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Prevalence of Microalbuminuria and Associated Risk Factors in HIV-Infected Children seen at a Tertiary Health Centre in the Niger Delta Region of Nigeria

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Human Immunodeficiency Virus (HIV) infection affects multiple organs, including the kidneys. One of the earliest signs of kidney disease related to HIV is the presence of proteinuria, which is preceded by microalbuminuria (MA). Detecting MA in its early stages and providing appropriate intervention can help slow down or even reverse the progression of kidney disease to end-stage renal disease (ESRD). Surprisingly, routine screening for MA is not yet a standard practice in the care of HIV-infected children.

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Aim: This study aimed to assess the prevalence of microalbuminuria and associated factors in children with HIV attending the paediatric infectious disease clinic (PIDC) at the Federal Medical Centre, Yenagoa (FMCY).

Methods and Materials: This was a comparative cross-sectional study conducted over a three-month period (18th October, 2021 to 10th January, 2022), involving 150 subjects, both human immunodeficiency virus infected and uninfected at the PIDC and children outpatient clinic (CHOP) of FMCY. The study involved 150 HIV-infected and 150 uninfected subjects. Subjects with normal urine specific gravity and who tested negative for protein, leukocytes, blood, nitrites, and glucose on urinalysis had their urine assessed for the presence of microalbuminuria using the Micral Test II. Those who tested positive for microalbuminuria had their glomerular filtration rate (GFR) estimated, and a renal ultrasound scan was performed. Bivariate logistic regression analyses was conducted to identify factors associated with microalbuminuria. Factors with statistical significance (*P* value less than .05) at the bivariate level were included in the multiple logistic regression analysis. The significance level was set at a *P* value less than .05.

Results: The prevalence of microalbuminuria among human immunodeficiency virus infected subjects (18.7%) was significantly higher than uninfected subjects (2.7%) ($P < 0.001$). The prevalence of microalbuminuria was significantly higher in human immunodeficiency virus infected subjects aged 11-15 years ($P = 0.018$), those who had been living with human immunodeficiency virus for over 10 years ($P = 0.042$), those on a regimen containing tenofovir ($P = 0.037$), and those with poor adherence to antiretroviral therapy ($P = 0.012$). Other factors significantly associated with a higher prevalence of microalbuminuria included clinical stage four human immunodeficiency virus disease ($P = 0.001$), advanced immunosuppression ($P = 0.016$), and an unsuppressed viral load ($P = 0.001$). The use of a tenofovir based regimen and having clinical stage four disease were the only predictors of microalbuminuria following multivariate logistic regression (Adjusted OR: 7.87, 95% CI: 1.88 – 70.48, $P = 0.045$, and OR: 14.71, 95% CI: 1.17 – 185.69, $P = 0.038$). Six HIV-infected subjects with microalbuminuria had mildly decreased eGFR with mean of 77.3 ± 10.8. Renal length and echogenicity were normal for all subjects with microalbuminuria.

Conclusion: Microalbuminuria was more prevalent in HIV-infected children compared to their uninfected counterparts, with clinical stage four disease being the most significant factor associated with microalbuminuria.

Keywords: HIV; microalbuminuria; kidney disease; children; antiretroviral therapy.

