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Risk of HCC With Hepatitis B Viremia Among HIV/HBV-Coinfected Persons in North America

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BACKGROUND AND AIMS: Chronic HBV is the predominant cause of HCC worldwide. Although HBV coinfection is common in HIV, the determinants of HCC in HIV/HBV coinfection are poorly characterized. We examined the predictors of HCC in a multicohort study of individuals coinfected with HIV/HBV.

APPROACH AND RESULTS: We included persons coinfected with HIV/HBV within 22 cohorts of the North American AIDS Cohort Collaboration on Research and Design (1995-2016). First occurrence of HCC was verified by medical record review and/or cancer registry. We used multivariable Cox regression to determine adjusted HRs (aHRs [95% CIs]) of factors assessed at cohort entry (age, sex, race, body mass index), ever during observation (heavy alcohol use, HCV), or time-updated (HIV RNA, CD4+ percentage, diabetes mellitus, HBV DNA). Among 8,354 individuals coinfected with HIV/HBV (median age, 43 years; 93% male; 52.4% non-White), 115 HCC cases were diagnosed over 65,392 person-years (incidence rate, 1.8 [95% CI, 1.5-2.1] events/1,000 person-years). Risk factors for HCC included age 40-49 years (aHR, 1.97 [1.22-3.17]), age ≥50 years (aHR, 2.55 [1.49-4.35]), HCV coinfection (aHR, 1.61 [1.07-2.40]), and heavy alcohol use (aHR, 1.52 [1.04-2.23]), while time-updated HIV RNA >500 copies/mL (aHR, 0.90 [0.56-1.43]) and time-updated CD4+ percentage <14% (aHR, 1.03 [0.56-1.90]) were not. The risk of HCC was increased with time-updated HBV DNA >200 IU/mL (aHR, 2.22 [1.42-3.47]) and was higher with each 1.0 $\log_{10}$ IU/mL increase in time-updated HBV DNA (aHR, 1.18 [1.05-1.34]). HBV suppression with HBV-active antiretroviral therapy (ART) for ≥1 year significantly reduced HCC risk (aHR, 0.42 [0.24-0.73]).

CONCLUSION: Individuals coinfected with HIV/HBV on ART with detectable HBV viremia remain at risk for HCC. To gain maximal benefit from ART for HCC prevention, sustained HBV suppression is necessary. (Hepatology 2021;74:1190-1202).

Liver cancer is the sixth most common cancer and third leading cause of cancer-related mortality worldwide.[1] Chronic HBV infection, both through inflammation and virally mediated pro-oncogenic mechanisms, is the most common cause of HCC.[2] Coinfection

Abbreviations: aHR, adjusted hazard ratio; ART, antiretroviral therapy; IQR, interquartile range; NA-ACCORD, North American AIDS Cohort Collaboration on Research and Design; TDF, tenofovir disoproxil fumarate.

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with chronic HBV is common among people living with HIV, with an estimated HBV prevalence of 5%-15%.[3] As the population of persons infected with HIV has aged during the antiretroviral therapy (ART) era, HCC has emerged as a leading cause of non-AIDS-defining cancer and cancer-attributable death.[4]

Despite the high prevalence of HBV coinfection, no population-based studies have examined the incidence rates and determinants of HCC exclusively among HIV/HBV-coinfected individuals. Existing knowledge of risk factors for HBV-associated HCC originates from native Asian or Caucasian cohorts without HIV infection.[5,6] Consequently, it remains unclear whether higher levels of HIV RNA, prolonged HIV viremia, and greater HIV-related immunosuppression contribute to the development of HCC in HBV coinfection. It is also unknown whether the biological gradient of risk for HCC with increasing HBV DNA levels, which has been observed among persons monoinfected with HBV, is present in HIV coinfection.[5]

In this multicohort study using data from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), we examined the incidence of HBV-associated HCC and evaluated the determinants of this malignancy, including HIV-related factors (HIV viremia, immunosuppression), HBV viremia, and traditional HCC risk factors, to help guide preventive measures and early identification of this cancer.

Materials and Methods

STUDY DESIGN AND DATA SOURCE

We performed a longitudinal cohort study of persons coinfected with HIV/HBV enrolled in 22 U.S. and Canadian cohorts of the NA-ACCORD from

Agency for Healthcare Research and Quality (90047713), the Health Resources and Services Administration (90051652), the Canadian Institutes of Health Research (CBR-86906, CBR-94036, HCP-97105, and TGF-96118), Ontario Ministry of Health and Long-Term Care, the Government of Alberta, Canada, the National Institute of Allergy and Infectious Diseases, National Cancer Institute, National Heart, Lung, and Blood Institute, Eunice Kennedy Shriver National Institute of Child Health & Human Development, National Human Genome Research Institute, National Institute for Mental Health, National Institute on Drug Abuse, National Institute on Aging, National Institute of Dental & Craniofacial Research, National Institute of Neurological Disorders and Stroke, National Institute of Nursing Research, National Institute on Alcohol Abuse and Alcoholism, National Institute on Deafness and Other Communication Disorders, and National Institute of Diabetes and Digestive and Kidney Diseases. The data were collected by cancer registries participating in the National Program of Cancer Registries of the Centers for Disease Control and Prevention.

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1995 to 2016. The NA-ACCORD is the largest consortium of interval and clinic-based HIV cohorts in the region.[7] At regular intervals, NA-ACCORD cohorts transfer demographic, diagnostic, medication, socio-behavioral, laboratory, and vital status information to the Data Management Core (University of Washington), which performs quality control for completeness and accuracy and harmonizes data across cohorts that are sent to the Epidemiology/Biostatistics Core (Johns Hopkins University), where analytic-ready summary files are created. NA-ACCORD research has been approved by the institutional review boards of each cohort. Informed consent was waived, given the de-identified nature of these data. This study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the University of Pennsylvania and University of Washington Institutional Review Boards.

