Cirrhosis and Hepatocellular Carcinoma in HIV-Infected Veterans With and Without the Hepatitis C Virus

A Cohort Study, 1992-2001

Thomas P. Giordano, MD, MPH; Jennifer R. Kramer, PhD, MPH; Julianne Souchek, PhD; Peter Richardson, PhD; Hashem B. El-Serag, MD, MPH

Background: Because they develop slowly and infrequently, the incidence and relative risk of cirrhosis and hepatocellular carcinoma (HCC) in patients with the human immunodeficiency virus (HIV) only and in patients coinfected with the hepatitis C virus (HCV) are not known.

Methods: By using national Veterans Health Administration administrative databases, we conducted a retrospective cohort study. Excluding patients with preexisting liver disease, 11,678 HIV-only and 4761 coinfected patients hospitalized between October 1, 1991, and September 30, 2000, were included. Incidence rates and adjusted hazard ratios (HRs) for nonalcoholic cirrhosis and HCC after discharge were calculated through September 30, 2001.

Results: The incidence rates of cirrhosis in the HIV-only and coinfected groups were 1.47 and 15.88 per 1000 person-years, respectively. In a Cox multivariate proportional hazards regression model, coinfected patients had an adjusted HR for cirrhosis of 9.24 compared with HIV-only patients (95% confidence interval, 6.92-12.33; \( P < .001 \)). The incidence rates of HCC in the HIV-only and coinfected groups were 0.20 and 1.32 per 1000 person-years, respectively. In a Cox multivariate proportional hazards regression model, coinfected patients had an adjusted HR for HCC of 5.35 compared with HIV-only patients (95% confidence interval, 2.34-12.20; \( P < .001 \)). Among patients identified during the highly active antiretroviral therapy era, the HR for cirrhosis was 19.06 (95% confidence interval, 10.14-35.85; \( P < .001 \)), while the HR for HCC was 5.07 (95% confidence interval, 1.72-14.99; \( P = .003 \)).

Conclusions: To our knowledge, this study is the largest longitudinal study to examine the incidence of nonalcoholic cirrhosis and HCC in HIV-only and HCV-coinfected patients. Hepatitis C virus coinfection dramatically promotes the development of HCC (5-fold) and of cirrhosis (10- to 20-fold), and is especially associated with cirrhosis in the highly active antiretroviral therapy era. Treatment of HCV in HIV-infected patients, while often unsuccessful, should be considered.

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O F PERSONS LIVING WITH the human immunodeficiency virus (HIV) in the United States and western Europe, 30% or more are coinfected with the hepatitis C virus (HCV). Among persons with HCV only, 8% to 24% will develop cirrhosis over 2 to 3 decades following infection. Once cirrhosis is established, hepatocellular carcinoma (HCC), which has a median survival of 8 months, occurs annually in 1% to 4% of the subjects. Human immunodeficiency virus likely accelerates the progression of HCV-related liver disease. Cirrhosis is an increasingly prevalent cause of morbidity in patients with HIV. However, because cirrhosis and HCC develop only after prolonged infection, they are relatively uncommon and little data are available on the incidence and relative risk of these conditions in HIV-infected and coinfected persons, especially from the highly active antiretroviral therapy (HAART) era. Most studies in these populations reporting on chronic liver disease outcomes are cross-sectional or case-control studies or are too small or have insufficient follow-up to compare incidence of chronic liver diseases. In the only large study of the risk of HCC in coinfected patients, including more than 300,000 persons with AIDS, 61 cases of HCC were observed. While coinfection with a hepatatrophic virus is expected to increase the risk of liver disease, the magnitude of the increased risk is unknown, especially in HIV-infected pa-
patients, in whom survival is decreased. There are scarce data to guide the clinician in determining the risk of cirrhosis and HCC in patients with HIV.

We hypothesized that in HIV-infected persons, HCV coinfection increases the risk of cirrhosis and HCC. We conducted a retrospective cohort study of all Veterans Health Administration (VA) patients hospitalized with HIV between October 1, 1991, and September 30, 2000, to quantify the incidence and relative risk of nonalcoholic cirrhosis and HCC after discharge in persons with and without HCV coinfection.

