

The Effect of HIV Coinfection on the Risk of Cirrhosis and Hepatocellular Carcinoma in U.S. Veterans with Hepatitis C

Jennifer R. Kramer, Ph.D., M.P.H., Thomas P. Giordano, M.D., M.P.H., Julianne Soucek, Ph.D., Peter Richardson, Ph.D., Lu-Yu Hwang, M.D., and Hashem B. El-Serag, M.D., M.P.H.
Houston Center for Quality of Care and Utilization Studies, Health Services Research and Development Service, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas; The Sections of Health Services Research, Infectious Diseases, and Gastroenterology, Department of Medicine, Baylor College of Medicine, Houston, Texas; and The University of Texas Health Science Center at Houston School of Public Health, Houston, Texas

- OBJECTIVES:** This study was conducted to determine whether HIV coinfection increases the risk of cirrhosis in HCV-infected patients in the HAART and pre-HAART eras. Further, the risk of hepatocellular carcinoma was also examined.
- METHODS:** This retrospective cohort study was conducted among HCV-infected veterans who were seen at one of the 172 Veterans Health Administration hospitals between October 1, 1991 and September 30, 2000. Patients with prerecorded advanced liver disease were excluded. Incidence rates, cumulative incidence, and Cox proportional hazard ratios were calculated.
- RESULTS:** There were 26,641 patients with HCV-only and 4,761 patients with HCV-HIV coinfection. The unadjusted incidence rate of cirrhosis was lower in patients with coinfection than HCV-only ($p < 0.01$). After controlling for demographics and confounders (including alcoholism and chronic hepatitis B), coinfection was not significantly associated with cirrhosis. However, there was an increased risk of cirrhosis in patients with coinfection compared to HCV-only during the pre-HAART era (before October 1, 1996) (hazard ratio = 1.48, 1.06–2.07, $p = 0.02$), but not among patients who entered the cohort during the HAART era. The unadjusted incidence rate of hepatocellular carcinoma in patients with coinfection and HCV-only was 1.3 and 2/1,000 person-years, respectively ($p = 0.04$). In the multivariate model, coinfection was not associated with hepatocellular carcinoma (hazard ratio = 0.84, $p = 0.40$).
- CONCLUSIONS:** Coinfection was a significant risk factor for cirrhosis only during the pre-HAART era and was not associated with hepatocellular carcinoma, irrespective of time period.

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INTRODUCTION

Coinfection with hepatitis C virus (HCV) and HIV is common because of the similar modes of transmission for both viruses. There are an estimated 240,000 persons with HCV and HIV coinfection in the United States (1). They comprise approximately 30% of the 800,000 persons infected with HIV and 6% of the 4 million infected with HCV.

The effect of HIV coinfection on the progression of HCV morbidity is not fully understood. The life expectancy of HIV infected individuals has been prolonged by the use of highly active antiretroviral therapy (HAART), and therefore

chronic HCV infection in these persons has become an increasingly important problem (2). Among HCV-infected persons, between 8 and 24% develop cirrhosis over two to three decades following the onset of HCV infection (3). Once cirrhosis is established, hepatocellular carcinoma (HCC) occurs at an annual rate of 1–4% (4, 5). Several studies examined the effect of HIV coinfection on the progression to liver disease in HCV infected patients and reported inconsistent findings (6–17). Many studies were performed before the HAART era, had a short duration of follow-up, if any, and/or did not adjust for potential confounders such as chronic hepatitis B virus (HBV) infection or alcohol consumption. Further, the majority of the studies examined small numbers of patients for short periods of follow-up and thus, were not able to investigate what effect, if any, HIV coinfection had on the development of HCC.

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We conducted a retrospective cohort study of all veteran patients hospitalized with HCV between 1992 and 2000 at any hospital of the Veterans Administration (VA) to examine the incidence and relative risk of cirrhosis and HCC after discharge in both persons with and without HIV coinfection.

