Renal outcomes in adults with HBV, HIV and HBV/HIV coinfection after 3 years of antiviral therapy in urban Tanzania

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Background: An enhanced understanding of renal outcomes in persons with chronic HBV, HIV, and HBV/HIV co-infection is needed to mitigate chronic kidney disease in regions where HBV and HIV are endemic.

Objectives: To investigate changes in estimated glomerular filtration rate (eGFR) in adults with HBV, HIV or HBV/HIV enrolled in a 3 year prospective cohort study of liver outcomes in Dar es Salaam, Tanzania and initiated on antiviral therapy.

Methods: We compared eGFR between and within groups over time using mixed-effects models.

Results: Four hundred and ninety-nine participants were included in the analysis (HBV: 164; HIV: 271; HBV/HIV: 64). Mean baseline eGFRs were 106.88, 106.03 and 107.18 mL/min/1.73 m^2, respectively. From baseline to Year 3, mean eGFR declined by 4.3 mL/min/1.73 m^2 (95% CI −9.3 to 0.7) and 3.7 (−7.8 to 0.5) in participants with HBV and HIV, respectively, and increased by 5.1 (−4.7 to 14.9) in those with HBV/HIV. In multivariable models, participants with HBV had lower eGFRs compared with those with HIV or HBV/HIV and, after adjusting for HBV DNA level and hepatitis B e antigen (HBeAg) status, significantly lower eGFRs than those with HBV/HIV at all follow-up visits.

Conclusions: In this Tanzanian cohort, coinfection with HBV/HIV did not appear to exacerbate renal dysfunction compared with those with either infection alone. Although overall changes in eGFR were small, persons with HBV experienced lower eGFRs throughout follow-up despite their younger age and similar baseline values. Longer-term studies are needed to evaluate continuing changes in eGFR and contributions from infection duration and other comorbidities.

Introduction

HIV continues to be a leading cause of morbidity and mortality in sub-Saharan Africa (SSA), affecting 25.6 million people in 2021.[1] Due to shared routes of transmission, chronic HBV is also highly prevalent, affecting approximately 9% of the general population and 15% of people with HIV (PWH).[2,3] Both HIV and HBV have been associated with a wide range of renal pathologies, and HBV/HIV coinfection may confer a greater risk of renal dysfunction than either infection alone.[4–7] In non-Tanzanian countries in SSA, the prevalence of chronic kidney disease (CKD) stage 2 or greater, i.e. estimated glomerular filtration rate (eGFR) < 90 mL/min/1.73 m^2, and CKD stage 3 or greater, i.e. eGFR

< 60 mL/min/1.73 m^2, have been estimated to be between 15.5% and 76.6% and 0.5% and 38.8%, respectively, in PWH.[8–15] Higher burdens of CKD have been reported in populations where HIV immunosuppression is more profound (e.g. treatment naive) or other competing risks for renal disease (e.g. hypertension, diabetes, schistosomiasis) exist.[16–18] In Tanzania, the prevalence of CKD stage 2 or greater and CKD stage 3 or greater have ranged from 29.2% (on ART) to 76.6% (not on ART) and 1.1% (on ART) to 21.1% (not on ART), respectively, in PWH.[19–21] The prevalence of CKD in persons with HBV in SSA and low- and middle-income countries (LMICs) has been less well characterized. A cross-sectional study of adults with chronic HBV in Cameroon found that 11.8% and 2.9% of participants had at least CKD stage 2

and 3, respectively, similar to reported rates from high-income countries (HICs).[22–25]

Causes of CKD in PWH include HIV-associated nephropathy (HIVAN), HIV immune complex kidney disease and comorbid conditions.[7] Genetic polymorphisms in the *APOL1* gene and ART-related nephrotoxicity such as proximal renal tubulopathy from tenofovir disoproxil fumarate or intratubular precipitation of PIs may further contribute to incident renal dysfunction.[26–31] HBV-related renal disease is largely attributed to the development of membranous nephropathy, membranoproliferative glomerulonephritis or polyarteritis nodosa, also reported in persons with HBV/HIV coinfection.[4,32] Although mechanisms of HBV-related glomerulopathy remain poorly understood, age at HBV acquisition has been identified as a major driver of HBV-associated glomerulonephritis.[33,34] HBV-related advanced liver disease may exacerbate renal dysfunction via haemodynamic changes and hepatorenal syndrome.[35] Additional epidemiological studies comparing renal outcomes in persons with HBV, HIV and HBV/HIV are needed to better understand the development and prevention of CKD in these populations.

In this study we examined changes in eGFR over 3 years in a longitudinal cohort of Tanzanian adults with HIV, HBV or HBV/HIV coinfection, and assessed differences across the three groups. We hypothesized that eGFR would be lower in persons with HBV/HIV due to more advanced immunosuppression and other virus-specific factors.

