Comparison of Hepatitis B Virus Infection in HIV-Infected and HIV-Uninfected Participants Enrolled in a Multinational Clinical Trial: HPTN 052

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Objective: Data comparing hepatitis B virus (HBV) infection in HIV-infected [HIV(+)], and HIV-uninfected [HIV(−)] individuals recruited into the same study are limited. HBV infection status and chronic hepatitis B (cHB) were characterized in a multinational clinical trial: HIV Prevention Trials Network (HPTN 052).

Method: HBV infection status at enrollment was compared between HIV(+) (N = 1241) and HIV(−) (N = 1232) from 7

HBV-endemic countries. Hepatitis B e antigen and plasma HBV DNA were determined in cHB. Median CD4, median plasma HIV RNA, and prevalence of transaminase elevation were compared in HIV(+) with and without cHB. Significance was assessed with χ^2, Fisher exact, and median tests.

Results: Among all participants, 33.6% had HBV exposure without cHB (8.9% isolated HBV core antibody, "HBcAb"; 24.7% HBcAb and anti-HB surface antibody positive, "recovered"), 4.3% had cHB,

8.9% were vaccinated, and 53.5% were uninfected. Data were similar among HIV(+) and HIV(−) except for isolated HBcAb, which was more prevalent in HIV(+) than HIV(−) [10.1% vs. 7.7%, $P = 0.046$]. Median HBV DNA trended higher in HIV(+) than in HIV(−). In HIV(+) with cHB versus those without cHB, transaminase elevations were more prevalent (alanine aminotransferase ≤ grade 2, 12% vs. 5.2%, $P = 0.037$; aspartate aminotransferase ≤ grade 2, 26% vs. 6.0%, $P < 0.001$), CD4 trended lower, and HIV RNA was similar.

Conclusions: HBV infection status did not differ by HIV infection status. HIV co-infection was associated with isolated HBcAb and a trend of increased HBV DNA. In HIV, cHB was associated with mild transaminase elevations and a trend toward lower CD4.

Key Words: HIV, HBV, CD4$^+$ cell count, chronic HBV infection, endemic HBV, prevalence of HBV infection, HIV/HBV co-infection

BACKGROUND

Human immunodeficiency virus type 1 (HIV-1) and hepatitis B virus (HBV) are transmitted through the same routes and are therefore common co-infections. HBV is endemic in areas of the world where HIV prevalence is highest. In these regions, HBV infection often occurs in the first 5 years of life and commonly results in the establishment of chronic infection. Approximately 90% of infants infected perinatally develop chronic hepatitis B (cHB); rates in children younger than age 5 are lower but substantial (~30%).[1] By contrast, acute HBV infection usually resolves spontaneously in adults with intact immunity.

Studies in Africa and Asia where HBV is endemic have documented the effects of HIV co-infection on cHB that was most likely acquired in childhood. Multiple features of HIV/HBV co-infection in these regions have been described, including impaired progression from active to inactive cHB, HBV reactivation among individuals with inactive cHB, reverse seroconversion (re-emergence of HBV after spontaneous resolution, due to reactivation of replication from residual HBV genomes retained in nuclei of quiescently infected hepatocytes), and increased prevalence of occult hepatitis B.[2] In active HBV infection, higher levels of HBV replication, manifested as higher HBV DNA levels in peripheral blood, have negative effects on outcomes such as hepatic fibrosis and cirrhosis, as described in studies of HIV co-infection from low prevalence and endemic regions.[3–6] HBV infection may also accelerate the course of HIV infection.[7,8]

Most reports of HIV/HBV co-infection in Africa and Asia are regionally restricted studies that compare features of cHB in HBV mono-infected subjects and HIV/HBV co-infected subjects who have a range of immune deficiencies, with moderately to severely reduced CD4$^+$ cell counts. Furthermore, mono-infected and co-infected study participants often come from different clinic populations, introducing potential bias in analyses. There is a paucity of data comparing prevalence of all states of HBV infection in HBV mono-infected and HIV/HBV co-infected individuals, and no studies exist that describe differences in cHB between HIV-infected and HIV-uninfected individuals in countries with intermediate to high HBV prevalence. The HIV Prevention Trials Network 052 (HPTN 052) study enrolled HIV-serodiscordant couples at sites in Africa, Asia, and Brazil.[9,10] This study offered the opportunity to characterize HBV infection in regions where HBV and HIV are endemic and allowed for a comparison of HBV monoinfection to HIV/HBV co-infection among participants recruited from the same populations. We compared the prevalence of different HBV infection states (chronic, recovered, isolated HBV core antibody [HBcAb], vaccinated, uninfected/unvaccinated) in HIV-infected and HIV-uninfected participants from 10 study sites in 7 countries and assessed clinical and laboratory characteristics of participants in these 2 groups who had cHB.