METHODS

Data Sources

This retrospective cohort study was conducted with data from national VA administrative databases and was approved by the Institutional Review Board for Human Subject Research for Baylor College of Medicine and Affiliated Hospitals. The VA's Patient Treatment File (PTF) contains discharge diagnoses that, since 1981, have been coded according to the 9th revision of the International Classification of Diseases (ICD-9). In 1997, VA started an Outpatient Clinic File (OPC) that contains a primary ICD-9 diagnosis code and up to nine additional diagnoses for each outpatient encounter. The Beneficiary Identification and Records Locator Subsystem Death File contains all deaths of veterans reported by the VA, the Social Security Administration, the Department of Veteran Affairs cemetery system, and funeral directors. Between 90% and 95% of deaths among veterans are captured by this file, which is updated twice monthly, as compared to the National Death Index (18).

Study Population and Outcomes

The sampling frame included all hospitalized veterans with HCV as indicated by ICD-9 codes 070.51, 070.54, 070.41, 070.44, and V02.62 in the PTF who were discharged alive between October 1, 1991 and September 30, 2000. Coinfection with HIV was defined by ICD-9 codes V08 or 042 in the PTF or OPC files. Because HIV and HCV share several modes of transmission, we assumed that patients with both infections were infected with both viruses at the time the first viral infection was identified. The two outcomes of the study were the presence of new cases of cirrhosis (571.5, 571.6 (these codes do not include alcoholic liver disease)) or HCC (155.0) diagnosed in the PTF or OPC during follow-up. The index hospitalization (date of enrollment in the study) was defined as the first hospitalization with either an HIV or HCV diagnosis. Follow-up began on the date of discharge from that hospitalization and ended either when an event occurred, the patient died, or if no event occurred on September 30, 2001. For length of follow-up when examining cirrhosis, patients were also censored if HCC occurred. To exclude nonincident cases of cirrhosis and HCC, we excluded patients with advanced liver diseases recorded in the PTF or OPC during the index hospitalization or the 4 yr before the index hospitalization, as indicated by any of the following diagnoses (ICD-9 codes): cirrhosis (571.5, 571.6), HCC (155.0), ascites (789.5), esophageal varices (456.1, 456.0, 456.2), hepatorenal syndrome (572.4), hepatic coma (572.2), hepatic infarction (573.4), acute liver failure (570), alcoholic liver disease (571.0, 571.1, 571.2, 571.3), and hemochromatosis (275.0).

Comorbidities

Comorbid or potentially confounding conditions ascertained included toxic or drug-related hepatitis (573.3), diabetes mellitus (250), and drug dependence (305.2, 305.3, 305.4, 305.5, 305.6, 305.7, 292, 304) diagnosed during the index hospitalization or the preceding 4 yr; and HBV infection (70.32, 070.33, V02.61), coagulation disorder (286), and alcoholism (291, 303, 305.0) diagnosed anytime during the 4 yr before the index hospitalization through the end of follow-up. Demographic features of patients collected at the index hospitalization included age, gender, race, marital status, and period of military service. Patients who entered the cohort before October 1, 1996, were considered to be in the pre-HAART era, while the remaining patients were considered in the HAART era.

Chart Validation Study

The medical records of a random sample of 300 patients (100 with HCV, 100 with HIV, and 100 with neither) seen at the Houston VA Medical Center between 1997 and 2000 identified by ICD-9 code in the PTF were reviewed for the presence of HCV or HIV laboratory tests. The presence of an HIV ICD-9 code was 98% predictive of a positive HIV laboratory test, while the absence of the code was 100% predictive of the absence of a positive HIV test. The presence of an HCV code was 94% predictive of a positive HCV laboratory test, while the absence of a code was 90% predictive of the absence of a positive test. Ninety-six percent of all patients with HIV were tested for HCV while 50% of patients with HCV were tested for HIV.

An additional chart validation study was performed to determine the validity of the ICD-9 code (155.0) for HCC. In the Houston VA Medical Center, 62 patients with ICD-9 code 155.0 were identified in the PTF or OPC Files during fiscal years 2000–2002. Medical records including histology, radiology, and laboratory tests were manually reviewed for the diagnosis of HCC. Eighty-four percent of the patients with the ICD-9 code 155.0 had a definitive diagnosis of HCC in the medical record.

