HIV and CKD in the Tenofovir Era: A Prospective Parallel-Group Cohort Study From Tanzania

Nicholas L.S. Roberts, Salama Fadhil,* Megan Willkens, Grace Ruselu, Bernard Desderius, Said Kanenda, Ladius Rudovick, Bazil B. Kavishe, Serena P. Koenig, Sri Lekha Tummalapalli, Myung Hee Lee, and Robert N. Peck*

Rationale & Objective: Longitudinal research on chronic kidney disease (CKD) in sub-Saharan Africa is sparse, especially among people living with HIV (PLWH). We evaluated the incidence of CKD among PLWH compared with HIV-uninfected controls in Tanzania.

Study Design: Prospective cohort study.

Setting & Participants: A total of 495 newly diagnosed PLWH who initiated antiretroviral therapy (ART) and 505 HIV-uninfected adults enrolled from public HIV clinics and followed from 2016-2021. The control group was recruited from HIV treatment partners from the same HIV clinics.

Exposures: Untreated HIV (at baseline), ART, sociodemographic information, health behaviors, hypertension, and diabetes.

Outcomes: Incident CKD, defined as a follow-up estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 with ≥25% reduction from baseline; annual eGFR change; incident albuminuria; 3-year all-cause mortality.

Analytical Approach: Multivariable Poisson and linear regression determined the association between HIV and other factors with a baseline prevalent reduced eGFR and albuminuria, incident CKD and albuminuria, and annual eGFR change. Cox hazard regression assessed the association between baseline CKD and mortality.

Results: Median age was 35 years and 67.5% were women. There were 101 incident CKD cases, 71 among PLWH and 30 among HIV-uninfected participants, equivalent to a CKD incidence of 57.9 per 1,000 person-years (95% CI, 44.4-71.4) and 26.2 per 1,000 person-years (95% CI, 16.8-35.5), respectively. PLWH had a more rapid eGFR decline (−6.65 vs −2.61 mL/min/1.73 m^2 per year). Female sex and older age were positively associated with incident CKD. Albuminuria incidence did not differ by HIV status. PLWH with albuminuria at baseline had higher mortality (HR, 2.13; 95% CI, 1.08-4.21).

Limitations: As an observational cohort study, there was no comparison group of HIV-positive participants on a nontenofovir disoproxil fumarate–based ART regimen.

Conclusions: PLWH receiving tenofovir disoproxil fumarate–based ART had a very high incidence of CKD and rapid eGFR decline. Conversely, albuminuria stabilized with ART use. Expanding access to less-nephrotoxic ART, such as tenofovir alafenamide, is urgently needed throughout sub-Saharan Africa.

Complete author and article information provided before references.

Correspondence to N.L.S. Roberts (nlr4002@med.cornell.edu)

**N.L.S.R. and S.F. contributed equally to this work.*

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Chronic kidney disease (CKD) is a leading cause of death and disability worldwide, with a disproportionate burden in low-income countries.[1,2] In sub-Saharan Africa, the burden of CKD is likely increasing as part of a growing noncommunicable disease epidemic, but robust primary epidemiologic data are lacking from the continent.[1,3] Data from sub-Saharan Africa are urgently needed to contextualize CKD interventions for African populations with high rates of endemic risk factors that are less common in high-income countries, in which most longitudinal studies of CKD have occurred.[3]

Managing CKD among people living with HIV (PLWH) in low-income countries has unique challenges owing to resource constraints and a lack of studies informing context-appropriate CKD screening and monitoring strategies.[4-6] In sub-Saharan Africa, including Tanzania, the first-line antiretroviral therapy (ART) regimen includes tenofovir disoproxil fumarate (TDF), which is more nephrotoxic than the alternative formulation, tenofovir alafenamide (TAF), which is preferred for patients with renal insufficiency and used more widely in high-income settings.[6-8] Recommendations from Kidney Disease: Improving Global Outcomes (KDIGO) advise screening for CKD at HIV diagnosis and ART initiation, monitoring for CKD annually in PLWH at a low risk, and avoiding nephrotoxic ART or adjusting the TDF dose in patients with an estimated glomerular filtration rate (eGFR) of <70 mL/min/1.73 m^2.[6] However, many HIV clinics in sub-Saharan Africa have limited laboratory capacity and routine kidney function testing is not regularly practiced, and patients who develop CKD likely continue on TDF.[9,10] TDF is also often only available in fixed-dose ART combinations throughout sub-Saharan Africa and dose adjustment is not possible, even when there is known renal insufficiency. Although CKD risk-prediction tools can guide the safety of TDF use, they are not validated in low-income country populations and require laboratory testing.[11,12] With a better understanding of the epidemiology of CKD among PLWH in sub-Saharan Africa, CKD identification and management can be scaled up and integrated into HIV clinics alongside other noncommunicable diseases such as hypertension and diabetes.[13]

PLAIN-LANGUAGE SUMMARY

Managing chronic kidney disease (CKD) among people living with HIV (PLWH) in sub-Saharan Africa is complex owing to resource constraints and sparse longitudinal data. Using a prospective cohort of 495 newly diagnosed PLWH who initiated tenofovir disoproxil fumarate–based antiretroviral therapy (ART) and 505 HIV-uninfected controls in Tanzania, we analyzed CKD incidence based on HIV status. The mean age of participants was 35 years and 67.5% were women. The incidence of CKD was over 2-fold greater among PLWH than among HIV-uninfected participants. PLWH also had a more rapid annual decline in kidney function. The high incidence of CKD among PLWH on tenofovir disoproxil fumarate–based ART indicates that expanding access to less-nephrotoxic ART regimens is warranted throughout sub-Saharan Africa.

