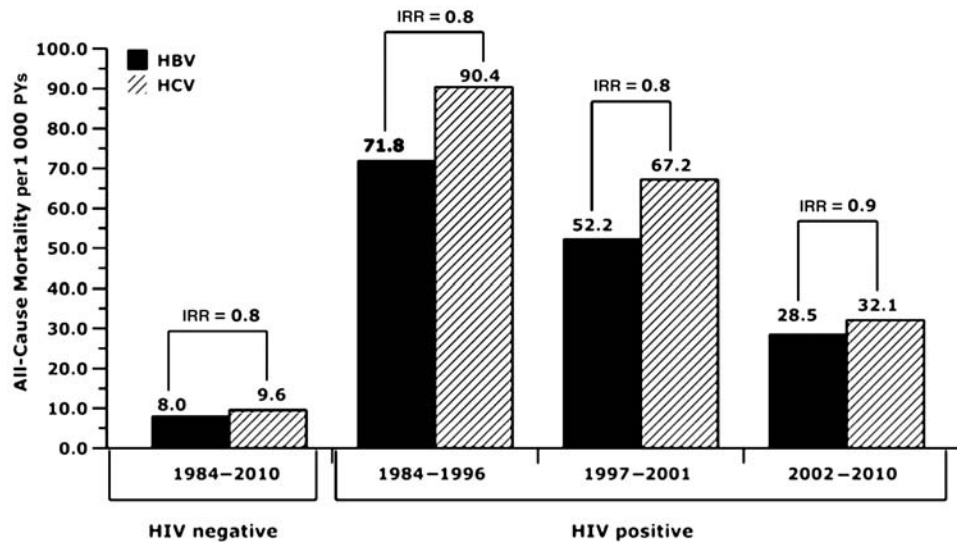


Figure 2. Time trend in all-cause mortality rates by hepatitis and human immunodeficiency virus type 1 status. Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IRR, incidence rate ratio; PY, person-year.

HBV-associated liver-related deaths since the introduction of more effective anti-HBV drugs, such as TDF. In contrast, during these same time periods, all-cause mortality consistently decreased in both HIV-HCV and HIV/HBV coinfecting subgroups (Figure 2). To determine whether TDF accounted for the decline in HBV-associated liver-related MR since 2002, we included TDF use as a time-varying covariate in a multivariable analysis restricted to HBV-infected subjects. There was a reduction in liver-related mortality with TDF use (IRR, 0.6; 95% CI, .16–2.3; $P = .5$); however, it was not statistically significant, likely due to limited power because only 56 subjects had used TDF, with a median use of 1.7 years.

DISCUSSION

This is the first study to clearly demonstrate that the risk of liver-related death is twice as high from CH-B than CH-C in HIV-infected and HIV-uninfected subjects. In the HIV-infected subjects, CH-B remained associated with an increased risk of liver death after accounting for potential confounders, including competing risks of death. Notably, liver-related death was strongly associated with lower CD4 cell counts. Thus, this study emphasizes the need for a more aggressive approach to the prevention, diagnosis, and treatment of CH-B, including increasing vaccination rates among all HBV-susceptible individuals. This is especially true in Asian and African countries where there is a high prevalence of CH-B, HIV infection, and HIV/HBV coinfection.

The biological basis for increased severity of liver disease from CH-B compared with CH-C is not immediately apparent.

It is unlikely to be due to differences in virulence of the 2 viruses because neither virus is cytopathic [15, 16]. Because it is the immune response to both viruses that is presumed to induce hepatocyte damage, it is plausible that HBV leads to a more robust T-cell response or a greater induction of cytokines. It is also plausible that the flares of hepatic inflammation, which are common in patients with CH-B, lead to more liver disease [17].

The finding that liver-related mortality was higher among men coinfecting with HIV was not surprising, but it was notable that men with CD4 T-cell counts <200 cells/mm³ or between 200–350 cells/mm³ had a 16- and 7-fold increased risk of liver death, respectively, compared with men with CD4 cell counts >350 . These data support that in individuals with chronic viral hepatitis, the severity of HIV-related immunosuppression affects the likelihood of liver death, which has been suggested by previous studies [4, 9–11]. These data also support recent trends toward earlier treatment of HIV in HBV-infected subjects [18].

