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# Renal health after long-term exposure to tenofovir disoproxil fumarate (TDF) in HIV/HBV positive adults in Ghana

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SUMMARY

*Objectives:* The study assessed markers of renal health in HIV/HBV co-infected patients receiving TDF-containing antiretroviral therapy in Ghana.
*Methods:* Urinary protein-to-creatinine ratio (uPCR) and albumin-to-protein ratio (uAPR) were measured cross-sectionally after a median of four years of TDF. At this time, alongside extensive laboratory testing, patients underwent evaluation of liver stiffness and blood pressure. The estimated glomerular filtration rate (eGFR) was measured longitudinally before and during TDF therapy.
*Results:* Among 101 participants (66% women, median age 44 years, median CD4 count 572 cells/mm$^3$) 21% and 17% had detectable HIV-1 RNA and HBV DNA, respectively. Overall 35% showed hypertension, 6% diabetes, 7% liver stiffness indicative of cirrhosis, and 18% urinary excretion of *Schistosoma* antigen. Tubular proteinuria occurred in 16% of patients and was independently predicted by female gender and hypertension. The eGFR declined by median 1.8 ml/min/year during TDF exposure (IQR −4.4, −0.0); more pronounced declines (≥5 ml/min/year) occurred in 22% of patients and were associated with receiving ritonavir-boosted lopinavir rather than efavirenz. HBV DNA, HBeAg, transaminases, and liver stiffness were not predictive of renal function abnormalities.
*Conclusions:* The findings mandate improved diagnosis and management of hypertension and suggest targeted laboratory monitoring of patients receiving TDF alongside a booster in sub-Saharan Africa.


## Introduction

Tenofovir disoproxil fumarate (TDF), the prodrug of the nucleotide analogue reverse transcriptase inhibitor (NRTI) tenofovir, is active against both HIV and HBV. TDF use as part of antiretroviral therapy (ART) carries a risk of proximal tubular dysfunction and declining glomerular filtration rate (GFR),[1–3] and monitoring of renal function is recommended during treatment.[4,5] The risk is related to both level and length of TDF exposure and is enhanced by co-administration of pharmacological boosters (e.g., ritonavir), low body weight, and pre-existing chronic kidney disease (CKD).[6–10] Whilst TDF discontinuation is generally associated with improved renal function, longer exposure and lower GFR at TDF interruption predict a reduced likelihood of GFR recovery.[6]

Whilst in North America and Western Europe tenofovir alafenamide fumarate (TAF) provides a recommended alternative formulation with a reduced potential for renal toxicity,[4,5] TAF is not currently available in resource-limited settings. The World Health Organisation (WHO) recommends TDF as the preferred NRTI for the treatment of HIV and HIV/HBV positive individuals in sub-Saharan Africa (SSA).[11] There are limited data on the occurrence of TDF-related renal adverse events in African populations and only a few reported long-term data. A study from Malawi, South Africa, and Zimbabwe showed similar rates of renal events over 196 weeks in patients randomised to either TDF plus emtricitabine

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(FTC) or zidovudine (ZDV) plus lamivudine (3TC), each in combination with efavirenz (EFV).[12] A cross-sectional study among HIV-positive subjects who had received ART for a median of 9.3 years in Uganda similarly found no differences in renal function when comparing regimens with and without TDF. [13] Neither study assessed the influence of concomitant use of ritonavir-boosted protease inhibitors (PI/r) or HBV co-infection on renal health. Short-term studies reported an increased risk of renal abnormalities with concomitant use of TDF and PI/r in SSA. In South Africa, HIV-1 positive adults on TDF experienced a small but significant decline in eGFR over a median of 13 months, and the decline was larger with concomitant PI use, older age, weight $<60$ kg, lower baseline eGFR, and CD4 counts $<200$ cells/mm$^3$.[9] In women receiving TDF in combination with either lopinavir/ritonavir (LPV/r) or nevirapine (NVP), renal events were predicted by LPV/r use, baseline HIV-1 RNA load, and baseline eGFR.[7]

By 2030, the number of patients requiring second-line ART in SSA is estimated to exceed 4 million, and an increasing number is likely to start therapy with PI/r.[14] At the same time, improved survival among people living with HIV in SSA is unmasking a substantial burden of co-morbidities, including HBV co-infection.[15] Limited data suggest that chronic hepatitis B may worsen renal outcomes. In one study in Zambia, HBV co-infection nearly doubled the odds of a reduced eGFR after adjusting for several factors, and the risk was higher among patients with raised serum transaminases.[16] Whilst the observation suggests a link between HBV disease activity and risk of renal dysfunction, published evidence has not been consistent.[17]

The aim of this study was to evaluate the renal function of HIV/HBV co-infected individuals receiving long-term TDF-containing ART in Ghana, integrating cross-sectionally measured tubular proteinuria (TuPr) and prospectively measured eGFR with markers of HIV and HBV status, and analysing the contributing role of PI/r use, hypertension, and diabetes.

