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A Comparison of Hepatitis B Virus Infection in HIV-infected and HIV-uninfected Participants Enrolled in a Multi-National Clinical Trial: HPTN 052

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Abstract

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 multi-national 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 seven HBV-endemic countries. Hepatitis B e antigen (HBeAg) 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 Chi-square, Fisher's 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 HBV core antibody (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 (ALT ≤ Grade 2, 12% vs. 5.2%, P=0.037; AST ≤ 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.

Keywords

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 via 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 five years of life and commonly results in the establishment of chronic infection. Approximately 90% of infants infected perinatally develop cHB; rates in children younger than age five are lower but substantial (~30%) [1]. In 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 mono-infection to HIV/HBV co-infection among participants recruited from the same populations. We compared the prevalence of different HBV infection states (chronic, recovered, isolated 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 two groups who had cHB.

METHODS

Study Participants

Participants were enrolled in HPTN 052, a multi-center 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 to 550 cells/mm^3 and reported no prior 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; 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 US 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 (ALT) and aspartate aminotransferase (AST). 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 Table 1. Participants with HBsAg were defined as having cHB since 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 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-HBV core antibody (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 Chi-square or Fisher's exact test (for categorical variables) and the median test (for continuous variables) [12]. For categorical variables, Fisher's exact test was used in place of the Chi-Square test whenever at least one cell had an expected value less than or equal to five.

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 sub-study. 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 gender (Table 1).

HBV Infection Status

Most participants (53.5%) had non-reactive 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 to HIV-uninfected participants (10.1% vs. 8.7%, p=0.046, Table 2). In an analysis of all participants by country (Supplemental Figure 1), prevalence of cHB and recovery from HBV infection was 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%–11% in other countries (Supplemental Figure 1). 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 Figure 2).

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 (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 $\log_{10}$ 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 to 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 two 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 compared to 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, South Africa), 2.9% B (Thailand), 17.4% C (Thailand), 14.5% D (India, 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 multi-national cohort. Sero-reactivity consistent with having been infected with HBV (cHB, isolated HBV core antibody, or recovered infection) was observed in 40% of the study population. Overall, the prevalence 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 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 prior 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 prior 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 prior to HIV infection, since most of the study sites included in this report were in areas where HBV transmission usually occurs perinatally or in early childhood. Additionally, HPTN 052 enrolled HIV-infected individuals with CD4 cell counts >350 cells/mm^3. In 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 genotypes (B, C, and D) found in these Asian countries. Interestingly, 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 to 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. Interestingly, previous studies comparing HIV/HBV co-infected to HBV-mono-infected individuals reported similar findings. Colin et al 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 HBV mono-infected group (n=67) was 7.1 log IU/ml and 6.7 log IU/ml (P=0.01) respectively [3]. These men were almost all HBeAg-positive (89%); these data are comparable to our HBeAg-positive group where we found HIV-HBV co-infected and HBV mono-infected participants with median HBV DNA 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 since there was a trend towards lower CD4+ T-cell counts in the HIV/HBV co-infected group compared to 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 since no individuals had ALT/AST 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 to 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 since 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 sub-analysis of HBeAg-positive and HBeAg-negative cHB. Finally, a correlation between abnormal serum transaminase levels and hepatitis C virus (HCV) infection, which has been demonstrated in HIV/HBV co-infected individuals, could not be addressed in this study as HCV testing was not performed.

In conclusion, in this multi-national cohort, HIV infection was associated with an increased prevalence of isolated HBcAb but not other HBV infection states. HBV DNA levels appeared to be higher in both HBeAg-negative and HBeAg-positive HIV-infected compared to 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Yim HJ, Lok AS. Natural history of chronic hepatitis B virus infection: what we knew in 1981 and what we know in 2005. Hepatology. 2006; 43:S173–181. [PubMed: 16447285]

2. Hoffmann CJ, Thio CL. Clinical implications of HIV and hepatitis B co-infection in Asia and Africa. Lancet Infect Dis. 2007; 7:402–409. [PubMed: 17521593]

3. Colin JF, Cazals-Hatem D, Loriot MA, Martinot-Peignoux M, Pham BN, Auperin A, et al. Influence of human immunodeficiency virus infection on chronic hepatitis B in homosexual men. Hepatology. 1999; 29:1306–1310. [PubMed: 10094979]

4. Thio CL, Seaberg EC, Skolasky R Jr, Phair J, Visscher B, Munoz A, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). Lancet. 2002; 360:1921–1926. [PubMed: 12493258]

5. Vinikoor MJ, Mulenga L, Siyunda A, Musukuma K, Chilengi R, Moore CB, et al. Association between hepatitis B co-infection and elevated liver stiffness among HIV-infected adults in Lusaka, Zambia. Trop Med Int Health. 2016; 6:12764.

