

The prevalence and risk factors for dyslipidaemia in human immunodeficiency virus-infected children on highly active antiretroviral therapy in Kano, Nigeria

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Abstract

Prolonged administration of Highly Active Anti Retroviral Therapy (HAART) is associated with metabolic side effects, especially dyslipidaemia, with potential increase in the risk of develop-

ment of cardiovascular disease as the affected children mature into adulthood. This study determined the prevalence and risk factors for dyslipidaemia among HIV infected children aged 2-15 years. The study was a comparative study conducted on children aged 2-15 years attending the Paediatric Infectious Disease Clinic of the Aminu Kano Teaching Hospital, Kano. Study subjects that fulfilled the inclusion criteria were recruited using systematic sampling technique. Serum lipid profile parameters were measured on blood samples from eighty HIV-infected children on HAART and eighty HIV-infected HAART naive children as patients and controls respectively. Data was analysed using the SPSS software for Windows version 16.0. P-values of <0.05 were considered as statistically significant. The overall prevalence of dyslipidaemia in HIV-infected children on HAART was 62.5% (95% CI: 51.8% - 73.1%), while 52.5% (95% CI: 41.5% - 63.4%) of the HIV-infected HAART naive children also had dyslipidaemia. The risk factors associated with hypercholesterolaemia were: age at commencement of HAART less than 2 years ($P<0.048$; Adjusted Odds Ratio, OR, of 0.38, 95% CI: 0.13-1.08) and PI-based HAART regimen ($P<0.001$; OR=0.18, 95% CI: 0.07-0.49), while age group greater than 5 years ($P<0.02$; OR=2.78 (95% CI: 0.76-10.23), duration of HIV diagnosis greater than one year ($P<0.02$ Fisher's exact) and duration of treatment on HAART for more than one year ($P<0.04$; OR=2.32, 95% CI: 0.14-38.99) were the risk factors associated with hypertriglyceridaemia among the HIV infected children on HAART. However, on multivariate analysis, PI-based HAART regimen was the only independent predictor of hypercholesterolaemia in the HAART treated children (OR=0.18, 95% CI: 0.07-0.49). Duration of diagnosis greater than 1 year was associated with hypercholesterolaemia in HAART naïve HIV-infected children ($P=0.05$).

The most common dyslipidaemia in HIV-infected children on HAART was hypertriglyceridaemia followed by hypercholesterolaemia while low HDL-cholesterol was the commonest lipid abnormality in the HIV-infected HAART naive children.

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Key words: Human immunodeficiency virus, highly active antiretroviral therapy (HAART), HAART-naive, Dyslipidaemia.

Contributions: AIOO, conceptualized and designed the study, acquired, analyzed and interpreted the data, drafted the article, revised it critically for important intellectual content, and approved the final submitted version; HHF designed the study, and acquired, analyzed and interpreted the data, drafted the article, revised it critically for important intellectual content, and approved the final submitted version; YIA designed the study, and acquired, analyzed and interpreted the data, drafted the article, revised it critically for important intellectual content, and approved the final submitted version; OOA and AHA analyzed and interpreted the data, drafted the article and revised it critically for important intellectual content, and approved the final submitted version.

Conflict of interest: The authors declare no conflict of interest

Funding: Self-funded.

Ethics approval and consent to participate: Ethical clearance for the study was obtained from the Research and Ethical Committee of the Hospital. Informed consent was also obtained from the parent(s) or care-giver(s) and assent was obtained for children older than eight years of age.

Received for publication: 5 February 2020.

Accepted for publication: 20 July 2020.

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Annals of African Medical Research 2020; 3:103

doi:10.4081/aamr.2020.103

Introduction

HIV infection has become a chronic disease in paediatric patients as access to Antiretroviral Therapy (ART) has significantly improved the prognosis and potential for long-term survival.¹ Highly Active Antiretroviral Therapy (HAART) which consists of Protease Inhibitors (PIs) or Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) in combination with Nucleoside Reverse Transcriptase Inhibitors (NRTIs) has led to dramatic improvements in the management of HIV-infected patients.² Although these anti-

retroviral therapies are usually well tolerated, previously unrecognized side effects are becoming more evident with their widespread usage.^{2,3} Frequently encountered metabolic side effects include dyslipidaemia, altered glucose metabolism, insulin resistance, elevated free fatty acids, fat redistribution syndrome or lipodystrophy, lactic acidosis and bone density abnormalities.⁴ These metabolic complications of ART have been well documented in adults, but paediatric cohort studies are limited.⁵ The NRTIs are closely linked to lipodystrophy and lactic acidosis, while the PIs have consistently been associated with increased cholesterol and triglycerides in children which may potentially increase the risk of cardiovascular disease as they mature into adulthood.⁵

