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Characterization of HIV-HBV co-infection in a multi-national HIV-infected cohort

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Abstract

Objective—To understand the HIV-hepatitis B virus (HBV) epidemic from a global perspective by clinically and virologically characterizing these viruses at the time of antiretroviral therapy (ART) initiation in a multi-national cohort.

Methods and design—HIV-infected subjects enrolled in two international studies were classified as HIV-HBV co-infected or HIV monoinfected prior to ART. HIV-HBV co-infected subjects were tested for HBV characteristics, hepatitis D virus (HDV), a novel non-invasive marker of liver disease, and drug-resistant HBV. Comparisons between discrete covariates used chi-square or Fisher's exact tests (and Jonchkheere-Terpstra for trend tests) while continuous covariates were compared using Wilcoxon Rank-Sum Test.

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Results—Of the 2105 HIV-infected subjects from 11 countries, the median age was 34 years and 63% were Black. The 115 HIV-HBV co-infected subjects had significantly higher ALT and AST values, lower body mass index, and lower CD4+ T-cell counts than HIV monoinfected subjects (median 159 cells/mL and 137 cells/mL, respectively, P=0.04). In the co-infected subjects, 49.6% had HBeAg-negative HBV, 60.2% had genotype A HBV, and 13% were HDV positive. Of the HBeAg-negative subjects, 66% had HBV DNA ≤2000 IU/ml compared to 5.2% of the HBeAg-positive subjects. Drug-resistant HBV was not detected.

Conclusions—Screening for HBV in HIV-infected patients in resource-limited settings is important since it is associated with lower CD4+ T-cell counts. In settings where HBV DNA is not available, HBeAg may be useful to assess the need for HBV treatment. Screening for drug-resistant HBV is not needed prior to starting ART in settings where this study was conducted.

Keywords

HIV; HBV; coinfection; global

Introduction

Chronic hepatitis B (CH-B), which is the leading cause of end stage liver disease worldwide, is common in human immunodeficiency virus type-1 (HIV)-infected individuals with a prevalence ranging from 5–20% in various studies of HIV-infected subjects [1–5]. Although co-infection with HIV and hepatitis B virus (HBV) is recognized as being common, there are limited data to provide an international perspective on this epidemic. Such a perspective is especially important as highly active antiretroviral therapy (HAART) is being introduced worldwide including in resource-limited settings with high HBV endemicity such as Asia and Africa. Since liver disease is a leading cause of non-AIDS death in HIV-infected patients receiving HAART, characterizing HBV prior to HAART is important in order to better understand the scope of the disease and to prioritize treatment needs in resource-limited settings.

Most studies of HIV-HBV co-infected subjects have been conducted in countries with low HBV endemicity and have shown a negative effect of HIV on CH-B with decreased hepatitis B e antigen (HBeAg) clearance, high HBV DNA levels, and increased risk for cirrhosis and liver-related death [6, 7]. Data from countries with low HBV endemicity are informative, but they represent HBV disease that occurs primarily in adulthood. In contrast, in countries with high HBV endemicity, transmission primarily occurs in infancy or early childhood; thus, in most of these cases, HBV has been present for years prior to HIV infection. It is not known if the worldwide epidemic is similar to what has been reported from countries with low HBV endemicity. One study from Nigeria suggests that this may not be the case since HBV DNA levels were lower than what has been seen in studies from North America and Europe [8]. Thus, data on HIV and HBV characteristics with a more global perspective in these co-infected individuals at the time HAART is initiated are needed.

Two randomized clinical trials of antiretroviral therapy were conducted by the Adult AIDS Clinical Trials Group (ACTG) in diverse resource-limited settings. The first, ACTG A5175, enrolled HIV-infected men and women worldwide to compare different initial HAART regimens [9]. The second, A5208, compared the response to first-line HAART in African women who had received single-dose nevirapine during a prior pregnancy to those who had not received nevirapine [10]. Both of these trials tested subjects for HBV at HAART initiation; thus, they are useful to characterize untreated HIV and HBV co-infection from a multi-national perspective.

Methods

Study subjects

The subjects participated in one of the following parent ACTG studies: 1) A5175, which was a randomized, open-label comparison of once-daily protease inhibitor or non-nucleoside reverse transcriptase inhibitor-containing regimens for HAART-naïve HIV-infected men and women (CD4 + T-cell count <300 cells/mm^3 and ALT/AST <5x upper limit of normal (ULN)) from Brazil, Haiti, India, Malawi, Peru, South Africa, Thailand, United States, and Zimbabwe, as previously described (n=1571) [9] or 2) A5208, which studied whether peripartum exposure to single-dose nevirapine diminished the response to a nevirapine-based initial HAART regimen (n=745), enrolled women with CD4+ T-cell count <200 cells/mm^3 and baseline AST/ALT <2.5x the ULN from the following African countries: South Africa, Kenya, Zimbabwe, Botswana, Zambia, Malawi, and Uganda, as previously described [10]. All A5175 sites and seven of the ten A5208 sites had local IRB approval for participation in this study. Informed consent was obtained from the study subjects in their native language, and the study was approved by the Johns Hopkins University IRB. Of the sites that participated, Brazil excluded people who had CH-B from enrolling in the parent study; thus, Brazilian participants were not included in prevalence estimates but are included in the HIV monoinfected study group. In addition, four of the 25 US sites, which enrolled 13% of the subjects from the US, excluded people with CH-B.

