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Renal Function Abnormalities in HIV-infected Children and Adolescents on Antiretroviral Therapy at the University of Abuja Teaching Hospital, Gwagwalada, Nigeria: A Cross-sectional Study

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Authors' contributions

This work was carried out in collaboration between all authors. Author AAO designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors JOL and DUI managed the analyses of the study. Author MSD managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To determine the degree of renal function abnormalities in HIV positive children and adolescents on highly active antiretroviral therapy in our health institution for baseline information and intervention.
Study Design: A cross sectional hospital based study.
Place and Duration of Study: Department of Paediatrics (Paediatric Outpatient Special Treatment Clinic), University of Abuja Teaching Hospital, Gwagwalada, and Zankli Hospital, Abuja.
Methodology: 161 HIV positive children and adolescents (103 males and 58 females, aged 6months to 18 years who were on highly active antiretroviral therapy overtime in our hospital were

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studied from February to May 2016. Clinical evaluation was carried out which included: blood and urine for urea, electrolytes, creatinine, CD4 cell count, viral load, microalbumin, protein, and heamaturia. Glomerular filtration rate estimate was also calculated with modified Schwartz equation, and kidney sizes assessed with a high-resolution real-time sonographic scanner.

Results: Of 161 patients studied, 137(85.1%) were on 1st line medications, 118 (73.3%) had normal eGFR of > 90 ml/min/1.73 m^2, 22(13.7%) had urine albumin creatinine ratio of >30 mg/gm, 18 (11.2%) had haematuria, and 11(6.8%) had proteinuria. High viral load, and low CD4 cell count were the two most important variables in this study with risk factor for microalbuminuria [OR 4.64 (CI 2.671–8.237), p value = 0.0001] for viral load, and [OR 3.69 (CI 1.938–7.774), p values=0.0001 for CD4 cell count. Other variables with risk factors for microalbuminuria are presence of haematuria [OR 2.22 (1.172–10.240), p value= 0.03]; systolic hypertension [OR 2.73 (1.832–6.244), p value= 0.007]; duration on HAART [OR 2.74 (0.630–7.283), p value =0.041], and types of 1st and 2nd line HAART [OR 2.30 (0.542-6.431), p value= 0.037].

Conclusion: Renal function abnormalities are common among HIV positive children and adolescents on highly active antiretroviral therapy without adequate viral suppression. Regular renal function monitoring to be institutionalized and supported in resource limited settings for earlier diagnosis to forestall development of chronic kidney disease.

Keywords: HIV infected; children; adolescents; estimated glomerular filtration rate; microalbinuria; proteinuria; haematuria.

1. INTRODUCTION

Globally over 3.4 million children are living with HIV infection at the end of 2011, 91% of whom are in sub- Saharan Africa which harbors only 10% of the world population [1,2]. Nigeria which ranks third in the continent is contributing 9% of the global HIV burden, with a sero-prevalence of 4.6%, and 220,000 of her children infected by 2011 [1,2]. The use of highly active anti-retroviral therapy (HAART) has dramatically decreased the incidence of morbidities associated with the infection especially that of HIV associated nephropathy (HIVAN), which is one of the commonest kidney diseases associated with HIV in the black descendants [3,4]. With the long-term use of HAART, drug toxicity and co-infection with chronic viral infections has resulted in an increase in the overall frequency of kidney diseases in HIV-infected individuals [5,6].

Kidney disease is widely recognized and frequent complication of HIV infection which can result from the infection itself, or from associated co-morbidities, malignancies, or adverse effects of therapeutics [7,8]. It often manifest as electrolyte abnormalities, urinary tract infections, renal tubular acidosis, acute kidney injury, treatment-related nephrotoxicity, infiltrative diseases of the kidney, and diseases of the glomeruli [9,10]. The later include chronic glomerular disorders such as HIVAN, HIV immune complex kidney disease (HIVICK), thrombotic microangiopathies including atypical forms of haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura, and IgA nephropathy [10]. HIVAN is the most common renal abnormality among HIV-infected adults in the black populations in the USA, is relatively rare in children, but reported in children in Nigeria and elsewhere, and affects primarily those of African descent [11-13].

