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Assessing Renal Impairment in Treatment-Naïve Adolescents Living with HIV Commencing Antiretroviral Therapy in Zimbabwe

Running Head: Renal Impairment in Adolescents with HIV

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Abstract

Objective: People living with HIV (PLWHIV) are increasingly experiencing non-communicable complications, including renal impairment, which are associated with worse clinical outcomes. Limited information exists surrounding renal impairment in paediatric PLWHIV, of which the majority live in sub-Saharan Africa, and further information is required to guide clinical practice. This study describes the prevalence of new or worsening renal impairment in adolescents commencing antiretroviral therapy (ART) in Zimbabwe and associated risk factors.

Design: Retrospective cohort study.

Methods: Data were collected between January 2010 to January 2019 from the medical records of adolescents aged 12-17 years initiating ART at an outpatient HIV clinic in Zimbabwe. Renal function (eGFR) was calculated using the Full Age Spectrum formula. Proteinuria was defined as a single urine dipstick score of ≥1+. Potential predictors of renal impairment at follow-up were assessed by logistical regression.

***Results*:** 266 adolescents were included in analysis. Baseline renal impairment (eGFR <90 ml/min/1.73m^2) and proteinuria were present in 13% and 7% of the cohort, respectively. After a median of 4.1 years (IQR 1.9, 6.9) following ART commencement, mean eGFR increased by 10 ml/min/1.73m^2 (p<0.01), and the prevalence of renal impairment decreased to 8% (p<0.01). Baseline renal impairment predicted renal impairment at follow-up (OR 8.98; 95%CI 2.81, 28.68; p<0.01). Proteinuria trended towards association with renal impairment at follow-up (OR 4.39; 95%CI 0.95, 20.31; p=0.06).

***Conclusions*:** Renal impairment is common in adolescent ART-naïve PLWHIV, and baseline renal impairment is associated with longstanding renal impairment, while baseline proteinuria trended towards an association with longstanding renal impairment.

***Key Words*:** HIV, Anti-retroviral therapy, Renal insufficiency, Proteinuria, Zimbabwe, sub-Saharan Africa

Introduction

Of the nearly 25 million people living with HIV (PLWHIV) in sub-Saharan Africa (SSA), approximately 5% are children (1). With the widespread implementation of antiretroviral therapy (ART) there has been a transition in the burden of HIV from infectious to non-infectious comorbidities, including kidney disease (2).

Rates of acute kidney injury and chronic kidney disease in PLWHIV have been reported to be nearly four-fold higher than the general population (3). Such complications may partly explain ongoing disparities in life expectancy despite effective ART, with acute renal failure increasing in-hospital mortality in PLWHIV six-fold (4, 5).

Data specific to paediatric populations are comparably limited. Children with end-stage renal disease from HIV-associated nephropathy (HIVAN) were reported to have a nine-fold higher mortality rate than those with renal failure secondary to focal segmental glomerular sclerosis (6). HIVAN is estimated to be present in up to 21-34% of children living with HIV in SSA (7-10), double that reported in the United States early in the AIDS epidemic (11-15). More recently, even mild renal impairment (eGFR <90 ml/min/1.73m^2) was shown to triple mortality risk in adolescent PLWHIV in SSA (16).

What remains poorly described are those risk factors which predispose paediatric patients to developing renal disease. This knowledge could help identify at-risk patients, allowing for early interventions to reduce the prevalence of new or worsening renal impairment and subsequent associated mortality. As such, here we describe the prevalence of, and risk factors for renal disease in adolescent PLWHIV commencing ART in Zimbabwe.

Methods

We conducted a retrospective review of medical records for ART-naïve adolescent PLWHIV at the Newlands Clinic in Harare, Zimbabwe, a non-government organization providing free HIV care to children, adolescents, and adults in the surrounding suburbs. Data were collected from clinic visits between January 2010 and January 2019. Eligible patients were between 12 and 17 years of age, ART-naïve at baseline, with measurements of CD4 count and serum creatinine prior to initiating ART. They required at least one CD4 count and serum creatinine measurement following commencement of ART. This study was granted ethical approval by the Medical Research Council of Zimbabwe (MRCZ/E/258), and research was conducted in accordance with the Declaration of Helsinki.