STUDY PATIENTS

The study population included individuals infected with HIV who had (1) age ≥18 years; (2) active HBV coinfection (defined by at least one of the following: positive HBsAg, positive HBeAg, or detectable HBV DNA) between January 1, 1995, and December 31, 2016; and (3) HIV RNA and CD4+ cell measurement during this period. To minimize the likelihood of including patients with acute HBV infection, we excluded patients who had an alanine aminotransferase or aspartate aminotransferase >1,000 U/L within ±30 days of their first HBsAg, HBeAg, or HBV DNA and no subsequent positive HBV laboratory test ≥6 months after the initial result.

To ensure prevalent HCC diagnoses were not misclassified as incident events, we defined the start of follow-up as 180 days after the latest of the date of NA-ACCORD enrollment, start of the HCC observation window for the patient's cohort (during which HCC diagnoses were ascertained), or assessment of HIV RNA or CD4+ cell measurements. We excluded patients who had HCC diagnosed before the start of follow-up. Follow-up continued until first occurrence of HCC, death, cohort-specific end date for reporting HCC diagnoses, date lost to follow-up (defined by NA-ACCORD as the earlier of the last HIV RNA or CD4+ cell measurement plus 540 days), or December 31, 2016.

MAIN STUDY OUTCOME

The primary outcome was incident HCC diagnosis. Within each cohort, HCC diagnoses were adjudicated based on cancer registry linkage or through comprehensive review of medical records by trained medical record abstracters under the supervision of a physician using a web-based standardized abstraction protocol to verify the diagnosis (i.e., histopathologic diagnosis, supportive radiographic imaging, or clinician-confirmed diagnosis), as previously described.[8]

COVARIATES

We examined age, sex, race/ethnicity, body mass index, HIV transmission risk factors, diabetes mellitus, alcohol use, chronic HCV infection, and use of ART. Diabetes was assessed throughout observation and defined by (1) hemoglobin A1c ≥6.5%, (2) prescription of specific antidiabetic medications (e.g., insulin), or (3) diabetes diagnosis plus prescription of diabetes-related medications.[9] Heavy alcohol use was defined as ever having had while under observation: (1) International Classification of Diseases, Ninth Revision, hospital or outpatient diagnosis of alcohol dependence/abuse; or (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.[10] Chronic HCV coinfection was defined by detectable HCV RNA or available HCV genotype recorded at any time during observation. ART was defined as use of three antiretrovirals from at least two classes or a triple nucleoside/nucleotide reverse-transcriptase inhibitor regimen (previously accepted as ART). We determined exposure to ART, HBV-active antiretrovirals (tenofovir disoproxil fumarate [TDF], lamivudine, emtricitabine), and entecavir throughout observation.

We examined all HIV RNA levels, CD4+ cell percentages, HBeAg, and quantitative and qualitative HBV DNA results before and during follow-up. We evaluated CD4+ cell percentage instead of absolute CD4+ cell count, because absolute CD4+ count may decrease during cirrhosis due to portal hypertension–induced splenic sequestration.[11] HIV RNA level

and CD4+ cell percentages were lagged by 180 days (approximate mean doubling time of <5 cm HCCs[12]) to reduce the possibility that HCC influenced these variables (i.e., reverse causality). Due to changes in the sensitivity of HIV RNA assays over time, detectable HIV was defined as >500 copies/mL. Hepatitis delta coinfection status was not available within the NA-ACCORD data.

STATISTICAL ANALYSIS

We first determined unadjusted incidence rates of HCC (events/1,000 person-years). We used multivariable Cox regression to determine aHRs (95% CIs) of HCC for risk factors of interest. HIV-related factors included detectable HIV RNA (>500 copies/mL) and CD4+ cell percentage, both time-updated. We examined traditional HCC risk factors including older age (≥40 years), male sex, race/ethnicity, obese body mass index (≥30 kg/m^2), time-updated diabetes mellitus, heavy alcohol use, and chronic HCV coinfection.[2] Baseline values of time-updated variables (i.e., HIV RNA, CD4+ cell percentage, and diabetes status) were carried forward until the date that a new value was recorded. The aHRs of HCC for time-updated variables therefore reflect associations between current values of that variable and HCC. Analyses additionally adjusted for the year that follow-up started. ART use was not included because of its collinearity with HIV RNA and CD4+ percentage. To evaluate fully the effects of HIV viremia on HCC, we also examined alternative definitions of HIV viremia as a (1) categorical variable (≤500; 501-10,000; >10,000 copies/mL); (2) continuous variable per 1.0 $\log_{10}$ copies/mL increase; and (3) cumulative value with increasing consecutive months of detectable HIV (compared to those with undetectable HIV), as previously described.[13] We performed two secondary analyses. First, we determined aHRs of HCC, accounting for death as a competing risk.[14] Second, to assess whether risk factors for HCC varied by presence of advanced hepatic fibrosis, we stratified our analysis by platelet count at start of follow-up (<150,000/μL; ≥150,000/μL), as platelet count <150,000/μL is associated with advanced hepatic fibrosis by liver biopsy (Ishak stage 4-6) among patients with chronic HBV and is a marker of cirrhosis-induced portal hypertension.[15] We chose not to adjust for platelet count in primary analyses, because cirrhosis is in the causal pathway to HCC and controlling for advanced hepatic fibrosis status could potentially adjust away associations between risk factors of interest and HCC, and might attenuate our ability to detect important clinical factors.

