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ASSESSMENT OF RENAL FUNCTION IN HIV INFECTED CHILDREN IN OWERRI, SOUTH- EAST NIGERIA

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ABSTRACT

Background:
Sub-Saharan Africa has the largest burden of paediatric HIV infection and renal disease is a major cause of morbidity and mortality in these children.

Materials and Methods:
This cross-sectional study was carried out at the Federal Medical Centre (FMC) Owerri between January and June 2015. It assessed renal function by determining the estimated GFR (eGFR) in HIV infected children and comparing it with that of apparently healthy age and sex matched HIV negative controls. Schwartz formula was used to estimate the glomerular filtration rates.

Results:
105 HAART naïve and 104 children on HAART were recruited consecutively and 209 matched for age and sex HIV negative children were involved in the study.
The mean eGFR of the HIV infected subjects (115.27±19.75ml/min/1.73m^2) was, significantly lower than that of HIV negative children (127.63±27.77ml/min/1.73m^2). The mean eGFR was significantly lower in the clinical and immunological advanced stages (106.93±19.97ml/min/1.73m^{2}and 110.54±19.80ml/min/1.73m^2 respectively) when compared to that observed in the non-advanced stages (116.56±19.75ml/min/1.73m^2 and 117.46±19.75ml/min/1.73m^2 respectively). In addition, the mean eGFR was higher in the subjects on HAART (118.37±19.79ml/min/1.73m^2) than that observed in the HAART naïve subjects (115.27±19.74ml/min/1.73m^2).

Conclusion:
This study showed that HIV infected children had decreased estimated GFR .Assessing renal function routinely would facilitate early detection and hence intervention thereby delaying progression to end stage renal disease in HIV infected children . This is important in a setting like ours where there are limited resources for renal replacement.
Key words. HIV infection, GFR, Renal function, Paediatric.

INTRODUCTION.

Kidney disease is an important cause of morbidity and mortality in HIV infected children, with its features ranging from asymptomatic microalbuminuria to Nephrotic syndrome and in some cases rapidly progressive renal insufficiency [1].Early detection and management can reduce morbidity and mortality but appropriate renal assessment is often overlooked in the management of these patients in many hospitals where standard protocols are not strictly observed. Renal assessment is important especially in children where lack of specific clinical features may mask the presence of renal disease. It is, therefore, important to monitor renal function in children with Human Immunodeficiency Virus (HIV) for early discovery of kidney damage. Early detection and treatment of renal disease will not only significantly increase renal survival but reduce direct and indirect financial and emotional cost of the disease to the children, care givers and community. This is more so in resource challenged countries such as Nigeria where renal replacement therapy which improves the lives of these patients is mostly unaffordable .

Unlike in adults, HIV associated nephropathy in children is usually not associated with obvious symptoms of oedema, hematuria or hypertension [2]. It is estimated that 13.3% to 31.6% of Nigerian children infected with HIV have renal disease.[3-5]

Various studies suggest that early initiation of highly active antiretroviral therapy (HAART) has beneficial effects on HIV disease progression and also slows the progression of nephropathy to end stage renal disease in children and adults.[3-7]

Estimates of glomerular filtration rate (GFR) are the best overall indices available to assess the level of kidney function in disease and health in an individual in a clinical setting. GFR is usually assessed using either exogenous or endogenous markers in their steady states.[8] As an index of kidney function, it may detect kidney disease; ascertain its severity and aid decisions about diagnosis, prognosis and treatment.[9] The ideal marker of GFR should be an endogenous molecule which is produced at a constant rate, cleared solely by the kidneys via free glomerulofiltration, and neither secreted by tubular cells, nor reabsorbed into the peritubular circulation.[8] A number of formulae have been devised to estimate GFR orcreatinine clearance values onthe basis of serum creatinine and include Cockcroft- Gault formula, Modification of Diet inRenal Disease (MDRD) formula, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, Mayo Quadratic formula and the Schwartz formula. However, the use of Schwartz formula is advocated.

There is a need for a baseline study to document the outcome of renal assessment of children infected with HIV/AIDS in OwerriSouth- East Nigeria. This study set to do just that.

Study area.

The study was carried out at the Paediatric HIV and the outpatient clinics of the Federal Medical Centre, Owerri, Imo State. The Federal Medical Centre is a tertiary health facility located centrally in Owerri, South –East Nigeria. It serves as a referral centre for hospitals from all over the state and its environs. While the Paediatric HIV clinic runs once a week on Thursdays, the Paediatric outpatient clinic runs daily from Mondays to Fridays .

Study design.

This was across-sectional case control study.The study population consisted of HIV infected children between the ages of 2 and 15 years attending the paediatric HIV clinic of the hospital and their age and sex matched controls (HIV negative children matched for sex and age with the subjects drawn from the paediatric outpatient clinic).Patients with known renal disease were not recruited into the control group.

