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Chronic kidney disease among children living with the human immunodeficiency virus in sub-Saharan Africa

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ABSTRACT

Background: Chronic kidney disease (CKD) remains an important comorbid condition in people living with HIV. However, data in children living with HIV/AIDS (CLWHA) in sub-Saharan Africa is limited. We sought to establish the prevalence and identify risk factors of CKD among CLWHA in SSA.

Methods: This was a retrospective chart review across five SSA countries HIV/AIDS care sites, March 2000 and June 2016.

Results: 4,859 children with at least two clinic visits were enrolled in the study. The median age at the first clinic visit was 5.7 (IQR; 2.5, 9.5) years, and median follow-up time was 22.6 (IQR 9.8, 46.1) months. 11.2% CLWHA had an eGFR of <60 mL/min/1.73m^2 on at least one clinic visit. The prevalence of CKD was 1.6%. In a multivariable Poisson regression analysis, CKD was associated with severe immunosuppression, incident rate ratio (IRR) 2.69 (95% CI, 1.11, 6.51). Risk of CKD decreased with increasing age (IRR 0.51 (95% CI, 0.39, 0.67). There was no association between CKD and ART regimen.

Conclusion: CKD was not as prevalent as previously reported in children in other studies. Kidney function monitoring should be incorporated into the pediatric HIV care monitoring guidelines to allow for better evaluation of kidney disease in CLWHA.

1. Introduction

The burden of human immunodeficiency virus (HIV) disease in sub-Saharan Africa (SSA) remains daunting with about 1.9 million children living with HIV/AIDS. The SSA region accounts for over 80% of new infections among 0-14-year-olds, producing an estimated 120,000 new cases annually [1]. With the widespread access and use of antiretroviral therapy (ART) regimens, enhanced infection prophylaxis (pre-exposure prophylaxis and prevention of mother-to-child transmission), children infected with HIV are living longer [2–4] and have increased risk of more chronic disease complications including an increased risk for chronic kidney disease (CKD) from medication toxicity, direct virus-associated nephropathy, and other comorbidities. In addition, common co-infections (e.g., gastroenteritis, opportunistic infections) and non-infectious causes (e.g., nephrotoxic medications) may also cause kidney damage and lead to CKD.

CKD remains an important comorbid condition in individuals living with HIV [5–8]. CKD is one of the most common chronic diseases among HIV-positive adults, with prevalence rates ranging from 3.5 to 48.5% [5,8,9]. Other common renal manifestations in individuals living with

Abbreviations: AIDS, Acquired Immunodeficiency Syndrome; BIPAI, Baylor International Pediatrics AIDS initiative; BP, Blood pressure; CD, Cluster of Differentiation; CKD, Chronic kidney disease; eGFR, Estimated glomerular function rate; ART, Highly active antiretroviral therapy; HIV, Human immunodeficiency virus; IQR, Interquartile range; IRB, Institutional review board; NNRTI, Non-nucleoside reverse transcriptase inhibitor; NRTI, Nucleoside reverse transcriptase inhibitor; PI, Protease inhibitor; TDF, Tenofovir; UNAIDS, Joint United Nations Programme on HIV/AIDS; WHO, World Health Organization.

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HIV include acute kidney injury, electrolyte and acid-base disturbances, drug-induced nephrotoxicity, interstitial nephritis, and various glomerular diseases associated with proteinuria [5,10]. Data on the prevalence of CKD in children under the age of 19 years with HIV, especially in resource-limited settings, is limited.

A study from Benin in children with HIV reported a prevalence of CKD of 10.7%. CKD was defined as an estimated glomerular filtration rate (eGFR) of less than 90 mL/min/1.73m^2. In the study of 205 ART-naïve HIV-infected children, CKD correlated positively with the level of immunosuppression [11]. In Nigeria, the prevalence of renal disease in 99 children with HIV on ART was 16.2%, with 5.1% having an eGFR less than 60 mL/min/1.73m^2 [2]. In Tanzania, a study conducted among 240 children with HIV (91% on ART), the prevalence of children with an eGFR less than 60 mL/min/1.73m^2 was 5.8% [12]. A study in the United States describing HIV-associated CKD in 192 children with HIV and adolescents on ART showed comparable results, with a CKD prevalence of 6% [13]. These studies show that CKD is not an uncommon occurrence among CLWHA.

