Prevalence and Factors Associated With Renal Dysfunction in HIV Positive Paediatric Patients on Highly Active Antiretroviral Therapy at the Paediatric Centre of Excellence of the University Teaching Hospital, in Lusaka, Zambia

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ABSTRACT

Background: Although sub-Saharan Africa has the largest number of children living with the Human Immunodeficiency Virus (HIV), little is known about the prevalence of HIV related kidney disease in these children despite the recognition of HIV infection as a strong risk factor for kidney disease. This study investigated the prevalence and factors associated with renal dysfunction in HIV positive paediatric patients on highly active antiretroviral therapy at the Paediatric Centre of Excellence (PCOE) of the University Teaching Hospital (UTH), Lusaka, Zambia.

Methodology- The study was a cross-sectional survey conducted at the PCOE of the UTH in Lusaka, Zambia. Enrolment of all eligible participants was from April to September 2014. The Inclusion criteria were patients aged 18 months to 16 years who consented or assented to the study and were on HAART. Renal dysfunction was defined as at least abnormal renal laboratory values in at least 1 of 3 measures of proteinuria, serum creatinine or Estimated Glomerular Filtration Rate (eGFR) 60mL/min/1.73m2 for the Age and height-adjusted value as defined by The Kidney Improving Global Outcomes (KDIGO) 2012 on two occasions. A file review and clinical evaluation were done by the study physician to determine the factors associated with renal dysfunction. Bloods were drawn for CD4 count, Haemoglobin (HB), Creatinine and Urine was taken for dipstick urinalysis.

Results- Of the 209 participants enrolled in this cross-sectional study, 105(50.2%) were females. This study found a prevalence of 8.1% (CI=5.0-12.5), of renal dysfunction among paediatric HIV patients, followed up at PCOE. Children aged 13 and above had on average 23 times greater odds for renal dysfunction [adjusted odds ratio (OR) = 23.76, and 95% confidence interval (CI) = (5.30 – 106.53), P-value <0.01] compared to children under 13 years old. Children receiving nephrotoxic HAART had on average 6 times greater odds for renal dysfunction [OR=5.55, CI= (1.57 – 19.65), P-value = 0.01] compared to children receiving Non-Nephrotoxic HAART.

Conclusion- The prevalence of renal dysfunction among paediatric HIV infected patients followed up at the PCOE at UTH in Lusaka Zambia is 8.1%, at 95% CI= (5.0-12.5) and associated factors include an increase in age and nephrotoxic HAART.

Keywords- Renal Dysfunction, Paediatric HIV patients, Highly Active Antiretroviral Therapy (HAART)

BACKGROUND

Although sub-Saharan Africa has the largest number of children living with the Human Immunodeficiency Virus (HIV), little is known about the prevalence of HIV related kidney disease in these children despite the recognition of HIV infection as a strong risk factor for kidney disease [1,2]. This study investigated the prevalence and factors associated with renal dysfunction in HIV positive paediatric patients on highly active antiretroviral therapy (HAART) at the Paediatric Centre of Excellence (PCOE) of the University Teaching Hospital (UTH), Lusaka, Zambia.

Renal impairment is an important comorbidity of HIV, whether due to direct effects of HIV on the kidney (e.g. HIV associated nephropathy-HIVAN) or due to factors related to HIV such as opportunistic infections (e.g. tuberculosis) or drug

toxicity (e.g. lopinavir/ritonavir [LPV/r], tenofovir [TDF]). Renal impairment is more common in HIV patients of African origin than among HIV patients of Caucasian origin and has been shown to be an important predictor of early mortality in patients starting antiretroviral therapy (ART) in western settings as well as in Africa [2,5].

The incidence and occurrence of renal disease has decreased since the widespread introduction of combination antiretroviral therapy (cART) [2-7], with studies suggesting that HAART reduces the incidence of HIVAN [5], possibly by slowing the decline in renal function [2-7]. Early stages of renal dysfunction are silent and only detectable through laboratory analyses; for example, the glomerular filtration rate (GFR) which can be estimated using serum creatinine and it correlates with the severity of kidney disease and typically decreases before the onset of symptoms of kidney failure [2-7].