METHODS

Study Participants

Participants were enrolled in HPTN 052, a multicenter randomized controlled trial that demonstrated the efficacy of early antiretroviral treatment (ART) for prevention of HIV transmission among HIV-serodiscordant couples (NCT 00074581).[9,10] At enrollment, HIV-infected index participants had CD4$^+$ cell counts between 350 and 550 cells/mm^3 and reported no previous ART use other than short-course ART for prevention of mother–child transmission. Participants from study sites in Africa (Lilongwe and Blantyre, Malawi; Soweto and Johannesburg, South Africa; Gaborone, Botswana; and Kisumu, Kenya), Asia (Chennai, India; Chiang Mai, Thailand), and South America (Rio de Janeiro, Brazil; Porto Alegre, Brazil) were included in this HBV study. Samples from Harare, Zimbabwe; Pune, India; and the United States were not available for this study. Demographic information (sex and age) for HIV-infected and HIV-uninfected participants was obtained from the parent study database.

Laboratory Testing

The following laboratory data for HIV-infected participants were obtained at enrollment by study sites during the trial: hepatitis B surface antigen (HBsAg), CD4$^+$ cell count, plasma HIV RNA level, and grade level elevations in alanine aminotransferase and aspartate aminotransferase. For HIV-infected participants with no detectable HBsAg and all HIV-uninfected participants, HBV infection status was determined by serologic testing of specimens collected at enrollment then stored at −70 to −90°C. This testing was performed at the HPTN Laboratory Center (Baltimore, MD) and other site laboratories. Testing sites and serologic assays used are shown in Supplemental Digital Content Table 1, http://links.lww.com/QAI/B69. Participants with HBsAg were defined as having cHB because it was likely that HBsAg persisted for >6 months, as per conventional definition, given that HBV transmission occurs during childhood in these areas where HBV is endemic. These participants were further tested for hepatitis B e antigen (HBeAg), plasma HBV DNA (COBAS AmpliPrep/COBAS TaqMan HBV Test, v2.0), and HBV genotype (direct sequencing of the HBV S gene[11]). Participants without detectable HBsAg were tested for total anti-HBcAb and anti–hepatitis B

surface antibody (anti-HBs). These participants were then classified as follows: recovered from HBV infection (detectable HBcAb and anti-HBs), previously HBV-infected/isolated HBcAb (HBcAb only), vaccinated (anti-HBs only), uninfected/unvaccinated (no detectable hepatitis B serologic markers).

Statistical Analysis

Characteristics of study participants were analyzed using the χ^2 or Fisher exact test (for categorical variables) and the median test (for continuous variables).[12] For categorical variables, Fisher exact test was used in place of the χ^2 test whenever at least 1 cell had an expected value less than or equal to 5.

Ethical Considerations

Written informed consent for the use of data and specimens was obtained from each participant in their native language at enrollment into HPTN 052. The HBV study protocol was approved by the Johns Hopkins Medicine Institutional Review Board.

RESULTS

Study Participants

HBV infection status was determined for 91.4% (2473/2704) of HPTN 052 participants enrolled at sites that participated in this substudy. Approximately half of the participants (1276/2473, 51%) were from Africa; the remainder were from India, Thailand, and Brazil (Table 1). HIV-infected and HIV-uninfected participants whose HBV status was determined were similar in number, median age, and sex (Table 1).

