Renal function and associated mortality risk in adults commencing HIV antiretroviral therapy in Zimbabwe

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Background: People with HIV (PWH) in sub-Saharan Africa appear to have a higher incidence of renal disease than other global regions but data are limited. This renal impairment may be associated with an increased mortality risk.

Aims: To define the prevalence of renal disease and explore its association with mortality risk in a cohort from Zimbabwe commencing antiretroviral therapy (ART) for HIV infection.

Methods: A retrospective study of all patients aged at least 18 years, commenced on ART for HIV infection at the Newlands Clinic in Harare, Zimbabwe between January 2007 and September 2019 was conducted. Data were extracted from electronic medical records. Patients with no baseline creatinine measurement were excluded. Baseline characteristics were assessed as potential predictors for mortality by Cox proportional hazard regression.

Results: Three thousand and thirty-nine patients were eligible for inclusion. Most were female (62.1%), with a median age of 36 years (IQR 30–43). At baseline, 7.3% had an estimated glomerular filtration rate (eGFR) 90 ml/min per 1.73 m^2 or less and 11.4% had proteinuria. Over a median follow-up period of 4.6 years (IQR 2.5–6.9), the mortality rate was 8.7%. One half of deaths (49.2%) occurred within the first year. In multivariable analysis, a baseline eGFR between 60 and 90 ml/min per 1.73 m^2 [hazard ratio 2.22, 95% confidence interval (CI) 1.46–3.33, $P < 0.001$] and proteinuria (hazard ratio 2.10, 95% CI 1.35–3.27, $P < 0.001$) were associated with increased mortality risk.

Conclusion: Baseline renal impairment was common. Both a reduced eGFR and proteinuria were independently associated with a doubling of mortality risk. These should serve as markers in the clinical setting of at-risk patients.

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Introduction

As of 2020, there were approximately 25 million people with HIV (PWH) in sub-Saharan Africa [1]. Prevalence estimates of renal disease in this population vary widely, reflected by the significant heterogeneity in the estimates of renal disease from the region, ranging from 20 to 77% [2–6]. Using pooled estimates, however, renal disease in PWH from sub-Sharan Africa is up to twice as prevalent than those from Europe or the Americas [7].

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Variation in prevalence estimates is partly a consequence of inconsistent study definitions of renal impairment, particularly the choice of estimating equation used to calculate estimated glomerular filtration rate (eGFR). Estimates using the Cockcroft−Gault equation are on average double those using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) or Modification of Diet in Renal Disease (MDRD) equations in sub-Saharan Africa, a trend not seen in most other global regions [3]. Even with consistent definitions, however, variability remains. This is likely explained by cohort differences, which seem to exhibit regional trends within sub-Saharan Africa [7].

Few studies have explored the consequences of renal impairment in PWH in sub-Saharan Africa but available data show increased mortality with just mild renal impairment and increasing risk with worsening degrees of renal impairment [2,3]. No studies from the region have yet reported the risk associated with proteinuria, another important marker of renal disease in the general population, and of pathological entities specific to PWH, including HIV-associated nephropathy (HIVAN) [8].

Overall, the prevalence of renal impairment in PWH in sub-Saharan Africa remains poorly defined. There are few data regarding the outcomes of PWH with renal impairment in the region. Moreover, these have only relied on measurements of serum creatine, which may not reflect the full spectrum of renal disease, particularly in HIV infection. Here we describe the prevalence of renal disease, in terms of reduced eGFR and proteinuria, and its association with mortality risk in a large retrospective cohort of PWH commencing antiretroviral therapy in Harare, Zimbabwe.

Methods

We conducted a retrospective cohort study to examine the prevalence of renal impairment and factors, which predict mortality amongst ART-naive patients commencing treatment for HIV infection at the Newlands clinic in Harare, Zimbabwe. Ethical approval was granted by the Medical Research Council of Zimbabwe (MRCZ/E/ 258). The study was conducted in accordance with the Declaration of Helsinki.

The Newlands Clinic is a charitable, not-for-profit, outpatient service focused on the management of PWH. The study included all adult patients commencing ART at the clinic between January 2007 and September 2019. Patients were excluded from the study if no baseline creatinine measurement was available. There was no minimum follow-up duration.