The primary aim of this study was to estimate the incidence of CKD in a longitudinal cohort of PLWH and HIV-uninfected adults and to identify other risk factors for incident CKD. We described the relationship between HIV and CKD in the following 3 analyses: the prevalence of CKD among ART-naive PLWH versus HIV-uninfected control participants at baseline; the incidence of CKD among PLWH after initiating ART, which was a TDF-based regimen for virtually all participants, versus HIV-uninfected participants; and the mortality of PLWH with CKD versus without CKD.

METHODS

Study Design and Population

This was a prospective cohort study of newly diagnosed PLWH and HIV-uninfected adults in northwest Tanzania. PLWH were enrolled from the following 3 urban public outpatient HIV clinics: Bugando Medical Centre, Igoma Health Center, and Nyamagana District Hospital. HIV-uninfected participants were recruited from the same HIV clinics and consisted of HIV-uninfected "treatment supporters," who were family members or neighbors designated to provide support, according to Tanzanian national guidelines.[7] We have previously shown that treatment supporters and PLWH have similar characteristics.[14] Inclusion and exclusion criteria are outlined in Item S1. In the incident CKD and albuminuria analyses, participants were excluded if they had an eGFR of <60 mL/min/1.73 m^2 or a urinary albumin-creatinine ratio (UACR) of ≥30 mg/g at baseline, respectively.

Study Procedures

Study procedures have been previously described.[15] Enrollment began in June 2016 and follow-up concluded in May 2021. Participants were seen at enrollment, 3 months, 6 months, and then every 6 months thereafter. At each study visit, a modified World Health Organization STEPwise Surveillance questionnaire was administered, which included questions regarding self-reported sex, socioeconomic status, diet, exercise, and HIV diagnosis and treatment.[16] Blood pressure (BP) was measured following the National Health and Nutrition Examination Survey procedures.[17] The average of the second and third BP measurements was used as the participant's BP. Blood and urine output were collected at the initial and final study visits. Serum creatinine level was measured using the A25 Analyzer (Biosystems), calibrated using the creatinine Jaffe 2 method. Urine albumin and creatinine were measured with the DCA Vantage Analyzer (Siemens Healthcare). Additional point-of-care laboratory tests were conducted at every visit (see Item S1 for additional laboratory procedure details).

Variable Definitions

Prevalent hypertension at baseline was defined as systolic BP > 140 mm Hg and/or diastolic BP > 90 mm Hg for 3 consecutive study visits, or use of antihypertensive medication, per World Health Organization guidelines.[16] Diabetes was defined as random blood glucose ≥ 200 mg/dL, fasting blood glucose ≥ 126 mg/dL, or a self-reported previous diagnosis of diabetes.[18] Anemia was defined as a hemoglobin level of <13.5 g/dL for male and <12 g/dL for female participants.[19]

We calculated the eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 creatinine equation.[20] UACR was equal to the urine albumin concentration in mg/dL over the urine creatinine concentration in g/dL. UACR and eGFR were categorized following the KDIGO CKD risk categories.[21] A reduced eGFR was defined as <60 mL/min/1.73 m^2. Incident CKD was defined as a reduced eGFR and a 25% decrease in eGFR from baseline, as has been done in other studies.[22,23] We performed a sensitivity analysis to assess the effect of the 25% decrease in eGFR compared with solely using a reduced eGFR at the final study visit as the definition of incident CKD. Albuminuria was defined as a UACR of ≥30 mg/g. We additionally calculated participants' annualized change in eGFR, which was equivalent to the difference between the first and second eGFR values divided by years of study enrollment. The mean annual change in eGFR was weighted by participant enrollment time.

Statistical Analysis

Differences in baseline characteristics between PLWH and HIV-uninfected groups were assessed using the χ^2 test. Differences in the distribution of KDIGO eGFR and UACR categories were assessed with the Fisher exact test owing to a small sample size in some categories. Poisson test of significance, accounting for participant enrollment time, was used to assess the differences in incidence between

groups. Stratified analysis was conducted to assess differences in CKD incidence based on age and sex, with the age cutoff set at the cohort's median age of 35 years.

We conducted sequential Poisson regression models to assess the association of HIV and other risk factors with prevalent and incident kidney disease. Outcome variables included a reduced eGFR at baseline, albuminuria at baseline, incident CKD, and incident albuminuria. Model 1 was adjusted for age and sex; model 2 was additionally adjusted for education, body mass index, alcohol use, tobacco use, hypertension, and diabetes. In the incident CKD models, we additionally adjusted for baseline eGFR and baseline albuminuria. We repeated each model stratified based on HIV status, with the addition of $CD4^+$ T-cell count as a covariate in the PLWH models. Confidence intervals were calculated with robust standard errors.

We modeled the effect of HIV on annual eGFR change with multivariable linear regression analysis using the same model 1 and model 2 covariate schema. We additionally assessed whether there was a significant difference in the annual change in eGFR between PLWH and HIV-uninfected participants when stratified based on baseline eGFR category (<60 mL/min/1.73 m^2, 60 to <90 mL/min/1.73 m^2, 90 to <120 mL/min/1.73 m^2, and ≥120 mL/min/1.73 m^2) using univariable linear regression with HIV as the sole covariate and multivariable regression with the model 2 covariates.