However, few studies have so far evaluated lipid profiles of children receiving HAART in sub-Saharan Africa, especially in Nigeria where over 90% of HIV-infected children reside. Most of the studies on lipid profiles of HIV-infected patients on HAART in Nigeria were done on the adult population.

As more children receive life-saving ARTs resulting in longer survival rates, understanding the adverse effects associated with exposure to ART is important for paediatricians and other health care workers who cater for these group of children and adolescents. It is thus imperative to determine these changes early so that timely intervention can be instituted to prevent complications and thus improve the quality of life of these children,⁶ hence the need for this study.

The aim of the study was to compare the prevalence and risk factors for dyslipidaemia among HIV-infected children on HAART and HIV-infected HAART naive children, aged 2-15 years, attending the Aminu Kano Teaching Hospital, Kano.

Materials and Methods

The study was carried out at the Paediatric Infectious Diseases Clinic (PIDC) of the Hospital on HIV infected children aged 2–15 years of age who were age- and sex- matched using systematic sampling technique. Eighty children receiving HAART for at least 3 months and 80 children not receiving ART were enrolled into the study from August, 2015 to March, 2016 as patients and controls respectively. HIV-infected children with confirmed renal disease, diabetes mellitus, cardiac disease or those on corticosteroids for at least one month prior to the commencement of the study were excluded from the study.

Ethical clearance for the study was obtained from the Research and Ethical Committee of the Hospital. Informed consent was also obtained from the parent(s) or care-giver(s) and assent was obtained for children older than eight years of age.

A proforma was used to collect information on each of the subjects at the time of recruitment. Socio-demographic data, including social class of the parents or caregivers, were recorded. The social class was classified using the Oyediji socio-economic classification scheme.⁷

Under strict aseptic conditions, after cleaning the blood collection site thoroughly with 70% alcohol, five milliliters of non fasting venous blood was collected from each subject by venepuncture using lithium heparin vacutainer tubes. All samples were separated and then centrifuged at 3000 revolutions per minute for 10 minutes and the separated plasma stored at -20°C until analysis. The plasma samples were later analyzed for Total Cholesterol (TC), Low Density Lipoprotein Cholesterol (LDL-C), High Density Lipoprotein Cholesterol (HDL-C) and Triglycerides (TG) by enzymatic assay methods^{8,9} on Cobas Integra 400 series Chemistry autoanalyser. Low density lipoprotein cholesterol level was calcu-

lated using the formula of Friedwald *et al.*¹⁰ Abnormal lipid levels, known as dyslipidaemia, were defined according to the National Cholesterol Education Programme (NCEP) guidelines. Subjects with values for TC \geq 200 mg/dL (5.2 mmol/L), LDL \geq 130 mg/dL (3.4 mmol/L), TG \geq 150 mg/dL (1.69 mmol/L) and HDL \leq 35 mg/dL (0.91 mmol/L) were considered to have dyslipidaemia.

Data obtained from the study were analyzed using the Statistical Package for Social Science (SPSS) software for Windows version 16.0 (University of Bristol). Data were presented in tables. Quantitative variables were summarized as mean \pm Standard Deviation (SD) or as median and inter-quantile range. Qualitative variables were described as frequencies and percentages. The Student "t" test was used to compare mean values of variables, while proportion and percentages were compared using Chi-square (χ^2) test. Multivariate analysis was used to determine the effects of independent variables such as age, duration of diagnosis of HIV, duration on HAART, type of HAART and Dyslipidaemia on the final outcome (*i.e.*, presence or absence of dyslipidaemia, which is the dependent variable). Level of statistical significance was set at $P\leq 0.05$.

Results

Table 1 shows the baseline characteristics of the study subjects. Both patients and controls had the same composition of sexes with an overall male:female ratio of 1.4:1.

The study subjects were mostly of low socio-economic class belonging to social class IV.