Sampling method.

105 consecutively registered HAART naïve and 104 consecutively registered HIV infected subjects on HAART attending clinic were recruited upon their consent. HIV negative children matched for age and sex were consecutively recruited from the children outpatient clinics as control groups. Age matching was done to the nearest half year for those less than 5 years and to the nearest year for those greater than or equal to 5 years.

Study procedure and data collection.

The study was carried out at the Paediatric HIV and outpatient clinics between January 9th and June 1st, 2015. Each recruited subject had a detailed history and a full physical examination documented. This was also done for the control at the paediatric outpatient clinics. The research proforma designed for this study was employed for collection of information about each subject. Variables documented in the proforma included socio demographic data (patient initials, hospital number, research number, age, gender, parents/care giver, address, occupation and education of the parents/care giver.

Socio economic stratification was based on the classification described by Oyedeji [10]The occupation and educational attainment of parents were used to determine the socioeconomic index score of the subjects.

Using the Schwartz formula, eGFR = K x height (cm)/ serum creatinine (mg/dl), the serum creatinine and height (or length) obtained for each participant were used to calculate their

glomerular filtration rate, taking into consideration the different values of constant "K" for age groups and gender: 0.55 in children 1-13 years and adolescent females above 13 years, 0.70 in adolescent males above 13 years. The estimated GFR (eGFR) was used to determine the renal function of the study population which was then classified based

Ethical considerations.

The ethical clearance and permission to conduct this study was obtained from the Ethical committee of the hospital.

Data analysis.

All completed questionnaires were coded before entries were made into the computer. Socio demographic, anthropometric and laboratory data were analyzed using the Statistical Package for Social Science (SPSS) version 20.0 for Windows ® (SPSS Inc., Chicago, IL, USA). Continuous variables such as the age, weight, height, body mass index (BMI) were analyzed and expressed as mean and standard deviations. Comparison of means such as eGFR of HIV infected subjects and HIV negative control, eGFRand clinical staging, eGFR and immunological staging and eGFR and use of HAART were done using 't' test for independent variables. Meanwhile, analysis of variance (ANOVA) was used to compare eGFR and duration on HAART. For categorical variables, chi-square 'x^{2}' test and odd's ratiotest were used. Significant levels were set at p-value of < 0.05 and 95% confidence interval.

Results

General characteristics of study population.

209 HIV infected subjects and 209 HIV negative apparently healthy matched for age and sex controls aged between 2 to 15 years were recruited for the study. Their general characteristics are as shown in table 1. There were 108 (51.67%) males with a mean age of 6.97 ±3.4 years and 101 (48.33%) females with a mean age of 7.07 ± 3.93 years. The male to female ratio was 1.1:1.

Renal function of the study population.

The mean eGFR of the HIV infected subjects was 115.27±19.75ml/min/1.73m^2. This was significantly lower than 127.63±27.77ml/min/1.73m^2 observed in the HIV negative control group (t-test=5.24, p=0.00). The estimated GFR of the HIV infected subjects ranged from 62.64-140.92 ml/min/1.73m2 while the estimated GFR of the control group ranged from 77.24-168.33 ml/min/1.73m2. None of the study population had eGFR<60ml/min/1.73m2. There was a significant relationship between the renal function and HIV infection (x2=10.65, p=0.00) as shown in Table 2.

Renal function of HIV- infected subjects and clinical staging of the disease.

The mean eGFR of the HIV infected subjects in the advanced stage was 106.93±19.97ml/min/1.73m2. This was significantly lower than 116.56±19.75ml/min/1.73m2 observed in the HIV infected subjects in the non-advanced stage (t-test=3.04, p=0.00). Table 3 shows the relationship between the estimated GFR and the clinical staging. There was a significant relationship between estimated GFR and clinical stage of HIV infection (x2=8.49, p=0.00).

Renal function of HIV-Infected subjects and HIV-associated immunodeficiency classification.

The mean eGFR of the HIV infected subjects in the advanced class was 110.54±19.80ml/min/1.73m2. This was significantly lower than 117.46±19.75ml/min/1.73m2 observed in the non-advanced class (t-test=2.30, p=0.02). Table 4 shows the relationship between the estimated GFR and HIV-associated immunodeficiency classification. There was a significant relationship between estimated GFR and HIV associated immunodeficiency classification of the HIV infected subjects (x2=5.77, p=0.02).