We assessed the association between a baseline reduced eGFR or albuminuria and mortality among PLWH using Cox proportional hazard regression analysis. Univariable models were conducted with reduced eGFR and albuminuria as predictors, respectively, followed by multivariable analyses that additionally adjusted for diabetes, hypertension, and $CD4^+$ T-cell count. Participants were censored at 3 years in mortality analyses. Complete-case analysis was used. Analyses were conducted using R statistical software (version 4.3.1; R Foundation for Statistical Computing).

Ethics

The study protocol and ethical consent forms were approved by Weill Cornell Medicine (IRB# 1506016328), the Tanzanian National Institute of Medical Research (Protocol NIMR/HQ/R.8c/Vol.1/1399), and Bugando Medical Centre (Protocol CREC/074/2015). All participants provided written informed consent. All PLWH were provided free treatment according to Tanzanian guidelines.[7]

RESULTS

Study Population

One thousand participants, including 495 PLWH and 505 HIV-uninfected adults, were enrolled. The median follow-up time was 3.6 years (interquartile range, 2.0-4.0). See Fig S1 for details on excluded participants.

Baseline Characteristics

Baseline participant characteristics are shown in Table 1. All participants were of Black African descent. Median ages of PLWH and HIV-uninfected participants were similar at 36 years (interquartile range, 29-43) and 35 years (interquartile range, 26-43), respectively. The majority of PLWH (69%) and HIV-uninfected participants (66%) were women. The prevalence of hypertension was lower among PLWH (4%) than HIV-uninfected participants (7%). Diabetes prevalence was low, at 2% in PLWH and 1% in HIV uninfected. PLWH had a lower prevalence of overweight and obese body mass index than HIV-uninfected participants. Thirteen participants never initiated ART. Of those who initiated ART, all but 3 were started on a TDF-based regimen (479/482; 99%).

Baseline CKD

Fig S2 displays the prevalence of CKD based on KDIGO risk category, stratified based on HIV status. At baseline, 82 (8%) participants had an eGFR of <60 mL/min/1.73 m^2 (41 PLWH and 41 HIV uninfected; $P = 0.91$). The prevalence of albuminuria was over 2-fold higher in PLWH compared with HIV-uninfected participants (14% vs 7%; $P < 0.001$). Four PLWH and 0 HIV-uninfected participants had an eGFR of <15 mL/min/1.73 m^2. Fourteen PLWH and 5 HIV-uninfected participants had a UACR of ≥300 mg/g.

HIV was associated with a higher adjusted prevalence ratio for albuminuria of 2.21 (95% confidence interval [CI], 1.47-3.32) after adjustment for age, sex, and other CKD risk factors (Table S1). Among PLWH, diabetes (adjusted prevalence ratio, 2.87; 95% CI, 1.14-7.25) and tobacco use (adjusted prevalence ratio, 2.32; 95% CI, 1.04-5.19) were associated with prevalent albuminuria (Table S1). A higher $CD4^+$ T-cell count had a negative association with albuminuria (adjusted prevalence ratio, 0.83 per 100 cells/mm^3; 95% CI, 0.74-0.92). HIV was not associated with a higher prevalence of a reduced eGFR (Table S2).

CKD Incidence Based on HIV Status

At the final study visit, the prevalence of a reduced eGFR was 25% (97/395) among PLWH and 13% (54/430) among HIV-uninfected participants (Fig S2). The prevalence of albuminuria was 11% (43/393) among PLWH and 7% (29/430) among HIV-uninfected participants. There were a total of 101 incident CKD cases, 71 among PLWH and 30 among HIV-uninfected participants (Table 2). CKD incidence was over 2-fold higher in PLWH at 57.9 per 1,000 person-years (95% CI, 44.4-71.4), compared with 26.2 per 1,000 person-years (95% CI, 16.8-35.5) in HIV-uninfected participants ($P < 0.001$). PLWH had a greater CKD incidence in every demographic group (Table 3). PLWH aged ≤35 years had a high incidence of 33.7 per 1,000 person-years (95% CI, 19.3-48.1), compared with 6.5 per 1,000 person-years (95% CI, 0.1-13.0) in HIV-uninfected adults aged ≤35 years.

