Effects of highly active antiretroviral therapy on renal function of HIV-infected under-fives in Southern Nigeria

Olugbenga M. Ajulo[1], Kayode M. Omole[2], Olanrewaju J. Moody[3], Regina Oladokun[4], Ofonime T. Dixon-Umo[5]

[1]Department of Clinical Pharmacy and Biopharmacy, Faculty of Pharmacy, University of Uyo, Uyo. AkwaIbom State. Nigeria.

[2]Department of Clinical Pharmacy and Pharmacy Administration,Faculty of Pharmacy, University of Ibadan,Ibadan. Oyo State. Nigeria.

[3]Department of Pharmacognosy,Faculty of Pharmacy, University of Ibadan,Ibadan. Oyo State. Nigeria.

[4]Department of Pediatrics, Faculty of Medicine, College of Medicine,University College Hospital, Ibadan. Oyo State. Nigeria.

[5]Department of Pediatrics,Faculty of Medicine, College of Medicine,University of Uyo Teaching Hospital, Uyo. Akwa-Ibom State. Nigeria.

Corresponding Author: Olugbenga M. Ajulo
E-mail: ajugbeng@gmail.com Phone: +2347030262468

ABSTRACT

Background: Toxicities from antiretrovirals caused clinically-relevant organ damage.

Objective: Study aimed at monitoring effects of Highly Active Antiretroviral Therapy (HAART) on kidney of HIV-infected under-fives in Southern Nigeria.

Methods: In Southern Nigeria, 238 under-fives were recruited. Institutional approval and written consent were obtained. Group A consisted of 91 HIV-infected children on HAART. Group B1 consisted of 24 HIV-exposed infants born to breast feeding HIV-mothers on HAART, who received nevirapine for first 6-week of life. Group B2 (18) and B3 (48) consisted of HIV-exposed children on co-trimoxazole at age 6-month and 18-month respectively. Group C consisted of 11 HIV-infected children on co-trimoxazole. Group D consisted of 46 seronegative children. A 2ml blood was collected from each participant during first phase of the study and was analysed for creatinine using Randox® kits. Group A returned for second and third phase of the study after 3 and 6 months respectively. Data was analysed by using ANOVA.

Results: Creatinine clearance was highest in group A (102.6±82.9ml/min/1.732m^2) suggesting normal renal function. Second phase, creatinine clearance of group A was reduced by 8.7% ($p>0.05$). Third phase, creatinine clearance was reduced by 25.4% ($p<0.05$) suggesting reduced renal function.

Conclusion: HAART was significantly associated with reduced renal function among HIV-infected under-fives in Southern Nigeria.

Key words: Under-five HIV children; kidney; creatinine; creatinine clearance; HAART.

Les effets de la thérapie antirétrovirale fortement active sur la fonction rénale des personnes de moins de cinq ans infectées par le VIH au sud du Nigeria

Auteur correspondant: Olugbenga Ajulo
E-mail: ajugbeng@gmail.com Téléphone: +2347030262468

RESUME

Contexte: Les toxicités provenant des antirétroviraux ont causé des lésions organiques de pertinence clinique.

Objective: L'étude a visé la suivie des effets de la thérapie antirétrovirale fortement active (HAART) sur les reins des enfants de moins de cinq infectés par le VIH au sud du Nigeria.

Méthodes: Au sud du Nigeria, 238 des moins de cinq ans ont été recensés. L'approbation institutionnelle et le consentement par écrit ont été obtenus. Le Groupe A comprenait 91 enfants infectés par VIH sur HAART. Le Groupe B1 comprenait 24 enfants exposés au VIH nés de mères VIH allaitant sur HAART, qui ont reçu la névirapine pendant les premiers 6 semaines de vie. Le Groupe B2 (18) et B3 (48) comprenaient des enfants exposés au VIH sur le co-trimoxazole à l'âge de 6 mois et 18 mois respectivement. Le Groupe C comprenait 11 enfants infectés par le VIH placés sur co-trimoxazole. Le Groupe D comprenait 46 enfants séronégatifs. 2ml de sang a été prélevé de chaque participant pendant la première phase de l'étude et a été analysé pour la créatinine en utilisant les trousses Randox®. Le Groupe A est revenu pour la deuxième et la troisième phase de l'étude après 3 et 6 mois respectivement. Les données ont été analysées à l'aide de ANOVA.

