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HBV Lamivudine Resistance among Hepatitis B and HIV Co-infected Patients Starting Lamivudine, Stavudine and Nevirapine in Kenya

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Abstract

Widespread use of lamivudine in antiretroviral therapy may lead to hepatitis B virus resistance in HIV-HBV co-infected patients from endemic settings where tenofovir is not readily available. We evaluated 389 Kenyan HIV-infected adults before and for 18 months after starting highly-active antiretroviral therapy with stavudine, lamivudine and nevirapine. Twenty-seven (6.9%) were HBsAg(+) and anti-HBs negative: 24 were HBeAg-negative, 18 had HBV DNA ≤10,000 IU/ml. Sustained HBV suppression to <100 IU/ml occurred in 89% of 19 evaluable patients. Resistance occurred in only 2 subjects, both with high baseline HBV DNA levels. Lamivudine resistance can emerge in the setting of incomplete HBV suppression but was infrequently observed among HIV-HBV co-infected patients with low baseline HBV DNA levels.

Keywords

HIV-1; HBV; lamivudine resistance

Introduction

Africa, in addition to carrying the largest global burden of HIV infection, is one of the largest reservoirs for chronic hepatitis B (HBV) infection (1). The impact of HIV infection on the course of chronic HBV infection in Africa has not been well studied.

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In Africa and most developing regions, for reasons of cost and availability, the most common regimen for initial antiretroviral therapy of HIV comprises lamivudine, stavudine and nevirapine, which includes just one active agent against HBV in lamivudine, the agent with the lowest genetic barrier for HBV resistance and associated with rapid development of resistance when used alone (2). Rates of HBV resistance as high as 20% per year of use have been reported with lamivudine monotherapy in HBV-HIV coinfected patients (3). Routine HBV screening is not currently available in most care settings in Africa so the extent of HBV coinfection and resistance are not known. Widespread HBV lamivudine resistance may limit future treatment options and contribute to potential liver-related morbidity in patients who have experienced successful suppression of HIV infection and extended survival.

We describe the clinical spectrum of HBV-HIV coinfection and the longitudinal development of HBV resistance in this prospective cohort of HBV-HIV coinfected patients started on lamivudine, stavudine and nevirapine in Kenya.

Methods

Patients at the Coptic Hope Center for Infectious Diseases in Nairobi, Kenya were enrolled in a randomized controlled trial from May 2006 to September 2008 that compared the impact of adherence counseling and alarm device on monthly pill count, HIV plasma RNA level and CD4 count over 18-month follow-up (4). Participants were eligible to start highly active antiretroviral therapy (HAART) consisting of stavudine, lamivudine and nevirapine based on Kenyan national guidelines at that time: CD4 count <250 cells/mm^3, CD4 count <350 cells/mm^3 with World Health Organization (WHO) clinical stage 3 or 4 disease. Those on anti-tuberculosis medications or pregnant at time of enrollment were excluded. Blood was drawn for CD4 cell counts and HIV viral load determination every six months; plasma was collected at months 0 (just before HAART initiation), 6, 12 and 18 for future analysis and stored at -80°C. Patients who missed monthly appointments for medication and pill bottle exchange were sought with active tracing and home visits. Date and cause of death were determined from contacts and hospital records when available. All subjects provided written informed consent. The institutional review boards of Kenyatta National Hospital and the University of Washington approved this study.

All testing of archived samples occurred in Seattle, WA after subjects completed follow-up and exited the main study. Available enrollment plasma samples were tested for hepatitis B surface antigen (HBsAg). Positive samples were tested for HBV surface antibody (anti-HBs). HBV carriers, defined as HBsAg-positive and anti-HBs-negative at baseline, underwent further HB e antigen (HBeAg) and anti-HBe antibody testing. Enzyme-linked immunoassay was used (DiaSorin): ETI-MAK-2 Plus and ETI-AB-AUK Plus for HBsAg and anti-HBs, ETI-EBK Plus and ETI-AB EBK Plus for HBeAg and anti-HBe.