Participants were classified as HIV-HBV co-infected if they were hepatitis B surface antigen (HBsAg) positive at the visit prior to randomization and positive for HBeAg, HBV DNA, or hepatitis B e antibody (anti-HBe) at the study entry visit. All others were classified as HIV monoinfected. Data abstracted from the parent study database included the following: age, sex, race, body-mass index (BMI), history of liver disease, hemoglobin, HIV disease stage, HIV RNA, CD4+ T-cell count, ALT, and AST. The HIV-HBV co-infected participants also had the following performed using study entry visit serum: HBeAg, anti-HBe, HBV genotype, HBV DNA, hepatitis D antibody (anti-HDV), hepatitis C virus (HCV) antibody (anti-HCV), HCV RNA if anti-HCV positive, HBV *Pol* sequencing, and a non-invasive marker of liver disease that correlates with liver disease [11]. This non-invasive marker measures the change in glycosylation of an immunoglobulin G reactive to specific alpha-galactose epitope, which is measured by reactivity to the fucose-binding lectin Aleuria aurantia lectin (AAL-reactivity). This marker was selected since other readily available markers use parameters such as platelets that are affected by HIV infection.

Laboratory testing

All specimens were stored at −80°C. Serological testing for HBeAg (ETI-EBK Plus, Diasorin, Stillwater MN or Abbott ARCHITECT® HBeAg v17.0, Abbott Park, IL), anti-HBe (ETI-AB-EBK Plus or Abbott ARCHITECT® Anti HBe v13.0), anti-HDV (ETI-AB-DELTAK-2, Diasorin, Stillwater, MN), and anti-HCV (Ortho HCV v3.0, Ortho Diagnostics, Raritan NJ) were performed according to manufacturer's instructions. HBV DNA testing was done with real-time PCR using either RealART™ HBV LC PCR v 3.0 (Qiagen, Valencia, CA) or Abbott RealTime HBV DNA (Abbott Molecular, Des Plains, IL). The highest common lower limit of detection of these assays was 200 IU/ml, which is the value used in the analyses. HBV genotype and drug-resistance mutations were determined by HBV *Pol* sequencing, performed as previously described [12]. HCV RNA was determined with the Abbott RealTime HCV RNA (Abbott Molecular, Des Plaines, IL), performed according to manufacturer's instructions. AAL-reactivity was tested as previously described [11] with values >5 representing cirrhosis, values 3–5 representing moderate liver disease, and values of 1–2 representing no or mild liver disease.

Statistical analysis

ALT and AST levels were graded according to standard ACTG definitions [13]. Comparisons between groups were made using chi-square or Fisher's exact test for discrete covariates and Wilcoxon Rank-Sum Test for continuous covariates. For 3-level ordinal group comparisons, the Jonchkheere-Terpstra trend test was performed. To test for associations of pre-treatment covariates with baseline HBV DNA level, linear regression modeling on the log 10 transformed HBV DNA was performed. Pre-treatment covariates tested include screening CD4 T-cell count category (< 50, 50–199, and 200–299), log10 HIV-1 RNA copies/mL, sex, age, BMI, anti-HDV, HBeAg, anti-HBe, HBV genotype, hemoglobin per 5 g/dL increase, creatinine clearance (Crockoft-Gault equation), ALT, and AST. *P*-values <0.05 were considered statistically significant and were not adjusted for multiplicity.

Results

A5175 and A5208 recruited 2316 participants of whom 2105 (90.9%) were enrolled in sites that obtained IRB approval for this substudy. Of these 2105 subjects, 115 (5.5%) were HIV-HBV coinfected. There was no significant difference in the prevalence of a positive HBsAg between the sites that did (6.7%) and did not (5.6%) have IRB approval for this substudy. The HIV-HBV co-infection prevalence varied with the highest prevalence in Zimbabwe (11%) and the lowest in Kenya (2.2%) (Table 1). The prevalence of HIV-HBV co-infection across continents was similar with Asia at 5.9%, Africa at 6.7%, Central/South America at 5.1% (excluding Brazil), and North America (US) at 4.8%. Anti-HCV was positive in 6 subjects who all had undetectable HCV RNA.

