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

Pediatric Nephrology
https://doi.org/10.1007/s00467-018-4080-6

ORIGINAL ARTICLE

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

Lisa Frigati[1,2,3] · Sana Mahtab[1] · Peter Nourse[1] · Patricio Ray[4] · Sofia Perrazzo[4] · Takwanisa Machemedze[1] · Nana-Akua Asafu Agyei[1] · Mark Cotton[2] · Landon Myer[5,6] · Heather Zar[1,3,7]

Received: 28 March 2018 / Revised: 6 August 2018 / Accepted: 3 September 2018

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/mm^3 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

✉ Lisa Frigati
frigati@sun.ac.za

[1] Department of Paediatrics and Child Health, Red Cross War Memorial Children's Hospital, University of Cape Town, Cape Town, South Africa

[2] Department of Paediatrics and Child Health, Tygerberg Hospital, Stellenbosch University, Cape Town, South Africa

[3] Research Centre for Adolescent and Child Health (REACH) and Medical Research (MRC) Unit on Child and Adolescent Health, Department of Pediatrics and Child Health, University of Cape Town, Rondebosch, Cape Town 7700, South Africa

[4] Center for Genetic Medicine Research and Division of Nephrology, Children's National Medical Center, and Department of Pediatrics, The George Washington University, Washington DC, WA, USA

[5] Division of Epidemiology and Biostatistics, School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa

[6] Centre for Infectious Diseases Epidemiology and Research, School of Public Health and Family Medicine, Cape Town, South Africa

[7] MRC Unit on Child and Adolescent Health, University of Cape Town, Cape Town, South Africa

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 antiretroviral 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].

Published online: 15 September 2018

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 > 95th 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/m^2 (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/mm^3 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 ≥ 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)	*P* 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 (*n*, %)			
< 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 (*n*, %)			
< 200	10 (2.0)	–	
200–499	73 (14.4)	–	
500–1000	315 (62.0)	–	
> 1000	110 (21.7)	–	
WHO HIV Staging (*n*, %)			
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 (*n*, %)	188 (37.4)	–	
3–5 years (*n*, %)	138 (27.4)	–	
6–14 years (*n*, %)	177(35.2)	–	
Duration on ARVs (years)			
Median (IQR)	7.6 (4.6–9.3)	–	
Current ARV regimen			
2 × NRTI + NNRTI (*n*, %)	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.

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

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.

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.

Funding The Cape Town Adolescent Antiretroviral Cohort is supported by National Institutes of Health grant R01HD074051 and the South African Medical Research Council. Lisa Frigati is supported by the South African Medical Research Council.

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.