Microscopic haematuria and proteinuria are the commonest presenting symptom of kidney disease in two African studies both of which usually proceeded by microalbuminuria (MA) [14,15]. They are believed to be precursors of HIV related renal disease for which early detection and intervention may prevent development of chronic kidney disease (CKD) and end stage renal disease (ESRD) in HIV infected children [14-16]. MA is a predictor, and sensitive marker of early or subclinical renal involvement in systemic and kidney diseases for which early detection is equally important in the prevention of CKD and its consequences [17]. Urine albumin-to-creatinine ratio (UACR) is the first method of preference to detect elevated protein in the urine.

A general lack of surveillance and reporting of kidney diseases in HIV-infected children on HAART exists in most developing regions of the world including Nigeria where HIV is highly prevalent. However, Iduoriyekemwen et al. [15] from Nigeria reported prevalence of renal disease in HIV-infected children on HAART to be 16.2%. CKD and end stage renal disease (ESRD) pose enormous physical and financial burden to patients and their families, and their treatment which relies on dialysis and

transplantation is out of reach to many families in resource poor countries like ours. Consequently, regular renal monitoring of HIV infected children and adolescent on HAART should be internalized for early intervention in order to guide against development of CKD and ESRD with its enormous financial management. We therefore conducted this present study to document the prevalence of structural and renal function abnormalities and their risk factors among HIV-infected children and adolescents on HAART at a tertiary health institution in Abuja, Nigeria.

2. MATERIALS AND METHODS

A cross sectional study was carried out at the paediatric out-patient special treatment clinic (POSTC) of the university of Abuja teaching hospital (UATH) over a 4 months period of February to May 2016. POSTC is an out-patient clinical service area where HIV infected children and exposed babies were followed up for treatment and monitoring. It has consulting rooms for the doctors, the nurses, and adherence counselors. Record clerks, pharmacists, and nutritionists are also at their disposal on week days (Monday-Friday, from 7.30 am to 4 pm.). UATH is a 350 bed capacity referral hospital, sub-serving the people of Federal Capital Territory (FCT) Abuja and five neighbouring states. Is one of the first centers to start offering free HIV/AIDS services in the country, through the President Emergency Plan for AIDs Relief (PEPFAR) since 2005.

The subjects were paediatric HIV infected patients 6 months to18 years diagnosed by either by serological method or by deoxy-ribonucleic acid (DNA) polymerase chain reaction (PCR) test and started on ARV therapy. Consecutive eligible children attending the POSTC were recruited and subsequently enrolled into the study after parents/caregivers have provided written informed consent and children 7 years and above provided verbal assent. Inclusion criteria for the study were: HIV infected children and adolescents from 6 months to 18 years of age on ARV therapy, patients/caregivers/children residing within FCT Abuja for easy collection of early morning urine, parents/caregivers acceptance to be part of the study, older children who gave ascent for the study. Exclusion criteria include those unwilling to participate in the study, exposed babies, those residing outside FCT, and patients with other forms of nephropathy such as nephrotic syndrome, acute glomerulo- nephritis, etc.

