Impact of Hepatitis B Virus Infection on Human Immunodeficiency Virus Response to Antiretroviral Therapy in Nigeria

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Background. As highly active antiretroviral therapy (ART) is introduced into areas of the world in which hepatitis B virus (HBV) infection is highly endemic, it is important to determine the influence of HBV on persons with human immunodeficiency virus (HIV) and HBV coinfection who are receiving ART.

Methods. We studied 1564 HIV-infected patients in Jos, Nigeria, who initiated ART. Participants with HIV-HBV coinfection had hepatitis B e antigen (HBeAg) and HBV DNA status determined. $CD4^+$ T cell count and HIV load at ART initiation were compared between individuals with HIV monoinfection and those with HIV-HBV coinfection with use of 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 median $CD4^+$ T cell count of the 262 participants with HIV-HBV coinfection (16.7%) was 107 cells/mL, compared with 130 cells/mL for participants with HIV monoinfection at ART initiation ($P < .001$). Participants with HIV-HBV coinfection also had higher HIV loads than did patients with HIV monoinfection (4.96 vs 4.75 $\log_{10}$ copies/mL; $p = .02$). Higher HBV DNA and detectable HBeAg levels were independently associated with lower $CD4^+$ T cell counts at ART initiation but not with higher HIV loads. In a multivariable model, HBeAg-positive patients were less likely than HBeAg-negative patients to suppress HIV replication to $\leqslant$400 copies/mL (odds ratio, 0.54; $P = .03$) 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. Among HIV-infected Nigerian individuals, HBV coinfection, especially among those with high levels of HBV replication, was associated with lower $CD4^+$ T cell counts at ART initiation, independent of HIV RNA level. Patients with HBeAg-positive status had a slower virological response to ART, compared with HBeAg-negative patients. Further work is needed to understand the effects of HBV on $CD4^+$ T cells.

The President's Emergency Plan for AIDS Relief (PEPFAR) has provided therapy for human immunodeficiency virus (HIV) infection to areas of the developing world where the HIV epidemic is increasing 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 coinfections that may influence responses in these settings. Chronic hepatitis B virus (HBV) infection is such a comorbidity, because many areas where HBV infection is highly endemic overlap with areas having high rates of HIV infection. Because ART use is rapidly escalating in such countries, it is important to understand the effects of HBV on HIV disease and on response to ART.

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

In Nigeria, a country where HBV and HIV infection prevalences are high, HBV coinfection occurs in 10%–70% of HIV-infected individuals [5–8]. Factors asso-

Received 6 April 2009; accepted 4 June 2009; electronically published 22 September 2009.

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Clinical Infectious Diseases 2009; 49:1268–73

1058-4838/2009/4908-0020$15.00
DOI: 10.1086/605675

ciated with mortality among Nigerian patients receiving ART include: tuberculosis, $CD4^+$ T cell count <50 cells/mL at ART initiation, male sex, age <30 years, and being unemployed [9]. However, data on how HBV infection 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, >300,000 eligible patients had initiated ART in Nigeria. Given the high level of HBV endemicity in Nigeria, we studied participants enrolled at one of the largest ART sites in the country, the Jos University Teaching Hospital (JUTH), to determine whether HBV infection influences HIV disease or the early response to ART in previously antiretroviral naive patients.

PATIENTS AND 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 plus emtracitabine) has been recommended as a first-line alternative in Nigeria, particularly for patients coinfected with hepatitis B virus. However, this study was conducted before the availability of tenofovir. To date, JUTH has initiated ART in 12,240 patients, with 9000 patients currently receiving drugs.

For this study, we included participants who had test results negative for hepatitis C virus antibody, who had initiated ART from October 2004 through June 2006, and who had a minimum of 6 months of follow-up while receiving ART. Patients were prospectively followed up 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 infection if they had test results positive for hepatitis B surface antigen (HBsAg) at the pre-ART (baseline) visit. All other participants were defined as HBV negative. All participants with HBV infection were further evaluated for hepatitis B e antigen (HBeAg), antibody to HBeAg (anti-HBe), and HBV DNA at the baseline visit. HIV load, $CD4^+$ T cell count, and alanine transaminase (ALT) level were determined at baseline, week 24 after ART initiation, and week 48 after ART initiation. 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 enzyme immunoassay (EIA) (Monolisa HBsAg Ultra 3; Bio-Rad). HBV DNA levels were determined using the Cobas Amplicor HBV Monitor, version 2.0 (Roche Diagnostics), 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 to quantify the HBV DNA. Hepatitis C antibody was tested with a third-generation EIA assay (Dia Pro; Diagnostic Bioprobes). HIV load was determined using the Roche Cobas Amplicor HIV-1 Monitor Test, version 1.5 (Roche Diagnostics) with a limit of detection of 400 copies/mL. $CD4^+$ T cell count was determined via flow cytometry (Partec).

