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Title: Response to LIVint-15-00100

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List of abbreviations: APRI (AST-to-platelet ratio), HAT (HIV-associated thrombocytopenia), HIV (human immunodeficiency virus), HBV (hepatitis B virus), HCV (hepatitis C virus)

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Although AST-to-platelet ratio index (APRI) and FIB-4 have been compared with liver biopsy in patients with hepatitis C virus (HCV), hepatitis B virus (HBV), HIV/HCV co-infection, and HIV/HBV co-infection, Johannessen and Lemoine stress that they have not been validated in HIV mono-infected populations in SSA. However, this is unlikely to occur because liver biopsy does not play a role in HIV management and the procedure carries its own risks for complication. Clinicians using APRI and FIB-4 in this setting should be aware of this limitation and should interpret test results in the context of each patient's clinical scenario.

While it elevates APRI or FIB-4 scores, HIV-associated thrombocytopenia (HAT) does not fully explain the association of these markers with mortality. In our analysis, an elevated APRI score at start of antiretroviral therapy predicted all-cause mortality — even among patients with WHO clinical stage 1 or 2 and CD4+ counts >200 cells/mm²

who were unlikely to have HAT [1]. In a sensitivity analysis not included in the primary manuscript, we replaced each patient's platelet count with the median value of $238 \times 10^9/L$. As expected, the percentage with APRI ≥ 1.5 decreased from 5.1% to 1.9%; however, the association with mortality was similar (adjusted hazard ratio 1.62; 95% CI, 1.29-2.05).

In their letter to the editor, Johannessen and Lemoine speculate that the excess mortality experienced by patients with elevated APRI was unlikely a direct result of liver disease. Unfortunately, as is common in Africa, causes of death were not available in our large observational cohort, making this a difficult question to answer. However liver-related mortality was plausible, since HIV itself can interact with and infect multiple liver cell types [2,3] with potential clinical consequences [4] that are not fully understood, and chronic HBV, the leading cause of advanced liver disease in Africa, was not comprehensively screened for in our cohort. Further investigation is needed to better understand the contribution of liver disease to all-cause mortality among patients on HIV treatment.

Finally, it is important to note that APRI and FIB-4 independently predicted ART mortality in our analysis and may thus have a prognostic role in HIV care in SSA. As our colleagues suggest, further research is certainly needed to better define underlying biological mechanisms to determine how to incorporate their use at scale. Given the limited capacity for diagnosis and management of liver disease, however, such non-invasive metrics appear highly promising for future work.

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