Table 1. Baseline Characteristics of the Cohort Based on HIV Status at Baseline

Baseline	HIV Uninfected	PLWH	*P* Value
N	505	495	
Demographics			
Sex			
Female	335 (66.3)	340 (68.7)	0.47
Male	170 (33.7)	155 (31.3)	
Age (y)	35 (26-43)	36 (29-43)	0.42
Education			
None	54 (10.7)	88 (17.8)	0.004
Primary	318 (63.0)	315 (63.6)	
Secondary or greater	133 (26.3)	92 (18.6)	
Health behaviors			
Current smoker	28 (5.5)	26 (5.3)	0.95
Current alcohol use	150 (29.7)	181 (36.6)	0.03
Comorbid conditions			
BMI category			
Underweight (<18.5 kg/m^2)	60 (11.9)	92 (18.6)	<0.001
Normal weight (18.5-25 kg/m^2)	269 (53.5)	283 (57.2)	
Overweight (25-30 kg/m^2)	123 (24.5)	72 (14.5)	
Obese (>30 kg/m^2)	51 (10.1)	48 (9.7)	
Systolic BP (mm Hg)	123.0 (112.0-134.0)	113.5 (103.8-124.5)	<0.001
Diastolic BP (mm Hg)	78.0 (71.5-85.0)	74.0 (67.8-82.0)	<0.001
Hypertension	36 (7.1)	19 (3.8)	0.03
Diabetes	5 (1.0)	10 (2.0)	0.28
Hemoglobin (mg/dL)	13.6 (12.6-14.8)	12.2 (10.5-13.8)	<0.001
Anemia	83 (16.4)	254 (51.3)	<0.001
Sickel cell			
Normal	332 (77.2)	316 (77.8)	0.25
Trait	96 (22.3)	84 (20.9)	
Disease	1 (0.2)	0 (0.0)	
CD4$^+$ (cells/mm^3)			-
>500		180 (36.4)	
201-500		166 (33.5)	
0-200		149 (30.1)	
ART regimen			
TDF exposure			-
Yes		479 (96.8)	
No: ART without TDF		3 (0.6)	
No: never started ART[a]		13 (2.6)	
Kidney function			
Creatinine (mg/dL)	0.93 (0.77-1.09)	0.87 (0.69-1.08)	0.37
eGFR (mL/min/1.73 m^2)	91.4 (75.8-111.6)	95.7 (75.0-117.5)	0.24
UACR (mg/g)	6 (4-9)	7 (5-15)	0.07

Note: The baseline demographic characteristics were broadly similar between PLWH and HIV-uninfected adults. Health-related covariates differed, and differences between cohorts were adjusted for in multivariable analyses. Almost the full cohort of PLWH (96.8%) was initiated on TDF-based ART regimens. Data are expressed as median (IQR) or n (%).

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; IQR, interquartile range; PLWH, people living with HIV; TDF, tenofovir disoproxil fumarate; UACR, urinary albumin-creatinine ratio.

[a]All 13 participants without ART information either died or were lost to follow up.

Female PLWH had a significantly higher CKD incidence than HIV-uninfected female participants (67.9 vs 36.6 per 1,000 person-years; incidence rate ratio [IRR], 1.86; 95% CI, 1.16-3.03; P = 0.008). Male PLWH had a higher CKD incidence (26.9 vs 7.3 per 1,000 person-years), but not to a statistically significant degree (IRR, 3.66; 95% CI, 0.88-21.41; P = 0.06).

PLWH had a higher risk of incident CKD after adjusting for age, sex, and other factors (IRR, 2.05; 95% CI, 1.38-3.06) (Table 4). Female sex (IRR, 3.06; 95% CI, 1.55-6.05) and age (IRR, 1.74 per 10-year increase; 95% CI, 1.45-2.08) were also associated with incident CKD. Among PLWH, female sex (IRR, 3.19; 95% CI, 1.42-7.20) and age (IRR, 1.66 per 10-year

Table 2. Incidence of Reduced eGFR and Albuminuria Among PLWH and HIV-Uninfected Community Controls

Outcome	Cohort	N	Incident Cases	PY	Incidence Per 1,000 PY (95% CI)	Incidence Rate Ratio (95% CI)	*P* Value Comparing HIV+ vs HIV-
CKD						2.21 (1.42-3.51)	<0.001
	HIV+	398	71	1,226	57.9 (44.4-71.4)		
	HIV-	393	30	1,146	26.2 (16.8-35.5)		
Albuminuria						1.31 (0.72-2.38)	0.40
	HIV+	375	29	1,169	24.8 (15.8-33.8)		
	HIV-	404	22	1,157	19.0 (11.1-26.9)		

Note: PLWH had a higher incidence of CKD, whereas the incidence of albuminuria did not differ between PLWH and HIV-uninfected participants. *P* value was calculated with a Poisson test of significance.
Abbreviations: CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; PLWH, people living with HIV; PY, person-years.

increase; 95% CI, 1.35-2.04) were positively associated with incident CKD (Table S3). HIV was not associated with incident albuminuria (Table S4). Baseline $CD4^+$ count was not associated with higher CKD incidence among PLWH (Table S5).

Annual eGFR Change Based on HIV Status

On average, PLWH had an average annual eGFR decline of -6.65 mL/min/1.73 m^2 per year, compared with -2.61 mL/min/1.73 m^2 per year in HIV-uninfected participants ($P < 0.001$). In multivariable linear regression, HIV was associated with a 2.81-mL/min/1.73 m^2 (95% CI, −3.92 to −1.69) greater decrease in eGFR per year (Table 4). HIV was specifically associated with a more rapid eGFR decline among those with an eGFR of 60 to <90 and 90 to <120 mL/min/1.73 m^2 at baseline (Fig 1) in analyses stratified based on baseline eGFR category. Baseline $CD4^+$ count was not associated with a more rapid eGFR decline (Table S5).

