Annals of Internal Medicine | ORIGINAL RESEARCH

Hepatic Decompensation in Antiretroviral-Treated Patients Co-Infected With HIV and Hepatitis C Virus Compared With Hepatitis C Virus–Monoinfected Patients

A Cohort Study

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Background: The incidence and determinants of hepatic decompensation have been incompletely examined among patients co-infected with HIV and hepatitis C virus (HCV) in the antiretroviral therapy (ART) era, and few studies have compared outcome rates with those of patients with chronic HCV alone.

Objective: To compare the incidence of hepatic decompensation between antiretroviral-treated patients co-infected with HIV and HCV and HCV-monoinfected patients and to evaluate factors associated with decompensation among co-infected patients receiving ART.

Design: Retrospective cohort study.

Setting: Veterans Health Administration.

Patients: 4280 co-infected patients who initiated ART and 6079 HCV-monoinfected patients receiving care between 1997 and 2010. All patients had detectable HCV RNA and were HCV treatment–naive.

Measurements: Incident hepatic decompensation, determined by diagnoses of ascites, spontaneous bacterial peritonitis, or esophageal variceal hemorrhage.

Results: The incidence of hepatic decompensation was greater among co-infected than monoinfected patients (7.4% vs. 4.8% at 10 years; $P < 0.001$). Compared with HCV-monoinfected patients, co-infected patients had a higher rate of hepatic decompensation (hazard ratio [HR] accounting for competing risks, 1.56 [95% CI, 1.31 to 1.86]). Co-infected patients who maintained HIV RNA levels less than 1000 copies/mL still had higher rates of decompensation than HCV-monoinfected patients (HR, 1.44 [CI, 1.05 to 1.99]). Baseline advanced hepatic fibrosis (FIB-4 score >3.25) (HR, 5.45 [CI, 3.79 to 7.84]), baseline hemoglobin level less than 100 g/L (HR, 2.24 [CI, 1.20 to 4.20]), diabetes mellitus (HR, 1.88 [CI, 1.38 to 2.56]), and nonblack race (HR, 2.12 [CI, 1.65 to 2.72]) were each associated with higher rates of decompensation among co-infected patients.

Limitation: Observational study of predominantly male patients.

Conclusion: Despite receiving ART, patients co-infected with HIV and HCV had higher rates of hepatic decompensation than HCV-monoinfected patients. Rates of decompensation were higher for co-infected patients with advanced liver fibrosis, severe anemia, diabetes, and nonblack race.

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Co-infection with chronic hepatitis C virus (HCV) occurs in 10% to 30% of HIV-infected patients (1–4). The course of chronic HCV is accelerated in patients co-infected with HIV, with more rapid progression of liver fibrosis than in HCV-monoinfected patients (5–7). Consequently, HCV-related liver complications, particularly hepatic decompensation (defined by the presence of ascites, spontaneous bacterial peritonitis, variceal hemorrhage, or hepatic encephalopathy [8]), have emerged as important causes of illness in co-infected patients (9, 10).

Despite the importance of HCV-related end-stage liver disease, few longitudinal studies have evaluated the incidence and determinants of hepatic decompensation among patients co-infected with HIV and HCV during the antiretroviral therapy (ART) era. Previous studies suggest that ART slows progression of HCV-associated liver fibrosis, possibly by reducing HIV-related inflammation and immune dysfunction and inhibiting the ability of HIV to directly infect hepatocytes (10–13). However, whether rates of hepatic decompensation and other severe liver events (for example, hepatocellular carcinoma [HCC] or liver-related death) in co-infected patients receiving ART are similar to those in HCV-monoinfected patients remains unclear. Furthermore, the determinants of hepatic decompensation among co-infected patients receiving ART are unknown. Determination of these factors could help define the mechanisms of decompensation in co-infected patients and could suggest interventions to reduce the risk for end-stage liver disease in this population.

We first compared the incidence of hepatic decompensation between antiretroviral-treated patients co-infected with HIV and HCV and HCV-monoinfected patients. We hypothesized that rates of decompensation would remain

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Context

Patients with HIV are often co-infected with hepatitis C virus (HCV). Whether treatment of HIV with antiretroviral therapy (ART) can improve HCV outcomes is a topic of interest.

Contribution

In a Veterans Affairs study, patients co-infected with HIV and HCV who had HIV RNA levels less than 1000 copies/mL had a lower rate of hepatic decompensation than those with less HIV suppression. However, the rate was still higher than that in HCV-monoinfected patients.

Caution

Few women were studied.

Implication

Patients co-infected with HIV and HCV remain at greater risk for poor outcomes from HCV infection than HCV-monoinfected patients despite viral suppression by ART.

—The Editors

higher in co-infected patients despite ART. We then evaluated host and viral factors associated with decompensation among co-infected patients.

METHODS

Study Design and Data Source

We conducted a retrospective cohort study among antiretroviral-treated patients co-infected with HIV and HCV and HCV-monoinfected patients in the VACS-VC (Veterans Aging Cohort Study Virtual Cohort) between 1 January 1997 and 30 September 2010 (14). The VACS-VC consists of electronic medical record data from HIV-infected patients receiving care at Veterans Affairs (VA) medical facilities across the United States. Each HIV-infected patient is matched on age, sex, race/ethnicity, and site to 2 HIV-uninfected persons. Data include hospital and outpatient diagnoses (recorded using International Classification of Diseases, Ninth Revision [ICD-9], codes), procedures (recorded using CPT [Current Procedural Terminology] codes), laboratory results, and pharmacy data. Clinically confirmed cancer diagnoses are available from the VA Central Cancer Registry. Deaths are identified from the VA Vital Status file, which uses data from the Social Security Death Master File, Medicare Vital Status Files, and VA Beneficiary Identification and Records Locator Subsystem. For patients who died, principal cause of death can be determined by linkage with the National Death Index (15). In addition, U.S. Medicare and Medicaid claims data are available for veterans also enrolled in these programs and have been merged with VACS-VC data.