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 was used for continuous variables. Linear regression analyses were used to determine whether HBeAg status or HBV DNA were associated with baseline $CD4^+$ T cell counts, HIV load, or ALT values. Logistic regression analyses were used to determine whether baseline HBV status, HBV DNA level, or HBeAg status influenced HIV load suppression or $CD4^+$ T cell count increase and to determine whether HBV DNA level or HBeAg status were associated with the risk of hepatotoxicity. An HBV DNA level ⩾20,000 IU/mL (~100,000 copies/mL) was classified as high on the basis of earlier literature that demonstrated a statistically significantly increased risk for hepatocellular carcinoma and cirrhosis at this level [11, 12]. All analyses were conducted using Stata software, version 10.1 (Stata).

RESULTS

Baseline characteristics. There were 1564 HIV-infected participants enrolled in this study; of those, 1302 (82.3%) were HBsAg negative at baseline (ie, they had HIV monoinfection). The remaining 262 individuals (16.7%) were HBsAg positive (ie, they had HIV-HBV coinfection) (Table 1). The median age was 35 years, and approximately two-thirds of the patients were female. A majority of the individuals with HIV-HBV coinfection had HBeAg-negative HBV (172 patients; 66%). Furthermore, most of those with HBeAg-negative HBV had HBV DNA levels <20,000 IU/mL (112 [65%] of 171 patients). In contrast, of the HBeAg-positive patients, 79 (88%) of 90 had HBV DNA levels ⩾20,000 IU/mL.

The median $CD4^+$ T cell count overall was 126 cells/mL (range, 2–1515 cells/mL), but it was significantly lower among the patients with HIV-HBV coinfection (107 cells/mL; range, 2–726 cells/mL) than it was among the patients with HIV monoinfection (130 cells/mL; range, 2–1515 cells/mL; $P =$

Table 1. Demographic Characteristics of the Study Cohort at Initiation of Antiretroviral Therapy

Variable	All patients (n = 1564)	HBsAg-negative patients (n = 1302)	HBsAg-positive patients (n = 262)	P[a]
Male sex, %	35	34	37	.43
Age, median years	35	34	33	.25
CD4$^+$ cell count, median cells/mL	126	130	107	.001
HIV RNA level, median log copies/mL	4.81	4.75	4.96	.003
ALT level, median U/mL	20	19	23	.002
ALT level >5 × ULN, %	18	16	25	.002

NOTE. ALT, alanine transaminase; HBsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus; ULN, upper limit of normal.

[a] P values are for comparison between HBsAg-negative and HBsAg-positive patients.

.001) (Table 1). The median HIV load in the cohort was 4.81 $\log_{10}$ copies/mL and was higher among those with HIV-HBV coinfection than it was among those with HIV monoinfection (4.96 vs 4.75 $\log_{10}$ copies/mL; $P = .02$). Notably, at baseline, 18% of the cohort had an elevated ALT level, and the proportion was greater in the group with HIV-HBV coinfection than it was in the group with HIV monoinfection (54% vs 16%; $P = .002$). Likewise, median ALT levels were higher among patients with HIV-HBV coinfection (23 IU/mL; range, 0–188 IU/mL) than they were among patients with HIV monoinfection (19 IU/mL; range, 0–1730 IU/mL; $P = .002$). A trend towards higher ALT levels was found among those with HBV DNA levels ⩾20,000 IU/mL ($P = .06$) and among the HBeAg-positive participants ($P = .02$).

Because HBV infection was associated with elevated HIV 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 patients with HIV-HBV coinfection, higher baseline HBV DNA levels were associated with lower baseline CD4$^+$ T cell counts (85 cells/mL vs 129 cells/mL; $P = .002$) (Table 2) but not with baseline HIV load.

HBeAg-positive patients had median baseline CD4$^+$ T cell counts of 80 cells/mL, compared with 119 cells/mL among those with HBeAg-negative disease ($P = .002$). HBeAg status at baseline did not affect HIV load levels. In a multivariable linear regression analysis, both HBeAg-positive status and HBV DNA level ⩾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 the CD4$^+$ T cell counts of individuals with HBeAg-negative status (95% CI, −164.8 to −33.4 cells/mL; $P = .003$). Those with an HBV DNA level ⩾20,000 IU/mL were predicted to have CD4$^+$ T cell counts that were 35 cells/mL lower than those of individuals with HBV DNA levels <20,000 IU/mL (95% CI, −66.5 to −4.6 cells/mL; $P = .03$). This model also indicated that the effect of HBV DNA count ⩾20,000 IU/mL on baseline CD4$^+$ cell count was statistically significantly different between individuals who were HBeAg positive and individuals who were HBeAg negative ($P = .03$).