The Baylor College of Medicine International Pediatric AIDS Initiative (BIPAI) is a network of independent, affiliated non-governmental organizations (NGOs) that provide comprehensive care and treatment to children, adolescents, and families living with HIV through clinical centers of excellence (COEs) in six SSA countries. Since 2000, the BIPAI COEs in SSA have provided direct care to over 90,000 people living with HIV and remains one of the world's largest networks of pediatric and adolescent HIV care and treatment. In partnership with their respective Ministries of Health, each COE provides free, comprehensive care for people living with HIV, using a standardized electronic medical record (EMR) system. The BIPAI COEs in SSA are located in Botswana (Gabarone, established 2000), Lesotho (Maseru, established 2005), Eswatini (Mbanane, established 2006), Malawi (Lilongwe, established 2006), Uganda (Kampala, established 2008), and Tanzania (Mbeya and Mwanza, established 2011).

The objective of this study was to estimate the prevalence of CKD among children under the age of 19 living with HIV who received care within the six BIPAI network COEs in five SSA countries from March 2000 to June 2016 and to establish the predictors or factors associated with development of CKD.

2. Methods

2.1. Patient population

This was a retrospective chart review of the existing de-identified clinical data of children living with HIV seen at BIPAI COEs between March 2000 and June 2016 in five SSA countries (Botswana, Lesotho, Eswatini, Uganda and Tanzania). Demographic and clinical data on children under the age of 19, with at least two clinic visits and serum creatinine measurements on two separate visits at least 90 days apart, were extracted from the clinical visits database. Since kidney function tests are not part of routine HIV/AIDS monitoring and only obtained at baseline or when clinically indicated, we expected that only a small proportion of patients would have serum creatinine values throughout the course of follow up. We excluded children without serum creatinine at two different time points and those with less than two clinic encounters.

2.2. CKD Definition

CKD was defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73m^2, measured at least three consecutive months apart. The eGFR was calculated using the modified Schwartz formula using serum creatinine [14]. The eGFR was used to categorize the children into stages of CKD: Grade 3a-eGFR between 45 and 59 mL/min/1.73m^2; Grade 3b-eGFR between 30 and 44 mL/min/1.73m^2; Grade 4-eGFR between 15 and 29 mL/min/1.73m^2; and Grade 5-eGFR less than 15 mL/min/1.73m^2.

2.3. Outcome measures

The primary outcome for our study was proportion of children with CKD (eGFR <60 mL/min/1.73m^2) for at least three months and factors that may be associated with CKD. The secondary outcome was to establish the proportion of children with an eGFR less than 60 mL/min/1.73m2 at any visit.

2.4. A priori variables

Factors identified *a priori* included age in years at HIV diagnosis and at initiation of ART; level of immune suppression based on CD4+ cell count at initiation of ART, categorized as no suppression, mild, advanced or severe immunosuppression; viral load measured only when clinically indicated, categorized as viral suppression or not, with viral suppression defined as a viral load count less than or equal to 1000 copies/mL or documented as undetectable; and duration on ART.

2.5. Statistical analysis

Continuous variables were reported as median and inter-quartile range (IQR) and tested between groups using the Wilcoxon Rank-Sum test. Categorical variables were reported as count (%) and tested by Chi-squared test or Fisher's exact test when expected cell counts were low. To determine independent associations with the primary outcome CKD, multivariable Poisson models with robust standard errors and adjustment for follow-up time were fit using all patients without missing ART regimens (n = 4795). The full model included age at ART initiation, gender, ART regimens (nucleoside reverse transcriptase inhibitor (NRTI) + boosted protease inhibitors (PI) at any visit, two NRTI + a non- nucleoside reverse transcriptase inhibitor (NNRTI) any visit, and other ART regimens (including integrase strand transfer inhibitor (INSTI)-based regimens) at any visit), absence of viral suppression (VL >1000 copies/mL) or missing viral load (vs viral suppression (VL<1000 copies/mL), and severe immunosuppression by CD4 percentage in children under five (<25% in <12 months, <20% in 12-35 months, and <15% in 36-59 months) and absolute CD4 count <200 cells/mm^3 for children >5 years (vs not severe or missing). Age at ART initiation was included in the model as a continuous variable instead of a categorical variable based on better model fit determined by AIC minimization. Adjusted associations were reported as risk ratios (95% confidence intervals). A two-sided p-value <0.05 was considered statistically significant. To visualize average trends in eGFR over the follow-up period, we fit generalized estimating equations predicting eGFR as a non-linear function of follow-up time (1st-4th order polynomial terms) and interaction with CKD group status. This model accounted for repeated measures within patient using an exchangeable correlation structure and robust sandwich estimator for variance. Statistical analyses were carried out using Stata 16 SE (StataCorp, 2020 College Station, TX) software.