HBV DNA quantitation was performed on plasma of carriers at all available time-points using an in-house real-time fluorescent-probe polymerase chain reaction (TaqMan) with dynamic range of 10 to 1 billion IU per ml. HBV polymerase gene sequencing was performed on plasma with detectable HBV DNA levels using the Abbott Molecular HBV RUO Sequencing (pol) reagent kit and an ABI 3730 instrument. The resulting sequence files were analyzed with ABI Seqscape software version 2.6 for the presence of specific drug mutations using a template supplied by Abbott Molecular. HBV genotype was assigned by determining the closest-match sequence against NCBI HBV genotyping reference sequences.

CD4 cell counts were measured by flow cytometry (Becton Dickinson FACScan). HIV-1 RNA levels were measured using Gen-Probe HIV-1 viral load assay (5).

Baseline characteristics were compared using nonparametric methods: Fisher's exact test for categorical variables and Mann-Whitney *U* test for continuous variables. Incidence of lamivudine resistance was estimated as cases over person-time at risk, censored at the last available sample tested. Cox proportional hazards models were used to assess difference in mortality by carrier status, adjusting for the assigned arm as well as imbalances in gender, baseline CD4 count, and cost of travel to clinic (dichotomized as <50 versus ≥50 Kenyan shillings or US $0.70) that were noted at $P \leq 0.1$ level. All analyses were conducted using Stata SE software, version 10.1 (StataCorp).

Results

A total of 389 subjects had archived plasma available for HBsAg testing at enrollment before HAART initiation. Of these 389, 27 were positive for HBsAg and negative for anti-HBs for an estimated prevalence of chronic HBV infection of 6.9% [95% confidence interval, 4.4%-9.5%]. Median age of chronic HBV carriers was 37 years (range 23-61). Thirteen (48%) were men (Table 1). HBV carriers were comparable to non-carriers with respect to baseline CD4 cell count, WHO stage, hemoglobin, weight and serum alanine aminotransferase (ALT) levels.

Of the 27 HBV carriers, 24 (89%) were hepatitis B e antigen (HBeAg) negative at baseline. Of the 21 carriers (78%) with detectable HBV DNA, only 9 (36%) had high HBV viral levels exceeding 10,000 IU/ml (Table 2). Baseline HBV viral levels varied widely among those with detectable HBV (range 12 IU/ml to 430 million IU/ml). All subjects with detectable HBV DNA had genotype A1 virus.

All 25 carriers with available baseline serum ALT had normal-range values: median 16 IU/L (range 2-34). No significant ALT elevations were observed during HAART among available measurements. Maximum ALT values exceeded 2-fold the upper limit of normal (>80 IU/L) in only two carriers (9%) during HAART with peak values of 95 and 150 IU/L.

HBV Lamivudine Resistance during HAART

Baseline HBV resistance testing revealed pre-treatment mutations in three subjects. Each subject had a single mutation: rtI233V, rtA181S, or rtV207I. These mutations have been associated with reduced *in vitro* susceptibility to adefovir (rtI233V, rtA181S) and lamivudine (rtV207I) in some reports (6-8).

We were able to assess HBV virologic response on HAART in 19 of the 27 carriers on follow-up (Table 2). Seventeen (89%) carriers were able to achieve and maintain HBV DNA suppression to <100 IU/ml.

Two participants had detectable HBV DNA >100 IU/ml during follow-up and were the only ones to develop lamivudine resistance on HAART. Both had high baseline HBV viral levels of 280,000 IU/ml and 430,000,000 IU/ml, HBeAg-negative and positive respectively, and neither had baseline mutations (Table 3). One patient demonstrated virologic breakthrough at month 12 with a concurrent rise in ALT (150 IU/L) and detection of dual reverse transcriptase mutations A200V + M204I. The other patient continued to show declining HBV DNA levels but was unable to achieve HBV viral suppression <100 IU/ml during the 18-month follow-up; lamivudine resistance with M204I was detected early by month 6 in that individual. Both patients maintained excellent HIV suppression through this time,

suggesting good adherence to therapy. The crude incidence rate for lamivudine resistance among HBV carriers was 7.5 per 100 person-years.