Statistical Analyses

We conducted univariate comparisons of the demographic and clinical characteristics of the HCV-only and HCV–HIV coinfecting patients. Continuous variables were compared using *t*-tests and categorical variables were compared with the χ^2 test. Incidence rates of the outcomes (cirrhosis and HCC) were calculated as well as incidence rate ratios comparing patients with HCV-only and HCV–HIV coinfection. The cumulative incidence for each outcome was calculated by Kaplan and Meier's Product-Limit estimator (19), and was stratified by HIV coinfection status. The log-rank test was used to compare the cumulative incidence between the HCV-only and HIV coinfecting groups (19). Graphs were also stratified by HAART era. For the pre-HAART era analyses, follow-up was right censored at September 30, 1996; therefore, outcomes that occurred after that date in these patients were

not counted. The HAART-era analyses only included patients whose date of discharge from the index hospitalization was after September 30, 1996, and were censored at September 30, 2001. Cox proportional hazards models were constructed to estimate the adjusted hazard ratio (HR) for each of the outcomes (19). Corresponding 95% confidence intervals (CI) and *p*-values were also calculated. Covariates considered in the models included the demographics and comorbidities defined earlier. The models were also stratified by HAART era as defined above. The log-log calculation was used to check the proportional hazard assumption. Incidence rates and incidence rate ratios were calculated by Stata software (Intercooled Stata 7.0, College Station, TX). All other calculations were performed using SAS statistical software version 8.1 (SAS Institute, Cary, NC).

RESULTS

We identified 43,406 subjects with HCV who were discharged alive from one of the 172 VA facilities between October 1, 1991 and September 30, 2000. Of those, 5,347 (12.3%) also had HIV coinfection, and the rest had HCV-only. After excluding patients with prerecorded advanced liver disease, the cohort consisted of 31,402 patients with HCV, of whom 4,761 (15.2%) also had HIV coinfection and 26,641 (84.8%) had HCV-only (Table 1). Patients with coinfection were on average 2.5 yr younger and were significantly more likely to be male, black (59% vs 33%), and Hispanic (10% vs 6%), than the HCV-only group. They were also significantly more likely to never have been married (31% vs 21%). Approximately half of the subjects in this cohort were first recognized in the pre-HAART era (before 1 October, 1996) (47.1%); however, more patients with coin-

fection had a pre-HAART index hospitalization than patients with HCV-only (58.3% vs 45.1%, $p < 0.0001$). Patients with HCV-only were more likely to have been diagnosed with toxic hepatitis and diabetes than patients with HCV-HIV coinfection (both variables, $p < 0.0001$). On the other hand, patients with HCV-HIV coinfection were more likely to have been diagnosed with chronic HBV than patients with HCV-only ($p < 0.0001$).

Cirrhosis

There were 2,414 patients diagnosed with cirrhosis during the course of the follow-up period with an incidence rate of 19.2/1,000 person-years (PY) of follow-up. The incidence rate of cirrhosis was lower in patients with HCV-HIV coinfection at 15.9/1,000 PY than in patients with HCV-only at 19.7/1,000 PY (Table 2). The incidence rate ratio of HCV-HIV coinfection to HCV-only was 0.81 (95% CI: 0.72–0.91, $p < 0.01$). During the HAART era the incidence rate ratio between the coinfecting and HCV-only patients was closer to one (RR = 0.92, 95% CI: 0.75–1.13, $p = 0.43$). During the pre-HAART era, the incidence rate of cirrhosis was substantially lower than in the HAART era (10.5/1,000 PY vs 21.6/1,000 PY). The incidence rate ratio between coinfecting and HCV-only infected patients was also close to one (RR = 1.07, 95% CI: 0.76–1.46, $p = 0.67$).

Figure 1A shows the Kaplan–Meier curves of the cumulative incidence of cirrhosis during the entire follow-up period. Patients with HCV-only had a significantly higher proportion of cirrhosis than patients with HCV-HIV coinfection (log rank $p = 0.0003$). After 1, 3, and 7 yr of follow-up respectively, 2.4%, 6.0%, and 12.4% of patients with HCV-only developed cirrhosis while 1.8%, 4.5%, and 10.7% of patients with HCV-HIV coinfection developed cirrhosis. When stratified by HAART era, the difference in the risk of cirrhosis between the two HIV infection status groups is diminished and is no longer statistically significant in either era (HAART era: log rank $p = 0.6913$; pre-HAART era: log rank $p = 0.9157$; Figure 1B). Regardless of coinfection status, the overall cirrhosis proportion is higher during the HAART era than during the pre-HAART era.

