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Determinants of Liver Complications Among HIV/Hepatitis B Virus-Coinfected Patients

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Abstract

Background: Hepatitis B virus (HBV) infection is a leading cause of end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC) in HIV. Factors contributing to the high rates of liver complications among HIV/HBV-coinfected individuals remain unknown.

Setting: North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD)

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Methods: We performed a retrospective cohort study among HIV/HBV-coinfected patients in ten US and Canadian cohorts of the NA-ACCORD that validated ESLD (ascites, spontaneous bacterial peritonitis, variceal hemorrhage, and/or hepatic encephalopathy) and HCC diagnoses from 1996–2010. Multivariable Cox regression was used to examine adjusted hazard ratios (aHRs with 95% CIs) of liver complications (first occurrence of ESLD or HCC) associated with hypothesized determinants and with increasing durations of HIV suppression (≤500 copies/mL).

Results: Among 3,573 HIV/HBV patients with 13,790 person-years of follow-up, 111 liver complications occurred (incidence rate=8.0 [95% CI, 6.6–9.7] events/1,000 person-years). Rates of liver complication were increased with non-black/non-Hispanic race (aHR=1.76 [1.13–2.74]), diabetes (aHR=2.07 [1.20–3.57]), lower time-updated CD4 cell count (<200 cells/mm^3: aHR=2.59 [1.36–4.91]; 201–499 cells/mm^3: aHR=1.75 [1.01–3.06] versus ≥500 cells/mm^3), heavy alcohol use (aHR=1.58 [1.04–2.39]), and higher FIB-4 at start of follow-up (>3.25: aHR=9.79 [5.73–16.74]; 1.45–3.25: aHR=3.20 [1.87–5.47] versus FIB-4 <1.45). HIV suppression for ≥6 months was associated with lower liver complication rates compared with those with unsuppressed HIV (aHR=0.56 [0.35–0.91]).

Conclusions: Non-black/non-Hispanic race, diabetes, lower CD4 cell count, heavy alcohol use, and advanced liver fibrosis were determinants of liver complications among HIV/HBV patients. Sustained HIV suppression should be a focus for HIV/HBV-coinfected patients to reduce the risks of ESLD/HCC.

Keywords

Hepatitis B; HIV; end-stage liver disease; hepatocellular carcinoma; coinfection

INTRODUCTION

Hepatitis B virus (HBV) infection is a leading cause of liver-related mortality worldwide. Many countries that have high HBV endemicity also carry an increased burden of HIV infection.[1] HIV accelerates progression of HBV-related liver fibrosis.[2] HIV/HBV-coinfected patients have a higher risk of cirrhosis and death from end-stage liver disease (ESLD) than those with HIV or HBV alone,[2–6] and higher rates of hepatocellular carcinoma (HCC) than those with HIV alone.[7] Consequently, ESLD and HCC have emerged as major causes of mortality among HIV/HBV-coinfected patients.[8] Rates of liver complications remain higher for HIV/HBV than HIV/hepatitis C virus (HCV)-coinfected patients, even with antiretroviral therapy (ART) that includes HBV-active medications (i.e., tenofovir disoproxil fumarate [TDF], lamivudine, emtricitabine).[9]

The impact of HIV-related factors, such as HIV viremia and low CD4 cell count, and other potential determinants of liver disease, such as heavy alcohol use, diabetes mellitus, and HCV coinfection, remain unclear in HIV/HBV-coinfected patients, primarily because large-scale, population-representative longitudinal studies specifically in this group have not yet been conducted. Identification of these contributing factors could help define the major determinants for the high rates of liver complications among HIV/HBV patients and guide interventions to reduce the risk of these events in this population.

We evaluated HIV-related and host factors associated with the development of liver complications, defined as a composite of first ESLD or HCC diagnosis, among HIV/HBV-coinfected patients in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD).[10] We examined the risk of liver complications associated with HBV-active ART compared with use of ART without an HBV-active agent. We also determined whether longer duration of HIV suppression with HBV-active ART reduced the risk of liver complications among HIV/HBV patients.

METHODS

Study Design and Data Source

We performed a retrospective cohort study of HIV/HBV-coinfected patients enrolled in ten United States (US) and Canadian cohorts of the NA-ACCORD that had access to both inpatient and outpatient electronic medical records to permit validation of ESLD and HCC diagnoses from 1996–2010 (Supplementary Table 1). The NA-ACCORD is the largest consortium of interval and clinic-based HIV cohorts from the US and Canada and is the North American region of the International Epidemiologic Databases to Evaluate AIDS (IeDEA).[10] At scheduled intervals, cohorts securely transfer demographic, diagnostic, medication, social-behavioral, laboratory, and vital status information to the Data Management Core (University of Washington), which performs quality control for completeness and accuracy before harmonization of data files by the Epidemiology/Biostatistics Core (Johns Hopkins University). NA-ACCORD research has been approved by the institutional review boards of each cohort. This study also was approved by the University of Pennsylvania and University of Washington Institutional Review Boards.

Study Patients

All HIV-infected patients ≥18 years of age were included if they had active HBV coinfection (defined by at least one of the following: positive HBV surface antigen [HBsAg], positive HBV e antigen [HBeAg], or detectable HBV DNA) and were members of an NA-ACCORD cohort that participated in the validation of ESLD and HCC diagnoses between January 1, 1996 and December 31, 2010. Patients were excluded if they had: 1) ESLD or HCC prior to start of follow-up (defined below), 2) no follow-up time, or 3) received care at a site within a cohort that did not participate in ESLD or HCC validation.