Methods

Study design and population

The analysis was conducted using longitudinal data collected from adults with HIV, HBV or HBV/HIV enrolled in a prospective cohort study of liver outcomes between September 2013 and December 2015 following written informed consent, which was subject to ethical reviews by the National Institute for Medical Research, Dar es Salaam, Tanzania, and Northwestern University.[36,37] Study participants were recruited from eight HIV Care and Treatment Clinics (CTCs) and an HBV clinic in Dar es Salaam. Study sites were supported by the Management and Development for Health (MDH) under the President's Emergency Plan for AIDS Relief. Inclusion criteria were: (i) adults at least 18 years of age; (ii) known HIV and HBV status; and (iii) antiretroviral (HIV, HBV/HIV) or antiviral (HBV) treatment naive. Chronic HBV was defined as hepatitis B surface antigen seropositivity on at least one occasion within the past 6 months. Participants were excluded if they were pregnant or had active TB, positive anti-hepatitis C antibody, known history of hepatocellular carcinoma, or clinical evidence of advanced liver disease (jaundice, hepatic encephalopathy, ascites, abnormal bleeding).[36]

Clinical protocols and participant follow-up

Participants were followed for 3 years after enrolment with annual study visits. Comprehensive history, examination and laboratory testing were performed at each visit. At the time of this study, clinical care of all PWH and HBV/HIV coinfection followed the 2013 WHO guidelines, and 2012 and revised 2015 Tanzanian National ART guidelines.[38–40] As part of routine clinical care, PWH and HBV/HIV were evaluated in the clinic monthly and received free refills and treatment-adherence counselling. PWH received semiannual clinical, immunological and virological monitoring and prophylaxis and treatment for opportunistic infections. Criteria for ART initiation included: (i) WHO HIV-related stages 3 (chronic HIV infection) and 4 (severely symptomatic HIV infection), regardless of

CD4+ T cell count; (ii) CD4+ T cell count < 500 cells/mm^3, regardless of WHO stage.[38–40] ART containing at least two anti-HBV agents, such as tenofovir disoproxil fumarate and lamivudine or emtricitabine, was recommended in all participants with HBV/HIV, regardless of CD4+ T cell count or WHO stage.[38–40] The recommended first-line ART regimen was the fixed-dose combination efavirenz/lamivudine/tenofovir disoproxil fumarate; alternative regimens included zidovudine/lamivudine/efavirenz, zidovudine/lamivudine/nevirapine and abacavir/lamivudine/lopinavir/ritonavir. Patients with chronic HBV were all initiated on lamivudine at enrolment according to local clinic protocols, as no national guidelines on HBV were available at the time. HBV DNA, HBeAg/anti-HBe and often ALT were also not routinely available and therefore not used to make any treatment decisions. Participants were followed monthly in clinic, and offered the option to switch to tenofovir disoproxil fumarate/emtricitabine when it became more widely available in Tanzania after 2014.

Laboratory tests performed for the study included: CD4+ T cell count (baseline only); HIV RNA quantification [Cobas Amplicor HIV-1 monitor test v2.0 (Roche Diagnostics Corp., Indianapolis, IN, USA; lower limit of detection 20 copies/mL)]; haemoglobin; platelets; AST; ALT; creatinine (Roche Cobas Integra 400+ Analyser); HBsAg (ABON HBsAg rapid test); HBeAg/anti-HBe (EIA assay Cobas e411); and HBV DNA (COBAS AmpliPrep TaqMan 96, v2.0; Roche Diagnostics GmbH, Mannheim, Germany; lower limit of detection 20 IU/mL). Testing was conducted at the MDH-supported Temeke Research Laboratory.

Outcomes and definitions

The primary outcome (eGFR) was determined using the CKD-EPI Creatinine Equation (2021) without race factor, as has been validated in similar studies.[41–43] For this analysis, we included any individual with at least one measure of serum creatinine at any point during four (baseline plus three follow-up) data collection visits from September 2013 to December 2018. CKD stages were defined using National Kidney Foundation eGFR thresholds.[41] Liver fibrosis was assessed using AST to platelet ratio index (APRI).[44] HIV and HBV virologic suppression were defined as HIV RNA <20 copies/mL and HBV DNA <20 IU/mL, the lower limits of detection, respectively. Deaths were recorded after notification by family members, friends or the participant-tracking team. Data collected to the point of withdrawal or last visit were included in analysis: by the study end, 47 participants had died (HBV: 4; HIV: 30; HBV/HIV: 13), 38 had withdrawn or moved away (HBV: 4; HIV: 26; HBV/HIV: 8) and 73 were lost to follow-up (HBV: 51; HIV: 18; HBV/HIV: 4).

