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Predictors of renal impairment and proteinuria after commencement of antiretroviral therapy in a Zimbabwean HIV cohort

Running title: Predictors of renal impairment and proteinuria on ART

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Abstract

Background: Renal disease prevalence varies widely amongst reported cohorts of people living with HIV (PLWHIV) in sub-Saharan Africa. Renal function testing is not routine in those commencing antiretroviral therapy (ART) in the region, however. Further data on renal disease prevalence and the change associated with ART use are therefore needed.

Aim: To explore changes in renal function and associated predictors after one year of antiretroviral therapy (ART) in an adult cohort of PLWHIV from Zimbabwe.

Methods: A retrospective analysis of patients who attended the Newlands Clinic between January 2007 and September 2019. Eligible patients were aged ≥18 years and had measures of serum creatinine at baseline and after one year of ART. Predictors of renal function change were assessed by multiple linear regression.

Results: 1729 patients were eligible for inclusion. Median age was 36 years (IQR 30 to 43) and 62.8% were female. After one year of ART, the proportion of patients with an eGFR <60 mL/min/1.73 did not significantly change (2.0 vs 1.2%, p=0.094), but there was a decrease in the proportion of patients with proteinuria (11.0 vs 5.6%, p<0.001). Hypertension (B = -6.43; 95%CI -8.97 to -3.89; p<0.001) and baseline proteinuria (B = -7.33; 95%CI -10.25 to -4.42; p <0.001) were negative predictors of change in eGFR from baseline, whereas diabetes status was not associated (p=0.476).

Conclusion: Proteinuria was common, but its prevalence halved after one year of ART. Screening for hypertension could be a simple way to identify patients at risk of renal function decline.

Introduction

Kidney disease is increasingly common amongst people living with HIV (PLWHIV) in both developed and developing settings (1). While estimates vary, PLWHIV in sub-Saharan Africa appear to be at particularly high risk of kidney disease as compared to other global regions (2, 3). This is of concern as, even in the absence of renal failure, kidney disease has been associated with an increased mortality risk in those commencing antiretroviral therapy (ART) in the region (4, 5).

As access to ART becomes increasingly available to PLWHIV in sub-Saharan Africa, the etiology of kidney disease is likely to shift from direct consequences of HIV infection and immunodeficiency to ART-related nephrotoxicity and the same non-infectious comorbidities of concern in the general population such as cardiovascular disease, diabetes, hypertension, which are increasing in prevalence in sub-Saharan Africa (3, 6). How this will impact upon the prevalence of kidney disease remains unclear and this is complicated by the lack of access to routine renal function testing. Further data on renal disease prevalence and risk of renal function decline in PLWHIV commencing ART in sub-Saharan African are needed.

Here we describe the prevalence of renal impairment and proteinuria at baseline and after one year of treatment and explore potential risk factors for worsening renal function, in a large cohort of PLWHIV commencing ART in Zimbabwe.

Methods

Study design and participants

We conducted a retrospective cohort study of ART naïve patients initiating treatment at the Newlands Clinic, Harare, Zimbabwe. The study included all ART naïve patients who attended the clinic between January 2007 and September 2019, aged ≥18 years at the time of ART initiation, and had a measure of serum creatinine at baseline and at one year after commencing ART. The Newlands Clinic is a charitable, not-for-profit, outpatient service dedicated to the management of PLWHIV in suburban Harare. 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.

Data collection and laboratory analysis

Demographic, laboratory and medical history data were extracted from the clinic's electronic medical records. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation with original adjustment for race (7). A patient was considered to have proteinuria if they had a positive urine dipstick (≥1+). Baseline values were those recorded on the day of starting ART or within the preceding month, selecting the value nearest to the starting date. Baseline renal function testing was conducted routinely for all clinic patients. Follow-up measures of serum creatinine, proteinuria and CD4 count were those available at one year from ART commencement ± three months. If there were multiple measures of serum creatinine and/or CD4 count, then the mean value was taken. Additionally, in the follow-up period, any positive dipstick was taken as evidence of proteinuria, even if there were additional negative dipstick tests.

Statistical analysis

Continuous variables are reported as mean (95%CI) or median (IQR), as appropriate. Changes in eGFR, CD4 count and categorical variables from baseline to follow-up were assessed by paired t-test, Mann-Whitney U test and chi-squared tests, respectively. Multiple regression was used to model predictors of change in renal function and logistic regression for predictors of proteinuria. For both analyses, potential predictors were first tested using in single variable models and those with $p<0.100$ were then included in the respective multivariable models.