Renal function of the HIV infected subjects and the use of HAART

The mean eGFR of the HAART naïve HIV infected subjects was 115.27±19.74ml/min/1.73m2 while the mean eGFR of the HIV infected subjects on HAART was 118.37±19.79ml/min/1.73m.2 The difference between the mean eGFR of the HAART naïve HIV infected subjects and HIV infected subjects on HAART was not statistically significant (t-test=1.13, p=0.26). Both means however were lower than the mean eGFR of 127.63±27.77ml/min/1.73m2 observed in the HIV negative control group. Table 5 shows the relationship between the eGFR of the HIV infected subjects and the use of HAART. There was no significant relationship between the eGFR and the use of HAART (x2=0.08, p=0.78).

Relationship between renal function and duration on HAART

The mean eGFR of the HIV infected subjects who had been on HAART for less than 2 years was 117.46±19.87ml/min/1.73m2, it was 114.55±20.32ml/min/1.73m2 for those who had been on HAART for 2-5 years and 110.76±19.48ml/min/1.73m2 for those who had been on HAART for more than 5 years. There was no significant difference in these mean values (ANOVA f=1.01, p=0.37). Table 6 shows the relationship between the estimated GFR and duration on HAART. There was no significant relationship between the estimated GFR and duration of treatment on HAART (x2=5.07, p=0.07)

Table I: General Characteristics of the Study Population

	HIV Infected n=209(%)	HIV negative n=209(%)
Age group		
2-5 years	90 (43.1)	90 (43.1)
6-10 years	75 (35.9)	75 (35.9)
11-15 years	44 (21.1)	44 (21.1)
Gender		
Male	108 (51.7)	108 (51.7)
Female	101 (48.3)	101 (48.3)
Socioeconomic Classification		
Upper (I,II)	28 (13.4)	75 (35.9)
Lower (III, IV, V)	181 (86.6)	134 (64.1)
Tribe		
Igbo	204 (97.6)	196 (93.8)
Yoruba	2 (1.0)	5 (2.4)
Hausa	1 (0.48)	2 (1.0)
Efik	1 (0.48)	0 (0)
Ikwerre	1 (0.48)	6 (2.9)
Place of Residence		
In State	193 (92.3)	206 (98.6)
Out of State	16 (7.7)	3 (1.4)
Orphan Status		
Non Orphan	166 (79.4)	202 (96.7)
Maternal Orphan	30 (14.4)	5 (2.4)
Paternal Orphan	10 (4.8)	2 (1.0)
Double Orphan	3 (1.4)	

Table 2: Estimated GFR of the Study Population

Estimated GFR*	HIV Infected n=209(%)	HIV negative n=209(%)	x^2	p-value	Odds ratio
Normal	157 (75.12)	183 (87.56)	10.65	0.00	2.33
Mildly decreased	52 (24.88)	26 (12.44)			

Table 3: Relationship between Estimated GFR of HIV-Infected Subjects and Clinical Staging

Clinical Staging	Estimated GFR*		x^2	p-value
	Normal	Mildly decreased		
Non-Advanced n=157(%)	126(80.25)	31(19.75)	8.49	0.00
Advanced n=52(%)	31(59.62)	21(40.38)		

Table 4: Relationship between Estimated GFR of HIV-Infected Subjects and HIV-associated Immunodeficiency classification

HIV associated immunodeficiency Classification	Estimated GFR*		x^2	p-value
	Normal	Mildly decreased		
Non-Advanced n=148 (%)	118(79.73)	30(20.27)	5.77	0.02
Advanced n= 61(%)	39(63.93)	22(36.07)		

Table 5: Relationship between Estimated GFR of the HIV Infected Subjects and Use of HAART

HAART Status	Estimated GFR*		x^2	p-value
	Normal	Mildly decreased		
HAART Naïve n= 105(%)	78 (74.29)	27 (25.71)	0.08	0.78
HAART n= 104(%)	79 (75.96)	25 (24.04)		

Table 6: Relationship between Estimated GFR and Duration on HAART

Duration on HAART (years)	Estimated GFR*		x^2	p-value
	Normal	Mildly decreased		
<2years n=46(%)	40(86.96)	6(13.04)	5.07	0.07
2-5years n=29(%)	21(72.41)	8(27.59)		
>5years n=29(%)	19(65.52)	10(34.48)		

Discussion

Renal complications are important causes of morbidity and mortality amongst HIV infected children and this study examined the renal function of HIV infected children as seen at the Paediatric HIV clinic of FMC Owerri. The mean eGFR in the HIV infected subjects in FMC Owerri was 115.27±19.75ml/min/1.73m^2. This was comparable to findings by Esezobor et al (96.8±36.1ml/min/1.73m^2) in Lagos, south-west Nigeria,[4] Ezeonwu et al (109.4±16.9 ml/min/1.73m^2) in Enugu south-east Nigeria[7] and Abiodun et al (102.7± 31.075ml/min/1.73m^2) in Benin south-south Nigeria.[12]

