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Impact of hepatitis B virus infection on HIV response to antiretroviral therapy in Nigeria

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Abstract

Background—As HAART is introduced into areas of the world with high hepatitis B virus (HBV) endemicity, it is important to determine the influence of HBV on HIV-HBV co-infected persons receiving antiretroviral therapy (ART).

Methods—We studied 1,564 HIV-infected subjects in Jos, Nigeria who initiated ART. HIV-HBV co-infected participants had HBeAg and HBV DNA status determined. CD4+ T-cell count and HIV viral load at ART initiation were compared between HIV mono-infected and HIV-HBV co-infected subjects using univariate methods. Regression analyses were used to determine if HBeAg status or HBV DNA at ART initiation were associated with baseline HIV parameters or ART response.

Results—The CD4+ T-cell counts of the 262 (16.7%) HIV-HBV co-infected participants was 107 cells/mL compared to 130 cells/mL in HIV monoinfected participants (p <0.001) at ART initiation. HIV-HBV co-infected participants also had higher HIV viral loads than HIV monoinfected subjects (4.96 vs. 4.75 $\log_{10}$ copies/mL; p = 0.02). Higher HBV DNA and detectable HBeAg were independently associated with lower CD4+ T-cell counts at ART initiation but not with higher HIV viral load. In a multivariable model, HBeAg-positive subjects were less likely to suppress HIV replication to ≤400 copies/ml (OR 0.54, p=0.03) at 24 weeks, but they had similar CD4+ T cell increases. At 48 weeks, there was no significant effect of HBeAg status on ART response.

Conclusions—In HIV-infected Nigerian individuals, HBV co-infection, especially in those with high levels of HBV replication, was associated with lower CD4+ T-cell counts at ART initiation independent of HIV RNA level. Subjects with HBeAg positive status had a slower virological response to ART. Further work is needed to understand the effects of HBV on CD4+ T-cells.

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Summary: In HIV-infected Nigerians, those with chronic hepatitis B have lower CD4+ Tcell counts prior to ART. Those with HBeAg+ chronic hepatitis B are slower to respond to ART. Chronic hepatitis B does not affect CD4+ T-cell increase with ART.

Conflict of interest

None of the authors have a conflict of interest relevant to this manuscript.

Keywords

hepatitis B; HIV; CD4 cell counts; antiretroviral therapy; Africa

Introduction

The President's Emergency Plan for AIDS Relief (PEPFAR) has provided HIV therapy to areas of the developing world where the HIV epidemic is rising and the cost of providing antiretroviral therapy (ART) is prohibitive. Early studies from such programs demonstrate a remarkable response to ART, but information is needed about co-infections that may influence responses in these settings. Chronic hepatitis B virus (HBV) infection is such a co-morbidity where high HBV endemicity overlaps with areas having high rates of HIV infection. As ART use is rapidly escalating in such countries, it is important to understand the effects of HBV on HIV disease and response to ART.

In studies where ART has been available for over a decade, such as those conducted in North America and Europe, HBV does not significantly impact the short- or long-term ART response [1,2]; however, there are limited data from countries with high HBV endemicity and other competing causes for liver disease [3,4].

In Nigeria, a country where HBV and HIV prevalence is high, HBV co-infection occurs in 10% to 70% of HIV-infected individuals [5–8]. Factors associated with mortality in Nigerian patients on ART include: tuberculosis, CD4+ T-cell count <50 cells/mL at ART initiation, male gender, age <30 years, and being unemployed [9]. However, data on how HBV affects HIV disease or response to ART in Nigeria are limited [10].

The Nigerian National ART program began in 2001 and PEPFAR funding for HIV/AIDS care and treatment activities started in September 2004, with later support provided by the Global Fund and Clinton Foundation. As of mid-2008, over 300,000 eligible patients had initiated ART in the country. Given the high HBV endemicity in Nigeria, we studied participants enrolled at one of the largest ART sites in the country, the Jos University Teaching Hospital (JUTH), in order to determine whether HBV influences HIV disease or the early response to ART in previously antiretroviral naïve patients.

Methods

Study participants

The AIDS Prevention Initiative in Nigeria (APIN)/Harvard PEPFAR program has been providing ART to HIV-infected patients in Nigeria free of charge. Patients enrolled in the program are treated according to Nigerian National ART Guidelines and international standards. Standard first-line ART regimens include stavudine or zidovudine, lamivudine, plus efavirenz or nevirapine. More recently, Truvada™ (tenofovir + emtracitabine) has been recommended as a first-line alternative in Nigeria, particularly for patients co-infected with hepatitis B. However, this study was conducted prior to the availability of tenofovir. To date, JUTH has initiated ART in 12,240 patients with 9,000 patients currently receiving drugs.