Because differences in age and other baseline characteristics (Table 1) of the two cohorts, the unadjusted analyses provide information of absolute risks, but relative risks should be interpreted with caution. Therefore, we performed a multivariate analysis. In the multivariate Cox proportional hazards model in the cohort over the entire follow-up period (Table 2), HCV-HIV coinfection was not a significant predictor of cirrhosis (HR = 0.99, 95% CI: 0.87–1.12, $p = 0.83$) while controlling for demographics (age, race, and gender) and other comorbidities (toxic hepatitis, chronic HBV, diabetes, coagulation disorder, drug dependence, and alcoholism). However, age, Hispanic ethnicity, toxic hepatitis, chronic HBV, diabetes, coagulation disorder, and alcoholism were significant positive predictors in the model. The model restricted to the HAART era showed similar findings to that of the entire cohort model. However, in the model restricted

Table 1 Demographic and Clinical Characteristics of a Cohort of 31,402 HCV Infected Veterans Hospitalized between October 1991 and September 2000

Characteristic	HCV and HIV Coinfection (%) (N = 4,761)	HCV-Only (%) (N = 26,641)	<i>p</i> - Value
Mean age (yr) (SD)	44.4 (7.0)	46.9 (9.1)	<0.0001
Male sex	98.5	97.6	0.0004
Race/ethnicity			
White	28.7	57.8	<0.0001
Black	58.6	32.7	
Hispanic	10.3	6.1	
Other/unknown	2.4	3.4	
Toxic hepatitis	4.0	8.8	<0.0001
Chronic HBV infection	13.6	8.4	<0.0001
Diabetes mellitus	9.1	14.9	<0.0001
Drug dependence	59.8	59.5	0.7144
Pre-HAART index hospitalization*	58.3	45.1	<0.0001

*Patients with an index hospitalization before October 1, 1996.

HCV = hepatitis C virus; HBV = hepatitis B virus; HAART = highly active antiretroviral therapy.

Table 2 Incidence Rates, Incidence Rate Ratios, and Adjusted Hazard Ratios of Cirrhosis and Hepatocellular Carcinoma in 26,641 HCV-Only and 4,761 HIV Coinfected Veterans

Outcome Event	HIV and HCV Coinfection		HCV-Only		HCV-HIV Coinfection vs HCV-Only	
	Number of Events	Incidence Rate Per 1,000 Person-Years	Number of Events	Incidence Rate Per 1,000 Person-Years	Incidence Rate Ratio (95% CI)	Adjusted Hazard Ratio [‡] (95% CI)
Cirrhosis, entire cohort	318	15.9	2,096	19.7	0.81 (0.72–0.91)	0.99 (0.87–1.12)
Cirrhosis, pre-HAART era [†]	48	10.8	231	10.1	1.07 (0.76–1.46)	1.48 (1.06–2.07)*
Cirrhosis, HAART era	111	20.7	788	22.4	0.92 (0.75–1.13)	1.15 (0.93–1.41)
HCC, entire cohort	27	1.3	221	2.0	0.67 (0.43–0.99)	0.84 (0.55–1.27)
HCC, HAART era	12	2.2	76	2.1	1.04 (0.51–1.92)	1.21 (0.64–2.28)

HCV = hepatitis C virus; CI = confidence interval; HAART = highly active antiretroviral therapy; HCC = hepatocellular carcinoma.

* p -value = 0.0216, all other p -values > 0.05

[†]Patients with an index hospitalization before October 1, 1996 with follow-up right censored; therefore, outcomes developing during the HAART era in these patients were not counted.

[‡]Adjusted hazard ratios derived from separate multivariate Cox proportional hazards models. Cirrhosis models adjusted for age, race, sex, toxic hepatitis, coagulation disorder, chronic HBV, diabetes mellitus, drug dependence, and alcoholism. HCC models adjusted for age, race, sex, chronic HBV, diabetes, coagulation disorder, drug dependence, and alcoholism.

HCC for pre-HAART era not shown due to small number of cases.

to the pre-HAART era, HCV-HIV coinfection was a significant predictor for cirrhosis (HR = 1.48, 95% CI: 1.06–2.07, $p = 0.02$). Other variables that had a significant positive association with cirrhosis in the pre-HAART era model were age, toxic hepatitis, chronic HBV, diabetes, and coagulation disorder.

