

Chronic Hepatitis B Virus Coinfection Is Associated With Renal Impairment Among Zambian HIV-Infected Adults

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Among 6789 HIV-infected Zambian adults screened for hepatitis B virus (HBV) coinfection, estimated glomerular filtration rate (eGFR) was 50–90 mL/minute/1.73 m² in 17.6% and <50 mL/minute/1.73 m² in 2.5%. Human immunodeficiency virus/HBV coinfection was associated with eGFR <50 mL/minute/1.73 m² (adjusted odds ratio, 1.96 [95% confidence interval, 1.34–2.86]), adjusted for age, sex, CD4⁺ count, and World Health Organization disease stage.

Keywords. HIV/AIDS; hepatitis B virus; renal dysfunction; Africa; tenofovir.

Approximately 3 million human immunodeficiency virus (HIV)-infected individuals in sub-Saharan Africa (SSA) are chronically coinfecting with hepatitis B virus (HBV) [1]. HIV/HBV coinfection is associated with increased incidence of serum aminotransferase elevations, delayed CD4⁺ count recovery, and increased all-cause mortality during antiretroviral therapy (ART) compared with HIV alone [2, 3]. Another potential complication of HIV/HBV coinfection is renal dysfunction. HBV monoinfection causes various forms of kidney disease [4], but little is known about HBV-related kidney disease in

the setting of HIV, particularly in SSA. Comorbid kidney disease in the setting of HIV/HBV is challenging to manage clinically because the preferred antiretroviral agent in coinfection, tenofovir disoproxil fumarate (TDF), is potentially nephrotoxic [5]. We investigated the prevalence of renal impairment among HIV-infected Zambian adults with and without HBV coinfection at the time of enrollment in HIV care.

METHODS

In their 2010 HIV treatment guidelines, the Zambian Ministry of Health recommended routine HBV screening of patients at the time of linkage to care [6]. During 2011–2013, this guideline was implemented among public-sector HIV care and treatment facilities in Zambia's capital, Lusaka [7]. We analyzed data from HIV-infected adults who enrolled in clinics that had the highest uptake of HBV screening during that time period. HBV testing took place at a reference laboratory using an enzyme-linked immunoassay (Access 2 Analyzer, Beckman Coulter) for the hepatitis B surface antigen (HBsAg).

Other enrollment procedures included World Health Organization (WHO) AIDS clinical staging and the measurement of hemoglobin, CD4⁺ T-cell count, creatinine, and alanine aminotransferase (ALT). For this analysis, we defined an elevated ALT level as grade 2 or higher according to the Division of AIDS criteria [8]. Using a single creatinine measurement made at enrollment and prior to receipt of any antiretroviral drugs (Olympus AU400 Analyzer, Beckman Coulter), we calculated each patient's estimated glomerular filtration rate (eGFR) with the Chronic Kidney Disease Epidemiology Collaboration formula [9]. We defined tuberculosis coinfection as having been referred to HIV care during tuberculosis treatment.

Using logistic regression, we modeled the factors associated with being screened for HBV at enrollment. We then determined the proportion of HBV-screened patients with chronic HBV coinfection, defined by having a single positive HBsAg test. We compared patient characteristics using the Wilcoxon rank-sum test for continuous variables and the χ^2 test for categorical variables, according to HBV status. We categorized eGFR as normal (>90 mL/minute/1.73 m²) [10], mildly impaired (50–90 mL/minute/1.73 m²), and moderate/severely impaired (<50 mL/minute/1.73 m²) [11]. To explore the association between HBV coinfection and eGFR <50 mL/minute/1.73 m²—the degree of impairment where TDF is relatively contraindicated—we fit a multivariable logistic regression

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model considering HBV coinfection as the primary exposure variable and including possible confounders including age, sex, WHO clinical stage, and CD4⁺ count. Under a subgroup analysis of the HBV-coinfected individuals, we assessed whether an elevated ALT level, a surrogate of liver disease, was associated with an eGFR <50 mL/minute/1.73 m².

In a sensitivity analysis, we estimated GFR using the Modification of Diet in Renal Disease (MDRD) study equation [12]. Prior to use, the dataset was stripped of personal identifying information. We used Stata version 12 for analysis (StataCorp, College Station, Texas). The ethics committees of the University of Zambia and the University of North Carolina at Chapel Hill approved our use of programmatic data in this analysis.