Résultats: La clairance de créatinine était la plus élevée dans le A (102.6±82.9ml/min/1.732m^2) indiquant une fonction rénal normale. La deuxième phase, la clairance de créatinine du groupe A a été réduite de 8.7% ($p>0.05$). La troisième phase, la clairance de créatinine a été réduite de 25.4% ($p<0.05$) indiquant une fonction rénale réduite.

Conclusion: HAART était considérablement associé à une fonction rénale réduite parmi les moins de cinq ans infectés par le VIH dans le sud du Nigéria.

Mots-clés: Enfants VIH de moins de cinq ans; rein; créatinine; clairance de créatinine; HAART.

INTRODUCTION

WHO stated that 2.1 million children were living with HIV/AIDS worldwide in 2007 while 2 million were claimed to be living in sub-Saharan Africa. Most of these children acquired HIV from their HIV-infected mothers during pregnancy, birth or breastfeeding. Successful interventions have reduced the risks of mother-to-child transmissions to 2%. An estimated 1,000 children get newly infected with HIV each day. The number of children receiving ART increased from about 75,000 in 2005 to almost 200,000 in 2007.[1]

The preferred option when choosing a first line regimen for infants and children is two nucleoside reverse transcriptase inhibitors (NRTIs) and a non-nucleoside reverse transcriptase inhibitor (NNRTI). These drugs prevent HIV replication by inhibition of the action of reverse transcriptase, the enzyme that HIV uses to make a DNA copy of its RNA. NRTI/NNRTI- based regimens are efficacious and generally less expensive; generic formulations are more often available and a cold chain is not required.[2]Accumulated toxicities from exposure to antiretroviral drugs for a long time caused clinically-relevant metabolic disturbances and end-organ damage. Direct toxicity of antiretroviral drugs also contributes to non-AID co-morbidities, although each successive generation of antiretroviral therapy has been associated with less toxicity. Tenofovir, which is now part of some first-line regimens and mostly used protease inhibitors have mild toxic effects on kidney function. Mild toxicities could lead to a large burden of disease when the drugs are used for decades, treatment guidelines now require regimens based on long-term toxicity and antiviral potency.[3]

The greatest improvements of HAART occurred in patients with renal dysfunction at baseline. This study suggested that the inability to monitor renal function should not be a contraindication to providing first-line HAART in poor countries. The pre-HAART prevalence of renal dysfunction in their study was greater than rates observed in United States which may be due to renal disease such as HIV-associated nephropathy which deteriorates with advanced HIV disease and the participants who featured advanced HIV disease at baseline. Besides, in the United States, conditions such as HIV-associated nephropathy occur mostly in individuals of African origin suggesting that Africans may also be at risk for this complication. In sub-Saharan Africa, the facility to monitor renal function is often limited. Their study suggested that renal function will improve in most patients with advanced HIV disease who received HAART. A rational approach of using standard weight-based dosing without adjustment for renal function at the initiation of HAART for patients known with renal dysfunction may not be necessary. This will avoid sub-optimal HAART dosing thereby preventing treatment failure based on viral load. Where monitoring facility is available, patients with renal dysfunction at HAART initiation may require repeat renal function testing during the first few months of treatment. If renal function does not improve despite HAART, antiretroviral dose adjustments based on renal function should be considered. They reported improved renal functions in the majority of participants while few participants had a significant decline in renal function despite achieving viral load suppression on HAART. The decline in renal function for a few participants may showed that the HIV- associated renal disease does not improve with HAART or other renal pathologies that would not be expected to respond to HAART.[4]