The median age of the 2105 subjects was 34 years and 39% were male (Table 2). The racial make-up was majority Black (62.7%) followed by Asian (17%), White (11.9%), and Other (7.4%). The HIV-HBV co-infected subjects had more Blacks and fewer Whites than the HIV monoinfected subjects (*P*=0.07). The BMIs were lower among the HIV-HBV co-infected (median 21.7) compared to the HIV monoinfected participants (median 22.4, *P*=0.02); however, the distribution of numbers in each BMI category (underweight, normal, overweight, and obese) was similar.

Liver function and HIV parameters

Given the entry criteria for the parent studies, only seven subjects had grade 3 to 4 elevations of ALT or AST, all of whom were HIV monoinfected. Although ALT and AST values were typically low (median 23 and 29 U/L, respectively), the distributions of these values were both higher among the HIV-HBV co-infected (median ALT 25.5 U/L, median AST 34 U/L) compared to the HIV monoinfected subjects (median ALT 23 U/L (*P*=0.03), median AST 28.8 U/L (*P*<0.001)) (Table 2).

The median CD4 T-cell count was 157 cells/mm^3 (interquartile range (IQR) 88–218 cells/mm^3) and was significantly lower in the HIV-HBV co-infected (137 cells/mm^3, IQR 68–210 cells/mm^3) than in the HIV monoinfected subjects (159 cells/mm^3 (IQR 90–218 cells/mm^3, *P* = 0.04) (Table 2). However, the two groups did not differ in HIV RNA level (median 5.10 and 5.05 log10 cp/ml, respectively *P*=0.23). Also, the CD4 T-cell differences between the groups could not be accounted for by differences in HBV prevalence by country (Figure 1). Consistent with the difference in CD4 T-cell counts, the HIV-HBV co-infected subjects had a higher prevalence of clinical AIDS, which was defined as WHO stage IV or history of AIDS, but the difference was not statistically significant (12.2% versus 8.6% in HIV-HBV co-infected and HIV monoinfected, respectively, *P*=0.19).

As a sensitivity analysis, we repeated the above analyses excluding participants from Brazil since they were all HIV monoinfected by that site's inclusion criteria. Comparisons between HIV monoinfected and HIV/HBV co-infected participants were similar with the following exceptions. The proportion of men was significantly higher in the HIV/HBV co-infected (46%) compared to the HIV monoinfected group (36%, P=0.02). The distribution of races between groups was attenuated (P=0.7). However, the difference in the ALT distribution was strengthened (P=0.002).

HBV characteristics in HIV-HBV co-infected subjects

From the study entry visit, serum was available for additional HBV testing in the 113 of the 115 HIV-HBV co-infected subjects. Approximately half, 57/113 (50.4%), were HBeAg-positive, and this proportion was similar in A5175 (51.8%) and A5208 (46.7%). The median age was 34 years in both the HBeAg-negative and –positive subjects and the proportion of females was similar between the HBeAg groups (48% and 52%). By country, subjects from Haiti (83%), India (69%), Kenya (67%), and Peru (83%) were predominantly HBeAg-positive, while those from Malawi (65%), Thailand (63%), and the United States (80%) were mainly HBeAg-negative.

HBV genotype could not be determined for 18 (16%) subjects due to low HBV DNA. Among observed genotypes, the most common were A (71.5%) and D (15.8%), but the distribution varied geographically with Africa having 95% genotype A, US with 78% genotype A, Thailand and India with 100% genotype C and D, respectively, and South and Central America with 55% genotype A, 27% genotype F, and 18% genotype E. Genotypes A and C were evenly divided between HBeAg-positive and −negative disease whereas D, E, and F were predominantly in HBeAg-positive subjects (Table 3).

Anti-HDV was detected in 15 of 113 (13.3%) HBV co-infected subjects, which is within the range of the prevalence reported in HBV monoinfection [14]. Anti-HDV was detected only among subjects from Botswana, Kenya, Peru, South Africa, Thailand, or Zimbabwe with Botswana having the highest relative number of subjects (three of four). When stratified by HBeAg status, a similar proportion of the HBeAg-negative and –positive subjects (14 and 12%, respectively) were anti-HDV positive.

HBV DNA was detected in 91.2% of the 113 co-infected subjects and was significantly more common in the HBeAg-positive (98.2%) compared to the HBeAg-negative subjects (83.9%, P=0.008) (Table 3). The median HBV DNA was significantly higher in the HBeAg-positive (median 7.96 log IU/ml) compared to the HBeAg-negative subjects (median 2.74 log IU/ml, P <0.001). In fact, 66.1% of HBeAg-negative subjects had an HBV DNA ≤2000 IU/ml, which is the level above which treatment should be considered in HBeAg-negative patients [15]. In contrast, only 5.2% of HBeAg-positive subjects had HBV DNA ≤2000 IU/ml. Only 12% of the HBeAg-positive subjects had values below the cut-off recommended by some treatment guidelines for HBeAg-positive monoinfected patients (20,000 IU/ml) [16]. Genotypes C, D, and F had a higher proportion of subjects with HBV DNA >20,000 IU/ml compared to the other genotypes (P =0.049).