Study Patients

Co-infected patients were included if they had detectable HCV RNA, had recently initiated ART (defined as use of ≥3 antiretrovirals from 2 classes [16] or ≥3 nucleoside analogues [a previously accepted ART regimen] [17]) within the VA system, had an HIV RNA level greater than 500 copies/mL within 180 days before starting ART (to identify those who newly initiated ART [18]), and had been observed for at least 12 months in the VACS-VC after starting ART. Monoinfected patients had detectable HCV RNA, no recorded HIV ICD-9 diagnosis or antiretroviral prescriptions, and at least 12 months of observation in the VACS-VC. Patients were excluded if, during the baseline period (defined in the Statistical Analysis section), they had hepatic decompensation, HCC, or liver transplantation or received interferon-based HCV therapy (because treatment reduces the risk for hepatic decompensation [19, 20]).

Study Outcomes

The primary outcome was incident hepatic decompensation, which was defined by 1 ICD-9 diagnosis of ascites, spontaneous bacterial peritonitis, or esophageal variceal hemorrhage at hospital discharge or 2 such outpatient diagnoses in the VACS-VC (**Supplement 1**, available at www.annals.org). A prior study validated this determination, with 91% of events confirmed by medical records (21). The requirement of 2 outpatient diagnoses aimed to exclude events that were suspected but not subsequently confirmed at follow-up visits. On the basis of the results of the prior validation study (21), we did not include ICD-9 diagnoses for hepatic encephalopathy and jaundice, which could indicate decompensation, because these diagnoses frequently were linked to unrelated conditions (for example, narcotic overuse, stroke recorded as encephalopathy, or biliary obstruction or atazanavir-associated hyperbilirubinemia recorded as jaundice). Date of decompensation was defined as the hospital discharge date (if identified by hospital diagnosis) or initial outpatient diagnosis date (if identified by outpatient diagnosis).

Secondary outcomes included incident hepatic decompensation (determined by the aforementioned ICD-9–based definition) within the VACS-VC, Medicare, or Medicaid data (to capture outcomes occurring at non-VA hospitals that did not result in transfer to a VA facility; this outcome was secondary because non-VA events have not been validated); HCC; and severe liver events, a composite outcome of hepatic decompensation within the VACS-VC, HCC, or liver-related death. Hepatocellular carcinoma was determined using the VA Central Cancer Registry, which confirmed diagnoses by histologic or cytologic evaluation or consistent radiography. We classified deaths as liver-related if the underlying cause from the National Death Index was recorded as hepatic decompensation, liver cancer, alcoholic liver disease, viral hepatitis, or nonalcoholic liver disease (**Supplement 1**) (15).

Table 1. **Characteristics of the Study Cohorts**

Characteristic	Antiretroviral-Treated Patients Co-infected With HIV/HCV (*n* = 4280)	HCV-Monoinfected Patients (*n* = 6079)
Median (IQR) baseline age, *y*	48 (44–52)	47 (43–50)
Male, *n (%)*	4214 (98.5)	6022 (99.1)
Race/ethnicity, *n (%)*		
Black	2788 (65.1)	3733 (61.4)
White	975 (22.8)	1775 (29.2)
Hispanic	414 (9.7)	477 (7.8)
Other/unknown	103 (2.4)	94 (1.5)
Baseline body mass index, *n (%)*		
<18.5 kg/m^2	135 (3.2)	107 (1.8)
18.5–24.9 kg/m^2	2184 (51.0)	2006 (33.0)
25–29.9 kg/m^2	1368 (32.0)	2242 (36.9)
≥30 kg/m^2	473 (11.1)	1669 (27.5)
Missing weight and/or height	120 (2.8)	55 (0.9)
Baseline diabetes mellitus, *n (%)*	318 (7.4)	453 (7.5)
Baseline history of alcohol dependence/abuse, *n (%)*	1130 (26.4)	1866 (30.7)
Baseline history of injection/noninjection drug use, *n (%)*	1501 (35.1)	2025 (33.3)
Baseline history of tobacco use, *n (%)*		
Current	2956 (69.1)	4457 (73.3)
Former	482 (11.3)	776 (12.8)
Never	486 (11.4)	650 (10.7)
Unknown	356 (8.2)	196 (3.2)
Median (IQR) follow-up, *y*	6.8 (3.6–10.1)	9.9 (6.0–12.4)
Total follow-up time, *person-years*	29 005	54 411
HCV genotype, *n (%)*		
1 or 4	2513 (58.7)	3648 (60.0)
2 or 3	315 (7.4)	513 (8.4)
Other	7 (0.2)	11 (0.2)
Missing	1445 (33.8)	1907 (31.4)
Baseline HCV RNA level, *n (%)**		
≥400 000 IU/mL and/or ≥1 000 000 copies/mL	3186 (74.5)	2309 (38.0)
<400 000 IU/mL and/or <1 000 000 copies/mL	450 (10.5)	2006 (33.0)
Qualitative HCV RNA result only	644 (15.0)	1764 (29.0)
Hepatitis B surface antigen, *n (%)*		
Positive (ever)	241 (5.6)	78 (1.3)
Negative	3992 (93.3)	5701 (93.8)
Never tested	47 (1.1)	300 (4.9)
Median (IQR) pre-ART HIV RNA level, *log copies/mL*	4.7 (4.0–5.1)	–
Pre-ART CD4 count, *n (%)*		
≥0.500 × 10^9 cells/L	391 (9.1)	–
0.350–0.499 × 10^9 cells/L	588 (13.7)	–
0.200–0.349 × 10^9 cells/L	1279 (29.9)	–
<0.200 × 10^9 cells/L	1921 (44.9)	–
Not tested at baseline	101 (2.4)	–
Most common baseline antiretroviral regimens, *n (%)*		
Nelfinavir–zidovudine–lamivudine	553 (12.9)	–
Efavirenz–zidovudine–lamivudine	551 (12.9)	–
Indinavir–zidovudine–lamivudine	545 (12.7)	–
Indinavir–stavudine–lamivudine	391 (9.1)	–
Efavirenz–tenofovir–lamivudine	268 (6.3)	–
Nevirapine–zidovudine–lamivudine	237 (5.5)	–

ART = antiretroviral therapy; HCV = hepatitis C virus; IQR = interquartile range.
* Based on highest result.

