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BRIEF REPORT

Who Is at Risk for New Hepatitis B Infections Among People With HIV?

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Hepatitis B virus (HBV) increases morbidity and mortality among people with HIV (PWH). We retrospectively analyzed HBV incidence among 5785 PWH. Fourteen had newly positive hepatitis B s antigen (mean 5.2 person-years of follow-up, 46.4/100 000 infections/year). These data show gaps in HBV vaccination and in the preventative efficacy of HBV-specific antiretroviral therapy.

Keywords. HBV; HBV vaccination; HIV; incident HBV infection.

Although the burden of hepatitis B virus (HBV) has decreased over time, new HBV infections still occur among people with HIV (PWH) [1–3]. These new HBV infections, which are vaccine preventable, thwart our efforts toward global hepatitis B elimination by the year 2030, proposed by World Health Organization (WHO) [4]. Antiretroviral therapies (ARTs) such as tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) or TDF/TAF combined with lamivudine (3TC) or emtricitabine (FTC) are highly effective at suppressing HBV with low risk of resistance. However, they are noncurative.

Studies examining the incidence of acute hepatitis B in those with HIV in the United States are limited. The incidence of acute HBV in a US-based cohort of PWH was 11–12 cases per 1000 person-years. In these cohorts, men who have sex with men (MSM) are more likely to acquire HBV than heterosexual men and women. Those with lower CD4 counts, those not on ART, and those using injection drugs also have higher incidence of HBV infection [5, 6]. We sought to examine the incidence of new HBSsAg positivity, which represents new hepatitis B infection, in a diverse cohort of PWH in Texas. Additionally, we examined factors that predict risk for acquiring HBV to inform strategies for hepatitis B elimination.

METHODS

Patient Consent

This study was conducted at Parkland Health & Hospital System (PHHS) and was approved by the Institutional Review Board; it was determined that a waiver of consent was appropriate given the retrospective nature of the data collection.

All adult PWH who received care from 01/01/2010 to 12/31/2018 at PHHS were included in this study. PWH were identified via electronic health record (EHR) query using International Classification of Diseases, Ninth and Tenth Revision (ICD-9 and ICD-10), codes and had 1–9 years of follow-up. Each PWH was assigned a study entry date associated with the first outpatient encounter for HIV-related care at each health care organization during the study period. We excluded those with existing HBV infection, as defined by hepatitis B s antigen (HBsAg) positivity within the first 6 months before study entry or 1 year after entry. Additionally, we excluded those with chronic HBV (HBV DNA+ or hepatitis B e antigen positive [HBeAg+]) within the first 6 months before study entry (see consort diagram, Figure 1). We had a final study population of 5785 adult PWH. Each patient was followed from study entry until the end of the study period, 12/31/2021; patients were censored at loss to follow-up (defined as not having any health care encounters for a ≥12-month period) and death.

EHRs were used to obtain data on demographics, insurance status, and comorbidities based on ICD-9 and -10 codes. Sociodemographic data, comorbidities, insurance status, severity of illness, laboratory and medication data, and other patient characteristics were collected at the time of study entry. Laboratory data included CD4 cell count, HIV viral load, HBsAg, hepatitis B virus s antibody (HBsAb), HBV DNA, HBeAg, aspartate aminotransferase (AST), alanine transaminase (ALT), and hepatitis B core total antibody. The primary outcome, new (either acute or recurrent) HBV infection, was defined as HBSAg-positive >12 months after study entry among those who were previously HBsAg-negative at baseline. Data were collected on ART components including agents with anti–hepatitis B activity such as 3TC, FTC, TDF, and TAF. As ART components often change over time, we examined ART use at baseline as well as at the time of seroconversion—that