The mean eGFR in the HIV infected subjects in this study was significantly lower when compared with the HIV negative control group (127.63±27.77ml/min/1.73m^2). This finding was similar to observations by Esezobor et al in Lagos, south-west Nigeria [4] and Eke et al in Port Harcourt south-south Nigeria.[13] The reason for the significantly lower eGFR in HIV infected subjects when compared to the controls would be as a result of the effect of virus on the Kidneys. Direct and indirect effects on the kidneys may be contributory factors to a reduced GFR in subjects. Direct effects like toxic consequences of viral replication, accumulated non-integrated viral DNA, accumulated viral RNA, aberrant host cell RNA and intracellular complexing of HIV envelope and CD4 receptors. The indirect effects include syncytia formation, autoantibodies, release of soluble toxic substances, innocent bystander cell killing, apoptosis, HIV infection of stem cells and super antigens. In addition, opportunistic infections and effects of nephrotoxic drug therapy in HIV infection may have contributed to this difference. This finding implies that patients with HIV infection may be at increased risk of a decreased renal function and hence progression to end stage renal disease. The significant reduction in GFR among HIV-infected children stable enough to attend the outpatient clinic probably indicates a chronic, rather than a rapidly evolving, reduction in GFR.

More of the HIV infected subjects (24.88%) had mildly decreased eGFR when compared with the control group (12.44%). This was statistically significant. The prevalence of mildly decreased eGFR in this study was lower than findings of Shah et al[14] where 44% of 28 HAART naïve subjects had mildly decreased eGFR. Although creatinine based Schwartz formula for GFR estimation was used in both studies, a higher sample size of 209 and inclusion of subjects on HAART in this present study may have accounted for the difference in findings.

None of the study population (test and control groups) had GFR less than 60ml/min/1.73m^2. This observation is similar to findings by Ezeonwu et al [7] in Enugu, also in south-east Nigeria, however, differs from the outcome of studies in Lagos and Benin ,south-west and south -south Nigeria where 13.3% and 10.7% of HIV positive subjects in the respective studies had estimated GFR of less than 60ml/min/1.73m^2 respectively. [4,12] Unlike our study, these other studies recruited HAART naïve subjects only and utilized Cystatin C based formulae. The use of serum creatinine-based Schwartz formula to estimate GFR which is known to overestimate GFR may also be a reason for higher values seen in this study.

[15] Treatment with HAART in HIV-infected subjects has been shown to suppress viral load and improve the renal function. Therefore, the inclusion of subjects on HAART in this study may have contributed to the higher mean values of eGFR and absence of subjects with eGFR lower than 60ml/min/1.73m^2. Ethnicity is reported to be one of the confounders in the comparison of renal function across ethnic groups.

The eGFR showed an inverse relationship with age, with younger subjects having higher values in the HIV infected subjects. This could be attributed to the effect of disease progression with age since majority of paediatric HIV is acquired by vertical transmission. Renal function is better preserved in HIV-positive children with high CD4 cell count. Other authors have also reported an independent association of lower GFR with increasing age.refs

Estimated GFR showed a significant association with both clinical and immunological stage of HIV disease. This is similar to reports by Iduoriyekemwen et al,3 Cheung et al, 16Winston et al,17Emem et al 18and Szczech et al,19 where renal function was significantly associated with severe immunodeficiency. In contrast, Esezobor et al4 reported a lack of a significant difference between the GFR in HIV-infected children with stage of HIV disease. The study by Esezobor et al, 4however, had a small sample size of only 60 subjects. A higher sample size of 209 subjects in this study may have increased the power and statistical significance of this study. Abiodun et al 12 and Wools-Kaloustain et al20on the other hand reported no association of kidney function with clinical staging but an association with immunological staging. Though renal pathology can occur at any stage of HIV infection, the significant relationship between estimated GFR and clinical and immunological staging seen in this study may indicate decreasing renal function with HIV disease progression.

This may be due to the fact that in advanced disease there is low CD4 count and high viral load, both of which predisposes the child to kidney damage. Also with immunosuppression, there is a higher prevalence of opportunistic infections and co-morbid factors which may affect renal function.

In this study, there was no significant association between the eGFR and the use of HAART or duration on HAART. This finding is similar to that documented by Ezeonwu et al.7 Majority of the subjects (44.23%) in this study had treatment duration of less than 2 years. This short duration of treatment with HAART may have contributed to this finding. It is also possible that other factors such as age, gender, CD4 cell count and stage of the disease may influence the effect of HAART treatment on renal function.

In conclusion, this study shows that infection with HIV increases the risk of having reduced renal function in children and with worsening disease condition, there is reduction in the estimated GFR. It is strongly recommended that a baseline and regular renal function monitoring of HIV infected children upon entry into care be instituted. This is more so in a setting like ours where renal replacement therapy is not available.

Conflict of intrest.

None declared by any of the authors

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