For this study, we included participants who were HCV antibody negative, initiated ART between October 2004 and June 2006, and had a minimum of six months of follow-up on ART. Subjects were prospectively followed from their ART initiation visit (defined as the baseline visit) until 48 weeks of therapy or until they were lost to follow-up, whichever came first.

A participant was defined as having HBV if the hepatitis B surface antigen (HBsAg) was positive at the pre-ART (baseline) visit. All other participants were defined as HBV negative. All HBV-infected participants were further evaluated with hepatitis B e antigen (HBeAg), antibody to HBeAg (anti-HBe), and HBV DNA at the baseline visit. HIV viral load, CD4+ T-cell count, and ALT were determined at baseline, week 24 post-ART, and week 48 post-ART. Hepatotoxicity was defined as ALT values that were ≥ 5-fold over the upper limit of normal (ULN) (41 IU/ml) for the APIN Plus/Harvard PEPFAR sites or ≥3.5-fold over ULN if baseline ALT values were above the ULN.

Patients were recruited for participation and enrolled in the ART program following written informed consent, which was subject to ethical review by the Institutional Review Boards at JUTH, the Harvard School of Public Health, and Johns Hopkins University.

Laboratory testing

HBsAg was determined using an EIA assay (MONOLISA HBsAg Ultra 3, Bio Rad, France. HBV DNA levels were determined using the COBAS® Amplicor HBV Monitor (v2.0, Roche Diagnostics GmbH, Mannheim, Germany), which has a lower limit of detection of 38 IU/ml and an upper limit of 3.8×10^4 IU/ml. Any samples that were above the upper limit were diluted in order to quantify the HBV DNA. Hepatitis C antibody was tested with a third generation EIA assay (DIA PRO Diagnostic Bioprobes, Milano, Italy). HIV viral load was determined using the Roche COBAS Amplicor HIV-1 Monitor Test v1.5 (Roche Diagnostics GmbH, Mannheim, Germany) with a limit of detection of 400 copies/mL. CD4+ T-cell count was determined via flow cytometry (Partec GmbH, Munster, Germany).

Statistical analysis

HBV and HIV characteristics at baseline were compared using nonparametric univariate methods; the Fisher's exact test was used to evaluate statistical significance for categorical variables and the Kruskal-Wallis test for continuous variables. Linear regression analyses were used to determine if HBeAg status or HBV DNA were associated with baseline CD4+ T-cell counts, HIV viral load, or ALT values. Logistic regression analyses were used to determine if baseline HBV status, HBV DNA level, or HBeAg status influenced HIV viral load suppression or CD4+ T-cell count increase and to determine if HBV DNA level or HBeAg status were associated with the risk of hepatotoxicity. An HBV DNA level ≥ 20,000 IU/ml (~100,000 cp/ml) was classified as high based on prior literature demonstrating significantly increased risk for hepatocellular carcinoma and cirrhosis at this level [11,12]. All analyses were conducted using Stata version 10.1 (College Station, TX).

Results

Baseline characteristics

There were 1,564 HIV-infected participants enrolled in this study; of those, 1,302 (82.3%) were HBsAg-negative at baseline (HIV mono-infected). The remaining 262 (16.7%) individuals were HBsAg-positive (HIV-HBV co-infected) (Table 1). The median age was 35 years and approximately two-thirds were female. A majority of the HIV-HBV co-infected individuals had HBeAg-negative HBV (n=172, 66%). Furthermore, most of those with HBeAg-negative HBV had HBV DNA levels <20,000 IU/ml (112 of 171, 65%). In contrast, of the HBeAg-positive subjects, 79/90 (88%) had HBV DNA ≥20,000 IU/ml.