Data Collection

Baseline data (**Table 1**) included age, sex, race/ethnicity, VA center patient volume, body mass index (BMI), diabetes mellitus, alcohol dependence or abuse, injection or noninjection drug use, hepatitis B surface antigen status, HCV genotype, HCV RNA level, pre-ART CD4 cell count, pre-ART plasma HIV RNA level, and baseline antiretroviral regimen. Diabetes was defined as a random glucose level of at least 200 mg/dL or antidiabetic medication use (22, 23). Alcohol dependence or abuse (24) and injection or noninjection drug use (24, 25) were defined by previously validated ICD-9 diagnoses (**Supplement 1**). Baseline serum creatinine, hemoglobin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels and platelet count were collected from dates closest to but before the start of follow-up. Baseline FIB-4 score, a noninvasive measure of advanced hepatic fibrosis, was determined as follows: [age in years × AST level in U/L] / [(platelet count in × 10^9/L) × (ALT level in U/L)$^{1/2}$] (26). Because liver fibrosis can progress by 1 stage

Table 2. **Incidence Rates, Standardized for Age and Race/Ethnicity, and Adjusted HRs for Specified Liver-Related Outcomes**

Outcome	Incidence Rate (95% CI), *events per 1000 person-years*		Adjusted HR (95% CI)*	
	Antiretroviral-Treated Patients Co-infected With HIV/HCV (n = 4280)	HCV-Monoinfected Patients (n = 6079)	Death Censored	Death as Competing Risk
Hepatic decompensation				
All patients (n = 10 359)	9.5 (7.6–11.9)	5.7 (4.4–7.4)	1.83 (1.54–2.18)	1.56 (1.31–1.86)
Patients with HIV/HCV				
HIV RNA level during follow-up				
<1000 copies/mL (n = 966†)	9.4 (5.4–16.2)	–‡	1.65 (1.20–2.27)	1.44 (1.05–1.99)
≥1000 copies/mL (n = 3180†)	9.6 (7.5–12.2)	–‡	1.87 (1.56–2.25)	1.59 (1.33–1.91)
Pre-ART CD4 count				
$\geq 0.500 \times 10^9$ cells/L (n = 391†)	8.8 (4.4–17.8)	–‡	1.56 (1.04–2.33)§	1.44 (0.96–2.17)§
$0.350–0.499 \times 10^9$ cells/L (n = 588†)	8.1 (4.4–14.8)	–‡	1.61 (1.13–2.28)§	1.44 (1.02–2.05)§
$0.200–0.349 \times 10^9$ cells/L (n = 1279†)	8.6 (5.6–13.1)	–‡	1.63 (1.26–2.11)§	1.45 (1.12–1.88)§
$<0.200 \times 10^9$ cells/L (n = 1921†)	10.9 (7.9–15.0)	–‡	2.03 (1.65–2.51)	1.71 (1.38–2.13)
Hepatocellular carcinoma (n = 10 359)	2.4 (1.7–3.4)	1.9 (1.3–2.6)	1.60 (1.16–2.21)	1.19 (0.88–1.61)
Severe liver events (n = 10 359)	12.9 (10.8–15.5)	8.1 (6.7–9.9)	1.77 (1.52–2.05)	1.47 (1.27–1.70)

ART = antiretroviral therapy; HCV = hepatitis C virus; HR = hazard ratio.
* HRs were adjusted for age, race, diabetes mellitus, body mass index, history of alcohol dependence/abuse, history of injection/noninjection drug use, and Veterans Affairs center patient volume. The proportion of HCV-monoinfected patients who had hemoglobin and hepatitis B surface antigen measured during the baseline period was small. As a result, these variables were not included in multivariable models comparing incidence rates of hepatic decompensation between antiretroviral-treated patients co-infected with HIV and HCV and HCV-monoinfected patients.
† Patients included in the subgroup of antiretroviral-treated patients co-infected with HIV and HCV for specified analysis.
‡ Unchanged from overall result of 5.7 events per 1000 person-years (CI, 4.4 to 7.4 events per 1000 person-years).
§ Because the HRs for strata $\geq 0.200 \times 10^9$ cells/L were indistinguishable, they are displayed as a single plot in the bottom panel of **Figure 2**.

as early as within 4 years for antiretroviral-treated patients co-infected with HIV and HCV (7) and within 5 years for HCV-monoinfected persons (27), we determined baseline FIB-4 scores by using ALT levels, AST levels, and platelet counts within a 2-year period around the start of follow-up. Scores less than 1.45 indicate no or minimal fibrosis, and scores greater than 3.25 indicate advanced hepatic fibrosis or cirrhosis in co-infected (26) and HCV-monoinfected patients (28).

Longitudinal data included hepatitis B surface antigen status, plasma HIV RNA level, diabetes, and liver transplantation (determined by diagnosis and procedural codes) (**Supplement 1**).

Statistical Analysis

The 12 months before the start of follow-up represented the baseline period for both cohorts. Follow-up began 12 months after ART initiation for co-infected patients and after 12 months in the VACS-VC for monoinfected patients. The rationale for defining the baseline period as the first year of receipt of ART for co-infected patients was that many of these patients initially entered care at the time of ART initiation, which was shortly after their HIV diagnosis. Follow-up continued until a study end point, death, initiation of HCV therapy, or the last visit before 30 September 2010, whichever came first.

For descriptive purposes, we estimated incidence rates (events per 1000 person-years) of end points with 95% CIs, standardized by the age and race/ethnicity distribution of co-infected patients (29). We then used Cox models to estimate adjusted hazard ratios (HRs) for outcomes in co-infected compared with monoinfected patients (30). We controlled for all available clinically relevant variables in **Table 1**. The proportionality of hazards was evaluated by plots of Schoenfeld residuals (31). In a sensitivity analysis, we addressed the potential for informative censoring by using inverse probability of censoring weights and Cox regression (**Supplement 2**, available at www.annals.org) (32).

Because mortality rates were higher for co-infected than for monoinfected patients and because death could be a competing risk for decompensation, we determined HRs for decompensation that accounted for death as a competing risk (33). We estimated the incidence of decompensation for both cohorts, standardized to the characteristics of patients in the overall sample based on the covariates in the Cox model (**Table 2**) and assuming that death was a competing risk.