1. INTRODUCTION

Human Immunodeficiency Virus (HIV) infection and Acquired Immune Deficiency Syndrome (AIDS) stand as significant global public health challenges, having claimed over 32 million lives to date [1]. According to the World Health Organization (WHO), there were 39 million people living with HIV/AIDS (PLHIV) in 2022, including 1.5 million children [1]. The first case of AIDS in Nigeria was reported in 1986, initiating a surge in national HIV prevalence from 1.8% in 1991 to a peak of 5.8% in 2001. Subsequently, the prevalence has steadily declined to the current figure of 1.5% in 2018 [2]. Nigeria bears the second-highest global HIV burden, with 1.9 million PLHIV as of 2018 [1]. Among Nigerian children aged 0–14 years, the HIV prevalence in 2018 was recorded at 0.2% [1]. Regional disparities are evident, with the South-South zone exhibiting the highest HIV prevalence (3.1%), followed by the North Central zone (2.0%) and the South East zone (1.9%) [2]. Lower prevalence rates are observed in the South West zone (1.1%), the North East zone (1.1%), and the North West zone (0.6%) [2]. Human immunodeficiency virus infection affects various organs within the body, including the kidneys [3]. Renal disease in HIV infected children can manifest in different forms, encompassing glomerular conditions like HIV-associated nephropathy (HIVAN), HIV immune complex kidney disease (HIVICK), thrombotic microangiopathy, as well as tubular-interstitial involvement and, less frequently, vasculitis [3]. Factors contributing to renal complications in HIV include the direct effect of the virus, opportunistic infections, immune dysregulation, and drug toxicity [3]. Microalbuminuria (MA) represents the earliest indicator of HIV-related kidney disease, denoting abnormal urinary albumin excretion without the presence of proteinuria.[4] Several studies on MA in HIV infected children have been carried out globally with varying prevalence rates ranging from 0 – 28.8%.[5–13] Majority of the studies however, were carried out before tenofovir containing regimen was introduced to the paediatric population and very few regional

studies compared the prevalence of MA to the individual antiretroviral treatment (ART) regimens. Also, in spite of these studies, periodic screening for MA has not been incorporated into routine care of HIV-infected children. This study aimed to determine the prevalence of MA and associated factors among HIV-infected children attending a paediatric infectious disease unit in a tertiary hospital in the Niger Delta region of Nigeria.

2. MATERIALS AND METHODS

2.1 Study Design and Area

It was a comparative cross-sectional, hospital-based study carried out over three months (18th October 2021-10th January 2022) in the Paediatric Infectious Disease Clinic (PIDC) and Children Out Patient/Consultant Outpatient Clinic (CHOP/COC) of the Federal Medical Centre, Yenagoa (FMCY), Bayelsa State. The FMCY is presently a 425 bedded Hospital, which provides quality tertiary health care services to meet the needs of the people of Bayelsa State and other neighbouring states [14]. Enrolment into the PIDC commenced in January 2010 and had 232 children living with HIV as at July 2020.

2.2 Study Population

The subjects for the study were children aged 18 months – 18 years with HIV infection who attended the PIDC of the FMCY during the study period. The control group were age and sex matched HIV-uninfected children who attended the CHOP/COC of FMCY during the study period.

2.2.1 Inclusion criteria

1. Those aged 18 months to 18 years who attended the PIDC during the study period.
2. Those whose caregivers/parents gave consent and those above the age of seven years that assented to the study.
3. Those with urine specific gravity (SG) of between 1.005-1.015.
4. Those with cluster of differentiation 4 (CD4/)viral load results within the past six months

2.2.2 Exclusion criteria

Subjects with the following were excluded:

Symptoms suggestive of urinary tract infection (UTI) e.g. dysuria, frequency, urgency, temperature >38^{o}C, menstruating females, chronic diseases such as diabetes mellitus, chronic kidney disease, sickle cell anaemia, conventional dipstick urine test positive for protein, blood, glucose, nitrite, leucocyte esterase and alkaline pH (>7.0). Also, those on anti-proteinuric drugs such as steroids, angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and those without CD4/viral load results within the past six months.

2.3 Sample Size Calculation

A sample size of 150 per group was calculated using the Pocock formula for prevalence studies involving two groups [15] with prevalences of MA in HIV-infected and uninfected as 11% and 2.5% from previous studies [8,12].

2.4 Sampling Technique

A convenience sampling technique was used to recruit subjects. All eligible subjects in the study group who attended the PIDC within the study period and who met the inclusion criteria were consecutively recruited until the sample size was obtained. Consecutive age and gender matched subjects in the control group who attended the CHOP/COC within the study period, who met the inclusion criteria and tested negative to retroviral screening using rapid test kits were also recruited until the sample size was obtained.