In Sub-Saharan Africa, a few studies describe the extent of renal disease in HIV-infected children. In Nigeria, Iduoriyekemwen et al. found the prevalence of the renal disease in HIV-infected children on highly active antiretroviral therapy (HAART) to be 16.2% [8]. It is anticipated that with the increased availability of HAART, the knowledge in diagnosing and treating renal disease in HIV-infected children will improve [1-5].

The prevalence rates of renal impairment in cohort studies of HIV-positive subjects have varied depending on the patients' clinical status, and the definition of renal impairment used [2-8]. This study aimed to investigate and determine the prevalence and factors associated with renal dysfunction in the HIV positive paediatric patients on highly active antiretroviral therapy presented to the PCOE at UTH in Lusaka.

MATERIALS AND METHODS

Study Design

This was a cross-sectional study conducted over six months from April to September 2014 targeting HIV positive children followed up at The UTH, PCOE in Lusaka Zambia between the age of 1year 6 months and 16 years.

The study site was an outpatient clinic in the Department of paediatrics at UTH, where about 4000 HIV positive children are followed up annually, in accordance with the Zambia National HIV guidelines adopted from WHO. The majority of patients seen in the PCOE clinic are on HAART and enrolments were done in the morning from Mondays to Fridays, with 10 patients being enrolled per day.

Eligibility

Inclusion Criteria

- All HIV positive children who followed up at UTH, PCOE in LUSAKA between the age of 18 months and 16 years old on HAART.

Exclusion Criteria

- HIV negative children.
- Refusal to take part in the study
- Children on Tuberculosis treatment, sickle cell disease, diabetes mellitus, acute illness/fever (axillary body temperature greater than 37.5^{o}c)
- Children known to have Hepatitis B were excluded from the study.
- Recent admission in the last four week

Sample Size

The following prevalence formula was used to calculate the sample size.

$$N = \frac{Z^2 \times P(1-P)}{(E)^2}$$

Where

N = sample required
Z =Z statistic =1.96 (95% C I)
P= expected prevalence 0.15 (assuming 15% renal dysfunction)
E= confidence interval 0.05

$$\text{Therefore } N = \frac{(1.96)^2 \times 0.15\ (1-0.15)}{(0.05)^2}$$

$$= \underline{\mathbf{196}}$$

Total sample considering a drop out of 5% = 1486 / (1-0.05) =<u>206</u>

Thus the sample size was calculated to be <u>206</u>

Sampling Methods

Convenient sampling method was used. All children attending the ART clinic at PCOE were invited to participate in the study. The first patient was invited to take part in the study; then, every alternate patient was invited to avoid selection bias. If a guardian and patient declined to be enrolled, the next possible participant was approached, and only 10 participants were enrolled per day. An

informed and signed consent/assent was obtained from the participants/guardians.

A questionnaire was administered, and the study physician clinically evaluated every enrolled child. Self-reported race and ethnicity information was provided by the parent, guardian, or subject. A maximum of 5mL of the blood sample was collected from each participant by vein puncture.

The blood samples were analyzed to measure serum creatinine while other results were obtained from the file to meet the 2 (two) required results within 3-6 months as per the study definition of renal dysfunction.

Urine samples were collected at the time of study and a urinalysis done on the spot. A second urinalysis was done on the next scheduled regular visit after three months to meet the two required urinalysis results as per study definition of renal dysfunction.

A file review was done to collect the relevant clinical data such as date of commencement of HAART, the HAART regimen details, other medications the participant was on and most recent Creatinine.

Study Definitions:

HAART was defined as a regimen that comprised at least three different ARVs from at least two drug classes (NRTI, NNRTI and PI).

