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Prevalence of risk factors for chronic kidney disease in South African youth with perinatally acquired HIV

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Abstract

Background Little is known about renal pathology among perinatally HIV-infected children and adolescents in Africa. We assessed the prevalence of risk factors for chronic kidney disease in South African children and adolescents with perinatally acquired HIV-1 (HIV+) on antiretroviral therapy (ART) and HIV-negative children and adolescents.

Methods HIV+ youth aged 9–14 years, on ART for > 6 months and age-matched HIV-negative children and adolescents were eligible for assessment of proteinuria and microalbuminuria using urine dipstick and Vantage analyser method. Blood pressure, estimated glomerular filtration rate, HIV-related variables and metabolic co-morbidities were assessed at enrolment.

Results Among 620 children and adolescents, 511 were HIV+. The median age was 12.0 years and 50% were female. In HIV+ children and adolescents, 425 (83.2%) had a CD4 count > 500 cells/mm³ and 391 (76.7%) had an undetectable viral load. The median duration of ART was 7.6 years (IQR 4.6–9.3) with 7 adolescents receiving Tenofovir. The prevalence of any proteinuria, microalbuminuria and hypertension was 6.6%, 8.5% and 13.9%, respectively, with no difference between HIV+ and negative children and adolescents. All participants had a normal glomerular filtration rate. There was no association between metabolic co-morbidities and microalbuminuria.

Conclusions Proteinuria and microalbuminuria appear to be uncommon in this population. Follow up of those with microalbuminuria may inform long-term outcomes and management of this growing population of HIV+ youth.

Keywords HIV · Perinatal · Children · Adolescents · Microalbuminuria · South Africa

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Introduction

In 2016, there were an estimated 2.1 million children younger than 15 years living with HIV, the majority of who live in sub-Saharan Africa (SSA) [1]. Prior to widespread access to anti-retroviral therapy (ART), the most common cause of chronic kidney disease (CKD) in HIV-infected children was HIV-associated nephropathy (HIVAN) [2]. Access to ART has markedly decreased the incidence of HIVAN and provides renal benefits to prevent CKD in HIV+ people. The benefits of ART on non-HIVAN renal diseases are not yet clear, but there may be beneficial renal effects by decreasing the inflammatory response associated with HIV infection. ART, specifically Tenofovir disoproxil fumarate (TDF), increases the risk of proteinuria in HIV+ children and adolescents [3, 4]. Despite the decrease in HIVAN, results from a large US cohort show that kidney disease is one of the ten most common non-infectious conditions occurring in children and adolescents with perinatally acquired HIV infection in the ART era, with an incidence rate of 2.6 per 100 patient-years [5].

However, there are few data from SSA on the impact of long-term ART use in perinatally infected HIV+ youth on renal disease. This is compounded by little surveillance of kidney disease in HIV+ children and adolescents in SSA [6]. Some South African studies suggest resolution of proteinuria after starting ART in children with HIVAN, with a study in KwaZulu Natal showing 30 (75%) of children had a greater than 50% reduction in proteinuria after starting ART [7].

Proteinuria is a marker of glomerular injury in HIV-related renal disease in children. However, the time from onset of proteinuria to development of CKD can vary from 5 months to 10 years, depending on whether the children receive appropriate ART [8, 9]. Microalbuminuria is a marker of endothelial and/or renal injury, associated with increased inflammatory activity [10, 11]. Previous studies in HIV+ adults have shown that decreased CD4 counts, higher HIV-RNA levels and non-nucleoside reverse transcriptase inhibitors are associated with increased prevalence of microalbuminuria [10]. Studies have reported that microalbuminuria is present in 11–15% of HIV-infected children on ART in the USA, Spain and Brazil [12–14]. However, an Indian study reported that in a cohort of HIV+ children on ART with a mean age of 11.5 years, 20% had microalbuminuria [15]. African studies report rates of microalbuminuria in children ranging from 28.8% in Tanzania [16] to 12% in Nigeria [17], although the majority were not on ART in the Nigerian study and viral load was unavailable in the Tanzanian study.

The primary aim of this study was to investigate the prevalence of proteinuria and microalbuminuria in a cohort of perinatally infected South African HIV+ adolescents on ART, compared to HIV-negative adolescents. A secondary aim was to describe the prevalence of other potential risk factors for CKD, such as hypertension and metabolic abnormalities.