Statistical analysis

Descriptive statistics were calculated to compare groups according to potential confounders. The nephro package was used for determination of CKD stages.[45] Mixed-effects models with random intercept for person were created to model eGFR over time and across groups and adjusted for potential confounders.[46] Models did not adjust for baseline eGFR as the primary goal was to detect any differences in eGFR over time across groups (Figure S1, available as Supplementary data at *JAC* Online). All models used second-degree polynomial terms for time, which was interacted with the group variable. In sensitivity analyses, we repeated models comparing eGFR across groups to include a random slope term for time. To facilitate comparisons, the emmeans package was used to calculate the marginal means per group at each timepoint and the differences across or within groups.[47] Multivariable analyses were conducted with complete cases then repeated with multiple imputation for missing values using the mice package[48] (see Supplementary Methods). HIV RNA and HBV DNA values <20 were imputed as 20 for the purpose of the analysis. Analyses were performed using R 4.3/RStudio.

Results

Five hundred and three participants were enrolled during the study period; four were missing all creatinine measures and excluded from final analysis. Of the remaining 499 participants, 164 (32.9%) had HBV, 271 (54.3%) had HIV and 64 (12.8%) had HBV/HIV (Table 1). All participants with HBV were initiated on lamivudine and 266 (98.2%) and 62 (96.9%) of participants with HIV and HBV/HIV, respectively, on a tenofovir disoproxil fumarate-containing regimen. Participants were followed for a median of 36.0 months (IQR 18.0–36.0) [(HBV: 35.0 (12.8–36.0); HIV: 36.0 (26.0–37.0); HIV/HBV: 34.5 (8.0–36.0); $P=0.009$]. Participants with HBV were younger [HBV: 33.16 years (SD 8.98); HIV: 38.73 (10.01); HBV/HIV: 37.14 (12.38); $P<0.001$], more likely to be male (HBV: 65.9%; HIV: 28.8%; HBV/HIV: 48.4%; $P<0.001$) and had a higher baseline BMI [HBV: 25.15 kg/m^2 (SD 4.81); HIV 22.73 (4.96); HBV/HIV 22.24 (4.23); $P<0.001$]. Baseline mean eGFR values were similar across groups [HBV: 106.88 mL/min/1.73 m^2 (SD 19.64); HIV: 106.03 (23.17); HBV/HIV: 107.18 (28.76); $P=0.898$]. Baseline mean APRI was highest in participants with HBV/HIV [HBV: 0.77 (SD 2.47), HIV: 0.35 (0.50), HBV/HIV: 1.00 (2.60); $P=0.008$].

Among participants with HIV (without or with HBV), baseline mean CD4 counts were similar [HIV: 237.16 cells/mm^3 (SD 170.63); HBV/HIV: 256.65 (207.41); $P=0.459$]. Participants with HIV alone had a higher baseline median HIV RNA [HIV: 5.0 log$_{10}$ copies/mL (IQR 4.6–5.4); HBV/HIV: 4.8 (3.8–5.4); $P=0.026$]. By Year 3, 148 (84.6%) and 24 (88.9%) of participants with HIV and HBV/HIV achieved HIV virological suppression, respectively. Among participants with HBV (without or with HIV), baseline median HBV DNA levels were similar [HBV: 2.8 log$_{10}$ copies/mL (IQR 1.8–3.7); HBV/HIV 2.8 (1.3–5.8); $P=0.254$]. By Year 3, 89 (87.3%) and 26 (100.0%) of participants with HBV and HBV/HIV achieved HBV virological suppression. Participants with HBV had lower HBeAg and higher anti-HBe positivity rates than those with coinfection at baseline and follow-up visits.

Comparison of eGFR across and within participant groups over time

Using mixed-effects models, we compared eGFR across groups at each timepoint, adjusting for baseline age, sex, BMI at time of visit, and baseline APRI (Figure 1). Participants with HBV had lower eGFR measures than those with HIV or HBV/HIV at all three follow-up visits; differences were statistically significant except at Year 3 when comparing participants with HIV with those with HBV (Table 2). Findings were similar using multiple imputation and complete case analysis, as well as with inclusion of a random slope term for time using multiple imputation (Table S1 and Figure S2).