2.6. Ethics and Consent

Ethical approval was obtained from the institutional review board at Baylor College of Medicine in addition to each of the relevant institutional review boards in Uganda, Lesotho, Botswana, Tanzania, and Eswatini. A waiver of informed consent was approved by all ethics committees as this was a retrospective chart review using only de-identified data.

3. Results

3.1. Patient characteristics

Of 13,237 children in care at BIPAI sites between March 2000 and June 2016, a total of 4,859 (37%) children with at least two serum creatinine measurements on separate clinic visit dates at least 90 days

Table 1
Patient demographics and characteristics.

	N = 4859
Gender, male n (%)	2386 (49)
Median age at first visit, years (IQR)	5.7 (2.5, 9.5)
Median age at last follow up, years (IQR)	8.2 (5.0, 12.4)
Numbers by clinic location	
Uganda	3182 (65)
Lesotho	1003 (21)
Botswana	613 (13)
Tanzania	30 (<1)
Eswatini	31 (<1)
Level of immunosuppression at initial serum creatinine n (%) (*n* = 4777)	
None	2356 (49)
Mild	600 (13)
Advanced	457 (10)
Severe	1364 (28)
Missing data	82
CD4 status at initial serum creatinine (median (IQR)	
CD4 percentage (<5 y)	24 (16, 33)
CD4 count (≥5 y)	729 (419, 1140)
Viral suppression n (%) (*n* = 2660)	
Yes (< 1000 copies/mL)	1564 (59)
No (≥ 1000 copies/mL)	1096 (41)
Missing data	2199
eGFR at enrollment (median, IQR)	117 (91, 141)
Age at ART initiation (median, IQR)	3.5 (1.4, 7.4)
ART reported during follow up, n (%) (*n* = 4795)[†]	
2NRTI-1NNRTI	2929 (61)
2NRTI-1PI	1518 (32)
Other ART combinations	284 (6)
ART regimen not specified	64 (1)
Tenofovir-containing ART regimen	
Yes	527 (11)
Nephrotoxic ART exposure during follow up[‡]	
Yes	2693 (56)
Patient status	
Active	4,104 (83.9)
Transferred out	526 (10.8)
Died	132 (2.7)
Lost to follow up	129 (2.6)
Proportion of CKD by country	
Lesotho	72 (7.2)
Botswana	2 (0.3)
Uganda	2 (0.1)
Eswatini	1 (3.2)
Tanzania	0 (0.0)

Level of immunosuppression is by CD4 count if ≥ 5y and CD4% if <5 y. [†]Specific ART regimen categories are not mutually exclusive; patients could receive more than one regimen during follow up. [‡] Nephrotoxic ART includes tenofovir, abacavir, indinavir, atazanavir, and efavirenz. CKD: chronic kidney disease, IQR: Interquartile range, NRTI: Nucleoside reverse transcriptase inhibitor, NNRTI: Non-nucleoside reverse transcriptase inhibitor, PI: Protease inhibitor, CD: Cluster of Differentiation. Other ART regimens included an integrase strand transfer inhibitor (INSTI).

apart were enrolled. All participants, (49% male) had at least two clinic visits. The majority of the children were from Uganda (65%), Lesotho (12%) and Botswana (13%). Less than 2% of the total study population was from Eswatini and Tanzania combined. 9.4% of children were under one year of age

The median ages at first clinic visit, ART initiation and last follow-up visit were 5.7 (IQR 2.5, 9.5) years, 3.5 (IQR 1.4, 7.4) years and 8.2 (IQR 5.0, 12.4) years, respectively. The median follow-up time was 22.6 (IQR 9.8, 46.1) months. Fifty-eight percent of patients had been initiated on ART prior to enrollment at the BIPAI sites, 7% were initiated on ART at their first visit and 35% were initiated on ART during subsequent visits.