6. Wandeler G, Mulenga L, Vinikoor MJ, Kovari H, Battegay M, Calmy A, et al. Liver fibrosis in treatment-naive HIV-infected and HIV/HBV co-infected patients: Zambia and Switzerland compared. Int J Infect Dis. 2016; 3:31155–31159.

7. Chun HM, Roediger MP, Hullsiek KH, Thio CL, Agan BK, Bradley WP, et al. Hepatitis B virus coinfection negatively impacts HIV outcomes in HIV seroconverters. J Infect Dis. 2012; 205:185–193. [PubMed: 22147794]

8. Tsai MS, Chang SY, Lo YC, Yang CJ, Sun HY, Liu WC, et al. Hepatitis B virus (HBV) coinfection accelerates immunologic progression in patients with primary HIV infection in an area of hyperendemicity for HBV infection. J Infect Dis. 2013; 208:1184–1186.

9. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011; 365:493–505. [PubMed: 21767103]

10. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Antiretroviral Therapy for the Prevention of HIV-1 Transmission. N Engl J Med. 2016; 375:830–839. [PubMed: 27424812]

11. Bartholomeusz A, Schaefer S. Hepatitis B virus genotypes: comparison of genotyping methods. Rev Med Virol. 2004; 14:3–16. [PubMed: 14716688]

12. Siegel, S., John, N., Castellan, J. Nonparametric Statistics for the Behavioral Sciences. McGraw-Hill, Inc; 1988. p. 124-128.

13. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatol. 2007; 45:507–539.

14. Thio CL, Smeaton L, Saulynas M, et al. Characterization of HIV-HBV coinfection in a multinational HIV-infected cohort. AIDS. 2013; 27:191–201. [PubMed: 23032418]

15. EASL 2017 Clinical practice guidelines on the management of hepatitis B virus infection. J Hepatol. Apr 18.2017 epub ahead of print.

16. Chandra N, Joshi N, Raju YS, Kumar A, Teja VD. Hepatitis B and/or C co-infection in HIV infected patients: a study in a tertiary care centre from South India. Indian J Med Res. 2013; 138:950–954. [PubMed: 24521641]

17. Khamduang W, Ngo-Giang-Huong N, Gaudy-Graffin C, Jourdain G, Suwankornsakul W, Jarupanich T, et al. Prevalence, risk factors, and impact of isolated antibody to hepatitis B core antigen and occult hepatitis B virus infection in HIV-1-infected pregnant women. Clin Infect Dis. 2013; 56:1704–1712. [PubMed: 23487379]

18. Martins S, Livramento A, Andrigueti M, Kretzer IF, Machado MJ, Spada C, et al. The prevalence of hepatitis B virus infection markers and socio-demographic risk factors in HIV-infected patients in Southern Brazil. Rev Soc Bras Med Trop. 2014; 47:552–558. [PubMed: 25467254]

19. Matthews PC, Geretti AM, Goulder PJ, Klenerman P. Epidemiology and impact of HIV coinfection with hepatitis B and hepatitis C viruses in Sub-Saharan Africa. J Clin Virol. 2014; 61:20–33. [PubMed: 24973812]

20. Peters PJ, McNicholl JM, Raengsakulrach B, Wasinrapee P, Mueanpai F, Ratanasuwan W, et al. An evaluation of hepatitis B virus diagnostic methods and responses to antiretroviral therapy among HIV-infected women in Thailand. J Int Assoc Provid AIDS Care. 2013; 12:349–353. [PubMed: 23792710]