Using similar methods, we compared eGFR within groups over time, adjusting for baseline age, sex, BMI at time of visit, and baseline APRI. From baseline to Year 3, mean eGFR declined by 4.3 mL/min/1.73 m^2 (95% CI −9.3 to 0.7) and 3.7 (−7.8 to 0.5) in participants with HBV and HIV, respectively, and increased by 5.1 (−4.7 to 14.9) in those with HBV/HIV; however, none of these changes were statistically significant (Table S2). Analogously, the proportion of participants with CKD stage 2 (eGFR < 60 mL/min/1.73 m^2) increased in the HBV and HIV groups (17.7%–25.0%

and 16.7%–26.8%, respectively) and decreased in the HBV/HIV group (12.5%–10.7%) from baseline to Year 3 (Table S3). In multivariable analyses of risk factors associated with eGFR, only older age was also associated with lower eGFR (beta −0.11; 95% CI −0.13 to −0.092; $P<0.0001$). Male sex (0.02; −0.01 to 0.058; $P=0.2298$), BMI (−0.02; −0.03 to 0; $P=0.0552$) and APRI (−0.01; −0.02 to 0; $P=0.0624$) were not associated with eGFR.

Subgroup analyses

We conducted further subgroup analyses to examine whether coinfection with HIV or HBV was associated with greater eGFR declines compared with either infection alone after adjusting for viral factors. In mixed-effect models comparing participants with HIV and HBV/HIV there were no significant differences in eGFR at any visit, adjusting for baseline HIV RNA (log-transformed), CD4 (square root), age, sex, BMI and APRI (Table S4). In the multivariable model using multiple imputation, older age was associated with lower eGFR (beta −0.12; 95% CI −0.14 to −0.10; $P<0.0001$) and higher CD4 count with higher eGFR (beta 0.00; 95% CI 0.00–0.01; $P=0.0479$). HIV RNA was not associated with eGFR.

When comparing participants with HBV and HBV/HIV, we observed significantly lower eGFRs among persons with HBV monoinfection at all visits, adjusting for baseline HBV DNA (log-transformed), HBeAg status, age, sex, BMI and APRI, corroborating findings in the overall model (Table S4). In the multivariable model using multiple imputation, older age was again associated with lower eGFR; HBV DNA and HBeAg status were not associated with eGFR.

Discussion

In this large Tanzanian cohort of adults with HIV, HBV or HBV/HIV, renal dysfunction was uncommon in all three groups and only small changes in eGFR were observed over the three years following antiviral initiation. Fewer than 4% had CKD stage 3 or greater at either baseline or Year 3 visits (Table S3). Contrary to expectations, HBV/HIV coinfection was not associated with any worsening of eGFR; in fact, slight improvements in eGFR were observed in persons with HIV and HBV/HIV, whereas continued declines were seen in those with HBV. These changes over time were not significant. Notably, persons with HBV had lower eGFRs compared with persons with HIV and HBV/HIV throughout follow-up.

In both persons with HIV and HBV/HIV, early improvements in eGFR were observed, followed by a return to baseline levels in those with HIV. We hypothesize that these initial improvements, also observed in other studies conducted in SSA,[19,49–52] were caused by decreased HIV viraemia and infection of renal epithelial cells, thereby reducing systemic and renal interstitial (as is present in HIVAN) inflammation.[53–58] Simultaneous declines in APRI following ART initiation, particularly among persons with HBV/HIV, suggest that decreased inflammation through HIV viraemia reduction may galvanize (some) recovery in organ function.[59,60] Some studies have observed progressive declines in eGFR despite ART; however, these may be indicative of more chronic damage from comorbidities, nephrotoxic drugs and intermittent viraemia.[26,61] Other explanations for the divergent results include differences in patient populations (LMIC versus HIC) and type of study (increased