2.5 Data Collection

After consent and assent were obtained, the biodata was obtained verbally from the caregivers/subjects while the other aspects of the clinical history were extracted from the case notes/care cards. The latest CD4 count/percentage within the past six months was used in classifying the immunological stage [16]. The viral load within the past six months was also noted. Viral suppression was defined as viral load <1000 copies/ml, no suppression ≥1000 copies/ml and undetectable levels as viral load <20 copies/ml according to WHO guidelines. Adherence was determined using the self-reporting method [17]. Adolescent patients and their parents/caregivers (for the younger subjects below 10 years of age) were asked to recall how many times they missed taking drugs as prescribed in the preceding two weeks [17]. Patients were classified as having good adherence if they scored ≥95% (did not miss more than one dose) and poor adherence if they

scored ≤95% (missed more than one dose) [17]. For the controls, retroviral screening was done using rapid test kits after pretest counselling at the PIDC after which their biodata was verbally obtained.

Anthropometric measurements including weight and height were taken using standard methods and the values obtained were used to calculate the body mass index (BMI). The weight was measured to the nearest 0.1kg while height was measured to the nearest 0.1cm. The calculated BMI was interpreted using the WHO BMI charts for age and sex as follows: obese: ≥95th percentile; overweight: 85th to <95th percentile; normal: 5th to <85th percentile; underweight: < 5th percentile [18]. Blood pressure (BP) was measured using standard methods with a mercury sphygmomanometer and stethoscope. The BP readings were classified according to the recommendations of the National Blood Pressure Education Program [19].

2.5.1 Urine collection

Each child was given a universal bottle (sample one) labelled with the study number. Those that could not produce urine immediately were encouraged to drink as much water as possible and wait for one hour for urine collection. The parents/subjects were instructed on how to collect about 10mililitres (ml) of midstream urine. They were advised to clean the tip of the penis or vulva with cotton wool soaked in clean water. About 10ml of urine was then collected after the first part of the urine had been passed with the sample bottle placed about two inches from the genitals avoiding contact with the perineum or adjacent skin. The collected urine was immediately handed over to the researchers/research assistants for testing.

2.5.2 Urine testing

About Five ml of the urine was transferred from sample one to another universal bottle labelled sample two. Then urinalysis was done on sample one using Medi-Test Combi 10R SGL. Those with negative urinalysis findings on sample one, had their sample two tested for MA using Micral Test stripR (batch number 47881801) [20]. All children with MA between 20 to 200mg/L were considered positive and referred to the paediatric nephrology clinic of the FMCY for appropriate management and follow up. Children with positive parameters for conventional dipstick were also referred to the paediatric nephrology clinic.

2.5.3 Blood sample collection, testing for serum creatinine and GFR estimation

Venous blood sample (two ml) was collected from subjects with microalbuminuria under standard procedure and sent to the chemical pathology laboratory of FMCY for serum creatinine analysis using standard protocols. The serum creatinine obtained was used to calculate the estimated glomerular filtration rate (eGFR) using the Schwartz formula. The estimated GFR obtained was classified according to the kidney disease improving outcome (KDIGO) clinical practice guideline for the evaluation and management of chronic kidney disease (CKD) [21].

2.5.4 Renal ultrasound scan

Renal sonogram was also done for subjects with MA in the Radiology department of FMCY by a consultant radiologist assisted by the researchers. A longitudinal scan of each kidney was done with the patient in prone position and the superior and inferior poles clearly identified and marked. The renal length in centimetres was taken as the longest distance between the poles (bipolar length) and this was compared with the normal renal length expected for the age as either normal, small or enlarged [22]. Renal cortical echogenicity was compared and graded with the echogenicity of the liver and renal medulla. Renal echogenicity was graded according to a standardized score with four categories [22].

2.6 Data Analysis

Data was analyzed using the Statistical Package for Social Science (SPSS) software for Windows version 26. The normality of distribution for quantitative variables was assessed using the Shapiro-Wilk test. The results indicated that the data were normally distributed. Subsequently, quantitative variables were summarized using mean and standard deviation and compared using Student t test. Qualitative variables were presented using frequencies and percentages. Chi-square test of proportion was used to assess difference between qualitative variables. Fisher's exact test was applied to correct Chi-squared test values when any cell had a value less than 5. Bivariate logistic regression analyses was conducted to identify factors associated with

microalbuminuria. Factors with statistical significance (*P* value less than .05) at the bivariate level were included in the multiple logistic regression analysis. Level of significance was set at P value less than .05.