HBV and response to ART. Although individuals with HIV-HBV coinfection initiated ART with higher baseline HIV loads, their overall response to ART was equivalent to that among those with HIV monoinfection. At 24 weeks after ART initiation, the proportion of patients with HIV load ⩽400 copies/mL was 70% in the HIV monoinfection group and 67% in the HIV-HBV coinfection group. At 48 weeks, the proportion was 73% in the HIV monoinfection group and 67% in the HIV-HBV coinfection group ($P > .05$).

To determine whether HBV DNA level or HBeAg status at baseline influenced ART response, we compared the proportion of patients who achieved viral suppression ⩽400 copies/mL with respect to 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 with those with ⩾20,000 IU/mL (Table 3). However, when stratified by HBeAg status, a lower proportion of HBeAg-positive individuals achieved HIV load ⩽400 copies/mL at 24 weeks, compared with either HBeAg-negative or HIV-monoinfected individuals ($P = .04$). Because baseline HIV load was also associated with decreased viral suppression at 24 weeks in univariate analyses, we constructed a multivariable logistic regression model with HBsAg-negative patients as the reference group. In this model, both baseline HIV load (odds ratio [OR], 0.78 per 1 log increase in baseline HIV load; 95% confidence interval [CI], 0.66–0.91; $P = .002$) and HBeAg-positive status (OR, 0.54; 95% CI, 0.31–0.92; $P = .03$) were independently associated with decreased likelihood of HIV load ⩽400 copies/mL at 24 weeks. By 48 weeks of therapy, 67% of both HBeAg-negative and HBeAg-positive patients with HIV coinfection achieved an undetectable HIV 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.

Table 2. Hepatitis B Virus (HBV) DNA and Hepatitis B e Antigen (HBeAg) Status among Patients with Human Immunodeficiency Virus (HIV) and HBV Coinfection Are Associated with HIV Disease Stage at Initiation of Antiretroviral Therapy

	HBV DNA level			HBeAg status		
Variable	<20,000 IU/mL (n = 120)	≥20,000 IU/mL (n = 131)	P	Negative (n = 171)	Positive (n = 90)	P
Median CD4$^+$ cell count, cells/mL	129	85	.002	119	80	.002
Median HIV RNA level, log copies/mL	4.99	4.97	.45	4.98	4.94	.44
Alanine transaminase level, median IU/mL	20	29	.06	21	32	.02

This cohort experienced good immune recovery while receiving ART, with mean CD4$^+$ T cell count 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 infection status and HBV DNA level did not affect the CD4$^+$ T cell count increase.

HBV and ART-related hepatotoxicity. At 24 weeks, the proportion of patients with hepatotoxicity was low, and hepatotoxicity was more common among those with HIV-HBV coinfection than it was among those with HIV monoinfection (3.1% vs 0.5%; $P = .01$). However, by 48 weeks, the percentage of patients with hepatotoxicity was <1% and was similar among both HIV-HBV–coinfected and HIV-monoinfected patients. This decrease in the prevalence of hepatotoxicity was not attributable to discontinuation of ART in those individuals with hepatotoxicity at week 24. Hepatotoxicity at 24 and 48 weeks of ART was not associated with baseline HBV DNA level or HBeAg status. In a logistic regression model, only elevated ALT level at baseline was predictive of 24-week hepatotoxicity.

DISCUSSION

Our results demonstrate that individuals with HIV-HBV coinfection in Nigeria had lower CD4$^+$ T cell counts and higher HIV loads at ART initiation than did those with HIV monoinfection. Furthermore, both high HBV DNA levels and the presence of HBeAg were independently associated with lower CD4$^+$ T cell counts. Of interest, these 2 HBV-related characteristics were not associated with the magnitude of the pre-ART HIV load; thus, differences in HIV load cannot account for the CD4$^+$ T cell associations. Virologic response to ART was diminished after 24 weeks of therapy in those individuals with HBeAg-positive HBV infection; however, by 48 weeks of therapy, no differences in response were detected.

This is, to our knowledge, the first study to demonstrate that individuals with HIV-HBV coinfection have statistically significantly lower CD4$^+$ T cell counts, compared with those of individuals with HIV monoinfection, at ART initiation. A few studies on HBV monoinfection support the hypothesis that HBV infection is associated with lower CD4$^+$ T cell counts. In a Thai study, individuals with HBV monoinfection had CD4$^+$ T cell counts that were lower than those of HBsAg-negative patients [13]. In univariate analysis, lower CD4$^+$ T cell counts were associated with high HBV DNA levels, detectable HBeAg, and age <20 years at the time of diagnosis of HBV infection. A study involving pregnant women from India found that CD4$^+$ T cell counts were lower in a group of 25 women with HBsAg than they were in a group of nearly 1100 women without HBsAg [14]. A study from Thailand demonstrated that treatment of an HBV infection led to statistically significant increases in CD4$^+$ T cell counts [15].