Next, to examine the effects of HBV viremia on HCC risk, we first restricted the sample to those who had quantitative HBV DNA measured before the end of follow-up. We constructed separate Cox models to examine aHRs of HCC associated with the following time-updated categories of HBV DNA: (1) >200 IU/mL; (2) ≤200; 201-2,000; >2,000 IU/mL; and (3) ≤200; 201-200,000; >200,000 IU/mL. We also determined the aHR of HCC with higher time-updated quantitative HBV DNA level (per 1.0 $\log_{10}$ IU/mL increase).

We then included those who had quantitative or qualitative HBV DNA assessed. We used Cox regression to evaluate the risk of HCC with time-updated detectable HBV (compared to those with undetectable HBV). We evaluated aHRs of HCC associated with increasing consecutive months of detectable HBV (compared to those with undetectable HBV). Given the potential impact of both HIV and HBV on development of HCC, we used Cox regression to evaluate the risk of HCC as a composite variable of time-updated detectable HIV and HBV with four categories: (1) detectable HIV and HBV; (2) undetectable HIV with detectable HBV; (3) detectable HIV with undetectable HBV; and (4) undetectable HIV and HBV. We then determined the aHRs of HCC for groups 1-3 compared to those with undetectable HIV and HBV.

Among individuals who received HBV-active ART (i.e., TDF, lamivudine, emtricitabine) or entecavir and who had quantitative or qualitative HBV DNA assessed, we determined whether the risk of HCC was reduced with increasing consecutive months of (1) undetectable HBV and (2) undetectable HIV and HBV. Consecutive months of undetectable viremia were counted until detectable HIV or HBV was observed. If undetectable viremia was again achieved, the consecutive months suppressed was restarted at 1 month.

Analyses evaluating HBV viremia were adjusted for time-updated HIV RNA, time-updated CD4+ percentage, and other HCC risk factors. Analyses were repeated, accounting for death as a competing risk and

stratified by platelet count (<150,000/μL; ≥150,000/μL) at start of follow-up. In the subgroup of persons who had HBeAg assessed, we performed an exploratory analysis examining the association between positive HBeAg status and HCC. Furthermore, to begin to explore the effect of advanced hepatic fibrosis on risk of HCC, we conducted an additional exploratory analysis evaluating the effect of baseline platelet count <150,000/μL on HCC risk.

We assessed the proportionality of hazards with log-log plots and Schoenfeld residuals. 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.[16] Results across the 10 data sets were combined to arrive at CIs that accounted for within–data set and across–data set variances. Data were analyzed using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

PATIENT CHARACTERISTICS

Among 130,594 persons with HIV in the 22 NA-ACCORD cohorts from 1995 to 2016, 10,661 (8.2%) were HBV-coinfected. After exclusions, 8,354 individuals coinfected with HIV/HBV remained in the sample (Fig. 1). The median age was 43 years, and participants were predominantly male (93.1%) and non-White (52.4%; Table 1). Heavy alcohol use was reported in 35.3%. A total of 1,806 (21.6%) had chronic HCV coinfection. At start of follow-up, the median HIV RNA was 2.6 $\log_{10}$ copies/mL, and the median CD4+ cell count was 354 cells/mm^3 (median percentage, 21.0%). At any time before or during follow-up, 3,054 (36.6%) had their quantitative HBV DNA assessed (median measures/patient, 2 [interquartile range (IQR), 1-5]), 2,795 (33.5%) had their qualitative HBV DNA assessed (median measures/patient, 3 [IQR, 1-6]), and 3,922 (47.0%) had their HBeAg tested. Among those who had HBeAg tested, 2,174 (55.4%) had a positive result.

At start of follow-up, 47.8% were on ART with lamivudine or emtricitabine as the only HBV-active antiretroviral; 26.7% received HBV-active ART with TDF plus either emtricitabine or lamivudine; 1.7% received HBV-active ART with TDF alone; and 4.0% were on ART without an HBV-active antiretroviral (Table 1). A total of 1,652 (19.8%) were not on ART at start of follow-up; of these, 1,277 (77.8%) started ART during follow-up. Among 1,985 (23.8%) patients not on an HBV-active antiretroviral at study entry, 1,509 (76.0%) received HBV-active ART during follow-up (1,143 TDF-based; 360 with lamivudine or emtricitabine alone). A total of 129 patients received entecavir during follow-up (of whom 118 [91.5%] were also on ART).

Among the 8,354 individuals, 115 (1.4%) developed HCC during 65,392 person-years of follow-up (incidence rate, 1.8 [95% CI, 1.5-2.1] events/1,000 person-years). The median duration of follow-up was 6.9 (IQR, 2.8-13.0) years.

RISK FACTORS FOR HCC

The risk of HCC was not increased with time-updated HIV RNA >500 copies/mL (aHR, 0.90 [0.56-1.43]; Table 2). Analyses evaluating alternative definitions of HIV viremia showed that the risk of HCC was not increased with higher time-updated HIV RNA (aHR, 1.03 [0.86-1.24] per 1.0 $\log_{10}$ copies/mL increase), higher category of time-updated HIV RNA (501-10,000 copies/mL: aHR, 0.59 [0.28-1.24]; >10,000 copies/mL: aHR, 1.16 [0.68-1.99] vs. ≤500 copies/mL), or greater consecutive months with detectable HIV (<12 months: aHR, 0.64 [0.30-1.38]; ≥12 months: aHR, 1.07 [0.64-1.79] vs. those with undetectable HIV). HCC risk was also not increased with CD4+ percentage <14% (aHR, 1.03 [0.56-1.90] vs. >28%). Several traditional risk factors for HCC were associated with increased HCC risk (Table 2), specifically age 40-49 years (aHR, 1.97 [1.22-3.17]), age ≥50 years (aHR, 2.55 [1.49-4.35]), heavy alcohol use (aHR, 1.52 [1.04-2.23]), and chronic HCV (aHR, 1.61 [1.07-2.40]). The risk of HCC was increased with diabetes, but the result did not meet statistical significance (aHR, 1.79 [0.95-3.38]).