In univariable analysis with log HBV DNA as the outcome, HBeAg-positive subjects had a 3.63 log IU/ml (95% confidence interval (CI) 2.95–4.32 log IU/mL) higher HBV DNA than those who were HBeAg-negative (P<0.01) (Figure 2a). Those with higher ALT and AST also had higher log HBV DNA values. When compared to subjects infected with genotype A, those infected with genotype D had a 1.61 log IU/ml higher HBV DNA (95% CI 0.21–3.01 log IU/mL) and those infected with genotypes C, E, or F had a 1.37 log IU/mL higher HBV DNA (95% CI −0.17–2.91 log IU/mL). In a multivariable model, only HBeAg status and AST remained significantly associated with higher HBV DNA (Figure 2b).

Of the 95 subjects with HBV *Pol* sequencing, none (95% CI 0–3.7%) had mutations in HBV *Pol* that are associated with known resistance to lamivudine, adefovir dipivoxil, or entecavir [17].

Liver disease characteristics in HIV-HBV co-infected subjects

AST values were higher in the HBeAg-positive (median 36.0 U/L) compared to the HBeAg-negative subjects (median 31.5 U/L, P=0.008) with a similar relationship in ALT (median 28.0 and 23.0 U/L, respectively, P=0.03) (Table 3). Liver disease was measured by AAL-reactivity in 103 subjects since the samples from India were not available for this assay. No or mild liver disease was present in 39 (37.8%), moderate liver disease in 48 (46.6%), and cirrhosis in 16 subjects (15.5%). All 16 with cirrhosis were from A5175, 15 of whom were Black. The 16 with AAL values consistent with cirrhosis (> 5) trended towards a lower albumin (3.29 g/dL) compared to the 87 without cirrhosis (3.62 g/dL)(P =0.06); however, none of these 16 subjects had clinical signs or symptoms of liver disease.

HIV disease characteristics in HIV-HBV co-infected subjects

Since the HIV-HBV co-infected subjects had lower CD4+ T-cell counts than the HIV monoinfected subjects, we further explored the relationship between HBV DNA and CD4+ T-cell counts amongst the co-infected subjects. The median CD4+ T-cell count did not differ by HBeAg status. To determine if CD4+ T-cell count was associated with HBV DNA, the CD4+ T-cell count was stratified into 3 groups of <50, 51–199, and >200 cells/mm^3. The proportion of subjects with HBV DNA >200, 000 IU/ml decreased significantly as CD4+ T-cell count increased (P=0.04) (Figure 3).

Discussion

This is the first multi-national study of HIV-HBV co-infected individuals characterizing both HBV and HIV parameters at the time of HAART initiation. Several notable findings include an association between HBV co-infection and lower CD4+ T-cell count especially those with high HBV DNA levels, the low HBV DNA levels in the majority of HBeAg-negative subjects, and the absence of drug-resistant HBV. Such characterization of HBV in HIV-infected patients at the time of HAART initiation advances our understanding of HBV in this setting in order to focus treatment efforts.

The association of lower CD4+ T-cell counts with HIV-HBV co-infection was first noted in a Nigerian study, but it was not clear if that finding was universal or specific to Nigeria [8]. This is the first multi-national study demonstrating that HIV-HBV co-infected subjects have lower CD4+ T-cell counts than HIV monoinfected subjects. If the finding were region-specific, then the association would have been diminished with the diverse countries included in this study. This finding is also robust because it was detected despite the fact that study entry criteria for the parent studies required a CD4+ T-cell count <300 cells/ mm^3 (for A5175) or 200 cells/ mm^3 (for A5208). Furthermore, this is the first study to demonstrate that the HIV-HBV co-infected subjects with CD4+ T-cell counts <50 cells/mm^3 were more likely to have high levels of HBV replication (HBV DNA >200, 000 IU/ml) than were those with higher CD4+ T-cell counts. One possible mechanism for this association is that CH-B may lead to immune activation, which increases CD4+ T-cell apoptosis. This association is not due to differences in geographical distribution of CD4+ T-cell counts among countries since those with higher HBV prevalence did not recruit subjects with lower CD4+ T-cell counts.

