No Impact of Hepatitis B Virus Infection on Early Mortality among HIV-infected Patients in Southern Africa

(Reply to Kouamé et al. Clin Infect Dis 2018)

Running title: Early mortality in HIV/HBV-coinfection

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DEAR EDITOR, We read with interest the informative article by Kouamé et al. describing mortality in HIV/Hepatitis B virus (HBV)-coinfected patients on antiretroviral therapy (ART) in West Africa (1). In line with studies from high-income countries, the results from the Temprano trial show that active HBV infection increases mortality among HIV-infected individuals (2). However, clinical trial data cannot be generalized to other clinical settings in sub-Saharan Africa (SSA), where resources for patient monitoring and management are limited and patient who initiate ART have often present with advanced stages of disease and comorbidities. Real-life data on the impact of HBV determinants on mortality from primary HIV care settings in SSA are scarce.

Since January 2013, we recruited consecutive HIV-infected patients at time of ART initiation into a prospective cohort in Lusaka, Zambia, and Ancuabe, a rural area in Mozambique, within the IeDEA collaboration (3). All patients were tested for the presence of chronic HBV infection, defined as a positive HBsAg rapid test (Determine®, Alere, Yavne, Israel), and HBV viral load (VL) was measured in HIV/HBV-coinfected individuals using quantitative real-time polymerase chain reaction (Roche, Indianapolis, USA) from plasma or dried blood spots (4). The systematic tracing of patients lost to follow-up (LTFU, ie. >3 months without a clinical visit) during the first year of ART was performed by phone calls or home visits. We used multivariable Cox proportional hazard methods to compare one-year mortality between HBV-infected and uninfected patients.

Fourteen percent (276/1,948) of the study participants were HBsAg-positive, of whom 137 (49.6%) had an HBV VL above 2000 IU/ml. Median age was 32 years (interquartile range [IQR] 26-40 years), median CD4 count 252 cells/µl (IQR 130-369), 38% had WHO stage 3 or 4, and 36% were female. There were no significant differences in CD4 cell counts, body mass index, age, and proportions with advanced HIV disease between groups. HBsAg-positive individuals were more likely to be male ($p<0.001$). After one year of ART, 129 (6.6%) patients had died, 113 (5.8%) were LTFU and 63 (3.2%) transferred or withdrew from the study. One-year mortality was 6.5% (95% confidence interval 5.4-7.8%) in HIV-infected patients, 8.7% (4.9-15.2%) in HIV/HBV-coinfected ones with HBV VL <2000 IU/ml, and 8.2% (95% CI 4.4-15.2%) in HIV/HBV-coinfected patients with HBV VL >2000 IU/ml. In multivariable analyses, HBsAg-positivity was not associated with mortality (Table).

As opposed to Kouamé et al., we did not find a significant difference in mortality between HIV-infected individuals with active HBV infection and HBV-uninfected ones in southern Africa. We provide robust mortality estimates from primary care clinical settings in SSA, as we limited the risk of under-estimating death rates by systematically tracing patients LTFU (5). Although the burden of liver-related mortality due to HBV infection is high in SSA (6), mortality of patients initiating ART outside of clinical trials remains driven by HIV-associated causes. As low-income countries are starting to implement the “treat all” strategy for HIV infection, the impact of HBV infection on

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clinical outcomes might become more evident. Therefore, long-term data from cohorts with intensive retention strategies will be crucial to inform monitoring of HIV/HBV-coinfected individuals in the near future.

Table. Risk factors for 1-year mortality, according to multivariable Cox proportional hazard regression analyses

	Deaths (%)	HR (95% CI)	p-value	aHR (95% CI)	p-value
HBsAg (%)					
negative	102/1673 (6.1)	Ref.		Ref.	
Positive	27/276 (9.8)	1.61 (1.05-2.45)	0.03	1.21 (0.74- 1.98)	0.45
WHO stage (%)					
1 or 2	50/1203 (4.2)	Ref.		Ref.	
3 or 4	79/732 (10.8)	2.69 (1.88-3.83)	<0.001	1.42 (0.93- 2.17)	0.10
CD4 cell count (%)					
≥200 cells/µl	41/973 (4.2)	Ref.		Ref.	
<200 cells/µl	71/640 (11.1)	2.76 (1.88-4.05)	<0.001	2.02 (1.33-3.07)	0.001
BMI (%)					
≥18.5 kg/m2	48/1275 (3.8)	Ref.		Ref.	
<18.5 kg/m^2	67/519 (12.9)	3.60 (2.49-5.22)	<0.001	2.66 (1.76- 4.02)	<0.001
Sex (%)					
Female	52/1240 (4.2)	Ref.		Ref.	
Male	77/708 (10.9)	2.63 (1.85-3.74)	<0.001	1.72 (1.13- 2.62)	0.01
Age (%)					
<30 years	43/772 (5.6)	Ref.		Ref.	
≥30 years	86/1176 (7.3)	1.29 (0.89-1.85)	0.18	0.97 (0.63- 1.50)	0.89

HBsAg: Hepatitis B surface antigen, WHO: World Health Organization, BMI: body mass index

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Conflict of Interest

All authors declare no conflict of interest.

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