Rho and Perazella (2007) emphasized that HAART regimens have nephrotoxic potential and are indicated in causing both acute and chronic kidney disease. Safe use of these drugs requires a firm knowledge of risk factors that lead to kidney injury such as patient-related characteristics and drug-related factors. Adefovir and tenofovir are associated with tubular toxicity in adults. Crystalluria, crystal nephropathy and nephrolithiasis have been established with indinavir in adults. Acute interstitial nephritis, although not common among antiretroviral agents, is seen with indinavir and atazanavir in immunocompromised adult patients. Enfuvirtide may rarely promote a glomerulopathy in adults. Frequent exposure to other nephrotoxic non-antiretroviral drugs also contributes to kidney disease. Identification and reversal of potentially modifiable risk factors prior to drug administration is important to limiting kidney injury. Recognition of drug-related nephrotoxicity will promote earlier resolution of acute kidney injury and reduce the development of chronic kidney disease.[5]

Although, the children have been exposed to HAART during pregnancy, breastfeeding and their commencement of HAART, there is no published data of effects of HAART on renal function of 0-5 year old children in Nigeria.The objective of the study is to evaluate the serum creatinine and creatinine clearance of the children as a means of determining their renal function.

METHODS

Study design:

This was a prospective quantitative observational study which was done by convenient sampling of under-fives.

Study setting:

This study was done in five selected HIV clinics in the following hospitals: University College Hospital, Ibadan, University of Uyo Teaching Hospital, Federal Medical Centre, Umuahia, Emmanuel Hospital, Eket and St Luke Hospital, Anua.

Population, sample and sampling

The study was done on 238 under-fives who were recruited through convenient sampling in Southern Nigeria.

Using assumed prevalence of HIV among 0-5 years to be 50 % in absence of known data in Nigeria.

$$n = \frac{z^2_{\alpha} p\, q}{d^2}$$

Therefore, the minimum sample size to show effect is 43 persons.[6] Since, there is no HIV prevalence value for 0-5 years in Nigeria; an assumption of 50 % prevalence was used. A total of 238 persons were recruited for the study to make up for withdrawal.

The recruited participants were selected into 6 categories by convenient sampling. Group A consisted of 91 HIV-infected infants and children on Highly Active Anti-retroviral Therapy (HAART).Group B1 consisted of 24 HIV-exposed infants born to breastfeeding HIV-mothers on HAART. These children were receiving single dose prophylactic nevirapine for first 6 weeks of life. They were 6 weeks old at the time of blood collection.Group B2 consisted of 18 HIV-exposed infants born to breastfeeding HIV-mothers on HAART. The children were receiving prophylactic co-trimoxazole and were 6 months old at the time of blood collection.Group B3 consisted of 48 HIV-exposed children born to breastfeeding HIV-mothers on HAART. The children were receiving prophylactic co-trimoxazole and were 18 months old at the time of blood collection. They had stopped breastfeeding at least 3 months before blood collection.Group C consisted of 11 HIV-infected children born to HIV-mothers on HAART. These children were receiving prophylactic co-trimoxazole because of their immunity.Group D consisted of 46 seronegative children born to seronegative parents. They served as the control group.

Ethical consideration

Institutional approval was obtained from all the study centres. Also, written consent was obtained from the care-givers of the participated under-five children.

Inclusion criteria

The inclusion criteria for participating in the study were: being 0-5 years old male and female, asymptomatic HIV-infected children in Stage 1, HIV-exposed children, seronegative children from seronegative mother.

Data collection

A 2ml blood sample was collected from each participant during first phase of the study and was analysed for creatinine using kits manufactured by Randox®. Creatinine clearance was calculated from the obtained creatinine by using Schwartz equation. HIV-infected children on HAART returned for second and third phases of the study after three and 6 months respectively.