Clinical evaluation and physical examination including blood pressure measurement, weight, and length/height were carried for all recruited subjects by the attending physician. The participants were clinically staged according to WHO clinical and immunological staging system. A clean catch midstream early morning urine sample was collected from older children and adolescents for proteinuria and haematuria using Combi 10. For infants, a clean-catch morning urine sample was also used. The parent/caregiver of the infant was advised to hold the child on her laps with the genitals exposed; urine that was spontaneously voided after drinking was caught in a urine container given prior to the test. HIVAN was diagnosed with nephrotic range proteinuria, hypoalbuminaemia and normal or low cholesterol levels [13,18-20]. The clinical entity called MA was defined as the presence of 30 to 300 mg albumin/g creatinine on a first morning urine specimen, [21-23] and was measured using automated Chemwell analyzer based on bromocresol green methodology, while Jaffe kinetic was used for creatinine. Microscopic haematuria was defined as the presence of 5 or more red blood cells (RBC) per high power field (phf) in two consecutive, fresh centrifuged specimens obtained at least 1 week apart, and proteinuria, a positive dipstick test of ≥+1 corresponding to ≥ 30 mg/dL, [15,24,25] Blood sample was also collected for serum electrolyte, urea and creatinine, and were analysed using Electrolyte Analyser (*model:1SE 6000 by SFRI Sarl France*). CKD was defined as: (1) evidence of structural or functional kidney damage (abnormal urinalysis, imaging studies, or histology) present for at least 3 months with or without a decreased glomerular filtration rate (GFR); or, (2) decreased kidney function (GFR <60 mL/min per 1.73 m^2), with or without evidence of kidney damage [22,23]. Estimated GFR (eGFR) was calculated using modified bedside Schwartz equation [25,26]. This was used to determine the severity of kidney disease. An eGFR of less than 60 ml per min per 1.73 sq m^2 for three months or more indicates CKD, and level less than 15 signals kidney failure. Normal range is from 90 to 120 ml per min per 1.73 sq m^2. Same blood sample collected was also use for $CD4^+$ T-cell count, and viral load (VL) for those who have not done theirs CD4 cell count in the last 3 months, and for those who have not done their viral load in the last 6 months. CD4 cell count was measured using automated Partec Cyflow easy count kit (*Partec code no. 05-8401 Western Germany*), VL measurement was with (*Roche Smp /prep /cobs*

Taqman 96, USA), and Seca beam weighing scale accurate to the nearest 0.01 kg was used for measuring their weight. For the sonographic assessment of kidney sizes, a high-resolution real-time sonographic scanner with 3.5-MHz convex transducers was used by a consultant radiologist.

Ethics clearance was obtained from the Ethics Committee of the health institution before the commencement of the study. Data analysis was conducted using SPSS version 21.0 that produced frequencies, percentages, means, and standard deviations. The tests for associations and differences were done by student t-test to compare continuous variables while association between categorical variables was determined using Chi-square and Fisher's exact tests. Univariable logistic regression and multivariable logistic models were performed to determine predictors of microalbuminuria, proteinuria, and haematuria. Crude and adjusted odds ratio (OR) were reported, p value of <0.05 was considered statistically significant.

3. RESULTS AND DISCUSSION

Characteristics of the study population based on 1st and 2nd line HAART was shown in Table 1. While more patients 137(85.1%) were on 1st line medications, more males 103(64.0%), and more Christians 110(68.3%) were the study participants. Their mean age, body weight, length/height, BMI, systolic and diastolic blood pressure were 10.13±4.5 years, 30.62±12.3 kg, 136.06±17.8 cm, 15.92±0.58 kg/m^2, 93.50±9.9 mmHg, and 56.43±10.3 mmHg respectively. Their mean CD4 cell count, VL, eGFR and UACR were

Table 1. Characteristics of the study population on first and second line antiretroviral therapy

Characteristics	1st line ARV (%)	2nd line ARV (%)	Total (%)	P value
Study population	137(85.1)	24(14.9)	161 (100.0)	.004
Age (years)	9.6±4.4	11±3.0	10.13±4.5	.386
Sex				
Male	90 (64.7)	13(59.1)	103(64.0)	.003
Female	49 (35.3)	9(40.9)	58(36.0)	.042
Religion				
Christianity	96 (69.1)	14(63.6)	110(68.3)	.038
Islam	43 (30.9)	8(36.4)	51(36.7)	.027
Anthropometry				
Weight (kg)	29.30±1.0	34.64±3.0	30.62±12.3	.058
Length/Height (cm)	133.13±1.66	143.48±3.7	36.06±17.8	.021
BMI (kg/m^2)	16.37±0.69	15.92±0.6	16.01±3.0	.821
ARV duration (years)	9.40 ± 0.56	6.41±0.28	7.91±3.2	.035
Blood pressure (mmHg)				
Systolic BP	93.04±1.82	94.91±2.2	93.50±9.9	.405
Diastolic BP	57.04±0.78	55.46±2.3	56.43±10.3	.463
Urea and Electrolytes				
Serum creatinine (mmol/l)	0.54±0.12	0.53±0.35	0.55±.15	.907
'' urea (mmol/l)	19.20±0.48	19.0±1.29	19.14±5.6	.200
'' sodium (mmol/l)	131.76±0.53	131.9±1.19	131.79±6.1	.914
'' bicarbonate (mmol/l)	21.88±0.34	20.59±0.56	21.73±3.87	.154
'' chloride (mmol/l)	99.27±0.37	99.23±0.83	99.16±4.29	.969
'' potassium (mmol/l)	3.9±0.91	3.79±1.61	3.74±1.52	.097
eGFR (ml/min/1.73 m^2)	109.53±33.6	111.01± 36.2	110.74±28.2	.753
Urine value & kidney size				
Right kidney length (cm)	8.12±1.4	8.43±0.9	8.09 ±1.24	.324
Right kidney width (cm)	3.40±0.52	3.65± 0.3	3.41±0.52	.391
Left kidney length (cm)	8.14±1.3	8.17±1.2	8.11±1.29	.042
Left kidney width (cm)	3.61±0.9	4.05± 0.6	3.62±0.90	.845
UACR(mg/g)	8.09±0.9	8.23±1.0	8.19±0.92	.876
CD4 and viral load				
CD4 (cells/µl)	963.80±40.40	925.10.9 ±10.9	944.49± 25.7	.027
Viral load (copies/ml)	15,702.73±79.4	3,732.03±15.82	9,717.38±47.2	.003