We also performed 3 subgroup analyses. First, because co-infected patients may have had varying antiretroviral adherence during follow-up or might have interrupted or discontinued ART, thus leading to virologic failure, we compared decompensation rates in the monoinfected cohort with those in subgroups of co-infected patients stratified by HIV RNA level during follow-up (<1000 copies/mL on all results during follow-up vs. ≥1000 copies/mL on any result during follow-up). This threshold was chosen because intermittent low-level HIV viremia less than 1000 copies/mL may occur among patients receiving ART and does not necessarily indicate HIV virologic failure (34). In a sensitivity analysis, we compared decompensation rates in the smaller subgroup of co-infected patients who maintained HIV RNA levels less than 400 copies/mL throughout follow-up (n = 386) compared with monoinfected patients. Second, we compared decompensation

rates in the monoinfected cohort with those in co-infected patients stratified by pre-ART CD4 count (<0.200, 0.200 to 0.349, 0.350 to 0.499, and ≥0.500 × 10^9 cells/L). Third, we evaluated the risk for decompensation between co-infected and monoinfected patients at the same baseline stage of liver fibrosis. This analysis focused on patients with no or minimal hepatic fibrosis (FIB-4 score <1.45) to fully evaluate the association between co-infection and decompensation.

Among co-infected patients, we used Cox and competing risk regression analyses to estimate HRs for decompensation for risk factors of interest. Hypothesized risk factors included baseline advanced hepatic fibrosis (FIB-4 score >3.25); baseline obesity (BMI ≥30 kg/m^2); baseline severe anemia (hemoglobin level <100 g/L); diabetes mellitus; active hepatitis B infection; nonblack race; pre-ART CD4 cell count; and HIV viremia copy-years, defined as the log copies of plasma HIV RNA per milliliter over time, which is a measure of cumulative plasma HIV burden (35). We estimated viremia copy-years by the cumulative annual HIV viral load based on the median value of each year of follow-up. Details are presented in **Supplement 3** (available at www.annals.org). Diabetes, hepatitis B, and HIV viremia copy-years were evaluated as time-varying covariates.

In a subgroup analysis among 3314 (77.4%) co-infected patients with baseline HCV RNA results reported in international units per milliliter, we evaluated the association between high baseline HCV RNA level (≥400 000 IU/mL) and decompensation. If multiple baseline HCV RNA loads were available, the highest result was analyzed.

We performed a simulation-based sensitivity analysis to examine the effect of unmeasured confounders on the HR for decompensation between co-infected and monoinfected patients (36). Details appear in **Supplement 4** (available at www.annals.org).

We used multiple imputation to address the potential bias of missing data by means of 10 imputations using all variables in **Table 1** and outcomes (37). We combined results across the 10 data sets to arrive at CIs that accounted for variances within and across data sets (38). Data were analyzed using SAS, version 9.2 (SAS Institute, Cary, North Carolina), and Stata 12.1 (StataCorp, College Station, Texas).

Regulatory Approvals

This study was approved by the Institutional Review Boards of the University of Pennsylvania and Philadelphia VA Medical Center.

Role of the Funding Source

This study was funded by the National Institutes of Health. The funding source had no role in data collection, analysis, or interpretation.

RESULTS

Patient Characteristics

Between 1997 and 2010, a total of 10 359 patients (4280 antiretroviral-treated patients co-infected with HIV and HCV and 6079 HCV-monoinfected patients) met our inclusion criteria (**Figure 1**). Absence of HCV RNA assessment was the most common reason for exclusion from both cohorts. There were no clinically relevant differences in the characteristics between included patients (**Table 1**) and those excluded due to absence of HCV RNA assessment in either cohort.

Table 1 summarizes the baseline cohort characteristics. Co-infected and monoinfected patients were similar in age, race/ethnicity, diabetes, history of alcohol dependence or abuse, and history of injection or noninjection drug use. Most patients in both cohorts were infected with HCV genotype 1. Co-infected patients more commonly had a high HCV RNA level. Follow-up was shorter for co-infected than monoinfected patients (6.8 vs. 9.9 years; $P <$ 0.001). During follow-up, 330 (7.7%) co-infected and 505 (8.3%) monoinfected patients initiated HCV therapy and were censored.

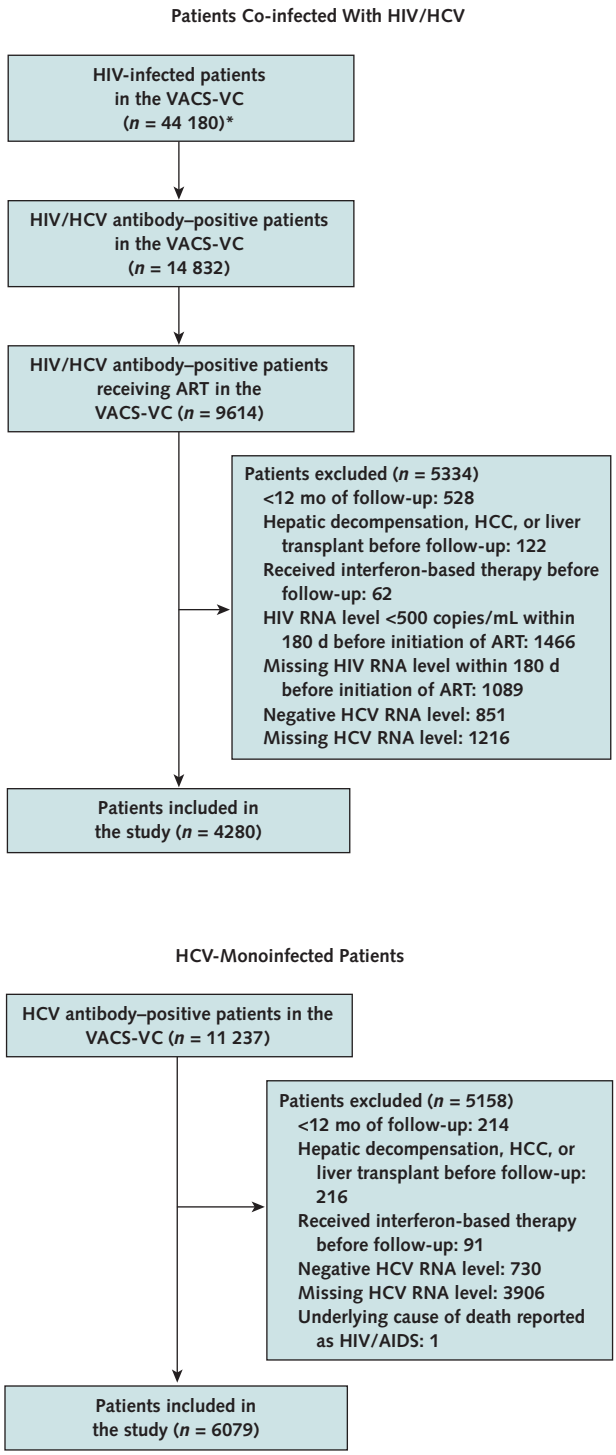
Baseline ART regimens prescribed to co-infected patients reflected the antiretroviral drugs used at the time of entry into the VACS-VC (**Table 1**). A relatively small number (162 [3.8%]) was prescribed a combination of abacavir, lamivudine, and zidovudine as the baseline regimen. Among the 241 co-infected patients who were positive for hepatitis B surface antigen, 207 (85.9%) received lamivudine alone, tenofovir plus emtricitabine, or tenofovir plus lamivudine as part of their baseline regimen. Co-infected patients had a median of 2.8 HIV RNA results (interquartile range [IQR], 1.8 to 3.8 results) measured each year during follow-up to assess HIV virologic response.