## Methods

### *Setting*

Eligible HIV/HBV co-infected positive adults ($\geq 18$ years) were drawn from the HEPIK (Hepatitis B Infection in Kumasi) prospective observational cohort based at the Komfo Anokye Teaching Hospital (KATH) in Kumasi, Ghana.[18,19] The cohort was established in 2010. Study visits took place at least once a year when participants underwent clinical assessment and sample collection. The last study visit occurred in November 2015. At study entry, upon detection of HBV co-infection, patients introduced TDF; subsequent management was at the discretion of the treating clinician. Between 2010 and 2015, monitoring for HIV-positive patients at KATH comprised routine measurements of haemoglobin, serum hepatic transaminases, and CD4 cell counts, and sporadic measurements of serum creatinine. Urine dipstick analysis, measurement of blood pressure in asymptomatic patients, and HIV/HBV virological monitoring were not part of routine care. No patient had access to TAF and TAF remains unavailable in Ghana in 2018. Ethical approval was granted by the Kwame Nkrumah University of Science and Technology, Ghana; all patients gave written informed consent.

### *Study population*

The analysis comprised HEPIK participants who at the last study visit (November 2015) were on stable TDF-containing ART. At this time, patients underwent study-related clinical assessment and sample collection. Adherence to ART was self-reported through an ordinal visual scale graded from 0 to 100%, in 10% increments. Transient elastography was performed using Fibroscan (Ecosens, France) and interpretative cut-offs applied as previously reported.[19,20] Blood pressure (BP) was measured with a manual sphygmomanometer; abnormal findings were confirmed after the patient had rested for $\geq 20$ min. Hypertension was graded as 1 (systolic 140–159 or diastolic 90–99 mmHg), 2 (systolic 160–179 or diastolic 100–109 mmHg) and 3 (systolic $\geq 180$ or diastolic $\geq 110$ mmHg).[21] Systolic BP $<140$ and/or diastolic BP $<90$ mmHg on antihypertensive therapy was scored as grade 1. Diabetes was defined by glycated haemoglobin (HbA1c) $\geq 48$ mmol/mol or receiving antidiabetic therapy.

### *Laboratory tests*

Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), haemoglobin, and CD4 cell counts were measured at the KATH diagnostic laboratory. Laboratory reference ranges are shown in *Supplementary Table 1*. Urine samples underwent dipstick analysis for proteinuria, haematuria, and glycosuria with Medi-Test Combi 5S (BHR Pharmaceuticals, Nuneaton, UK), and testing for *Schistosoma* circulating cathodic antigen (Ag) with the Urine-CCA Cassette test (Rapid Medical Diagnostics, Pretoria, South Africa).[22] Plasma was separated from whole blood in EDTA within one hour of collection and stored immediately at $-80$ °C. Frozen aliquots of whole EDTA blood, plasma, serum, and urine were shipped to the UK for further testing. In the UK, plasma HIV-1 RNA and HBV DNA were quantified by the RealTime HIV-1 and HBV assays (Abbott Diagnostics, Maidenhead, UK), as previously described.[19] Hepatitis B e antigen (HBeAg) was measured by Architect (Abbott Diagnostics). Creatinine, urinary protein-to-creatinine ratio (uPCR), urinary albumin-to-creatinine ratio (uACR, performed if uPCR $>20$ mg/mmol), and HbA1c were measured in the accredited diagnostic laboratory of the Royal Liverpool University Hospital, Liverpool, UK. TuPr was defined as uPCR $>20$ mg/mmol with uACR/uPCR ratio $<0.4$;[23] significant TuPr was defined by uPCR $>30$ mg/mmol with uACR/uPCR ratio $<0.4$. The eGFR was calculated using the CKD epidemiology collaboration-derived equation (CKD-EPI); the ethnicity factor was applied (x1.21).[24] Reduction in eGFR was classed as grade 2, 3, or 4 based on readings of 60–89, 30–59, and $<30$ ml/min/1.73 m$^2$, respectively.[21] In addition to blood samples collected in November 2015, stored samples collected between 2010 and 2015 were retrieved and serum creatinine was measured retrospectively to calculate changes in eGFR over time. A rapid eGFR decline (RD-eGFR) was defined as a mean decline $>5$ ml/min/1.73 m$^2$/year.[10]

### *Analysis*

Patients' characteristics according to the presence or absence of TuPr or RD-eGFR were compared by the Fisher's, Chi-squared, or Mann–Whitney–Wilcoxon test, as appropriate. Factors associated with TuPr or RD-eGFR and factors associated with changes in eGFR over time were investigated in logistic and linear regression analyses, respectively. Each multivariable model explored factors associated with renal outcomes by stepwise selection. TuPr was not included in the analysis of factor associated with eGFR variation and vice versa, as potential collinearity between the two could not be excluded. This approach resulted in the inclusion of gender and hypertension for TuPr; receipt of LPV/r and CD4 cell count for changes in eGFR; and receipt of LPV/r, duration of HIV diagnosis, and CD4 cell count for RD-eGFR. The robustness of the results was investigated in models that serially added all variables showing $p<0.2$ in the univariate analysis, including *Schistosoma* Ag test, liver stiffness, AST, and HbA1c for TuPr; ALT for changes in eGFR; and adherence for RD-eGFR. Haemoglobin was not included in the multivariable model for RD-eGFR as potentially part of the casual