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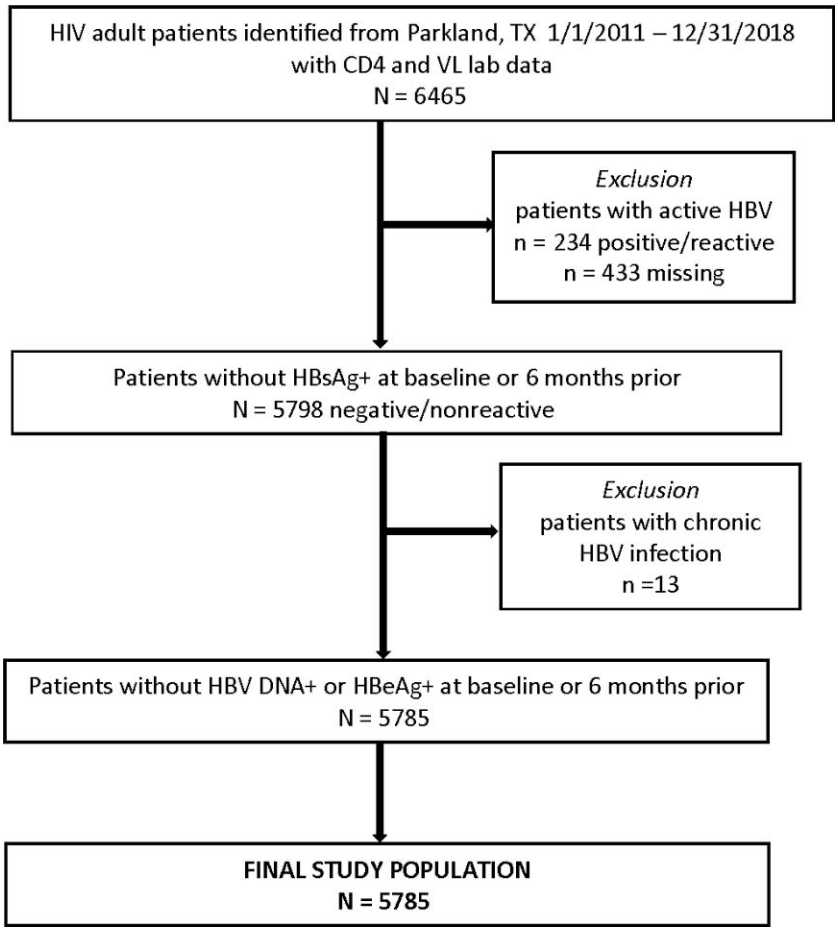

Figure 1. Flowchart of patient selection. Inclusion criteria were adult and PWH. Excluded were CD4 count, viral load, active HBV, and chronic HBV. Abbreviations: HBeAg, hepatitis B virus e antigen; HBsAg, hepatitis B virus s antigen; HBV, hepatitis B virus; PWH, people with HIV; VL, viral load.

is, at the time of new HBV. Similarly, we collected HIV and laboratory values at baseline and at the time closest to 3 months after a positive HBsAg test. Specifically, we examined the HIV load, CD4 count, AST, ALT, and medications prescribed for the patients. Medications prescribed 6 months before an HBsAg-positive test were captured in the data set (Table 1).

RESULTS

A total of 5785 PWH were included in the cohort. Of these, 74% were male, 43% were <34 years of age, 55% were Black, 21% were Hispanic/Latinx, and 70% were uninsured. Comorbidities were common; 47% had a history of or active opportunistic infections, 75% had a mental health or psychiatric diagnosis, and 31% had AIDS (CD4 <200 cells/mm^3) at baseline. HBsAb was >10 mIU/mL in 48% at baseline, rendering them immune to new infection, and only 16% had an HIV viral load <50 copies/μL at baseline. Within the first 2 years, 85% were placed on ART with components active against HBV (Table 1).

We examined the development of new HBsAg+ over the course of follow-up. Fourteen patients developed a new positive HBsAg during follow-up, an incidence of 46.4/10 000 patients/year over an average follow-up of 5.2 years.