3. RESULTS

3.1 Age and Gender Distribution of the Study Participants

A total of 300 children (150 HIV infected and 150 HIV uninfected), were recruited for the study. As shown in Table 1, 74 (49.3%) of the HIV infected subjects were males while 76 (50.7%) were females with a male to female ratio of 1:1.02. The HIV uninfected also had similar male to female ratio of 1:1.02. The mean age of the HIV infected and uninfected subjects were 9.73 ± 3.99 and 9.59 ± 3.69 respectively. The age category 11 – 15 years had the highest percentage frequency in the HIV infected (53.2%) while the age category 6 – 10 years was highest in the HIV uninfected (53.5%).

3.2 Prevalence of Microalbuminuria

Thirty-two subjects, both HIV-infected and uninfected (10.7%) tested positive for microalbuminuria. The prevalence of microalbuminuria was significantly higher in the HIV infected subjects 28 (18.7%) compared to the HIV uninfected subjects four (2.7%) (*P* <0.001) (Table 2).

Table 1. Age and gender distribution of the study subjects

Characteristics	HIV infected	HIV uninfected	Total	χ^2	*P* value
	N (%)	N (%)	N (%)		
Age					
≤5 years	27 (52.9)	24 (47.1)	51 (100.0)	1.19	0.754
6 -10 years	59 (46.5)	68 (53.5)	127 (100.0)		
11 -15 years	50 (53.2)	44 (46.8)	94 (100.0)		
>15 years	14 (50.0)	14 (50.0)	28 (100.0)		
Gender					
Female	76 (50.0)	76 (50.0)	152 (100.0)	0.00	1.000
Male	74 (50.0)	74 (50.0)	148 (100.0)		

Table 2. Prevalence of microalbuminuria in the study subjects

Microalbuminuria	HIV infected	HIV uninfected	Total	Fisher's exact	*P* value
	N (%)	N (%)	N (%)		
Positive	28 (18.7)	4 (2.7)	32 (10.7)	18.51	<0.001*
Negative	122 (81.3)	146 (97.3)	268 (89.3)		
Total	150 (100.0)	150 (100.0)	300 (100.0)		

Table 3. Association between microalbuminuria and age/gender

Characteristics	Microalbuminuria		Crude Odds Ratio	95% CI	*P* value
	Yes N (%)	No N (%)			
Age (years)					
≤5	1 (3.7)	26 (96.3)	1		
6 – 10	9 (1.3)	50 (84.7)	4.68	0.56 – 38.98	0.154
11 – 15	16 (32.0)	34 (68.0)	12.24	1.52 – 98.31	0.018*
>15	2 (14.3)	12 (85.7)	4.33	0.36 – 52.58	0.250
Gender					
Female	11 (14.5)	65 (85.5)	1		
Male	17 (23.0)	57 (77.0)	1.58	0.75 – 3.32	0.232

*CI is confidence interval, * is statistically significant*

Table 4. Association between microalbuminuria and age at HIV diagnosis, mode of transmission and duration of infection

Characteristics	Microalbuminuria		Crude Odds Ratio	95% CI	*P* value
	Yes N (%)	No N (%)			
Age at diagnosis					
<5years	17 (15.7)	91 (84.3)	0.84	0.17 – 4.24	0.833
5 – 10 years	9 (29.0)	22 (71.0)	1.84	0.33 – 10.25	0.486
>10 years	2 (18.2)	9 (81.8)	1		
Mode of infection					
Vertical	27 (18.7)	117 (81.3)	1.15	0.13 – 10.26	0.898
Horizontal	1 (16.7)	5 (83.3)	1		
Duration of infection					
<5years	2 (7.4)	25 (92.6)	1		
5 – 10 years	10 (14.9)	57 (85.1)	2.19	0.45 – 10.75	0.333
>10 years	16 (28.6)	40 (71.4)	5.00	1.06 – 23.62	0.042*

*CI is confidence interval, * is statistically significant*

Table 5. Association between microalbuminuria and type of treatment regimen, duration on treatment and adherence

