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Chronic hepatitis B increases mortality and complexity among HIV-co-infected patients in South Africa: a cohort study

Kavindhran Velen, MPH[1], **Salome Charalambous, MBBCh, PhD**[1,3], **Craig Innes, MBBCh, MSc**[1], **Gavin J Churchyard, MBBCh, PhD**[1,3], **Christopher J Hoffmann, MD, MPH**[1,2,3]

[1]The Aurum Institute, Johannesburg, South Africa

[2]Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

[3]School of Public Health, University of the Witwatersrand, Johannesburg, South Africa

Abstract

We evaluated mortality and single drug substitutions up to three years from ART initiation (median follow-up 2.75 years, interquartile range: 2–3) among patients with and without chronic hepatitis B (CHB) enrolled in a workplace HIV care program in South Africa. Mortality was increased for CHB patients with HBV DNA levels >10,000 copies/ml (adjusted hazard ratio 3.1; 95% confidence interval: 1.2–8.0) compared with non-CHB patients. We did not observe a similar difference between non-CHB patients and those with CHB and HBV DNA <10,000 copies/mL (adjusted hazard ratio 0.70; 95% confidence interval: 0.2–2.3). Single drug substitutions occurred more frequently among co-infected patients regardless of HBV DNA level. Our findings suggest CHB may increase mortality and complicate antiretroviral therapy management.

Keywords

hepatitis B; HIV; Africa; mortality; antiretroviral therapy

Background

Sub-Saharan Africa has the highest burden of HIV infection in the world and is a setting where chronic hepatitis B (CHB) is highly endemic.(1–4) For example: in South Africa the adult HIV prevalence is around 12% (5) and between 3.5% and 17% of HIV-infected individuals are co-infected with CHB.(6, 7) CHB can lead to substantial morbidity including end stage liver disease and hepatocellular carcinoma. It is well described in high income countries that CHB increases mortality among HIV-co-infected patients on and off of antiretroviral therapy (ART). (8–12) In Africa, the clinical relevance of CHB in HIV-CHB co-infection is less clear (13) including whether CHB increases mortality among patients receiving ART.(14–17) A differential mortality effect in African settings compared to

Corresponding Author: Christopher J Hoffmann, The Aurum Institute, The Ridge, 29 Queens Road, Parktown, South Africa 2193. Tel: +27 010 590 1394; fax: +27 086 594 6544; choffmann@auruminstitute.org.

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Europe and North America is plausible due to differences in overall mortality, competing causes of death, and the epidemiology of hepatitis B in Africa compared to Europe and North America.

Given continued uncertainty in the clinical importance of CHB co-infection among HIV-infected individuals in sub-Saharan Africa, we compared mortality and the frequency of single drug substitutions - as a proxy of clinical complexity - by CHB status and HBV DNA level. We conducted retrospective hepatitis B surface antigen (HBsAg) testing on stored plasma samples from a prospective cohort receiving routine management of ART in a workplace HIV care program in South Africa.

Methods

The study population consisted of HIV-infected adult patients enrolled in a workplace HIV care program operating in two Provinces in South Africa with large mining operations and initiated on ART between 2002 and 2010 (13, 18) who also had pre-ART serum samples retrospectively tested for HBsAg. During the study period, patients in the HIV care program were initiated on ART if they had a CD4 count <250 cells/mm^3 or a CD4 count <350 cells/mm^3 with WHO stage III or any CD4 and WHO stage IV clinical condition. The ART regimen consisted of zidovudine or stavudine and lamivudine, and efavirenz or nevirapine prior to June 2007 at which time it shifted to tenofovir, lamivudine or emtricitabine, and efavirenz or nevirapine. There was no regimen modification based on hepatitis B status and hepatitis B testing was not part of routine care. Routine care included a CD4 cell count and HIV RNA level at baseline, at 6 weeks and then every 6 months. HBV testing was done on a random selection (by random number generation) of 20% of patients with retrievable stored serum specimens obtained prior to ART initiation. Approvals for this study were obtained from the University of Kwa-Zulu Natal Biomedical Research Ethics Committee and the Johns Hopkins Institutional Review Board.