Follow-up began at NA-ACCORD enrollment, start of ESLD and HCC observation windows for the patient's cohort (time period during which these events were ascertained[9]), or January 1, 1996, whichever occurred last. Follow-up continued until first occurrence of: ESLD, HCC, death, cohort-specific end date for reporting validated ESLD/HCC diagnoses, date lost to follow-up (defined by NA-ACCORD as the earlier of the last CD4 count or HIV RNA plus 540 days), or December 31, 2010.

Main Study Outcomes

The primary outcome was an incident liver complication, defined as a composite of first occurrence of an ESLD or HCC diagnosis. We chose to examine a composite of ESLD or HCC because these events equally represent important liver complications.

ESLD and HCC events were confirmed using a method we previously described.[11,12] Patients were centrally screened for possible ESLD or HCC from 1996–2010 based on: 1) relevant hospital or outpatient diagnoses (i.e., ascites, spontaneous bacterial peritonitis, variceal hemorrhage, hepatic encephalopathy, end-stage liver disease, hepatorenal syndrome, HCC) or procedures (i.e., paracentesis, transjugular intrahepatic portosystemic shunt, liver transplant), or 2) presence of significant liver fibrosis determined by ≥2 measurements of aspartate aminotransferase (AST)-to-platelet ratio index (APRI) >1.5[13] or ≥2 measurements of Fibrosis-4 Index for Liver Fibrosis (FIB-4) >3.25[14,15] >180 days apart *plus* ≥2 laboratory results indicating impaired hepatic function (i.e., total bilirubin ≥5.0 mg/dL, albumin ≤2.0 mg/dL, or international normalized ratio [INR] ≥1.7) >180 days apart. APRI was calculated using AST and platelet count: (AST [U/L]/upper limit of normal [considered as 40 U/L])/(platelet count [10^9/L] × 100).[13] APRI >1.5 identifies significant liver fibrosis (METAVIR stages F2-F4). FIB-4 was determined using AST, alanine aminotransferase (ALT), platelet count, and age: (age [years] × AST [U/L])/(platelet count [10^9/L]) × (ALT [U/L])$^{1/2}$).[14,15] FIB-4 >3.25 indicates advanced hepatic fibrosis/cirrhosis (METAVIR stages F3-F4).

Patients who screened positive for possible ESLD or HCC had all medical records reviewed by a clinician in each cohort. ESLD was defined by a clinical complication of cirrhosis (ascites, spontaneous bacterial peritonitis, variceal hemorrhage, or hepatic encephalopathy). HCC was determined by review of medical records and pathology reports or by cancer registry linkage.[12] The earliest date of ESLD or HCC diagnosis represented the liver complication date.

Data Collection

We collected age at start of follow-up, sex, race/ethnicity, HIV transmission risk factors, diabetes mellitus, heavy alcohol use, and use of ART. Sex, race/ethnicity, and HIV risk factors were determined via self-report at enrollment. Diabetes was assessed throughout observation and defined by: 1) hemoglobin A1c ≥6.5%, 2) prescription of certain anti-diabetic medications, or 3) diabetes diagnosis plus prescription of certain anti-diabetic medications.[16] Heavy alcohol use was defined as ever having had while under observation: 1) inpatient or outpatient International Classification of Diseases, Ninth Revision (ICD-9) diagnosis of alcohol dependence/abuse; 2) ≥3 drinks/day or ≥7 drinks/week for females; ≥4 drinks/day or ≥14 drinks/week for males on the self-reported Alcohol Use Disorders Identification Test-Consumption questionnaire;[17] or 3) documentation of alcohol intoxication, dependence, or abuse identified during medical record review to confirm ESLD or HCC diagnoses.[9] ART was defined as use of three antiretrovirals from at least two classes[18] or a triple nucleoside/nucleotide reverse transcriptase inhibitor regimen (previously accepted as ART[19]). We determined exposure to ART, HBV-active antiretrovirals (TDF, lamivudine, emtricitabine), or entecavir throughout observation.

All HIV RNA, CD4 cell count, HBsAg, HBeAg, and HBV DNA results before and during follow-up were collected. Due to changes in the sensitivity of HIV RNA assays over time, HIV suppression was defined as ≤500 copies/mL. HCV coinfection was defined by detectable HCV RNA or available HCV genotype recorded at any time during observation.

HCV treatment before or during follow-up was ascertained. FIB-4 was determined using the closest AST, ALT, and platelet counts within 24 months before or after start of follow-up.

Statistical Analysis

We calculated unadjusted incidence rates of liver complications, overall and by ART era (1996–2001, 2002–2005, 2006–2010). We used multivariable Cox regression to examine adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) of liver complications associated with risk factors of interest. HIV-related factors included time-updated HIV viremia (>500 copies/mL) and time-updated lower CD4 cell count. Traditional liver disease risk factors included age ≥40 years, male sex, black/non-Hispanic race/ethnicity (versus non-black/non-Hispanic and Hispanic), time-updated diabetes status, heavy alcohol use, HCV coinfection, and advanced liver fibrosis by FIB-4. Analyses were adjusted for year of start of follow-up. We did not include ART as a covariate because of its effects on HIV RNA and CD4 count and collinearity with both variables. HBV DNA and HBeAg were measured too infrequently in clinical practice to evaluate as determinants of liver complications.