Characteristics	Microalbuminuria		Crude Odds Ratio	95% CI	*P* value
	Yes N (%)	No N (%)			
Treatment Regimen					
ABC/3TC/EFV	7 (11.7)	53 (88.3)	1		
TDF/3TC/DTG	16 (27.1)	43 (72.9)	2.82	1.06 – 7.47	0.037*
ABC/3TC/DTG	2 (14.3)	12 (85.7)	1.26	0.23 – 6.85	0.788
ABC/3TC/LPV/r	3 (17.6)	14 (82.4)	1.62	0.37 – 7.09	0.520
Duration on HAART					
<5years	10 (16.4)	51 (83.6)	1		
5 – 10 years	11 (16.7)	55 (83.3)	1.02	0.40 – 2.60	0.367
>10 years	7 (30.4)	16 (69.6)	2.23	0.73 – 6.82	0.159
Adherence to HAART					
Good	20 (15.4)	110 (84.6)	1		
Poor	8 (40.0)	12 (60.0)	3.70	1.33 – 10.00	0.012*

*CI is confidence interval, * is statistically significant*

3.3 Association Between Micro-albuminuria and Age/Gender

Those aged 11 – 15 years were seven point five times more likely to have MA than those aged 6 – 10 years and >15 years. Microalbuminuria was twelve times more likely in those aged 11 – 15 years than those aged ≤5 years (OR:12.24; 95% CI:1.52 – 98.31; *P* = 0.018) [Table 3]. The odds of having MA was not statistically significant across gender (OR: 1.58; 95%CI: 0.75 – 3.32; *P* = 0.232) [Table 3].

3.4 Association between Micro-albuminuria and Age at HIV Diagnosis, Mode of Transmission and Duration of Infection

There was no significant difference in the odds of having MA based on age at diagnosis and mode of infection. Microalbuminuria was three and five times more likely to be present in those whose duration of infection was >10 years than those with duration between 5 – 10 years and <5 years respectively. (OR: 5.00; 95% CI: 1.06 – 23.62; *P* = 0.042) [Table 4].

3.5 Association Between Micro-albuminuria and type of Treatment Regimen, Duration on Treatment and Adherence

As shown in Table 5, those on TDF/3TC/DTG were three times more likely to have MA than those on other regimen (OR:2.82; 95% CI: 1.06 – 7.47; *P* = 0.037). Though not statistically significant, MA was twice more likely to be present in those whose duration on HAART was >10 years than those with lesser duration (OR: 2.23; 95% CI: 0.73 – 6.82; *P* = 0.159). Those

Table 6. Association between microalbuminuria and clinical, immunologic and virologic disease staging in the HIV-infected subjects

Characteristics	Microalbuminuria		Crude Odds Ratio	95% CI	*P* value
	Yes N (%)	No N (%)			
Clinical Stage					
Stage 1	12 (18.2)	54 (81.8)	1		
Stage 2	0 (0.0)	39 (100.0)	0.00	-	-
Stage 3	6 (20.7)	23 (79.3)	1.17	0.39 – 3.51	0.774
Stage 4	10 (62.5)	6 (37.5)	7.50	2.28-24.65	0.001*
CD4 Count					
Not Significant	15 (13.4)	97 (86.6)	1		
Mild	3 (27.3)	8 (72.7)	2.43	0.58-10.17	0.226
Advanced	7 (36.8)	12 (63.2)	3.77	1.28-11.10	0.016*
Severe	3 (37.5)	5 (62.5)	3.88	0.84-17.94	0.083
Viral load					
Undetected	0 (0.0)	11 (100.0)	0.00	-	-
Suppressed	14 (13.3)	91 (86.7)	1		
Not Suppressed	14 (41.2)	20 (58.8)	4.55	1.89-11.11	0.001*

*ABC: Abacavir, 3TC: Lamivudine, DTG: Dolutegravir, LPVr: Lopinavir/ritonavir, TDF: Tenofovir, CI is confidence interval, * is statistically significant*

with poor adherence to HAART were three times more likely to have microalbuminuria than those with good adherence (OR: 3.70; 95% CI: 1.33 – 10.00; *P* = 0.012).