Results

Baseline characteristics

1,729 patients were included in the analysis. The median age was 36 years (IQR 30 to 43) and the majority of patients (62.8%) were female. Mean BMI was 23.7 kg/m^2 (95%CI 22.9 to 24.6). Nearly one fifth of patients (17.7%) had a background of hypertension. Diabetes mellitus was less common, affecting only 2.2% of patients. Nearly half of patients (49.0%) were WHO Stage I at initiation of ART, followed by Stage II (21.8%), Stage III (19.6%) and

Stage IV (9.6%). Most patients (92.2%) were commenced on an ART regimen containing tenofovir disoproxil, with the remainder being on alternative regimens or missing ART data. A similar proportion of those patients (91.8%) with a baseline eGFR <90 mL/min/1.73m^2 were on a tenofovir disoproxil containing regimen.

Kidney function and proteinuria
At the time of ART initiation, mean eGFR was 131 mL/min/1.73m^2 (95%CI 129 to 132), decreasing to 126 mL/min/1.73m^2 (95%CI 125 to 127) after one year of ART). Although there was a numerical reduction in the proportion of patients with an eGFR <60 mL/min/1.73m^2, this did not reach statistical significance (p=0.094) (Table 1). Of the 21 patients with an eGFR <60 mL/min/1.73m^2 at follow-up, only one had an eGFR <60 at baseline. The proportion of patients with proteinuria halved from baseline to follow-up at one year (11.0 vs 5.6%, p<0.001). Proteinuria at follow-up was a new feature for most patients, with only 12 of the 96 patients having proteinuria which persisted from baseline. At baseline, males were more likely to have proteinuria than females (16.3 vs 10.3%, p=0.002), whereas this trend was reversed at follow-up (4.0 vs 7.0%, p=0.020).

Predictors of change in kidney function and proteinuria
In multiple regression, hypertension (B = -6.43; 95%CI -8.97 to -3.89; p<0.001) and baseline proteinuria (B = -7.33; 95%CI -10.25 to -4.42; p <0.001) were significant negative predictors of change in eGFR from baseline (Table 2). There was no significant association with diabetes status, however (p=0.476). A small negative association with baseline eGFR (B = -1.01; 95%CI -1.04 to -0.98; p<0.001) was also noted, likely representing regression to the mean. None of these factors were predictors of proteinuria after one year of ART (Table 3). Risk of proteinuria at follow-up was nearly doubled by female sex (OR 1.90; 95%CI 1.18 to 3.06; p=0.009), while age was associated with a slight risk increase (OR 1.02; 95%CI 1.00 to 1.05; p=0.022).

Discussion
In this large cohort of ART naïve patients from Zimbabwe, we found a low prevalence of moderate to severe renal impairment, defined as an eGFR <60 mL/min/1.73m^2, of 2.1% at the time of ART initiation. Despite a modest decrease in mean eGFR, there was no increase in the proportion of patients with an eGFR <60 mL/min/1.73m^2. Proteinuria was more common, affecting 11.0% of patients, which halved after one year of ART.

Estimates of the prevalence of renal impairment among ART-naïve patients in sub-Saharan Africa vary considerably. Mild renal impairment (eGFR <90ml/min/1.73m^2) is very common, present in up to 75% of patients in some series (4). The proportion with an eGFR <60 mL/min/1.73m^2 is less considerably less, however, ranging from 1.9% to 23.4% (8-11). Some of this variation is likely artifactual, a consequence of using different estimating equations for glomerular filtration rate (5, 12). There is also geographic variation in prevalence (9), the latter which may partly reflect differences in genetic predisposition (13, 14).

The effect of commencing ART on renal function appears dependent on the degree of baseline renal impairment (8, 11). In multiple sub-Saharan African cohorts, patients with an eGFR <60ml/min/1.73m^2 experienced an improvement in eGFR following commencement

of ART, even when the cause of the underlying kidney disease was unknown (8, 12, 15). In contrast, those without baseline renal impairment have been shown to experience a modest reduction in eGFR, regardless of ART regimen (8). This effect is not restricted to sub-Saharan Africa (16). Given the low prevalence of patients with a baseline eGFR <60 in our cohort mL/min/1.73m^2, the small decrease in mean eGFR observed (-5 mL/min/1.73m^2) is consistent with these previously reported trends.

Limited data previously suggested a high prevalence (45.9%) of proteinuria among ART naïve patients in Harare, Zimbabwe (17). Although these data were collected from an outpatient setting, the small sample size may have resulted in selection bias. Our cohort is an order of magnitude larger and so the 11.0% prevalence of proteinuria likely better reflects the overall rate in PLWHIV in Zimbabwe. Importantly, both the previous and our current study used urinary dipstick to quantify proteinuria. The sensitivity of this method to detect albuminuria (albumin to creatinine ratio ≥30 mg/g) has been reported to be as low as 44.9% (18). Similarly, urinary dipsticks are poorly sensitive for the tubular proteinuria associated with the use of tenofovir disoproxil (19). Thus, our data may underestimate the true prevalence of proteinuria at baseline and after one year of ART.