Of the 14 PWH who developed new HBV after being HBV-negative at baseline, 11 were men and 3 were women (Table 1). At baseline 5 people had an HBsAb level >10 mIU/mL, and 8 had a reactive total core antibody. The average time to HbsAg conversion was 4.9 years. Three people developed a new reactive total core and IgM antibodies after previously being negative. Two who had been core-negative at baseline did not develop a reactive core total antibody or IgM at the time of seroconversion. None had an undetectable HIV viral load (value <50), and 9 had a CD4 count <200. Four people who had prior HBsAb immunity with a value of >10 mIU/mL lost immunity by the time of seroconversion, while 2 people with prior immunity had unknown HBsAb levels at seroconversion. Eight people in this cohort showed signs of hepatocellular injury (AST and/or ALT level 3 times the upper limit of normal or >105 U/L) at the time of diagnosis.

Table 1. Demographics and Laboratory Data of Patients who Developed New HBsAg

					Before Seroconversion					After Seroconversion							
	Age	Race/ Ethnicity	Sex	HIV Risk Factors	Hep B Vaccination Status	HBV-Active ART	HBsAb, mIU/mL	HBcAb Total	Years to New HBsAg	HBcAb Total	HBc IgM	HIV Viral Load, Copies/ mL	CD4 Count, Cells/ mm^3	AST/ ALT Levels, U/L	HBsAb, mIU/mL	HBV DNA, Copies/ mL	HBeAg
1	25	White, non-Hispanic	Male	SUD	…	Yes[a]	<4.23	Not done	1.93	New positive	Positive	187 025	168	825/1824	26.6	>170 000 000	Not done
2	33	Unknown, Hispanic	Male	MSM	1 dose	No	<4.23	Negative	1.25	New positive	Positive	41 834	357	2339/ 3492	Not done	418 240	Not done
3	27	Black, non-Hispanic	Female	Heterosexual	…	No	26.5	Negative	3.71	New positive	Positive	17 385	321	22/15	<1.0	1 147 557	Positive
4	29	White, non-Hispanic	Male	MSM	…	Yes[a]	<4.23	Negative	3.63	Negative	Not done	735 480	47	42/31	<1.0	311 070	Positive
5	31	White, non-Hispanic	Male	MSM	…	Yes[a]	308	Negative	4.63	Negative	Not done	78 416	189	157/175	4.38	4 240 000	Positive
6	38	Black, non-Hispanic	Male	Cocaine	…	Yes[a]	<4.23	Reactive	2.29	Remained positive	Positive	11 018	11	49/42	<1.0	>170 000 000	Positive
7	50	Black, non-Hispanic	Male	MSM	…	Yes	<4.23	Reactive	3.77	Remained positive	Positive	5642	135	463/448	<4.23	Not done	Not done
8	49	Black, non-Hispanic	Female	Heterosexual	1 dose	No[b]	18.3	Reactive	2.76	Remained positive	Nonreactive	72	427	25/24	Not done	>170 000 000	Positive
9	28	Black, non-Hispanic	Male	MSM	…	No[b]	58.3	Reactive	12.26	Remained positive	Not done	75 270	37	48/50	Not done	7 756 038	Not done
10	27	Black, non-Hispanic	Male	MSM/SUD	1 dose	No[b]	0.1	Reactive	7.99	Remained positive	Nonreactive	39 154	559	20/17	4.53	249	Negative
11	46	White, Hispanic	Female	IDU	…	Yes[a]	85.7	Reactive	4.53	Remained positive	Nonreactive	288 988	24	133/78	3.82	1000	Positive
12	50	White, Hispanic	Male	MSM	…	Yes[a]	15.1	Reactive	7.75	Remained positive	Nonreactive	1 705 472	57	21/21	<1.00	793 000 000	Not done
13	46	Black, non-Hispanic	Male	SUD	…	Yes[a]	2	Reactive	10.00	Remained positive	Nonreactive	82 093	60	81/82	Not done	>170 000 000	Not done
14	28	Black, non-Hispanic	Male	SUD	…	Yes	4.23	Negative	1.72	New positive	Positive	8736	390	27/25	<3.1	511 377	Positive

Abbreviations: ART, antiretroviral therapy (with activity against HBV [tenofovir-containing regimens]); AST, aspartate aminotransferase; ALT, alanine transaminase; HBcAg, hepatitis B virus c antigen; HBsAg, hepatitis B virus s antigen; HBV, hepatitis B virus; IDU, intravenous drug use; IgM, immunoglobulin M; MSM, men who have sex with men; SUD, substance use disorder.