21. Phuangchoei P, Chotiyaputta W, Chayakulkeeree M. Clinical characteristics of hepatitis B and C virus infections in HIV-infected patients. J Med Assoc Thai. 2015; 98:226–231. [PubMed: 25920291]
22. Saha D, Pal A, Biswas A, Panigrahi R, Sarkar N, Sarkar J, et al. Characterization of treatment-naive HIV/HBV co-infected patients attending ART clinic of a tertiary healthcare centre in eastern India. PLoS One. 2013; 8:e73613. doi:73610.71371/journal.pone.0073613. [PubMed: 24023688]
23. Saravanan S, Velu V, Kumarasamy N, Nandakumar S, Murugavel KG, Balakrishnan P, et al. Coinfection of hepatitis B and hepatitis C virus in HIV-infected patients in south India. World J Gastroenterol. 2007; 13:5015–5020. [PubMed: 17854146]
24. Stabinski L, O'Connor S, Barnhart M, Kahn RJ, Hamm TE. Prevalence of HIV and hepatitis B virus co-infection in sub-Saharan Africa and the potential impact and program feasibility of hepatitis B surface antigen screening in resource-limited settings. J Acquir Immune Defic Syndr. 2015; 68:S274–285. [PubMed: 25768867]
25. Sungkanuparph S, Vibhagool A, Manosuthi W, Kiertiburanakul S, Atamasirikul K, Aumkhyan A, et al. Prevalence of hepatitis B virus and hepatitis C virus co-infection with human immunodeficiency virus in Thai patients: a tertiary-care-based study. J Med Assoc Thai. 2004; 87:1349–1354. [PubMed: 15825712]
26. French AL, Operskalski E, Peters M, Strickler HD, Tien PC, Sharp GB, et al. Isolated hepatitis B core antibody is associated with HIV and ongoing but not resolved hepatitis C virus infection in a cohort of US women. J Infect Dis. 2007; 195:1437–1442. [PubMed: 17436223]
27. Liang SH, Chen TJ, Lee SS, Tseng FC, Huang CK, Lai CH, et al. Risk factors of isolated antibody against core antigen of hepatitis B virus: association with HIV infection and age but not hepatitis C virus infection. J Acquir Immune Defic Syndr. 2010; 54:122–128. [PubMed: 20386111]
28. Witt MD, Lewis RJ, Rieg G, Seaberg EC, Rinaldo CR, Thio CL. Predictors of the isolated hepatitis B core antibody pattern in HIV-infected and -uninfected men in the multicenter AIDS cohort study. Clin Infect Dis. 2013; 56:606–612. [PubMed: 23090927]
29. French AL, Lin MY, Evans CT, Benning L, Glesby MJ, Young MA, et al. Long-term serologic follow-up of isolated hepatitis B core antibody in HIV-infected and HIV-uninfected women. Clin Infect Dis. 2009; 49:148–154. [PubMed: 19480573]
30. Attia KA, Eholie S, Messou E, Danel C, Polneau S, Chenal H, et al. Prevalence and virological profiles of hepatitis B infection in human immunodeficiency virus patients. World J Hepatol. 2012; 4:218–223. [PubMed: 22855697]
31. Rodriguez-Mendez ML, Gonzalez-Quintela A, Aguilera A, Barrio E. Prevalence, patterns, and course of past hepatitis B virus infection in intravenous drug users with HIV-1 infection. Am J Gastroenterol. 2000; 95:1316–1322. [PubMed: 10811346]
32. Webale MK, Budambula V, Lihana R, Musumba FO, Nyamache AK, Budambula NL, et al. Hepatitis B virus sero-profiles and genotypes in HIV-1 infected and uninfected injection and Non-injection drug users from coastal Kenya. BMC Infect Dis. 2015; 15:299.doi: 10.1186/s12879-12015-11060-12873 [PubMed: 26223795]
33. Bihl F, Martinetti G, Wandeler G, et al. HBV genotypes and response to tenofovir disoproxil fumarate in HIV/HBV-coinfected persons. BMC Gastroenterol. 2015; 15:79. [PubMed: 26152237]
34. Dao DY, Balko J, Attar N, et al. Hepatitis B virus genotype G: prevalence and impact in patients co-infected with human immunodeficiency virus. J Med Virol. 2011; 83:1551–1558. [PubMed: 21739445]
35. van der Kuyl AC, Zorgdrager F, Hogema B, et al. High prevalence of hepatitis B virus dual infection with genotypes A and G in HIV-1 infected men in Amsterdam, the Netherlands, during 2000–2011. BMC Infect Dis. 2013; 13:540. [PubMed: 24225261]
36. DallaPiazza M, Amorosa VK, Localio R, Kostman JR, Lo Re V 3rd. Prevalence and risk factors for significant liver fibrosis among HIV-monoinfected patients. BMC Infect Dis. 2010; 10:116. [PubMed: 20465840]
37. Price JC, Seaberg EC, Badri S, Witt MD, D'Acunto K, Thio CL. HIV monoinfection is associated with increased aspartate aminotransferase-to-platelet ratio index, a surrogate marker for hepatic fibrosis. J Infect Dis. 2012; 205:1005–1013. [PubMed: 22291196]

38. Price JC, Seaberg EC, Phair JP, Witt MD, Koletar SL, Thio CL. Brief Report: Highly Active Antiretroviral Therapy Mitigates Liver Disease in HIV Infection. J Acquir Immune Defic Syndr. 2016; 72:319–323. [PubMed: 26945179]

39. Panel on Antiretroviral Guidelines for Adults and Adolescents. [Accessed 16 June 2017] Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. 2016. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

40. Andersson MI, Preiser W, Van Rensburg C, Taljaard J, Hoffmann CJ. The HIV/HBV co-infected patient: Time for proactive management. S Afr Med J. 2015; 105:281–282. [PubMed: 26294869]

41. European AIDS Clinical Society. [Accessed 16 June 2017] European AIDS Clinical Society Guidelines version 8.0. 2015. http://www.eacsociety.org/files/guidelines_8_0-english_web.pdf

Table 1
Study participants with complete HBV serologic test results

The table shows the number and percentage of participants with complete hepatitis B virus (HBV) test results by HBV status. Percentages are shown for each column.