**Table 1**
Characteristics of HIV/HBV positive patients with long-term TDF exposure according to the detection of tubular proteinuria (TuPr; $n = 101$ evaluated) and rapidly declining estimated glomerular filtration rate (RD-eGFR; $n = 97$ evaluated).[a]

| | | Total $N = 101$ | With TuPr $N = 16$ | Without TuPr $N = 85$ | $p$ | With RD-eGFR $N = 21$ | Without RD-eGFR $N = 76$ | $p$ |
|---|---|---|---|---|---|---|---|---|
| Female gender, *n* (%) | | 67 (66.3) | 15 (93.8) | 52 (61.2) | 0.01 | 16 (76.2) | 48 (63.2) | 0.31 |
| Age, median years (IQR) | | 44 (39, 48) | 47 (38, 52) | 44 (39, 48) | 0.63 | 44 (40, 47) | 45 (39, 48) | 0.45 |
| BMI, median kg/m$^2$ (IQR) | | 23.5 (20.4, 27.3) | 23.4 (20.7, 28.1) | 23.5 (20.4, 27.1) | 0.84 | 22.6 (20.8, 28.6) | 23.3 (20.1, 27.1) | 0.54 |
| Duration HIV diagnosis, median years (IQR) | | 8.3 (6.6, 10.2) | 8.2 (6.6, 9.4) | 8.4 (6.6, 10.3) | 0.96 | 7.5 (5.3, 9.4) | 8.4 (6.9, 10.3) | 0.16 |
| ART duration, median years (IQR) | | 7.9 (6.0, 9.2) | 7.9 (5.2, 8.8) | 7.8 (6.3, 9.3) | 0.71 | 7.4 (5.1, 8.8) | 7.9 (6.2, 9.2) | 0.40 |
| TDF duration, median years (IQR) | | 4.0 (3.8, 4.1) | 4.0 (3.8, 4.1) | 4.0 (3.8, 4.1) | 0.45 | 4.0 (3.8, 4.2) | 4.0 (3.8, 4.1) | 0.99 |
| Prior ZDV, *n* (%) | | 89 (88.1) | 14 (87.5) | 75 (88.2) | 1.00 | 19 (90.5) | 67 (88.2) | 1.00 |
| Prior d4T, *n* (%) | | 48 (47.5) | 8 (50.0) | 40 (47.1) | 1.00 | 7 (33.3) | 39 (51.3) | 0.22 |
| Receiving EFV, *n* (%) | | 87 (86.1) | 15 (93.8) | 72 (84.7) | 0.50 | 12 (57.1) | 72 (94.7) | < 0.001 |
| Receiving NVP, *n* (%) | | 4 (4.0) | 0 (0) | 4 (4.7) | 1.00 | 4 (19.1) | 0 (0) | 0.02 |
| Receiving LPV/r, *n* (%) | | 10 (9.9) | 1 (6.3) | 9 (10.6) | 1.00 | 5 (23.8) | 4 (5.3) | 0.02 |
| Adherence ≥ 90%, *n* (%) | | 86 (86.9) | 15 (93.8) | 71 (83.5) | 0.69 | 16 (76.2) | 66 (86.8) | 0.15 |
| Haemoglobin, median g/dl (IQR) | | 13.2 (11.6, 14.6) | 12.0 (11.1, 14.4) | 13.2 (11.7, 14.7) | 0.34 | 11.7 (11.4, 13.7) | 13.4 (11.8, 14.7) | 0.07 |
| CD4 count, median cells/mm$^3$ (IQR) | | 572 (383, 716) | 593 (302, 639) | 565 (391, 717) | 0.47 | 572 (391, 749) | 559 (370, 711) | 0.78 |
| HIV-1 RNA > 40 copies/ml, *n* (%) | | 21 (20.8) | 4 (25.0) | 17 (20.0) | 0.74 | 6 (28.6) | 14 (18.4) | 0.36 |
| HIV-1 RNA > 1000 copies/ml, *n* (%) | | 14 (13.9) | 3 (18.8) | 11 (12.9) | 0.69 | 2 (9.5) | 12 (15.8) | 0.73 |
| HBV DNA > 15 IU/ml, *n* (%) | | 15 (14.9) | 2 (12.5) | 13 (15.3) | 1.00 | 3 (14.3) | 11 (14.7) | 1.00 |
| HBV DNA > 2000 IU/ml, *n* (%) | | 6 (5.9) | 1 (6.3) | 5 (5.9) | 1.00 | 3 (14.3) | 3 (4.0) | 0.11 |
| Liver stiffness, median kPa (IQR) | | 4.6 (3.8, 5.8) | 4.8 (3.1, 5.5) | 4.5 (3.8, 5.9) | 0.86 | 4.6 (3.9, 6.1) | 4.6 (3.8, 5.7) | 0.87 |
| Liver stiffness kPa > 9.4, *n* (%) | | 7 (6.9) | 2 (12.5) | 5 (5.9) | 0.29 | 1 (4.8) | 5 (6.6) | 1.00 |
| AST, median IU/l (IQR) | | 31 (23, 38) | 31 (22, 39) | 27 (25, 35) | 0.83 | 30 (24, 37) | 31 (23, 39) | 0.98 |
| ALT, median IU/l (IQR) | | 24 (18, 33) | 23 (16, 30) | 24 (18, 36) | 0.42 | 26 (17, 32) | 24 (18, 36) | 0.89 |
| HBeAg positive, *n* (%) | | 11 (10.9) | 1 (6.3) | 10 (11.8) | 0.63 | 3 (14.3) | 8 (10.5) | 0.61 |
| Systolic BP, median mmHg (IQR) | | 122 (112, 145) | 148 (122, 160) | 121 (110, 137) | < 0.01 | 126 (118, 130) | 122 (110, 147) | 0.64 |
| Diastolic BP, median mmHg (IQR) | | 80 (71, 90) | 90 (77, 110) | 80 (70, 88) | 0.02 | 78 (74, 86) | 80 (70, 93) | 0.90 |
| Hypertension, *n* (%) | Any grade | 35 (35.0) | 10 (62.5) | 25 (29.4) | 0.02 | 6 (28.6) | 28 (36.8) | 0.61 |
| | Grade 1 | 13 (13.0)[b] | 2 (12.5) | 11 (12.9) | – | 2 (9.5) | 11 (14.5) | – |
| | Grade 2 | 12 (12.0) | 3 (18.8) | 9 (10.6) | – | 2 (9.5) | 10 (13.2) | – |
| | Grade 3 | 10 (10.0) | 5 (31.3) | 5 (5.9) | – | 2 (9.5) | 7 (9.2) | – |
| | NA | 1 (1.0) | 0 (0) | 1 (1.2) | – | 0 (0) | 0 (0) | – |
| Hb1Ac, median mmol/mol (IQR) | | 33 (31–38) | 35 (31, 38) | 33 (31, 38) | 0.55 | 34 (32, 39) | 33 (30, 38) | 0.15 |
| Diabetes, *n* (%) | | 6 (5.9)[c] | 2 (12.5) | 4 (4.7) | 0.24 | 2 (9.5) | 4 (5.3) | 0.61 |
| *Schistosoma* Ag positive, *n* (%) | | 18 (17.8) | 5 (31.3) | 13 (15.3) | 0.16 | 5 (23.8) | 12 (15.8) | 0.52 |