Hepatocellular Carcinoma

There were 248 cases of HCC diagnosed in the cohort during the entire follow-up period with an incidence rate of 1.9/1,000 PY of follow-up. The incidence rate was 1.3/1,000 PY in patients with HCV-HIV coinfection and 2.0/1,000 PY in patients with HCV-only (Table 2). The incidence rate ratio comparing HIV coinfecting and HCV-only infected patients was 0.67 (95% CI: 0.43–0.99, $p = 0.04$). However, during the HAART era the incidence rate ratio was 1.04 (95% CI: 0.51–1.92, $p = 0.87$).

Figure 2 shows that patients with HCV-only have a higher cumulative incidence of HCC than those with HCV-HIV coinfection (log rank $p = 0.0463$). After 1, 3, and 7 yr of follow-up respectively, 0.3%, 0.5%, and 1.4% of patients with HCV-only and 0.1%, 0.3%, and 0.9% of patients with HCV-HIV coinfection developed HCC.

Again, due to differences in baseline characteristics, we performed a multivariate Cox proportional hazards analysis. In the multivariate models, HCV-HIV coinfection was neither a significant predictor for the development of HCC during the entire follow-up period, nor in the HAART or pre-HAART eras (Table 2). In the entire cohort model, age, chronic HBV, and coagulation disorder had a significant positive association with the development of HCC.

DISCUSSION

This is the first study to examine cirrhosis and HCC in patients with HCV-HIV coinfection using nationwide data sets in the United States. It is also the first large study to examine these outcomes in both the pre-HAART and HAART

eras. This study demonstrates that cirrhosis and HCC are important sequelae in patients with HCV and HCV-HIV coinfection. However, the findings also indicate that HCV-HIV coinfection was a significant risk factor for the development of cirrhosis only during the pre-HAART era, and HCV-HIV coinfection seemed to be not significantly associated with the development of HCC, irrespective of time period. The incidence of cirrhosis was significantly lower in the patients with HCV-HIV coinfection than in the patients with HCV-only. These differences may be related to the fact that patients with HCV-HIV coinfection were significantly younger, had a different racial distribution, were more likely to be infected in the pre-HAART era, and had less comorbid disorders than patients with HCV-only. When controlling for these differences in the multivariate analysis, patients with HCV-HIV coinfection had no greater risk of developing cirrhosis than those with HCV-only during the entire follow-up period. However, there was a significant interaction between HAART era and risk of cirrhosis. During the pre-HAART era there was a small but significant increased risk of developing cirrhosis for HCV-HIV coinfecting patients compared to patients with HCV-only; however, this increased risk all but disappeared during the HAART era. This finding is corroborated by several studies conducted during the pre-HAART era that reported a 3–7 fold increased risk of cirrhosis among patients with HCV-HIV coinfection (9–11).

One could speculate the reason for the increased risk of cirrhosis in the pre-HAART era, and the lack of such risk during the HAART era. Although it is uncertain whether HCV viral load plays an important role in the progression of HCV-related liver disease, it has been reported that HIV-related immunosuppression causes an elevation of HCV RNA levels (20, 21). It is possible that HAART, by reducing HIV RNA levels, may indirectly reduce HCV RNA levels (22). Also, HAART may have a beneficial impact on the progression of HCV-related liver disease. One study reported that patients with HCV-HIV coinfection who were not treated with protease inhibitors were almost five times more likely to progress