ARV use was divided into mutually exclusive categories:

1. **Nephrotoxic HAART**: Nephrotoxic HAART was defined as any HAART regimen that included tenofovir and lopinavir/ritonavir
2. **Non-Nephrotoxic HAART**: Non-nephrotoxic HAART was defined as any HAART regimen that excluded those classified as nephrotoxic above.

The use of herbal medication and non-steroidal anti-inflammatory drugs (NSAIDs) was included as exposure to Nephrotoxic agents.

Definition of Renal Dysfunction

Renal dysfunction was defined as; abnormal renal laboratory values in at least 1 of 3 measures as in agreement with the kidney improving global outcomes (KDIGO) 2012 on two occasions:

1. **Urine protein content:** Cut off for increased urine protein was ≥+1.
2. **Serum creatinine (Cr):** Cut-offs for increased serum Creatinine was age-adjusted:
   ≥ 62 umol/l. (0.7mg/dl) for children 1–12 years.
   ≥ 88 umol/l. (1.0 mg/dl) for adolescents ≥13 years–19 years.
3. **Estimated Glomerular Filtration Rate (eGFR);** eGFR was computed using the Schwartz formula. The cut off for decreased eGFR was <60mL/min/1.73m^2 for the Age and height-adjusted value.

Data Management and **Statistical Analysis**

A standardized data entry questionnaire for each study participant was used for data collection and was identified by numbers. No personal details that could help identify participants appeared on the form. Double data entry was performed, and databases matched. Data was entered on an Epi Info database.

The data was analyzed using SPSS version 22.0. Frequency tables were used to describe the socio-demographic characteristics. Chi-square tables were used to test for associations for categorical variables while t-tests were used to make associations for continuous variables. The effect size was measured using odds ratios.

Data were analyzed based on gender; age group at study time; race/ethnicity; WHO clinical and immunological stage and nephrotoxic medication exposure at the time of the study.

In the final set of analyses, the compared risk of renal toxicities for subjects taking Nephrotoxic-HAART and other Nephrotoxic medications concurrently, was compared with non-Nephrotoxic HAART.

All analyses were restricted to participants with confirmed HIV diagnosis on HAART.

Ethical Issues

Ethical clearance was sought from the Research Ethics Committee (ERES), **Ref. no 2013-Nov-014.** Permission to carry out the study was sought from, The Department of Paediatrics and Child Health at UTH and PCOE. The purpose and procedures of the study were fully explained by the study physician and a written informed consent/ assent obtained from the guardian/parent and the participant where appropriate. It was emphasized that participation in the study was purely voluntary and that participants could withdraw from the study at any point.

RESULTS

Social-Demographic Characteristics of the Participants

Race, Sex and Age distribution

All the 209 participants enrolled in this study were black Africans and Lusaka province residents in Zambia with a confirmed HIV diagnosis. Of the 209 recruited participants in this study, there were 105 (50.2%) female children and 104 (49.8%) male children, P-value = 0.95. The mean age at enrolment onto the study was 9.3 years (SD=3.84), while the minimum and maximum years were two years and 15.1 years, respectively.

Clinical Characteristics of Participants

Temperature and Weight-for-Height (Nutritional Status)

All participants had a normal body temperature as those with fever were excluded. The mean body temperature (axillary) was 35.9^{o}C (SD=0.51), while the minimum and maximum body temperature measures were 35^{o}C and 37^{o}C, respectively.

Participants enrolled into the study had a fair nutritional status with, 48 of the 209 (23%) children in enrolled into the study having a weight-for-height score < -1 SD, while the remaining 161of the 209 (77%) had median weight-for-height standard deviation (SD).

Age at diagnosis and age at of starting HAART

The mean age at diagnosis with HIV in the participants was 4.8 years (SD=3.55), while the minimum and maximum ages were 0.2 years and 13 years, respectively. The mean age for starting on HAART was 5.3 years (SD=3.80), while the minimum and maximum ages for starting on HAART were 0.4 years and 13 years, respectively.