Methods

Study population

This study included all participants enrolled in the Cape Town Adolescent Antiretroviral cohort (CTAAC), a longitudinal cohort study which enrolled 515 HIV+ children and adolescents aged 9–14 years on ART for over 6 months from 7 sites in Cape Town, South Africa, and 110 age-matched HIV-negative youth of similar ethnicity from July 2013 to March 2015 [18].

Ethical approval was given by the Faculty of Health Sciences, University of Cape Town and Stellenbosch University, Human Research Ethics Committee (051/2013). Parents gave informed consent and assent was taken from all adolescents. All HIV+ participants knew their HIV status as a pre-requisite to study enrolment.

Primary outcome

The primary outcome of interest was proteinuria defined as > 500 mg/dl and measured by dipstick or microalbuminuria defined as a urinary albumin/creatinine ratio of > 30 mg/g [19, 20].

Sociodemographic data were collected as part of the enrolment questionnaire, and the participants' clinical records were reviewed at their primary treatment facility.

Physical examination, including Tanner staging, World Health Organisation (WHO) HIV staging, blood pressure (BP) and anthropometry, was performed at enrolment. Weight was measured in kilograms on a Scales 2000[®] digital scale to the nearest 0.1 kg. The standing height was measured using a stadiometer with a moveable headboard in centimetres. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). BMI was classified according to WHO reference standards [19, 21]. BP was measured using an electronic sphygmomanometer (Spot Vital Signs, Welch Allyn[®]) validated in children [22]. Hypertension was defined as a single blood pressure measurement > 95 th percentile for height, age and sex [23].

All anthropometric measures were performed by one of two trained study nurses in order to ensure standardisation of measures.

Laboratory measures included viral load (Roche COBAS Ampliprep/Taqman[®]) and CD4 count (Beckman Coulter[®]) in the HIV infected, as well as urea and electrolytes. Abnormal total cholesterol (TC), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) were defined as > 5.18 , < 1.03 and > 3.37 mmol/L, respectively. Abnormal triglycerides were defined as > 2.85 mmol/L if age < 10 years or > 3.89 mmol/L if age ≥ 10 years at the time of baseline investigations [24]. Insulin was measured using an electrochemiluminescence immunoassay (Cobas 6000, Roche USA[®]) and glucose using the enzymatic method (Roche Cobas 6000, Roche USA[®]). An abnormal highly sensitive (hs) CRP (Ultrasensitive CRP) was defined as a hs-CRP between 1 and 5.0 mg/L.

Serum creatinine was measured in micromoles per litre by the enzymatic method. The modified Schwarz formula was used to estimate glomerular filtration rate (GFR) [25]. A GFR below 90 ml/min/ 1.73m^2 was considered abnormal. If creatinine measures were unavailable at enrolment, GFR was calculated from clinical and laboratory measures performed at the 6-month visit.

Urine was obtained from an early morning sample (as far as possible) and was tested with Multistix[®] dipstick for proteinuria. Proteinuria was defined as > 500 mg/dL. Laboratory analysis of microalbuminuria was done using the Siemens DCA Vantage Analyser[®]. Microalbuminuria was defined as an albumin/creatinine ratio of > 30 mg/g.

Statistical analysis

Baseline variables were compared between groups using *t* tests, Wilcoxon and chi-square tests and odds ratios where appropriate. Univariate analysis was performed to evaluate factors associated with microalbuminuria in HIV-infected children and adolescents. Covariates considered for associations with microalbuminuria included anthropometry, HIV laboratory parameters, metabolic parameters and duration and type of ART. Statistical analysis was performed using Stata version 14.1. StataCorpInc. College Station, Texas USA.

Results

Six hundred and twenty participants (511 HIV+ and 109 HIV-uninfected children and adolescents) had samples available for microalbuminuria. Median age and sex were similar between those with and without HIV infection (Table 1). The median BMI and median height, 17.1 (IQR 15.9–18.9) vs. 18.7 kg/m² (16.8–21.5), $p < 0.01$, and 140.2 (IQR 132.5–147.6) vs. 142.8 (IQR 136.5–155 cm), $p = < 0.01$, were lower in HIV+ than in HIV- adolescents.

Puberty was delayed in HIV+ youth, with half (49.7%) being Tanner Stage 1 compared to 32.4% HIV negative adolescents ($p < 0.01$).