Presence of HBsAg was determined from plasma specimens stored at −70°C and collected between 6 months prior to ART initiation and two weeks after ART initiation. HBsAg was tested using the ADVIA Centaur automated immunoassay system (Bayer Diagnostics). Patients who were positive for HBsAg had a pre-ART sample tested for HBV DNA using the Versant HBV DNA Quantitative Assay, version 3.0 (Bayer Diagnostics); the lower limit of detection for this assay was 2000 copies/mL.(13)

Ascertainment of patient death was determined through available clinical records and linkage with the South African National vital status registry using available national identification numbers. We used inverse probability weighting to adjust for mortality based on participants with known or unknown national identification numbers (19, 20). The database was closed on 30 August 2011. Cause of death was unavailable.

We compared patient characteristics using Chi-squared testing based on HBsAg status. The date of ART initiation was used to define entry into observation. Exit from observation was the earliest date amongst death, ART discontinuation, 6 months after last documented visit, or two years after ART initiation. We assessed association with mortality and CHB status –

CHB negative, CHB with HBV DNA ≤10,000 copies/mL, and CHB with HBV DNA >10,000 copies/mL. We used the 10,000 copies/mL cut-off (roughly 2,000 IU/mL) based on the increased risk for hepatocellular carcinoma and cirrhosis with levels greater than 10,000 copies/mL.(21, 22) We calculated hazard ratios and adjusted hazard ratios using Cox proportional hazards modeling, controlling for site level effects and region of origin, using shared frailty. In addition, to assess for a change in CHB association with mortality over time on ART (non-proportional hazards) we created a dichotomous time variable: ≤3 months and >3 months on ART. This period was selected in order to have a sufficient number of deaths in each CHB category during each time interval. As a proxy for clinical complexity, we compared single drug substitution by CHB status – CHB negative, CHB with HBV DNA ≤10,000 copies/mL, and CHB with HBV DNA >10,000 copies/mL. For this analysis, we used a competing-risks time-to-event framework, with death considered a competing risk, with robust estimates at site level.

Results

Of the 8,711 patients enrolled in the HIV workplace program, 1,484 patients met the criteria for inclusion in the study. A total of 7,227 patients failed to meet enrollment criteria because we did not perform pre-ART HBsAg testing (they were not randomly selected or they lacked a pre-ART serum specimen). Among those excluded, there were fewer men versus included patients (89% compared to 94%, $p<0.001$) and the median CD4 count was lower (119 cells/mm^3 compared to 133 cells/mm^3, $p<0.001$). The age distribution was similar ($p=0.1$). Among the included patients, the median age was 44 years [interquartile range (IQR): 38, 51] and the median CD4 count at ART initiation was 133 cells/mm^3 (IQR: 72, 205). There were 248 (16%) patients who had a serum sample that tested HBsAg positive and 236 (88%) had HBV DNA results; 87 (37%) had HBV DNA levels of >10,000 copies/ml. The initial nucleoside reverse transcriptase inhibitor was zidovudine for 1,306 (88%), stavudine for 154 (10.4%), and tenofovir for 24 (1.6%) patients; 1,388 (93.5%) received efavirenz and 96 (6.5%) received nevirapine. A greater proportion of patients with CHB had HIV RNA >100,000 c/mL and higher WHO clinical stages (Table 1). The median follow-up time was 2.75 years (IQR: 2.0, 3.0).

There were 121 deaths over the three years of follow-up. The mortality rate for CHB patients with DNA levels of >10,000 copies/ml was 3.0 per 100 PYRs [95% confidence interval (CI): 1.4–6.7], for CHB patients with DNA levels ≤10,000 copies/ml was 2.6 per 100 PYRs (95% CI: 2.1–5.3), and for non-CHB patients was 2.2 per 100 PYRs (95% CI: 1.1–4.1).

In the multivariable Cox proportional hazards model, the hazard ratio was 3.1 (95% CI: 1.2–8.0) for CHB patients with DNA levels >10,000 copies/ml compared with non-CHB patients as the referent group (Table 2). The adjusted hazard ratio remained unchanged during the first three months compared to greater than three months on ART (p value for interaction between time on ART, CHB status, and mortality = 0.9). There was no association with mortality among patients with CHB and HBV DNA ≤10,000 copies/mL [the adjusted hazard ratio was 0.7 (95% CI: 0.2, 2.3)]. Additional associations with mortality were higher WHO clinical stage at ART initiation and lower time-updated CD4 count.