Data collection

Data were extracted from the electronic medical records of the Newlands Clinic over a median follow-up of 4.1 years (IQR 1.9, 6.9). Participant censorship was at death, loss to follow-up, or transfer of care out of the clinic. CD4 counts were obtained using the CyFlow Counter II (Sysmex, Germany), with severe immunodeficiency being defined as having a CD4 count <200

cells/μL. Prior to 2015, serum creatinine was measured by Reflotron Sprint (Roche, Switzerland), and later measured by a COBAS Integra 400 Plus (Roche, Switzerland). Estimated GFR was calculated using the Full Age Spectrum Formula (17), with renal impairment being defined as an eGFR <90 mL/min/1.73m^2. Urine protein was analyzed using the Combur10 Test UX dipstick read on a Urisys 1100 (Roche, Switzerland). Proteinuria was defined as a single urine dipstick score of ≥1+.

Data analysis

Statistical analyses were conducted using IBM SPSS Statistics 27. Prior to analyses, values for creatinine, eGFR and CD4 count were transformed to fit normal distribution. Creatinine and eGFR were transformed using $\log_{10}$ values, and the square root of the CD4 count was used. The mean and confidence limits of the transformed creatinine, eGFR and CD4 count were calculated, and then back-transformed for reporting purposes. Patient demographic data were compared by unpaired t-test or chi-square test. Baseline measurements were compared to the last available measure for each patient in the study period. Within-group comparisons were made using paired t-tests, whereas comparisons between groups in subgroup analyses utilized unpaired t-tests. In examining predictors of renal impairment, univariate logistical regressions were conducted. Potential predictors of renal impairment at follow-up included baseline eGFR <90 ml/min/1.73m^2, WHO disease stage, baseline CD4 count <200 cells/μL, baseline proteinuria, age, and sex. Variables with $p<0.1$ in univariate models were then progressively included in multivariable logistical regression analyses until the best fit model was produced using the Akaike Information Criterion.

Results

Between January 2010 and January 2019, 284 adolescents with HIV between the ages of 12 and 17 years commenced ART at the Newlands Clinic. Eighteen patients did not have follow-up eGFR data and were excluded from analysis. A total of 266 patients were included in the study, with a median follow-up time of 4.1 years (IQR 1.9, 6.9).

Baseline characteristics are presented in Table 1. The prevalence of baseline renal impairment in this cohort was 13%. Males were substantially more likely than females to have renal impairment at baseline (21.7% vs 6.2%, $p<0.01$) despite being a similar age ($p=0.53$) and having a similar WHO stage distribution ($p=0.30$) and CD4 count ($p=0.15$).

Proteinuria was present in 7% of the cohort. Adolescents with baseline proteinuria had similar age ($p=0.51$), sex distribution ($p=0.88$), WHO stage distribution ($p=0.23$) and prevalence of baseline renal impairment ($p=0.79$) compared to those without proteinuria. Individuals with baseline severe immunodeficiency (CD4 count <200 cells/μL) had a greater prevalence of proteinuria (23% vs 5%, $p<0.01$).

From baseline to last available follow-up, mean eGFR increased by 10 ml/min/1.73m^2 (IQR 7, 13; $p<0.01$). The increase was similar in those with and without baseline renal

impairment (16 vs 9 ml/min/1.73m^2; p=0.17). There was an 8% prevalence of renal impairment at last follow-up (p<0.01 compared to baseline). Of the 21 individuals with renal impairment at follow-up, 10 (48%) also had renal impairment at baseline. At last follow-up there were 15 individuals with proteinuria. Of the 14 individuals with proteinuria at baseline, seven no longer had detectable proteinuria at last follow-up, while eight individuals developed new proteinuria.