Baseline Kidney Dysfunction and All-Cause Mortality

PLWH with a reduced eGFR or albuminuria at baseline were at a greater risk of mortality in the 3 years after HIV diagnosis than PLWH with normal kidney function (Fig 2). Almost one-fifth (13/67; 19%) of PLWH with albuminuria died, compared with 6% (27/426) of PLWH without albuminuria. The mortality rate of PLWH with albuminuria was equal to 103.4 deaths per 1,000 person-years. In Cox hazard regression analysis, albuminuria had a hazard ratio of 2.13 (95% CI, 1.08-4.21) after adjustment for age, sex, hypertension, diabetes, and $CD4^+$ count (Table S6). PLWH with a reduced eGFR at baseline had a higher mortality rate than PLWH with a normal eGFR (75.0 vs 33.7 deaths per 1,000 person-years), although a reduced eGFR was not a significant factor in multivariable Cox hazards regression analysis (hazard ratio, 1.10; 95% CI, 0.44-2.73).

Sensitivity Analysis

Removing the requirement for a 25% decrease from the definition of incident CKD did not substantially alter the results (Table S7). The association between HIV and incident CKD was similar (IRR, 1.95; 95% CI, 1.39-2.75) (Table S8).

DISCUSSION

In this prospective, longitudinal cohort study of PLWH and HIV-uninfected controls recruited from public HIV clinics in sub-Saharan Africa, we found PLWH

Table 3. Incidence of CKD Based on Age Group and Sex Between PLWH and HIV-Uninfected Community Controls

	Full Cohort Incidence Per 1,000 Person-Years (95% CI)	PLWH Incidence Per 1,000 Person-Years (95% CI)	HIV Uninfected Incidence Per 1,000 Person-Years (95% CI)	Incidence Rate Ratio (95% CI)	*P* Value for Difference in Incidence	*P* Value for Interaction
All	42.6 (34.3-50.9)	57.9 (44.4-71.4)	26.2 (16.8-35.5)	2.21 (1.42-3.51)	<0.001	
Based on age						0.13
≤35 y	20.2 (12.3-28.2)	33.7 (19.3-48.1)	6.5 (0.1-13.0)	5.15 (1.74-20.62)	<0.001	
>35 y	66.8 (51.8-81.8)	83.0 (60.0-106.0)	48.6 (29.9-67.3)	1.71 (1.04-2.86)	0.03	
Based on sex						0.61
Female	54.0 (42.9-65.2)	67.9 (51.1-84.6)	36.6 (22.8-50.4)	1.85 (1.16-3.03)	0.008	
Male	15.6 (6.4-24.8)	26.9 (8.2-45.5)	7.3 (0.0-15.6)	3.66 (0.88-21.41)	0.06	

Note: PLWH had a greater incidence of CKD compared with HIV-uninfected participants in the full cohort and every demographic subgroup. Significance testing for the difference in the CKD incidence between PLWH and HIV-uninfected adults was done with the Poisson test of significance. Interaction testing was done with multivariable regression modeling, which included HIV, sex, and age as covariates with an interaction term between HIV and age group or sex. Neither the interaction between HIV and age nor that between HIV and sex was statistically significant.
Abbreviations: CI, confidence interval; CKD, chronic kidney disease; PLWH, people living with HIV.

Table 4. Association of HIV and Incident CKD and Annual Change in eGFR After Adjusting for Demographics and Other Risk Factors at Baseline

	Incident CKD		Annual Change in eGFR	
Variable	**Model 1 (n = 791)**	**Model 2 (n = 790)**	**Model 1 (n = 823)**	**Model 2 (n = 822)**
HIV+	2.07 (1.40-3.04)[a]	2.05 (1.38-3.06)[a]	-3.66 (-5.12 to -2.20)[a]	-2.81 (-3.92 to -1.69)[a]
Age (per 10 y)	1.74 (1.49-2.04)[a]	1.74 (1.45-2.08)[a]	0.73 (0.07-1.39)[a]	-2.08 (-2.69 to -1.47)[a]
Female sex	2.97 (1.64-5.35)[a]	3.06 (1.55-6.05)[a]	-1.78 (-3.38 to -0.17)[a]	-0.68 (-2.00 to 0.64)
Less than secondary education		1.08 (0.62-1.87)		0.31 (-0.97 to 1.59)
BMI		0.99 (0.96-1.02)		-0.05 (-0.18 to 0.07)
Current alcohol use		0.90 (0.60-1.36)		-0.58 (-1.75 to 0.59)
Current tobacco use		1.07 (0.30-3.86)		1.84 (-0.51 to 4.19)
Hypertension		1.19 (0.68-2.09)		-0.47 (-2.59 to 1.65)
Diabetes		0.95 (0.21-4.25)		-2.41 (-7.18 to 2.35)
Baseline eGFR (per 10 mL/min/1.73 m^2)		1.00 (0.91-1.10)		-2.98 (-3.25 to -2.71)[a]
Albuminuria		1.50 (0.83-2.72)		-0.27 (-2.53 to 1.98)

Note: PLWH had a higher incidence of CKD and magnitude of annual eGFR decline. The incident CKD model was a multivariable Poisson regression analysis conducted among those with an eGFR of ≥60 mL/min/1.73 m^2 at baseline; annual change in eGFR model was a multivariable linear regression analysis conducted in all participants with 2 eGFR values. In the "Incident CKD" columns, data are adjusted incidence rate ratios and 95% confidence intervals from Poisson regression analysis. In the "Annual change in eGFR" model columns, the values are adjusted beta coefficients and 95% confidence intervals from multivariable linear regression.
Abbreviations: BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; PLWH, people living with HIV.
[a]Values significant to $P < 0.05$.

experienced over a 2-fold greater risk of CKD than HIV-uninfected participants. The strong association between HIV and incident CKD remained statistically significant after adjusting for potential confounders. PLWH on ART also experienced a very rapid annual eGFR decline that was significantly faster than the eGFR decline of HIV-uninfected controls. In addition, albuminuria was associated with early mortality in PLWH. These results demonstrate that PLWH on TDF-based ART are at a higher risk of CKD in sub-Saharan Africa than HIV-uninfected adults, and interventions to reduce nephrotoxicity and scale up CKD screening in routine HIV care are warranted.