ART regimen use was reported in 4,795 (97%) of children, with the majority (61%) on two nucleoside reverse transcriptase inhibitors (NRTI) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) at some point during follow up. Thirty-two percent were on 2 NRTIs and a boosted protease inhibitor (PI), and 4% were on other regimens. Eleven percent (527) of patients were on a tenofovir disoproxil fumarate (TDF) containing ART regimens at one point in time. Of the 1.3% (64 of 4859) of patients missing ART regimen data, none had CKD.

3.2. CKD prevalence

In the entire cohort, 545 children (11.2%) had an estimated GFR ≤60 mL/min/1.73m^2 on at least one clinic visit during the follow-up period with serum creatinine back to normal range on subsequent testing. Only 1.6% (77 of 4,859) had CKD. Lesotho had the highest CKD prevalence at 7.2% (72/1003)). CKD prevalence was 3.2% (1/31), 0.3% (2/613), and 0.1% (2/3182) in Eswatini, Botswana, and Uganda, respectively. None of the children in Tanzania had CKD.

Children who met the criteria for CKD were likely to be younger at first visit (median age 0.8 (IQR 0.5, 1.8) years) compared to the children without CKD (median age 5.8 (IQR 2.6, 9.6) years), Rank sum $p < 0.001$. Among those with CKD, the median age at which the first eGFR was ≤60

Table 2
Comparing CKD to non-CKD populations.

	CKD, $N = 77$ n (%)	Non-CKD, $N = 4782$ n (%)	p-value
Median age, IQR (years)	0.8 (0.5, 1.8)	5.8 (2.6, 9.6)	<0.0001
Gender, male	36 (47)	2350 (49)	0.677
Age at first eGFR<60	0.9 (0.5, 2.2)		
eGFR at first visit (mL/min/1.73m^2) median (IQR)	52 (45, 62)	118 (92, 142)	<0.0001
Initial eGFR‡			
≥90	4 (5)	3652 (76)	<0.0001
60-90	18 (23)	912 (19)	
30-59	52 (68)	196 (4)	
15-29	2 (3)	21 (<1)	
<15	1 (1)	1 (<1)	
Nadir CD4 (Median (IQR)			
CD4 percentage	22 (15, 31)	24 (16, 32)	0.402
CD4 absolute count	872 (540, 1479)	740 (442, 1118)	0.005
HIV disease stage by CD4 count at time of initial eGFR			
Stage I (normal)	4 (5)	3652 (76)	0.0001
Stage II	18 (23)	912 (19)	
Stage III	52 (68)	196 (4)	
Stage IV	3 (4)	22 (<1)	
Length on ART, median (IQR)	1.4 (0.8, 2.7)	3.0 (1.2, 6.1)	

‡eGFR using initial patient serum creatinine
IQR: Interquartile range, eGFR: estimated glomerular filtration rate, ART: highly active antiretroviral therapy, CKD: chronic kidney disease, HIV: Human immunodeficiency virus.

mL/min/1.73m^2 was 0.9 (IQR 0.5, 2.2) years, and they did not differ by gender. All children who had CKD were on ART.

3.3. Level of immunosuppression by CD4+, viral suppression, and ART as predictors of CKD

After identifying children with CKD, we evaluated the relationship between CD4 and CKD regardless of when the serum creatinine was drawn. CD4+ cell counts were available for 98% (4,700/4,859) of the children. Among children with CD4+ cell counts at the time of ART initiation, 28% (1,327 of 4,700) had severe immunodeficiency by CD4 percentage if under the age of five and absolute count if ≥ 5 years at some point during their clinical follow-up. Children with severe immunosuppression (CD4% <25% in <12 months, <20% in 12-35 months, and <15% in 36-59 months) and absolute CD4 count <200 cells/mm^3 for children >5 years) were more likely to have CKD, Fisher's Exact $p < 0.001$ (Table 2).

Our cohort included viral load data on 55% (2,660 of 4,859) of participants. Ninety-one percent (70 of 77) of those with CKD and 45% (2,129 of 4,782) of those without CKD had viral loads. The median viral load count for each patient across all visits was 0 (IQR 0, 26186). Viral suppression (VL< 1000 copies/mL) was observed in 59% of patients. Viral load and creatinine are typically measured following national guidelines which may have varied across countries hence introducing bias in the analysis.

We observed that children with CKD had been on ART for a shorter time (median time 1.4, IQR (0.8-2.7) years compared with 3.0, IQR (1.2, 6.1) years in the non-CKD group, Rank sum $p < 0.001$).