The low levels of HBV DNA in a large proportion of individuals was unexpected since HIV-HBV co-infection is associated with higher HBV DNA in subjects from areas of the

world with low HBV endemicity [6]. In our study, 16% of the HBeAg negative subjects had an undetectable HBV DNA, and an additional 50% had a HBV DNA <2000 IU/ml, which is the level above which treatment is considered. In contrast, the majority of HBeAg-positive subjects (75%) had detectable HBV DNA levels that were >200,000 IU/ml. These findings are supported by the multivariable analysis demonstrating that HBeAg-positive status was the only factor associated with higher HBV DNA levels. The low HBV DNA in this cohort is not simply due to exclusion of subjects with higher ALT or AST levels since studies from Nigeria and South Africa that did not exclude such patients also show low HBV DNA in a substantial proportion of HIV-HBV co-infected subjects [8, 18]. In the Nigerian study, these low levels were also found primarily in HBeAg-negative subjects, but HBeAg was not determined in the other study. Taken together, these studies suggest that determining HBeAg may provide a strategy to prioritize the need for HBV treatment in HIV-infected individuals when HBV DNA assays are not available in resource-limited settings.

In our study, no subject had pre-existing drug-resistant mutations in the majority population of the quasispecies. In two prior Japanese studies of therapy naïve subjects, the prevalence of drug-resistant mutants using population sequencing was 0 and 1.6% [19, 20]. One of these studies used a second assay that could detect as little as 0.001% of mutant virus and found that 11% of subjects had a drug-resistant virus in the minority population [19]. However, whether such low levels of virus lead to HBV treatment failure is not known. One study found lamivudine-resistant strains in 10 of 20 HIV-HBV co-infected patients prior to therapy, but the pattern of mutations was identical in the majority of the tested samples suggesting that contamination may explain this high prevalence [21]. Our study does not support the need for HBV drug-resistance testing prior to starting anti-HBV therapy.

Our study had several limitations. First, the inclusion criteria of the parent antiretroviral treatment trials may have skewed our study population. Even though both parent studies were focused on participants with CD4 T-cell counts < 300 cells/mm^3, we were still able to see an association between CD4 T-cell count and HBV infection. The exclusion of subjects with very high AST and ALT, may have underestimated the prevalence of CH-B especially those with HBeAg-positive disease. However, we believe that this exclusion did not substantially alter the HBV DNA findings or the association with lower CD4+ T-cell counts, as discussed above. In addition, HIV-HBV co-infected subjects are recognized to have lower ALT levels than are HBV monoinfected subjects despite higher HBV DNA levels [6]. Second, we were not able to characterize liver disease using a liver biopsy since biopsies were not feasible and are not readily available in resource-limited countries. However, we did use a non-invasive marker of liver disease (AAL reactivity) that correlates with the level of fibrosis [11] and does not use platelet count, which can be affected by HIV. About 15% of the cohort had a level of AAL reactivity that was consistent with cirrhosis, which was almost exclusively found in subjects of African descent; however, the only sign of liver disease in these subjects was a trend towards lower albumin. This prevalence is similar to that described in HBV monoinfected cohorts with ALT cut-offs that were lower at <2x the ULN [22]. A Ugandan study found a 17% prevalence of significant fibrosis in HIV mono-infected subjects [23]; thus, the cirrhosis prevalence in our study of HIV-HBV co-infected individuals is possible. Further studies are needed to characterize liver disease in HIV-HBV co-infected subjects from resource-limited settings including those with high ALT/AST levels. Third, we did not find an association in the multivariable analysis with HBV genotype and HBV DNA, but these data are limited by the inability to genotype 16% of the subjects. This lack of association was also seen in a study from Denmark of 784 HBV monoinfected patients [24]. However, in another study HBV DNA levels were the highest in HBeAg-positive subjects with HBV genotype D [25].

In summary, we found a variable prevalence (2–11%) of hepatitis B in HIV-infected subjects from diverse settings prior to starting HAART. Thus, it is important for providers to know the prevalence of HBV in their country. HBV DNA levels were relatively low in HBeAg negative subjects; thus, this serologic marker may be useful in prioritizing patients on their need for HBV treatment in settings where HBV DNA is not available. HIV-HBV co-infection, especially those with high HBV DNA, was associated with lower CD4+ T-cell counts prior to HAART initiation, which emphasizes the need for HBV testing in HIV-infected patients. Further work is needed to study HIV-HBV co-infection in subjects with high ALT/AST levels, to understand the mechanism for CD4 + T-cell loss in HIV-HBV co-infection, and to optimize treatment for HIV-HBV co-infection in resource-limited settings.