	All N=2,473[a]	**HIV-infected N=1,241**[b]	**HIV-uninfected N=1,232**[c]
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)

[a] Of 2,704 enrolled (91.5%)

[b] Of 1,346 enrolled (92.1%)

[c] Of 1,358 enrolled (90.7%)

Table 2

HBV infection status of HIV-infected and HIV-uninfected participants

The table shows the number and percentage of participants with different HBV infection status. Percentages are shown for each column. Abbreviations: cHB: chronic HBV infection; HBeAg: HBV e antigen.

	All N=2,473	HIV-infected N=1,241	HIV-uninfected N=1,232	p-value[a]
Uninfected/unvaccinated	1,324 (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[b]
HBeAg-positive	30 (1.2)	19 (1.5)	11 (0.9)	0.206[c]
HBeAg-negative	76 (3.1)	39 (3.1)	37 (3.0)	
Isolated HBcAb	220 (8.9)	125 (10.1)	95 (7.7)	0.046[d]
Recovered from HBV infection	612 (24.7)	324 (26.1)	288 (23.4)	

[a]Chi square tests for all comparisons were conducted using the entire sample (n=2,473) unless otherwise stated.

[b]P value for HIV-infected vs. HIV-uninfected participants with cHB.

[c]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.

[d]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

The table shows HBV DNA levels in HIV-infected and HIV-uninfected participants with HBeAg-positive and HBeAg-negative cHB. Percentages are shown for each column. Abbreviations: HBeAg: HBV e antigen; HBV: hepatitis B virus; IQR: inter-quartile range.

	HBeAg-Positive (N=30)		HBeAg-Negative (N=76)		p-value
	HIV-infected	HIV-uninfected	HIV-infected	HIV-uninfected	
Median HBV DNA (IQR)[a,b]	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[a]
HBV DNA detectable	18/19 (94.7%)	11/11 (100%)	34/39 (87%)	28/37 (76%)	0.691[c]
HBV DNA ≥1.3 and ≤3.3[b]	0/19 (0%)	1/11 (9.1%)	21/39 (53.8%)	19/37 (51.3%)	
HBV DNA >3.3[b]	18/19 (94.7%)	10/11 (90.9%)	13/39 (33.3%)	9/37 (24.3%)	0.453[d]
HBV DNA >5.3[b]	15/19 (78.9%)	8/11 (72.7%)	1/39 (2.6%)	3/37 (8.1%)	1.000[e] 0.35[f]

[a]The Median test was used to compare differences in median HBV DNA by infection status, among HBeAg-positive participants (N=30).

[b]Units for HBV DNA: $\log_{10}$ IU/mL.

[c]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).

[d]The Chi-square test was used to compare HBV DNA > 3.3 by HIV infection status, among participants who were negative for HBeAg (N=76).

[e]The Fisher test was used to compare HBV DNA > 5.3 by HIV infection status, among participants who were positive for HBeAg (N=30).

[f]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).

Table 4

Characteristics of HIV-infected participants with cHB and other HBV infection states

The table shows median CD4 cell count, median HIV RNA, and proportion (percentage for each column) of HIV-infected participants with cHB and other hepatitis B infection states. Abbreviations: cHB: chronic hepatitis B virus (HBV) infection; HBe Ag: HBV e antigen; IQR: interquartile range; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

	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[a] 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)[b]	7/58 (12%)[c]	4/19 (21%)	3/39 (8%)	20/324 (6%)	8/125 (6%)	27/615 (4%)	7/118 (6%)
AST elevation (≤ Grade 2)[b]	15/58 (26%)[d]	5/19 (26%)	10/39 (26%)	21/324 (6%)	12/124 (10%)	31/614 (5%)	7/118 (6%)

[a] 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.

[b] 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 non-missing data.

[c] ALT elevation (≤ Grade 2) cHB compared to non-cHB (12% vs. 5.2%), p-value = 0.0374 (Fisher's Exact test).

[d] AST elevation (≤ Grade 2) cHB compared to non-cHB, (26% vs. 6.0%), p-value <0.001 (Fisher's Exact test).