One study of occult hepatitis B (defined as the presence of HBV DNA in the absence of HBsAg) in HIV infection also supports our data. Nine patients with occult hepatitis B had CD4$^+$ T cell counts that were lower than those of 184 patients without occult hepatitis B [16]. However, 2 studies of HIV-HBV coinfection did not identify differences in CD4$^+$ T cell counts before ART initiation [3,4]. These studies may not have detected a difference because they both involved patient groups that were smaller than our Nigerian cohort, and the patients may have had different HBV disease characteristics. In the study involving African miners, 40 patients had high HBV DNA levels, but the HBeAg status of the patients was not determined [4]. In the Thai study, the HBV DNA levels and HBeAg status of the patients were not determined, so data from their population cannot be directly compared to data from our study [3].

One interpretation of the association of lower CD4$^+$ T cell counts with higher HBV DNA levels and the 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 that have demonstrated 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, because it is uncommon for HIV to infect hepatocytes, which is the cell type with the most HBV. Our data do not support this mechanism, because high HBV DNA levels and HBeAg-positive status were not associated with higher HIV 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

Table 3. Hepatitis B Virus (HBV) and Antiretroviral Therapy (ART) Response

Variable	HBsAg-negative patients	HBsAg-positive patients			
		HBV DNA level		HBeAg negative	HBeAg positive
		<20,000 IU/mL	⩾20,000 IU/mL		
24 Weeks of ART					
HIV RNA level ⩽400 copies/mL, % of patients	70	70	63	74	55[a]
Change in CD4+ cell count, median cells/mL	86	83	89	87	71
48 Weeks of ART					
HIV RNA ⩽400 copies/mL, % of patients	73	68	67	67	67
Change in CD4+ cell count, median cells/mL	125	109	112	107	113

NOTE. HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus.

[a] $P = .04$ between HBeAg-positive and HBeAg-negative patients. All other Pvalues are >.05.

activation. Several studies on HBV monoinfection 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. Last, it is possible that the patients with HIV-HBV coinfection had advanced liver disease, which could lower CD4+ T cell counts because of splenic sequestration. We were unable to test this hypothesis, because liver biopsies were not performed and platelet counts were unavailable for calculation of the FIB-4 index or the ALT/platelet ratio index (abbreviated APRI) as surrogate marker for liver disease.

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

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

A major strength of this study is that, to our knowledge, this is the largest study involving individuals with HIV-HBV coinfection who initiated ART and had HBV status carefully characterized before ART initiation. Furthermore, because this study was performed in an area of the world in which HBV and HIV infection are highly endemic, the results are applicable to similar regions. A limitation of this study includes the 48-week follow-up period, which prevented us from determining whether HBV and HBeAg status affect longer-term HIV infection outcomes. Furthermore, we could not determine the impact of long-term lamivudine monotherapy for HBV infection. A second limitation is that we do not have data on opportunistic infections that may have occurred before study entry, so we cannot determine whether the lower CD4+ T cell counts associated with HBV coinfection were clinically significant. Our study suggests that further examination of incident opportunistic infections in the setting of HIV-HBV coinfection is warranted. Third, we did not have data regarding CD4+ cell percentages and could not determine whether they were also lower for those individuals with HBV coinfection. A final limitation is that we do not have accurate mortality data, so we are unable to determine the impact of HIV-HBV coinfection on AIDS-related and non–AIDS-related mortality during ART.

In summary, we found that HIV-infected Nigerians with HBV coinfection had lower CD4+ T cell counts at ART initiation. High HBV replication, as measured by HBV DNA levels and HBeAg-positive status, were independently associated with lower CD4+ T cell counts. Furthermore, HBeAg-positive status

decreased the likelihood of achieving undetectable HIV load after 24 weeks of ART. Fortunately, this difference in response disappeared at 48 weeks of ART. Our data emphasize the need for additional detailed studies of HIV-HBV coinfection to understand the impact of HBV on $CD4^+$ T cells and ART response.

Acknowledgments

We thank all patients and staff in the AIDS Prevention Initiative in Nigeria/Harvard President's Emergency Plan for AIDS Relief program at Jos University Teaching Hospital and Camilla Graham, for her help in establishing these and related collaborative studies.

Financial support. National Institutes of Health (U01 AI38858) and the Health Resources and Services Administration (cooperative agreement no. U51HA02522).

Potential conflicts of interest. All authors: no conflicts.

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