3.6 Association between Micro-albuminuria and Clinical, Immunologic and Virologic Disease Staging in the HIV Infected Subjects

Microalbuminuria was seven times more likely to be present in those with stage four disease than those with stage three and one (OR: 7.50; 95% CI: 2.28-24.65; *P* = 0.001*) Those with advanced immunosuppression were two and three times more likely to have MA than those with mild and not significant immunosuppression respectively (OR: 3.77; 95% CI: 1.28-11.10; *P* = 0.016) [Table 6]. Those with unsuppressed viral load were four times more likely to have MA than those with suppressed viral load (OR: 4.55; 95% CI: 1.89-11.11; *P* = 0.001) [Table 6].

3.7 Multivariate Logistic Regression Analysis of Factors with Significant Association with Microalbuminuria in the HIV-infected Subjects

Factors that showed significant association with microalbuminuria in the HIV-infected subjects at the bivariate analysis: age group, duration of infection, type of antiretroviral treatment (ART) regimen, adherence, clinical stage, CD4 count and viral load were used as independent variables in a multivariate binary logistic regression. Tenofovir containing regimen and clinical stage four disease were the only two factors with significant statistical association with microalbuminuria (adjusted OR: 7.87, 95% CI: 1.88 – 70.48, *P* = 0.045 and OR: 14.71, 95% CI: 1.17 – 185.69, *P* = 0.038) (Table 7).

3.8 Mean Estimated GFR and Categories of the Subjects with Micro-albuminuria

The mean GFR for the HIV infected subjects with microalbuminuria (112.5 ± 25.1ml/min/1.73m^2) was significantly lower when compared to the HIV uninfected subjects with microalbuminuria (153.0 ± 23.3ml/min/1.73m^2) (*P* = 0.005). Six (21.4%) of HIV infected subjects who tested positive for microalbuminuria had mildly decreased GFR compared to 0% of their uninfected counterparts who had microalbuminuria. This difference was however not statistically significant (*P* = 0.566).

3.9 Renal length and Echogenicity of the Subjects with Microalbuminuria

Ultrasound scan of the kidneys was done for those with MA but two (HIV uninfected) subjects did not show up for the scan. The mean length of the right kidney for the HIV infected subjects was 8.9 ± 1.10cm compared to 9.8 ± 0.42cm for the HIV uninfected subjects. This difference was not

Table 7. Multivariate logistic regression analysis of factors with significant association with microalbuminuria in the HIV-infected subjects

Factors	β -coefficient	Adjusted Odds Ratio	95% CI	*P* value
Gender				
Female		1		
Male	0.71	2.04	0.62 – 6.74	0.242
Age group				
≤5 years		1		
6 – 10 years	-2.41	0.09	0.01 – 12.27	0.337
11 – 15 years	-1.74	0.18	0.01 – 42.64	0.534
>15 years		2.32	0.27 – 19.95	0.444
Duration of Infection				
<5 years		1		
5 – 10 years	-1.99	0.14	0.01 – 2.69	0.190
>10 years	1.79	5.99	0.05 – 805.61	0.474
Treatment Regimen				
ABC/3TC/EFV		1		
TDF/3TC/DTG	2.06	7.87	1.88 – 70.48	0.045*
ABC/3TC/DTG	0.16	1.18	0.09 – 14.38	0.898
ABC/3TC/LPV/r	1.06	1.21	0.52 – 6.18	0.109
Adherence				
Good		1		
Poor	0.96	2.62	0.27 – 24.84	0.401
Clinical Stage				
Stage 1		1		
Stage 2		0.00	-	-
Stage 3	0.57	0.57	0.08 – 3.80	0.559
Stage 4	2.69	14.71	1.17 – 185.69	0.038*
CD4 Count				
Not significant		1		
Mild	0.54	1.72	0.12 – 25.77	0.694
Advanced	1.03	2.79	0.20 – 39.03	0.446
Severe	0.62	1.85	0.08 – 42.43	0.700
Viral Load				
Undetected		1		
Suppressed		0.00	-	-
Not suppressed	0.21	1.23	0.09 – 16.67	0.876

*CI is Confidence Interval, * is statistically significant*

statistically significant (*P* = 0.282). The mean length of the left kidney for the HIV infected subjects was 9.45 ± 0.98cm compared to 10.2 ± 0.28cm for the HIV uninfected subjects. This difference was also not statistically significant (*P* = 0.300). All 30 participants scanned had normal (grade 0) renal echogenicity.