ALT: Alanine transaminase, AST: Aspartate transaminase, ALP: Alkaline phosphatase, BMI: Body mass index

also 944.49±25.7 cells/µl, 9,717.38±47.2 copies/ml, 110.74±28.2 ml/min/1.73 sq m^2, and 8.19±0.92 mg/gm respectively. Most of the study participants 138(85.7%) were in WHO stage 1 clinical disease, most 118 (73.3%) also had a normal eGFR of > 90 ml/min/1.73 sq m^2. Only 2(1.2%) had a mean eGFR of <60 ml/min/1.73 sq m^2. 22(13.7%) of the study participants had MA (UACR) of >30 mg/gm, 18 (11.2%) had haematuria, and 11(6.8%) had proteinuria. Their mean right and left kidney sizes were within normal limit (8.27±1.15cm x 3.52±0.41cm and 8.15±1.25cm x 3.62±0.9), so also was their mean serum electrolyte, urea, and creatinine. However, 35 (21.7%) had increased echogenicity with 1(0.6%) had gross kidney enlargement, 2(1.2%) had high urea of > 40 mmol/L, and 2 (1.2%) also showed creatinine of > 1.2 mmol/L.

Table 2 shows the renal function tests based on the age ranges of the study population. It was not surprising that there was statistical significant difference between the ages of the patients, their length/height, their systolic and diastolic blood pressure, and the sizes of their right and left kidney sizes for the different age ranges of the study participants because of their age differences. There was however statistical significant difference in VL for the difference age ranges, a study variable that is not influenced by age (P=0.002).

Table 3 is the representation of renal function tests and types of 1st and 2nd line HAART. No significant difference was seen in renal function tests among the study population on 1st and 2nd line HAART except for their V (P= 0.002 for 1st line, and 0.004 for the 2nd line).

Table 4 shows factors associated with MA. It was observed that MA was significantly associated with the following variables: duration of HAART [< 10 yrs Vs > 10 yrs] (p=0.046), type of 1st and 2nd line HAART (p=0.023), CD4 % age [>25% Vs <25%] (p= 0.001), VL [<20 Vs > 20] (P=0.001), presence of haematuria (p=0.011), and systolic blood pressure [> and < 95th centile] (p=0.027). Children with higher VL (of >20 copies/ml) had over 4 fold increase likelihood of having MA when compared to those with VL of <20 copies/ml. Children with CD4 %age (<25 %) had also greater than 3 fold likelihood of having MA when compared to their counterpart with CD4 % age of ≥25 %. Greater than 1.5 fold likelihood of MA was also seen in children with haematuria and those with systolic blood pressure of > 95th centile.