Table 1. Characteristics over 3 years by group

Characteristic	All participants (N=499)	HBV (n=164)	HIV (n=271)	HBV/HIV (n=64)	P value
Age (years) at baseline, mean (SD)	36.70 (10.32)	33.16 (8.98)	38.73 (10.01)	37.14 (12.38)	<0.001
Male sex, **n** (%)	217 (43.5)	108 (65.9)	78 (28.8)	31 (48.4)	<0.001
BMI (kg/m²), mean (SD)					
Baseline	23.47 (4.96)	25.15 (4.81)	22.73 (4.96)	22.24 (4.23)	<0.001
Year 1	25.37 (5.04)	26.19 (4.88)	25.02 (5.14)	24.50 (4.76)	0.058
Year 2	25.68 (5.33)	25.88 (4.82)	25.83 (5.70)	24.16 (4.94)	0.236
Year 3	25.70 (5.07)	25.63 (4.59)	25.76 (5.32)	25.53 (5.27)	0.962
Estimates of renal function					
Creatinine (mg/dL), mean (SD)					
Baseline	0.83 (0.36)	0.88 (0.23)	0.79 (0.40)	0.84 (0.44)	0.033
Year 1	0.81 (0.23)	0.91 (0.21)	0.76 (0.22)	0.71 (0.23)	<0.001
Year 2	0.79 (0.23)	0.88 (0.21)	0.74 (0.22)	0.75 (0.27)	<0.001
Year 3	0.84 (0.21)	0.93 (0.20)	0.80 (0.21)	0.75 (0.14)	<0.001
CKD-EPI (2021) eGFR (mL/min/1.73 m²), mean (SD)					
Baseline	106.45 (22.85)	106.88 (19.64)	106.03 (23.17)	107.18 (28.76)	0.898
Year 1	105.43 (20.90)	102.43 (19.26)	105.12 (21.19)	115.71 (21.52)	0.001
Year 2	105.82 (21.02)	104.35 (20.24)	105.78 (21.57)	110.73 (20.62)	0.282
Year 3	100.97 (19.63)	100.01 (18.91)	100.36 (20.66)	108.45 (13.55)	0.106
CKD stage at baseline, **n** (%)					
1	397 (79.7)	133 (81.1)	214 (79.3)	50 (78.1)	0.324[a]
2	82 (16.5)	29 (17.7)	45 (16.7)	8 (12.5)	
3a	11 (2.2)	2 (1.2)	5 (1.9)	4 (6.2)	
3b	4 (0.8)	0 (0)	3 (1.1)	1 (1.6)	
4	3 (0.6)	0 (0)	2 (0.7)	1 (1.6)	
5	1 (0.2)	0 (0)	1 (0.4)	0 (0)	
APRI score					
Baseline	0.56 (1.71)	0.77 (2.47)	0.35 (0.50)	1.00 (2.60)	0.008
Year 1	0.33 (0.22)	0.34 (0.16)	0.32 (0.25)	0.33 (0.25)	0.657
Year 2	0.32 (0.26)	0.36 (0.32)	0.30 (0.23)	0.29 (0.18)	0.098
Year 3	0.31 (0.19)	0.33 (0.17)	0.30 (0.21)	0.29 (0.17)	0.271
HIV parameters					
HIV RNA (copies/mL), median (IQR)					
Baseline	90163.00 (27961.50–266943.00)	NA	96536.50 (35717.25–275191.75)	57035.00 (5689.00–249926.00)	0.026
Year 1	20.00 (20.00–58.00)	NA	20.00 (20.00–65.00)	20.00 (20.00–20.25)	0.217
Year 2	20.00 (20.00–20.00)	NA	20.00 (20.00–20.00)	20.00 (20.00–20.00)	0.350

Continued

Table 1. *Continued*

Characteristic	All participants (N=499)	HBV (n=164)	HIV (n=271)	HBV/HIV (n=64)	P value
Year 3	20.00 (20.00–20.00)	NA	20.00 (20.00–20.00)	20.00 (20.00–20.00)	0.552
HIV suppressed (≤20 copies/mL), *n* (%)					
Baseline	4 (1.3)	NA	1 (0.4)	3 (5.3)	0.024[a]
Year 1	155 (64.3)	NA	122 (61.9)	33 (75.0)	0.144
Year 2	170 (82.1)	NA	142 (81.1)	28 (87.5)	0.540
Year 3	172 (85.1)	NA	148 (84.6)	24 (88.9)	0.767[a]
CD4 count (cells/mm^3) at baseline, mean (SD)	240.53 (177.33)	NA	237.16 (170.63)	256.65 (207.41)	0.459
HBV parameters					
HBV DNA (IU/mL), median (IQR)					
Baseline	634.00 (38.25–10217.50)	613.00 (61.00–4567.00)	NA	655.00 (20.00–580006.50)	0.254
Year 1	20.00 (20.00–20.00)	20.00 (20.00–20.00)	NA	20.00 (20.00–20.00)	0.902
Year 2	20.00 (20.00–20.00)	20.00 (20.00–20.00)	NA	20.00 (20.00–20.00)	0.806
Year 3	20.00 (20.00–20.00)	20.00 (20.00–20.00)	NA	20.00 (20.00–20.00)	0.056
HBV suppressed (≤20 IU/mL), *n* (%)					
Baseline	50 (22.1)	33 (20.2)	NA	17 (27.0)	0.360
Year 1	138 (79.3)	104 (79.4)	NA	34 (79.1)	1
Year 2	120 (82.8)	91 (82.7)	NA	29 (82.9)	1
Year 3	115 (89.8)	89 (87.3)	NA	26 (100.0)	0.120[a]
HBeAg positive, *n* (%)					
Baseline	38 (16.7)	16 (9.8)	NA	22 (34.4)	<0.001
Year 1	15 (8.6)	4 (3.1)	NA	11 (25.0)	<0.001[a]
Year 2	12 (8.0)	6 (5.3)	NA	6 (16.2)	0.076[a]
Year 3	7 (5.3)	4 (3.8)	NA	3 (10.7)	0.335[a]
HBeAb positive, *n* (%)					
Baseline	213 (93.4)	162 (98.8)	NA	51 (79.7)	<0.001[a]
Year 1	161 (92.0)	127 (96.9)	NA	34 (77.3)	<0.001[a]
Year 2	144 (96.0)	113 (100.0)	NA	31 (83.8)	<0.001[a]
Year 3	124 (93.9)	104 (100.0)	NA	20 (71.4)	<0.001
Tenofovir disoproxil fumarate-containing regimen, *n* (%)					
Baseline	328 (65.7)	0 (0)	266 (98.2)	62 (96.9)	<0.001
Year 3	335 (98.2)	105 (100.0)	197 (97.0)	39 (100.0)	0.107[a]