METHODS

STUDY DESIGN AND DATA SOURCES

This retrospective cohort study of US veterans was conducted with data from national VA databases. The VA’s Patient Treatment File (PTF) contains discharge diagnoses that are coded according to the International Classification of Diseases, Ninth Revision (ICD-9). In October 1996, the VA started an Outpatient Clinic file that contains up to 10 ICD-9 diagnosis codes for each outpatient encounter. The Beneficiary Identification and Records Locator Subsystem Death File contains all deaths of veterans reported by VA Medical Centers, the Social Security Administration, the VA cemetery system, and funeral directors. Between 90% and 95% of deaths among veterans are captured by this file or the PTF compared with the National Death Index.

STUDY POPULATION

The study cohort was all veterans with HIV, as indicated by ICD-9 codes V08 or 042, discharged alive after hospitalization between October 1, 1991, and September 30, 2000. Coinfection with HCV was defined by ICD-9 codes 070.41, 070.44, 070.51, 070.54, and V02.62. Because HIV and HCV share several modes of transmission, we assumed that a person who was ultimately diagnosed as having both infections was likely infected with both viruses at the time the first viral infection was identified. The index hospitalization, therefore, was the first hospitalization during the specified interval with an HIV or HCV diagnosis, and follow-up began on the date of discharge from that hospitalization and ended on September 30, 2001. We extracted medical diagnoses from the PTF and Outpatient Clinic file during the 4-year period before the index hospitalization and all medical diagnoses and deaths occurring between the index hospitalization and the end of follow-up. To exclude nonincidence cases of cirrhosis and HCC, we excluded patients with advanced liver diseases recorded during the index hospitalization or the 4 years before the index hospitalization, as indicated by any of the following diagnoses (ICD-9 codes): cirrhosis (571.5 and 571.6), HCC (155.0), ascites (789.5), esophageal varices (456.0, 456.1, and 456.2), hepatorenal syndrome (572.4), hepatic coma (572.2), hepatic infarction (573.4), acute liver failure (570), and alcoholic liver disease (573.0, 571.1, 571.2, and 571.3). Patients diagnosed as having HIV-2 (ICD-9 code 079.33) at any time in their records were excluded.

HIV DISEASE SEVERITY, COMORBIDITIES, PRE-HAART AND HAART ERAS, AND OUTCOMES

The severity of HIV at the index hospitalization was determined using the previously validated Severity Classification System for AIDS Hospitalizations (SCAH). The SCAH is constructed from selected ICD-9 codes recorded during the index hospitalization, and is predictive of short- and long-term mortality in patients with HIV.19,20 We modified the SCAH by removing codes for hepatitis, because they are examined separately in this study, and codes for severe liver diseases, because patients with these conditions were excluded from the study, as previously described. Comorbid or potentially confounding conditions ascertained included toxic or drug-related hepatitis (ICD-9 code 573.3) and diabetes mellitus (ICD-9 code 250), diagnosed during the index hospitalization or the preceding 4 years; and chronic hepatitis B infection (ICD-9 code 70.32, 070.33, or V02.61) and coagulation disorders (ICD-9 code 286), diagnosed anytime from the 4 years before the index hospitalization through the end of follow-up. The pre-HAART era analyses included patients whose HIV diagnosis was recorded before October 1, 1996, and follow-up for these analyses was terminated at September 30, 1996. The HAART era analyses included patients whose HIV diagnosis was recorded on or after October 1, 1996, with follow-up through September 30, 2001. The primary outcomes of the study were new diagnoses of nonalcoholic cirrhosis (ICD-9 code 571.5 or 571.6) or HCC (ICD-9 code 155.0) during follow-up. These diagnoses could be associated with an outpatient or an inpatient encounter, and need not have been the primary diagnosis. Diagnoses of alcoholic cirrhosis were not considered an outcome.

VALIDATION STUDY

The medical records of a random sample of 300 patients (100 with HCV, 100 with HIV, and 100 with neither) identified in the PTF were reviewed. The presence of an HIV ICD-9 code was 98% predictive of a positive HIV laboratory test result, while the absence of the code was 100% predictive of the absence of a positive HIV test result. The presence of an HCV code was 94% predictive of a positive HCV laboratory test result, while the absence of a code was 90% predictive of the absence of a positive test result. Of all patients with HIV, 96% were tested for HCV.