Table 2. Age distribution of study population and renal functions

Parameter	6 mths – 5 yrs (n=24)	6 yrs – 10 yrs (n=72)	11 yrs – 15 yrs (n=53)	16 yrs - 18 yrs (n=12)	P value
Wt (kg)	17.0±0.6	25.5±0.9	37.3±1.4	51.0±3.1	.000
Lt/Ht (cm)	110.4±1.9	130.9±1.4	145.0±2.7	157.9±4.5	.000
BMI (kg/m^2)	14.9±0.3	16.9±0.4	17.9±3.8	18.7±1.18	.821
SBP(mmHg)	85.0±1.7	90.3±0.9	98.8±1.1	103.3±2.2	.013
DPP (mmHg)	53.6±1.7	54.9±1.0	60.4±1.4	58.8±0.7	.024
Serum creatinine (mmol/l)	0.6±0.0	0.6±0.0	0.5±0.1	0.4±0.0	.751
” urea (mmol/l)	19.6±1.2	19.5±0.8	19.1±0.8	16.7±1.4	.132
” sodium (mmol/l)	132.5±0.9	131.5±0.8	131.6±0.9	132.6±0.8	.652
” potassium (mmol/l)	3.5±0.7	3.8±1.6	3.7±0.6	3.1±0.7	.977
” NaHCo3 (mmol/l)	21.74±1.2	22.0±0.4	21.1±0.5	22.3±0.9	.935
” chloride (mmol/l)	96.75±0.3	99.1±0.4	99.7±0.8	98.9±1.2	.782
eGFR (ml/min/1.73 sq m^2)	113.0±34.8	100.7±27.1	128.6±43.6	117.17±31.8	.075
UACR (mg/g)	6.87±1.1	9.67±3.7	6.77±1.9	5.96±0.8	.473
Length of Rt Kidney (cm)	7.83±0.1	8.2±0.2	8.28±0.18	8.4±0.3	.207
Width of Rt Kidney (cm)	3.5±0.1	3.3±0.1	3.5±0.07	3.4±0.1	.498
Length of Lt Kidney (cm)	8.05±0.3	8.0±0.2	8.17±0.18	8.3±0.3	.031
Width of Lt Kidney (cm)	3.55±0.1	3.6±0.1	3.57±0.87	3.9±0.6	.201
CD4 cell count (ul/ml)	1,202.9±10.9	933.6±57.0	937.8±59.2	711.3±10.7	.063
Viral Load (copies/ml)	2869.1±596.6	9561.9±883.5	4980.5±582.9	57.5±12.4	.002

BMI: Body mass index, SBP: Systolic blood pressure, DPP: Diastolic blood pressure, eGFR: Estimated glomerular filtration rate, NaHCo3: Sodium bicarbonate, UACR: Urine albumin creatinine ratio

Table 3. Renal function tests and type of 1st and 2nd line HAART

	1ST Line HAART				2ND Line HAART				
E/U/C (mmol/l)	**AZT+3TC+ NVP (n= 88)**	**ABC+3TC+ NVP(n= 45)**	**D4T+3TC+ EFV (n= 4)**	**P value**	**AZT+3TC+ LP/r (n= 11)**	**ABC+3TC+ LP/r (n= 6)**	**TDF+3TC+ LP/r (n= 4)**	**TDF+EMT+ LP/r (n=3)**	**P value**
urea	19.2±5.5	19.01±2.4	20.0±0.1	.258	19.3±1.6	18.0±2.8	22.0±1.9	19.1±0.4	**.324**
creatinine	0.55±0.5	0.55±0.5	0.42±0.03	.040	0.56±0.1	0.48±0.1	0.52±0.1	**0.51±0.1**	.025
Na+	131.75±6.1	128.75±9.6	134.01±2.1	.557	133.2±4.5	127.7±11.3	132.5±2.8	**131.7±6.1**	.468
K+	3.78±0.8	3.6±0.7	4.2±0.5	.841	3.02±1.1	2.27±0.3	4.8±0.4	3.8±0.7	.881
NaHco3	21.74±4.1	19.4±4.8	22.1±2.2	.826	21.8±4.1	21.7±2.8	20.8±4.7	21.1±1.6	.725
Cl	99.51±5.0	96.5±1.29	97.11±8.3	.793	98.7±0.8	99.7±1.4	99.7±1.8	99.2±1.0	.655
eGFR(ml/min/1.73 sq m^2)	109.53±33.6	140.80±5.24	157.35±14.1	.388	105.7±5.0	139.4±18.7	107.7±11.9	121.5±7.8	.458
UACR (mg/g)	8.09±0.9	14.4±6.7	10.2±2.1	.506	7.4±1.2	5.9±2.1	17.1±5.9	2.5±1.7	.335
CD4 +(ul/ml)	889.47±36.3	869.5±211.6	1185.51±6.1	.909	892.7±35.9	901.7±13.3	1183.7±12.8	938.5±14.5	.835
VL(copies/ml)	6699.4±34.2	281.67±22.8	59.0±2.1	.002	2994±35.6	481.1±15.8	54.7±2.8	20.0±0.0	.004