Schwartz equation:

Creatinine clearance (ml/min/1.732m^2) = $\frac{[\text{length (cm)} * k]}{\text{Serum creatinine}}$

K=0.45 for infants 1 to 52 weeks old,K=0.55 for children 1 to 13 years old.[7]

Serum creatinine was measured in µmol/L. Conversion of µmol/L to mg/dL was done by dividing the value of creatinine by 88.4.

Data analysis

The obtained data were analysed using descriptive statistics and Analysis of variance (ANOVA). SPSS version 20 software was used.

RESULTS

First phase of blood collection

Two hundred and thirty-eight (238) study participants comprising 118 (49.6%) boys and 120 (50.4%) girls were recruited for the study in Southern Nigeria during the first phase of blood collection. The study participants were recruited at a mean age of 26.3±20.6months with mean weight of 13.3kg. The body mass index was highest in group B3 (23.8±9.2kg/m^2) followed by group C (21.5±7.7kg/m^2), group B2 (20.2±8.9kg/m^2), group B1 (19.4±9.7kg/m^2), group A (19.0±10.9kg/m^2) and group D (16.9±3.2kg/m^2) respectively (Fig. 3). The mean baseline CD4 count for the study participants who received highly active antiretroviral therapy (HAART) was 945cells/mm^3 during the first phase of blood collection (Table 1).

The body mass index of study participants receiving different HAART combinations were evaluated as thus ABC+ 3TC + LPv/rtv (14.4kg/m^2), D4T + 3TC + NVP (15.6kg/m^2), AZT + 3TC + NVP (19.9kg/m^2), EFV + AZT + 3TC (15.9kg/m^2), ABC + 3TC + AZT (17.6kg/m^2) and AZT + 3TC + LPv/rtv (16.9kg/m^2) (Table 2).

The kidney function test showed that creatinine was highest in group D (58.7±24.7µmol/L) followed by

group C (54.3±23.0µmol/L), group B3 (54.1±23.0µmol/L), group A (53.7±22.4µmol/L), group B2 (39.1±16.4µmol/L) and group B1 (38.7±11.6µmol/L) respectively (Fig. 1). Creatinine clearance was highest in group A (102.6±82.9ml/min/1.732m^2) followed by group D (84.4±52.1ml/min/1.732m^2), group C (74.7±20.2ml/min/1.732m^2), group B1 (71.8±72.5ml/min/1.732m^2), group B2 (69.6±33.0ml/min/1.732m^2) and group B3 (67.5±31.8ml/min/1.732m^2) respectively (Fig. 2). The statistical analysis of variance was used to compare the means among the groups using IBM SPSS version 20, the results showed that creatinine ($p<0.05$), creatinine clearance ($p<0.05$) and BMI ($p>0.05$)were significant (Table 3).

Table 1: Characteristics of study participants during first phase in Southern Nigeria

Characteristics	N=238
Male	118 (49.5%)
Female	120 (50.4%)
Mean age (months)	26.3±20.6
Average Weight (Kg)	13.3±7.5
BMI (A)	18.9±10.9
BMI (B1)	19.4±9.7
BMI (B2)	20.2±8.9
BMI (B3)	24.1±9.3
BMI (C)	21.7±7.7
BMI (D)	17.1±2.8
Mean baseline CD4 (cells/mm^3)	945±548.2
Stage	1

BMI- Body mass index

Table 2: HAART Combinations received by HIV-infected children in Southern Nigeria

S/NO	Haart Combinations	Number Of Participants (percentage)	BMI Of Participants Who Took HAART Combinations (kg/m^2)
1	ABC+ 3TC + LPv/rtv	6(6.5%)	14.4
2	D4T + 3TC + NVP	3(3.3%)	15.6
3	AZT + 3TC + NVP	72(79.1%)	19.9
4	EFV + AZT + 3TC	5(5.4%)	15.9
5	ABC + 3TC + AZT	2(2.2%)	17.6
6	AZT + 3TC + LPv/rtv	3(3.3%)	16.9

ABC= Abacavir, 3TC= Lamivudine, LPv= Lopinavir, rtv= Ritonavir, D4T= Stavudine, NVP= Nevirapine, AZT= Zidovudine, EFV= Efavirenz