STATISTICAL ANALYSIS

For univariate comparisons of baseline characteristics between HIV-only and coinfected patients, continuous data were compared using t tests and categorical data were compared using the χ² test. The incidence rate was calculated using the incidence density method, and 95% confidence intervals were estimated assuming a Poisson distribution. The cumulative incidence for each outcome was calculated by the Kaplan-Meier survival method, and the log-rank test was used to compare cumulative incidences. Cox proportional hazards regression models were constructed to estimate the adjusted hazard ratio (HR) of the outcomes. Covariates considered in the models included coinfection status, age, race (white, black, Hispanic, and other or unknown), sex, SCAH score, and the comorbidities defined earlier. The log-log calculation was used to check the proportional hazard assumption. All calculations were performed using SAS statistical software, version 8.1 (SAS Institute Inc, Cary, NC).

RESULTS

BASELINE CHARACTERISTICS

The initial cohort included 18,391 patients, but 310 diagnosed as having HIV-2 and 1,642 with preexisting liver disease were excluded. The analysis cohort, thus, in-
cluded 16439 patients. Of these patients, 4761 had HCV and HIV, while 11678 had HIV only. The HIV-only and coinfected patients were a similar age, but compared with HIV-only patients, coinfected patients were less often diagnosed as having HIV during the pre-HAART era and were less often female, although the overall proportion of females in each group was 2% or less (Table 1). Coinfected patients were more often black or Hispanic, and more often had a coagulation disorder and a chronic hepatitis B infection. They also had lower SCAH scores, indicating that they had less advanced HIV.

**CIRRHOSIS**

With 59482 total person-years of follow-up and a mean of 3.4 and 4.2 years of follow-up in the HIV-only and coinfected groups, respectively, the incidences of cirrhosis were 1.47 and 15.88 per 1000 person-years, respectively (Table 2). The incidence rate ratio of cirrhosis for coinfected patients relative to HIV-only patients was 10.80. During the pre-HAART era, with a total of 13437 person-years of follow-up and a mean of 1.3 and 1.6 years of follow-up in the HIV-only and coinfected groups, respectively, the incidences of cirrhosis were 3.09 and 10.71 per 1000 person-years, respectively, yielding an incidence rate ratio of 3.46. In the HAART era, with 17366 total person-years of follow-up and a mean of 2.7 years of follow-up in each group, the incidence of cirrhosis in the HIV-only group was 0.92 per 1000 person-years, while in the coinfected group, it was 20.63 per 1000 person-years, yielding an incidence rate ratio of 22.48.

By using the Kaplan-Meier method, the unadjusted cumulative incidence of developing cirrhosis was higher in the coinfected group than in the HIV-only group (Figure 1A; P<.001). For example, the 3-year cumulative incidence of cirrhosis was 0.5% in HIV-only patients, while it was 4.5% in coinfected patients. In the pre-HAART era, the 3-year cumulative incidence of cirrhosis was 1.2% in HIV-only patients, while it was 3.4% in coinfected patients (Figure 1B; P<.001). For patients diagnosed as having HIV in the HAART era, the 3-year cumulative incidence of cirrhosis was 0.3% in HIV-only patients, while it was 6.1% in coinfected patients (Figure 1C; P<.001).

In univariate and multivariate Cox proportional hazards regression modeling, coinfection, age, race, diabetes mellitus, coagulation disorders, and hepatitis B were associated with cirrhosis. After adjusting for these variables, and for sex and HIV disease severity, the HR for cirrhosis for coinfected patients relative to HIV-only patients was 9.24 (Table 2). In the pre-HAART era, the HR was 2.84, while among patients from the HAART era, it was 19.06. Because the Outpatient Clinic data were available only in the HAART era, we conducted an analysis that used cirrhosis diagnoses contained in the inpatient PTF data for pre-HAART and HAART analyses, but did not include Outpatient Clinic data. The HR for cirrhosis in coinfected patients relative to HIV-only patients in the HAART era was 9.37 (95% confidence interval, 4.81-18.26), still increased compared with the pre-HAART estimate of 2.84.