We performed four sensitivity analyses to assess the robustness of our results. First, we repeated our analysis accounting for death as a competing risk.[20] Second, since our definition of HBV infection might have misclassified some patients with acute HBV infection as having chronic HBV, we repeated our analysis after excluding patients who had an ALT or AST >1,000 U/L within +/−30 days of their qualifying HBV laboratory test (since aminotransferase elevations of this degree are typically observed during acute HBV infection[21]). Third, since duration of diabetes might affect the risk of liver complications, we determined the time since the first observed diabetes diagnosis for each patient and repeated the primary analysis, replacing time-updated diabetes with duration of diabetes diagnosis. We determined the aHR of liver complications for every 12 months of diabetes. Finally, since the accuracy of FIB-4 among HIV/HBV-coinfected patients is unclear, we repeated our analysis substituting FIB-4 first with platelet count at start of follow-up (<150,000/μL versus ≥150,000/μL) and then with both AST (per 10 U/L increase) and platelet count (per 20,000/μL decrease), since both variables were associated with advanced hepatic fibrosis in a recent analysis of HIV/HBV patients in the Hepatitis B Research Network.[22]

Next, we examined the effect of HBV-active ART on the risk of liver complications. Among patients who received ART, we examined the aHRs of liver complications with use of ART that included: 1) an HBV-active antiretroviral, or 2) either TDF or entecavir, compared to ART use without an HBV-active antiretroviral, adjusting for all variables in the above risk factor analysis.

We then performed multivariable Cox regression to examine if increasing consecutive time with suppressed HIV RNA (≤500 copies/mL) during HBV-active ART was associated with a lower risk of HBV-related liver complications. We restricted the cohort to patients who received HBV-active ART to determine the effect of HIV suppression during treatment for both HIV and HBV infection. We evaluated consecutive, rather than cumulative, months of HIV suppression because the latter measure might include periods of interruption in HIV suppression, which could attenuate the beneficial effects of HIV suppression on risk of liver complications. HIV suppression was evaluated as a time-updated variable. Once a patient

had suppressed HIV, consecutive months were counted until an HIV RNA >500 copies/mL was identified, at which time the patient was classified as unsuppressed. If HIV suppression was again achieved, the consecutive months suppressed was restarted at one month. In an initial model (model #1), we evaluated HRs of liver complications with increasing categories of HIV suppression (<6 months; 6–11 months; 12–17 months; 18–23 months; ≥24 months) compared with persons with unsuppressed HIV, adjusting for all other variables in our prior risk factor analyses. Because aHRs of liver complications for categories of HIV suppression of ≥6 months were not statistically different, in a subsequent model (model #2), we dichotomized our results at 6 months (<6 months; ≥6 months). Analyses were repeated accounting for death as a competing risk.

We implemented multiple imputation using chained equations to address the potential bias of missing risk factor data, by means of 10 imputations using all variables in Table 1.[23] For laboratory covariates, we imputed values that were not measured at baseline and carried those forward until first measurement. Results across the 10 datasets were combined to arrive at CIs that accounted for within- and across-dataset variances.[24] Data were analyzed using SAS 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Patient Characteristics

Among 54,415 HIV-infected patients in the ten cohorts, 5,134 (9.4%) were HBV-coinfected. Of these, 1,561 were excluded because they did not meet eligibility (Figure 1), leaving 3,573 HIV/HBV-coinfected patients in the sample.

This cohort was predominantly <40 years of age, male, and non-white/non-Hispanic (Table 1). The most common risk factor for HIV transmission included men who have sex with men (51.6%). Heavy alcohol use was reported in 25.1%, and 17.9% had HCV coinfection. Among HCV-infected individuals, only (3.7%) were treated for HCV during the study period. At start of follow-up, 53.7% had HIV RNA >500 copies/mL, and 29.1% had a CD4 count <200 cells/mm^3. Advanced hepatic fibrosis/cirrhosis by FIB-4 was present in 9.3%.

At start of follow-up, 35.9% were on ART with lamivudine or emtricitabine as the only HBV-active antiretroviral, 21.2% received TDF-based ART, and 6.8% were on ART without an HBV-active antiretroviral. Notably, 36.0% (n=1,287) were not on ART at start of follow-up; of these, 742 (57.7%) started ART during follow-up. Among 1,530 patients not on an HBV-active antiretroviral at study entry, 916 (59.9%) received HBV-active ART during follow-up (613 TDF-based; 303 with lamivudine or emtricitabine alone). Twelve patients received entecavir during follow-up.

Within the cohort, 3,227 (90.3%) had HBsAg status determined, 1,163 (32.6%) had HBV DNA assessed, and 1,152 (32.2%) had HBeAg tested at any time before or during follow-up. HBV DNA was detectable in 741 (63.7%) of those assessed. Among those who had HBeAg tested, 783 (68.0%) had a positive result.