The plasma concentrations of lipid profile parameters were higher in children receiving HAART compared to the HAART naive children and the differences were statistically significant for all the parameters except HDL-cholesterol (Table 2).

Fifty out of the eighty HIV-infected children on HAART had at least one abnormal lipid profile parameter, resulting in a prevalence of 62.5% (95% CI: 51.8% - 73.1%). While the prevalence of dyslipidaemia in HIV-infected HAART naive children was 52.5% (95% CI: 41.5% - 63.4%).

The most common dyslipidaemia in patients on HAART was hypertriglyceridaemia followed by hypercholesterolaemia, while low HDL-cholesterol was the commonest lipid abnormality in the HAART naive children (Table 3).

Commencement of HAART at age less than 2 years and PI-based HAART regimen were found to be significantly associated with hypercholesterolaemia in the patients on HAART (Table 4).

Duration of diagnosis greater than 1 year was associated with hypercholesterolaemia in HAART naïve HIV-infected children ($P=0.05$).

After controlling for possible confounders such as age and sex, only PI-based HAART regimen remained the predictor for hypercholesterolaemia among the HIV infected children on HAART ($P=0.001$; OR=0.18, 95% CI: 0.07 - 0.49) while non PI-based regimen was protective against hypercholesterolaemia among the HIV- infected children on HAART (Table 5).

Tables 6 shows the risk factors associated with Hypertriglyceridaemia amongst the HIV-infected children on HAART.

The children who were older than 5 years of age ($P=0.02$; OR=2.78, 95% CI: 0.76-10.23), duration of diagnosis of HIV infection greater than 1 year ($P=0.02$; OR=2.23, 95% CI: 0.14 - 38.99) and duration on HAART regimen greater than 1 year ($P=0.04$) were found to be the factors significantly associated with hypertriglyceridaemia (Table 7).

Discussion

Total cholesterol, LDL-cholesterol and triglycerides levels were found to be significantly higher among the studied children on HAART compared to HAART naïve children. However, the levels of HDL-cholesterol did not differ between the two groups. The elevations in serum lipids in HIV infection could be due to the replication of HIV in human T-cells.¹¹ These elevations are further worsened by the use of HAART.^{12,13} A similar pattern of dyslipidaemia was reported in a group of HIV-infected adults in a Nigerian population by Awah *et al* in Asaba.¹⁴

The high prevalence of dyslipidaemia noted in this study can

be attributed to the combination therapy of the HAART regimen, particularly the PI based antiretroviral drugs (lopinavir/ritonavir-based combinations) which are known to have lipid sparing effects. Also, the high prevalence of dyslipidaemia may be attributed to the long duration of treatment with HAART as this study showed the mean duration of treatment of about five years.

This study also showed that duration of diagnosis greater than 1 year was significantly associated with dyslipidaemia. Previous studies have shown that unfavourable lipid concentrations could begin to manifest within three to twelve months of commencement of PI-based therapy and the manifestation could be faster in those with ritonavir-based combinations.¹⁵ The studies conducted by

Table 1. Baseline characteristics of study subjects.

Baseline characteristics	HAART (n= 80)	HAART NAIVE (n= 80)
Mean age in years (SD)	9.08 ± 3.8	9.00 ± 3.67
Gender		
Male	47 (58.7%)	47 (58.7%)
Female	33 (41.3%)	33 (41.3%)
Socio-economic class		
I	12 (15.0%)	2 (2.5%)
II	13 (16.2%)	3 (3.8%)
III	22 (27.5%)	23 (28.7%)
IV	26 (32.5%)	40 (50.0%)
V	7 (8.8%)	12 (15.0%)
Medical history		
Age at diagnosis [Median (IQR)]	30 (48)	72 (58)
Duration of diagnosis[Mean±SD](mo)	65.4(39.2)	37.8(31.7)
Age at commencement of ART[Mean±SD] (mo)	49.8(44.03)	NA
Duration on ART[Mean±SD] (mo)	59.61(40.7)	NA
HAART regimen		
First line	46(57.5%)	NA
Second line	34(42.5%)	NA
Duration on current ART(mo)	30.8(17.8)	NA

mo -months NA= not applicable.

Table 2. Serum lipid profile (Mean ± SD) of study subjects by group.