Our finding of an increased risk of liver-related mortality in CH-B was suggested by the Data Collection on Adverse Events of Anti-HIV Drugs study (D:A:D). In this study, of 2482 deaths among 33 308 individuals, the relative risk of liver-related death in those with viral hepatitis compared with those without was 2.37 for subjects with CH-B and 1.67 for those with CH-C [11]. Another study, which compared liver-related mortality in 72 HBV/HIV and 256 HCV/HIV coinfecting individuals receiving care at an HIV/hepatitis clinic, found a similar proportion of deaths from liver disease in the 2 groups (15% of HIV/HBV-coinfecting individuals vs 13% of

HIV/HCV-coinfected individuals) [8]. However, these patients were heterogeneous; thus, the results may have been confounded by increased use of excessive alcohol in the CH-C group compared with the CH-B group (25% vs 13%) and the use of HBV-active agents in the CH-B group. The French Mortality 2000 study, which found liver-related death in 31% of 235 HIV/HCV-coinfected and 22% of 64 HIV/HBV-coinfected individuals, was limited by small numbers of participants with CH-B and lack of adjustment for potential confounding factors, including high rates of excessive alcohol use (62%) in the CH-C group compared with the CH-B group (9%) [7]. In addition, the French study enrolled from clinics throughout France; thus, the HCV- and HBV-infected groups may have been selected from different populations, which was not accounted for. Our study design has clear advantages over these other studies, including a study population that was recruited and prospectively followed in the same manner, with similar numbers of men with CH-B or CH-C, similar rates of alcohol use between groups, and adjustment for potential confounders of liver-related mortality. In addition, this is, to our knowledge, the first study comparing liver-related mortality in CH-B and CH-C groups that accounted for competing causes of death.

Among HIV-1-infected men, the observed increased liver-related MRs after introduction of HAART were present in both HBV- and HCV-infected individuals and are consistent with findings from other cohorts [19, 20]. These increases have been attributed to many factors, including reduction in AIDS-associated mortality, which permitted development of complications from liver disease; increased use of alcohol among HIV-infected persons due to improved health; and hepatotoxicity associated with antiretroviral drugs, which was more frequent in early HAART therapy and is more severe in patients coinfecting with hepatitis viruses [19, 21–23]. Of note, alcohol use is unlikely to have played a significant role in liver-related mortality in our study given low levels of alcohol use in the MACS. The more recent downward trend in liver-related MR in our study is consistent with findings from a hospital cohort in Spain [24] and may be related to improvements in care of HIV, including a reduction in the use of earlier antiretroviral drugs, which were associated with more hepatotoxicity [25]. It is, however, interesting to note that although liver-related MRs dropped in the current HAART era compared with the pre-HAART era in the CH-B group, rates remained similar in the CH-C group. These temporal trends suggest a potential beneficial effect of the use of HBV-active agents as part of HAART in HBV-infected individuals.

There are inherent limitations of this study due to its observational nature. It was not possible to ascertain the onset of HBV or HCV infection; thus, we were unable to directly adjust for duration of hepatitis infection. However, it is

unlikely that our findings are due to longer duration of CH-B because stratification of liver-related mortality by calendar period (Figure 1) revealed an increased risk of liver-related death from CH-B in all time periods, with the largest difference between 1984 and 1996. Second, although the duration of follow-up in this study was longer for the CH-B group, adjustment for age and period of study recruitment should account for some of this difference. Third, HBV DNA levels were not uniformly available and thus were not taken into account when classifying subjects. However, if we classified people with low or undetectable levels of HBV DNA as being CH-B, the actual risk of liver death from CH-B with high levels of replication would be even greater than we report. Similarly, serial, HBsAg, and HCV RNA testing were not uniformly obtained, so some individuals may have recovered from either infection. Individuals are, however, more likely to spontaneously recover from HBV than HCV. Thus, the chances for misclassification of individuals with acute hepatitis as chronic hepatitis are higher for CH-B than for CH-C, so the risk of liver death from CH-B would be even greater than we have reported if there was misclassification. Fourth, this study was in a cohort of men who have sex with men, the majority of whom were infected with HIV. Further studies are needed to determine whether the results are applicable to women, HIV-uninfected individuals, or to men who are infected with HBV or HCV through other routes.

This study clearly demonstrates that CH-B carries a greater risk of death from liver disease than does CH-C. More emphasis needs to be placed on more-effective global HBV screening and increased efforts for vaccination and treatment of HBV infection worldwide.

Notes

Acknowledgments. Data in this manuscript were collected by the Multicenter AIDS Cohort Study (MACS) with centers principal investigators at the Johns Hopkins Bloomberg School of Public Health Joseph B. Margolick, Lisa P. Jacobson; Howard Brown Health Center, Feinberg School of Medicine, Northwestern University, and Cook County Bureau of Health Services (John P. Phair, Steven M. Wolinsky); University of California, Los Angeles (Roger Detels); and University of Pittsburgh (Charles R. Rinaldo).

Financial support. The MACS is funded by the National Institute of Allergy and Infectious Diseases, with additional supplemental funding from the National Cancer Institute (UO1-AI-35042, U11-RR025005 [GCRC], UO1-AI-35043, UO1-AI-35039, UO1-AI-35040, and UO1-AI-35041).

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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