Table 3: Comparison of kidney function and BMI of study participants in Southern Nigeria during first phase

Group	Number Of Participants	Kidney Function Test		BMI (Kg/m^2)
		Creatinine (µMOL/L)	Clearance ($ML/MIN/1.732M^2$)	
A	91	53.7±22.4	102.6±82.9	18.9±10.9
B1	24	38.7±11.6	71.8±72.5	19.4±9.7
B2	18	39.1±16.4	69.6±33.0	20.2±8.9
B3	48	54.1±23.0	67.5±31.8	24.1±9.3
C	11	54.3±23.0	74.6±20.3	21.5±7.7
D	46	58.7±24.7	85.5±52.6	17.1±2.8
P-VAUE (ANOVA)		P<0.05	P<0.05	p>0.05

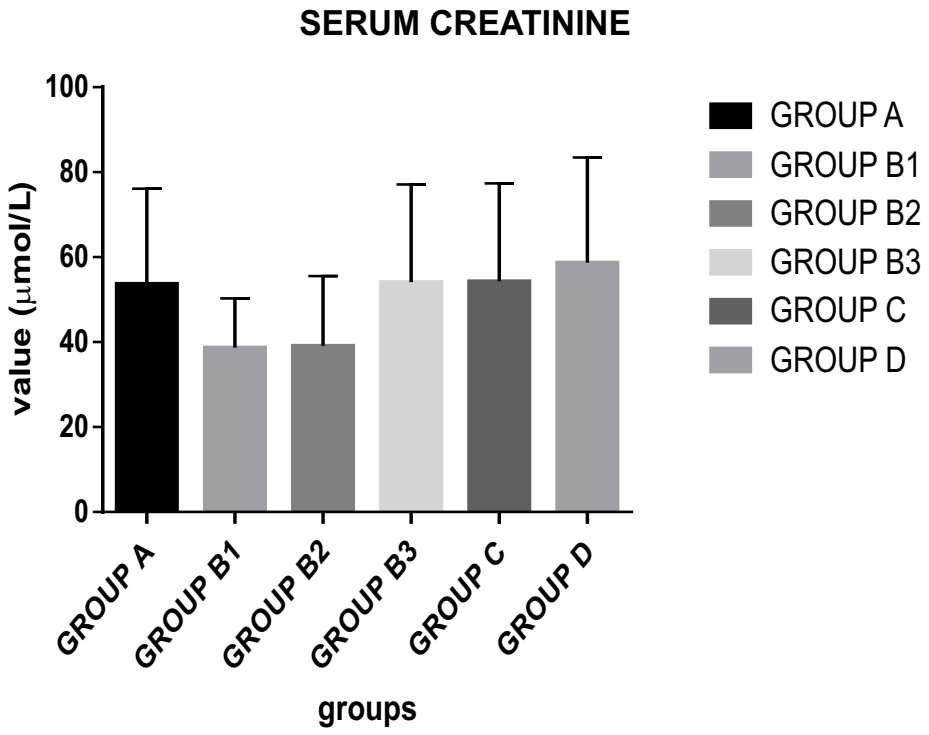

Fig. 1: Comparison of serum creatinine among groups during first phase in Southern Nigeria