Duration from diagnosis to starting HAART and Duration on HAART

The median duration from the age of diagnosis of HIV to starting HAART was 0.1 years, with the minimum being immediately following diagnosis, i.e. within a month of diagnosis and maximum five years after diagnosis. The mean duration on HAART was 4.1 years (SD=2.32), while the minimum was 0.4 years, and the maximum was ten years.

WHO clinical stage of HIV

The majority of the enrolled children (70.3%) were WHO clinical stage 1 of HIV and about 23.4 % were in WHO clinical stage 2 of HIV. 3.8% and 2.4% of the participants were in WHO clinical stage 3 and 4, respectively, as shown in table 1(WHO Clinical staging).

HAART and Other Drugs

About 29.7% of the children enrolled in this study were on nephrotoxic HAART as per the study definition of this study, the remaining 70.3% were on non-nephrotoxic HAART regimen. About one-quarter (25.8%) of all the children enrolled in this study were on LPV/r containing regimens of HAART, and only 5% were on TDF containing regimens of HAART, as shown in table 2. About 55% of the participants were on Cotrimoxazole, and no patient reported having used any herbal medication and NSAIDs in the 4 (four) months before enrolment into this study.

Laboratory Characteristics Of Participants Biochemistry

Serum Creatinine adjusted for age

There were 8 (3.8%) children who had high Creatinine for Age on two (2) occasions over a period of 3months hence they were classified as having renal dysfunction as per study definition(s). Only 2 participants had an abnormal creatinine adjusted for age on one occasion only; hence they did not meet the criteria for renal dysfunction.

Estimated Glomerular Filtration Rate (eGFR)

There were 8 (3.8%) children classified as having renal dysfunction based on eGFR results as per study definition(s) on the basis that they had eGFR on two occasions less than 60 in mL/min/1.73m^{2}.

Urinalysis results for participants

There were 17 (8.13%) children diagnosed with renal dysfunction based on proteinuria as per study definition. 2 participants were diagnosed with a urinary tract infection(UTI) and treated for it. 3 (three) participants had one-off proteinuria either in test one or repeat test (test Two). Haematuria was a note in 3 (1.4%) participants at least on one occasion. All participant that had Haematuria were found to have had renal dysfunction as per study definition.

Prevalence and Association of Study Variables with Renal Dysfunction

The prevalence of renal dysfunction in HIV infected children at the PCOE in UTH, Lusaka, was found to be 8.1%, (CI- 5.0-12.5), based on urinalysis proteinuria, age-adjusted serum creatinine and eGFR as per study definition. All the participants with renal dysfunction had proteinuria on two occasions while only 8 out of the 17 (47%) had an abnormal creatinine and eGFR on two occasions.

Factors Associated with Renal Dysfunction

At 5% significance level after bivariate and multivariate analysis, Age, HAART, WHO stage and HB were found to be significantly associated with renal dysfunction as shown in table 4(Bivariate analysis) and table 5 (Multivariate analysis).

DISCUSSION

Prevalence of renal dysfunction

The Prevalence of renal dysfunction in HIV infected children on HAART at the PCOE in UTH, Lusaka, was found to be 8.1%, at 95% confidence interval, CI= (5.0-12.5) based on proteinuria, age-adjusted serum creatinine and estimated glomerular filtration rate as per study definition, this finding was similar and within range, as has been documented in other studies of 2 % to 34% prevalence of renal dysfunction in HIV infected children in who are on HAART depending on the definition of renal dysfunction used [2,13,16-21]. Differences in the criteria for defining renal disease in the various studies have accounted for the differences in prevalence hence in this study we used an internationally standardized definition of Renal dysfunction by KIDGO to avoid this variance in prevalence due to definitions of renal dysfunction used.

Factors associated with renal dysfunction

The male: female ratio (52.9% being male) of the children with renal disease in this study did not differ significantly statically with a p value=0.78. However, this contrasts with most other studies, where there is usually a male preponderance of renal dysfunction [7,8,9] but equal male: female ratio has also been reported previously in several studies [10-14].