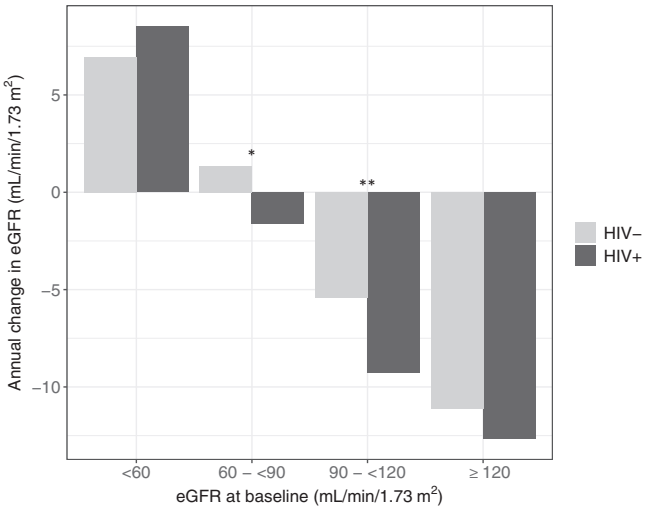

Figure 1. The mean annual change in eGFR based on baseline eGFR category, weighted by enrollment time, stratified based on HIV status at baseline. HIV was associated with a greater average eGFR decline for every eGFR category at baseline, except for those with a reduced eGFR of <60 mL/min/1.73 m^2. The difference was significant in the 60- to <90-mL/min/1.73 m^2 group, 90- to <120-mL/min/1.73 m^2 group, and the overall cohort. The Y axis represents the weighted mean of the annual change in eGFR, weighted by participant enrollment time. *P* values are from univariable linear regression. The same strata had significant differences between PLWH and HIV-uninfected participants when adjusting for model 2 covariates in multivariable linear regression (*P* in the order of the figure categories: 0.62, 0.01, 0.02, and 0.33). *$P < 0.01$; **$P < 0.001$. Abbreviations: eGFR, estimated glomerular filtration rate; PLWH, people living with HIV.

The incidence of CKD among PLWH in our cohort was very high compared with similar cohorts in high-income settings, which is especially worrisome because of the limited availability of laboratory-based kidney function monitoring, less-nephrotoxic ART medications, and renal replacement therapy. One meta-analysis estimated the incidence of PLWH globally and in Africa to be 12.5 (95% CI, 9.0-17.4) and 13.2 (95% CI, 3.7-46.8) per 1,000 person-years, respectively.[24] Multiple reasons may underlie the high incidence among PLWH in our cohort, including that they were all ART naive at baseline, that many had advanced HIV disease, and that they were all initiated on a TDF-based ART regimen. Our results were comparable with those of a study from South Africa that found the CKD incidence among 15,000 ART-naive patients starting TDF-containing ART to be 58.9 (95% CI, 55.5-62.5) per 1,000 person-years.[25] Although that study lacked an HIV-uninfected control group, together, the 2 studies demonstrate the elevated risk of CKD among PLWH on TDF across multiple sub-Saharan African settings.

The high CKD incidence and rapid eGFR decline among PLWH highlight the urgent need for early detection of CKD in PLWH and prompt initiation of kidney protective therapies in those with kidney disease. These