HBV Infection Status

Most participants (53.5%) had nonreactive test results for all markers of HBV infection and were classified as uninfected (Table 2). Among participants with serologic evidence of HBV infection, 4.3% had cHB, 8.9% had isolated HBcAb, and 24.7% had recovered. Evidence of vaccination was found in 8.5% of all participants. These distributions were similar in HIV-infected and HIV-uninfected participants, with the exception of isolated HBcAb, which was more prevalent in HIV-infected compared with HIV-uninfected participants (10.1% vs. 8.7%, $P = 0.046$, Table 2). In an analysis of all participants by country (Supplemental Digital Content Fig. 1, http://links.lww.com/QAI/B69), prevalence of cHB and recovery from HBV infection were highest in Thailand (cHB, 11%; recovery, 33%) and Kenya (cHB, 11%; recovery, 46%). Serologic evidence of vaccination was highest in Brazil (21%) and ranged from 1% to 11% in other countries (Supplemental Digital Content Fig. 1, http://links.lww.com/QAI/B69). A comparison of HBV infection states among HIV-infected and HIV-uninfected participants by country showed no common trends in prevalence across the different study sites (Supplemental Digital Content, Fig. 2, http://links.lww.com/QAI/B69).

Analysis of HBeAg status among participants with cHB demonstrated that HBeAg-negative infections were more prevalent than HBeAg-positive infections among all (71.7%), HIV-infected (67.2%), and HIV-uninfected participants (77.0%, Table 2). Most HBeAg-positive participants were HIV-infected participants (63.3%, Table 2). However, this was due largely to the high prevalence of HBeAg-positive/HIV-infected participants in Thailand and India (8 HBeAg-positive cHB infections, 7/8 in HIV-infected subjects). At other sites, the proportion of HIV-infected and HIV-uninfected subjects was similar for HBeAg-positive and HBeAg-negative participants.

cHB in HIV-Infected and HIV-Uninfected Participants

Among participants with HBeAg-positive cHB, HIV-infected individuals had higher plasma HBV DNA than HIV-uninfected individuals; however, the difference was not statistically significant (median 8.1 $\log_{10}$ IU/mL vs. 6.6

TABLE 1. Study Participants With Complete HBV Serologic Test Results

	All (N = 2473)*	HIV Infected (N = 1241)†	HIV Uninfected (N = 1232)‡
Age, median	32 (27–39)	33 (27–39)	32 (27–40)
Male (%)	51.4	49.6	53.2
Country of origin (N, column %)			
Botswana	132 (5.3)	65 (5.2)	67 (5.4)
Kenya	105 (4.2)	52 (4.2)	53 (4.3)
Malawi	865 (35)	432 (34.8)	433 (35.1)
South Africa	174 (7)	92 (7.4)	82 (6.7)
India	497 (20.1)	249 (20.1)	248 (20.1)
Thailand	205 (8.3)	103 (8.3)	102 (8.3)
Brazil	495 (20.1)	248 (20)	247 (20.1)

*Of 2704 enrolled (91.5%).
†Of 1346 enrolled (92.1%).
‡Of 1358 enrolled (90.7%).

TABLE 2. HBV Infection Status of HIV-Infected and HIV-Uninfected Participants

	All (N = 2473)	HIV Infected (N = 1241)	HIV Uninfected (N = 1232)	P*
Uninfected/unvaccinated	1324 (53.5)	616 (49.6)	708 (57.5)	
Vaccinated	211 (8.5)	118 (9.5)	93 (7.5)	
cHB	106 (4.3)	58 (4.7)	48 (3.9)	0.392†
HBeAg positive	30 (1.2)	19 (1.5)	11 (0.9)	0.206‡
HBeAg negative	76 (3.1)	39 (3.1)	37 (3.0)	
Isolated HBcAb	220 (8.9)	125 (10.1)	95 (7.7)	0.046§
Recovered from HBV infection	612 (24.7)	324 (26.1)	288 (23.4)	

*Chi-square tests for all comparisons were conducted using the entire sample (n = 2473) unless otherwise stated.
†P value for HIV-infected vs. HIV-uninfected participants with cHB.
‡P value for HIV-infected vs. HIV-uninfected participants with cHB infection who were positive for HBeAg (N = 30). The P value for HBeAg-positive vs. HBeAg-negative among all 106 participants with cHB is 0.367.
§P value for HIV-infected vs. HIV-uninfected participants with isolated HBcAb.