[a] TuPr proteinuria was defined as uPCR ≥ 20 mg/mmol and uACR/uPCR < 0.4; RD-eGFR was defined as ≥ 5 ml/min eGFR decline per year.
[b] Comprising 4 subjects with normal readings while on anti-hypertensive medication.
[c] Comprising 2 subjects with normal readings while on oral hypoglycaemic medication. uPCR = urinary protein/creatinine ratio; uACR = urinary albumin/creatinine ratio; IQR = interquartile range; BMI = body mass index; ART = antiretroviral therapy; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine; d4T = stavudine; EFV = efavirenz; NVP = nevirapine; LPV/r = ritonavir-boosted lopinavir; AST = aspartate transaminase; ALT = alanine transaminase; BP = blood pressure; NA = not available; Hb1Ac = glycated haemoglobin; Ag = Antigen.

pathway of the outcome. The distribution of residuals was assessed for each linear regression, and indicated a good model fit. Performance of dipstick proteinuria (≥ 0.3 g/l), glycosuria (1.1 mmol/l) and haematuria (≥ 10 cells/μl) as predictors of TuPr was estimated through a receiver operating characteristic (ROC) analysis. Analyses were performed with STATA v.14.

## Results

### *Characteristics of the study population*

The study population comprised 101 subjects that had received TDF for a median of 4.0 years (IQR 3.8–4.1) (Table 1). All subjects were also receiving 3TC and most were receiving EFV (87/101, 86.1%). Ten (9.9%) were on LPV/r, having received the PI/r for a median of 4.4 years (IQR 3.7–5.5). Plasma HIV-1 RNA was detected in 21/101 (20.8%) subjects at median levels of 4.2 $\log_{10}$ copies/ml (IQR 2.1–5.1). HBV DNA was detected in 15/101 (14.9%) subjects at median levels of 2.7 $\log_{10}$ IU/ml (IQR 1.7–3.8). Hypertension of any grade was diagnosed in 35/100 (35.0%) subjects. There were 9/101 (8.9%) patients on anti-hypertensive drugs (nifedipine, losartan, bendroflumethiazide) and five of these had elevated blood pressure of grade 1 ($n = 1$), 2 ($n = 3$), or 3 ($n = 1$). Diabetes was diagnosed in 6/101 (5.9%) subjects. There were 3/101 (3.0%) patients on oral hypoglycaemic drugs (metformin, glibenclamide) and one of these had abnormal Hb1Ac levels (80 mmol/mol). The urinary *Schistosoma* Ag was reactive in 18/101 (17.8%) subjects. None of the participants was taking other regular medications.

### *Markers of renal health*

#### *Tubular proteinuria*

The uPCR was median 13 mg/mmol (IQR 13–20) and was > 20 mg/mmol in 28/101 (27.7%) patients and > 50 mg/mmol in 13/101 (12.9%) patients (Table 2). Among subjects with uPCR > 20 mg/mmol, the uACR was median 0.33 mg/mmol (IQR 0.17–0.49). TuPr was diagnosed in 16/101 (15.8%) subjects, including 9/101 (8.9%) with significant TuPr (*Supplementary Table 2*). TuPr was significantly more prevalent in women and patients with hypertension and the association was confirmed after adjustment (Table 3). The univariate analysis showed trends for an association between TuPr and higher liver stiffness, higher HbA1c levels, and a positive *Schistosoma* Ag test. Separate models adjusting for these variables confirmed that gender and hypertension were each independently associated with TuPr (*Supplementary Table 3*).