3.4. Risk factors for CKD

Multivariable Poisson models with robust standard error (SE) and adjusted for follow-up times were fit with all patients with ART regimen data, a total of 4795 patients (64 were missing ART data). The incidence of CKD decreased by 50% for every one-year increase in age, incident rate ratio (IRR) 0.51 (95% CI, 0.39, 0.67). The risk of CKD in severely immunosuppressed children was more than double that of the children without severe immunosuppression, IRR 2.69, 95% CI, 1.11, 6.51). There was no association between CKD and ART regimens, and we did not find an association between tenofovir (TDF) exposure and CKD. The frequency of kidney function monitoring did not differ by ART regimen.

3.5. Risk factors for eGFR <60 mL/min/1.73m^2 at anytime

A total of 11.2% of children had an eGFR less than 60 mL/min/1.73m^2 on at least one clinic visit. Using a multivariable Poisson regression, we found that increasing age was similarly protective against low eGFR, as observed with the primary outcome of CKD. For every one-year increase in age, the incidence rate of eGFR <60 mL/min/1.73m^2 decreased by 30%, IRR 0.71, (95% CI, 0.62, 0.80).

Among the children with viral loads, virological failure was significantly associated with an eGFR <60 mL/min/1.73m^2 at any visit compared to those who were virally suppressed, adjusted IRR 2.39 (95% CI, 1.29, 4.40, p-value 0.005).

Exposure to other regimes such as integrase inhibitor-containing regimens or protease inhibitor-containing regimens was protective against eGFR <60 mL/min/1.73m^2. However, only 2 patients had ever been on integrase inhibitor-containing regimens and majority in this group were on protease inhibitor-containing regimens. Tenofovir (TDF) exposure was not associated with low eGFR (Table 3). All children on TDF had serum creatinine measured at all visits.

Using a fit generalized estimating equations predicting eGFR as a non-linear function of follow-up time, we observed that the eGFR among the CKD group declined over the first 36 months of follow-up compared to the non-CKD group (Fig. 1).

4. Discussion

There is limited data from SSA on CKD among children living with HIV. Early identification of potentially modifiable predictors of CKD may allow targeted approaches to slow or even halt disease progression in care settings where access to chronic dialysis and renal transplantation is limited. We therefore sought to determine the prevalence of, and the factors associated with, CKD among children living with HIV followed at six BIPAI network sites in SSA. The prevalence of CKD in our retrospective study was 1.6%. CKD was associated with severe immunosuppression, supporting previous studies on the topic [2,12,15].

The prevalence of CKD in our cohort is much lower than that of 5-16% reported in previous pediatric studies in SSA [2,11,13]. These previous studies were conducted in smaller patient populations. The rela-

Table 3
Adjusted risk factors associated with CKD and impaired kidney function (eGFR<60 at any visit) from multivariable Poisson regression models among $n = 4795$ patients with known ART regimen.

	CKD confirmed over 3+ months Incident rate ratios (95% CI)	Impaired kidney function (eGFR<60 mL/min/1.73m^2) at any visit Incident rate ratios (95% CI)
Age at first visit, years	**0.51 (0.39-0.67)**	**0.71 (0.62-0.80)**
Gender, male	0.66 (0.28-1.56)	0.66 (0.57-1.71)
ART at any visit‡		
2NRTI-1NNRTI	1.11 (0.43-2.83)	0.60 (0.29-1.23)
21NRTI-1PI	0.71 (0.29-1.73)	**0.42 (0.23-0.75)**
Other ART combinations	0.66 (0.06-7.66)	**0.13 (0.03-0.63)**
Viral suppression		
Yes	0.32 (0.02-4.84)	**3.52 (1.67-7.42)**
Missing	**43.84 (13.38-143.58)**	**23.88 (12.47-45.76)**
Severe immunosuppression (by CD4 category)	**2.69 (1.11-6.51)**	**2.39 (1.29-4.40)**

CKD: chronic kidney disease, IQR: Interquartile range, NRTI: Nucleoside reverse transcriptase inhibitor, NNRTI: Non-nucleoside reverse transcriptase inhibitor, PI: Protease inhibitor, Other ART regimens: integrase inhibitor-containing regimens and protease inhibitor-containing regimens. CD: Cluster of Differentiation. ‡ reference group is no ART.