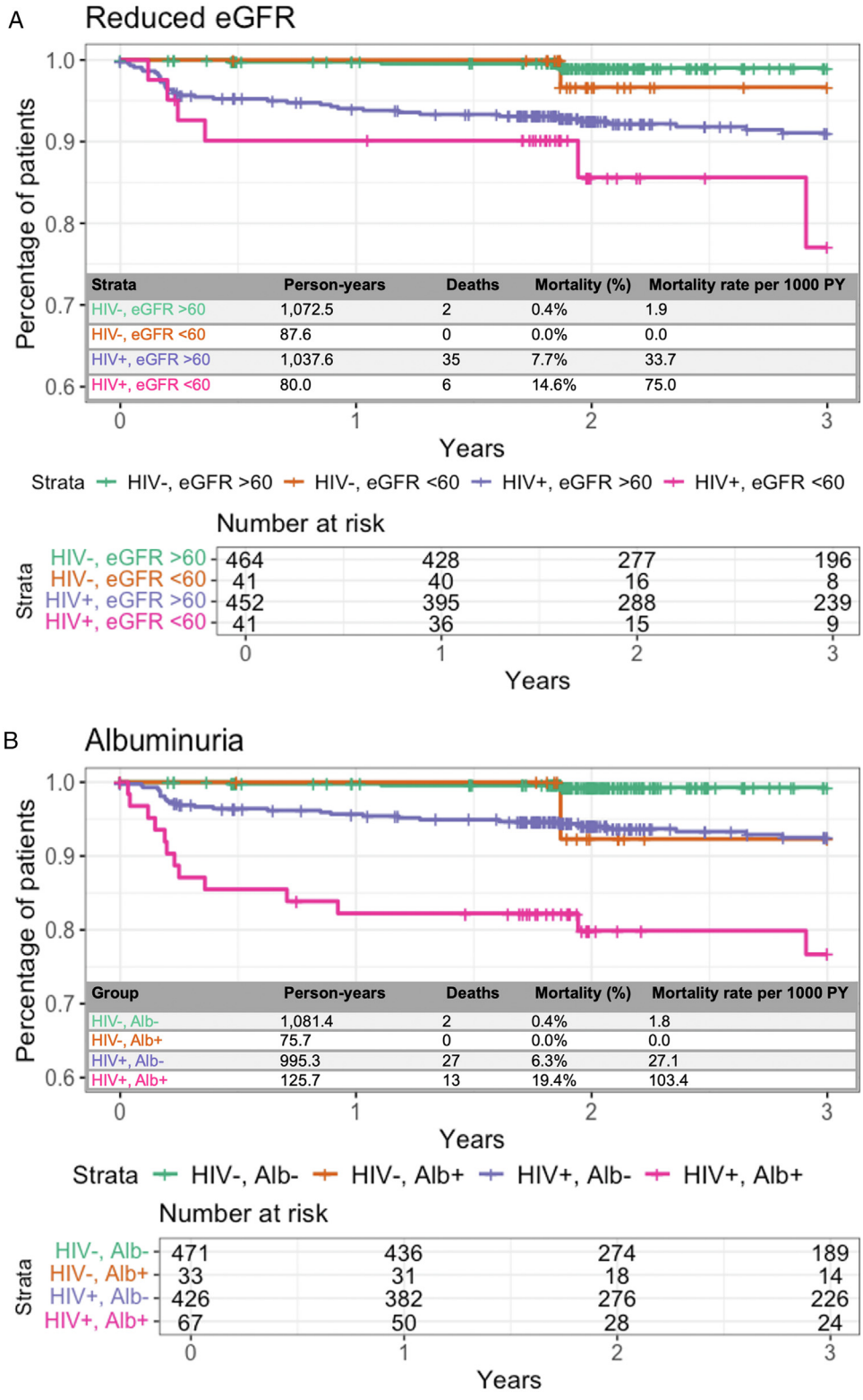

Figure 2. Kaplan-Meier curves demonstrating the association of (A) reduced eGFR and (B) albuminuria at baseline with death among PLWH and HIV-uninfected adults. PLWH with either a reduced eGFR or reduced albuminuria at baseline had a higher all-cause mortality rate than PLWH with normal kidney function. Abbreviations: Alb, albuminuria; eGFR, estimated glomerular filtration rate; PLWH, people living with HIV.

include metabolic risk factor control and lifestyle interventions, renin-angiotensin system inhibitors, and sodium-glucose cotransporter 2 inhibitors. However, accessing these medications can be challenging in a setting with limited primary and nephrology care,[26] common shortages in first-line noncommunicable disease therapy,[27] and in which 49% of the population live on less than $2.15 per day.[28] In addition, although TAF is recommended by the World Health Organization for patients with renal insufficiency,[8] TAF is unavailable in Tanzania and PLWH with renal insufficiency often remain on a TDF-based regimen. KDIGO recommends TDF dose adjustment in settings in which TAF is unavailable[6]; however, this is difficult in resource-constrained settings in which creatinine clearance screening is not routinely performed.[9,10] Alternative doses of TDF are also often unavailable in many HIV clinics throughout sub-Saharan Africa, where fixed-dose combination ART is preferred by both providers and patients. At the end of our study, one-quarter of PLWH had a reduced eGFR (n = 97), of whom 96% (n = 93) were still on high-dose TDF. Only 4 participants had been switched to TDF-free regimens containing abacavir or zidovudine. Our results argue for expanded access to TAF-containing ART regimens in sub-Saharan Africa, according to World Health Organization guidelines, so that clinicians can have greater access to less-nephrotoxic ART for patients who develop CKD. Further economic analyses and clinical trials are warranted to optimize specific guidelines on the expansion of TAF in sub-Saharan Africa.

Women had almost triple the risk of incident CKD compared with men after adjusting for other risk factors. This disparity is concerning among PLWH because 80% of new HIV infections in Tanzania occur in women.[29] The elevated risk of CKD among female PLWH has been shown previously; women with HIV in 1 large US cohort had a 61% higher CKD risk compared with men.[30] There are multiple hypotheses for this gender disparity, including that women have higher plasma drug concentrations of TDF than men at the same dose and have greater levels of systemic inflammation from HIV, even when virally suppressed.[31,32] Women in sub-Saharan Africa also have a high burden of nontraditional risk factors unrelated to HIV, such as pregnancy complications, including hypertensive disorders of pregnancy,[33,34] traditional medication use, and exposure to environmental pollutants. Women also may have a higher incidence of CKD of unknown etiology.[35,36] Further research studying the burden and etiology of CKD in women in sub-Saharan Africa as a high-risk group is needed.

Strengths of this study include that it was a longitudinal cohort study made up of half PLWH and half HIV-uninfected community controls recruited from 3 large public outpatient HIV clinics in sub-Saharan Africa, in which there is a paucity of longitudinal data on CKD. By enrolling a control group that had a similar prevalence of a reduced eGFR at baseline, we demonstrate that the higher risk of CKD and rapid eGFR decline were specific to PLWH on ART. Our study captured risk factors at different stages throughout the time course of HIV infection and adds to the growing research base on CKD and HIV in sub-Saharan Africa.