Systolic blood pressure was lower in HIV+ than in HIV negative (105 (IQR 98–112) vs. 108 mmHg (100–118), $p < 0.01$). Eighty-six participants had hypertension (67 HIV+ and 19 HIV-, 13.1 vs 17.4%, $p = 0.24$), of whom 1 had proteinuria and 7 had microalbuminuria.

Rates of hypertriglyceridaemia (OR = 4.56, CI 1.08–19.16, $p = 0.04$) and hypercholesterolaemia (OR = 7.42, CI 1.78–30.81, $p < 0.01$) were higher in HIV+ participants than those who were HIV-. HIV+ children and adolescents had higher rates of raised hs-CRP (OR = 2.23, CI 1.41–3.51, $p < 0.01$).

Over 80% of HIV+ participants had CD4 cell counts > 500 cells/mm³ and 76.7% had a viral load < 50 copies/mL at enrolment.

The median duration of ART was 7.6 years (IQR 4.6–9.3), and the median age at ART initiation was 4.3 years (IQR 2.3–7.5). Three hundred five (60.5%) were on an Efavirenz-based ART regimen with the remainder 188 (37.3%) on a lopinavir/ritonavir-based regimen. Only 7 (1.4%) adolescents were on TDF.

There was no difference in the prevalence of proteinuria between HIV+ and HIV-negative participants (5.9 vs. 10.1%; $p = 0.11$). Two HIV+ participants had 2+ proteinuria and 1 had 3+ proteinuria. No HIV-negative participant had 2+ or 3+ proteinuria. No participant had been referred for a kidney biopsy prior to the study.

The overall prevalence of microalbuminuria was 8.5% with no difference between HIV+ and HIV-uninfected adolescents ($p = 0.8$, OR = 0.9, CI 0.44–1.87). Female sex was predictive of

microalbuminuria regardless of HIV status, OR = 3.81 (CI 2.01–7.41). There was no difference in microalbuminuria according to age, in fact younger children (9–11 years) had a higher prevalence of microalbuminuria than those who were older (12–14 years): 10.3 vs. 6.4%, $p = 0.11$. No participant on TDF had microalbuminuria. All participants had a normal GFR. There were no significant associations between metabolic parameters and microalbuminuria in HIV+ youth (Table 2).

Discussion

The prevalence of proteinuria in the cohort of South African HIV+ youth on ART of 6.6% is similar to a cohort of HIV+ and negative children living in the USA (9%) [26]. This similar prevalence in SA adolescents is surprising, as proteinuria is more frequent in people of African ancestry [27], and the US cohort only had 50% African American children, while almost all our participants were Black African. Furthermore, we found no difference in the prevalence of proteinuria between HIV+ and HIV- South African adolescents; however, only HIV+ children had $\geq 2+$ proteinuria on urine dipstick analysis.

The prevalence of microalbuminuria (8%) in this South African cohort is also lower than the 15% prevalence reported in healthy US children and adolescents in the National Health and Nutrition Survey (NHANES) but is closer to the 7.3% prevalence in healthy adults between the ages of 20 and 39 years in the same study [28]. We found that female sex predicted microalbuminuria regardless of HIV status, as in the NHANES study where females between the ages of 6 and 19 years of age had a similar microalbuminuria prevalence to 60–79-year-old women [28]. The reason for females having a higher prevalence of microalbuminuria is unknown.

Other studies have reported a prevalence of microalbuminuria between 10 and 30% in African HIV+ children [12, 13, 17]. The lower prevalence found in this cohort could be due to children starting ART relatively earlier than in other African cohorts, or fewer children receiving a TDF-based regimen. South African HIV guidelines recommend Abacavir in first-line therapy and switching to TDF is only recommended for adolescents above 15 years of age and 40 kg, as the current available formulation only allows for adult dosing.

Many adolescents switching to TDF have been on Lopinavir/ritonavir (LPV/r) since childhood. Concomitant LPV/r can increase TDF levels by more than 50%. Although only seven participants were on TDF at the time of this analysis, it will be important to monitor renal function, as around 40% of HIV+ youth in our cohort were on protease inhibitor regimens and are likely to switch to TDF in the near future as they reach guideline criteria.