TABLE 3. Plasma HBV DNA Levels of HIV-Infected and HIV-Uninfected Participants With cHB

| | HBeAg Positive (N = 30) | | HBeAg Negative (N = 76) | | |
	HIV Infected	HIV Uninfected	HIV Infected	HIV Uninfected	P
Median HBV DNA (IQR)*†	8.1 (6.1–8.6)	6.6 (5.1–8.3)	2.6 (1.6–3.5)	2.6 (1.6–3.5)	0.449*
HBV DNA detectable	18/19 (94.7%)	11/11 (100%)	34/39 (87%)	28/37 (76%)	0.691‡
HBV DNA ≥1.3 and ≤3.3†	0/19 (0%)	1/11 (9.1%)	21/39 (53.8%)	19/37 (51.3%)	
HBV DNA >3.3†	18/19 (94.7%)	10/11 (90.9%)	13/39 (33.3%)	9/37 (24.3%)	0.453§
HBV DNA >5.3†	15/19 (78.9%)	8/11 (72.7%)	1/39 (2.6%)	3/37 (8.1%)	1.000‖
					0.35¶

*The median test was used to compare differences in median HBV DNA by infection status, among HBeAg-positive participants (N = 30).
†Units for HBV DNA: $\log_{10}$ IU/mL.
‡The Fisher test was used to compare differences in HBV DNA detection by HIV infection status, among participants who were negative for HBeAg (N = 76).
§The χ^2 test was used to compare HBV DNA >3.3 by HIV infection status, among participants who were negative for HBeAg (N = 76).
‖The Fisher test was used to compare HBV DNA >5.3 by HIV infection status, among participants who were positive for HBeAg (N = 30).
¶The Fisher test was used to compare HBV DNA >5.3 by infection status, by HIV infection status, among participants who were negative for HBeAg (N = 76).
IQR, interquartile range.

$\log_{10}$ IU/mL, $P = 0.45$, Table 3), and high HBV DNA levels (defined conventionally as >5.3 $\log_{10}$ IU/mL or 200,000 IU/mL[13,14]) were observed in equivalent proportions of HIV-infected and HIV-uninfected individuals (Table 3). Among participants with HBeAg-negative cHB, a greater percentage of HIV-infected individuals had detectable HBV DNA compared with HIV-uninfected individuals, but this also was not statistically significant (87.1% vs. 75.6%, $P = 0.69$). Likewise, a greater proportion of HIV-infected individuals had HBV DNA levels >3.3 $\log_{10}$ IU/mL, the threshold for considering initiation of treatment for HBeAg-negative cHB[13,15] (Table 3), but this difference did not reach statistical significance. The median HBV DNA level was similar in these 2 groups.

Transaminase levels were available only for the HIV-infected participants; thus, these characteristics were compared in HIV-infected participants with and without cHB. The prevalence of mildly elevated transaminase levels, (≤grade 2), was greater in participants with cHB compared with those without cHB (12% vs. 5.2% $P = 0.037$, Table 4). Markers of HIV infection were also compared in HIV-infected participants with and without cHB (Table 4). CD4$^+$ cell counts trended lower in HIV-infected

participants with cHB (particularly HBeAg-positive cHB, 353 vs. 431 cells/mm^3 in HBeAg-positive vs. those without cHB, $P = 0.17$, Table 4 footnote). HIV RNA levels were comparable between HIV-infected participants with and without cHB.

HBV genotype A was the most common genotype detected, reflecting the proportion of subjects from Africa with cHB. Overall, the distribution was 62.3% A (Brazil, Kenya, Malawi, and South Africa), 2.9% B (Thailand), 17.4% C (Thailand), 14.5% D (India and Botswana), and 2.9% E (Malawi).

DISCUSSION

HBV is a complex infection, with multiple phases and different recovery outcomes depending on age of acquisition. HBV prevalence was high in this multinational cohort. Seroreactivity consistent with having been infected with HBV (cHB, isolated HBcAb, or recovered infection) was observed in 40% of the study population. Overall, the prevalences of different phases of infection in this cohort were consistent with those reported previously for individual countries.[16–25]

We found that isolated HBcAb was more prevalent in HIV-infected than HIV-uninfected participants. Although this