Our study had several limitations. First, the CKD-EPI creatinine-based equations have been found to overestimate eGFR in African populations.[37] Our eGFR results could therefore be underestimating the true burden of CKD in the cohort. Second, some participants may have had acute kidney injury rather than CKD, which is a well-recognized limitation of many longitudinal cohort studies. Third, kidney biopsy was not available in our Tanzanian research setting and confirmation of CKD etiology via biopsy was not feasible. Urinary biomarker panels that could have assessed for specific indicators of TDF-related nephrotoxicity beyond UACR or serum creatinine were also not available. *APOL1* genotyping was also not performed and is an important area for future study from longitudinal cohorts based in sub-Saharan Africa. Furthermore, because virtually all participants were on standard-of-care first-line TDF-based ART regimens, the study was not designed to specifically assess the effect of TDF on kidney function. Additional longitudinal research and clinical trials are warranted.

In conclusion, in this longitudinal cohort, PLWH on ART had a very high CKD incidence and a rapid eGFR decline. PLWH with albuminuria at the time of ART initiation were at a higher risk of mortality. International guidelines for the diagnosis and treatment of CKD among PLWH should recognize the limited diagnostic capacity and lack of treatment alternatives of HIV clinics in sub-Saharan Africa and tailor guidelines to these settings, given they are where the majority of PLWH globally seek care. Expanded TAF availability, increased laboratory capacity, and integration of CKD preventative services into routine HIV care are urgently needed.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Item S1: Supplementary Methods.

Figure S1: Flow chart of included and excluded participants in 3 respective analyses assessing (1) prevalence of reduced eGFR at baseline, (2) prevalence of albuminuria at baseline, (3) incidence of CKD, and (4) incidence of albuminuria.

Figure S2: Prevalence of CKD at initial and final study visits stratified by KDIGO risk categories based on eGFR and UACR levels.

Table S1: Association Between Covariates and Albuminuria at Baseline Among All Participants Together and Stratified by HIV Status in Poisson Regression Analyses.

Table S2: Association Between Covariates and Reduced Egfr at Baseline Among All Participants Together and Stratified by HIV Status in Poisson Regression Analyses.

Table S3: Association Between Covariates and Incident CKD Among PLWH and HIV-Uninfected Participants in Stratified Poisson Regression Analyses.

Table S4: Association Between Covariates and Incident Albuminuria Among All Participants Together and Stratified by HIV Status in Poisson Regression Analyses.

Table S5: Incidence of CKD and Annual Change in eGFR Among PLWH Stratified by Baseline $CD4^+$ Count.

Table S6: Cox Proportional Hazard Results for All-Cause Mortality Among PLWH at Baseline.

Table S7: Sensitivity Analysis Results Demonstrating the Incidence of CKD Defined Using Solely eGFR <60 mL/min/1.73 m^2.

Table S8: Sensitivity Analysis Results Assessing the Association of Covariates With CKD Incidence, Defined Using Solely Reduced eGFR <60 mL/min/1.73 m^2 in Poisson Regression Analyses.

ARTICLE INFORMATION

Authors' Full Names and Academic Degrees: Nicholas L.S. Roberts, MPH, Salama Fadhil, BA, Megan Willkens, BS, Grace Ruselu, MD, Bernard Desderius, MD, Said Kanenda, MD, Ladius Rudovick, MD, Bazil B. Kavishe, MD, PhD, Serena P. Koenig, MD, Sri Lekha Tummalapalli, MD, Myung Hee Lee, and Robert N. Peck, MD, PhD.

Authors' Affiliations: Center for Global Health (NLSR, MW, MHL, RNP), Weill Cornell Medicine, New York, NY; Department of Internal Medicine (NLSR, SF, GR, BD, SK, LR, RNP), Bugando Medical Centre and Weill Bugando School of Medicine, Mwanza, Tanzania; Mwanza Intervention Trials Unit (SF, GR, BBK, RNP), National Institute for Medical Research, Mwanza, Tanzania; Division of Infectious Diseases (BD), Department of Internal Medicine, Bugando Medical Centre and Weill Bugando School of Medicine, Mwanza, Tanzania; Division of Nephrology (SK, LR), Department of Internal Medicine, Bugando Medical Centre and Weill Bugando School of Medicine, Mwanza, Tanzania; Division of Infectious Diseases and Division of Global Health Equity (SPK), Brigham and Women's Hospital, Boston, MA; Division of Healthcare Delivery Science and Innovation (SLT), Department of Population Health Sciences, Weill Cornell Medicine, New York, NY; Division of Nephrology and Hypertension (SLT), Weill Cornell Medicine, New York, NY; and The Rogosin Institute (SLT), New York, NY.

Address for Correspondence: Nicholas L.S. Roberts, MPH, Center for Global Health, Weill Cornell Medicine, 402 East 67th Street, 2nd Floor, New York, NY 10065. Email: nlr4002@med.cornell.edu

Authors' Contributions: Research idea and study design: NLSR, SF, RNP; data acquisition: NLSR, SF, MW, GR, RNP; data analysis/interpretation: NLSR, SF, BD, SK, LR, BBK, SPK, SLT, MHL, RNP; statistical analysis: NLSR, MHL; supervision or mentorship: MHL, RNP. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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