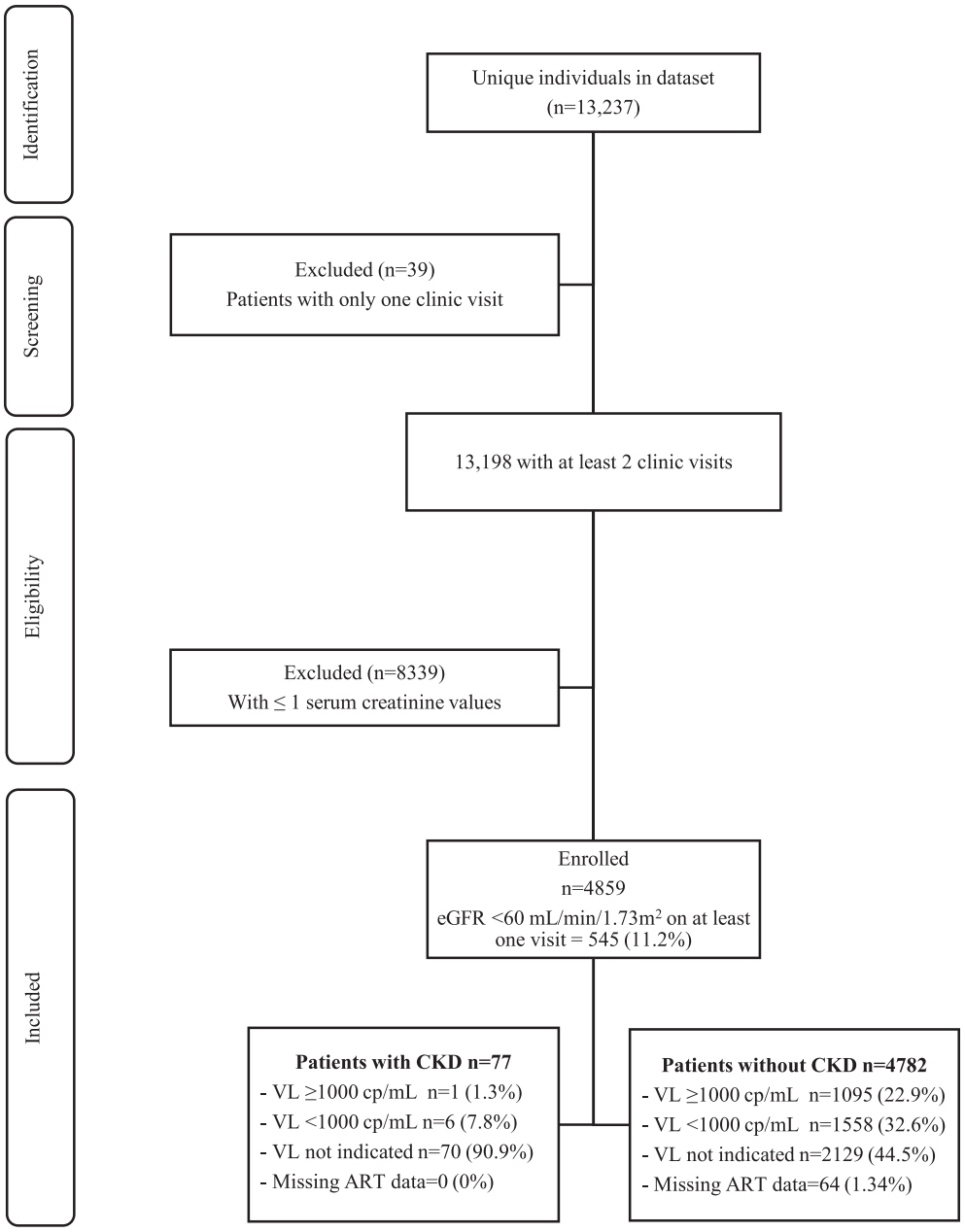

Fig. 1. Consort diagram; This figure displays a consort diagram of the study population selection process. CKD: chronic kidney disease. VL: viral load.