4. DISCUSSION

Microalbuminuria was found to be common among HIV infected children in this study with a prevalence of 18.7%. This finding buttresses the need for routine screening for MA in HIV-infected children in this setting so as to institute early treatment in order to prevent further progression. Studies with similar prevalence to the index study include that of Ihekaike et al. in Jos (22.2%), Fredrick et al. in Tanzania (20.4%) and Sharma et al. in India (20.5%) [9,11,13]. The reported prevalence in the index study is higher than that by Ezeonwu et al. in Enugu (0%) and Mudi et al. in Kano (6.7%) [5,7]. The index study despite using the same micral test, relatively similar sample size and similar exclusion criteria, reported higher prevalence than the study by Ezeonwu et al. [7]. This difference in prevalence may be attributed to the fact that the subjects in the index study had higher mean duration of HIV infection (6.14 ± 3.31 years) compared to 1.75 ±

1.33 years in the study by Ezeonwu et al. [7]. When compared to the study by Mudi et al. in Kano, the index study used random spot urine sample rather than first morning sample which was used in the study by Mudi et al. [5]. The use of first morning urine sample excludes transient causes of MA such as postural changes and vigorous exercise [4]. The prevalence of MA in the index study was lower than that reported by Mosten et al. in Tanzania (28%) [10]. This difference could be attributed to the smaller sample size (150 HIV infected children) used in the index study compared to 330 in the study by Mosten et al. [10]. Also, micral test strip was used in the index study compared to hemocue albumin analyzer used by Mosten et al. [10]. Hemocue albumin analyzer gives exact values of urine microalbumin [10].

The prevalence of MA in the HIV uninfected subjects in the index study was 2.7% which is seven times less than that of the HIV infected subjects. This finding is not surprising as both HIV and its treatment are known to affect the kidneys [6]. Similar prevalence of MA in HIV uninfected subjects have been reported by Ekulu et al. in Congo (2.5%) [12].

In the index study, the prevalence of MA was higher in males compared to females, though, statistically not significant. This male predilection has been attributed to hormonal and renal structural differences [8]. Male hormones tend to initiate podocyte apoptosis [8]. This pattern aligns with findings from previous studies [6,9–12].

Microalbuminuria was found to be more prevalent in older HIV infected subjects in the present study. The reason for this finding may be because older children may have had HIV infection for a longer duration, with longer exposure to ARVs and thus are more likely to have MA [6]. This finding is consistent with studies done by Okechukwu et al. in Abuja, Fredrick et al. in Tanzania and Sharma et al. in India [6,9,11]. However, Iduoriyekemwen et al. in Benin city, found a higher prevalence of MA in the younger age group [8]. The reason for this contrasting finding is not obvious. It could be due to the lower mean age of the study subjects in the Benin City study (6.6 ± 3.5 years) compared to 9.73 ± 3.99 years in the index study [8]. While majority of the study subjects in the index study were six years and above, almost half of the subjects in the Benin City study [8] were less than six years [8].

In this present study, there was a linear relationship between duration of HIV infection and the prevalence of MA. It was observed that the prevalence of microalbuminuria was significantly higher in those with duration of HIV infection of more than 10 years. This suggests that there could be progression of renal damage with longer duration of HIV infection. This is similar to previous studies by Ihekaike et al. in Jos and Fredrick et al. in Tanzania [9,13].

In the index study, MA prevalence was significantly higher in subjects with clinical stage 4 disease, advanced immunosuppression and unsuppressed viral load. The association of advanced clinical disease with MA can be explained by the fact that as the disease progresses there is profound immune suppression favouring unchecked viral replication and hence kidney involvement. This finding is consistent with those of other studies [6,8–11]. On the contrary, Mudi et al. found no association between the clinical stage of HIV and MA in their study in Kano [5].

The use of tenofovir containing regimen was significantly associated with MA in the present study. This finding is significant as tenofovir has been fully introduced to the paediatric population. Tenofovir causes renal cell mitochondrial DNA damage leading to oxidative respiratory chain dysfunction [23]. Because of a shortage of adenosine triphosphate (ATP) production, tubular cells cannot properly ensure reabsorption of ions and small molecules, such as microalbumin, potassium, glucose, phosphate, uric acid and amino acids [23]. Therefore, these molecules are secreted in abnormal quantities in the urine [23]. This is consistent with findings in previous studies done by Saez Llorens et al. in Panama and Riordan et al. in United Kingdom [24,25].