The low prevalence of diabetes mellitus in our population similar to other sub-Saharan African cohorts (20). Hypertension was common, affecting nearly one fifth of patients, and predicted poorer renal function at one year. Similar findings regarding hypertension were reported in cohorts from Uganda and Zimbabwe and Kenya (9, 11). This is of particular importance given the increasing prevalence of hypertension in sub-Saharan Africa, where most cases remain undiagnosed and uncontrolled (21). This offers a simple potential screening approach to identify patients at risk of deteriorating renal function, even in the absence of routine renal function testing.

As few patients were on ART regimens not containing tenofovir disoproxil, we are unable to draw any conclusions regarding the relationship between the use such regimens with renal impairment and proteinuria. Such regimens, however, do not appear to attenuate the improvement in eGFR seen in other ART naïve cohorts in sub-Saharan African (8), nor increase the risk of renal dysfunction at follow-up (22).

Our data demonstrate that in a Zimbabwean treatment naïve cohort of PLWHIV hypertension and proteinuria were common and predicted loss of renal function after one year of ART. Where renal function testing may be limited by resource constraints, our results suggest that it is safe to commence ART without baseline renal function testing and that screening for hypertension may also be useful to identify patients at risk of renal function decline.

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TABLE 1 Renal function parameters at baseline and after 1 year of antiretroviral therapy ($n = 1729$)

Variable	Baseline	1 year	*P* value
CD4 count (cells/μl)	233 (113–392)	341 (214–481)	<0.001
Proteinuria (urine dipstick reading ≥1+)	191 (11.0)	96 (5.6)	<0.001
eGFR (ml/min/1.73 m^2)			
<30	9 (0.5)	6 (0.3)	0.094
30–59	26 (1.5)	15 (0.9)	
60–90	75 (4.3)	97 (5.6)	
>90	1619 (93.4)	1611 (93.2)	

Note: Values are median (IQR) or *n* (%).
Abbreviation: eGFR, estimated glomerular filtration rate.

TABLE 2 Predictors of change in estimated glomerular filtration rate from baseline after 1 year of antiretroviral therapy

Predictor	B (single variable)	*P* value	B (multivariable)	β	*P* value
Gender (female)	5.72 (1.55 to 8.80)	0.005	0.96 (−0.97 to 2.90)	0.01	0.328
Age	−1.33 (−1.49 to −1.17)	<0.001	−1.22 (1.32 to −1.12)	−0.340	<0.001
BMI	0.06 (−0.07 to 0.19)	0.350	–	–	–
DM	−14.84 (−26.78 to −2.91)	0.015	2.27 (−3.98 to 8.53)	0.01	0.476
HTN	−15.50 (−20.03 to −10.96)	<0.001	−6.43 (−8.97 to −3.89)	−0.07	<0.001
WHO stage					
I	Reference	–	–	–	–
II	0.721 (−3.58 to 5.02)	0.742	–	–	–
III	−3.30 (−7.78 to 1.18)	0.148	–	–	–
IV	−4.86 (−10.90 to 1.19)	0.115	–	–	–
Baseline proteinuria	−15.05 (−20.60 to −9.50)	<0.001	−7.33 (−10.25 to −4.42)	−0.06	<0.001
Baseline eGFR	−1.01 (−1.04 to −0.97)	<0.001	−1.01 (−1.04 to −0.98)	−0.77	<0.001
Baseline CD4 count	0.11 (0.00 to 0.20)	0.010	0.00 (0.00 to 0.01)	0.02	0.079

Abbreviations: BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HTN, hypertension; WHO, World Health Organization.

TABLE 3 Predictors of proteinuria after 1 year of antiretroviral therapy

Predictor	OR (single variable)	*P* value	OR (multivariable)	*P* value
Gender (female)	1.73 (1.08–2.78)	0.021	1.90 (1.18–3.06)	0.009
Age	1.02 (1.00–1.04)	0.022	1.025 (1.00–1.05)	0.022
DM	0.94 (0.22–3.98)	0.937	–	–
HTN	1.60 (0.99–2.58)	0.056	1.24 (0.74–2.01)	0.421
BMI	1.00 (0.98–1.02)	0.777	–	–
WHO stage				
I	Reference	–	–	–
II	1.07 (0.62–1.85)	0.805	–	–
III	1.07 (0.61–1.89)	0.807	–	–
IV	1.23 (0.60–2.50)	0.571	–	–
Baseline proteinuria	1.16 (0.621–2.17)	0.641	–	–
Baseline eGFR	1.00 (0.99–1.00)	0.168	–	–
Baseline CD4 count	1.00 (1.00–1.00)	0.460	–	–

Abbreviations: DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HTN, hypertension; OR, odds ratio; WHO, World Health Organization.