There were 164 single-drug substitutions over the three years of ART follow-up. The rate of single-drug substitution was higher in CHB patients (4.2 per 100 PYRs; 95% CI: 2.8–6.4) when compared to non-CHB patients (1.8 per 100 PYRs; 95% CI: 1.4–2.4). The single-drug substitution rate was similar by HBV DNA level [patients with HBV DNA >10,000 copies/ml had a rate of 5.0 per 100 PYRs (95% CI: 2.6–9.5) compared to a rate of 3.8 per 100 PYRs (95% CI: 2.2–6.6) for patients with CHB and HBV DNA ≤10,000 copies/mL]. The breakdown of agents substituted from was as follows: zidovudine 72, stavudine 50, tenofovir 8, efavirenz 20, and nevirapine 14 substitutions. In the multivariable competing risks regression model, the hazard ratio for having a single-drug substitution for CHB patients with HBV DNA levels of ≤10,000 copies/ml was 2.2 (95% CI: 1.2–4.1) and for CHB patients with DNA levels >10,000 copies/ml was 2.3 (95% CI: 1.1–4.7) when compared to the referent group of non-CHB patients (Table 2). Also associated with single-drug substitutions was lower time-updated CD4 count.

Discussion

We observed an association between increased mortality and CHB when the HBV DNA level was >10,000 c/mL. We believe that our observation of an increased effect size between CHB and mortality with higher HBV DNA levels supports the validity of our findings and makes an important contribution to understanding HIV-CHB co-infection in Africa. Furthermore, single drug substitutions occurred more commonly with co-infection, suggesting that in addition to increased mortality, co-infection was associated with additional clinical management challenges.

CHB has been reported to increase mortality among HIV-co-infected populations in Europe and North America. However, there is uncertainty regarding the mortality effect of CHB among ART patients in Africa.(14–17) Our finding of increased mortality with CHB is consistent with some prior studies from low and middle income countries (LMIC).(14, 15, 17) Notably our study added to understanding in that we included the comparison of HBV DNA levels and identified an association with mortality only among patients with CHB and a higher HBV DNA concentration prior to ART initiation. This is consistent with more active HBV disease and HBV contributing to the deaths. Our findings contrast with a smaller study that reported no difference in mortality by CHB status.(16) The effect of HBV-active agents on HBV-associated mortality is unclear from our study. All of the patients we analyzed received a deoxycytidine nucleoside analogue (either lamivudine or emtricitabine) and very few received tenofovir. Thus we were unable to compare outcomes by agent in our cohort. It is plausible that mortality would have been higher without the use of a deoxycytidine nucleoside analogue or would have been lower had all patients received tenofovir.

Over the first three years of ART, patients with CHB were more likely to have a single agent substitution. This finding was similar to a European study which found the frequency of substitution of at least one ART agent was higher among patients co-infected with hepatitis B and HIV. (23) Similar studies are not available from Africa. Agent substitutions are important in LMIC settings because they may require a higher level of clinical expertise than

is often available where HIV care is part of chronic disease management provided at the primary care level by nurses.

There are certain limitations to this study. First, this cohort primarily consisted of men and thus the results do not necessarily extend to women. (13) Second, CHB infection was assessed by a single HBsAg assay potentially leading to the classification of individuals with acute hepatitis B infection as having CHB. (24) We presume that minimal misclassification occurred because hepatitis B transmission usually occurs during childhood in southern Africa; thus, it is unlikely that the individuals identified as HBsAg positive had acute HBV infection.(13) Third, characteristics between patients with and without CHB differed in HIV RNA; a characteristic generally associated with increased mortality. Although we did not identify confounding from any factors as an explanation for the associations between CHB and mortality and single drug substitution, it is possible that unaccounted for residual confounding may have contributed to our findings. Forth, we did not have data on the reasons for single agent substitutions or on cause of death.

In conclusion, CHB appeared to increase mortality and complicate HIV care, an important finding with implications for CHB assessment among ART patients. In settings with a high prevalence of CHB, earlier initiation and use of tenofovir as a standard part of first-line ART may be important for reducing mortality. In addition, optimizing ART care overall, including assuring that a larger fraction of individuals who meet local ART initiation criteria are started on ART, are likely important aspects of reducing HIV associated mortality in Africa. Patient knowledge of their HIV-CHB co-infection may serve as added motivation for care seeking and continued engagement in care. Continued monitoring and assessment of the role of chronic co-morbidities, including CHB, on outcomes should be incorporated into care programs.

