Early Mortality Risk of HIV/Hepatitis B Virus co-Infected Patients Initiating ART in Kenya

Murithi Mbae[1*], Kirwa Kiprono Elisha[2], Amos Ndhere[2], Ndwiga Stanley Mugambi[2], Ram Yogev[3,4], Robert L Murphy[3], Joseph N Jarvis[1,5,6]

[1] Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, [2] African Infectious Diseases Village Clinics, [3] Northwestern University Feinberg School of Medicine, [4] Ann & Robert H. Lurie Children's Hospital of Chicago, [5] Botswana-Upenn Partnership, [6] Perelman School of Medicine, University of Pennsylvania. *This work was carried out as part of Dr Murithi Mbae's MSc in Tropical Medicine and International Health at LSHTM. The African Villages Clinic was funded by the Ann and Robert H. Lurie Foundation

Introduction

Hepatitis B virus (HBV) co-infection, common in HIV-infected patients in sub-Saharan Africa[1], is associated with impaired immunological recovery while on antiretroviral treatment (ART)[1,2], and worse clinical outcomes, even in the context of effective ART[3]. A clear association between HBV co-infection and early mortality has not been shown in African settings and the impact of tenofovir-containing ART on outcomes is unknown[1].

Methods

We performed a retrospective analysis of programmatic data from the African Infectious Disease Village Clinics, Kajiado district, Rift Valley province, Kenya, **to determine The prevalence of hepatitis B surface antigen (HBsAg) in a cohort of patients enrolling in an ART programme** between 2003 and 2012. The clinic serves a predominantly rural Maasai population (approximate pop. 200,000). ART was prescribed according to WHO and Kenyan guidelines, with a CD4 starting threshold of <200 cells/μL until 2007, increased to 250 cells/μL between 2007 and 2010, and 350 cells/μL thereafter. First-line ART regimens consisted of D4T or AZT plus lamivudine, with efavirenz or nevirapine until 2010, when tenofovir based regimens were introduced. All patients were screened for Hepatitis B at baseline (immunochromatographic lateral flow assay, Bionike Inc). Patients were followed 3-monthly with CD4 (Guava PCA, EMD Millipore) and viral load (Cavidi ExaVirLoad) monitoring. Data were prospectively collected in an electronic database and exported as CSV files for analysis in STATA. **Clinical outcomes, immunological and virological responses to ART were compared between HIV mono-infected and HIV/HBV co-infected patients using Cox regression.** The impact of tenofovir-containing ART on outcomes was determined in an analysis adjusting for confounders relating to time and indication (sex, age, baseline CD4 count, calendar year, and baseline creatinine). Ethical clearance was given by the LSHTM and Moi University RECs.

Results

7,155 patients were enrolled in the cohort and followed for 12,408 person years, with a mean duration of follow-up of 633 days. **HBsAg was detected in 451/7155 (6.3%, 95%CI 5.8-6.9%) of patients.** HBsAg prevalence was higher in men than women (9.2% versus 5.0%, p<0.001) and increased with age. HBsAg positivity was associated with increased risk of death in crude analysis (HR 1.84, 95%CI 1.4-2.5, p<0.001).

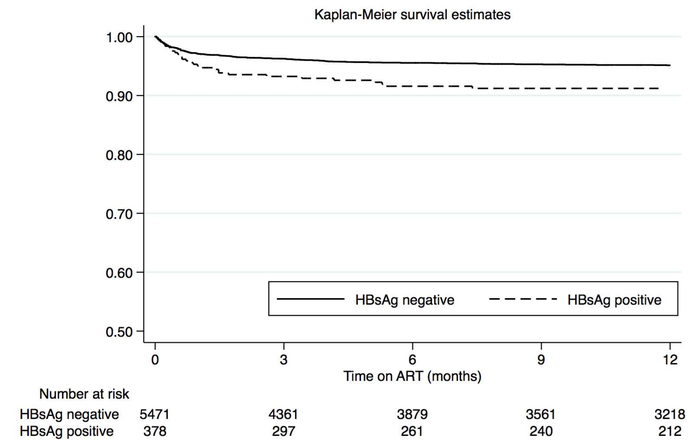

Fig. 1 Kaplan-Meier Survival curves showing the excess mortality risk in Hepatitis B surface antigen positive patients during the first year of ART in a Kenyan cohort.