Liver Complications

Among the 3,573 patients, 111 (3.0%) developed a liver complication (90 with ESLD only; 11 with HCC only; 10 with both) during 13,790 person-years of follow-up (incidence rate=8.0 [95% CI, 6.6–9.7] events/1,000 person-years). The median (interquartile range) duration of follow-up was 3.0 (1.8–5.0) years. The incidence rate of ESLD was 7.2 (95% CI, 5.9–8.8) events/1,000 person-years. The most frequent first ESLD event was ascites (n=74, 74%), followed by variceal hemorrhage (n=17, 17%), hepatic encephalopathy (n=13, 13%), and spontaneous bacterial peritonitis (n=4, 4%). Four patients had concurrent ascites and hepatic encephalopathy at presentation, three had ascites and spontaneous bacterial peritonitis, and one had ascites and variceal hemorrhage. There were no differences in types of ESLD events by ART era. The incidence rate of HCC was 1.5 (95% CI, 0.9–2.3) events/1,000 person-years. Rates of liver complications during follow-up did not significantly differ in magnitude by ART era (Figure 2; Supplementary Table 2).

Determinants of Liver Complications

Non-black/non-Hispanic race, time-updated diabetes, heavy alcohol use, lower time-updated CD4 count, and higher FIB-4 at start of follow-up were significant determinants of liver complications (Table 2). Analyses accounting for the competing risk of death showed similar results (Supplementary Table 3). Results were also similar after patients with ALT or AST >1,000 U/L within +/−30 days of their qualifying HBV laboratory test (n=95) were excluded (Supplementary Table 4). When duration of diabetes was examined in place of time-updated diabetes, the risk of liver complications was increased with longer diabetes duration (aHR, 1.12 [95% CI, 1.05–1.20] per 12 months of diabetes). When platelet count at start of follow-up was substituted for FIB-4, platelets <150,000/μL were associated with an increased risk of liver complications (aHR, 5.78 [95% CI, 3.61–9.24]). When FIB-4 was replaced with both AST and platelet count at start of follow-up, the risk of liver complications was increased with higher AST (aHR, 1.04 [95% CI, 1.02–1.05] per 10 U/L increase) and lower platelet count (aHR, 1.25 [95% CI, 1.16–1.33] per 20,000/μL decrease).

The risk of liver complications was reduced with use of ART that included an HBV-active antiretroviral (aHR, 0.47 [95% CI, 0.16–1.36]) or ART that included either TDF or entecavir (aHR, 0.36 [95% CI, 0.12–1.03]) compared with those receiving ART without an HBV-active antiretroviral, but results were not statistically significant.

Association Between HIV RNA Suppression and Liver Complications

Among 3,385 HIV/HBV-coinfected persons who received HBV-active ART during follow-up, HIV suppression for ≥6 months was associated with a lower risk of liver complications compared with those with unsuppressed HIV (Table 3). Results were similar in analyses accounting for competing risk of death (Supplementary Table 5).

DISCUSSION

This is the first population-representative cohort study to evaluate rates and determinants of liver complications exclusively among HIV/HBV-coinfected individuals from North America. We observed high rates of liver complications in our cohort. Non-black/non-

Hispanic race, diabetes, heavy alcohol use, lower CD4 cell count, and higher FIB-4 were significant risk factors for liver complications. Importantly, maintaining HIV suppression for ≥6 months with HBV-active ART significantly decreased the risk of liver complications.

The high rate of liver complications among coinfected individuals in this study may have been driven by lack of receipt of HBV-active ART during the observation period. By end of follow-up, 5.3% of patients had not received HBV-active ART, despite guidelines recommending that all HIV/HBV patients be considered for dual therapy.[18] Some of these patients may have had contraindications to HBV-active ART (e.g., underlying nephrotoxicity or HIV mutations conferring antiretroviral resistance). The risk of liver complications was reduced with ART that included an HBV-active antiretroviral, particularly TDF, though these results did not achieve statistical significance, likely due to the short (median, 3.0 years) duration of follow-up. Future studies with longer follow-up should evaluate the extent to which HBV-active and TDF-based ART decrease the risk of liver complications.

We found that coinfected patients with ≥6 months of HIV suppression during HBV-active ART were significantly less likely to develop liver complications, highlighting the importance of HIV control to limit progression of liver disease. HIV viremia has been linked with hepatic fibrogenesis.[25] Early and late HIV suppression with ART is associated also with lower cancer incidence, though to a greater degree for AIDS-defining cancers.[26] Our study shows that initiation of ART and maintenance of HIV suppression should remain a key goal for HIV/HBV patients to reduce the risk of ESLD and HCC.

Lower CD4 cell count was a strong determinant of liver complications. This finding is consistent with a prior study in the Multicenter AIDS Cohort Study that found that liver-related death was associated with lower CD4 counts among HIV/viral hepatitis-coinfected patients.[27] However, it remains unclear if the association between low CD4 count and increased risk of liver complications is due to immunosuppression or if the low CD4 count is a marker of advanced liver disease, since cirrhosis-induced portal hypertension can lead to low CD4 counts via splenic sequestration.[28] Additional studies are needed to determine the effects of immunosuppression on risk of liver complications among HIV/HBV-coinfected persons.

We identified non-black/non-Hispanic race as a determinant of liver complications. No studies have examined racial/ethnic differences in HBV-related liver complications in HIV. Recent studies among HIV/HCV-coinfected patients reveal that persons of non-black race have a higher risk of hepatic decompensation[29] and liver-related death.[30] More research is needed to determine the impact of race/ethnicity on risk of liver complications in HIV/HBV coinfection.