NA=not applicable. Additional data on CKD stages by group at Years 1, 2 and 3 visits are available in Table S3.
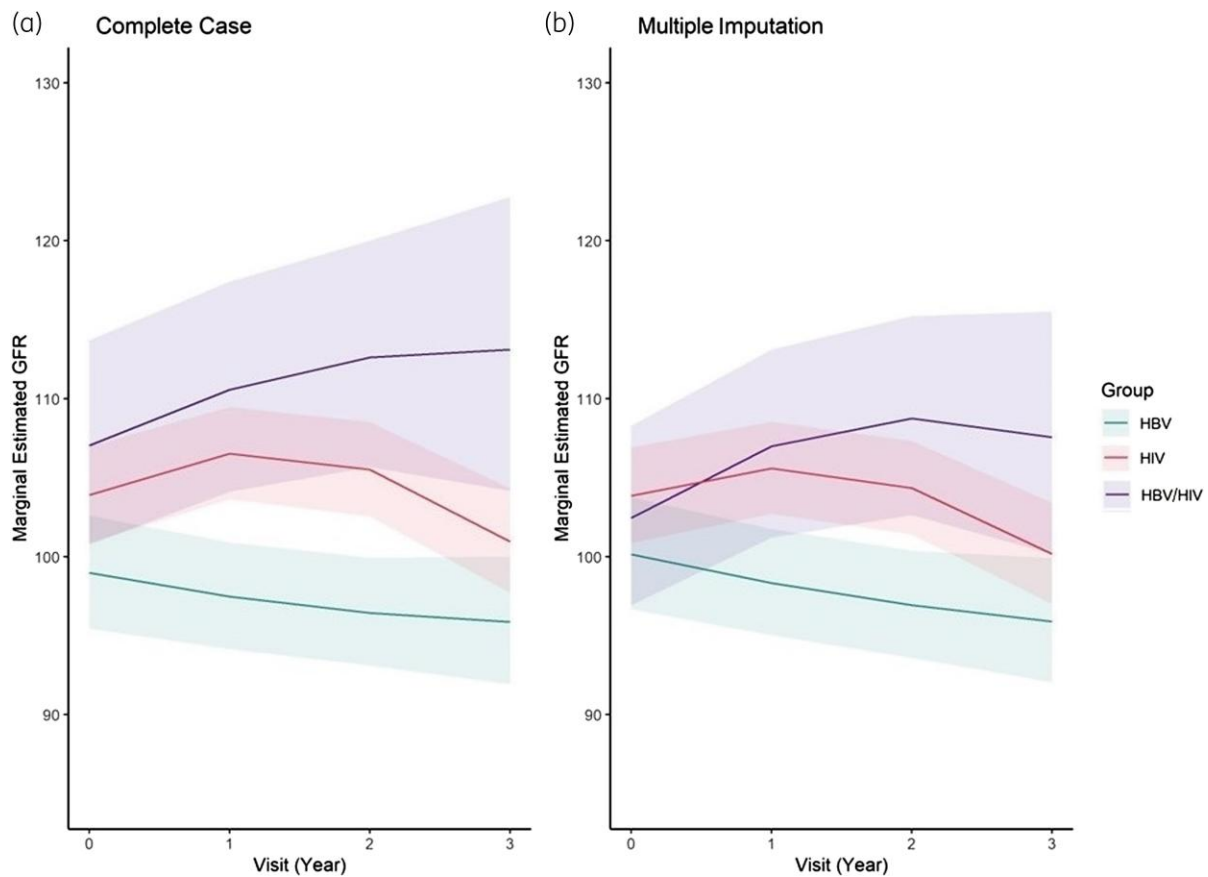[a]The chi-squared approximation may be incorrect due to missing data.

Figure 1. Mixed-effects models of eGFR over time by group (HBV, HIV and HBV/HIV) using complete case analysis (left) and multiple imputation (right). x-axis = time (years); y-axis = eGFR (mL/min/1.73 m^2). Lines (with ribbons) represent mean eGFR (with 95% CI) for the group and time after multivariable adjustment.