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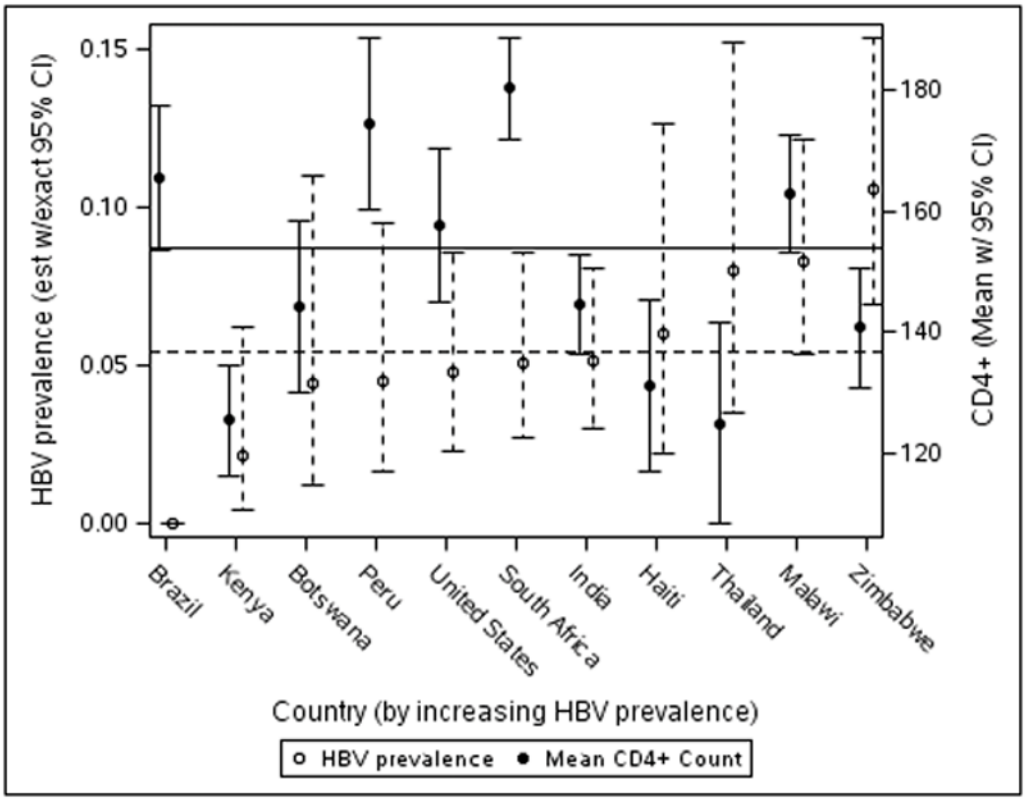
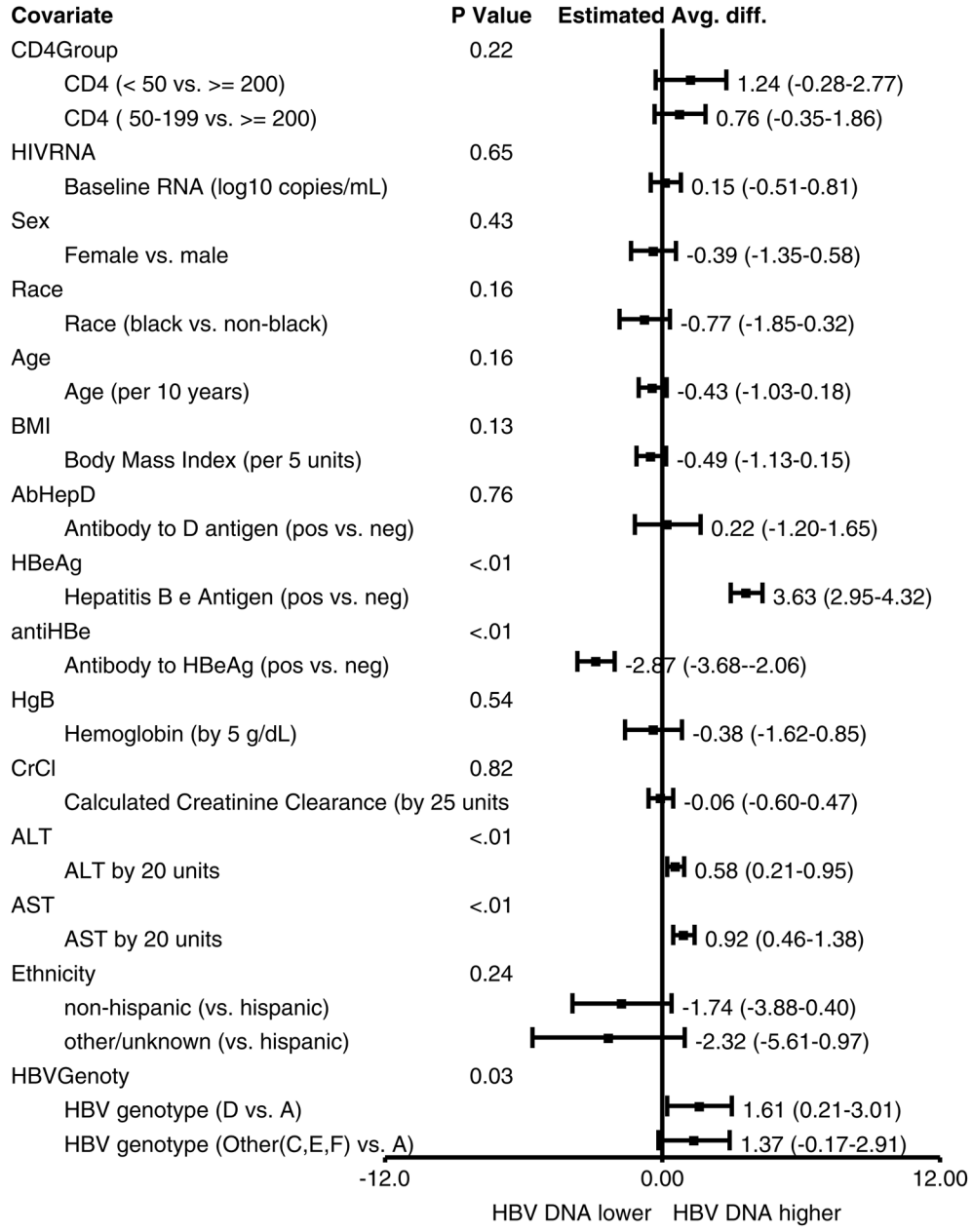