Among persons who had a quantitative HBV DNA assessed during follow-up (n = 3,054; Table 3), the risk of HCC increased with higher time-updated HBV DNA (aHR, 1.18 [1.05-1.34] per 1.0 $\log_{10}$ IU/mL increase). HBV DNA >200 IU/mL was associated with a 2.7-fold increased risk of HCC (aHR, 2.70 [1.23-5.93]). The risk was especially elevated at HBV DNA >200,000 IU/mL (aHR, 4.34 [1.72-10.94]).

TABLE 1. Baseline Characteristics of Persons Coinfected With HIV/HBV in the NA-ACCORD (1995-2016)

Characteristic	(n = 8,354)
Age (n, %)	
Median (years, IQR)	42.9 (36.2-49.2)
<40 years	3,224 (38.6%)
40-49 years	3,204 (38.4%)
≥50 years	1,926 (23.1%)
Male sex (n, %)	7,775 (93.1%)
Race (n, %)	
White	3,973 (47.6%)
Black or African American	3,421 (41.0%)
Asian/Pacific Islander	126 (1.4%)
Multiracial, Other, Unknown	834 (10.0%)
Hispanic (n, %)	665 (8.4%)
Body mass index (n, %)	
Median (IQR)	24.4 (22.0-27.3)
Underweight (<18.50 kg/m^2)	273 (3.6%)
Normal weight (18.50-24.99 kg/m^2)	4,041 (52.6%)
Overweight (25.00-29.99 kg/m^2)	2,435 (31.7%)
Obesity (≥30.00 kg/m^2)	929 (12.1%)
Missing	676 (8.1%)
Diabetes mellitus (n, %)	523 (6.3%)
Heavy alcohol use (n, %)	
Ever	2,946 (35.3%)
Never	5,207 (62.3%)
No data on alcohol use available	201 (2.4%)
HIV transmission risk factors (n, %)	
Men who have sex with men	3,939 (47.2%)
History of injection drug use	1,806 (21.6%)
Recipient of blood transfusion	31 (0.4%)
Heterosexual contact	842 (10.1%)
Other	151 (1.8%)
Unknown	2,020 (24.2%)
Chronic HCV infection (n, %)	1,803 (21.6%)
HIV RNA (n, %)	
Median ($\log_{10}$ copies/mL, IQR)	2.6 (1.7-4.1)
≤500 copies/mL	4,567 (54.7%)
>500 copies/mL	3,787 (45.3%)
Absolute CD4+ cell count (n, %)	
Median (cells/mm^3, IQR)	354.0 (184.0-557.0)
≥500 cells/mm^3	2,626 (31.4%)
200-499 cells/mm^3	3,450 (41.3%)
<200 cells/mm^3	2,278 (27.3%)
CD4+ cell percentage (n, %)	
Median (%, IQR)	21.0 (12.2-30.0)
≥28%	2,539 (30.4%)
14%-27.99%	3,454 (41.3%)
<14%	2,361 (28.3%)
Platelet count (n, %)	
<150,000/μL	1,584 (19.0%)
≥150,000/μL	6,285 (75.2%)
Not assessed at start of follow-up	485 (5.8%)
HBV DNA	
Median HBV DNA ($\log_{10}$ IU/mL, IQR)	2.0 (1.3-5.0)
Quantitative HBV DNA (initial assessment during observation; n, %)	3,054 (36.6%)
≤200 IU/mL	1,688 (55.3%)
201-2,000 IU/mL	215 (7.0%)
>2,000 IU/mL	1,151 (37.7%)
Assessed only for qualitative HBV DNA during observation (n, %)	2,307 (27.6%)
Never assessed for quantitative or qualitative HBV DNA during observation (n, %)	2,993 (35.8%)
HBeAg (n, %)	
Negative	1,748 (20.9%)
Positive	2,174 (26.0%)
Never tested before or during follow-up	4,432 (53.1%)
On ART at start of follow-up (n, %)	6,702 (80.2%)
Anti-HBV ART regimen at start of follow-up (n, %)*	
Lamivudine or emtricitabine alone	3,997 (47.8%)
TDF alone	142 (1.7%)
TDF + (lamivudine or emtricitabine)	2,230 (26.7%)
On ART, but no anti-HBV antiretroviral	333 (4.0%)
Not on ART	1,652 (19.8%)
Year at start of follow-up (n, %)	
1995-2000	2,490 (29.8%)
2001-2006	3,398 (40.7%)
2007-2016	2,466 (29.5%)

Note: Age was measured as year of baseline – year of birth. Sex, race/ethnicity, and history of injection drug use were collected at enrollment into the NA-ACCORD. History of heavy alcohol use was defined as ever having reported while under observation in the NA-ACCORD: (1) inpatient or outpatient diagnosis of alcohol dependence/abuse; or (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. HIV transmission risk factors were not mutually exclusive. Diabetes mellitus was defined by (1) hemoglobin A1c ≥6.5%, (2) prescription of certain antidiabetic medications, or (3) diabetes diagnosis plus prescription of certain antidiabetic medications. Chronic HCV infection was defined by detectable HCV RNA or available HCV genotype recorded at any time during observation. ART was measured as a combination of three antiretroviral agents from at least two classes or a triple nucleoside/nucleotide reverse-transcriptase inhibitor regimen.
*Results represent initial ART regimen.