Lipid profile (mmol/L)	HAART	HAART NAIVE	T test	P value
Total Cholesterol	5.34 ± 1.30	4.16 ± 0.9	6.58	0.001
LDL-Cholesterol	3.52 ± 1.17	2.51 ± 0.88	6.17	.001
HDL-Cholesterol	0.92 ± 0.34	0.86 ± 0.23	1.31	0.193
Triglycerides	1.88 ± 0.58	1.67 ± 0.53	2.39	0.018

Table 3. Prevalence of Dyslipidaemia among the study subjects.

Variable	HAART n (%)	HAART NAIVE n (%)	P value
Total Cholesterol			
High	38 (47.5)	9 (11.3)	0.001
Normal	42 (52.5)	71 (88.7)	
HDL Cholesterol			
Low	43 (53.8)	42 (52.5)	0.980
Normal	37 (46.2)	38 (47.5)	
LDL Cholesterol			
High	33 (41.3)	14 (17.5)	0.001
Normal	47 (58.7)	66 (82.5)	
Triglyceride			
High	50 (62.5)	38 (47.5)	0.014
Normal	30 (37.5)	42 (52.5)	

Table 4. Risk factors for hypercholesterolaemia in children on HAART.

Variable	High TC n(%)	Normal TC n(%)	TOTAL n= 80	Test statistic χ^2	P value
Age					
≥5years	29(43.9)	37(56.1)	66	1.92	0.17
< 5years	9(64.3)	5(35.7)	14		
Gender					
Male	20(42.6)	27(57.4)	47	1.12	0.29
Female	18(54.6)	12(45.4)	33		
Age at diagnosis					
≥2years	22(42.3)	30(57.7)	52	1.61	0.21
<2years	16(57.1)	12(42.9)	28		
Duration of diagnosis					
≥1year	38(50.0)	38(50.0)	76		0.12
<1year	0	4(100.0)	4		
Age at HAART					
≥2 years	21(39.6)	32(60.4)	53	3.91	0.048
<2years	17(63.0)	10(37.0)	27		
Duration on HAART					
≥1year	34(49.3)	35(50.7)	69	0.63	0.43
<1year	4(36.4)	7(63.4)	11		
HAARTRegimen					
PI based	24 (70.6)	10 (29.4)	34	12.64	0.001
Non PI based	14(30.4)	32(69.6)	46		

Table 5. Multivariate analyses for risk factors for hypercholesterolaemia in children on HAART.

Risk factor for Hypercholesterolaemia	Adjusted Odds Ratio (95%CI)	p value
Age at HAART (years)		
Less than 2 (referent)		
Greater than or equal to 2	0.38(0.13-1.08)	0.07
HAART Regimen		
PI based (referent)		
Non-PI based	0.18(0.07-0.49)	0.001

Table 6. Risk Factors for Hypertriglyceridaemia in children on HAART.

Variable	High TC n(%)	Normal TC n(%)	TOTAL n= 80	Test statistic χ^2	P value
Age Group					
≥5years	45(68.2)	21(31.8)	66	5.20	0.02
<5years	5(35.2)	9(64.3)	14		
Gender					
Male	30(63.8)	17(36.2)	47	0.09	0.77
Female	20(60.6)	13(39.4)	33		
Age at diagnosis					
≥2years	33(63.5)	19(36.5)	52	0.06	0.81
<2years	17(60.7)	11(39.30)	28		
Duration of diagnosis					
≥ 1year	50(65.8)	26(34.2)	76		0.02
< 1year	0	4(100.0)	4		
Age at HAART					
≥ 2 years	33(62.3)	20(37.7)	53	0.004	0.95
< 2 years	17(63.0)	10(37.0)	27		
Duration on HAART					
≥ 1year	49(65.3)	26(34.7)	75	4.11	0.04
< 1year	1(20.0)	4(80.0)	5		
HAARTRegimen					
PI based	19(55.9)	15(44.1)	34	1.11	0.29
Non PI based	31(67.4)	15(32.6)	46		

Table 7. Multivariate analyses of risk factors for hypertriglyceridaemia in children on HAART.

Risk factor for Hypercholesterolaemia	Adjusted Odds Ratio (95%CI)	p value
Age Group (years)		
Less than 5	2.78 (0.76-10.23)	0.12
Greater than or equal to 5 (referent)		
Duration on HAART (year)		
Less than 1	2.32 (0.14-38.99)	0.56
Greater than 1		

Vigano *et al.*¹⁶ and Farley *et al.*¹⁷ also reported similar findings of higher prevalence of lipid disorders among HIV-infected children and adolescents on HAART.

