

Hepatic Decompensation in Patients With HIV/Hepatitis B Virus (HBV)/Hepatitis C Virus (HCV) Triple Infection Versus HIV/HCV Coinfection and the Effect of Anti-HBV Nucleos(t)ide Therapy

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The incidence rate of hepatic decompensation was higher in patients with human immunodeficiency virus (HIV)/hepatitis B virus (HBV)/hepatitis C virus (HCV) triple infection than in those with HIV/HCV coinfection (24.1 vs 10.8 events per 1000 person-years; hazard ratio [HR], 1.89; 95% confidence interval [CI], 1.12–3.18). Compared with HIV/HCV-infected patients, the rate of decompensation was increased among HIV/HBV/HCV-infected patients receiving no anti-HBV therapy (HR, 2.48; 95% CI, 1.37–4.49) but not among those who did receive such therapy (HR, 1.09; 95% CI, .40–2.97)

Keywords. end-stage liver disease; hepatic decompensation; hepatitis B; hepatitis C; HIV.

Owing to shared routes of transmission, hepatitis B virus (HBV) infection may also be present in patients with human immunodeficiency virus (HIV)/hepatitis C virus (HCV) coinfection

[1–5]. However, few studies have compared rates of hepatic decompensation between patients with HIV/HBV/HCV triple infection and those with HIV/HCV dual infection. Mechanistically, HBV infection could either increase or have little effect on the rate of hepatic decompensation among HIV/HCV-coinfected persons. Chronic HBV infection might exacerbate immune-mediated hepatic inflammation and fibrosis and increase the risk of hepatic decompensation in HIV/HCV-infected patients [6]. Alternatively, because replication of one hepatitis virus usually predominates over the other in coinfecting persons [7–10], the reciprocal inhibitory effect of hepatitis viruses might lead to comparable decompensation rates in HIV/HBV/HCV-infected and HIV/HCV-infected patients. Moreover, it remains unclear whether rates of decompensation in HIV/HBV/HCV-infected patients receiving anti-HBV nucleos(t)ide analogue therapy are similar to those of HIV/HCV-infected patients.

We first compared rates of hepatic decompensation in HIV/HBV/HCV-infected and HIV/HCV-infected patients. We then determined the risk of decompensation associated with anti-HBV nucleos(t)ide analogue-untreated and treated HIV/HBV/HCV infection compared with HIV/HCV infection.

METHODS

We conducted a retrospective cohort study among patients with HIV/HBV/HCV triple infection and those with HIV/HCV coinfection in the Veterans Health Administration (VA) between 1 October 2005 and 28 February 2012. Data within the VA's national Medical SAS Dataset, Pharmacy Benefits Management files, and Decision Support System were evaluated [11, 12], including hospital and outpatient *International Classification of Diseases, Ninth Revision* (ICD-9) diagnoses, laboratory results, and dispensed medications. Death date was determined using the VA Vital Status file. This study was approved by the University of Pennsylvania Institutional Review Board.

HIV/HBV/HCV-infected patients had: (1) HIV (HIV ICD-9 diagnosis, positive HIV antibody/RNA result, or prescriptions for antiretroviral therapy (ART), defined as use of ≥ 3 antiretrovirals from 2 classes [13]); (2) detectable HCV RNA (HCV RNA >650 IU/mL or positive qualitative HCV RNA result); (3) chronic HBV (2 chronic HBV ICD-9 diagnoses, 2 positive HBV surface antigen results, or a positive HBV surface antigen result and chronic HBV ICD-9 diagnosis that each had to be recorded >6 months apart, or a prescription for a nonantiretroviral anti-HBV nucleos(t)ide analogue [ie, adefovir, entecavir, or telbivudine]),

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and (4) ≥ 12 months in the VA system. HIV/HCV-infected patients had: (1) HIV infection; (2) detectable HCV RNA; (3) ≥ 12 months in the VA system; and (4) no chronic HBV ICD-9 diagnosis, positive HBV surface antigen, or prescriptions for nonnucleos(t)ide analogues. Previously validated ICD-9 diagnoses used to identify HIV [14] and chronic HBV [15] are listed in [Supplementary Appendix 1](#). Patients were excluded if they had hepatic decompensation or had received interferon-based HCV therapy (because treatment reduces the risk of end-stage liver disease [16, 17]) before the start of follow-up.

Follow-up for both cohorts began after 12 months in the VA system. The 12 months before the start of follow-up represented the baseline period. Follow-up continued until first hepatic decompensation (defined below), death, HCV treatment initiation, or last visit before 28 February 2012.

The primary outcome was incident hepatic decompensation, defined by 1 hospital discharge ICD-9 diagnosis or ≥ 2 outpatient ICD-9 diagnoses of ascites, spontaneous bacterial peritonitis, or esophageal variceal hemorrhage ([Supplementary Appendix 2](#)). A prior study validated this definition, with 91% of events confirmed by medical records [18]. Two outpatient diagnoses were required to exclude events that might be suspected, but not confirmed, at follow-up visits. Based on the results of the prior validation study [18], we did not include ICD-9 diagnoses for hepatic encephalopathy or jaundice, which could indicate decompensation, because these diagnoses were often linked to unrelated conditions (eg, narcotic overuse, stroke recorded as encephalopathy, biliary obstruction, or atazanavir-associated hyperbilirubinemia recorded as jaundice). The decompensation date was defined as the hospital discharge date (if identified by hospital diagnosis) or initial outpatient diagnosis date (if identified by outpatient diagnoses).