Table 2. Mixed-effects models of eGFR and differences (compared with participants with HBV) using multiple imputation ($n = 499$)

	Unadjusted eGFR (95% CI)	Adjusted eGFR (95% CI)	Difference (95% CI)	*P* value
Baseline				
HBV	104.4 (100.4–108.5)	100.2 (96.7–103.8)	reference	
HIV	102.3 (99.2–105.4)	103.9 (100.9–106.9)	3.7 (−2.1 to 9.5)	0.296
HBV/HIV	102.6 (96.4–109.2)	102.5 (96.9–108.3)	2.3 (−5.7 to 10.3)	0.779
Year 1				
HBV	102.1 (98.3–106.0)	98.3 (95.0–101.8)	reference	
HIV	103.2 (100.1–106.3)	105.6 (102.7–108.6)	7.3 (1.7–12.8)	0.006
HBV/HIV	107.0 (100.4–114.1)	107.0 (101.2–113.1)	8.7 (0.5–16.8)	0.035
Year 2				
HBV	100.5 (96.7–104.5)	96.9 (93.6–100.4)	reference	
HIV	101.6 (98.5–104.8)	104.3 (101.4–107.3)	7.4 (1.8–13.0)	0.005
HBV/HIV	108.3 (101.4–115.7)	108.8 (102.6–115.2)	11.8 (3.3–20.4)	0.004
Year 3				
HBV	99.5 (95.2–104.1)	95.9 (92.0–99.9)	reference	
HIV	97.6 (94.4–101.0)	100.2 (97.0–103.4)	4.3 (−2 to 10.5)	0.243
HBV/HIV	106.3 (98.1–115.1)	107.6 (100.2–115.5)	11.7 (1.4–22.0)	0.022

Unadjusted model adjusts for time, group and random intercept for person. Adjusted model additionally adjusts for age (baseline), sex (baseline), BMI (at time of visit) and APRI (baseline). Similar findings were observed using complete case analysis ($n = 440$).

representation of HIVAN in prospective cohorts initiating ART versus CKD due to other comorbidities in retrospective cohorts).[29]

Several studies have reported inverse associations between HIV viraemia and eGFR;[55,56,62,63] however, we did not observe an independent effect of HIV RNA level on eGFR in subgroup analysis of participants with HIV and HBV/HIV. A longitudinal cohort study conducted in the USA (Choi *et al*.[61]) similarly reported no association between viral load and eGFR in mixed-effects models adjusted for baseline age, sex, race, time-updated viral load, CD4 count, ART use and comorbidities. A consistent relationship between CD4 count and eGFR has also not been established across studies; although Choi *et al*. found no association between CD4 and eGFR, Reid *et al*.[49] and Mocroft *et al*.[5] observed greater increases in eGFR in participants with higher baseline CD4 and lower odds of CKD progression in participants with higher CD4 nadir, respectively. We identified a similar positive association between CD4 and eGFR in participants with HIV and HBV/HIV.

In contrast to previous reports where coinfection with HBV has been associated with greater risk of renal dysfunction than HIV alone, we found no significant differences in eGFR between persons with HIV and HBV/HIV. In a Zambian study of 6789 PWH (11.8% with HBV/HIV), coinfection with HBV was associated with greater odds of eGFR < 50 mL/min/1.73 m^2 [adjusted OR (AOR) 1.96; 95% CI 1.34–2.86] than HIV alone, adjusting for age, sex, CD4 count and WHO clinical stage.[6] Due to its cross-sectional design, the study was unable to assess changes in eGFR following ART initiation; data on viral load, infection duration and antiviral duration were also not available. Similarly, in a secondary analysis of 3441 PWH (3.3% with HBV/HIV) in Denmark, England and Australia, coinfection with HBV was associated with greater odds of progressive CKD (defined as end-stage renal disease, renal death, or 25% eGFR decline to a level or from a baseline of <60 mL/min/1.73 m^2) (AOR 2.26; 95% CI 1.15–4.44), adjusting for HIV parameters and antihypertensive and lipid-lowering therapies.[5] Due to a relatively small number of participants with HBV/HIV, however, they were unable to further investigate the role of HBV viraemia during follow-up (median 16 months and 7 years in the SMART and ESPRIT trials, respectively). Other prospective cohort studies of persons with HBV/HIV have also identified age (younger and older), male sex, higher BMI and previous AIDS-defining illness as risk factors for eGFR decline; in one of these studies, undetectable HBV DNA on treatment was found to be protective.[64,65]

Somewhat unexpectedly, in our study, participants with HBV had the largest, albeit small, declines in eGFR and significantly lower eGFRs at all follow-up visits compared with other groups, despite their younger age, higher baseline BMI and relatively short exposure to tenofovir disoproxil fumarate [median 18.7 months (IQR 15.1–22.6)]. Large cohort studies of persons with chronic HBV in HICs have observed comparable declines in eGFR following tenofovir disoproxil fumarate initiation,[66–71] and others comparing tenofovir disoproxil fumarate with no treatment reported no differences in rates of renal dysfunction over time.[24,25] Risk of eGFR loss despite HBV treatment has been associated with baseline renal dysfunction, age, diabetes, hypertension and diuretic use.[66,68–71] We similarly observed a significant inverse association between age and eGFR in participants with HBV monoinfection. HBV duration (which we were unable to measure) may be an important contributor to eGFR declines.