The median CD4+ T-cell count overall was 126 cells/mL (range 2–1,515 cells/mL) but was significantly lower in the HIV-HBV co-infected subjects (107 cells/mL; range 2–726 cells/mL) compared to the HIV mono-infected subjects (130 cells/mL, range 2–1,515 cells/mL; $p = 0.001$) (Table 1). The median HIV viral load in the cohort was 4.81 $\log_{10}$ cp/mL and was

higher in those with HIV-HBV co-infection compared to those with HIV mono-infection (4.96 vs. 4.75 $\log_{10}$ copies/mL; $p = 0.02$). Notably, at baseline 18% of the cohort had an elevated ALT and the proportion was greater in the HIV-HBV co-infected compared to the HIV mono-infected group (54% versus 16%, $p = 0.002$). Likewise, median ALT levels were higher in HIV-HBV co-infected compared to HIV mono-infected subjects (23, range 0–188 versus 19 IU/ml, range 0=1730; $p = 0.002$). A trend towards higher ALT values was found in those with HBV DNA ≥ 20,000 IU/ml ($p = 0.06$) and in the HBeAg-positive participants ($p= 0.02$).

Since HBV was associated with elevated HIV viral load and lower CD4+ T-cell counts at baseline, we determined whether the level of HBV replication, measured by HBeAg and HBV DNA levels, differentially affected these baseline HIV parameters. Among the HIV-HBV co-infected subjects, higher baseline HBV DNA levels were associated with lower baseline CD4 + T-cell count (85 cells/mL compared to 129 cells/mL, $p= 0.002$) (Table 2) but not with baseline HIV viral load.

HBeAg-positive subjects had baseline CD4+ T-cell counts of 80 cells/mL compared to 119 cells/mL in those with HBeAg-negative disease ($p =0.002$). HBeAg status at baseline did not affect HIV viral load levels. In a multivariable linear regression analysis, both HBeAg-positive status and HBV DNA ≥20,000 IU/mL were independently associated with lower CD4+ T-cell counts. HBeAg-positive patients were predicted to have CD4+ T-cell counts that were 99 cells/mL lower than those with HBeAg-negative status (95% CI: −164.8, -33.4; $p=0.003$). Those with an HBV DNA ≥20,000 IU/mL were predicted to have CD4+ T-cell counts that were 35 cells/mL lower than those with HBV DNA levels <20,000 IU/mL (95% CI: −66.5, −4.6; $p=0.03$). This model also indicated that the effect of HBV DNA count ≥20,000 IU/mL on baseline CD4 count was significantly different between those that were HBeAg-positive versus HBeAg-negative.

HBV and response to ART

Although HIV-HBV co-infected individuals initiated ART with higher baseline HIV viral loads, their overall response to ART was equivalent to those with HIV monoinfection. At 24 weeks post-ART, the proportion of patients with HIV viral load ≤400 cp/ml was 70% in the HIV mono-infected group and 67% in those with HIV-HBV co-infection. At 48 weeks the proportion was 73% and 67% in the two groups, respectively ($p>0.05$).

In order to determine if HBV DNA level or HBeAg status at baseline influenced ART response, we compared the proportions of subjects who achieved viral suppression ≤400 copies/mL by these HBV categories. There was no significant difference in the proportions at 24 or 48 weeks when comparing patients with HBV DNA <20,000 IU/ml to those with ≥20,000 IU/ml (Table 3). However, when stratified by HBeAg status, a lower proportion of HBeAg-positive individuals achieved HIV viral load ≤400 cp/ml at 24 weeks compared to either HBeAg-negative or HIV mono-infected individuals ($p=0.04$). Since baseline HIV viral load was also associated with decreased viral suppression at 24 weeks in univariate analyses, we constructed a multivariable logistic regression model with HBsAg-negative subjects as the reference group. In this model, both baseline HIV viral load (OR = 0.78 per 1 log increase in baseline HIV viral load; 95% CI: 0.66, 0.91; $p = 0.002$) and HBeAg-positive status (OR = 0.54; 95% CI: 0.31, 0.92; $p = 0.03$) were independently associated with decreased likelihood of HIV viral load ≤400 cp/mL at 24 weeks. By 48 weeks of therapy, 67% of both HBeAg-negative and positive HIV co-infected subjects achieved an undetectable HIV viral load. Evaluation of univariate results at week 24 versus week 48 determined that loss of statistical significance at week 48 was not explained by loss to follow-up or differences in patient values at the time points.

This cohort experienced good immune recovery on ART with mean CD4+ T-cell increases of 86 cells/mL at 24 weeks and 125 cells/mL at 48 weeks. Lower baseline CD4+ T-cell counts

were associated with a less robust CD4+ T-cell recovery, but HBV status and HBV DNA level did not affect the CD4+ T-cell count rise.