The Median Age of 10.0 years among the children infected with HIV with renal disease in this study is higher compared to the Lagos study with a median age of 5.5 years and a Jamaican study of 5.0 years [10,15]. The finding that renal dysfunction was more prevalent in the older age group children who were on HAART was not surprising as the mean age at diagnosis and starting HAART was higher compared to those who did not have renal dysfunction and may be attributed to longer periods of unsuppressed viral replication [7,8]. Renal disease in HIV is generally viewed as a late complication, which is therefore expected at a much older age [1-5]. This finding may be because all of the study children acquired the infection by vertical transmission and living longer with the infection. It is possible that the acquisition of HIV when the kidneys are still developing may predispose to the renal disease earlier than that observed in adults [8].

This study illustrated that older children infected with HIV were more likely to have renal dysfunction. Children aged 13 years and above had on average 23 times greater odds for renal dysfunction [adjusted odds ratio (OR) = 23.76, and 95% confidence interval (CI) = (5.30 – 106.53), P-value <0.01] compared to children under 13 years old. These findings are similar to Phelps et al who documented that, in children, a renal disease associated with HIV progresses at a slower rate than in adults, with most children developing proteinuria within 2-5 years after HIV infection [16]. After the onset of proteinuria, end-stage renal disease can develop within three years. However, the progression rate depends on the underlying cause of the disease and the presence of other AIDS-associated illnesses [5-10]. It is a well-known fact that ART prolongs survival and decreases the risk and halts renal disease progression [1-5].

The majority of the participant enrolled in this study were in WHO stage 1and 2 at 70.3% and 23.8% respectively. The reason for this may be effective adherence to cART, the rapid response to cART noted in children compared to adults on cART when it comes to clinical improvement of the WHO staging and the selection criteria used. This study showed that a higher WHO clinical stage was associated with renal dysfunction, and this was in keeping with other studies. McCulloch et al and Kala et al both showed that a WHO clinical stage of 3 and 4 was associated with a higher prevalence of renal dysfunction [4, 5]. it was noted that children with the WHO stage greater

than I had on average 58% increased odds for renal dysfunction than children with WHO stage I, but this was not statistically significant [OR=1.58, CI= (0.46 – 5.50), P-value = 0.47].

In this study, children receiving Nephrotoxic HAART per study definition had on average six times greater odds of renal dysfunction [OR=5.55, (CI=1.57 – 19.65), P-value = 0.01] compared to children receiving Non-Nephrotoxic HAART. This was in agreement with other studies such as the study by Dontrelle et al, which showed a reduction in renal function in paediatric HIV patients on Nephrotoxic HAART [25]. Lopinavir/Ritonavir was found to be associated with renal dysfunction with a P-value< 0.01. In literature, Lopinavir/Ritonavir is rarely associated with renal dysfunction as it is 80-90% metabolized and excreted in the liver while only 10-20% of it is metabolized excreted by the Kidneys. Lopinavir and other protease inhibitors have documented to cause renal dysfunction by causing nephrocalcinosis and renal stones[21-25].

Despite finding an association between the type of HAART and renal dysfunction, there was no association noted in this study between the duration the participants had been on HAART and renal dysfunction with a P-value of 0.13. The short mean duration on HAART of 3.3 years may be why the duration on HAART did not show any association with renal dysfunction. However, this finding may be due to the well-documented fact that HAART prevents and halts renal dysfunction progression. [5,7]

Conclusion

This study has demonstrated renal dysfunction among CLHIV who are followed at the UTH in accordance with a widely accepted definition of renal dysfunction in agreement with the kidney improving global outcomes (KDIGO) 2012. Finding of this study justify the need for screening CLHIV for renal dysfunction before starting HAART and after that annually in order to facilitate earlier detection and management of renal dysfunction in these children.

In conclusion, the prevalence of renal dysfunction in HIV infected children on HAART at the PCOE in UTH, Lusaka, was found to be 8.1%, at 95% confidence interval, CI= (5.0-12.5). Increase in Age, WHO stage greater than 1 (one), and nephrotoxic HAART, were associated with renal dysfunction among HIV paediatric patients on HAART in this study.