Unlike a similar study in the USA where HIV+ youth tended to have more microalbuminuria, we found no difference in the

Table 1 Baseline characteristics of youth living with perinatally acquired HIV and HIV-uninfected youth

	HIV-infected Adolescents (511)	HIV-uninfected Adolescents (109)	<i>P</i> value
Female	249 (48.7)	60 (55.1)	0.23
Age (years)	12.0 (10.7–13.3)	11.8 (10.1–13.4)	0.40
Black African	473 (92.6)	109 (100)	0.00
BMI (kg/m ²)	17.1 (15.9–18.9)	18.7 (16.8–21.5)	<0.01
BMI Z score	−0.19 (−0.93 to 0.4)	0.36 (−0.43 to 1.0)	<0.01
Height (cm)	140.2 (132.5–147.6)	142.8 (136.5 to 155)	<0.01
Height Z score	−1.27 (−2.09 to −6.2)	−0.59 (−1.22 to 0.03)	<0.01
Prepubertal (Tanner 1)	252 (50.3)	35 (32.41)	<0.01
Pubertal (Tanner 2–5)	249 (49.7)	73 (67.59)	
Tanner 4 and 5	62 (12.38)	21 (19.44)	0.05
Metabolic comorbidities			
Triglycerides (mmol/L)	0.9 (0.7–1.1)	0.7 (0.5–0.85)	<0.01
Hypertriglyceridaemia	40 (7.9)	2(1.9)	0.02
Total cholesterol (mmol/L)	4.1 (3.6–4.7)	3.8 (3.4–4.25)	<0.01
Hypercholesterolaemia	61 (12.3)	2 (1.9)	<0.01
LDL (mmol/L)	2.2 (1.8–2.6)	2 (1.6–2.4)	0.01
High LDL	28 (5.6)	2 (1.9)	0.10
HDL (mmol/L)	1.5 (1.2–1.7)	1.45 (1.2–1.7)	0.51
Low HDL	56 (11.3)	5 (4.63)	0.04
Increased HOMA-IR	78 (20.7)	14 (22.6)	0.74
Systolic BP (mmHg)	105 (98–112)	108 (100–118)	<0.01
Diastolic BP (mmHg)	67 (61–73)	69 (64–74)	0.05
Hypertension	67 (13.1)	19(17.4)	0.24
Highly sensitive CRP	217 (42.5)	33 (30.3)	0.02
Other laboratory values			
Sodium	137 (136–139)	137 (136–139)	0.32
Urea	3.2(2.7–3.9)	3.4 (2.7–3.9)	0.46
Creatinine (serum)	40 (36–46)	44(39–50.5)	<0.01
Glomerular filtration rate	128.5 (114.6–143.7)	122.0 (109.0–138.0)	0.07
Haematuria	8 (1.57)	5 (4.63)	0.04
Any proteinuria	30 (5.9)	11 (10.1)	0.11
Trace	24	8	
1 plus	3	3	
2 plus	2	0	
3 plus	1	0	
Microalbuminuria	43 (8)	10 (9)	0.80
Proteinuria no microalbuminuria	13 (2.5)	4 (3.7)	0.51
Microalbuminuria no protein	26 (5.1)	3 (2.7)	0.30
Microalbuminuria 9–11 years	27 (62.8)	4 (40.0)	0.19
Microalbuminuria 12–14 years	16 (37.2)	6 (60.0)	
HIV-related characteristics			
Viral Load (<i>n</i> , %)			
< 50 copies/ml	391 (76.7)	–	
50–1000 copies/ml	56 (11.0)	–	
1001–10,000 copies/ml	36 (7.1)	–	
> 10,000 copies/ml	27 (5.3)	–	
CD4 count (<i>n</i> , %)			
< 200	10 (2.0)	–	
200–499	73 (14.4)	–	
500–1000	315 (62.0)	–	
> 1000	110 (21.7)	–	
WHO HIV Staging (<i>n</i> , %)			
Stage I	34 (7.0)	–	
Stage II	50 (10.3)	–	
Stage III	291 (59.8)	–	
Stage IV	112 (23.0)	–	
Age at initiation of ARVs			
Median (IQR)	4.3 (2.3–7.5)	–	
0–2 years (<i>n</i> , %)	188 (37.4)	–	
3–5 years (<i>n</i> , %)	138 (27.4)	–	
6–14 years (<i>n</i> , %)	177(35.2)	–	
Duration on ARVs (years)			
Median (IQR)	7.6 (4.6–9.3)	–	
Current ARV regimen			
2 × NRTI + NNRTI (<i>n</i> , %)	305 (60.5)	–	