#### *Changes in eGFR over time*

At the last study visit, the eGFR was median 103 ml/min/1.73 m$^2$ (IQR 92–116) and was < 90 ml/min in 22/101 (21.8%) subjects, including 4/101 (4.0%) subjects with levels < 30 ml/min (Table 2). The analysis of changes in eGFR over time comprised 90 subjects with data from three time points (T0, T1, T2) and seven subjects with data from two time points

**Table 2**
Relationship between markers of renal health in HIV/HBV positive patients with long-term TDF exposure.

| | | Total $N=101$ | With TuPr $N=16$ | Without TuPr $N=85$ | $p$ | With RD-eGFR $N=21$ | Without RD-eGFR $N=76$ | $p$ |
|---|---|---|---|---|---|---|---|---|
| Serum creatinine | Median µmol/l (IQR) | 78 (66, 87) | 74 (64, 81) | 79 (67, 90) | 0.11 | 82 (75, 103) | 77 (64, 85) | – |
| eGFR | Median ml/min (IQR) | 103 (92, 116) | 105 (88, 124) | 103 (93, 116) | 0.97 | 92.3 (81.3, 105) | 107 (94.1, 117) | – |
| ≥90 ml/min | *n* (%) | 79 (78.2) | 12 (75.0) | 67 (78.8) | 0.75 | 12 (57.1) | 63 (82.9) | – |
| 60–89 ml/min | *n* (%) | 18 (17.8) | 3 (18.8) | 15 (17.7) | | 7 (33.3) | 11 (14.5) | – |
| 30–60 ml/min | *n* (%) | 4 (4.0) | 1 (6.3) | 3 (3.5) | | 2 (9.5) | 2 (2.6) | – |
| Change over time | Median ml/min (IQR) | −1.8 (−4.4, −0.0) | −2.4 (−5.8, −1.0) | −1.7 (−4.3, +0.3) | 0.49 | −7.12 (−7.48, −5.79) | −1.20 (−2.82, +0.92) | – |
| Rapid decline ($n=97$) | *n* (%) | 21 (21.6) | 4 (25.0) | 17 (20.0) | 0.12 | 21 (100) | 0 (0) | – |
| uPCR | Median mg/mmol (IQR) | 13 (10, 20) | 32 (24, 56) | 12 (9, 17) | – | 13 (9, 18) | 14 (10, 21) | 0.30 |
| >20 mg/mmol | *n* (%) | 28 (27.7) | 16 (100) | 12 (14.1) | – | 5 (23.8) | 21 (27.6) | 1.00 |
| ≥50 mg/mmol | *n* (%) | 13 (12.9) | 5 (31.3) | 8 (9.4) | – | 3 (14.3) | 10 (13.2) | 1.00 |
| Tubular proteinuria | *n* (%) | 16 (15.8) | 16 (100) | 0 (0) | – | 4 (19.1) | 10 (13.2) | 0.50 |
| Dipstick protein | *n* (%) | 15 (14.9) | 4 (25.0) | 11 (12.9) | 0.25 | 3 (14.3) | 12 (15.8) | 1.00 |
| Dipstick RBC | *n* (%) | 12 (11.9) | 5 (31.3) | 7 (8.2) | 0.02 | 3 (14.3) | 8 (10.5) | 0.70 |
| Dipstick glucose | *n* (%) | 17 (16.8) | 4 (25.0) | 13 (15.3) | 0.46 | 5 (23.8) | 11 (14.5) | 0.33 |

TuPr = tubular proteinuria; RD-eGFR = rapid declining estimated glomerular filtration rate; IQR = inter-quartile range; uPCR = urinary protein/creatinine ratio; RBC = red blood cells.

**Table 3**
Logistic regression analysis of factors associated with TuPr and RD-eGFR in HIV/HBV positive patients with long-term TDF exposure.[a]

| | | Factors associated with TuPr | | | | | | Factors associated with RD-eGFR | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Univariate analysis | | | Multivariable analysis[a] | | | Univariate analysis | | | Multivariable analysis[a] | | |
| | | OR | 95% CI | $p$ | OR | 95% CI | $p$ | OR | 95% CI | $p$ | OR | 95% CI | $p$ |
| Gender | Female vs. male | 9.52 | 1.20, 75.5 | 0.03 | 9.65 | 1.19, 78.5 | 0.03 | 1.87 | 0.62, 5.65 | 0.27 | | | |
| Age | Per 5 years older | 1.14 | 0.81, 1.60 | 0.46 | | | | 0.88 | 0.64, 1.21 | 0.43 | | | |
| BMI | Per kg/m$^2$ higher | 1.00 | 0.90, 1.12 | 0.95 | | | | 1.03 | 0.94, 1.14 | 0.50 | | | |
| Duration HIV diagnosis | Per year longer | 0.96 | 0.77, 1.21 | 0.74 | | | | 0.85 | 0.69, 1.06 | 0.15 | 0.83 | 0.66, 1.05 | 0.12 |
| ART duration | Per year longer | 0.93 | 0.74, 1.17 | 0.53 | | | | 0.90 | 0.73, 1.13 | 0.37 | | | |
| TDF duration | Per year longer | 0.66 | 0.18, 2.42 | 0.53 | | | | 0.80 | 0.26, 2.46 | 0.70 | | | |
| Third antiretroviral | LPV/r vs. NNRTI | 0.56 | 0.07, 4.78 | 0.60 | | | | 5.63 | 1.36, 23.3 | 0.02 | 6.14 | 1.42, 26.5 | 0.02 |
| Adherence | ≥90% vs. <90% | 2.54 | 0.31, 21.0 | 0.39 | | | | 0.39 | 0.11, 1.35 | 0.14 | | | |
| Haemoglobin | Per g/dl higher | 0.90 | 0.74, 1.10 | 0.30 | | | | 0.84 | 0.68, 1.03 | 0.09 | | | |
| CD4 count | Per 50 cells/mm$^3$ higher | 0.96 | 0.86, 1.06 | 0.42 | | | | 1.02 | 0.93, 1.11 | 0.70 | | | |
| HIV-1 RNA | Per $\log_{10}$ copies/ml higher | 1.10 | 0.70, 1.72 | 0.68 | | | | 0.89 | 0.56, 1.42 | 0.63 | | | |
| HBV DNA | Per $\log_{10}$ IU/ml higher | 0.88 | 0.45, 1.72 | 0.70 | | | | 1.21 | 0.81, 1.82 | 0.36 | | | |
| Liver stiffness | Per one kPa higher | 1.05 | 0.98, 1.14 | 0.16 | | | | 1.04 | 0.97, 1.11 | 0.23 | | | |
| AST | Per 10 IU/l higher | 0.75 | 0.49, 1.15 | 0.19 | | | | 1.05 | 0.84, 1.31 | 0.64 | | | |
| ALT | Per 10 IU/l higher | 1.06 | 0.83, 1.35 | 0.65 | | | | 0.92 | 0.68, 1.25 | 0.61 | | | |
| HBeAg | Yes vs. no | 0.52 | 0.06, 4.40 | 0.55 | | | | 1.46 | 0.35, 6.08 | 0.61 | | | |
| Hypertension | Yes vs. no | 3.93 | 1.29, 12.0 | 0.02 | 3.51 | 1.08, 11.4 | 0.04 | 0.69 | 0.24, 1.97 | 0.48 | | | |
| Hb1Ac | Per 5 mmol/mol higher | 1.16 | 0.95, 1.42 | 0.14 | | | | 1.06 | 0.89, 1.27 | 0.52 | | | |
| Diabetes | Yes vs. no | 2.89 | 0.48, 17.3 | 0.25 | | | | 1.89 | 0.32, 11.1 | 0.48 | | | |
| *Schistosoma* Ag | Positive vs. negative | 2.52 | 0.75, 8.45 | 0.14 | | | | 1.67 | 0.51, 5.42 | 0.40 | | | |