**HEPATOCELLULAR CARCINOMA**

With 60003 total person-years of follow-up, and a mean of 3.4 and 4.3 years of follow-up in the HIV-only and coinfected groups, respectively, the incidences of HCC were 0.20 and 1.32 per 1000 person-years, respectively (Table 2). The incidence rate ratio of HCC for coinfected relative to HIV-only patients was 6.50. With 13482 person-years of follow-up in the pre-HAART era, only 5 patients were diagnosed as having HCC (1 in the HIV-only group and 4 in the coinfected group); therefore, further analyses of those data are not presented. Among persons diagnosed as having HIV during the HAART era, with 17488 total person-years of follow-up and a mean of 2.7 and 2.8 years of follow-up in the HIV-only and coinfected groups, respectively, the incidences of HCC were 0.42 and 2.18 per 1000 person-years, respectively, for an incidence rate ratio of 5.23 (Table 2).

In the Kaplan-Meier analysis, the unadjusted cumulative incidence of HCC was higher in the coinfected group than in the HIV-only group (Figure 2A; P<.001). For example, the 3-year cumulative incidence of HCC was 0.6% in HIV-only patients, while it was 0.30% in coinfected patients. The 3-year risk of HCC for HAART-era patients was 0.1% in HIV-only patients, while it was 0.4% in coinfected patients (Figure 2B; P<.001).

In univariate Cox proportional hazards regression models, coinfection (P = .002), age (P = .01), coagulation disorders (P<.001), and chronic hepatitis B (P<.001) were associated with HCC; other factors considered were of
low significance (**P > 0.25**). In a Cox multivariate proportional hazards regression model, after adjusting for these factors and HIV disease severity, the HR for HCC for coinfected patients relative to HIV-only patients was **5.35** (Table 2). In patients diagnosed as having HIV during the HAART era, the HR was **5.07**.

**COMMENT**

Hepatitis C virus infection dramatically increased the risk of cirrhosis and HCC in persons with HIV, especially during the HAART era. Three measures of disease burden were used, including calculating incidence rates, Kaplan-Meier cumulative incidence rates, and adjusted HRs from Cox proportional hazards regression modeling. With each measure, HCV coinfection compared with infection with HIV alone increased the risk of nonalcoholic cirrhosis approximately 10-fold, increased the risk of cirrhosis during the HAART era approximately 20-fold, and increased the risk of HCC approximately 5-fold.

The relative risk of cirrhosis observed in the HIV Outpatient Study cohort during the HAART era was approximately 10-fold higher in persons with HCV. In the present study, with a similar duration of follow-up, the incidence rate was approximately 20-fold higher with coinfection. The veterans in this study are older and may have had other comorbidities that contributed to the differing point estimates. The confidence interval for the relative risk in the HIV Outpatient Study was broad (95% confidence interval, 2.97-34.28), and included our value; thus, statistically, the results from both studies are consistent, with our result being more precise.

In our study, there was no increase in the incidence of cirrhosis in the HIV-only group from the pre-HAART to the HAART era. On the other hand, in coinfected patients, the rate of cirrhosis increased from the pre-HAART to the HAART era. One intuitive explanation is that improved survival in the HAART era led to longer exposure to HCV and, hence, a higher rate of cirrhosis. However, the risk of cirrhosis increased in the HAART era, even after adjusting for survival time, as is evident in the Kaplan-Meier and Cox proportional hazards regression analyses. These results suggest that HAART accelerates the development of cirrhosis in the setting of HCV infection, perhaps as a result of toxicity or immune reconstitution. Alternatively, it is possible that physicians in the HAART era diagnosed cirrhosis more frequently than in the pre-HAART era, because of increased awareness of HCV, concerns about HAART-related adverse effects, or increased availability of treatment for HCV. Further studies are needed to clarify this issue.

The dramatically increased relative risk of cirrhosis observed with HCV coinfection, especially in the HAART era, must be viewed in the context of the absolute risk. The 3-year incidence of cirrhosis in coinfected veterans in the HAART era is 6%, which is less than the 3-year risk of an AIDS-defining illness in nearly all persons who meet the recommended criteria for HAART. For example, the 3-year risk of an AIDS-defining illness in an untreated person with moderately advanced HIV (a CD4 cell count between 201/µL and 350/µL and an HIV viral load between 20001 and 550000 copies per milliliter) is 36%. Thus, the benefit of HAART will likely outweigh the risk of cirrhosis for all patients but those in the earliest stages of HIV disease, even if HAART were causally related to the increase in cirrhosis risk.