Among those who had quantitative or qualitative HBV DNA assessed during follow-up (n = 5,316; Table 4), the risk of HCC was increased with ≥1 year of detectable HBV (aHR, 2.15 [1.34-3.42]) but not

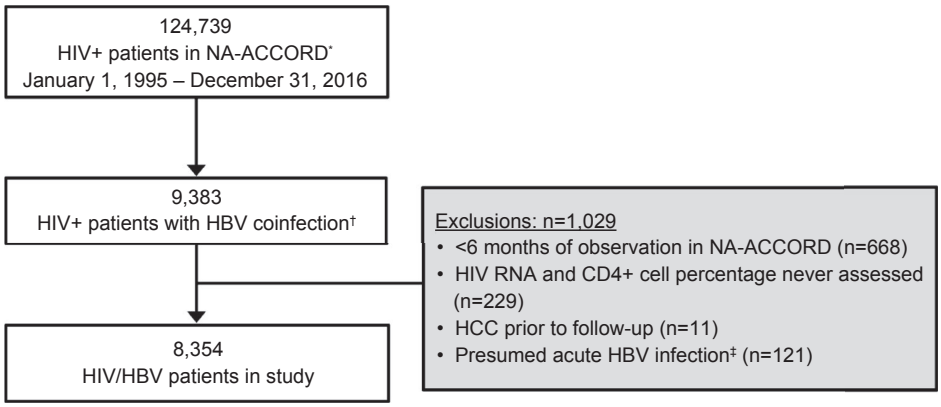

FIG. 1. Selection of persons coinfected with HIV/HBV within the NA-ACCORD (1995-2016). *Includes 22 contributing cohorts: ALIVE, CWRU/PCRD, FENWAY, HOMER, HOPS, JHHCC, KPMAS, KPNC, MACS, MCHS-II, MONT, OHTN, RRC, SAC, SCOPE, UAB, UCHCC, UCSD, UW, VAND, VACS, WIHS. †HBV co-infection determined by an ever positive for HBV surface antigen, HBV e antigen, or HBV DNA. ‡Presumed acute HBV infection defined as alanine aminotransferase or aspartate aminotransferase >1,000 U/L within ±30 days of the first positive HBV laboratory test (HBV surface antigen, HBV e antigen, or HBV DNA) with no subsequent positive HBV laboratory test ≥6 months after the initial result. Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; NA-ACCORD, North American AIDS Cohort Collaboration on Research and Design; RNA, ribonucleic acid.

with <1 year (aHR, 2.02 [0.95-4.32) compared to those with consistently undetectable HBV (test for trend $P = 0.0012$). In the analysis examining combined HIV and HBV viremia, the highest risk of HCC was observed among coinfected patients with both detectable HIV and HBV (aHR, 2.21 [1.17-4.18]; Table 4) compared to those with both undetectable HIV and HBV. Patients with undetectable HIV but detectable HBV also had significantly elevated HCC risk (aHR, 1.77 [1.07-2.92]), but the risk of HCC was not increased with detectable HIV but undetectable HBV (aHR, 0.27 [0.06-1.14]).

For persons who received HBV-active ART and who had quantitative or qualitative HBV DNA assessed (n = 4,891; Table 5), increasing consecutive months of undetectable HBV was associated with a lower risk of HCC compared to those with detectable HBV (Table 5; test for trend $P = 0.0024$). This pattern was also seen when evaluating consecutive months of combined HIV and HBV suppression. The risk of HCC was significantly reduced with ≥1 year of suppression of both viruses (Supporting Table S1).

Similar findings were observed in competing risk analyses (Supporting Tables S2-S4). Among persons with platelet counts ≥150,000/μL at start of follow-up, age ≥40 years, HCV coinfection, and heavy alcohol use remained risk factors for HCC, while time-updated HIV RNA >500 copies/mL and CD4+ percentage <14% were not (Supporting Table S5). Within this subgroup, associations with HCC were slightly stronger for time-updated detectable HBV DNA and detectable HIV/HBV (Supporting Table S6) as well as increasing consecutive years with both undetectable HIV and HBV (Supporting Table S7).

Finally, in our exploratory analysis examining the association between positive HBeAg status and HCC among persons who had HBeAg assessed, we observed no increased risk of HCC with HBeAg-positive status after adjustment for HIV-related and traditional HCC risk factors (aHR, 1.47 [0.92-2.35]). In a separate exploratory analysis, baseline platelet count <150,000/μL was strongly associated with an increased risk of HCC (aHR, 4.05 [2.62-6.26]), after adjusting for detectable HBV, detectable HIV, CD4+ percentage, and traditional HCC risk factors (Supporting Table S8). When accounting for competing risks, the results of these analyses were nearly identical.

Discussion

In this large sample of HIV/HBV-coinfected persons from North America, we found that all detectable measures of HBV viremia, including time-updated detectable HBV >200 IU/mL, higher current HBV

TABLE 2. Factors Associated With HCC Among Persons Coinfected With HIV/HBV in the NA-ACCORD (1995-2016) (n = 8,354; 115 Incident HCC Events Identified)