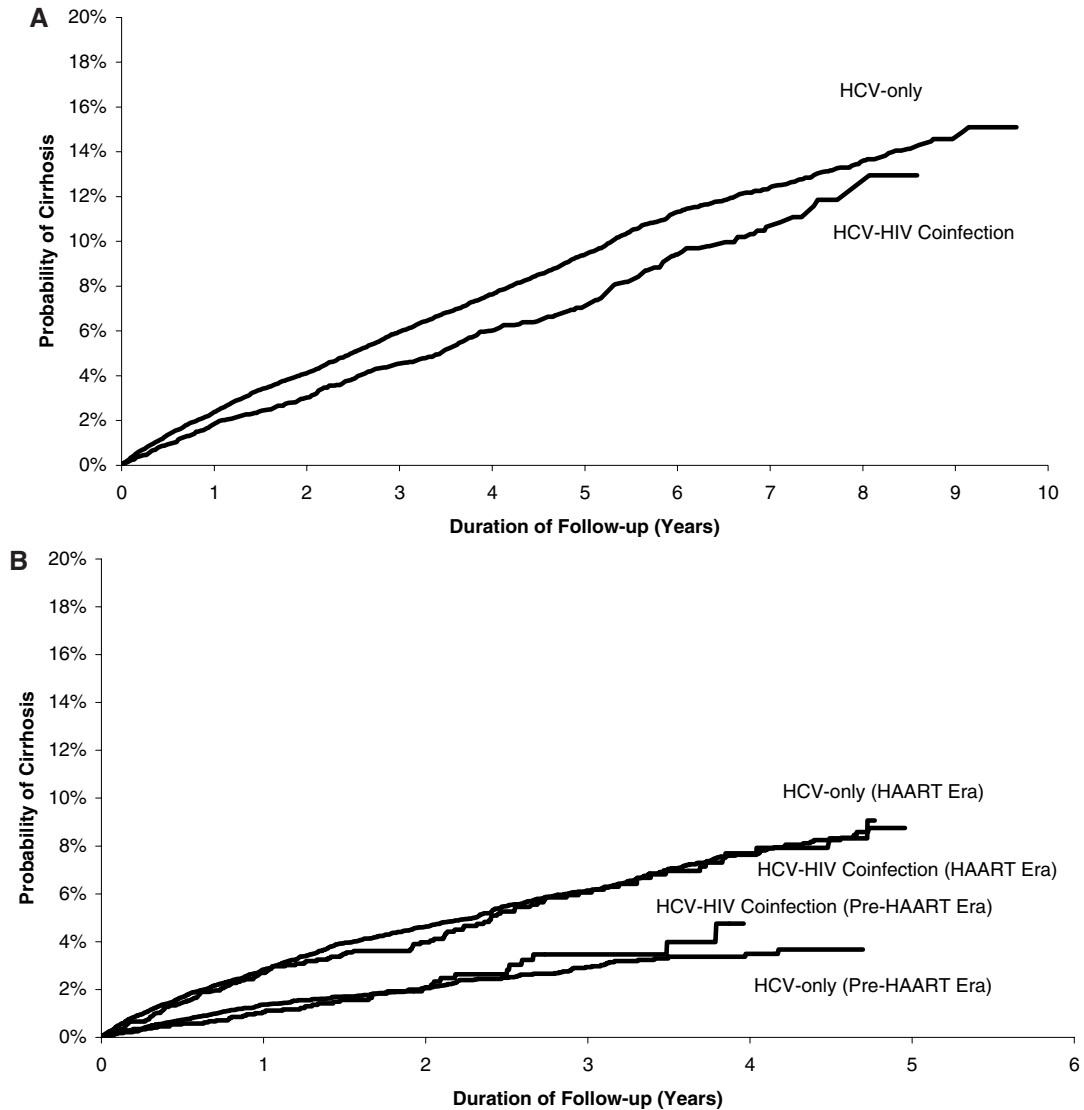


Figure 1. (A) Cumulative incidence (unadjusted) of cirrhosis in patients with HCV-HIV coinfection ($N = 4,761$) compared to patients with HCV-only ($N = 26,641$). All patients were identified at VA hospitals from October 1, 1991 to September 30, 2000 with follow-up through September 30, 2001. Difference was statistically significant, log-rank test p -value < 0.0001 . (B) Cumulative incidence (unadjusted) of cirrhosis in patients with HCV-HIV coinfection compared to patients with HCV-only during the HAART era and pre-HAART era. All patients were identified at VA hospitals from October 1, 1991 to September 30, 2000 with follow-up through September 30, 2001. Difference was not statistically significant in either era. HAART era: log-rank test p -value = 0.6913; pre-HAART era: log-rank test p -value = 0.9157. HCV = hepatitis C virus; VA = Veterans Administration; HAART = highly active antiretroviral therapy.