Table 1 (continued)

	HIV-infected Adolescents (511)	HIV-uninfected Adolescents (109)	P value
2 X NRTI + PI (n, %)	188 (37.3)	–	
Others (n, %)	10 (2.0)	–	
Currently on TDF (n, %)			
Yes	7 (1.4)	–	

All continuous variables expressed as median (interquartile range) or mean (SD) and categorical variables as number (%)

ABC abacavir, AZT zidovudine, ART antiretroviral treatment, BMI body mass index, D4T stavudine, DDI didanosine, HDL high-density lipoprotein cholesterol, HOMA homeostatic model assessment, LDL low-density lipoprotein cholesterol, NRTI nucleoside reverse transcriptase inhibitor, NNRTI non-nucleoside reverse transcriptase inhibitor, PI protease inhibitor, WHO World Health Organization, YLHIV youth living with perinatally acquired HIV

prevalence of microalbuminuria between HIV+ and negative children and adolescents [28].

GFR was also normal with no difference between those with or without HIV. Other cohorts have reported similar findings [13, 14, 26].

HIV+ youth had a lower BMI and were significantly shorter than HIV-negative youth. In addition, HIV+ youth had higher rates of hypertriglyceridaemia, hypercholesterolaemia and hs-CRP, although these comorbidities were not associated with

microalbuminuria (Table 2). Higher rates of lipid abnormalities in HIV+ youth may be expected due to protease inhibitor-based regimens. The fact that hs-CRP was not associated with microalbuminuria was unexpected as it may reflect chronic inflammation, a risk factor for chronic kidney disease.

The low prevalence of renal abnormalities in this cohort is reassuring and most likely reflects the relatively long use of ART. Further long-term study of this cohort and in particular those participants with microalbuminuria will be important for early identification of those who are at risk for developing renal dysfunction.

Strengths of this study are the inclusion of HIV-negative adolescents as a comparison group and the large sample size. However, the study was limited by each participant only having had one measurement of BP, proteinuria and microalbuminuria at the enrolment visit. Additional limitations include lack of measurement of isotope GFR and protein/creatinine measurement. Urine samples were obtained on arrival in the morning but not all samples were ‘early’ morning urines if participants were delayed.

Table 2 Univariate analysis for microalbuminuria in HIV-infected children and adolescents

	Unadjusted OR (CI)	p value
Age, years	0.88 (0.72–1.07)	0.188
Gender		
Male	Ref	
Female	4.45 (2.09–9.48)	<0.001
Blood pressure (mmHg)		
Systolic	1.01 (0.97–1.03)	0.903
Diastolic	0.99 (0.95–1.02)	0.528
Normal	Ref	
Hypertension	0.86 (0.33–2.27)	0.763
Growth measures		
BMI Z score	0.86 (0.65–1.14)	0.295
Laboratory measures		
Normal triglycerides	Ref	
Hypertriglyceridaemia	1.61 (0.59–4.34)	0.351
Normal total cholesterol	Ref	
Hypercholesterolaemia	0.74 (0.25–2.14)	0.572
Normal LDL	Ref	
High LDL	1.89 (0.62–5.73)	0.261
Normal HDL	Ref	
Low HDL	0.58 (0.17–1.95)	0.382
hsCRP		
Normal (< 1)	Ref	
High risk (1–5.99)	0.91 (0.44–1.84)	0.778
Active infection (≥ 6)	1.54 (0.67–3.51)	0.309

BMI body mass index, HDL high density lipoprotein cholesterol, hsCRP highly sensitive CRP, LDL low-density lipoprotein cholesterol, OR odds ratio, CI confidence intervals

Conclusions

Proteinuria or microalbuminuria was equally uncommon in HIV+ youth and HIV-negative adolescents. Assessing for microalbuminuria may allow identification of those at risk of HIVAN in order to implement more intensive follow up. Follow up of participants, especially as they are routinely switched to a TDF-containing ART regimen, may inform long-term outcomes and potential strategies for screening and management of this growing population of HIV-infected youth.

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Compliance with ethical standards

Ethical approval was given by the Faculty of Health Sciences, University of Cape Town and Stellenbosch University, Human Research Ethics

Committee (051/2013). Parents gave informed consent and assent was taken from all adolescents.

Conflict of interest The authors declare that they have no conflict of interest.

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