Data were extracted from the clinic's electronic medical records, including demographic information, diabetes status, renal function indicators and CD4$^+$ cell count. Proteinuria was measured using Combur10 Test UX by (Roche, Switzerland) and read using a Urisys 1100 (Roche, Switzerland). Proteinuria was defined as at least 1+ on dipstick. Creatinine and CD4$^+$ cell counts were measured in the clinic's on-site laboratory. These values were collected at baseline and at subsequent follow-up appointments, which occurred at approximately 6-monthly intervals. Note that CD4$^+$ cell count was not routinely rechecked until 1 year after ART initiation. Subsequent measures of proteinuria were at the discretion of the clinician. Longitudinal proteinuria data were, therefore, available for only a portion of patients, and likely biased towards those with or at high risk of renal disease. Thus, they were not used to inform this analysis. Where deaths were not actively reported to the clinic, mortality status was ascertained retrospectively for patients who did not attend planned follow-up.

Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation [9]. Normal renal function was defined as an eGFR greater than 90, mild impairment as 60−90 and moderate−severe impairment as less than 60 ml/min per 1.73 m^2.

Statistical analysis

Values are presented as mean [95% confidence interval (CI)] or median (IQR) as appropriate. Baseline values were those recorded on the day of starting ART or the most recent within the preceding month, selecting the value nearest to the starting date. Follow-up measures of creatinine were attributed to the nearest 6-monthly time point, in accordance with the clinic's follow-up schedule. Where multiple measures existed for a single time point, the mean value was taken.

Differences in creatinine and CD4$^+$ cell count at different time points were assessed by t test. Kaplan−Meier survival curve comparison was by logrank test or logrank test for trend, as indicated. Potential predictors of mortality were assessed by Cox proportional hazards regression. Those predictors with a P less than 0.1 in bivariate analysis were included in the multivariate analysis. For all analyses, P less than 0.05 was considered statistically significant.

Results

A total of 3048 adult patients were commenced on antiretroviral therapy at the Newlands Clinic between January 2007 and September 2019. Nine patients did not have baseline creatinine measurements available, and were therefore, excluded from further analysis. The remaining 3039 patients were followed-up for a median of 4.6 years (IQR 2.5−6.9).

Table 1. Baseline patient characteristics (*n* = 3039).

Characteristic	Number (%)
Gender (female)	1888 (62.1)
Age (years)	
18–29	705 (24.7)
30–39	1207 (39.7)
40–49	748 (24.6)
50+	320 (10.5)
Diabetes mellitus	73 (2.4)
Proteinuria (*n* = 3012)	344 (11.4)
eGFR (ml/min per 1.73 m^2)	
<60	56 (1.8)
60–90	166 (5.5)
>90	2817 (92.7)
WHO stage (*n* = 2909)	
I	1391 (47.8)
II	605 (20.8)
III	593 (20.4)
IV	320 (11.0)
CD4$^+$ cell count <200 cells/μl	1359 (44.7)

eGFR, estimated glomerular filtration rate.

Baseline characteristics are shown in Table 1. The majority of the cohort was female (62.1%), with a median age of 36 years (IQR 30–43 years). A tenth of the cohort was aged 50 years or older at baseline. Pre-existing renal impairment was common, with nearly a fifth of patients (17.5%) having an eGFR less than 90 ml/min per 1.73 m^2 or proteinuria. Severe immunodeficiency (CD4$^+$ cell count <200 cells/μl) was noted in nearly half of patients (44.7%).

The mortality rate over the follow-up period was 8.8%, with approximately half of all deaths (50.4%) occurring within 1 year of commencing ART. No formal reporting mechanisms for cause of death were in place, hence 30.5% of deaths were of unknown cause. Infection (27.4%) and malignancy (10.5%) were the most common known causes. Kaplan−Meier survival curves are shown for patients by baseline eGFR and proteinuria status in Fig. 1. A Cox proportional hazards analysis was performed to determine, which baseline characteristics were associated with increased mortality risk (Table 2). In multivariate analysis, as compared with normal renal function (baseline eGFR >90 ml/min per 1.73 m^2), an eGFR of 60−90 ml/min per 1.73 m^2 was associated with an increased risk (hazard ratio 2.22, 95% CI 1.46−3.33, $P < 0.001$), whereas risk with an eGFR less than 60 ml/min per 1.73 m^2 was not significantly different ($P = 0.696$). Proteinuria was similarly associated with more two-fold increased risk of mortality (hazard ratio 2.10, 95% CI 1.35−3.27, $P < 0.001$).