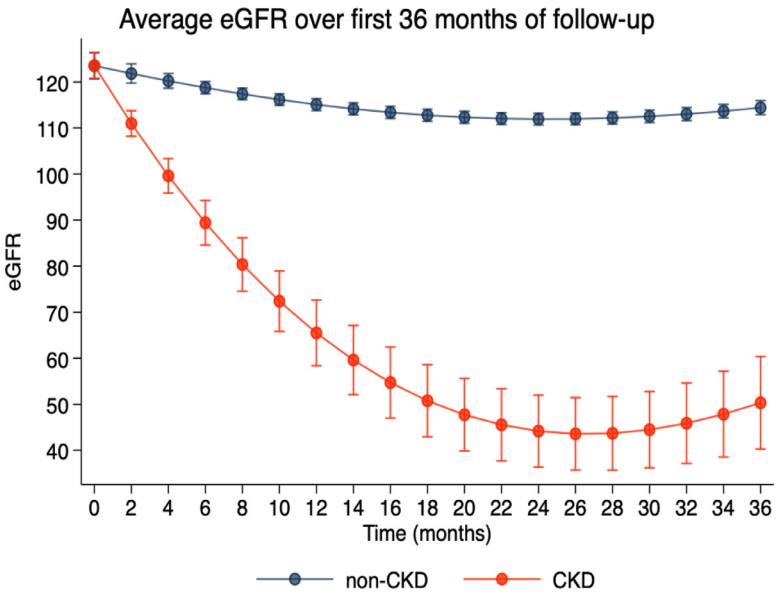

Fig. 2. Estimated glomerular filtration rate overtime among CKD and non-CKD groups.

tively low prevalence of CKD in our study compared to other studies may be due to the use of different cut-offs for eGFR (<60 mL/min/1.73m^2), not including proteinuria or microalbuminuria in the definition of CKD unless they met our CKD definition criterion, and also possibly because there were more children on optimal ART regimens in this cohort. In a study conducted in South African youths with perinatally acquired HIV, with a median age of 12 years, proteinuria and microalbuminuria were prevalent, however all children had normal eGFR [16]. This may suggest that just eGFR is insufficient to screen for CKD and that serial microalbuminuria and proteinuria, which are not part of the current monitoring practice at our study sites, should be considered in addition to serum creatinine. Renal function should also be evaluated periodically in these children. In our study population, only 37% of children had a serum creatinine checked on at least two occasions during the follow up period.

The highest prevalence of CKD in our cohort is in Lesotho (7.2%), where the HIV prevalence in children 0 to 14 years was estimated to be 2.1% in 2016 [17]. The prevalence of CKD was lower in Eswatini (3.2%), Botswana (0.3%), and Uganda (0.1%). This difference could be due to variations in implementation and scale-up of robust early HIV testing and counseling programs, and earlier universal access and implementation of optimal antiretroviral therapy for children with HIV. The role of ART in CKD development remains unclear. Some studies have shown that early initiation of ART may slow progression of CKD [18] while others found that duration of ART, particularly when nephrotoxic agents such as TDF are used, increase the risk of CKD development [19]. Regardless, this underscores the importance of regular monitoring of kidney function to allow timely identification of CKD when it occurs. Limited use of known nephrotoxic antiretroviral therapy such as TDF could also explain the lower CKD prevalence in this cohort. The substantial heterogeneity in the CKD prevalence among the clinic sites could also be due to missing data and/or regional differences in practice and/or variations in *APOL1* risk alleles, a known risk factor for kidney disease in SSA populations [20]. We are not aware of any genetic tests including *APOL1* risk alleles in this study cohort.

In our study, children with CKD were likely to be younger when compared to those without CKD. This is contrary to findings in previous studies where the median age of CKD and/or proteinuria in children living with HIV is early to late teenage years [13], and we found that increasing age was a protective factor against CKD in our multivariate models. This may indirectly be related to the duration of ART exposure with increasing age, or the introduction of better tolerated ART in the older weight brands. Surprisingly, there was no clear association between age with length of follow up, and age at first visit with length of follow up.

Similar to studies by Kalayjian et al and Mocroft et al in adults [21,22], and Iduoriyekemwen et al in children [2,23,24], we found that the risk factors for CKD in children living with HIV were advanced HIV stages (severe immunosuppression), and shorter duration of ART exposure. Abiodun et al, reported an association between advanced HIV stage and CKD in children older than five years. However, this association was not present in children younger than five [11]. Other studies have demonstrated an association between advanced HIV disease and microalbuminuria or proteinuria which are surrogate markers for CKD, especially when persistently present [12,25]. These tests were not performed in our cohort.

Like Woolnough et al. and Hsu et al., we found no association between TDF exposure and CKD in our cohort [26,27]. However, only 11% of our cohort had previously received TDF and had switched to other ART regimens for unknown reasons and we did not analyze the duration on TDF-containing therapy. Changing ART regimen may have contributed to lower prevalence rates.