Early childhood acquisition is the most common route of HBV transmission in SSA, therefore it is likely that participants in our study had been living with HBV for some time and eGFR declines were more age-related. In a Cameroonian cross-sectional study of persons with chronic HBV (1.8% had HBV/HIV), in addition to older age and use of traditional herbs, longer duration of HBV was associated with eGFR < 60 mL/min/1.73 m^2 (AOR 2.00; 95% CI 1.04–3.88); coinfection with HIV was not included in multivariable analysis.[22]

Few studies (and to our knowledge none in SSA) have compared eGFR in persons with HBV monoinfection with those with HBV/HIV or HIV. In an Italian cohort of 34 participants with HBV and 44 with HBV/HIV who initiated tenofovir disoproxil fumarate and were followed for 5 years, a larger decline in eGFR (104–81 mL/min/1.73 m^2) was observed in those with HBV using generalized linear mixed models adjusted for exposure to nephrotoxic drugs (ACE inhibitors, cyclosporine and diuretics) and comorbidities (diabetes, hypertension, cirrhosis).[72] Age was not included in the model and may have been a confounder as median age was higher in the HBV group. In a French cohort of 50 participants with HBV, 194 with HIV, and 85 with HBV/HIV who initiated tenofovir disoproxil fumarate and were followed for 2.7 years, participants with HBV had lower eGFRs at baseline and last follow-up (93–87 mL/min/1.73 m^2).[73] Declines in eGFR were associated with older age, non-African origin, higher baseline eGFR and longer tenofovir disoproxil fumarate administration —but not type of infection. In subgroup analysis of participants with HBV and HBV/HIV, HBV DNA level > 2000 IU/mL was associated with eGFR decline. In our study, HBV DNA level and HBeAg positivity were not independently associated with changes in eGFR in participants with HBV and HBV/HIV, perhaps due to lack of power in the setting of study attrition over time.

To our knowledge, this is the largest longitudinal cohort study comparing renal outcomes among persons with HBV, HIV and HBV/HIV. As with other studies, we observed an inverse association between age and eGFR. In fact, this was the only risk factor that was independently associated with eGFR in our cohort across all models after adjusting for other confounders. Older age is a well-known risk factor for renal dysfunction observed in both LMICs and HICs and in populations with and without HIV.[6,13,30,52,74,75] Due to a lack of available data, we were unable to examine the role of other comorbidities associated with renal dysfunction (e.g. duration of HIV or HBV infection, diabetes, hypertension, hepatitis C coinfection, nephrotoxic medications and area deprivation index).[28,61,76,77] Treatment adherence was not measured in this study but was unlikely to have explained differences in eGFR between participants with HBV and HBV/HIV at follow-up due to comparable rates of HBV virological suppression (Table 1), even at Year 1, and adjustment for HBV DNA level in subgroup analysis (Table S4). We were unable to account for the effect of tenofovir disoproxil fumarate exposure on eGFR in HBV participants, as almost all switched to tenofovir disoproxil fumarate/emtricitabine by Year 3. Thus, not enough participants remained on a non-tenofovir disoproxil fumarate-containing regimen to serve as a control. In addition, we were unable to model eGFR before and after switch to tenofovir disoproxil fumarate among HBV participants using an interrupted time-series approach as this requires multiple pre-tenofovir disoproxil fumarate measurements, which were not available in our data.

Longer-term assessments are needed to examine the effects of tenofovir disoproxil fumarate and comorbidities on changes in renal function. Finally, we caution that changes in renal function may not be accurately reflected by serum creatinine and eGFR, especially in PWH.[78] Future studies including 24 h urine collection for creatinine clearance are needed to help differentiate clinically insignificant changes in serum creatinine and eGFR from true renal dysfunction.

Conclusions

In this Tanzanian cohort of persons with HIV, HBV and HBV/HIV, we observed no significant changes in eGFR following treatment initiation; furthermore, HBV/HIV coinfection did not adversely impact eGFR compared with either infection alone. The relatively lower eGFRs among persons with HBV monoinfection highlight a need for closer monitoring of renal function, as well as HBV parameters in this population, in addition to longer-term studies examining risk factors associated with renal dysfunction.

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Supplementary data

Figures S1 and S2 and Tables S1 to S4 are available as Supplementary data at *JAC* Online.

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