Figure 1.
Distribution of HBV prevalence and mean CD4+ T-cell count by country. There is no clear relationship between HBV prevalence and mean CD4+ T-cell count.

Figure 2a: Univariable Linear Regression Models



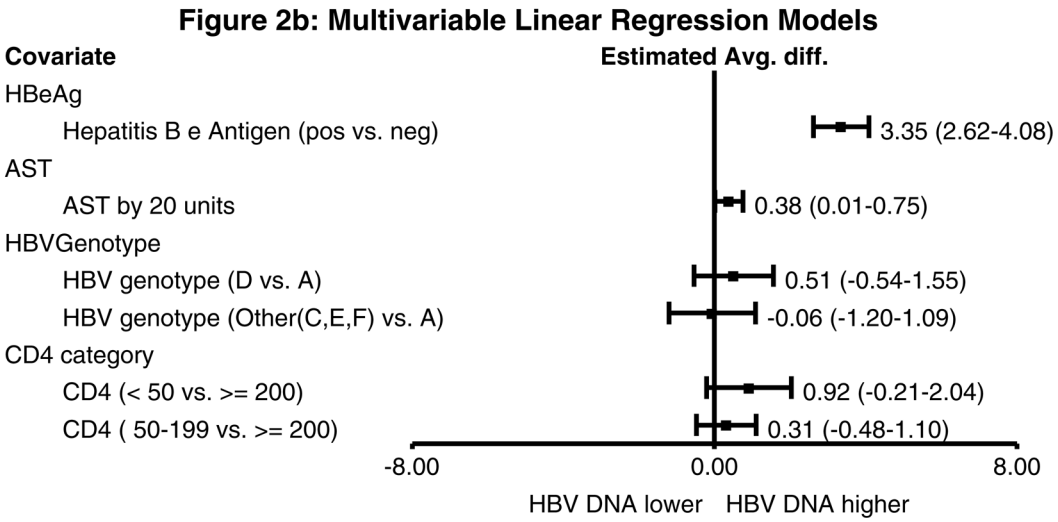


Figure 2.

Figure 2a. Univariable linear regression models with log HBV DNA as the outcome. HBeAg positive status was associated with a 3.63 log IU/ml higher HBV DNA, anti-HBe positive status was associated with a 2.87 log IU/ml lower HBV DNA, both ALT and AST were associated with higher HBV DNA levels, and non-A genotype HBV was associated with higher HBV DNA levels.

Figure 2b. Multivariable linear regression models with log HBV DNA as the outcome. The associated variables from the univariable models were included in this model and CD4 count was forced into the model. Anti-HBe was not included since it is collinear with HBeAg status. HBeAg-positive status was associated with a significantly higher HBV DNA level (3.35 log IU/ml higher compared to HBeAg-negative subjects). AST was also associated with higher HBV DNA level.

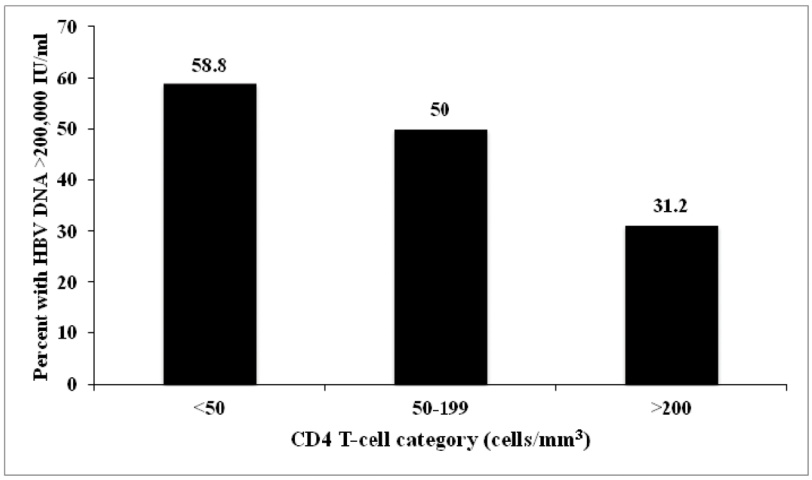


Figure 3.