TABLE 4. Characteristics of HIV-Infected Participants With cHB and Other HBV Infection States

	cHB (N = 58)	cHB, HBeAg Positive (N = 19)	cHB, HBeAg Negative (N = 39)	Recovered (N = 324)	Isolated HBcAb (N = 125)	Uninfected, Unvaccinated (N = 616)	Vaccinated (N = 118)
Median CD4* cell count, cells/mm^3 (IQR)	398 (340–494)	353 (321–482)	407 (340–514)	430 (365–509)	442 (370–516)	424 (360–519)	444 (378–533)
Median HIV RNA, copies/mL (IQR)	4.4 (3.7–4.8)	4.5 (3.5–4.8)	4.3 (3.7–4.9)	4.4 (3.8–4.9)	4.7 (4.2–5.1)	4.5 (3.9–4.9)	4.3 (3.7–4.8)
ALT elevation (≤grade 2)†	7/58 (12%)‡	4/19 (21%)	3/39 (8%)	20/324 (6%)	8/125 (6%)	27/615 (4%)	7/118 (6%)
AST elevation (≤grade 2)†	15/58 (26%)§	5/19 (26%)	10/39 (26%)	21/324 (6%)	12/124 (10%)	31/614 (5%)	7/118 (6%)

*Comparison of median CD4$^+$ cell counts in different groups: cHB vs. non-cHB, 398 vs. 431 cells/mm^3, $P = 0.146$; HBeAg-positive cHB vs. non-cHB, 353 vs. 431 cells/mm^3, $P = 0.171$; HBeAg-negative cHB vs. non-cHB, 407 vs. 431 cells/mm^3, $P = 0.525$.
†Transaminases were determined only in HIV-infected participants at enrollment and were reported by grade level abnormality, according to the upper level of normal (ULN) at each site. Grade 1 elevation, 1.25 to <2.5 times ULN. Grade 2 elevation, 2.5 to <5.0 times ULN. There were 1 and 3 missing ALT and AST values, respectively; denominator and percentage calculations reflect only the nonmissing data.
‡ALT elevation (≤grade 2) cHB compared with non-cHB (12% vs. 5.2%), P value = 0.0374 (Fisher exact test).
§AST elevation (≤grade 2) cHB compared with non-cHB, (26% vs. 6.0%), P value <0.001 (Fisher exact test).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; IQR, interquartile range.

could represent test artifact (false positive total core antibody), it is notable that previous studies have also documented this finding.[26–28] Given the high probability of previous exposure to hepatitis B, isolated HBcAb likely represents recovery from a past HBV infection with loss of anti-HBs. Even in the United States, where the likelihood of HBV exposure is lower, isolated HBcAb most often represented transition from a state of previous immunity.[28,29] The prevalence of other HBV infection states was largely similar between HIV/HBV co-infected and HBV mono-infected participants. These data differ from previous studies that suggested that HIV infection is associated with a higher prevalence of some HBV infection states (cHB and recent infection) with lower prevalence of recovered HBV infection.[2,30–32] The disparity in findings may reflect differences in study populations that include temporal differences in HIV/HBV co-infection acquisition and degree of immune impairment. In our study, HBV infection was likely acquired years before HIV infection because most of the study sites included in this report were in areas where HBV transmission usually occurs perinatally or in early childhood. In addition, HPTN 052 enrolled HIV-infected individuals with CD4$^+$ cell counts >350 cells/mm^3. By contrast, previous studies investigated the relationship between HIV and HBV infection in adults with moderately to severely decreased CD4$^+$ cell counts who were actively engaged in drug use or had multiple sexual partners.[31,32] Contemporaneous or proximal HIV/HBV infection in those studies, in combination with marked immune deficits, could account for differences between previous studies and ours. In this report, HBeAg-positive cHB was more prevalent in HIV/HBV co-infected participants than in HBV mono-infected participants in Thailand and India, but not in other countries. Further research is needed to investigate whether this association correlates with HBV geno-types (B, C, and D) found in these Asian countries. Of interest, we did not note any HBV genotype G infections, although this genotype has been described alone and in combination with genotype A in other studies of HIV/HBV co-infection.[33–35]