There was a small initial decline in eGFR in the first 6 months after commencing ART of −4.4 ml/min per 1.73 m^2 (95% CI −5.9 to −2.9, $P < 0.001$), which generally persisted throughout the study period but was not statistically significant at the 6, 6.5, 9 and 9.5-year time points. There was a rapid improvement in eGFR for patients with a baseline eGFR 60−90 and less than 60 ml/min per 1.73 m^2. Within 6 months of commencing ART,
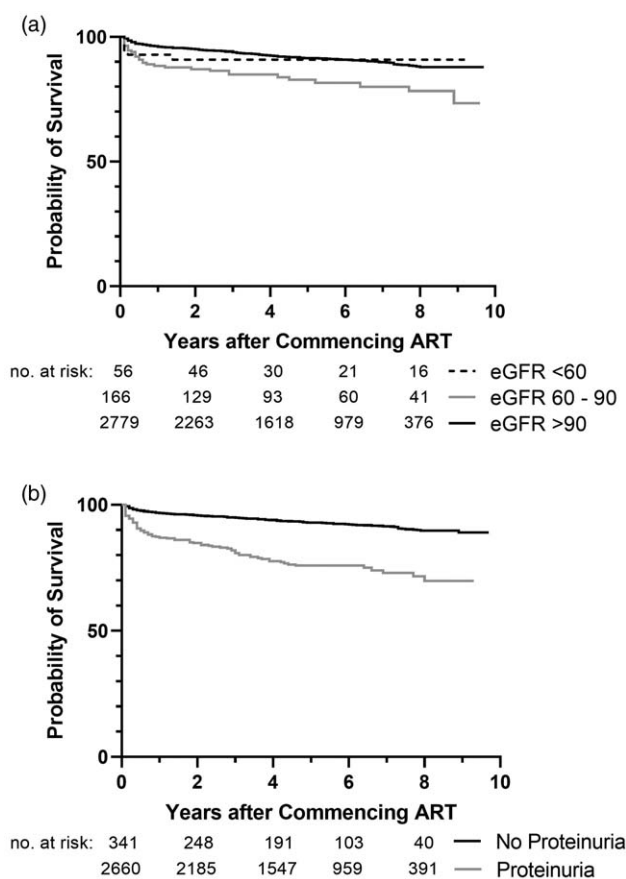

Fig. 1. Kaplan−Meir survival curves based on baseline estimated glomerular filtration rate in ml/min per 1.73 m^2 (a) and baseline proteinuria as at least 1+ on urinary dipstick (b). eGFR, estimated glomerular filtration rate. Statistical significance by logrank test for trend (a) and logrank test (b) was $P = 0.005$ and P less than 0.001, respectively.

mean eGFR of both groups did not significantly differ from those with a baseline eGFR greater than 90 ml/min per 1.73 m^2 ($P = 0.650$ and $P = 0.106$, respectively).

There was no significant difference in baseline eGFR between those with proteinuria and those without ($P = 0.433$). After 6 months of ART, the mean difference in eGFR increased to 9.9 ml/min per 1.73 m^2 (95% CI 5.6−14.3; $P < 0.001$) for those with baseline proteinuria. This persisted at a similar magnitude across the study period, although was no longer statistically significant after year 8 (Fig. 2a).

Baseline mean CD4$^+$ cell count was 279 cells/μl (95% CI 271−287). There were interval increases at 1, 1.5 and 2 years ($P < 0.001$ for all), after which the CD4$^+$ cell count plateaued. After 2 years of ART, mean CD4$^+$ cell count had increased by 169 cells/μl (95% CI 160−178, $P < 0.001$) from baseline. Patients with proteinuria had a baseline CD4$^+$ cell count of 63 cells/μl (95% CI 31−95, $P < 0.001$) less than those without proteinuria. Although this trend continued throughout the follow-up period, it was no longer statistically significant after year 3 (Fig. 2b).