HBV and ART-related hepatotoxicity

At 24 weeks, the proportion of patients with hepatotoxicity was low and was more common in those with HIV-HBV co-infection than those with HIV mono-infection (3.1% versus 0.5%, respectively; p=0.01). However, by 48 weeks, the number of patients with hepatotoxicity was <1% and was similar regardless of HBV status. This decrease in hepatotoxicity was not due to discontinuation of ART in those with hepatotoxicity at week 24. Hepatotoxicity at 24 and 48 weeks was not associated with baseline HBV DNA or HBeAg status. In a logistic regression model, only elevated ALT at baseline was predictive of 24-week hepatotoxicity.

Discussion

Our results demonstrate that HIV-HBV co-infected Nigerians had lower CD4+ T-cell counts and higher HIV viral loads at ART initiation as compared to those who were HIV mono-infected. Furthermore, both high HBV DNA and presence of HBeAg were independently associated with lower CD4+ T-cell counts. Interestingly, these two HBV characteristics were not associated with the magnitude of the pre-ART HIV viral load; thus, differences in HIV viral load cannot account for the CD4+ T-cell associations. Virologic response to ART was diminished after 24 weeks of therapy in those with HBeAg-positive HBV; however, by 48 weeks of therapy, no differences in response were detected.

This is the first study to demonstrate that HIV-HBV co-infected individuals have statistically significant lower CD4+ T-cell counts compared to HIV mono-infected subjects at ART initiation. A few studies on HBV mono-infection support the hypothesis that HBV is associated with lower CD4+ T-cell counts. In a Thai study, HBV mono-infected individuals had lower CD4+ T-cells compared to HBsAg-negative subjects [13]; this association was strongest in those with high HBV DNA, detectable HBeAg, and HBV infection before the age of 20. A study of pregnant Indian women found that CD4+ T-cell counts were lower in 25 women with HBsAg compared to nearly 1,100 women without HBsAg [14]. A study from Thailand demonstrated that treatment of an HBV infection led to significant increases in CD4+ T-cell counts [15].

One study of occult hepatitis B, defined as presence of HBV DNA in the absence of HBsAg, in HIV infection also supports our data. Nine subjects with occult hepatitis B had lower CD4 + T-cell counts when compared to 184 subjects without occult hepatitis B [16]. However, two HIV-HBV co-infected studies did not identify differences in CD4+ T-cell counts prior to ART initiation [3,4]. These studies may not have detected a difference since they were both smaller than our Nigerian cohort and the subjects may have had different HBV disease characteristics. In the study of African miners, 40 subjects had high HBV DNA, but the HBeAg status of the subjects was not determined [4]. In the Thai study, the HBV DNA levels and HBeAg status of the subjects were not determined, so their population cannot be directly compared to our study [3].

One interpretation of the association between lower CD4+ T-cell counts with higher HBV DNA and presence of HBeAg is that HBV replication increases HIV RNA replication, which lowers CD4+ T-cell counts. Support for this hypothesis comes from in vitro studies demonstrating that the HBV X protein serves as a transactivator of HIV transcription [17–19]. However, whether this interaction has biological relevance in vivo is suspect since it is uncommon for HIV to infect hepatocytes, the cell type with the most HBV. Our data do not support this mechanism since high HBV DNA and HBeAg-positive status were not associated with higher HIV viral loads, which one would expect if HBV increased HIV replication. An

alternative explanation is that HBV leads to increased apoptosis of CD4+ T-cells through increased T-cell activation. Several studies on HBV mono-infection support the idea that HBV leads to an overall increase in T-cell activation [20,21]. Another potential explanation is that HBV infection may alter the cytokine milieu leading to a change in the production or destruction of CD4+ T-cells. Lastly, it is possible that the HIV-HBV co-infected patients had advanced liver disease, which could lower CD4+ T-cell counts due to splenic sequestration. We were unable to test this hypothesis since liver biopsies were not done and platelet counts were unavailable for calculation of the FIB-4 index or the APRI (ALT/platelet ratio), as a surrogate marker for liver disease.