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Table 1:

Patient characteristics by CHB status

Characteristic	HBsAg (-ve) (n=1,236)	HBsAg (≤10,000) (n=163)	HBsAg (>10,000) (n=85)	p-value
Gender, *n (%)*				0.1
Men	1,155 (93.4)	157 (96.3)	80 (94.1)	
Women	81 (6.6)	6 (3.7)	5 (5.9)	
Age, *n (%)*				<0.001
≤42 years	505 (40.9)	70 (42.9)	43 (50.6)	
>42 years	731 (59.1)	93 (57.1)	42 (49.4)	
Year of ART initiation, *n (%)*				0.05
2002–2003	201 (16.3)	25 (15.3)	15 (17.6)	
2004	316 (25.6)	44 (27.0)	19 (22.4)	
2005	397 (32.1)	56 (34.4)	35 (41.2)	
2006–2010	322 (26.0)	38 (23.3)	16 (18.8)	
CD4 count at ART initiation, cells/mm^3, *n (%)*				0.1
<100	429 (34.7)	44 (27.0)	40 (47.1)	
101–250	542 (43.9)	83 (50.9)	29 (34.1)	
>250	156 (12.6)	20 (12.3)	9 (10.6)	
Missing	109 (8.8)	16 (9.8)	7 (8.2)	
Median (IQR)	135 (70–208)	138 (90–202)	106 (64–170)	
HIV RNA at ART initiation, c/mL, *n (%)*				<0.001
<1000	19 (1.5)	1 (0.6)	0 (0)	
1000–50000	266 (21.5)	27 (16.6)	7 (8.2)	
50001–100000	117 (9.5)	14 (8.6)	2 (2.4)	
>100000	213 (17.3)	33 (20.2)	17 (20.0)	
Missing	621 (50.2)	88 (54.0)	59 (69.4)	
Log_{10} Median (IQR)	4.8 (4.3–5.2)	4.9 (4.3–5.3)	5.1 (4.7–5.3)	
NRTI at ART initiation				<0.001
Zidovudine	1,093 (88.4)	133 (81.6)	80 (94.1)	
Stavudine	125 (10.1)	26 (16.0)	3 (3.5)	
Tenofovir	18 (1.5)	4 (2.4)	2 (2.4)	
NNRTI at ART initiation				<0.001
Efavirenz	1,157 (93.6)	158 (96.9)	73 (85.9)	
Nevirapine	79 (6.4)	5 (3.1)	12 (14.1)	
WHO clinical stage, *n (%)*				<0.001
I & II	369 (29.9)	41 (25.2)	16 (18.8)	
III & IV	341 (27.6)	49 (30.1)	16 (18.8)	
Missing	526 (42.5)	73 (44.7)	53 (62.4)	
Previous history of TB, *n (%)*				0.03
Yes	91 (7.4)	10 (6.1)	2 (2.4)	
No	1,145 (92.6)	153 (93.9)	83 (97.6)	

Table 2.

Univariable and multivariable competing-risk regression model for single agent substitution and Cox proportional hazard model for Mortality

	Mortality				Single-drug substitution			
	Univariable		Multivariable		Univariable		Multivariable	
	Hazard ratio	p-value	Hazard ratio	p-value	Hazard ratio	p-value	Hazard ratio	p-value
Chronic hepatitis B								
Negative	Ref.		Ref.		Ref.		Ref.	
≤10,000 copies/mL	0.7 (0.2–2.3)	0.5	0.7 (0.2–2.3)	0.5	2.1 (1.2–3.9)	0.01	2.2 (1.2–4.1)	0.01
>10,000 copies/mL	2.6 (1.0–6.7)	0.05	3.1 (1.2–8.0)	0.02	2.6 (1.3–5.3)	0.01	2.3 (1.1–4.7)	0.02
WHO stage at ART initiation		<0.001		<0.001		0.03		0.002
I and II	Ref.		Ref.		Ref.		Ref.	
III and IV	1.9 (1.1–3.7)		1.9 (1.1–3.6)		0.4 (0.1–0.9)		0.3 (0.1–0.8)	
Age (years)		0.8		0.8		0.6		0.8
≤42	Ref.		Ref.		Ref.		Ref.	
>42	0.9 (0.5–1.8)		0.9 (0.4–1.9)		0.9 (0.6–1.4)		1.1 (0.6–1.8)	
Time-updated CD4, cells/mm^3		0.06		0.003		0.003		0.002
<100	16.0 (3.1–45.6)		7.5 (1.4–39.2)		4.5 (1.9–10.2)		5.3 (2.3–12.3)	
101–250	3.8 (0.7–20.8)		2.4 (0.4–13.0)		2.0 (0.9–4.1)		2.1 (1.1–4.5)	
>250	Ref.		Ref.		Ref.		Ref.	

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