E/U/C: Electrolyte/ urea/ creatinine, Na+: Sodium, K+: Potassium, eGFR: Estimated glomerular filtration rate, VL: Viral load

Table 4. Factors associated with microalbunuria (n=22)

Variables	N (%)	Microalbunria present (%)	P value
Age in years			
<5 years	24 (14.9)	2(8.3)	
5-10 years	72(44.7)	9(12.5)	
>10 years	65(40.4)	11(16.9)	.525
Sex			
Male	103(64.0)	15(14.7)	
Female	58(36.0)	7(12.1)	.296
Religion			
Christian	110(68.3)	13(11.8)	
Moslem	51(31.7--)	9(17.6)	.122
Duration on HAART			
<10 years	146 (90.7)	18(12.3)	
>10 years	15(9.3)	4(26.7)	.046
Type of HAART			
1st line	137(85.1)	16(11.7)	
2nd line	24(14.9)	6(25.0)	.023
CD4 cell count			
< 25%	67 (41.6)	17(25.4)	
>25%	94(58.4)	5(5.3)	.001
Viral load	**--**		
<20	75 (46.6)	3(4.0)	
>20	86(53.4)	19(22.1)	.001
Presence of haematuria			
Yes	18 (11.2)	12(66.7)	
No	143 (88.8)	8(5.6)	.011
Systolic blood pressure			
< 95th centile	145 (90.1)	12(8.2)	
>95th centile	16 (9.9)	8(50.0)	.027
Renal echogenicity			
Normal	128 (78.3)	18(14.3)	
Increased	35 (21.7)	4(11.4)	.742

Table 5 showed multivariate logistic regression and risk factor for MA. High VL and low CD4 cell count were the two most important variables with risk factor for MA in this study [OR 4.6 (CI 2.671–8.237); aOR 6.54 (CI 3.761–13.246)), P = 0.0001] for VL, and [OR 3.69 (CI 1.938–7.774); aOR 5.13 (2.369–14.326), P=0.0001 for CD4 cell count. Other variables with risk factors include; presence of haematuria [OR 2.22 (1.172–10.240); aOR 3.84 (0.173–14.153), P= 0.03]; systolic hypertension [OR 2.73 (1.832–6.244); aOR 2.76(1.186-12.974), P= 0.007]; duration on HAART [OR 2.74 (0.630–7.283); aOR 3.19 (1.0345–7.820), P =0.041], and types of 1st and 2nd line HAART [OR 2.30 (0.542-6.431); aOR 2.76(1.579-8.381), P= 0.037].

3.1 Discussion

MA has been reported to be predictor, and sensitive marker of early or subclinical renal involvement in systemic and many HIV kidney diseases. This was seen in 13.7% in this study. The finding was similar to 11.1%, 12.0% earlier reported among HIV positive children in Nigeria studies, [14,24] and 15% from USA. [20] It was however lower than 20.4% from Tanzania, [16] 25.0% from South Africa, [27] 28.8% from another Tanzania study, [28] and 35.6% among HIV adults in Ilorin, Nigeria. [29] The high prevalence found in this study was however much higher than 0% recorded at Enugu in Nigeria, [30] and 6.7% from Kano, Nigeria. [31] The differences in the prevalence of MA among HIV positive children across the country and the globe may not be unrelated to the different cut-off values used for defining MA form different studies, different methods used in assaying MA, the differences in the sample size and study population of various studies, and weather study population was HAART naïve or not.