Mortality

Five HBV carriers died during follow-up – 3 within 4 months of follow-up (range 0.5 to 10.4 months). All were HBeAg-negative and 4 had detectable HBV DNA, range 71 to 350,000 IU/ml. All had low baseline CD4 counts: 96, 193, 160, 16 and 16 cells/mm^3. Baseline ALT values did not differ significantly from other carriers. Cause of death could not be ascertained.

The 18-month mortality rate was higher for HBV carriers than non-carriers at 21.7% versus 8.9%, log-rank *P*-value = .045. A multivariable model that included the main study interventions of counseling and alarm use as well as gender, baseline CD4 count and cost of travel to clinic yielded an adjusted hazard ratio (HR) of 2.9 (95% CI 1.1-7.6, *P*= .032) for death.

Discussion

We outline the emergence of HBV drug resistance following first-line lamivudine-containing HAART in HIV-HBV co-infected patients in Kenya. The prevalence of chronic HBV infection was 6.9% in our cohort and comparable to recent estimates of HBsAg seroprevalence from Kenya (9, 10) and Tanzania (11). In contrast to HBV-HIV coinfected cohorts from Europe (12) or Asia (13), the majority (89%) of our HBV carriers were HBeAg-negative as has been observed with genotype A1 HBV (14) as well as in other HBV-HIV-coinfected cohorts in Africa (11, 15, 16). Only a third had high baseline HBV DNA levels >10,000 IU/ml.

Seventeen (89%) of the 19 evaluable patients achieved complete HBV viral suppression on lamivudine. Our estimated incidence rate of lamivudine resistance (7.5 per 100 person-years) was lower than the estimated 18-20% per year reported in other HIV-HBV coinfected populations in Europe (3), US, Australia (17) or West Africa (18). The higher rate of sustained HBV suppression might be attributable to lower baseline HBV viral levels in our patients, which has been shown to be associated with greater durability of lamivudine (19, 20). HBeAg-negative carriers have also been reported to have lower rates of early lamivudine resistance with a rate of 10% in 2.5 years in one cohort (21) though this was not noted in other larger cohorts (22, 23). A cross-sectional study of HIV-HBV coinfected patients from Thailand did suggest that HBeAg-negative status was a protective factor for the risk of lamivudine resistance (24).

We also observed a higher mortality rate of 21.7% in HBV carriers compared with 8.9% in non-carriers (adjusted HR 2.9 (95% CI 1.1-7.6, *P*= .032). Excess mortality in HBV-HIV coinfected patients has been reported, both for all-cause (rate ratio, RR 1.4-1.7) (25-28) and liver-related (RR 3.6-8.3) (25, 29, 30) mortality in more developed settings. Two studies, in South Africa and Tanzania, also observed a trend toward excess mortality in HBV-HIV coinfected patients compared with HIV-monoinfected patients starting HAART (RR ~1.3) (11, 31). Whether the deaths among our HBV carriers were liver-related is not known.

The strength of our study lay in our ability to test specimens collected prospectively and follow the evolution of resistance over time, as well as to conduct active tracing of those lost to follow-up. Our study was limited by small numbers, loss to follow-up and missing data – 3 of 8 patients with high baseline HBV viremia (>100,000 IU/ml) had no subsequent samples. There were constraints with respect to accurate ascertainment of cause of death. We also lacked data on cofactors such as alcohol use or schistosomiasis. Severity of liver

disease by histology or noninvasive testing could not be evaluated in our cohort. Finally, antiviral resistance was determined by consensus sequencing, which may have lower sensitivity in detecting minor variants with resistance mutations (32).