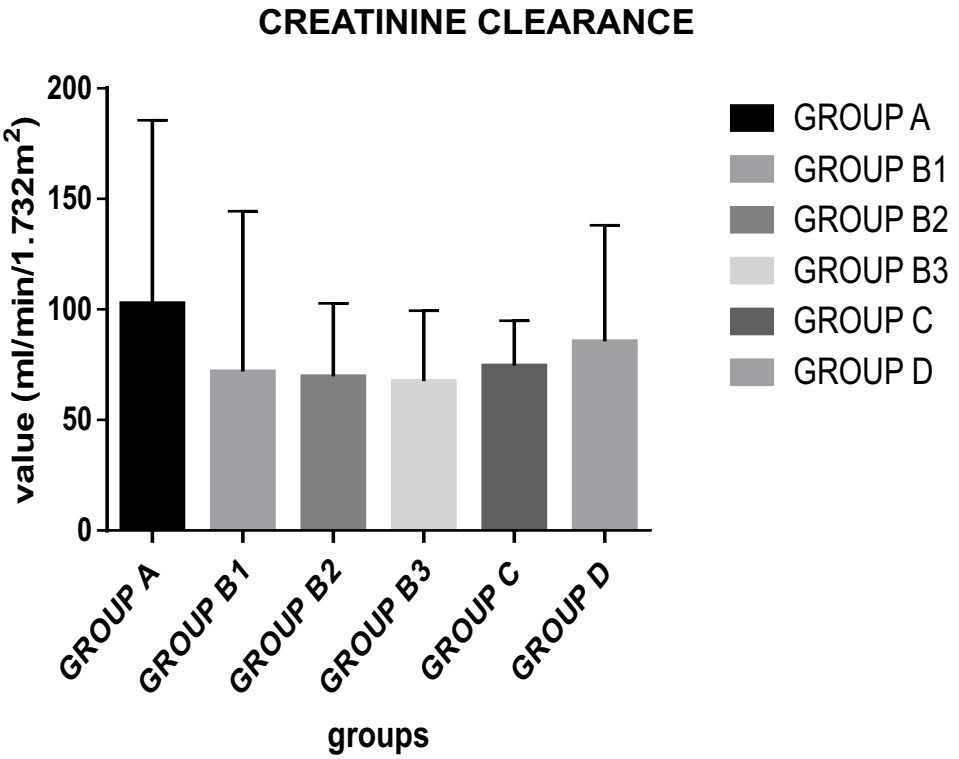

Fig. 2: Comparison of creatinine clearance among groups during first phase in Southern Nigeria