[a]Off medications.

[b]Non-HBV ART.

Three patients received a single dose of hep B vaccine before HBV infection. All patients had detectable HBV DNA at the time of seroconversion (13/13, 1 missing value). Seven were HBeAg-positive at the time of seroconversion, while for 7 others those lab data were missing.

DISCUSSION

The incidence of new HBV infection seen in this cohort of PWH, 46.4/10 000 patients/year, is 100-fold higher than the incidence in the general population of Texas, where the rate of acute hepatitis B ranged from 0.8 per 100 000 in 2011 to 0.2 per 100 000 in 2019 [7]. In the United States, the Centers for Disease Control and Prevention estimates a new hepatitis B infection case count of 1 per 100 000, with most cases occurring in those 30–59 years of age, with the most significant risk factor being injection drug use [8]. The impact of HIV/HBV coinfection is avoidable with vaccination against HBV. However, data show that less than half of PWH have been fully vaccinated [9, 10]. Our findings highlight the importance of reduction of HBV risk through vaccination. This aligns with the WHO hepatitis B elimination strategy, which proposes to reduce new infections by 90% between 2022 and 2030 through increasing access to hepatitis B testing, vaccination, and treatment [11].

The uptake of HBV vaccination in those with new infections in this cohort was poor. Six of 14 had HBsAb levels >10 mIU/mL before seroconversion, which should be protective, and none were measured in the 2 years before seroconversion, implying that protective Abs may have waned. Only 3 PWH received 1 dose of an HBV vaccine before seroconversion. Our findings highlight the need for increased vaccine uptake and imply that regular assessment of HBsAb for evidence of waning vaccine efficacy and revaccination may be helpful.

The HBV-specific medications TDF and TAF can reduce the risk of HBV infection and prevent transmission, as demonstrated with mother-to-child transmission [12, 13]. In a recent retrospective analysis among MSM, TDF and TAF were found to reduce the risk of new HBV infection [14]. However, this strategy requires adherence to ART. High HIV viral load measurements were seen among PWH with incident infections in this cohort: All were >50 and 13/14 were >1000 copies/mL, implying nonadherence to ART. For this cohort, even if they were receiving TDF or TAF, the protective effect was limited. It is also notable that 5 of 14 seroconversions occurred in PWH with CD4+ cell counts >200 cells/mm^3, demonstrating risk even for those without immunocompromise.

This study has limitations, including the retrospective data collection, which may introduce bias and misclassification. Our cohort does not have reliable capture of data on HIV or HBV transmission routes or ongoing behavioral risks. There may be under-representation of acute HBV infection as testing was not done systematically. Our analysis is also limited in its ability to determine whether new infections were secondary to waning of HBSab levels and the need for boosting new infections with S-gene mutations, which allow for vaccine escape [15], or, for those with prior positive HBcAb, transition to immune-active infection.

Regardless of these limitations, this is a large cohort of PWH in whom we have longitudinal data to inform us on the incidence of HBV infections among PWH. The high incidence, especially among those not immune at baseline, raises the importance of improving hepatitis B vaccination among PWH. Low rates of vaccination among PWH have been documented in the United States [16]. We noted evidence of nonadherence to ART in patients with newly acquired HBV infection. Improving strategies to implement hepatitis B vaccination and supporting adherence to ART regimens with anti-HBV activity in PWH at highest risk are needed to reduce new HBV infections.

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