In the present study, the mean eGFR of the HIV-infected subjects with MA was significantly lower than their uninfected counterparts. Mild renal impairment in this study (defined as eGFR of between 60-90ml/min/m2) [21] was noted in 21.4% of the HIV-infected subjects with MA. This finding further buttresses the fact that MA is an early marker of glomerular dysfunction. This underscores the need for routine screening of all children infected with HIV for latent renal damage. Similar findings have been reported by Okechukwu et al. in Abuja and Fredrick et al. in Tanzania [6,9]. This is lower than that reported by Ahoui et al. in Benin Republic (38.5%) but higher than report by Esezobor et al. in Lagos (13.3%) [26,27]. The varying rates is as a result

of the different eGFR cut off values for renal impairment, the methods used in estimating GFR and the stage of HIV associated kidney disease of the subjects. The eGFR cut off values for the index study was higher (60 – 90) than the cut off values from the Lagos study (30 – 60), [27] but similar to that of the Benin Republic study [26]. Also, while the index study used the creatinine-based formula for GFR estimation, the Lagos study [27] used Cystatin C. The use of Cystatin C-based formula has been argued to be more accurate than the GFR derived from the widely used creatinine-based formula because it is less affected by non-glomerular factors such as lean mass, diet, and tubular secretion [8].

Renal ultrasound examination of 30 subjects with MA in the index study revealed normal renal length and echogenicity in all (100%) of them. Ultrasound findings of HIV related kidney disease include normal or enlarged kidneys with increased echogenicity [22]. The findings of normal renal length and echogenicity in this study buttresses the fact that MA is an early manifestation of HIV related kidney disease. Ahoui et al. in Benin Republic reported increased echogenicity in 25.6% of their subjects [26]. Other studies with finding of increased echogenicity include; Okechukwu et al. in Abuja (4.7%), Fredrick et al. in Tanzania (39.2%) [6,9]. Increased echogenicity is a late manifestation of HIV related kidney disease which the subjects in the index study did not have. Ahoui et al. in Benin Republic studied subjects with fully established HIV related kidney disease which may account for the high prevalence of increased echogenicity in their study compared to the index study [26].

The limitations of this current study include the fact that the study was cross sectional, thereby limiting longitudinal follow up of children with positive MA. Additionally, the testing for MA was conducted on random spot samples, as opposed to first morning urine samples, which may have included cases of transient albuminuria. Estimated GFR was only done for subjects with positive MA due to cost implications. This limitation restricted the comparison of renal function between subjects who tested positive and those who tested negative for MA, respectively. Furthermore, renal ultrasound scans were exclusively conducted for subjects with positive MA due to cost constraints. This restriction also hindered the comparison of renal function between subjects with and without MA, respectively.

5. CONCLUSION

Microalbuminuria was more prevalent in HIV-infected children than their uninfected counterparts and clinical stage four disease was the single most significant factor associated with MA. Measurement of MA (instead of the dipstick urinalysis) should be included in the routine investigations for better management of HIV-infected children. This could help identify those susceptible to development of renal disease early and prophylactic measures initiated. HIV-infected children with clinical stage 4 disease, advanced immunosuppression, unsuppressed viral load and those on tenofovir containing regimen may benefit from having their MA assessed for early management and control.

CONSENT AND ETHICAL APPROVAL

Ethical approval for the study was obtained from the Research and Ethics Committee of FMCY (FMCY/REC/ECC/2021/OCTOBER/272). Written informed consent/assent was also obtained from parents/caregivers of the study subjects. All information obtained from the subjects were treated as confidential. Feedback of the outcome of the study was given to caregivers of subjects. Children with microalbuminuria were referred to the paediatric nephrology unit of the FMCY for further evaluation, management and follow up. Children with positive parameters for conventional dipstick (haematuria, proteinuria, pyuria, positive nitrite) were also referred to the paediatric nephrology clinic. The costs of the investigations done during the study were borne by the researchers.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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