[a] Variables were identified for inclusion in the multivariable model using stepwise selection (p value entry and exit <0.2); the multivariable analysis of RD-eGFR excluded haemoglobin; OR = odds ratio; CI = confidence interval; BMI = body mass index; ART = antiretroviral therapy; TDF = tenofovir disoproxil fumarate; LPV/r = ritonavir-boosted lopinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; AST = aspartate transaminase; ALT = alanine transaminase; Hb1Ac = glycated haemoglobin; Ag = antigen.

(T0 and T2). T0 occurred prior to TDF introduction (median −0.2 months; IQR −2.2, −0.1), whereas T1 and T2 occurred a median of 8.1 months (IQR 5.9–10.9) and 4.0 years (IQR 3.8–4.1) after TDF introduction, respectively. By univariate linear regression analysis, receiving LPV/r at T2 was associated with a larger eGFR decline, and the association persisted after adjusting for CD4 cell counts (Table 4). Of the total population on LPV/r, four subjects had started LPV/r prior to T0, five between T0 and T1, and one between T1 and T2. The univariate analysis indicated a trend for an association between changes in eGFR and ALT levels. A separate model adjusting for CD4 cell counts and ALT levels confirmed the independent association between LPV/r and eGFR decline (coefficient −3.31; 95% CI −5.87, −0.75; $p=0.01$); no other independent predictors were identified (not shown).

A diagnosis of RD-eGFR was made in 21/97 (21.6%) subjects. Patients with RD-eGFR were more likely to be receiving LPV/r, and the association persisted after adjustment (Table 3). Among the four subjects with eGFR <60 ml/min at T2, two had experienced RD-eGFR, whereas the other two had a low eGFR at T0. In the main logistic regression model, receiving LPV/r independently increased the risk of RD-eGFR after adjusting for duration of HIV diagnosis. A separate model also adjusting for adherence confirmed the findings with an odds ratio (OR) of 5.27 (95% CI 1.13–24.5; $p=0.03$) (not shown).

### *Relationship between TuPr, eGFR, and urinary dipstick results*

Median eGFR and prevalence of eGFR <90 ml/min were similar in subjects with and without TuPr (Table 2). Changes in eGFR were slightly greater in subjects with TuPr (median −2.4 ml/min/year) than in those without TuPr (median −1.7 ml/min/year). As a result, a diagnosis of RD-eGFR was made in a slightly larger proportion of subjects with TuPr (4/16; 25.0%) than in those without TuPr (17/85; 20.0%). Patients with TuPr showed increased prevalence of dipstick

**Table 4**
Linear regression analysis of factors associated with changes in eGFR in HIV/HBV positive patients with long-term TDF exposure.