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	3,224	25	26,141	1.0 (0.6-1.4)	Reference	Reference
40-49 years	3,204	56	26,221	2.1 (1.6-2.8)	2.21 (1.38-3.54)	1.97 (1.22-3.17)
≥50 years	1,926	34	13,029	2.6 (1.8-3.6)	2.82 (1.68-4.73)	2.55 (1.49-4.35)
Sex						
Female	579	3	4,364	0.7 (0.1-2.0)	Reference	Reference
Male	7,775	112	61,028	1.8 (1.5-2.2)	2.61 (0.83-8.21)	1.92 (0.60-6.14)
Race						
Non-White	4,381	51	33,540	1.5 (1.1-2.0)	Reference	Reference
White	3,973	64	31,852	2.0 (1.5-2.6)	1.30 (0.90-1.88)	1.38 (0.94-2.03)
Body mass index						
Not obese (<30 kg/m^2)	6,749	95	54,954	1.7 (1.4-2.1)	Reference	Reference
Obese (≥30 kg/m^2)	929	12	7,218	1.7 (0.9-2.9)	0.98 (0.54-1.79)	1.00 (0.55-1.83)
Time-updated diabetes mellitus‡						
No	7,903	104	62,138	1.7 (1.4-2.0)	Reference	Reference
Yes	449	11	3,253	3.4 (1.7-6.1)	2.08 (1.12-3.87)	1.79 (0.95-3.38)
Heavy alcohol use§						
No	5,207	51	36,804	1.4 (1.0-1.8)	Reference	Reference
Yes	2,946	63	27,103	2.3 (1.8-3.0)	1.62 (1.12-2.35)	1.52 (1.04-2.23)
Chronic HCV infection‖						
No	6,551	75	50,504	1.5 (1.2-1.9)	Reference	Reference
Yes	1,803	40	14,888	2.7 (1.9-3.7)	1.79 (1.22-2.63)	1.61 (1.07-2.40)
Time-updated HIV RNA						
≤500 copies/mL	7,436	87	45,829	1.9 (1.5-2.3)	Reference	Reference
>500 copies/mL	6,719	28	19,563	1.4 (1.0-2.1)	0.89 (0.57-1.37)	0.90 (0.56-1.43)
Time-updated CD4+ cell percentage						
>28%	4,961	40	25,873	1.5 (1.1-2.1)	Reference	Reference
14%-28%	6,219	59	27,469	2.1 (1.6-2.8)	1.47 (0.98-2.21)	1.47 (0.97-2.21)
<14%	3,973	16	12,049	1.3 (0.8-2.2)	0.98 (0.55-1.76)	1.03 (0.56-1.90)
Year at start of follow-up (per year)	—	—	—	—	0.96 (0.91-1.02)	0.95 (0.89-1.01)

*For time-updated variables, a given patient may be included within more than one category.
†HRs adjusted for all other risk factors listed in this table.
‡Diabetes mellitus was defined by (1) hemoglobin A1c ≥6.5%, (2) prescription of antidiabetic medication, or (3) record of a diabetes diagnosis plus the prescription of diabetes-related medication before start of follow-up.
§History of heavy alcohol use defined as ever having reported while under observation in the NA-ACCORD: (1) inpatient or outpatient diagnosis of alcohol dependence/abuse; or (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.
‖Chronic HCV infection was defined by detectable HCV RNA or available HCV genotype recorded at any time during observation.

DNA, and greater consecutive months of detectable HBV, were associated with increased risk of HCC. There was a biological gradient of risk of HCC with higher HBV DNA, especially at levels >200,000 IU/mL. Notably, neither CD4+ percentage nor any definition of HIV viremia was associated with increased HCC risk. In analyses evaluating both detectable HIV and HBV, the risk of HCC was highest when HBV viremia was detectable. Finally, sustained HBV suppression with HBV-active ART for ≥1 year was associated with a 58% reduction in HCC risk.

These findings complement and extend existing knowledge of HBV natural history, and do so specifically for persons coinfected with HIV. The REVEAL-HBV study from Taiwan provided important initial data on the role of HBV replication on

TABLE 3. Risk of Incident HCC Associated With Different Categories of Time-Updated HBV DNA Among Persons Coinfected With HIV/HBV Who Had Quantitative HBV DNA Measured Before Follow-up in the NA-ACCORD (1995-2016) (n = 3,054; 30 Incident HCC Events Identified)

Characteristic	No. Exposed*	No. Events	Person-Time	Incidence Rate (95% CI), Events/1,000 Person-Years	Unadjusted HR (95% CI)	Adjusted HR† (95% CI)
Time-updated HBV DNA, 200 IU/mL cutoff						
≤200 IU/mL	2,355	17	15,844.9	1.1 (0.6-1.7)	Reference	Reference
>200 IU/mL	1,468	13	5,031.4	2.6 (1.4-4.4)	2.60 (1.25-5.41)	2.70 (1.23-5.93)
Time-updated HBV DNA, 2,000 IU/mL cutoff						
≤200 IU/mL	2,355	17	15,844.9	1.1 (0.6-1.7)	Reference	Reference
201-2,000 IU/mL	596	2	973.1	2.1 (0.2-7.4)	2.11 (0.48-9.17)	2.20 (0.50-9.59)
>2,000 IU/mL	1,232	11	4,058.3	2.7 (1.4-4.8)	2.72 (1.26-5.86)	2.85 (1.24-6.57)
Time-updated HBV DNA, 200,000 IU/mL cutoff						
≤200 IU/mL	2,355	17	15,844.9	1.1 (0.6-1.7)	Reference	Reference
201-200,000 IU/mL	1,122	5	2,924.0	1.7 (0.6-4.0)	1.71 (0.63-4.67)	1.77 (0.63-4.94)
200,000 IU/mL	774	8	2,107.4	3.8 (1.6-7.5)	3.87 (1.66-9.06)	4.34 (1.72-10.94)

*Because HBV DNA is a time-updated variable, a given patient may be included within more than one category.
†HRs adjusted for age and year at start of follow-up.