Diabetes, as well as increasing duration of diagnosis, were independently associated with an increased risk for liver complications. Prior cohort studies show that diabetes increases risk of ESLD among HCV-monoinfected[31] and HIV/HCV-coinfected patients.[29] Diabetes can promote hepatic steatosis, which contributes to hepatic fibrosis.[32] Diabetes may also induce hepatic fibrosis independent of steatosis via stimulation of hepatic stellate cells by insulin.[33] Cirrhosis can further promote development of glucose intolerance and diabetes,[34] making it

difficult to interpret associations between diabetes and ESLD, especially in cross-sectional and case-control studies. The longitudinal design of our study and time-updated manner in which diabetes was evaluated overcomes this limitation.

Higher FIB-4, a non-invasive index of hepatic fibrosis, was also a determinant of liver complications. Cirrhosis is a well-recognized risk factor for hepatic decompensation and HCC.[35] HIV providers could calculate FIB-4 for their HIV/HBV patients, particularly when transient elastography or other modalities for assessing hepatic fibrosis are unavailable. Increased FIB-4 should prompt clinicians and patients to address modifiable risk factors for ESLD and identify those who should be followed closely for this outcome.

We also examined the effects of heavy alcohol use and HCV coinfection on liver complications among HIV/HBV patients. Similar to findings in HBV-monoinfected patients,[36] heavy alcohol use was an important determinant of ESLD/HCC. Interestingly, HCV coinfection was associated with a modest, but non-significant, increase in risk of liver complications. Among HIV-uninfected persons, HCV coinfection increases rates of cirrhosis and HCC compared to HBV monoinfection.[37] However, interference between HBV and HCV in coinfected patients resulting in suppression of viral replication has been described,[38] which could have resulted in attenuation of the effect of HCV coinfection in our analysis. Additional studies should examine the risk of liver complications with HCV coinfection among HIV/HBV patients.

This study had a number of strengths. It included a large, representative sample of HIV/HBV patients from across the US and Canada; evaluated previously unexamined determinants of ESLD/HCC among HIV/HBV patients; accounted for time-varying covariates; and ascertained validated ESLD and HCC endpoints using standardized criteria across the participating sites. Results were robust in sensitivity analyses.

The study has several potential limitations. First, ESLD and HCC diagnoses were validated through 2010, which prevented inclusion of HIV/HBV patients receiving more modern ART and HBV treatment regimens. However, the greater variability in HIV suppression during the study period enhanced statistical power to evaluate associations between HIV suppression and liver complication risk. Second, by allowing patients with only one measurement of HBsAg, HBeAg, or HBV DNA into the cohort, we may have included some patients with acute HBV infection. However, we performed a sensitivity analysis excluding those with concomitant liver aminotransferases >1,000 U/L, who might have had acute HBV and not progress to chronic infection, and results were similar to the primary analysis. Third, the accuracy of FIB-4 among HIV/HBV-coinfected patients, particularly during HBV-active ART, is unclear and has not been validated compared to liver biopsy. Liver fibrosis may have been misclassified by FIB-4 due to conditions that decrease platelets or increase liver aminotransferases. Finally, data on body mass index and hepatitis delta virus were unavailable, and HBV DNA and HBeAg were measured too infrequently to examine as determinants of liver complications. Future studies should evaluate these variables and examine whether there is a biological gradient of risk for liver complications with increasing HBV DNA.

In summary, HIV/HBV-coinfected patients in the NA-ACCORD experienced high rates of ESLD and HCC events. In addition to non-black/non-Hispanic race, diabetes, heavy alcohol use, and higher FIB-4, lower cell CD4 count and longer consecutive time with HIV suppression were important HIV-related determinants of liver complications. Initiation of HBV-active ART and sustained HIV suppression should be a focus for HIV/HBV patients to reduce the risk of ESLD and HCC. Future studies should evaluate how HBV DNA and different HBV-active ART regimens impact on liver complications among HIV/HBV-coinfected patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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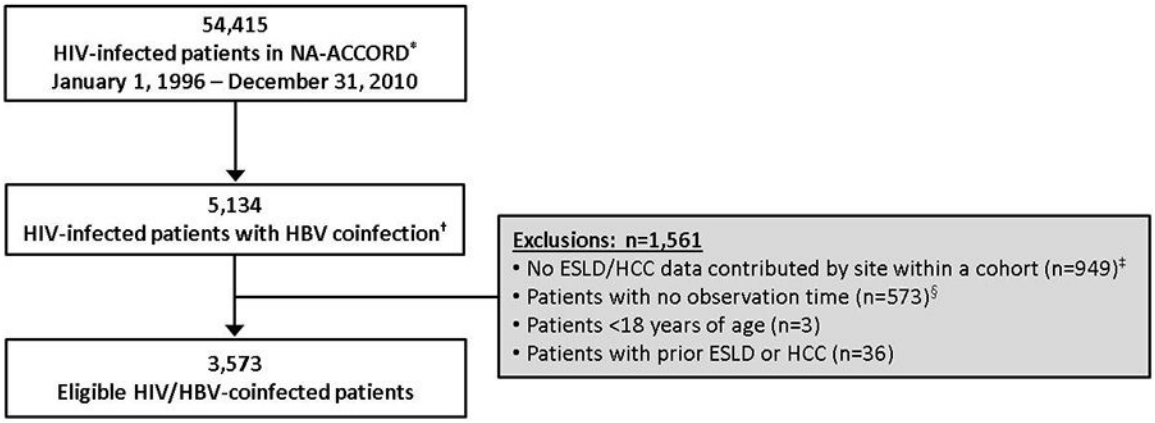

Figure 1.