It is encouraging that overall HBV did not have a negative impact on response to ART at 48 weeks. However, we did find that at 24 weeks of ART, those individuals who were HBeAg-positive were nearly half as likely to have HIV viral load suppression compared to HBV-uninfected, even when controlling for baseline viral load. This difference disappeared by 48 weeks; thus, these HBeAg-positive subjects had a slower virologic response to ART. The delayed response was not simply due to higher HBV DNA levels in this group since there was no association between HBV DNA and decreased HIV suppression at 24 weeks. A longer follow-up is needed to determine if HBeAg-positive subjects are less likely to maintain long-term ART responses. Further study is also needed to determine if HBeAg-positive subjects would still have a delayed response to ART if a more potent anti-HBV drug were part of the HIV regimen. This is the first study to find a differential effect of HBeAg status on early ART response. Several studies have found that HBV co-infection did not affect HIV viral load suppression with ART, but they did not divide subjects by HBeAg status [3,22]. A study of South African miners found that HBV DNA levels did not affect HIV viral load suppression, but HBeAg was not evaluated [4].

The low rate of hepatotoxicity even in those with HBV coinfection is encouraging as ART is becoming more widespread in areas where HBV is endemic. We found that elevated baseline ALT was associated with increased risk for hepatotoxicity, so these are the individuals in whom close monitoring of ALT upon ART initiation is advisable. Our results are also consistent with a South African study demonstrating a low hepatotoxicity rate [4]. In that study, hepatotoxicity was associated with use of tuberculosis medications, but we were unable to assess for concomitant medications as these data were not collected.

A major strength of this study is that this is the largest study of HIV-HBV co-infected individuals initiating ART with carefully characterized HBV status prior to ART initiation. Furthermore, since this study was performed in an area of the world where HBV and HIV are highly endemic, the results are applicable to other similar regions. A limitation of this study includes the 48-week follow-up, so we could not determine whether HBV and HBeAg status affect longer-term HIV outcomes. Furthermore, we could not determine the impact of long-term lamivudine monotherapy for HBV. A second limitation is that we do not have data on opportunistic infections prior to study entry, so we cannot determine if the lower CD4+ T-cell counts with HBV co-infection were clinically significant. Our study suggests that further examination of incident opportunistic infections in the setting of HIV-HBV co-infection is warranted. Third, we did not have CD4 percentages to determine if they were also lower in those with HBV co-infection. A final limitation is that we do not have accurate mortality data, so we are unable to determine the impact of HIV-HBV co-infection on AIDS and non-AIDS mortality during ART.

In summary, we found that HIV-infected Nigerians with HBV co-infection had lower CD4+ T-cell counts at ART initiation. High HBV replication, as measured by HBV DNA and HBeAg positive status, were independently associated with lower CD4+ T-cells. Furthermore, HBeAg positive status decreased the likelihood of achieving undetectable HIV viral load after 24 weeks

of ART. Fortunately, this difference in response disappeared at 48 weeks of ART. Our data emphasize the need for further detailed studies of HIV-HBV co-infection in order to understand the impact of HBV on CD4+ T-cells and ART response.

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Table 1

Demographics of cohort at initiation of ART

	All n= 1,564	**HBsAg- n=1,302**	**HBsAg+ n= 262**	***p*** *
Male gender (%)	35	34	37	0.43
Median age (years)	35	34	33	0.25
Median CD4 count (c/mL)	126	130	107	0.001
Median HIV RNA (log cp/mL)	4.81	4.75	4.96	0.003
Median ALT (U/mL)	20	19	23	0.002
ALT >5x ULN (%)	18	16	25	0.002

* *P*-values represent comparison between HBsAg-negative and HBsAg-positive subjects

Table 2

HBV DNA and HBeAg status in HIV-HBV co-infected subjects are associated with HIV disease stage at initiation of ART

	HBV DNA (IU/mL)			HBeAg status		
	<20,000 n=120	**≥20,000 n=131**	***p***	**Negative n=171**	**Positive n=90**	***p***
Median CD4 count (c/mL)	129	85	0.002	119	80	0.002
Median HIV RNA (log cp/mL)	4.99	4.97	0.45	4.98	4.94	0.44
Median ALT (IU/mL)	20	29	0.06	21	32	0.02

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Table 3

Hepatitis B and ART response

	HBsAg-negative	HBsAg-positive			
		HBV DNA (IU/mL)		HBeAg	
		<20,000	≥20,000	Negative	Positive
24 weeks					
HIV RNA ≤400 cp/ml (%)	70	70	63	74	55*
Δ median CD4 count (c/mL)	86	83	89	87	71
48 weeks					
HIV RNA ≤400 cp/mL (%)	73	68	67	67	67
Δ median CD4 count (c/mL)	125	109	112	107	113

*P=0.04 between HBeAg+ and HBeAg−. All other P-values are >0.05.

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