Among participants with HBeAg-positive cHB, higher plasma HBV DNA levels were observed in the HIV-infected compared with the HIV-uninfected participants; in HBeAg-negative participants, a higher proportion of the HIV/HBV co-infected had detectable HBV DNA. The lack of statistical significance of these differences may be due to the sample size. Of interest, previous studies comparing HIV/HBV co-infected to HBV mono-infected individuals reported similar findings. Colin et al[3] studied a cohort of men who have sex with men in France and found that the median HBV DNA in the HIV–HBV co-infected group (n = 65) and the median in HBV mono-infected group (n = 67) were 7.1 log IU/mL and 6.7 log IU/mL (P = 0.01) respectively. These men were almost all HBeAg positive (89%); these data are comparable with our HBeAg-positive group where we found HIV–HBV co-infected and HBV–mono-infected participants with median HBV DNA levels of 8.1 and 6.6 log IU/mL, respectively. Among participants with HBeAg-negative cHB, median plasma HBV DNA levels were similar in HIV/HBV co-infected and HIV-uninfected participants; however, a slightly greater proportion of HIV/HBV co-infected participants had detectable HBV DNA with levels >2000 IU/mL, suggesting that mild to moderate immune impairment

may result in ineffective suppression of HBV mutant viruses that fail to express HBeAg.

Previous HIV/HBV co-infection studies demonstrated that cHB is associated with acceleration of HIV disease progression.[7,8] This finding is supported by our data because there was a trend toward lower CD4$^+$ T-cell counts in the HIV/HBV co-infected group compared with the HIV mono-infected groups. An alternative explanation for these lower CD4$^+$ cell counts is the development of cirrhosis with resultant splenic sequestration leading to lower white blood cells and lower absolute CD4$^+$ counts in HIV-infected individuals with cHB; however, this is less likely because no individuals had alanine aminotransferase /aspartate aminotransferase elevations greater than grade 2.

Although HIV infection in the absence of HBV infection can lead to liver disease,[36–38] we found that a greater proportion of HIV-infected participants with cHB had mild transaminase elevations compared with HIV mono-infected participants. In our study, a similar prevalence of low-grade transaminase elevations was observed in HIV-infected participants with HBeAg-positive and HBeAg-negative cHB; these groups had significantly different plasma HBV DNA levels (8.1 vs. 2.6 log$_{10}$ IU/mL), suggesting that adverse effects on liver may potentially occur even with low-level HBV replication among individuals with only mild to moderate declines in CD4$^+$ cells. Alternatively, the small sample size may have obscured potential differences between HBeAg-positive and HBeAg-negative cHB in the setting of HIV infection. Our findings of transaminase elevations and enhanced CD4$^+$ cell depletion substantiate recommendations to treat HIV infection in all HIV/HBV co-infected individuals, regardless of CD4$^+$ cell count.[39–41]

Our study had a number of limitations. Enrollment of HIV-infected participants with cHB in HPTN 052 was at the discretion of each site investigator; this could have led to ascertainment bias. Individuals with documented or suspected acute hepatitis within 30 days of enrollment and those with injection drug use within 5 years of enrollment were excluded from enrollment in HPTN 052. These individuals would also have been at risk of recent HBV acquisition; therefore, acute HBV infection could not be characterized accurately in this study. Individuals who had occult HBV, with no other markers of HBV infection other than a low level of detectable HBV DNA in peripheral blood, would not have been identified in this study because HBV DNA measurement was performed only in participants with detectable HBsAg. The effects of cHB on liver could not be compared between HIV/HBV co-infected and HBV mono-infected participants because serum transaminases were not measured in HIV-uninfected participants in HPTN 052. Small sample size precluded definitive conclusions regarding differences in HBV DNA levels between HIV-infected and HIV-uninfected individuals in the subanalysis of HBeAg-positive and HBeAg-negative cHB. Finally, a correlation between abnormal serum transaminase levels and hepatitis C virus infection, which has been demonstrated in HIV/HBV co-infected individuals, could not be addressed in this study as hepatitis C virus testing was not performed.

In conclusion, in this multinational cohort, HIV infection was associated with an increased prevalence of isolated HBcAb but not other HBV infection states. HBV DNA levels

seemed to be higher in both HBeAg-negative and HBeAg-positive HIV-infected compared with HIV-uninfected participants with cHB. Further work is needed to determine whether this reflects a diminished immune response to HBV even when $CD4^+$ cells are only moderately diminished, higher levels of HBV replication, or both of these factors.

ACKNOWLEDGMENTS

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