Selection of HIV/hepatitis B virus-coinfected patients within the North American AIDS Cohort Collaboration on Research and Design (January 1996 - December 2010) for inclusion in the study.

Abbreviations: ESLD, end-stage liver disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; NA-ACORD, North American AIDS Cohort Collaboration on research and Design

*Includes data from ten cohorts that participated in validation of end-stage liver disease and hepatocellular carcinoma diagnoses: HIV Research Network; Johns Hopkins HIV Clinical Cohort; Kaiser Permanente Northern California; Montreal Chest Institute Immunodeficiency Service Cohort; Southern Alberta Clinic Cohort; University of Alabama at Birmingham 1917 Clinic Cohort; University of North Carolina at Chapel Hill HIV Clinical Cohort; University of Washington HIV Cohort; Vanderbilt-Meharry Center for AIDS Research Cohort; Veteran's Aging Cohort Study 8-Site Study.

†HBV co-infection determined by ever positive for HBV surface antigen, HBV e antigen, or HBV DNA.

‡Patients at a site within a cohort that did not participate in ESLD or HCC validation.

§Patients with no observation time did not have follow-up during the period in which ESLD/HCC events were ascertained.

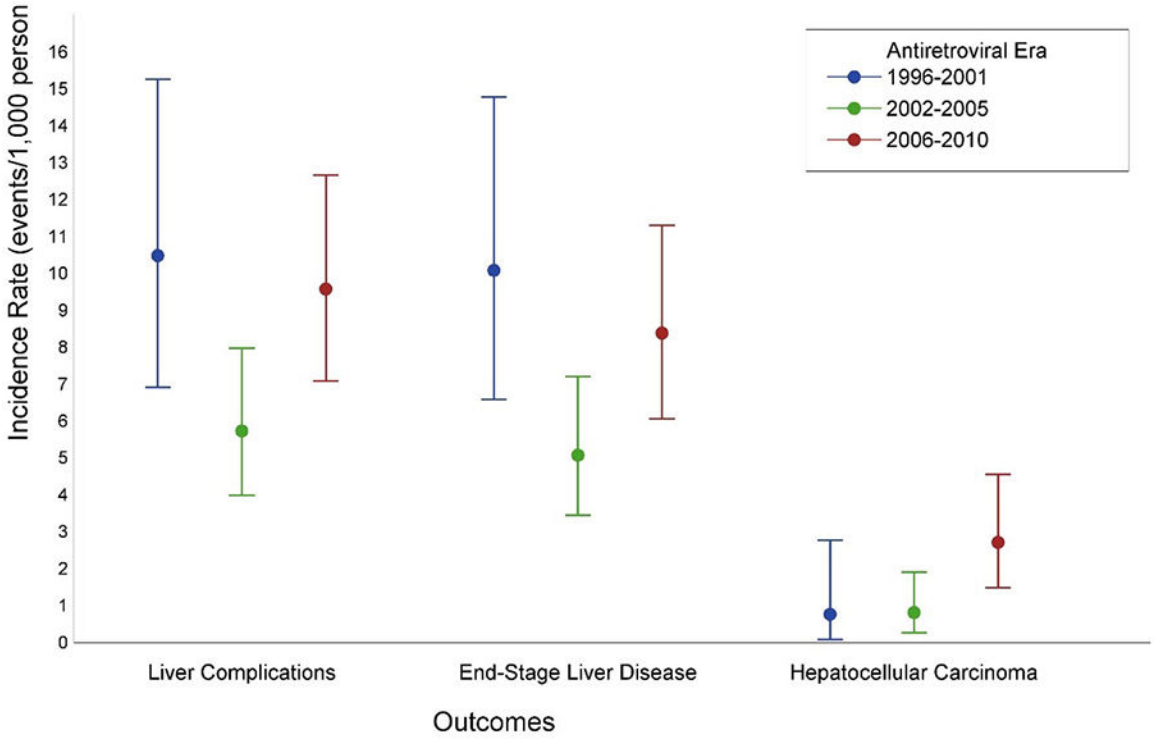

Figure 2.

Incidence rates and 95% confidence intervals of liver complications (composite of first occurrence of end-stage liver disease or hepatocellular carcinoma diagnosis), end-stage liver disease, and hepatocellular carcinoma among HIV/hepatitis B virus-coinfected patients in the North American AIDS Cohort Collaboration on Research and Design (January 1996 - December 2010), by antiretroviral therapy era (1996–2001, 2002–2005, 2006–2010).

Table 1.

Characteristics of HIV/hepatitis B virus-coinfected patients within the North American AIDS Cohort Collaboration on Research and Design (1996 – 2010) at start of follow-up.