Univariate and multivariable logistical regression data are presented in Table 2. Neither WHO clinical stage, age, nor sex were associated with renal impairment at follow-up. In multivariable logistical regression, a baseline eGFR <90 ml/min/1.73m^2 was associated with an approximately nine-fold increase in likelihood of renal impairment at follow-up (OR 8.98; 95%CI 2.81, 28.68; p<0.01); baseline proteinuria approached association with a more than four-fold increased likelihood of renal impairment at follow-up (OR 4.39; 95%CI 0.95, 20.31; p=0.06). Baseline CD4 count <200 cells/μL was excluded from multivariable analysis, as its inclusion was associated with a greater Akaike Information Criterion, suggesting the model had a poorer statistical fit compared to when it was not included in analysis.

Discussion

In this cohort of 266 ART-naïve adolescent PLWHIV in Zimbabwe, baseline renal impairment and proteinuria were common, present in 13% and 7% of patients, respectively. Following ART there was a significant improvement in eGFR and reduction in prevalence of renal impairment. Baseline eGFR <90 ml/min/1.73m^2 was associated with an increased risk of eGFR <90 ml/min/1.73m^2 at follow-up, whereas baseline proteinuria trended towards an association with long-standing renal impairment. To the knowledge of the authors, this is the first study to examine prevalence and risk factors of renal impairment in a large adolescent cohort of ART-naïve PLWHIV in SSA.

The prevalence of baseline renal impairment in the present study was lower than other paediatric HIV cohorts from SSA, which reported baseline renal impairment in 35% and 65% of patients with median ages of 7.5 years (18, 19). This may be a result of these studies calculating eGFR using the modified Counahan-Barratt and modified Schwartz formulas, respectively, which may underestimate eGFR by more than 20% in sick children (20). The discrepancy may also reflect differences in study design, as these studies included children already receiving ART and thus at risk of potential ART-induced nephrotoxicity (21). Regional differences in rates of renal impairment across SSA may also partly explain the variability in findings (22).

The male preponderance for renal impairment in our cohort may be partly explained by HIVAN, which has been shown to be more than twice as common in males (7, 23, 24). Although there was no difference in the prevalence of proteinuria between males and females in our cohort at baseline, this does not preclude differences in the amounts of proteinuria. Unfortunately, this data was unavailable for analysis.

The 7% prevalence of proteinuria in the cohort at baseline is consistent with other studies examining paediatric PLWHIV across SSA, reporting proteinuria in 3-8% of patients (18, 19, 25, 26). Proteinuria trended towards predicting renal impairment at follow-up. Proteinuria has been associated with a doubling of risk of acute kidney injury in adult PLWHIV (27). Proteinuria is also associated with a more than two-fold increased risk of developing chronic kidney disease in PLWHIV (28, 29), in addition to being a consequence of HIVAN (30). This is further supported by the finding that the prevalence of proteinuria was significantly greater in those with baseline severe immunodeficiency, a risk factor for HIVAN (31). However, immunodeficiency is also associated with increased rates of urinary tract infections, which may also lead to proteinuria (18).

There was an increase in eGFR following initiation of ART, consistent with other paediatric (16) and adult cohorts of PLWHIV across SSA (32-34). Despite improvements in eGFR, approximately one-third of adolescents with renal impairment at baseline continued to have renal impairment at last follow-up. This may be partly due to some patients developing chronic kidney disease, or the impact of some ART medications such as tenofovir disoproxil fumarate which have nephrotoxic effects (35, 36). However, this study did not examine prescribed ART medications.

One limitation of this study is that it examined outpatients at a single clinic in Zimbabwe, and thus may not be representative of the larger SSA region or those receiving inpatient care. However, reports of other cohorts have found similar prevalence of proteinuria and improvements in eGFR with ART (16, 18, 19, 25, 26). Additionally, the present study noted a similar baseline eGFR to another cohort of adolescent PLWHIV in SSA (25). Combined with the large sample size, this suggests that the results of the current study are likely generalizable to the broader population of SSA. An additional limitation is that proteinuria data was not collected in all adolescents and was determined by a single urine dipstick measure. Further, eGFR was used as a sole marker of renal function, which can underestimate the prevalence of renal disease in undernourished individuals (37). Despite this, eGFR remains a convenient indicator of renal function, particularly in resource-limited settings. Lastly, there was no baseline data available for HIV viral load or underlying factors which can contribute to renal dysfunction in PLWHIV including BMI, presence of hypertension or diabetes mellitus, ART selection, and concomitant medication. This limits the ability to better contextualize the data. However, the prevalence of these risk factors is expected to be low in this population (38, 39). Despite these limitations, the present study is strengthened by a large sample size with complete data over a four-year follow-up period, with the data reflecting outpatients in a community setting.