| | | Univariate analysis | | | Multivariable analysis[a] | | |
|---|---|---|---|---|---|---|---|
| | | Coefficient | 95% CI | *p* | Coefficient | 95% CI | *p* |
| Gender | Female vs. male | −0.55 | −2.14, + 1.04 | 0.50 | | | |
| Age | Per 5 years older | +0.02 | −0.07, + 0.12 | 0.63 | | | |
| BMI | Per kg/m$^2$ higher | +0.04 | −0.11, + 0.20 | 0.57 | | | |
| Duration HIV diagnosis | Per year longer | −0.02 | −0.36, + 0.33 | 0.93 | | | |
| ART duration | Per year longer | −0.12 | −0.46, + 0.22 | 0.48 | | | |
| TDF duration | Per year longer | −1.16 | −3.65, + 1.33 | 0.36 | | | |
| Third antiretroviral | LPV/r vs. NNRTI | −3.12 | −5.64, −0.60 | 0.02 | −3.51 | −6.04, −0.98 | 0.01 |
| Adherence | ≥ 90% vs. < 90% | +1.12 | −1.10, + 3.34 | 0.32 | | | |
| Haemoglobin | Per g/dl higher | +0.13 | −0.15, + 0.41 | 0.35 | | | |
| CD4 count | Per 50 cells/mm$^3$ higher | −0.09 | −0.23, + 0.05 | 0.20 | −0.12 | −0.26, + 0.01 | 0.08 |
| HIV-1 RNA | Per $\log_{10}$ copies/ml higher | +1.02 | −1.11, + 3.16 | 0.34 | | | |
| HBV DNA | Per $\log_{10}$ IU/ml higher | −0.22 | −0.95, + 0.51 | 0.55 | | | |
| Liver stiffness | Per kPa higher | +0.10 | −0.24, + 0.44 | 0.56 | | | |
| AST | Per 10 IU/l higher | −0.10 | −0.47, + 0.27 | 0.61 | | | |
| ALT | Per 10 IU/l higher | +0.31 | −0.13, + 0.76 | 0.17 | | | |
| HBeAg | Yes vs. no | −0.52 | −2.91, + 1.87 | 0.67 | | | |
| Hypertension | Yes vs. no | −0.01 | −1.59, + 1.57 | 0.99 | | | |
| Hb1Ac | Per 5 mmol/mol higher | +0.02 | −0.13, + 0.16 | 0.83 | | | |
| Diabetes | Yes vs. no | −0.61 | −3.74, + 2.52 | 0.70 | | | |
| *Schistosoma* Ag | Positive vs. negative | −0.36 | −2.35, + 1.62 | 0.72 | | | |

[a] All variables with $p < 0.20$ in the univariate analysis were considered for inclusion using a stepwise selection with $p$ of exit < 0.2; CI = confidence interval; BMI = body mass index; ART = antiretroviral therapy; LPV/r = ritonavir-boosted lopinavir; NNRTI = non-nucleoside reverse-transcriptase inhibitor; AST = aspartate transaminase; ALT = alanine transaminase; Hb1Ac = glycated haemoglobin.

haematuria, and to a lesser extent increased prevalence of dipstick proteinuria. The ROC analysis indicated poor agreement between TuPr and dipstick proteinuria, glycosuria and haematuria, with an area under the curve (*r*) of 0.56, 0.55, and 0.61, respectively (*Supplementary Figure 1*). A diagnosis of RD-eGFR was not associated with clear dipstick patterns, although prevalence of glycosuria was higher than in patients without RD-eGFR. A detailed summary of urinary dipstick results in relation to a diagnosis of TuPr, RD-GFR, hypertension, diabetes, or *Schistosoma* Ag positivity is presented in **Supplementary Table 4**.

## Discussion

Among HIV/HBV co-infected subjects on long-term TDF-containing ART prevalence of TuPr was 15.8%, and the risk was highest among women and those with hypertension. There was an overall modest eGFR decline over time (1.8 ml/min per year of TDF), but 21.6% of participants experienced a more pronounced decline (≥ 5 ml/min per year). Despite the small number of patients on LPV/r, a strong association was detected between a larger eGFR decline and receiving LPV/r. There was limited overlap between TuPr and RD-eGFR, pointing at the different impact of promoting factors. In addition, there was no clear evidence of an effect of HBV disease activity on the two renal markers, as expressed by HBV DNA load, HBeAg status, transaminase levels, and liver stiffness. Urinary dipstick failed to accurately predict TuPr, although was able to point to important co-morbidities (i.e., proteinuria with hypertension and schistosomiasis, glycosuria with hypertension and diabetes).

Previous studies conducted predominantly in HIV-positive patients of white ethnicity reported tubular dysfunction in 7-22% of subjects receiving TDF-containing ART for up to nearly five years.[25–28] Prevalence of TuPr in the Kumasi cohort after a median of four years of TDF was close to the upper limit of the reported range, and hypertension increased the risk by over four-fold. There is a growing burden of hypertension across West Africa, and whilst the determinants remain to be fully established, the attributable mortality is estimated to have increased by over 100% between 1990 and 2015.[29] The prevalence of diagnosed hypertension can reach 54% in the general population[30] and hypertension is estimated to account for 32% of all cases of CKD in Ghana.[31] A third of patients in our study had hypertension, although only a few reported a previous diagnosis and fewer still were receiving anti-hypertensive medication. A similar high rate of untreated hypertension among HIV-positive patients has been reported from other regions of SSA.[32] While we found no evidence of related clinical events among patients still attending for care, the findings clearly highlight the urgent need to introduce routine blood pressure screening in African HIV care settings.

There was also a strong association between TuPr and female gender, although the large confidence interval prevented an accurate estimation of the magnitude of the risk. Previous studies investigating factors associated with tubulopathy in HIV-positive subjects did not identify an effect of gender but included predominantly Caucasian males.[26,33,34] An association between female gender and risk of renal disease has been described, which may reflect the influence of sex hormones on several biological processes involved in kidney injury.[35] It could also be speculated that greater adherence or lower body weight among women may have increased TDF exposure relative to men, increasing the risk of tubulopathy. In SSA, women have been reported to have greater adherence to ART than men[36] and a similar trend was present in our cohort, with adherence rates ≥ 90% by visual scale reported in 91% of women and 79% of men respectively. The BMI however did not show an association with renal abnormalities, being higher in women than in men (24.2 vs. 21.4 km/m$^2$). Data from bigger cohorts are needed to confirm the role of gender in increasing the risk of tubular proteinuria among HIV-positive people on TDF-containing ART.