Hepatic Decompensation

Hepatic decompensation occurred more frequently in antiretroviral-treated co-infected patients (271 [6.3%]) than among monoinfected patients (305 [5.0%]) ($P =$ 0.004). At the time of initial decompensation, variceal hemorrhage was less common among co-infected patients (71 [26.2%] vs. 168 [55.1%]; $P <$ 0.001). However, similar proportions of co-infected and monoinfected patients presented with ascites (226 [83.4%] vs. 236 [77.4%]; $P =$ 0.070) and spontaneous bacterial peritonitis (48 [17.7%] vs. 68 [22.3%]; $P =$ 0.171). Among those who presented with ascites, similar proportions of co-infected and monoinfected patients had the diagnosis recorded in the inpatient setting (145 [64.2%] vs. 133 [56.4%]; $P =$ 0.087).

After adjustment for age, race/ethnicity, diabetes, BMI, history of alcohol abuse and injection or noninjection drug use, and VA center patient volume, co-infected patients receiving ART had a higher rate of decompensation than monoinfected patients (HR, 1.83 [95% CI, 1.54

Figure 1. **Study flow diagram.**



ART = antiretroviral therapy; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; VACS-VC = Veterans Aging Cohort Study Virtual Cohort.
* HIV infection determined by diagnosis codes from the International Classification of Diseases, Ninth Revision.

to 2.18]). This association was almost identical when we expanded our outcome to include events from VA, Medicare, or Medicaid data (HR, 1.85 [CI, 1.59 to 2.18]) and remained when we treated death as a competing risk (HR, 1.56 [CI, 1.31 to 1.86]). Hazard ratios that were adjusted for informative censoring differed little (data not shown). The standardized cumulative incidence of decompensation was higher among co-infected than monoinfected patients at 10 years (7.4% vs. 4.8%; $P < 0.001$) (**Figure 2** [*top*]).

In subgroup analyses, rates of decompensation remained higher in co-infected patients who maintained HIV RNA levels less than 1000 copies/mL throughout follow-up compared with monoinfected patients (**Table 2** and **Figure 2** [*middle*]). Similar results were observed when co-infected patients with HIV RNA levels less than 400 copies/mL throughout follow-up were compared with HCV-monoinfected patients (data not shown). Across strata of pre-ART CD4 cell count, the HR for decompensation was highest for co-infected patients with a pre-ART CD4 count less than 0.200×10^9 cells/L compared with monoinfected persons (**Table 2** and **Figure 2** [*bottom*]). Among those with a baseline FIB-4 score less than 1.45, the risk for decompensation remained higher in co-infected than monoinfected patients (adjusted HR, 1.98 [CI, 1.23 to 3.18]).

Hepatocellular Carcinoma

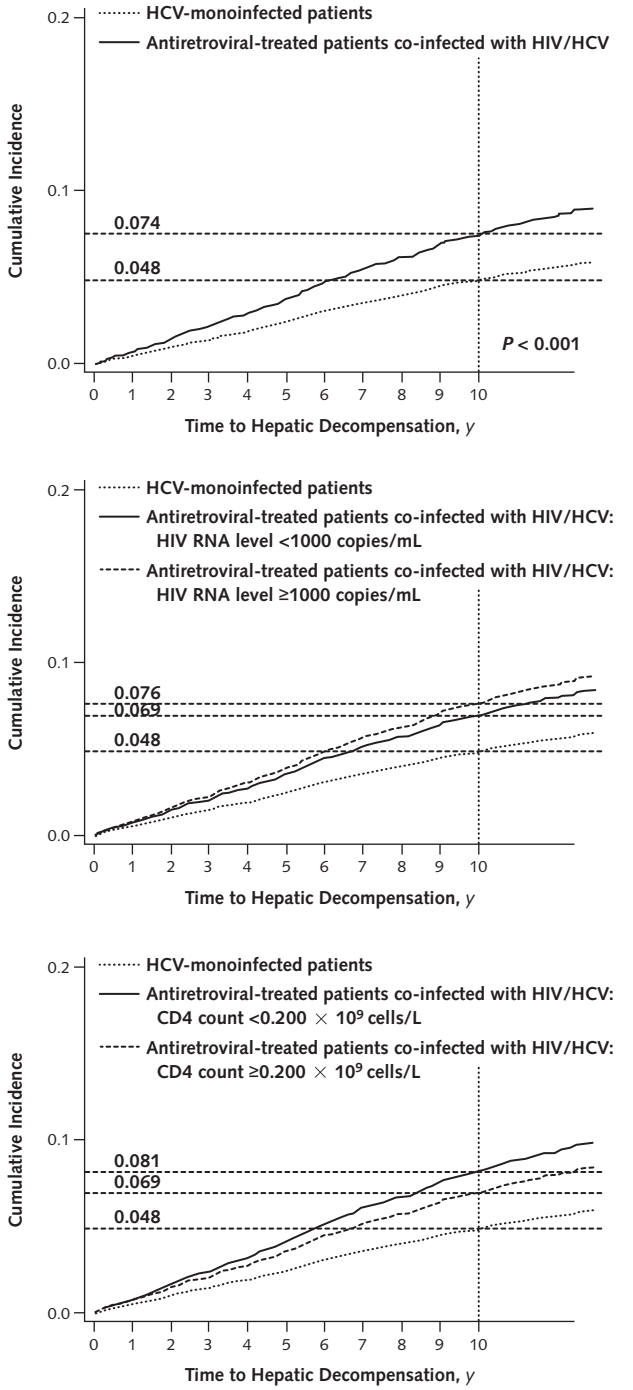
The proportions of co-infected and monoinfected patients who developed HCC were similar (74 [1.7%] vs. 100 [1.6%]; $P = 0.74$). After adjustment for age, race, diabetes, BMI, alcohol abuse, injection or noninjection drug use, and VA center patient volume, rates of HCC were higher for co-infected patients (HR, 1.60 [CI, 1.16 to 2.21]). This association did not remain significant in a competing risk analysis (**Table 2**). Median survival after HCC diagnosis was shorter for co-infected patients (8.7 months [IQR, 2.3 to 27.3 months] vs. 14.2 months [IQR, 3.8 to 101.8 months]), but this difference was not significant ($P = 0.22$). There were no important differences in age at diagnosis, race, BMI, diabetes, or alcohol abuse between co-infected and monoinfected patients with HCC (**Appendix Table 1**, available at www.annals.org).