Table 5. Multivariated logistic regression and risk factor for microalbuminuria

Variable	Crude OR (95 % CI)	P value	Adjusted OR (95% CI)	P value
Duration on HAART				
<10years	Ref			
>10years	2.736 (0.630–7.283)	.023	3.187 (1.0345–7.820)	.041
Type of HAART				
1st line	Ref			
2nd line	2.296 (0.542-6.431)	.021	2.756(1.579-8.381)	.037
CD4 cell count				
<25%	Ref			
>25%	3.686 (1.938–7.774)	<.0001	5.134 (2.369–14.326)	<.0001
Viral load				
<20	Ref			
>20	4.635 (2.671–8.237)	<.0001	6.544 (3.761–13.246)	<.0001
Presence of Haematuria				
No	Ref			
Yes	2.227 (1.172–10.240)	.034	3.844 (0.173–14.153)	.013
Systolic blood pressure				
<95th centile	Ref			
>95th centile	2.731 (1.832–6.244)	.018	2.756(1.186-12.974)	.007
Age of patients				
<5 years	Ref			
5-10 years	1.088 (0.712–2.673)	.619	2.144 (2.278–8.724)	.224
>10 years	1.432 (0.843–3.254)	.273	3.220 (1.254–9.711)	.043

Variables with strong association with MA are VL [OR 4.635 (2.671–8.237), P <0.0001] and CD4 cell count [OR 3.686 (1.938–7.7740), P <0.0001] in this study. Other variables with some degree of association included: duration on HAART [OR 2.296 (0.542-6.431), P =0.023)], type of used HAART [OR 2.296 (0.542-6.431), P =0.021], presence of haematuria [OR 2.227 (1.172–10.240), P=0.034], and presence of systolic hypertension [OR 2.731 (1.832–6.244), P=0.018]. While CD4 cell count determines the degree of immune suppression of an individual, VL is an indicator of the extent of viral suppression. High VL and low CD4 cell are not only indicator of advance HIV disease, but also well-established risk factors for the development of HIVAN. HIVAN is the most aggressive kidney disease affecting 10% of HIV-infected adults [6,9]. The true prevalence of paediatric age group is unknown because kidney biopsies are not regularly performed in all HIV-infected patients with proteinuria and haematuria [8,10,19,21]. Hence the following criteria was adopted and in used for diagnosis of HIVAN in children: the presence of persistent proteinuria defined as UPCR≥0.2 for 3 months or more in the absence of acute infection especially in children of African descent, urine sediment with urine microcysts, highly echogenic kidneys by serial renal ultrasound at 3 months apart, and black race with history of nephrotic-range proteinuria with or without oedema or hypertension [12]. In the present study aside from MA that was detected in 13.7% of the study population, haematuria and proteinuria were also documented in 11.2% and 6.8% respectively. This finding was similar to proteinuria of 5% reported from Zimbabwe, [32] 7.1% from Tanzania [20] and 12.0% [24] in one Nigerian study. Higher values of 37.9% was observed by Esezobor et al, [33] 33.0% by Chaparro et al, [22] and 100% each among positive children with HIVAN in Nigerian and Indian studies [13,34]. Haematuria of 11.2% documented in this study was also seen in similar other studies. 12.5% among HIV positive children by Senguttuvan et al. [35] from India, and 4.2% in Tanzania by Fredric et al. [16] Microscopic haematuria, with proteinuria (75%) or without (50%) was the commonest presenting symptom of kidney disease in two African studies

thus noting its importance as early sign and symptom in patients with HIVAN and other HIV-related kidney diseases [10,22]. The subsequent development of nephrotic syndrome and CKD represent the commonest manifestations of HIV-related glomerular disease [10]. CKD in children with HIV infection usually has an insidious onset [36]. The strategy to minimize kidney damage is by screening urine for haematuria, proteinuria and even MA, as MA was reported in association with nephropathy in South Africa study by Han et al. [14] in 24 % of cases.