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TABLES

Table 1: WHO clinical stage distribution of participants.

WHO Clinical Stage	Frequency	Percent
1	147	70.3
2	49	23.4
3	8	3.8
4	5	2.4
Total	209	100.0

Table 2: Type of HAART distribution among participants

HAART	Frequency	Percent
Nephrotoxic	62	29.7
Non-Nephrotoxic	147	70.3
Total	205	100.0

Table 2: The prevalence of renal dysfunction

Condition	Mode of diagnosis	Number (%)
Renal dysfunction		17 (8.13%)
	Proteinuria	17 (8.13%)
	Creatinine	8 (3.83%)
	eGFR	8 (3.83%)
No Renal dysfunction		192 (91.9%)

NB: Renal dysfunction defined as at least an abnormal renal laboratory values in at least 1 of 3 measures of either proteinuria, serum creatinine or eGFR

Table 4: **Bivariate analysis results for factors associated with renal dysfunction**

Variable	No Renal Dysfunction	Renal Dysfunction	P-value
Categorical variables			
Age group			
0 < 13 years	153 (79.7%)	6 (35.3%)	<0.01[c]
≥ 13 years	39 (20.3%)	11 (64.7%)	
Sex			
Female	97 (50.5%)	8 (47.1%)	0.78[c]
Male	95 (49.5%)	9 (52.9%)	
HAART			
Nephrotoxic HAART	51 (26.6%)	11 (64.7%)	< 0.01[c]
Lopinavir/R(LPV/R)	43(22.4%)	6(35.5%)	<0.01[f]
Tenofovir (TDF)	11(5.7%)	0(0%)	0.61[f]
Non-Nephrotoxic HAART	141 (73.4%)	6 (35.3%)	
DURATION on HAART			
< 5 Years	122(63.5%)	14(82.4%)	0.12[c]
> 5 Years	70 (36.5%)	3(17.6%)	
Cotrimoxazole			
On Cotrimoxazole	103 (53.6%)	5 (29.4%)	0.18[c]
Not Cotrimoxazole	89 (46.4%)	12 (70.6%)	
Weight-for-height			
< -1SD	42 (21.9%)	6 (35.3%)	0.23[f]
Median	150 (78.1%)	11 (64.7%)	
WHO Stage			
Stage I	138 (71.9%)	9 (52.9%)	0.10[c]
Other stages	54 (28.1%)	8 (47.1%)	
Continuous variables			
Mean study CD4 (SD)	883.5 (526.70)	816.2 (538.47)	0.90[t]
Mean HB (SD)	12.1 (1.26)	11.2 (0.40)	<0.01[t]
Mean enrolment age (SD)	9.3 (3.63)	10.0 (5.81)	0.61[t]
Mean age at diagnosis (SD)	4.7 (3.37)	6.6 (4.88)	0.12[t]
Mean age starting HAART (SD)	5.2 (3.69)	6.7 (4.82)	0.23[t]
Mean duration on HAART (SD)	4.1 (2.35)	3.3 (1.81)	0.13[t]
Mean body temperature (SD)	35.9 (0.52)	35.8 (0.41)	0.39[t]

[c]=Chi-square; [f]=Fisher's exact; [t]=T-test

Table 5: Multivariate logistic regression analysis predicting renal dysfunction

Variable	Unadjusted Odds Ratio	Adjusted Odds Ratio	P-value
Age			
< 13 Years	1	1	
≥ 13 Years	7.19 (2.50 - 20.66)	23.76 (5.30 - 106.53)	<0.01
HAART			
Non-Nephrotoxic	1	1	
Nephrotoxic	5.07 (1.78 - 14.41)	5.55 (1.57 - 19.65)	0.01
WHO Stage			
Stage I	1	1	
Stage ≥ II	2.27 (0.83 - 6.19)	1.58 (0.46 - 5.50)	0.47
HB	0.55 (0.36 - 0.85)	0.28 (0.14 - 0.55)	<0.01