to cirrhosis (RR = 4.74, 95% CI: 1.34–16.67) (23). The authors speculate that improvements in patients' immune status or a direct impact of protease inhibitor therapy on cytokine expression may be important factors. Moreover, in our study we observed an increase in the incidence of cirrhosis and HCC in the HAART era in both coinfecting and HCV-only patients; however, the significance of this is difficult to determine. This increase in incidence from the pre-HAART to HAART era may be due to an ascertainment bias since the outpatient data from the OPC became available in 1997, shortly after the beginning of the HAART era, hence allowing for a greater chance of recording a liver disease diagnosis. The overall increase of cirrhosis during the HAART era could

also be due to the increased detection and awareness of HCV-related sequelae. In addition, it could reflect a cohort effect since the HCV epidemic began in the 1960s, and therefore, progressively increasing numbers of HCV infected patients are likely to develop cirrhosis during more recent times. Regardless of the reason for the higher incidence of cirrhosis in the HAART era in both groups, we saw no evidence that HIV coinfection increased the risk of cirrhosis in the HAART era.

The current study is the largest cohort to evaluate the effect of HCV-HIV coinfection on the development of HCC. The overall incidence rate for HCC in the entire study cohort was 1.9/1,000 PY, which might be an underestimate due to the relatively young age of this cohort and only having an

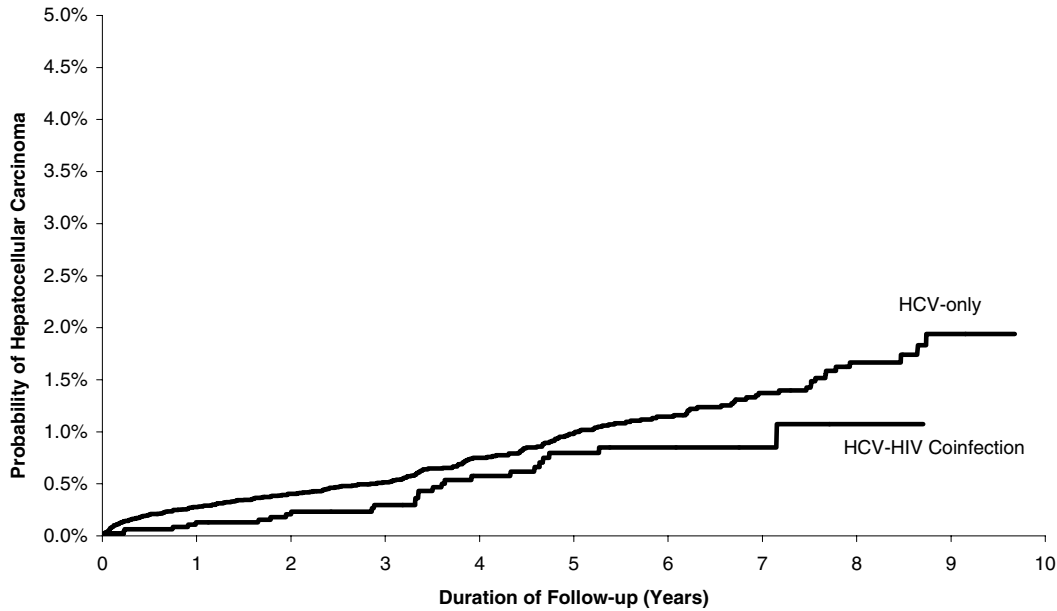


Figure 2. Cumulative incidence (unadjusted) of hepatocellular carcinoma in patients with HCV–HIV coinfection (N = 4,761) compared to patients with HCV-only (N = 26,641). All patients were identified at VA hospitals from October 1, 1991 to September 30, 2000 with follow-up through September 30, 2001. Difference was statistically significant, log-rank test p -value = 0.0463. HCV = hepatitis C virus; VA = Veterans Administration; HAART = highly active antiretroviral therapy.

average of 4 yr of follow-up. However, the incidence rate of HCC in patients with HCV–HIV coinfection was lower than in patients with HCV-only (1.3/1,000 PY vs 2.0/1,000 PY, $p = 0.04$). Since we assembled a large cohort of infected patients who accrued several years of follow-up, the study had a sufficient number of cases of HCC that were ascertained and analyzed to provide 80% power to detect a RR of 1.5 between the two groups. This does not apply to the stratified analysis by HAART era, which most likely has reduced power due to small number of cases. However, after adjusting for demographic and confounding variables, patients with HCV–HIV coinfection are not significantly different from patients with HCV-only with respect to progression to HCC. This is consistent with the findings of no significant increase in risk of cirrhosis since HCC develops in patients with cirrhosis. Since there were a sufficient number of HCC cases (more than 10 cases per covariate) this model was adequately fitted (24).