Frequency (in percent) of subjects with HBV DNA >200,000 IU/ml by CD4+ T-cell category. Subjects with CD4 T-cells <50 cells/mm^3 had the highest proportion with HBV DNA >200, 000 IU/ml.

Table 1

Distribution of study subjects by country

Country	HIV monoinfected Number (% of group)	HIV-HBV co-infected Number (% of group)	HIV-HBV co-infected Estimated Prevalence (%) (95% CI)
Africa			
Botswana	86 (4)	4 (3)	4.4 (1.2–11.0)
Kenya	135 (7)	3 (3)	2.2 (0.5–6.2)
Malawi	265 (13)	24 (21)	8.3 (5.4–12.0)
South Africa	314 (16)	17 (15)	5.1 (3.0–8.1)
Zimbabwe	203 (10)	24 (21)	11.0 (6.9–15)
South/Central America			
Brazil	231 (12)	0*	N/A
Haiti	94 (5)	6 (5)	6 (2.2–13.0)
Peru	128 (6)	6 (5)	4.5 (1.7–9.5)
North America			
United States	200 (10)	10 (9)	4.8 (2.3–8.6)
Asia			
India	242 (12)	13 (11)	5.1 (2.7–8.6)
Thailand	92 (5)	8 (6)	8.0 (3.5–15.0)

*excluded HIV-HBV co-infected subjects at enrollment

Table 2

Characteristics of study subjects

	HIV monoinfected N=1990	HIV-HBV co-infected N=115	*P*
Age (IQR) (years) *	34 (29–40)	34 (30–40)	0.53
Male sex (%)	39	47	0.09
Race			0.07
Black (%)	62.1	73.9	
White (%)	12.5	2.6	
Asian (%)	16.9	18.2	
Other (%)	7.5	5.2	
BMI (IQR) *	22.4 (20.3–25.3)	21.7 (19.8–24.0)	0.02
ALT (IQR) * (U/L)	23 (16.5–35.0)	25.5 (19.0–38.0)	0.03
Normal	1804 (91.0%)	100 (87.0%)	0.14
Mild	154 (7.8%)	11 (9.6%)	
Moderate	20 (1.0%)	4 (3.5%)	
Severe	3 (0.2%)	0 (0.0%)	
Life Threatening	1 (0.01%)	0 (0.0%)	
AST (IQR) * (U/L)	28.8 (23.0–38.0)	34 (27.0–44.0)	<0.001
Normal	1703 (85.9%)	86 (74.8%)	0.001
Mild	242 (12.2%)	28 (24.3%)	
Moderate	35 (1.8%)	1 (0.9%)	
Severe	2 (0.1%)	0 (0.0%)	
Life Threatening	1 (0.1%)	0 (0.0%)	
HIV characteristics			
CD4 T-cell count (IQR) (cells/mm^3) *	159 (90,218)	137 (68,210)	0.04
HIV RNA (IQR) (log cp/ml) *	5.1 (4.6–5.5)	5.1 (4.6–5.6)	0.23
WHO Stage IV or clinical AIDS (%)	8.6	12.2	0.19

* median values

Table 3

HBV Characteristics in HIV-HBV co-infected subjects by HBeAg status

	Overall N=113	HBeAg-negative N=56	HBeAg-positive N=57
Median ALT (IQR)(U/L) *	25.5 (19.0–38.0)	23 (17.5–33.0)	28 (21.9–49.0)
Median AST (IQR)(U/L) *	34.0 (27.0–44.0)	31.5 (24.0–40.0)	36 (29.0–55.0)
Detectable HBV DNA (>200 IU/ml (%)) *	91.2	83.9	98.2
Median HBV DNA (IQR)(log IU/ml) *	5.1 (2.7–8.1)	2.7 (2.3–4.4)	8.0 (5.6–8.6)
HBV genotype (number) †			
A	68	33	35
C	5	2	3
D	15	4	11
E	4	1	3
F	3	0	3
AAL reactivity (number) ‡			
1–2	39	18	21
3–5	48	26	22
>5	16	8	8

* $P < 0.05$ comparing HBeAg-negative to HBeAg-positive

† HBV genotype not determined in 15 due to inability to amplify

‡ Missing in 12 subjects