Table 2. Cox proportional hazard regression of potential predictors mortality in adults commencing antiretroviral therapy.

		Bivariate		Multivariate	
Predictor		HR (95% CI)	P value	HR (95% CI)	P value
Gender (female)		0.60 (0.47–0.76)	**<0.001**	0.83 (0.64–1.10)	0.193
Age (years)		1.03 (1.02–1.04)	**<0.001**	1.02 (1.01–1.04)	**<0.001**
Diabetes mellitus		1.74 (0.95–3.19)	0.071	1.12 (0.59–2.16)	0.724
WHO stage	I (reference)	–	–	–	–
	II	2.53 (1.66–3.87)	**<0.001**	2.10 (1.35–3.27)	**0.001**
	III	4.74 (3.24–6.92)	**<0.001**	3.10 (2.06–4.68)	**<0.001**
	IV	9.10 (6.22–13.15)	**<0.001**	5.36 (3.52–8.16)	**<0.001**
Proteinuria		4.01 (3.07–5.24)	**<0.001**	2.10 (1.35–3.27)	**<0.001**
eGFR (ml/min per 1.73 m^2)	>90 (reference)	–	–	–	–
	60–90	2.23 (1.52–3.27)	**<0.001**	2.22 (1.46–3.33)	**<0.001**
	<60	1.10 (0.45–2.66)	0.840	1.22 (0.45–3.30)	0.696
CD4$^+$ cell count (<200) cells/μl		3.60 (2.73–4.74)	**<0.001**	1.79 (1.31–2.45)	**<0.001**

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.
Significant P-values are indicated in bold.

Discussion

In our large cohort of adult patients commenced on ART in the Newlands Clinic in Harare, Zimbabwe, renal disease was common, with nearly one in five patents having a reduced eGFR and/or proteinuria. Over median follow-up period of 4.6 years, there was a mortality rate of 8.8%, with approximately half of deaths occurring within the first year. Both reduced baseline eGFR and proteinuria were predictors of mortality, each associated with more than a two-fold increased mortality risk.

The 7.3% prevalence of impaired eGFR in our population was lower than comparable studies, with estimates ranging from 20 to 77% [2–6]. This low value may have been because of the use of the CKD-EPI estimating equation in our analysis. A recent meta-analysis of chronic kidney disease in PWH found good concordance between estimating equations in North America and Europe. In sub-Saharan Africa, however, chronic kidney disease prevalence was nearly double when measured by the

Cockcroft–Gault equation, as compared with either the CKD-EPI or MDRD equation [7].

Although we did not observe an overall increase in eGFR after the commencement of ART, in contrast to other studies from the region [5,6,10], this was likely a consequence of few patients in our cohort having moderate or severely reduced baseline eGFR. Improvements in eGFR in other cohorts were limited to these subgroups [5,10] and a similar trend was indeed present in our study population.

The accuracy of all GFR-estimating equations is increasingly in question and their use in an African context warrants special consideration [11]. Individuals from sub-Saharan Africa were not included in the derivation cohorts for the CKD-EPI and MDRD equations and subsequent attempts to validate these equations in populations from the region have failed [12,13]. Despite this limitation, these estimating equations still may have clinical utility in identifying patients from the region with increased mortality risk.
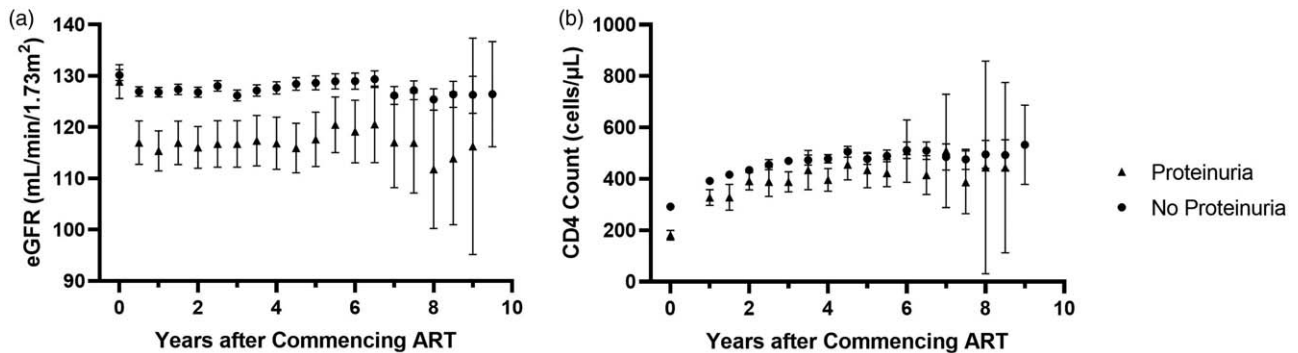