A previous study of the general population in the same region of Ghana showed that approximately 2% of adults (mean age 55 years) had an eGFR < 60 ml/min.[37] This compares with a prevalence of 4% in our study, where the mean age was 45 years, suggesting a greater burden of renal disease. It should be noted that after a median of four years of exposure to TDF, there was only a modest decline in eGFR, which is in line with the reported overall good safety profile of TDF.[38] Importantly, and consistent with previous data,[7,9] there was evidence that the eGFR decline was greater

in patients receiving LPV/r. Concomitant treatment with LPV/r may indirectly increase the risk of renal damage by boosting TDF exposure through reduced excretion or increased reabsorption, whilst other PIs may have a more direct nephrotoxic potential.[39] As the impact of concomitant PI may differ by type, it will be important to monitor the relative impact of atazanavir and darunavir, which are becoming available across SSA.[40]

CKD is estimated to have an overall prevalence of 14% across populations of SSA, although attention has been drawn to the poor quality of the data and the need for more information using validated measures of kidney function.[30] In addition to the direct effect of poorly controlled HIV, rising prevalence of CKD in SSA may be fuelled by increasing urbanisation, dietary changes, and growing rates of tobacco consumption, obesity, diabetes and hypertension acting on a background of longer life-expectancy[30] and genetic predisposition to renal disease.[41] There are limited data suggesting that diabetes is a significant contributor to renal disease in HIV-positive African cohorts.[30,42] Although numbers were small, in our study there appeared to be a role for diabetes as a determinant of renal abnormalities, again pointing at the importance of screening for co-morbidities in HIV care settings.

A previous study suggested a role for HBV co-infection in increasing the risk of renal disease in Zambian HIV-positive adults.[16] Reassuringly, we detected no indication that HBV status increased the risk of renal function abnormalities. Among infectious co-morbidities with a potential impact on renal health, high rates of *Schistosoma* infection may play a role in Ghana. In Kumasi, prevalence rates of 21% have been described among hospital attendees, although varying considerably according to likelihood of exposure to contaminated water.[43] *S. haematobium*, which causes chronic infection of the urinary tract tends to prevail over *S. mansoni*,[44] although immunological-mediated impairment of glomerular and tubular function has also been associated with infection by *S. mansoni*.[45] Our data documented a reactive CCA-test in 17.8% of subjects, which suggest a high burden of infection. A reactive CCA-test was often accompanied by dipstick proteinuria and haematuria, and carried a 2.5-fold increase in the odds of tubular proteinuria. Data are needed to ascertain the impact of specific *Schistosoma* treatment on urinary findings.

There are limitations of this study. As it is often the case with cohorts in SSA, we observed a significant loss to follow-up (26%) and a documented mortality rate of at least 8% over five years. While some subjects may have moved to a different part of the country, most loss is believed to reflect undocumented mortality. Patients with severe renal impairment or complications of undiagnosed hypertension or diabetes might have died, leading to an underestimation of the burden of disease. Our data therefore should be interpreted as providing estimates for patients who continued to engage with HIV care. Tests not available in Kumasi were performed on frozen samples and sample volume restricted the number of tests. Ideally, additional measures of tubular function and explorative biomarkers of renal function might have been considered, while more frequent measurements of eGFR over time may have allowed increased confidence in the estimates. Further, a diagnosis of hypertension was based on two separate measurements on the same day, and repeated measurements over time would have improved diagnostic accuracy. Overall small study numbers meant that confidence intervals were wide, although associations were controlled for carefully. Despite these limitations, the data have important implications for the management of HIV-positive patients in SSA, and identify several important research needs. Among subjects retained into care, long-term TDF use appeared overall safe, especially in the context of EFV-containing ART. Attention should be paid to optimising blood pressure control, starting from the introduction of routine blood pressure monitoring. Regular measurements of eGFR should also be introduced, and prioritised for patients receiving TDF with a booster. The use of urinary dipstick was effective in detecting evidence of hypertension, diabetes and possible schistosomiasis, and should be included in routine care to improve diagnosis and management of prevalent co-morbidities. In our cohort, one in five individuals had detectable HIV viral load, typically coinciding with a detectable HBV DNA, and optimising control of virus replication remains a key priority. For patients with renal toxicity, where HBV co-infection and lack of entecavir make TDF discontinuation undesirable, reducing the dose of TDF could potentially improve renal safety[46]. The potential cost-benefits of enabling access to TAF for HIV-positive patients in SSA who are at risk of progressive renal dysfunction remain to be determined.

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## Conflict of interests

GV and AB have received funding to attend conferences from Gilead Sciences. CS has received honoraria for preparing educational materials for Gilead Sciences and ViiV Healthcare. FAP has received research funding from ViiV Healthcare, Gilead Sciences, and Janssen; funding to attend conferences from Gilead Sciences; and consultancy and speaker's fees from Gilead Sciences, ViiV Healthcare and MSD. AMG reports consultancy and speaker fees from Abbott Diagnostics, AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, and ViiV Healthcare. The University of Liverpool is the recipient of research funds from Bristol-Myers Squibb, Gilead, Janssen, and ViiV for studies of which AMG is the principal investigator. AMG is employed as an expert scientist by Roche Pharma Research and Early Discovery; Roche had no involvement in the study. All other authors declare no competing interests.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2018.03.001.

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