References

1. UNAIDS W (2017) Fact sheet: world AIDS day 2017. Global HIV statistics
2. McCulloch MI, Ray PE (2008) Kidney disease in HIV-positive children. Semin Nephrol 28:585–594
3. Purswani M, Patel K, Kopp JB, Seage IIIGR, Chernoff MC, Hazra R, Siberry GK, Mofenson LM, Scott GB, Van Dyke RB (2013) Tenofovir treatment duration predicts proteinuria in a multi-ethnic United States cohort of children and adolescents with perinatal HIV-1 infection. Pediatr Infect Dis J 32:495
4. Lim Y, Lyall H, Foster C (2015) Tenofovir-associated nephrotoxicity in children with perinatally-acquired HIV infection: a single-centre cohort study. Clin Drug Invest 35:327–333
5. Nachman SA, Chernoff M, Gona P, Van Dyke RB, Dankner WM, Seage GR, Oleske J, Williams PL (2009) Incidence of noninfectious conditions in perinatally HIV-infected children and adolescents in the HAART era. Arch Pediatr Adolesc Med 163:164–171
6. Naicker S, Fabian J (2010) Risk factors for the development of chronic kidney disease with HIV/AIDS. Clin Nephrol 74:S51–S56
7. Ramsuran D, Bhimma R, Ramdial PK, Naicker E, Adhikari M, Deonarain J, Sing Y, Naicker T (2012) The spectrum of HIV-related nephropathy in children. Pediatr Nephrol 27:821–827
8. Ray PE, Rakusan T, Loechelt BJ, Selby DM, Liu X-H, Chandra RS (1998) Human immunodeficiency virus (HIV)-associated nephropathy in children from the Washington, DC area: 12 years' experience. Semin Nephrol 18:396–405
9. Anochie IC, Eke FU, Okpere AN (2008) Human immunodeficiency virus-associated nephropathy (HIVAN) in Nigerian children. Pediatr Nephrol 23:117–122
10. Szczech LA, Gupta SK, Habash R, Guasch A, Kalayjian R, Appel R, Fields TA, Svetkey LP, Flanagan KH, Klotman PE (2004) The clinical epidemiology and course of the spectrum of renal diseases associated with HIV infection. Kidney Int 66:1145–1152
11. Kim PS, Woods C, Dutcher L, Georgoff P, Rosenberg A, Mican JAM, Kopp JB, Smith MA, Hadigan C (2011) Increased prevalence of albuminuria in HIV-infected adults with diabetes. PLoS One 6:e24610
12. Dimock D, Thomas V, Cushing A, Purdy JB, Worrell C, Kopp JB, Hazra R, Hadigan C (2011) Longitudinal assessment of metabolic abnormalities in adolescents and young adults with HIV-infection acquired perinatally or in early childhood. Metabolism 60:874–880
13. Deyà-Martínez À, Noguera-Julian A, Vila J, Vila A, Valls A, Sánchez E, Jiménez R, Fortuny C (2014) The role of albuminuria in the follow-up of HIV-infected pediatric patients. Pediatr Nephrol 29:1561–1566
14. Leão FVF, de Menezes Succi RC, Machado DM, Gouvêa AFTB, do Carmo FB, Beltrão SV, de Paula Cançado MA, de Abreu Carvalhaes JT (2016) Renal abnormalities in a cohort of HIV-infected children and adolescents. Pediatr Nephrol 31:773–778
15. Sharma G, Mathai SS (2017) Prevalence of asymptomatic microalbuminuria in HIV positive children in India. Indian J Pediatr 84:417–419
16. Mosten IK, Hamel BC, Kinabo GD (2015) Prevalence of persistent microalbuminuria and associated factors among HIV infected children attending a tertiary hospital in Northern Tanzania: a cross sectional, analytical study. Pan Afr Med J 20:251
17. Eke F, Anochie I, Okpere A, Eneh A, Ugwu R, Ejilemele A, Ugboma H (2010) Microalbuminuria in children with human immunodeficiency virus (HIV) infection in Port Harcourt. Nigeria Niger J Med 19:298–301
18. Githinji LN, Gray DM, Hlengwa S, Myer L, Zar HJ (2017) Lung function in South African adolescents infected perinatally with HIV and treated long-term with antiretroviral therapy. Ann Am Thorac Soc 14:722–729
19. Silverstein J, Klingensmith G, Copeland K, Plotnick L, Kaufman F, Laffel L, Deeb L, Grey M, Anderson B, Holzmeister LA (2005) Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. Diabetes Care 28:186–212
20. Babazono T, Takahashi C, Iwamoto Y (2004) Definition of microalbuminuria in first-morning and random spot urine in diabetic patients. Diabetes Care 27:1838–1839
21. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J (2007) Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ 85:660–667
22. Alpert BS (2007) Validation of the Welch Allyn spot vital signs blood pressure device according to the ANSI/AAMI SP10: 2002. Accuracy and cost-efficiency successfully combined. Blood Press Monit 12:345–347
23. Falkner B, Daniels SR, Flynn JT, Gidding S, Green LA, Ingelfinger JR, Lauer RM, Morgenstern BZ, Portman RJ, Prineas RJ (2004) The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 114:555–576
24. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute (2011) Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics 128:S213
25. Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL (2009) New equations to estimate GFR in children with CKD. J Am Soc Nephrol 20:629–637
26. Unsal AB, Mattingly AS, Jones SE, Purdy JB, Reynolds JC, Kopp JB, Hazra R, Hadigan CM (2017) Effect of antiretroviral therapy on bone and renal health in young adults infected with HIV in early life. J Clin Endocrinol Metab 102:2896–2904
27. Rosenberg AZ, Naicker S, Winkler CA, Kopp JB (2015) HIV-associated nephropathies: epidemiology, pathology, mechanisms and treatment. Nat Rev Nephrol 11:150
28. Centers for Disease Control and Prevention (1996) The third National Health and Nutrition Examination Survey (NHANES III 1988–94) reference manuals and reports [CD-ROM]. Bethesda, MD: Centers for Disease Control and Prevention