Severe Liver Events and Death

Severe liver events were more common in co-infected than monoinfected patients (373 [8.7%] vs. 433 [7.1%]; $P = 0.003$), and co-infected patients had a higher risk for this end point (**Table 2**). Liver transplantation was less common among co-infected patients (5 [0.1%] vs. 26 [0.4%]; $P = 0.004$).

Death occurred more frequently among co-infected patients (1407 [32.9%] vs. 934 [15.4%]; $P < 0.001$), and HIV/AIDS (46.3%) was most commonly recorded as the underlying cause of death in this cohort. Liver disease (20.1%) was most commonly recorded as the cause of

Figure 2. **Standardized cumulative incidences of hepatic decompensation, based on competing risk regression analyses.**



ART = antiretroviral therapy; HCV = hepatitis C virus.
Top. Antiretroviral-treated patients co-infected with HIV and HCV (*solid line*) and HCV-monoinfected patients (*dotted line*). *Middle.* Co-infected patients with HIV RNA levels ≥1000 copies/mL on any HIV RNA test result during follow-up (*dashed line*), co-infected patients with HIV RNA levels <1000 copies/mL on all HIV RNA test results throughout follow-up (*solid line*), and HCV-monoinfected patients (*dotted line*). *Bottom.* Co-infected patients with pre-ART CD4 T-lymphocyte counts $<0.200 \times 10^9$ cells/L (*solid line*), co-infected patients with pre-ART CD4 T-lymphocyte counts $\geq 0.200 \times 10^9$ cells/L (*dashed line*), and HCV-monoinfected patients (*dotted line*). Strata for CD4 counts $\geq 0.200 \times 10^9$ cells/L were collapsed into a single plot because these hazard ratios were indistinguishable (see **Table 2**).

death in monoinfected patients (**Appendix Table 2**, available at www.annals.org).

Factors Associated With Decompensation Among Co-infected Patients

Baseline advanced hepatic fibrosis, baseline hemoglobin level less than 100 g/L, diabetes, and nonblack race were risk factors for decompensation (**Table 3**). The hazard for HIV viremia copy-years greater than 6 log copy-years/mL was approximately twice that of the reference group (<2 log copy-years/mL), but these results did not approach statistical significance.

The incidence of decompensation was similar between co-infected patients with baseline HCV RNA levels of 400 000 IU/mL or greater and those with levels less than 400 000 IU/mL (5.8% [169/2936] vs. 6.9% [26/378]; HR, 0.78 [CI, 0.52 to 1.18]). Results were similar for competing risk regression analyses (data not shown).

DISCUSSION

In this study, antiretroviral-treated patients co-infected with HIV and HCV had higher rates of hepatic decompensation and severe liver events than HCV-monoinfected patients. Co-infected patients who maintained HIV RNA levels less than 1000 copies/mL or less than 400 copies/mL over the median 6.8 years of follow-up still had higher rates of decompensation, suggesting that HIV viral suppression below these thresholds with ART is not sufficient to reduce rates of end-stage liver disease to those of HCV-monoinfected patients. Furthermore, among patients with minimal or no fibrosis at baseline, the risk for decompensation remained higher for co-infected patients. Rates of decompensation were highest for patients with pre-ART CD4 counts less than 0.200×10^9 cells/L compared with monoinfected patients. Finally, among co-infected patients receiving ART, baseline advanced liver fibrosis, severe anemia, diabetes, and nonblack race were each associated with higher rates of decompensation.

Our analyses examining the risk for decompensation between co-infected and monoinfected patients did not control for baseline stage of hepatic fibrosis because the development of liver fibrosis is in the causal pathway to hepatic decompensation. Thus, controlling for baseline hepatic fibrosis could adjust away an association between treated HIV and decompensated cirrhosis. We conducted a secondary analysis restricted to patients with minimal or no liver fibrosis (FIB-4 score <1.45) at baseline. Antiretroviral-treated co-infected patients continued to have an increased risk for hepatic decompensation compared with monoinfected patients.

Table 3. **Factors Associated With Hepatic Decompensation Among 4280 Antiretroviral-Treated Patients Co-infected With HIV and HCV**

Characteristic	Adjusted HR (95% CI)*	
	Death Censored	Death as Competing Risk
Body mass index		
<18.5 kg/m^2	0.58 (0.22–1.52)	0.46 (0.17–1.23)
18.5–24.9 kg/m^2	Referent	Referent
25–29.9 kg/m^2	1.09 (0.83–1.42)	1.13 (0.86–1.47)
≥30 kg/m^2	1.04 (0.69–1.56)	1.07 (0.71–1.62)
Diabetes mellitus†		
Absent	Referent	Referent
Present	1.88 (1.39–2.53)	1.88 (1.38–2.56)
FIB-4 score		
<1.45	Referent	Referent
1.45–3.25	1.99 (1.39–2.85)	1.91 (1.33–2.73)
>3.25	6.54 (4.56–9.39)	5.45 (3.79–7.84)
Hemoglobin level		
≥100 g/L	Referent	Referent
<100 g/L	3.50 (1.97–6.24)	2.24 (1.20–4.20)
Hepatitis B surface antigen†		
Absent	Referent	Referent
Present	1.04 (0.61–1.77)	0.98 (0.57–1.69)
Race		
Black	Referent	Referent
Nonblack	2.14 (1.67–2.75)	2.12 (1.65–2.72)
HIV viremia copy-years†		
<2 log copy-years/mL	Referent	Referent
2–6 log copy-years/mL	1.37 (0.67–2.77)	1.64 (0.84–3.23)
≥6 log copy-years/mL	2.01 (0.66–6.12)	2.06 (0.69–6.10)
Pre-ART CD4 count‡		
≥0.200 × 10^9 cells/L	Referent	Referent
<0.200 × 10^9 cells/L	1.22 (0.95–1.56)	1.17 (0.91–1.49)