In addition, we found that 11.2% of children in this cohort had an eGFR below 60 mL/min/1.73m^2 at one point in time during follow up which may suggest an increased risk of acute kidney injury (AKI) in these children. AKI, a common complication in HIV infected individuals can be due to the HIV infection itself, other comorbidities such as gastroenteritis, ART through direct tubular toxicity, interstitial nephritis, or crystal-induced obstruction [28]. AKI is associated with an increased risk for CKD and in one study in HIV+ adults; the hazard ratio was 2.4 [29]. This also, underscores the importance of screening children living with HIV for renal dysfunction through both urine protein and/or microalbuminuria, as well as renal function assays.

Our study was not without limitations. Firstly, follow up time was relatively short with only 37% of children having serum creatinine obtained at least twice during the study period. These laboratory studies were likely obtained only when clinically indicated which may introduce a source of selection bias. This may also reflect variations in clinical practices that have changed over time as well as availability of testing. Short follow up time may have limited identification of incident cases. At least annual monitoring of kidney function is recommended and every 3-6 months for patients on TDF as was done for children on TDF in this study [6,30]. Secondly, serum creatinine by gender, illness severity, nutritional status/diet, muscle mass and certain medications,

making it a less accurate estimation of GFR. In a population such as ours where undernutrition is prevalent, it is possible that serum creatinine overestimates kidney function resulting in CKD under diagnosis. Data on nutritional status for our cohort was not available and cystatin which is increasingly used nowadays was not standard of care in SSA at the time this data was obtained. Thirdly, our study was limited in that it did not include blood pressure or urinalyses data. It is possible that data on microalbuminuria and proteinuria were obtained as point of care readings and tests only when clinically indicated, and data were not systematically captured in the electronic records. Urine dipsticks are widely available and affordable and can be used to screen for proteinuria, identifying patients that need further evaluation.

Fourthly, the inevitable variations in country practices and guidelines over time and across sites could have introduced inherent sampling bias. For example, it is possible that patients with CKD were sicker than those without CKD and therefore more likely to have laboratory monitoring including viral loads. We were not able to assess the relationship between viral load and CKD because viral loads were not routinely obtained, as this was not the standard of care during the majority of the study period. Estimates beyond 36 months of follow-up are not shown in Fig. 2 due to sparse data and limited inference possibly from highly imprecise estimates. In addition, the impact of comorbidities and other non-ART medications was not assessed. To our knowledge, no kidney biopsies were performed on these children so we are not able to determine the proportion of CKD that is attributable to HIV-associated nephropathy.

5. Conclusion

Individuals living with HIV are at an increased risk for developing CKD. The prevalence in children may not be as high as previously reported; however early detection may delay disease progression. Individuals with advanced HIV stages are more likely to develop CKD. Early ART initiation may decrease the risk of CKD especially if the combination regimen does not contain nephrotoxic medications.

Incorporation of systematic screening for pediatric CKD into the monitoring protocols for all children with HIV should be considered. The current World Health Organization (WHO) consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring recommend against initiating TDF if the estimated GFR is < 50 mL/min, presence of uncontrolled hypertension, or existing kidney failure [31]. Monitoring could be as basic as routine blood pressure checks, evaluation for proteinuria and microalbuminuria, and at a minimum, annual kidney function tests regardless of ART regimen to allow for early detection of CKD and timely interventions to delay its progression.

Our findings prompt additional studies to examine the incidence of AKI in children living with HIV and its association with CKD, and risk factors in a more systematic and standardized manner.

Authors' contributions

P.D.I., P.S. and M.C.B. conceptualized the study. C.S.B. participated in formal data analysis. P.D.I. wrote the original draft. R.S.W., P.J.E., S.P.H., K.K., B.L., T.St., T.Se., L.T., and H.H. are BIPAI affiliates who participated in data validation, manuscript review, and editing. All authors read, edited, and approved the final manuscript.

Ethics approval and consent to participate

Ethics approval was obtained from the institutional review board at Baylor College of Medicine in addition to each of the relevant institutional review boards in Uganda, Lesotho, Botswana, Tanzania, and Eswatini. A waiver of informed consent was approved by all ethics committees as this was a retrospective chart review using only de-identified data.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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