Renal impairment was common in adolescents commencing ART, and remained in approximately one-third of these patients despite ART. Baseline renal impairment was the sole predictor of longstanding renal dysfunction, while baseline proteinuria trended towards an association with longstanding renal dysfunction. These findings are important and may have implications for clinical practice. Future studies are needed to examine interventions targeted

at eGFR and proteinuria to determine if modification of these variables is effective in improving health outcomes in this population.

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Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

BB was involved in the design of the study, analysis and interpretation of data, and development of the report. DD was involved in the design of the study, analysis and interpretation of data, and development of the report. TS was involved in interpretation of data and development of the report. CC was involved in interpretation of data and development of the report. RD was involved in interpretation of data and development of the report. DG was involved in the design of the study, interpretation of data, and development of the report. All authors provided approval of the final report for publication.

Data Availability

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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Table 1. Patient characteristics of adolescent PLWHIV commencing antiretroviral therapy in Zimbabwe

	Entire cohort		eGFR >90 ml/min/1.73m^2		eGFR <90 ml/min/1.73m^2		p-value
Variable	n		n		n		
Age (years)	266	14.0 (13.0, 16.0)	231	14.0 (13.0, 16.0)	35	13.0 (13.0, 14.0)	**0.01**
Sex (Female - n)	266	146 (55%)	231	137 (59%)	35	9 (26%)	**<0.01**
WHO Stage (n)	243		213		30		0.60
Stage 1		90 (37%)		81 (38%)		9 (30%)	
Stage 2		79 (32%)		70 (33%)		9 (30%)	
Stage 3		65 (27%)		55 (26%)		10 (33%)	
Stage 4		9 (4%)		7 (3%)		2 (7%)	
eGFR (ml/min/1.73m^2)*	266	117.1 (101.8, 136.8)	231	125.7 (107.7, 140.1)	35	73.5 (70.7, 86.5)	**<0.01**
eGFR <90 ml/min/1.73m^2 (n)	266	35 (13%)	-		-		
Creatinine (µmol/L)*	266	48.5 (43.0, 56.0)	231	48.5 (43.0, 56.0)	35	79.7 (65.0, 85.0)	**<0.01**
CD4 count (cells/µL)¥	266	420 (286, 589)	231	426 (304, 588)	35	380 (197, 633)	0.46
CD4 <200 cells/µL (n)	266	36 (14%)	231	27 (12%)	35	9 (26%)	0.30
Proteinuria (n)	199	14 (7%)	175	12 (7%)	24	2 (8%)	0.79

Age is expressed as Median (IQR). eGFR, creatinine and CD4 count are expressed as Mean (IQR). * Data were back-transformed from log_{10} transformation

¥ Data were back-transformed from square root transformation. PLWHIV, people living with HIV; WHO, World Health Organization; eGFR, estimated glomerular filtration rate.

Table 2. Predictors of eGFR <90 ml/min/1.73m^2 at follow-up in adolescent PLWHIV commenced on antiretroviral therapy.

	Univariate		Multivariable	
Variable	Odds Ratio (95%CI)	p-value	Odds Ratio (95%CI)	p-value
Age	0.89 (0.68, 1.18)	0.42		
Sex	0.73 (0.29, 1.83)	0.50		
WHO Stage 2	0.62 (0.18, 2.10)	0.44		
WHO Stage 3 and 4	1.40 (0.52, 3.81)	0.51		
Baseline eGFR <90 ml/min/1.73m^2	8.00 (3.09, 20.71)	**<0.01**	8.98 (2.81, 28.68)	**<0.01**
Baseline proteinuria	3.93 (0.97, 16.01)	0.06	4.39 (0.95, 20.31)	0.06
Baseline CD4 <200 cells/μL	4.03 (1.50, 10.88)	**<0.01**		

WHO, World Health Organization; eGFR, estimated glomerular filtration rate.