Lamivudine resistance did emerge as an early finding in this Kenyan cohort in those HBV-HIV coinfected patients with high baseline HBV DNA levels who did not completely suppress within the first year of therapy. However we did not observe lamivudine resistance among patients who had low baseline HBV DNA levels, nearly all of whom were HBeAg-negative. Although our results are not generalizable to regions such as Asia where high HBV viral levels and HBeAg-positive infection predominate, or to other regions in Africa where different genotypes (e.g. A3, D and E) are encountered, they suggest that HBV treatment outcomes in this region may be quite distinct from what has generally been described. The World Health Organization 2010 guidelines on HAART recommend tenofovir in combination with either lamivudine or emtricitabine as the first-line component to HAART in patients found to be HBV-HIV coinfected. A larger cohort would need to be studied and the long-term durability of HBV suppression in HBeAg-negative patients with low HBV levels confirmed before lamivudine monotherapy could be considered an alternative.

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Table 1
Baseline characteristics of chronic HBV carriers compared with non-carriers

Characteristic	Chronic HBV carriers N=27	Non-carriers N=362	*P*
Age, years	37 (31, 43)	36 (30, 42)	.85
Gender, no. (%)			
Women	14 (52)	242 (67)	.11
Men	13 (48)	120 (33)	
Cost of travel to clinic, no. (%)			
< 50 Kenyan shillings (US $0.70)	10 (37)	139 (38)	.90
≥ 50 Kenyan shillings (US $0.70)	17 (63)	223 (62)	
WHO stage, no. (%)			
Stage 1	11 (41)	132 (37)	
Stage 2	9 (33)	130 (36)	.72
Stage 3	6 (22)	92 (25)	
Stage 4	1 (4)	7 (2)	
CD4 cell count, cells/mm^3	122 (75, 197)	115 (60, 179)	.76
Hemoglobin, g/dl	12.1 (11, 13.7)	12.3 (10.6, 13.9)	.78
Weight, kg	66 (60, 68)	61 (53, 69)	.14
Baseline ALT, IU/L	15.8 (12.3, 24.1)	15.8 (10.4, 25)	.97

All values in median and IQR, interquartile range (25th & 75th percentiles) unless otherwise indicated.

Table 2

Hepatitis B e antigen/antibody status and HBV DNA levels (IU/ml) among chronic HBV carriers

Participant	HBeAg	Anti-HBe	Month 0	Month 6	Month 12	Month 18
1	−	−	<10	<10	<10	<10
2	−	−	<10	<10	<10	<10
3	−	−	<10	<10	<10	<10
4	−	−	<10	---	---	---
5	−	−	<10	---	---	---
6	−	+/−	<10	<10	<10	<10
7	−	+	12	<10	<10	<10
8	−	+	24	<10	<10	<10
9	−	+	71	<10	---	---
10	−	+	480	<10	<10	<10
11	−	+	530	<10	<10	<10
12	−	+	1,100	---	---	---
13	−	+	1,300	19	<10	<10
14	−	+	2,400	---	---	---
15	−	+/−	3,200	<10	<10	<10
16	−	+	3,600	---	---	---
17	−	+	5,800	<10	---	---
18	−	+	10,000	79	68	28
19	−	+	25,000	<10	<10	<10
20	−	+	210,000	<10	<10	<10
21	−	+	210,000	20	66	51
22	−	+	280,000	86	288	478,000,000
23	−	+	350,000	---	---	---
24	+	−	1,100,000	---	---	---
26	−	+	230,000,000	26	13	28
26	+	−	310,000,000	---	---	---
27	+	−	430,000,000	3,407	2,027	576

HBeAg, hepatitis B e antigen. Anti-HBe, hepatitis B e antibody. +, positive; −, negative; +/−, equivocal. ---, samples not available.

Table 3

Laboratory trends of the two HBV carriers with lamivudine resistance

Participant		HBV DNA level (IU/ml)	HBV Mutations	Serum ALT (IU/L)	HIV RNA level (copies/ml)
22	Month 0	280,000	None	24	614,000
	Month 6	86	None	9	78
	Month 12	288	A200V + M204I	150	34
	Month 18	478,000,000	A200V + M204I	80	2
27	Month 0	430,000,000	None	34	194,300
	Month 6	3,407	M204I	39	26
	Month 12	2,027	M204I	28	14
	Month 18	576	M204I	38	84

HBV, hepatitis B virus. HIV, human immunodeficiency virus. ALT, alanine aminotransferase.