The prevalence of the various forms of dyslipidaemia observed in this study are similar to the findings of Amaya *et al.*¹⁸ in a study conducted on a group of 40 HIV-infected children in the United States of America on PI- and non PI-based HAART regimens. They reported a prevalence of hypercholesterolaemia and hypertriglyceridaemia of 68% and 28% respectively. Also in Uganda, Piloya *et al.*¹⁹ reported a prevalence of hypercholesterolaemia of 16.8% and hypertriglyceridaemia of 83.2%. The differences in prevalence rates could be due to varying effects of the antiretroviral drugs, particularly the PIs.²⁰ Various types of diets could also be associated with the pathogenesis of HAART-related dyslipidaemia, as the children studied were from different parts of the world.²⁰

Lower serum lipid levels were found among the HIV-infected HAART naïve children compared to the HAART treated group in this study. Similarly, Chantry *et al.*,²¹ in the USA also reported lower serum lipid levels in HAART naïve children.

Hypertriglyceridaemia and low HDL-cholesterol were the most common form of lipid abnormalities observed among the studied HAART naïve group. Similar findings were also reported by Kanjanavanit *et al.*²² in a group of 274 HIV-infected HAART naïve Thai and Cambodian children aged 1 to 12 years.

In the HAART treated group, total cholesterol was found to be significantly elevated in the children on PI-based HAART regimen (which also contains NRTIs) compared to the children on the non-PI-based HAART regimen (which contains both NRTIs and NNRTI). However, there was no significant difference in the elevated triglyceride levels among the two groups. This observation corroborates the findings of Brewinski *et al.*,²³ in a cohort of HIV-infected Latin American children on PI-based HAART regime which showed that the children were at increased risk of hypercholesterolaemia and hypertriglyceridaemia compared with the children that were on NNRTI-containing HAART regimen.

Factors associated with hypercholesterolaemia and hypertriglyceridaemia among the HIV- infected children on HAART noted in this study were age at commencement of HAART greater than 2 years, PI-based HAART regimen, age group greater than 5 years, duration of HIV diagnosis greater than 1 year and duration of treatment with HAART of more than 1 year. However, after controlling for confounders on multivariate analysis, PI-based HAART regimen was the only factor found to be independently associated with hypercholesterolaemia in HAART treated group. Farley *et al.*,¹⁷ in a large group of 1,812 HIV-infected children in the USA, found that the use of PI-based HAART regimen, ages from 4 to <6 years, HIV-1 RNA <400 copies/mL, good adherence and the use of NNRTI were independently associated with hypercholesterolaemia.

No significant relationship was observed between gender, hypercholesterolaemia and hypertriglyceridaemia in this study. This was similar to the findings of Brewinski *et al.*,²³ in a group of HIV infected Latin American children. In this study, there was also no significant association between socio-economic class, hypercholesterolaemia and hypertriglyceridaemia. This could be due to exposure of the children to the same staple food within the community. Though a greater proportion of the children were in social class 4 and 5, almost all the children recruited for the study lived within Kano metropolis which is an urban settlement.

Conclusions

The aim of the study was to compare the prevalence and risk factors for dyslipidaemia among HIV-infected children on HAART and HIV-infected HAART naïve children aged 2-15 years attending the Aminu Kano Teaching Hospital, Kano.

It could be concluded from the observations made in this study that the prevalence of dyslipidaemia was higher in the HIV infected HAART treated children than the HIV infected HAART naïve children. Also, the prevalence of hypercholesterolaemia was higher in patients on PI-based HAART regimen than those on non -PI-based HAART regimen. The risk factor strongly associated with dyslipidaemia was PI-based HAART regimen. Other risk factors for dyslipidaemia identified in the study were age group greater than 5 years, commencement of HAART in children greater than 2 years of age, duration of HIV diagnosis more than 1 year and duration of treatment on HAART for more than 1 year.

Recommendations

All HIV positive children should have pre-HAART baseline lipid profiles measured followed by periodic assessments. The treatment regimen with the lowest risk for dyslipidaemia should be offered to patients as the second line treatment option. Patients identified with dyslipidaemia should be commenced immediately on the various treatment options available for children and adolescents.

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