RESULTS

From January 2011 to December 2013, within 7 Lusaka urban district facilities, 6839 of 13 138 (52.1%) HIV-infected adults were screened for HBV at enrollment into HIV care. Initial ALT level and CD4⁺ T-cell count were not associated with being screened for HBV coinfection (both $P > .05$), but age ≥ 30 years (adjusted odds ratio [AOR], 1.11; 95% confidence interval [CI], 1.03–1.20), male sex (AOR, 1.14; 95% CI, 1.06–1.23), and WHO stage 1 or 2 (AOR, 1.32; 95% CI, 1.22–1.43) were associated with an increased likelihood of HBsAg screening. Patients with tuberculosis were less likely to be tested for HBsAg (AOR, 0.70; 95% CI, .62–.80).

Among HBsAg-tested patients, 50 (0.7%) had unavailable results due to insufficient specimen volume, and the remaining patients (N = 6789) comprised the analysis cohort. Among the analysis cohort, the median age was 34 years (interquartile range [IQR], 28–40), 56% were women, and 799 (11.8%) were HBV coinfecting. Men were more likely than women to be HBV coinfecting (14.6% vs 9.5%, $P < .001$). HBV-coinfected patients had lower median CD4⁺ counts (194 vs 252 cells/ μ L) and were more likely to have tuberculosis coinfection (9.9% vs 6.9%) compared to those with HIV alone (all $P < .001$).

At enrollment, the median eGFR among those in the analysis cohort was 111 mL/minute/1.73 m² (IQR, 94–129); 1195 (17.6%) had an eGFR of 50–90 mL/minute/1.73 m², and 172 (2.5%) patients had an eGFR <50 mL/minute/1.73 m². Factors associated with eGFR <50 were increased age, male sex, reduced CD4⁺ count, WHO stage 3 or 4, and HBV coinfection (all $P < .001$; Table 1). Compared to those infected with HIV alone, HIV/HBV-coinfected patients had 2-fold odds of eGFR <50 mL/minute/1.73 m² (4.9% vs 2.2%, $P < .001$). After adjustment for age, sex, CD4⁺ count, and WHO stage, HBV coinfection remained associated with an eGFR <50 mL/minute/1.73 m² (AOR, 1.96; 95% CI, 1.34–2.86; Table 1).

Among HIV-HBV patients, 61 (7.7%) had an elevated ALT level at enrollment compared with 158 (2.7%) in the HIV-

Table 1. Risk Factors for Baseline Moderate/Severe Renal Dysfunction Among 6789 HIV-Infected Zambian Adults

Risk Factor	No. (%) With Renal Dysfunction	Bivariable Analysis, OR (95% CI)	Multivariable Analysis, OR (95% CI)
HBV coinfection			
No	133 (2.2)	1	1
Yes	39 (4.9)	2.26 (1.57–3.25)	1.96 (1.34–2.86)
Age, y			
16–39	80 (1.6)	1	1
40–49	54 (4.0)	2.59 (1.82–3.68)	2.32 (1.63–3.32)
≥ 50	38 (8.1)	5.41 (3.63–8.06)	5.01 (3.32–7.55)
Sex			
Female	71 (1.9)	1	1
Male	101 (3.4)	1.84 (1.36–2.51)	1.34 (.97–1.84)
WHO clinical stage			
1–2	62 (1.4)	1	1
3–4	110 (4.4)	3.16 (2.30–4.33)	2.07 (1.49–2.89)
CD4 ⁺ count, cells/ μ L			
≥ 200	24 (1.2)	1	1
50–200	47 (4.8)	3.81 (2.62–5.52)	2.89 (1.98–4.24)
<50	24 (7.7)	6.11 (3.99–9.36)	4.06 (2.60–6.34)

Estimated glomerular filtration rate of <50 mL/minute/1.73 m² was based on the Chronic Kidney Disease Epidemiology Collaboration formula.