Baseline data included age, sex, race, ethnicity, body mass index, diabetes mellitus, alcohol dependence/abuse, injection/noninjection drug use, HCV RNA level, hepatitis delta virus ICD-9 diagnosis, CD4 cell count, plasma HIV RNA, use of antiretroviral medications, and use of anti-HBV nucleos(t)ide analogues (ie, adefovir, emtricitabine, entecavir, lamivudine, telbivudine, or tenofovir). Diabetes [19], alcohol dependence/abuse [20], and injection/noninjection drug use [20, 21] were defined by validated ICD-9 diagnoses.

We estimated incidence rates (events per 1000 person-years) of hepatic decompensation with 95% confidence intervals (CIs) in each cohort. We used Cox regression to estimate adjusted hazard ratios (HRs) of decompensation in triply versus dually infected patients [22]. Potential confounders evaluated included age, race, ethnicity, body mass index, diabetes, alcohol dependence/abuse, drug use, and HCV RNA level. We then used Cox regression to determine the risk of decompensation in anti-HBV nucleos(t)ide analogue-untreated and treated HIV/

HBV/HCV-infected patients compared with HIV/HCV-infected patients. Proportionality of hazards was evaluated using plots of Schoenfeld residuals [23]. Data were analyzed using SAS software (version 9.2; SAS Institute).

RESULTS

Between 2005 and 2012, a total of 5051 patients (149 with HIV/ HBV/HCV and 4902 with HIV/HCV infection) met inclusion criteria ([Supplementary Figure 1](#)). Triply infected patients were more commonly white and Hispanic and more frequently had diabetes, alcohol and drug dependence/abuse, and an HCV RNA level $< 800\,000$ IU/mL (Table 1). Similar proportions of both cohorts had HIV RNA < 75 copies/mL and CD4 counts < 200 cells/mm³, but HIV/HBV/HCV-infected patients were more frequently prescribed ART during the baseline period. Among the 149 triply infected patients, 63 (42.3%) received an anti-HBV nucleos(t)ide analogue as part of their baseline ART regimen, most commonly tenofovir in combination with either emtricitabine or lamivudine. Seventeen HIV/HBV/HCV-infected patients (11.4%) also had a diagnosis of hepatitis delta virus infection.

The median follow-up time was longer for triply infected than for dually infected patients (4.6 vs 4.4 years; $P = .03$). During follow-up, 15 (10.1%) of the HIV/HBV/HCV-infected and 544 (11.1%) of the HIV/HCV-infected patients started HCV therapy and were censored. A higher proportion of triply infected patients died during follow-up (13 [8.7%] vs 209 [4.3%]; $P = .009$).

Hepatic decompensation occurred more frequently in triply than in dually infected patients (16 [10.7%] vs 230 [4.7%]; $P = .02$). At the time of initial decompensation, spontaneous bacterial peritonitis was less common among triply infected patients (0/16 [0.0%] vs 18/230 [7.8%]; $P < .001$). Similar proportions of triply and dually infected patients with hepatic decompensation presented with ascites (13/16 [81.3%] vs 176/230 [76.5%]; $P = .63$) and variceal hemorrhage (6/16 [37.5%] vs 68/230 [29.6%]; $P = .53$). The unadjusted incidence rate of hepatic decompensation was higher in triply than in dually infected patients (24.1 vs 10.8 events per 1000 person-years). After adjustment for baseline age, ethnicity, diabetes, history of alcohol abuse, and HCV RNA level, HIV/HBV/HCV-infected patients had a higher rate of decompensation than HIV/HCV-infected patients (HR, 1.89; 95% CI, 1.12–3.18).

Compared to findings in HIV/HCV-infected patients, the rate of decompensation was increased for triply infected patients with no anti-HBV nucleos(t)ide analogue use (HR, 2.48; 95% CI, 1.37–4.49) but not for those receiving an anti-HBV nucleos(t)ide analogue (HR, 1.09; 95% CI, .40–2.97), after controlling for age, ethnicity, diabetes, history of alcohol abuse, and HCV RNA level. No differences in the frequency of decompensation were observed by anti-HBV regimen prescribed.