Fig. 2. Mean estimated glomerular filtration rate (a) and CD4$^+$ cell count (b) after commencing antiretroviral therapy by baseline proteinuria status (defined as ≥1+ on urine dipstick). eGFR, estimated glomerular filtration rate. Error bars show 95% confidence interval (CI).

In our cohort, mildly impaired renal function was associated with a 2.2-fold increased mortality risk, this was greater than the 1.4-fold increase noted by Mulenga *et al.* [10] and may be explained by their use of the CG equation, which may have classed patients with normal eGFR using the CKD-EPI equation as having an impaired eGFR. Mortality risk in patients commencing ART appears to increase with the severity of baseline renal impairment [3,10]. Although this same association was not noted in our cohort, this is likely a consequence of few patients in our cohort having moderately or severely reduced baseline eGFR.

We did not explore the effect of high eGFR values in our study. In a large cohort study of over 27 000 PWH in the UK, a U-shaped trend in mortality risk was observed, with patients at either extreme of eGFR being at increased risk [14]. Routine proteinuria data was unavailable for that study but a separate meta-analysis of renal disease in the general population found that an eGFR at least 05 ml/min per 1.73 m^2 was only associated with a greater mortality risk when there was concomitant proteinuria [15]. Although high eGFR values may represent pathological hyperfiltration [14], these findings need to be interpreted with caution. Neither the CDK-EPI nor the MRDR equations used by these studies are validated for eGFR values in this range [9].

Baseline proteinuria was associated with more than a doubling of mortality risk in our study, comparable with the risk associated with a low baseline eGFR. We believe we are the first to report on the association between proteinuria and mortality in PWH in the sub-Saharan region. The risk increase was similar, though to that reported in other cohorts from other global regions [16,17].

Proteinuria is of particular concern in PWH, partly because of it being a clinical feature of HIVAN [8]. Although we did not have renal biopsy findings available to us, multiple case series from sub-Saharan Africa have reported HIVAN as the most common histological diagnosis in PWH with persistent proteinuria [8]. This may be of particular relevance to Western African populations who are at increased risk of HIVAN because of a high prevalence of particular alleles of the *APOL1* gene as compared with other sub-Saharan regions [18]. Despite modern ART, HIVAN continues to have a poor prognosis. In one French case series, where 83% of patients were of African origin, median time to end-stage renal failure was only 40 months [19].

The main limitation to of our study was its data having been derived from a single site. Sub-Saharan Africa is diverse, and this may limit generalizability of our findings. Data on ART regimens were not available for our analysis. As such, we were unable to draw any conclusions regarding the relationship between the use of TDF-containing ART regimens and eGFR, proteinuria or

mortality in this cohort. However, TDF-containing ART regimens do not appear to attenuate the improvement in eGFR seen in ART-naive cohorts in sub-Saharan Africa [10], nor increase the risk of renal impairment at follow-up [6].

The absence of regular proteinuria measurements meant we were unable to identify patients with persistent proteinuria, a key clinical feature of HIVAN [8]. The use of urine dipsticks for patient monitoring precluded the detection of microalbuminuria in our study, which has also been associated with an increased mortality risk in PWH [16]. Longitudinal assessment of proteinuria, with laboratory quantification, would, therefore, be important avenue for future study.

Reduced eGFR and proteinuria were each associated with more than a two-fold increased risk mortality in this large cohort of PWH from Zimbabwe. This underscores the importance of ensuring access to routine testing of both these parameters in PWH and the presence of either may warrant more rigorous follow-up of patients.

Conflicts of interest
There are no conflicts of interest.

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