ART = antiretroviral therapy; HCV = hepatitis C virus; HR = hazard ratio.
* Adjusted for all other risk factors as well as history of alcohol dependence/abuse, history of injection/noninjection drug use, age, serum creatinine level, and Veterans Affairs center patient volume.
† Evaluated as time-varying covariate.
‡ Measured ≤180 d before initiation of ART.

The mechanisms for the higher rates of hepatic decompensation in co-infected patients receiving ART remain unclear. HIV-related immune dysregulation, HIV-mediated depletion of CD4 cells in the gastrointestinal tract with resultant microbial translocation, oxidative stress related to co-infection with HIV and HCV, and HIV-induced hepatocyte apoptosis have been implicated in the pathogenesis of progressive hepatic disease in patients co-infected with HIV and HCV (13). Other cofactors, such as hepatic steatosis and cumulative exposure to potentially hepatotoxic medications, particularly selected antiretroviral drugs (39–41), might also accelerate liver disease progression in co-infected patients.

We found that variceal hemorrhage was less commonly an initial presenting decompensation event among co-infected patients. A similar finding was reported in a cohort study of Spanish patients who were co-infected with HIV and HCV (42). Prior studies have suggested that HIV infection is associated with protein C deficiency (43–45) and protein S deficiency (46), which can promote hypercoagulability and reduce the likelihood of variceal bleeding among co-infected patients.

We found a higher rate of HCC in co-infected patients receiving ART than in HCV-monoinfected patients, but this difference was not statistically significant after adjustment for competing risk. A prior cohort study conducted between 1992 and 2000 showed that co-infection with HIV and HCV was not associated with an increased risk for HCC compared with HCV monoinfection in either the pre-ART or ART eras (47). As life expectancy continues to increase among patients co-infected with HIV and HCV, clinically important differences in rates of HCC may become apparent in the future.

We identified several important factors associated with hepatic decompensation in co-infected patients. Diabetes is associated with hepatic steatosis (48), which could promote hepatic inflammation and accelerate liver fibrosis progression (49). Diabetes might also induce hepatic fibrosis independent of steatosis via stimulation of hepatic stellate cells by insulin (50, 51). Severe anemia might be a marker of advanced HCV-associated liver disease, potentially indicating blood loss from variceal bleeding. Alternatively, anemia may be a marker for systemic inflammation (52), which may promote hepatic fibrosis. Nonblack HCV-infected patients have been reported to have stronger HCV-specific immunity than black patients (53), which could result in increased immune-mediated hepatic inflammation and accelerated liver fibrosis progression.

Our results suggest that the highest level of HIV viremia copy-years (>6 log copy-years/mL of HIV RNA) might increase the risk for hepatic decompensation. However, plasma viral loads were measured infrequently in many patients, with variable numbers and timing. Given our additional finding of a higher risk for decompensation in co-infected patients with pre-ART CD4 counts less than 0.200 × 10^9 cells/L than in monoinfected patients, suppression of HIV while receiving ART and resultant immune reconstitution should remain a key goal for patients co-infected with HIV and HCV to possibly reduce the risk for end-stage liver disease.

Neither hepatitis B infection nor HCV RNA level was associated with hepatic decompensation among co-infected patients. Most co-infected patients (85.9%) who were positive for hepatitis B surface antigen received hepatitis B–active ART, and this might have mitigated the association between hepatitis B and decompensation. Future analyses should test this hypothesis. Moreover, although several studies in HCV-monoinfected patients have suggested that higher HCV RNA levels are associated with more advanced liver fibrosis (54–56) or death from end-stage liver disease (57), most have found no association between

HCV RNA level and liver disease severity (58–62). Our results are consistent with these findings.

Our results have important clinical implications. The finding that antiretroviral-treated co-infected patients who maintained an HIV RNA level less than 1000 copies/mL had lower rates of hepatic decompensation than those who did not achieve HIV suppression below this level suggests that suppression of HIV RNA with ART is an important factor in slowing progression of HCV-related liver fibrosis. This observation supports current management guidelines that recommend initiation of ART among patients co-infected with HIV and HCV, regardless of CD4 cell count (16, 63). Furthermore, the increased rate of hepatic decompensation among co-infected patients should prompt earlier consideration of initiation of HCV therapy to try to reduce the risk for liver complications (19, 20). Recent clinical trials evaluating boceprevir- and telaprevir-based antiviral therapy among patients co-infected with HIV and HCV genotype 1 show sustained HCV virologic response rates that are similar to those of HCV-monoinfected patients (64, 65). Providers might also address modifiable risk factors, such as diabetes, to try to decrease the risk for end-stage liver disease.

This study has several potential limitations. First, decompensation outcomes could have been misclassified. However, hepatic decompensation was identified using a validated definition (21). We might have underestimated the number of decompensation events because our definition did not include hepatic encephalopathy; however, the negative predictive value of our validated definition exceeded 99% (21). In addition, the incidence rates of decompensation among co-infected (9.5 per 1000 person-years) and monoinfected (5.7 per 1000 person-years) patients in this study were similar to those reported in other cohorts of co-infected (11.6 per 1000 person-years [10]) and monoinfected (3.4 per 1000 person-years [62]) patients. The potential exists for differential ascertainment of outcomes if patients in one of the cohorts more frequently presented to non-VA hospitals for care. To address this issue, we evaluated incident decompensation events within the VA system and in the U.S. Medicare and Medicaid programs, as well as liver-related deaths within a composite severe liver event outcome. The association between antiretroviral-treated co-infection and these composite end points remained in both analyses. Second, residual confounding by unmeasured factors (for example, duration of HCV infection or alcohol dependence or drug use during follow-up) is possible. However, sensitivity analyses (**Supplement** 4) suggested that our results were robust to the potential bias from unobserved confounders. Third, the median follow-up among the monoinfected patients was longer than that for the co-infected patients. However, both cohorts included patients in all age groups and produced risk sets of adequate size for all combinations of decompensation risk factors across age groups; therefore, they covered the spectrum of risk among young, middle-aged, and older HCV-infected patients. Finally, our study sample predominantly comprised male U.S. veterans, so results may not be generalizable to women. Because progression of HCV-related liver fibrosis differs by sex (60, 66, 67), future epidemiologic analyses should evaluate end-stage liver disease events among women co-infected with HIV and HCV and HCV-monoinfected women.