Characteristic	HIV/HBV Coinfected Overall (n=3,573)
Age (n, %)	
< 40 years	1,562 (43.7%)
40 – 49 years	1,368 (38.3%)
≥ 50 years	643 (18.0%)
Male sex (n, %)	3,096 (86.6%)
Race/ethnicity (n, %)	
White, non-Hispanic	1,334 (37.3%)
Black or African American, non-Hispanic	1,393 (39.0%)
Hispanic	528 (14.8%)
Asian/Pacific Islander	63 (1.8%)
Multiracial	1 (0.0%)
Other	53 (1.5%)
Not reported	201 (5.6%)
History of heavy alcohol use (n, %)	
Never	2,518 (70.5%)
Ever	896 (25.1%)
Not assessed	159 (4.5%)
HIV transmission risk factors (n, %)	
Men who have sex with men	1,844 (51.6%)
History of injection drug use	769 (21.5%)
Receipt of blood transfusion, etc.	44 (1.2%)
Heterosexual contact	881 (24.7%)
Other	61 (1.7%)
Unknown	342 (9.6%)
Diabetes mellitus (n, %)	159 (4.5%)
Hepatitis C virus coinfection (n, %)	641 (17.9%)
HIV RNA (n, %)	
Median (log_{10} copies/mL, IQR)	3.5 (2.3–4.7)
≤500 copies/mL	1,310 (36.7%)
>500 copies/mL	1,918 (53.7%)
Not assessed at start of follow-up	345 (9.7%)
CD4 cell count (n, %)	
Median (cells/mm^3, IQR)	332.0 (160.0–519.0)
<200 cells/mm^3	1,040 (29.1%)
200 – 499 cells/mm^3	1,470 (41.1%)
≥ 500 cells/mm^3	938 (26.3%)
Not assessed at start of follow-up	125 (3.5%)

Characteristic	HIV/HBV Coinfected Overall (n=3,573)
FIB-4 (n, %)	
< 1.45	2,076 (58.1%)
1.45 – 3.25	953 (26.7%)
> 3.25	334 (9.3%)
Not assessed at start of follow-up	210 (5.9%)
Year of start of follow-up (n, %)	
1996 – 2001	1,286 (36.0%)
2002 – 2005	1,131 (31.7%)
2006 – 2010	1,156 (32.4%)
HBV-active ART regimen (n, %)	
Lamivudine or emtricitabine alone	1,284 (35.9%)
Tenofovir alone	75 (2.1%)
Tenofovir + (lamivudine or emtricitabine)	684 (19.1%)
On ART without an HBV antiretroviral	243 (6.8%)
Not on ART at start of follow-up	1,287 (36.0%)
ART classes prescribed (n, %)	
Protease inhibitor	1,136 (41.6%)
Non-nucleoside reverse transcriptase inhibitor	751 (27.5%)
Nucleoside reverse transcriptase inhibitor	100 (3.7%)
Other	139 (5.1%)

Abbreviations: ART=antiretroviral therapy; HBV=hepatitis B virus; HIV=human immunodeficiency virus; IQR=interquartile range

Age was measured as year at start of follow-up - year of birth.

Sex, race/ethnicity, and history of injection drug use were collected at enrollment into the NA-ACCORD and are time-fixed.

History of heavy alcohol use was defined as ever having reported while under observation in the NA-ACCORD: 1) inpatient or outpatient International Classification of Diseases, Ninth Revision (ICD-9) diagnosis of alcohol dependence/abuse; 2) ≥3 drinks/day or ≥7 drinks/week for females; ≥4 drinks/day or ≥14 drinks/week for males on the self-reported Alcohol Use Disorders Identification Test-Consumption questionnaire; or 3) documentation of alcohol intoxication, dependence, or abuse identified during medical record review to confirm ESLD or HCC diagnoses.

HIV transmission risk factors were not mutually exclusive.

Diabetes mellitus was defined by: 1) hemoglobin A1c >6.5%, 2) prescription of anti-diabetic medication, or 3) diabetes diagnosis plus prescription of a diabetes-related medication prior to start of follow-up.

Hepatitis C virus infection was defined by detectable HCV RNA or available HCV genotype recorded at any time during observation.

HIV RNA and CD4 cell count were measured as the closest value prior to, or within two months after, start of follow-up.

ART was measured as a combination of 3 antiretroviral agents from at least 2 classes or a triple nucleoside/nucleotide reverse transcriptase inhibitor regimen containing abacavir or tenofovir.

FIB-4 is a non-invasive score to estimate the amount of liver fibrosis, calculated by: (age [years] × AST [U/L]) / ((platelet count [10^9/L]) × (ALT [U/L])$^{1/2}$). FIB-4 was estimated using aspartate aminotransferase, alanine aminotransferase, and platelet count measurements that were recorded as the closest values within 24 months before or after the start of follow-up.

Table 2.

Factors associated with liver complications, defined by first occurrence of end-stage liver disease or hepatocellular carcinoma, among HIV/hepatitis B virus-coinfected patients within the North American AIDS Cohort Collaboration on Research and Design (1996 – 2010; n=3,573).