Abbreviations: CI, confidence interval; HBV, hepatitis B virus; HIV, human immunodeficiency virus; OR, odds ratio; WHO, World Health Organization.

monoinfected group. Independent of age, sex, CD4⁺ count, and WHO stage, an elevated ALT level was associated with an eGFR <50 mL/minute/1.73 m² among HIV/HBV-coinfected patients (AOR, 4.03; 95% CI, 1.60–10.13). When we repeated analyses using the MDRD formula, the proportion of patients with renal impairment and the association between HBsAg and eGFR <50 mL/minute/1.73 m² was similar (Supplementary Table 1).

DISCUSSION

Among HIV-infected Zambian adults in this analysis, HBV coinfection was associated with increased odds of baseline eGFR <50 mL/minute/1.73 m², the threshold at which TDF use is discouraged by the WHO's HIV treatment guidelines. Interestingly, HIV/HBV-coinfected patients with elevated ALT levels appeared more likely to have an eGFR <50 mL/minute/1.73 m², suggesting a possible link between HBV-related liver disease activity and renal dysfunction.

Strengths of our study included its relatively large size and its external validity for primary care settings in SSA. We also note several limitations. Our study was limited by its cross-sectional nature. As our analysis relied on the initial eGFR at enrollment, we could not distinguish acute from chronic kidney disease. Although HBV is an established cause of renal disease, we were

unable to attribute causality to HBV coinfection. We adjusted models for factors known to be associated with impaired renal function in HIV patients, but unobserved factors may have resulted in residual confounding. In addition, urinalysis and/or renal biopsy data would have strengthened our study as it may have allowed us to differentiate HBV-associated nephropathy from HIV-associated kidney diseases; however, such diagnostic tests are limited in settings such as ours. In the period of our analysis, only 52% of HIV care enrollees were screened for HBsAg. Although a patient's initial ALT level was not associated, the probability of HBsAg testing increased with age, a risk factor for eGFR <50 mL/minute/1.73 m². Therefore, we could not exclude selection bias as a factor in the observed association between HBV and renal dysfunction.

Nevertheless, our results suggest that HBV coinfection may be an important risk factor for renal disease in HIV-infected individuals and that the degree of HBV-related liver disease may be associated with renal dysfunction. At HIV care enrollment, the likelihood of an eGFR <50 mL/minute/1.73 m² was doubled for patients with HIV/HBV coinfection, and was even higher in the subset of dually infected patients with an elevated ALT. These results support others in the medical literature. In France, among 137 HIV/HBV-coinfecting patients in a well-characterized cohort study, investigators demonstrated that significant hepatic fibrosis, based on the Fibrometer score, was associated with increased risk of developing renal impairment during ART (adjusted hazard ratio, 3.74; 95% CI, 1.57–8.92) [13]. However, among 114 HIV/HBV-coinfecting participants in a clinical trial, despite being more likely to experience an eGFR decline compared to those with HIV alone, HBV DNA level, hyaluronic acid, AST-to-platelet ratio, and FIB-4 were not associated with the likelihood of kidney disease development [14]. More investigation is needed to confirm our findings and to delineate which HBV-coinfecting patients are at highest risk to develop renal disease.

Although only 5% of HIV/HBV-coinfecting patients had an eGFR <50 mL/minute/1.73 m² in our study, an estimated 3 million dually infected patients live in resource-constrained settings. For this reason, guidelines are needed to address the management of this challenging clinical scenario. Whenever HIV infection is complicated by an eGFR <50 mL/minute/1.73 m², WHO and Zambian guidelines recommend non-TDF-containing regimens that include either lamivudine or emtricitabine [11]. This is suboptimal in HIV/HBV coinfection because resistant HBV viruses emerge when either is the sole HBV-active agent in the regimen. Dose adjustment of TDF is also possible, but this is unlikely to be a widely implementable strategy in overburdened ART programs where fixed-dose combination pills are predominant. Unfortunately, entecavir, a drug that is often used in such situations in upper-income settings, is rarely available in SSA.

In summary, in this Lusaka cohort, HBV coinfection was associated with having an eGFR <50 mL/minute/1.73 m², the threshold at which TDF should be withheld per guidelines. Additional investigation and clinical guidance is needed for resource-constrained settings with significant HIV/HBV burden.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (<http://cid.oxfordjournals.org>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Disclaimer. The funders had no role in study design, data collection and analysis, the decision to publish, or the preparation of the manuscript.

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