The overall incidence of HCC in the entire cohort was **0.58 per 1000 person-years**, and persons with coinfection had 6.5 times the risk of HCC compared with persons with HIV only. In the only previous study to assess the incidence of HCC in persons with HIV and HCV coinfection, the incidence of HCC was as high as **0.19** per 1000 person-years, and coinfection was estimated to increase the risk of HCC 2.4-fold. However, that study
only included patients with AIDS, limiting its time-forward follow-up and not allowing it to capture events in persons without AIDS, and the median age at study enrollment was 37 years. In contrast, most patients in the present study did not have advanced HIV, and their mean age was 44 years. Thus, the patients in our study likely had a longer follow-up and longer exposure to HCV, important determinants of the risk of HCC. Finally, the previous study used data from the pre-HAART era only.

To our knowledge, this study is the largest of HIV and HCV–coinfected patients. However, it has several limitations that should be acknowledged. First, it includes only US veterans being cared for in VA facilities and does not include many women, which may limit its generalizability. The VA cares for approximately 5% of all HIV-infected persons in care in the United States, and these results are applicable to them. Second, data on whether patients were treated with antiviral therapy were not available. Anti-HCV treatment is not commonly prescribed to coinfected patients in VA facilities, and because anti-HCV therapy is protective of cirrhosis, such treatment would bias our results toward the null. We used the HAART era as a surrogate for HAART use, a validated method. If patients with HCV were less likely to receive HAART and HAART is associated with cirrhosis, then again our results are underestimates of the true rate of cirrhosis. Third, we did not have accurate data on the amount and type of alcohol use. We, therefore, excluded patients with evidence of alcoholic liver disease and alcoholic cirrhosis at baseline and did not include alcoholic cirrhosis as an outcome; these exclusions may not have excluded all cases of alcoholic cirrhosis. We are also unaware that the amount of alcohol use would differ substantially by HCV status in this population. Fourth, no data were available on CD4 cell count or HIV viral load. Because all patients were hospitalized at the start of follow-up, we were able to use the SCAH score as a surrogate for HIV disease severity; this score was highly predictive of long-term mortality (data not shown). Last, we were unable to document that all patients with HIV were tested for HCV, so coinfected patients might be classified as having HIV only. The validation study indicates that this misclassification should be uncommon;

Figure 1. Kaplan-Meier cumulative risk of cirrhosis among veterans with hepatitis C virus (HCV) and human immunodeficiency virus (HIV) coinfection or with HIV only, in all patients (A), during the pre–highly active antiretroviral therapy (HAART) era (B), and during the HAART era (C). The log-rank test was significant (P<.001) for A–C. All curves are truncated at the point at which there are fewer than 100 persons in follow-up.

Figure 2. Kaplan-Meier cumulative risk of hepatocellular carcinoma among veterans with hepatitis C virus (HCV) and human immunodeficiency virus (HIV) coinfection or with HIV only, in all patients (A) and during the highly active antiretroviral therapy era (B). The log-rank test was significant (P<.001) for A and B. All curves are truncated at the point at which there are fewer than 100 persons in follow-up.
in any case, this misclassification would also bias our results toward the null.

To our knowledge, this study provides the first estimate of the incidence of nonalcoholic cirrhosis and HCC in HIV-infected and HCV-coinfected veterans, and is the largest study of these outcomes that includes patients with HIV only and HCV coinfection followed up longitudinally. Hepatitis C virus increases the risk of cirrhosis 10- to 20-fold, and increases the risk of HCC 5-fold. Whether HAART itself contributes to these risks is unclear, and these increased risks cannot overshadow the tremendous benefit of HAART. While treatment for HCV is often unsuccessful and accompanied by morbidity, it is recommended that treatment be considered in all patients with coinfection.2,7 The findings of this study corroborate that recommendation, especially in persons with or at high risk for cirrhosis, who can tolerate treatment, and who otherwise have a good prognosis.

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Correspondence: Thomas P. Giordano, MD, MPH, Houston Center for Quality of Care and Utilization Studies, Department of Veterans Affairs Medical Center (152), 2002 Holcombe Blvd, Houston, TX 77030 (tpg@bcm.tmc.edu).

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REFERENCES