This study is limited by several factors. First, selection bias may have occurred because all VA patients were probably not tested for HCV; therefore, those tested may be different in some way than patients who were not, and in turn, not included in our study. It is also possible that not all of the HCV-only patients were truly HIV negative since our chart validation study indicated that 50% of patients with HCV had been tested for HIV. This would reduce the observed difference between the two groups. Given the relatively low incidence of cirrhosis and HCC (10% and 1%, respectively after 7 yr of follow-up in this study) with minor differences related to HIV infection status, it would take several hundred patients to be misclassified as HIV negative for at least 7 yr, and for

HIV to have a true deleterious effects to significantly change the current results. Further, since we used all the available inpatient and outpatient medical diagnoses in defining the infection status, it is improbable that a significant proportion of hospitalized patients and those seen in several encounters at the VA medical care system carry undiagnosed HIV. Another potential bias is the lack of HCV RNA as a marker of ongoing infection since approximately 30% of all anti-HCV positive patients are expected to be HCV RNA negative. This may overestimate the number of HCV positive patients and hence explain the relatively low overall incidence rates of cirrhosis and HCC in this study, but this bias is likely to be nondifferential between the coinfecting and HCV-only groups. Third, receipt of HAART was not measured directly. However, it is likely that a large population of patients with HIV and an indication for HAART receiving care at a VA facility are prescribed HAART because all FDA-approved antiretroviral drugs are given free of charge (25). Fourth, the outcomes, cirrhosis, and HCC, were defined by ICD-9 codes. We conducted a validation study of the code for HCC and found it to be highly predictive of HCC (84%). In addition, previous studies of HCC show similar temporal trends between HCC identified in the PTF by ICD-9 code 155.0 and those histologically confirmed in the SEER registry (26). The codes for cirrhosis and HCC were in place before the beginning of the study and did not undergo any changes during the follow-up period.

The exact date of infection with HCV or HIV was not known, and therefore the inception point of follow-up was estimated by the index hospitalization date. This most likely underestimated the duration of infection and may have caused

a bias, the direction of which is difficult to determine. It is possible that in the early years of the study, patients with HCV-only were diagnosed with HCV when they presented with clinically evident liver disease. On the other hand, patients with HCV-HIV coinfection were more likely to get tested for HCV for screening purposes only. If this were true, the patients with HCV-only may have a more advanced stage of their HCV-related liver disease than patients with HCV-HIV coinfection. To mitigate this potential bias, we removed patients with preexisting liver disease at or before the inception point for follow-up. Furthermore, we made an assumption that at the index date when the first infection was recorded both infections were already present. The accuracy of this assumption is unknown; however, a sensitivity analysis was conducted, which used as the inception point the date when both infections were documented in the medical records. The results were essentially the same as in the main analysis except that there was a slight increase in the risk for cirrhosis among patients with HCV-HIV coinfection in the entire cohort. Finally, this cohort was comprised of mostly low-income veteran men, and therefore, the results of this study may not be generalizable to women or nonveterans.

In conclusion, our study, which uses nationwide information from a comprehensive care setting, found little evidence that HIV coinfection accelerates HCV disease progression in this cohort, especially during the HAART era. Future studies are needed to evaluate the effect of HIV coinfection on HCV-related disease progression in patients on HAART. However, clinically evident cirrhosis and HCC are important causes of morbidity in HCV-infected patients irrespective of HIV infection status. Further, given the prolonged survival of HIV-infected patients successfully treated with HAART, a risk of cirrhosis of 20/1000 person-years as was observed in this study is clinically important. It is clear from this as well as other studies that HCV-infected patients with HIV coinfection have at least a similar incidence of cirrhosis and HCC to patients with HCV alone. Therefore, although treatment for HCV has limited efficacy especially in HIV infected patients, we recommend that treatment be considered in all patients with HCV. In addition, given the increased number of cases of cirrhosis and HCC expected to occur among HCV-infected patients with HIV coinfection, the scientific and ethical issues surrounding liver transplantation should continue to be examined.

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Reprint requests and correspondence: Hashem B. El-Serag, M.D., M.P.H., Houston Center for Quality of Care and Utilization Studies, Michael E. DeBakey Veterans Affairs Medical Center (152), Houston, TX 77030.

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