Among those initiating ART (n=6,214), HBsAg positive patients (n=419) had significantly impaired immunological recovery within the first year of ART compared to HBsAg negative patients (median CD4 cell count increase 110 cells/μLvs135 cells/μL, p=0.03), despite similar rates of virological suppression (90% vs 88%, p=0.32). **HBsAg positivity remained an independent predictor of early mortality in adjusted analysis (aHR1.84, 95%CI 1.3-2.6, p=0.001).**

Baseline ALT was higher in HBsAg positive patients (27 IU/L vs 23 IU/L, p<0.001), however this difference was not clinically significant, and there was no evidence for severe liver disease in the HBsAg positive patients during the first year of ART.

Among patients initiating tenofovir-containing regimens (n=3,125), HBsAg positivity (n=350) was no longer significantly associated with increased risk of mortality (aHR 1.45, 95%CI 0.9-2.2, p=0.1) in contrast to the markedly increased risk in patients receiving non-tenofovir based regimens (aHR 3.32, 95%CI 1.8-6.2, p<0.001, p-value for interaction = 0.03).

Table 1. Associations between Hepatitis B surface antigen status and outcome in a cohort of 7155 HIV-infected Kenyans

	HBsAg +ve	HBsAg -ve	*p-value*	TDF	No TDF	*p-value*
Age (years)	38 (32-45)	36 (30-44)	*<0.001*	37 (31-44)	36 (30-43)	*<0.001*
Sex (% male, *n*)	46% (209)	31% (2057)	*<0.001*	34% (1034)	30% (951)	*0.009*
CD4 count (cells/mL)	145 (61-299)	167 (67-347)	*0.01*	167 (69-327)	137 (59-276)	*<0.001*
HIVviral load (Log_{10}Copies/mL)	4.76 (3.7-5.2)	4.59 (3.3-5.3)	*0.07*	4.64 (3.3-5.2)	4.73 (3.7-5.3)	*<0.001*
CD4 increase in year 1(cells/mL)	110 (41-208)	135 (48-251)	*0.03*	128 (43-224)	140 (50-267)	*<0.001*
HIV viral suppression in year 1(%, *n*)	90.4% (263)	88.5% (3784)	*0.32*	89.5% (1927)	87.8% (2118)	*0.07*
Mortality in year 1 (%, *n*)	9.3% (42)	5.3% (356)	*<0.001*	4.8% (148)	4.1% (127)	*0.16*
HBsAg and Mortality	**aHR of death**	**95% CI**	***p-value***			
All patients	1.84	1.3-2.6	*0.001*	All adjusted analyses were restricted to patients initiating ART and adjusted for age, sex, CD4 count at ART initiation, baseline creatinine, and calendar year. When tenofovir use was included as an interacting term there was significant evidence for interaction *(p=0.03)*.		
Not on TDF	3.32	1.8-6.2	*<0.001*			
On TDF	1.45	0.9-2.2	*0.1*			

All results are median (interquartile range) or percentage (number) unless otherwise indicated. HBsAg = Hepatitis B virus surface antigen. TDF – tenofovirdisoproxilfumarate. aHR = adjusted hazard ratio, derived from a Cox regression model.

Conclusions

Hepatitis B co-infection was associated with impaired immunological responses to ART and increased risk of mortality in this large cohort of Kenyans initiating ART, despite adequate HIV virological suppression and no evidence for severe liver disease. Use of tenofovir-containing regimens significantly reduced mortality risk in HIV/HBV co-infected patients. **Any move away from tenofovir containing first-line ART in sub-Saharan Africa must be combined with Hepatitis B surface antigen screening to enable effective treatment of individuals with HIV/HBV co-infection.**

References

1. Hawkins et al. Prevalence of hepatitis B co-infection and response to antiretroviral therapy among HIV-infected patients in Tanzania. AIDS. 2013;27:919–927. 2. Wandeler et al. Hepatitis B virus infection is associated with impaired immunological recovery during antiretroviral therapy in the Swiss HIV cohort study. JID. 2013 Nov 1;208(9):1454-8. 3. Stabinski et al. Prevalence of HIV and hepatitis B virus co-infection in sub-Saharan Africa and the potential impact and program feasibility of hepatitis B surface antigen screening in resource-limited settings. JAIDS. 2015 Apr 15;68 S274-85.