TABLE 4. Risk of HCC Associated With Time-Updated HBV DNA Level and Time-Updated Detectable HIV and HBV Status Among Persons Coinfected With HIV/HBV Who Had Quantitative or Qualitative HBV DNA Assessed in the NA-ACCORD (1995-2016) (n = 5,316; 87 Incident HCC Events Identified)

Characteristic	No. Exposed*	No. Events	Person-Time	Incidence Rate (95% CI), Events/1,000 Person-Years	Unadjusted HR (95% CI)	Adjusted HR† (95% CI)
Time-updated HBV DNA						
Undetectable	3,656	44	22,692	1.9 (1.4-2.6)	Reference	Reference
Detectable	3,364	43	12,850	3.3 (2.4-4.5)	1.87 (1.22-2.85)	2.22 (1.42-3.47)
Time-updated detectable HIV and HBV status‡						
Undetectable HIV and HBV	3,494	42	19,164	2.2 (1.6-3.0)	Reference	Reference
Detectable HIV, undetectable HBV	1,881	2	3,529	0.6 (0.07-2.0)	0.29 (0.07-1.21)	0.27 (0.06-1.14)
Undetectable HIV, detectable HBV	2,835	27	8,510	3.2 (2.1-4.6)	1.55 (0.95-2.52)	1.77 (1.07-2.92)
Detectable HIV and HBV	2,480	16	4,340	3.7 (2.1-6.0)	1.93 (1.07-3.49)	2.21 (1.17-4.18)

*Because HIV RNA and HBV DNA are time-updated variables, a given patient may be included within more than one category.
†Model evaluating time-updated HBV DNA was adjusted for age, sex, race/ethnicity, diabetes, time-updated HIV RNA, time-updated CD4+ cell percentage, heavy alcohol use, and year at start of follow-up. Model evaluating time-updated detectable HIV and HBV status was adjusted for age, sex, race/ethnicity, diabetes, time-updated CD4+ cell percentage, heavy alcohol use, and year at start of follow-up.
‡Detectable HIV = HIV RNA >500 copies/mL; detectable HBV = HBV DNA identified on quantitative or qualitative assay; undetectable HIV = HIV RNA ≤500 copies/mL; and undetectable HBV = no HBV DNA identified on quantitative or qualitative assay.

HCC development in the pre-HBV antiviral therapy era.[5] This study demonstrated a strong relationship between baseline HBV DNA level and risk of HCC among persons with chronic HBV monoinfection. A threshold for increased HCC risk was observed at 2,000 IU/mL, with incrementally greater risk for HCC with higher levels of HBV DNA. Additionally, persistent HBV viremia during follow-up, particularly at higher HBV DNA levels and for longer duration, was found to be a risk factor for incident HCC and later for recurrent HCC.[17,18]

Our study shows that HBV viremia is associated with HCC risk in a large, racially diverse cohort of adults outside of Asia. The epidemiology of HBV infection is distinctly different in Asia, where most HBV infections are acquired perinatally followed by years of immune tolerance. In contrast, horizontal HBV transmission through sexual or parenteral routes is more common in Western countries. Despite this difference in acquisition and natural history, HBV viremia remained adversely associated with HCC

TABLE 5. Risk of HCC Associated With Different Categories of Increasing Consecutive Months With Undetectable HBV DNA and, Separately, Both Undetectable HIV RNA and HBV DNA, Among Persons Coinfected With HIV/HBV Who Had Quantitative or Qualitative HBV DNA Assessed and Received HBV-Active Antiretroviral Therapy in the NA-ACCORD (1995-2016) (n = 4,891; 78 Incident HCC Events Identified)

Characteristic*	No. Exposed†	No. Events	Person-Time	Incidence Rate (95% CI), Events/1,000 Person-Years	Unadjusted HR (95% CI)	Adjusted HR‡ (95% CI)
Duration of undetectable HBV§						
Detectable HBV	3,226	38	11,529	3.3 (2.3-4.5)	Reference	Reference
Undetectable HBV for <1 year	3,263	13	3,110	4.2 (2.2-7.1)	1.41 (0.74-2.69)	1.12 (0.55-2.28)
Undetectable HBV for ≥1 year	2,843	27	15,481	1.7 (1.1-2.5)	0.50 (0.30-0.82)	0.42 (0.24-0.73)
Duration of undetectable HBV‖						
Detectable HBV	3,226	38	11,529	3.3 (2.3-4.5)	Reference	Reference
Undetectable HBV for <1 year	3,263	13	3,110	4.2 (2.2-7.1)	1.42 (0.75-2.71)	1.14 (0.56-2.31)
Undetectable HBV for 1-4 years	2,843	12	7,107	1.7 (0.9-2.9)	0.56 (0.29-1.08)	0.55 (0.28-1.07)
Undetectable HBV for ≥4 years	1,773	15	8,374	1.8 (1.0-3.0)	0.45 (0.25-0.84)	0.34 (0.17-0.67)
Duration of undetectable HIV and HBV¶						
Detectable HIV and HBV	4,181	40	13,923	2.9 (2.1-3.9)	Reference	Reference
Undetectable HIV and HBV for <1 year	3,145	15	4,068	3.7 (2.1-6.1)	1.34 (0.74-2.44)	1.25 (0.68-2.29)
Undetectable HIV and HBV for ≥1 year	2,609	23	11,996	1.9 (1.2-2.9)	0.62 (0.37-1.05)	0.51 (0.29-0.91)
Duration of undetectable HIV and HBV#						
Detectable HIV and HBV	4,181	40	13,923	2.9 (2.1-3.9)	Reference	Reference
Undetectable HIV and HBV for <1 year	3,145	15	4,068	3.7 (2.1-6.1)	1.34 (0.74-2.45)	1.24 (0.68-2.29)
Undetectable HIV and HBV for 1-4 years	2,609	13	6,597	2.0 (1.0-3.4)	0.70 (0.37-1.32)	0.64 (0.34-1.23)
Undetectable HIV and HBV for ≥4 years	1,396	10	5,399	1.9 (0.9-3.4)	0.54 (0.26-1.10)	0.38 (0.17-0.83)

*Detectable HIV = HIV RNA >500 copies/mL; detectable HBV = HBV DNA identified on quantitative or qualitative assay; undetectable HIV = HIV RNA ≤500 copies/mL; and undetectable HBV = no HBV DNA identified on quantitative or qualitative assay.
†Because HIV RNA and HBV DNA are time-updated variables, a given patient may be included within more than one category.
‡Models were adjusted for age, sex, race/ethnicity, diabetes, time-updated HIV RNA, time-updated CD4+ cell percentage, heavy alcohol use, and year at start of follow-up.
§Test for trend: $P = 0.0024$.
‖Test for trend: $P = 0.0010$.
¶Test for trend: $P = 0.0314$.
#Test for trend: $P = 0.0132$.

in this non-Asian, HIV-infected population, with a threshold of risk that may begin as low as 200 IU/mL.