Characteristic	No. Exposed	No. Events	Person-Time	Incidence Rate (95% CI), Events/ 1,000 Person-Years	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)
Age						
<40 years	1,562	45	6,471.3	7.0 (5.1–9.3)	Ref	Ref
≥40 years	2,011	66	7,318.8	9.0 (7.0–11.5)	1.44 (0.99–2.10)	0.87 (0.56–1.34)
Sex						
Female	477	8	1,817.2	4.4 (1.9–8.7)	Ref	Ref
Male	3,096	103	11,972.9	8.6 (7.0–10.4)	1.83 (0.89–3.77)	1.12 (0.54–2.35)
Race						
Black, non-Hispanic	1,393	36	5,872.3	6.1 (4.3–8.5)	Ref	Ref
Hispanic	528	6	1,678.4	3.6 (1.3–7.8)	0.67 (0.28–1.62)	0.85 (0.35–2.06)
Non-black, non-Hispanic	1,652	69	6,239.3	11.1 (8.6–14.0)	1.69 (1.13–2.53)	1.76 (1.13–2.74)
Diabetes mellitus†‡						
No	3,414	94	12,682.1	7.4 (6.0–9.1)	Ref	Ref
Yes	298	17	1,048.6	16.2 (9.4–26.0)	2.02 (1.21–3.39)	2.07 (1.20–3.57)
HCV coinfection§						
No	2,923	81	11,053.2	7.3 (5.8–9.1)	Ref	Ref
Yes	641	30	2,716.6	11.0 (7.5–15.8)	1.50 (0.98–2.28)	1.28 (0.82–1.99)
Current HIV RNA†						
≤500 copies/mL	2,737	61	7,582.5	8.0 (6.2–10.3)	Ref	Ref
>500 copies/mL	2,664	49	5,651.2	8.7 (6.4–11.5)	1.10 (0.75–1.60)	1.03 (0.67–1.58)
Current CD4 cell count†						
≥500 cells/mm^3	1,799	17	4,268.7	4.0 (2.3–6.4)	Ref	Ref
200 – 499 cells/mm^3	2,615	51	6,175.1	8.3 (6.1–10.9)	2.14 (1.24–3.70)	1.75 (1.01–3.06)
<200 cells/mm^3	1,640	43	3,082.4	14.0 (10.1–18.8)	3.58 (2.05–6.27)	2.59 (1.36–4.91)
Heavy alcohol use//						
No	2,518	53	8,876.9	6.0 (4.5–7.8)	Ref	Ref
Yes	896	52	3,994.8	13.0 (9.7–17.1)	1.98 (1.34–2.94)	1.58 (1.04–2.39)
FIB-4 at start of follow-up¶						
< 1.45	2,076	22	8,032.4	2.7 (1.7–4.1)	Ref	Ref
1.45 – 3.25	953	39	3,735.7	10.4 (7.4–14.3)	3.48 (2.07–5.83)	3.20 (1.87–5.47)
> 3.25	334	44	1,180.3	37.3 (27.1–50.0)	11.69 (7.17–19.07)	9.79 (5.73–16.74)
Year of start of follow-up						
1996 – 2001	1,286	69	7,559.4	9.1 (7.1–11.6)	Ref	Ref
2002 – 2005	1,131	27	4,406.5	6.1 (4.0–8.9)	0.82 (0.51–1.33)	0.72 (0.45–1.15)
2006 – 2010	1,156	15	1,824.2	8.2 (4.6–13.6)	1.36 (0.70–2.65)	1.52 (0.78–2.98)

Abbreviations: CI=confidence interval; FIB-4=Fibrosis-4 Index for Liver Fibrosis; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HR=hazard ratio

[*] Hazard ratios adjusted for all other risk factors and based on 10 imputations.

[†] Evaluated as a time-varying covariate.

[‡] Diabetes mellitus was defined by: 1) hemoglobin A1c >6.5%, 2) prescription of anti-diabetic medication, or 3) record of a diabetes diagnosis plus the prescription of diabetes-related medication prior to start of follow-up.

[§] Hepatitis C virus coinfection defined by detectable HCV RNA or available HCV genotype recorded at any time during observation.

[//] History of heavy alcohol use was defined as ever having reported while under observation in the NA-ACCORD: 1) inpatient or outpatient International Classification of Diseases, Ninth Revision (ICD-9) diagnosis of alcohol dependence/abuse; 2) ≥3 drinks/day or ≥7 drinks/week for females; ≥4 drinks/day or ≥14 drinks/week for males on the self-reported Alcohol Use Disorders Identification Test-Consumption questionnaire; or 3) documentation of alcohol intoxication, dependence, or abuse identified during medical record review to confirm ESLD or HCC diagnoses.

[¶] FIB-4 is a non-invasive score to estimate the amount of liver fibrosis, calculated by: (age [years] × aspartate aminotransferase [U/L]) / ((platelet count [10^9/L]) × (alanine aminotransferase [U/L]))$^{1/2}$). FIB-4 was estimated using aspartate aminotransferase, alanine aminotransferase, and platelet count measurements that were recorded as the closest values within 24 months before or after the start of follow-up.

Table 3.

Adjusted hazard ratios of liver complications associated with increasing consecutive months of HIV suppression compared with persons with unsuppressed HIV among HIV/hepatitis B virus-coinfected patients who received HBV-active antiretroviral therapy within the North American AIDS Cohort Collaboration on Research and Design (1996 – 2010; n=3,385).

HIV RNA Suppression	Adjusted Hazard Ratio (95% CI) of Liver Complications*	
	Model #1†	Model #2‡
Unsuppressed	Ref	Ref
<6 months	1.06 (0.59–1.91)	1.06 (0.59–1.92)
≥6 months	-	0.56 (0.35–0.91)
6–11 months	0.49 (0.20–1.21)	-
12–17 months	0.37 (0.12–1.09)	-
18–23 months	0.34 (0.10–1.18)	-
≥24 months	0.71 (0.40–1.27)	-

Abbreviations: HIV=human immunodeficiency virus

*Analyses adjusted for age, sex, race, time-updated diabetes mellitus, hepatitis C virus coinfection, time-updated CD4 cell count, heavy alcohol use, FIB-4 at start of follow-up, and year of start of follow-up.

†test for trend p=0.06

‡test for trend p=0.02