This study has several strengths. It is, to our knowledge, the largest study to evaluate liver-related events among antiretroviral-treated co-infected patients and to compare outcomes with those of HCV-monoinfected persons. It had a long duration of follow-up, evaluated validated end points (21), accounted for time-varying covariates, and identified decompensations and liver-related deaths outside the VA system, ensuring that few outcomes were missed.

In conclusion, we found that patients co-infected with HIV and HCV who were receiving ART had higher rates of hepatic decompensation and severe liver events than HCV-monoinfected patients. Among co-infected patients receiving ART, baseline advanced liver fibrosis, severe anemia, diabetes, and nonblack race were associated with higher rates of decompensation. Clinicians should address modifiable risk factors and consider treatment of HCV infection in co-infected patients to reduce rates of hepatic decompensation.

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Appendix Table 1. **Characteristics of Patients With Hepatocellular Carcinoma***

Characteristic	Antiretroviral-Treated Patients Co-infected With HIV/HCV (*n* = 74)	HCV-Monoinfected Patients (*n* = 100)
Median (IQR) age at diagnosis, *y*	57 (54–61)	56 (54–59)
Male	74 (100.0)	100 (100.0)
Race/ethnicity		
Black	49 (66.2)	59 (59.0)
White	14 (18.9)	28 (28.0)
Hispanic	11 (14.9)	12 (12.0)
Other/unknown	0 (0.0)	1 (1.0)
Body mass index		
<18.5 kg/m^2	3 (4.1)	2 (2.0)
18.5–24.9 kg/m^2	37 (50.0)	28 (28.0)
25–29.9 kg/m^2	29 (39.2)	32 (32.0)
≥30 kg/m^2	4 (5.4)	37 (37.0)
Missing	1 (1.4)	1 (1.0)
Diabetes mellitus	10 (13.5)	9 (9.0)
History of alcohol dependence/abuse	19 (25.7)	35 (35.0)
History of drug abuse	25 (33.8)	29 (29.0)
Hepatitis B surface antigen status		
Positive	9 (12.2)	1 (1.0)
Negative	64 (86.5)	19 (19.0)
Not tested at baseline	1 (1.4)	80 (80.0)
Median (IQR) pre-ART HIV RNA level, *log copies/mL*	4.3 (3.8–5.0)	–
CD4 count at diagnosis		
≥0.500 × 10^9 cells/L	9 (12.2)	–
0.350–0.499 × 10^9 cells/L	11 (14.9)	–
0.200–0.349 × 10^9 cells/L	25 (33.8)	–
<0.200 × 10^9 cells/L	28 (37.8)	–
Missing	1 (1.4)	–

ART = antiretroviral therapy; HCV = hepatitis C virus; IQR = interquartile range.
* Data are numbers (percentages) unless otherwise indicated.

Appendix Table 2. Causes of Death

Cause*	Deaths, *n (%)*	
	Antiretroviral-Treated Patients Co-infected With HIV/HCV (*n* = 1407)	HCV-Monoinfected Patients (*n* = 934)
Liver-related	110 (7.8)	188 (20.1)
Alcoholic liver disease	16 (1.1)	30 (3.2)
Hepatic decompensation†	13 (0.9)	18 (1.9)
Hepatitis C	20 (1.4)	35 (3.7)
Other viral hepatitis	1 (0.1)	3 (0.3)
Liver cancer‡	35 (2.5)	61 (6.5)
Nonalcoholic liver disease§	25 (1.8)	41 (4.4)
Accidents (unintentional injury)	65 (4.6)	66 (7.1)
Intentional self-harm (suicide)	8 (0.6)	10 (1.1)
Assault (homicide)	14 (1.0)	10 (1.1)
Cardiovascular disease	121 (8.6)	176 (18.8)
Other circulatory disorders	0 (0.0)	2 (0.2)
Diabetes mellitus	9 (0.6)	35 (3.7)
HIV/AIDS	652 (46.3)	NA
Infection‖	37 (2.6)	40 (4.3)
Infectious, parasitic disease	27 (1.9)	31 (3.3)
Meningitis	0 (0.0)	1 (0.1)
Influenza, pneumonia	10 (0.7)	8 (0.9)
Malignant lymphoid neoplasms	8 (0.6)	8 (0.9)
Other malignant neoplasms	84 (6.0)	101 (10.8)
In situ or benign neoplasms	1 (0.1)	3 (0.3)
Nephritis, nephrotic syndrome	21 (1.5)	18 (1.9)
Noninfectious respiratory	16 (1.1)	27 (2.9)
Chronic lower respiratory	11 (0.8)	17 (1.8)
Pneumonitis	3 (0.2)	3 (0.3)
Other respiratory system	2 (0.1)	7 (0.7)
Mental and behavioral disorders¶	19 (1.4)	26 (2.8)
Other	67 (4.8)	72 (7.7)
Not reported	175 (12.4)	152 (16.3)

HCV = hepatitis C virus; NA = not applicable.
* Classified using categories determined by the National Center for Health Statistics.
† Includes cases in which ascites, spontaneous bacterial peritonitis, esophageal variceal hemorrhage, hepatic encephalopathy, hepatic failure, or end-stage liver disease was identified as the underlying cause of death on the death certificate.
‡ Includes cases in which hepatocellular carcinoma or another malignant neoplasm of the liver was identified as the underlying cause of death on the death certificate.
§ Includes cases in which a diagnosis of toxic liver disease or another specified or unspecified chronic hepatitis was identified as the underlying cause of death on the death certificate.
‖ Excludes HIV-related and viral hepatitis–related diagnoses.
¶ Deaths from psychoactive substance use related to mental and behavioral disorders.