Our findings also provide some insight into the association between HBV viremia and excess mortality among people living with HIV and HBV that has been observed in a variety of cohort studies from Africa and Europe.[19-21] In these studies, the probability of death increased at HBV DNA levels >2,000 IU/mL, and in one study, was incrementally higher with every 1.0 $\log_{10}$ IU/mL increase of HBV DNA.[19] HCC, a lethal cancer with high case fatality, may be more challenging to diagnose and treat in the setting of HIV,[22,23] and may have been a contributing factor to the increased mortality observed in these studies.

Notably, in contrast to REVEAL-HBV, our sample of HIV/HBV-coinfected individuals was a mostly treated cohort, with 76% on HBV-active ART at start of follow-up and 76% of those not on HBV-active ART at baseline, initiating this therapy during follow-up. This observation highlights that antiviral therapy reduces, but does not eliminate, the risk of HCC. The overall incidence of HCC in our study was comparable to estimates reported among patients with monoinfected HBV without cirrhosis receiving TDF.[24-26] Interestingly, HBV viremia was a stronger predictor of HCC than HIV viremia in our cohort, which underscores the necessity of HBV-specific control with HBV-active ART to reduce HCC risk. Just

as suboptimal adherence on HBV antiviral therapy and HBV viremia have been shown to have detrimental effects on development of HCC,[27] so can persistent HBV viremia during HBV-active ART. These data highlight the importance of ongoing HBV DNA monitoring and optimization of HBV-active ART to achieve HBV DNA suppression, through maximal adherence and use of tenofovir-based ART.

As a corollary to our findings on HBV viremia, we found that sustained HBV suppression had a protective association with HCC risk. The potential for antiviral therapy to prevent liver cancer was first noted in a randomized, controlled trial of lamivudine in patients with chronic HBV and advanced hepatic fibrosis, which reported a 51% reduction in HCC risk with lamivudine.[28] Multiple observational studies in HBV monoinfection have since demonstrated that prolonged use of the more potent and durable antiviral nucleos(t)ide analogues tenofovir or entecavir is associated with a reduction in risk of HCC by as much as 70%.[6,25,26] Our findings suggest that patients coinfected with HIV/HBV are most likely to derive protective benefit from HBV-active ART when they have maintained HBV suppression beyond a year. We observed even lower hazard ratios with longer durations of HBV suppression.

Older age, heavy alcohol use, and chronic HCV coinfection—all known risk factors for HCC in cohorts with monoinfected HBV[29]—also significantly increased the risk of HCC in our cohort of persons coinfected with HIV/HBV. Heavy alcohol use and HCV coinfection were prevalent in our cohort and may continue to influence the natural history of HCC despite HBV suppression. Our findings suggest that avoiding excessive alcohol consumption and initiating antiviral therapy for chronic HCV infection might help to reduce the risk of HCC among persons coinfected with HIV/HBV.

Our study has several limitations. First, clinical factors were prospectively collected as part of routine clinical care, not per standardized protocol, which explains why HBV DNA monitoring was inconsistently performed. Second, we did not have data on hepatitis delta coinfection, HBV genotype, or NAFLD, which have all been shown to be associated with increased risk of HCC.[30,31] Third, we used thrombocytopenia as a surrogate for advanced hepatic fibrosis, because cirrhosis diagnoses were not available and because aspartate aminotransferase–to-platelet ratio index and Fibrosis-4 Index for hepatic fibrosis, which are commonly used noninvasive measures of hepatic fibrosis, perform poorly in determining cirrhosis among patients coinfected with HIV/HBV.[32] Platelet count <150,000/μL is associated with advanced hepatic fibrosis, as determined by liver biopsy among patients with chronic HBV, and is a marker of portal hypertension.[15] Fourth, chronic HCV infection was determined by detectable HCV RNA or genotype. HCV antibody–positive persons who were never assessed for HCV RNA or genotype might have been misclassified as uninfected. Finally, our cohorts represent the North American demographic of individuals coinfected with HIV/HBV. Our results may not be generalizable to other geographic regions.

A major strength of this study is examination of validated cancer diagnoses within a large multicohort population of persons coinfected with HIV/HBV who were followed over an extended length of time. Our evaluation of individual-level clinical data, as well as time-updated measures of HBV DNA, HIV RNA, and CD4+ percentage, enabled a comprehensive and granular examination of HCC risk factors. Use of lagged HIV RNA and CD4+ percentage minimized the potential for reverse causality. Care was also taken to account for competing risk of death in our analyses.

Our findings highlight the burden of HCC on individuals coinfected with HIV/HBV in the ART era. In the absence of a cure for chronic HBV infection, prevention of HBV with immunization, early identification of HBV coinfection, and prompt initiation of HBV-active ART remain essential to preventing HBV-associated HCC. To gain maximal benefit from ART for HCC prevention, sustained and ideally uninterrupted suppression of HBV may be necessary over years. Further work is needed to determine how best to intervene with risk factor modification, antiviral therapy, and HCC screening to reduce the impact of this major cancer among persons coinfected with HIV/HBV.

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