MA which usually precedes microscopic haematuria and proteinuria are the commonest presenting symptom of kidney disease in two African studies [14,15]. VL and CD4cell count are two variables that had highest risk factor for MA. This finding was in consistent with report by Esezobor et al. [33] in Nigerian where 37.9 % of 29 children with proteinuria had severe immunosuppression when compared to 11.9 % of 59 with milder immunosuppression. Chaparro et al. [22] reported similar association between proteinuria and low CD4 count and high viral load in a landmark study of proteinuria in HIV infected children conducted in Miami, USA. Patients with CD4 percent <25 % was also found to have a higher prevalence of both MA and proteinuria in Tanzanian study [16]. HIV viral burden and immunosuppression are well-established risk factors for the development of HIVAN and the main reasons for its decline with HAART [37,38]. Consistent with this clinical evidence is the fact that infection of kidney epithelial cells is now well documented as a reservoir for HIV-1. Aside from immune suppression, other contributing factors to kidney disease in HIV infected includes: ARV agents used, others drugs such as aminoglycosides, antifungals (amphotericin B), antivirals (acyclovir), anti-tuberculosis drugs, anti-inflammatory drugs used for the patients, and combinations of all these. Some of these contributing factors were also documented in this present study where type of ARV used, duration of time patient was on HAART, and hypertension was found to be a risk factor of MA (an earliest manifestation of renal diseases in HIV positive patients). Renal toxicity arising from ARV drugs has been reported. Infants with perinatal HIV-1 infection are started on combination ARV therapy as soon as the diagnosis is established and will remain on medications for the rest of their life. Unfortunately, there is a paucity of data on ARV toxicity in children. A comprehensive review by Jao and Wyatt [17] has described kidney toxicity with all classes of ARVs, except for the integrase inhibitors and the CCR5 antagonists. Tenofovir is one of the most widely used ARV agents in adults. Until recently, it was used only in children ≥12 years, and in 2012, received approval for use in children ≥2 years of age in USA. It causes proximal renal tubular toxicity and with acute tubular injury, there is reduced glomerular filtration rate, presenting as acute kidney injury.

The eGFR which indicates the severity of kidney disease is the best test to measure the level of kidney function and stage of kidney disease. Values of 60 ml/min/1.73 sq m^2 or less for three months or more with high levels of urine albumin (MA) indicates chronic kidney disease (CKD). Person with a high MA in their urine is at an increased risk of having CKD progress to kidney failure. Serum creatinine is also a window into the state of the function and structure of the kidney. An elevated serum creatinine signifies kidney injury. Studies have shown that elevated serum creatinine during hospitalization is an independent risk factor for mortality, progression to CKD, end-stage renal disease, and reduced long-term survival. In the present study, though the mean eGFR, UACR, electrolytes, blood urea, creatinine, and kidney sizes were within normal values, however 1.2% of the study population had an eGFR of less than 60 ml/min/1.73 sq m^2, 13.7% had MA, 1.2% had elevated serum creatinine and urea, while and 0.6% showed gross kidney enlargement. All these indicating injury to the kidney, and compromization of kidney function. In an Indian study by Shah et al. [34] they observed that 44.0% of their study population had abnormal GFR. Also in a Nigerian study by Eke et al. [24] of the 12% in their study population that had MA, 16.7% of same study had elevated serum creatinine of 400 micrommo/L, urea of 20 mmol/L and a GFR of 69 ml/min/1.73m^2 all signifying stage 2 kidney damage and renal failure. In yet another Nigerian study, [13] though eGFR, and MA were not measured, they noted that 90% of their patients were in renal failure, with elevated serum creatinine of 6.3–24 mg/dl and serum urea of 70–120 mg/dl. All the findings in these studies including the present one though in small number of study population signifies serious renal involvement in HIV positive children, and calls for internalization of regular renal function monitoring tests for early detection and treatment. This call is supported by hyperechoic findings on abdominal ultrasound and grossly enlarged kidney in one of the patient in this study and elsewhere.

4. CONCLUSION

Renal function abnormalities are common in HIV positive children on HAART without adequate viral suppression. There is need to internalization and support regular monitoring for early detection to prevent development to chronic kidney disease.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Approval was obtain from the ethical committee of University of Abuja Teaching Hospital, Gwagealada and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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