Table 1. Baseline Characteristics of Study Cohorts

Characteristic	HIV/HBV/HCV-Infected Patients (n = 149)	HIV/HCV-Infected Patients (n = 4902)	P Value
Age, median (IQR), y	52 (48–56)	53 (49–57)	.19
Male sex, No. (%)	146 (98.0)	4790 (97.7)	.83
Race, No. (%)			
Black	62 (41.6)	2106 (43.0)	.74
White	51 (34.2)	878 (17.9)	<.001
Other/unknown	36 (24.2)	1918 (39.1)	<.001
Hispanic ethnicity	32 (21.5)	286 (5.8)	<.001
BMI, median (IQR), kg/m ²	25.3 (22.6–28.5)	25.7 (23.2–28.9)	.22
Diabetes mellitus, No. (%)	31 (20.8)	681 (13.9)	.02
History of alcohol dependence/abuse, No. (%)	46 (30.9)	1027 (21.0)	.004
History of injection/noninjection drug use, No. (%)	88 (59.1)	1961 (40.0)	<.001
HCV RNA level, No. (%) ^a			
≥800 000 IU/mL	96 (64.4)	3529 (72.0)	.04
<800 000 IU/mL	43 (28.9)	1061 (21.6)	.04
Qualitative result only	10 (6.7)	312 (6.4)	.86
HIV RNA level			
Median (IQR), log copies/mL	4.1 (2.8–5)	4.3 (2.7–5)	.75
<75 copies/mL, No. (%)	60 (40.3)	1657 (33.8)	.10
CD4 cell count			
Median (IQR), cells/mm ³	356 (206–561)	378 (204–568)	.81
<200 cells/mm ³ , No. (%)	15 (10.1)	492 (10.0)	.99
Prescribed ART, No. (%)			
During baseline period	84 (56.4)	2332 (47.6)	.03
Ever	114 (76.5)	3470 (70.8)	.13
Anti-HBV nucleos(t)ide analogue use, No. (%) ^b			
During baseline period	63 (42.3)	1510 (30.8)	.003
Ever	103 (69.1)	2809 (57.3)	.004
Baseline anti-HBV nucleos(t)ide analogue regimens, No. (%) ^c			
Tenofovir and emtricitabine	30 (20.1)	789 (16.1)	.20
Tenofovir and lamivudine	24 (16.1)	464 (9.5)	.007
Tenofovir alone	0 (0.0)	5 (0.1)	.047
Lamivudine alone	1 (0.7)	65 (1.3)	.49
Other	18 (12.1)	449 (9.2)	.23

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range.

^a Based on highest baseline HCV RNA result.

^b Defined by dispensed prescription for adefovir, emtricitabine, entecavir, lamivudine, telbivudine, or tenofovir.

^c Patients may have been receiving >1 regimen during the baseline period.

DISCUSSION

In this study, HIV/HBV/HCV-infected patients had higher rates of hepatic decompensation than HIV/HCV-infected patients. Specifically, the risk of decompensation was increased among triply infected patients who did not receive an anti-HBV-active nucleos(t)ide analogue.

Our findings are consistent with those of prior studies evaluating liver-related outcomes among HIV/HBV/HCV-infected

patients. A cohort study from the United States found that liver-related deaths occurred more frequently among patients with HIV/HBV/HCV infection than among those with either HIV/HCV or HIV infection alone [1]. Similarly, a cross-sectional study from Spain showed that HIV/HBV/HCV-infected patients had a higher prevalence of cirrhosis than HIV/HBV- or HIV/HCV-infected patients [2]. Another cohort study from Spain observed that HIV/HBV/HCV-infected patients had higher rates of cirrhosis and hepatic decompensation than HIV/HBV-infected patients [24].

Our observation that HIV/HBV/HCV-infected patients receiving anti-HBV nucleos(t)ide analogue therapy did not have a higher rate of decompensation than HIV/HCV-infected patients demonstrates the effect of anti-HBV treatment on liver-related complications. This finding supports the recommendation that all HIV/HBV-coinfected patients should start and continue anti-HBV-active ART, regardless of CD4 count [13]. These guidelines state that the optimal ART regimen for HBV-coinfected persons should include tenofovir and emtricitabine (or lamivudine) as the preferred nucleos(t)ide backbone. If tenofovir cannot safely be used, entecavir is an alternative if used with a fully suppressive ART regimen.

This study has several potential limitations. Decompensation outcomes could have been misclassified, but the risk of misclassification was minimized by using a previously validated definition [18, 25]. Because this definition did not include hepatic encephalopathy diagnoses, the number of decompensation events might have been underestimated. However, the negative predictive value of the definition exceeded 99% [18]. Second, residual confounding by unmeasured factors (eg, duration of HIV infection and viral hepatitis, tobacco use, and alcohol dependence/drug use during follow-up) is possible. Moreover, hepatitis B e antigen, hepatitis B e antibody, and hepatitis B DNA were only rarely measured in clinical practice, so we could not evaluate the influence of these variables on decompensation events, particularly the effectiveness of anti-HBV-active ART. Finally, our sample included predominantly male US veterans, and results may not be generalizable to women.

In conclusion, HIV/HBV/HCV-infected patients had higher rates of hepatic decompensation than HIV/HCV-infected patients. The risk of decompensation was increased among triply infected patients who did not receive anti-HBV nucleos(t)ide analogue therapy. Providers should ensure that HIV/HBV/HCV-infected patients receive anti-HBV-active ART to reduce rates of decompensated cirrhosis in this population.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (<http://cid.oxfordjournals.org>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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