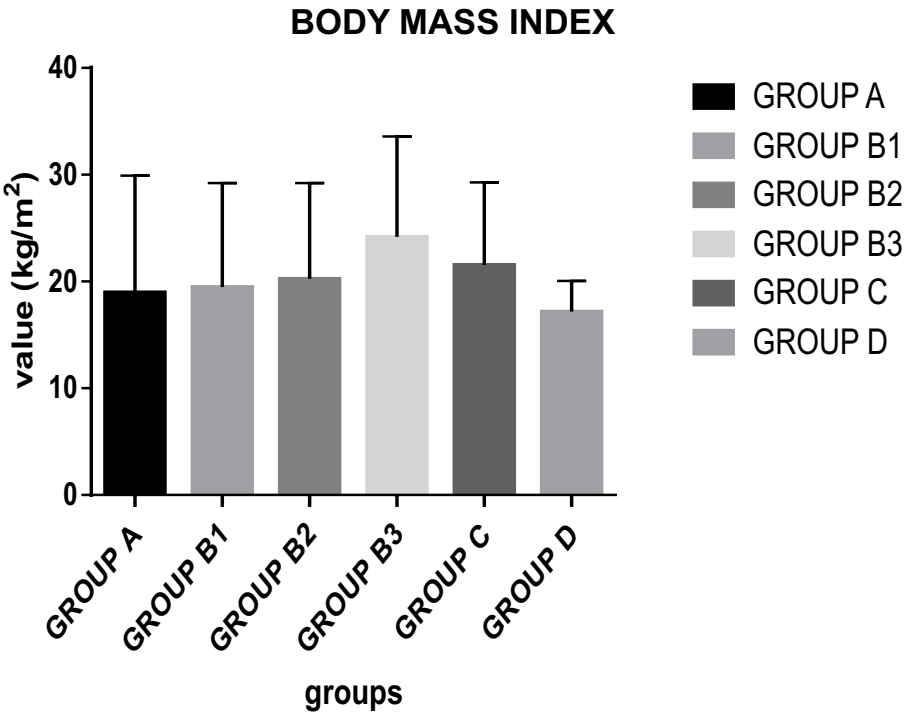

Fig. 3: Comparison of BMI among groups during first phase in Southern Nigeria

Second phase of blood collection

Out of ninety-one (91) HIV-infected children aged 0-5 years on HAART that were recruited for the study during the first phase of blood collection in Southern Nigeria, 59 (64.8%) children returned for the second phase of blood collection. Thirty-three boys and 26 girls who were receiving HAART participated in the second phase of blood collection with a mean age of 50.5months and mean weight of 17.1kg. The BMI of study participants was 18.2±3.6kg/m^2 and their CD4 count was 897.1cells/mm^3(Table 4).

The blood chemistry result of HIV-infected children on HAART during second phase of blood collection was creatinine (65.7±32.8µmol/L), creatinine clearance (91.3±80.7ml/min/1.732m^2) (Fig. 4) and BMI (18.2±3.6kg/m^2) (Fig. 5). Comparing with the first phase, BMI and creatinine clearance were reduced by 3.5% ($p>0.05$) and 8.7% ($p>0.05$) respectively while creatinine was increased by 22.9% ($p<0.05$) respectively (Table 5).

Third phase of blood collection

Out of the 91 study participants that were recruited for the study during the first phase of blood collection, 56 (61.5%) study participants returned to participate in the third phase. Thirty-two (57.1%) boys and 24 (42.8%) girls participated during the third phase of blood collection. The study participants had a mean age of 52.9months, mean weight of 16.8kg, mean BMI of 17.1±2.6kg/m^2 and mean CD4 count of 999.2cells/mm^3 (Table 4).

The blood chemistry result for children on HAART during third phase of blood collection was creatinine (66.7±32.4µmol/L), creatinine clearance (74.7±40.4ml/min/1.732m^2) (Fig. 4) and BMI (17.1±2.6kg/m^2) (Fig. 5). Comparing with the first phase BMI and creatinine clearance were reduced by 9.4% ($p<0.05$) and 25.4% ($p<0.05$) respectively while creatinine was increased by24.2% ($p<0.05$) (Table 5).

Five (5.5%) of the HIV-infected children on HAART died before the completion of the study. Post-mortem finding was not done because the study protocol did not cover that aspect.

Table 4 - Characteristics of HIV-infected children on HAART during second and third phase in Southern Nigeria

Characteristics	Second Phase*	Third Phase*
Number of participants	59	56
Male	33 (55.9%)	32 (57.1%)
Female	26 (44.0%)	24 (42.8%)
Mean age (months)	50.5±18.6	52.9±20.6
Average weight (kg)	17.1±4.8	16.8±4.0
BMI (kg/m^2)	18.3±3.7	17.1±2.5
Mean CD4 (cells/mm^3)	897.1±503.0	999.2± 551.6
Stage	1	1

BMI= Body mass index *Second phase of blood collection

Table 5: Impacts of HAART on kidney of HIV-infected children on HAART in Southern Nigeria

Phase	Group		Kidney Function Test			Efficacy
		Number of participants	Creatinine (µMOL/L)	Clearance (ML/MIN/1.732M2)	BMI (KG/M^2)	Cd4 Count ($CELLS/MM^3$)
FIRST PHASE	A	91	53.7±22.4	102.6±82.9	18.9±10.9	945.0±548.2
SECOND PHASE	A	59	66.0±32.9	91.4±81.4	18.3±3.7	897.1±503.0
% INCREASE OF GRP A IN PHASE II OVER PHASE I			22.9% (p<0.05)	-8.7% (p>0.05)	-3.5% (p>0.05)	-5.0%
THIRD PHASE	A	56	66.7±32.4	74.7±40.4	17.1±2.6	999.2±551.6
% INCREASE OF GRP A IN PHASE III OVER PHASE I			24.2% (p<0.05)	-25.4% (p<0.05)	-9.4% (p<0.05)	5.7%

GRP= Group, First phase= First phase of blood collection

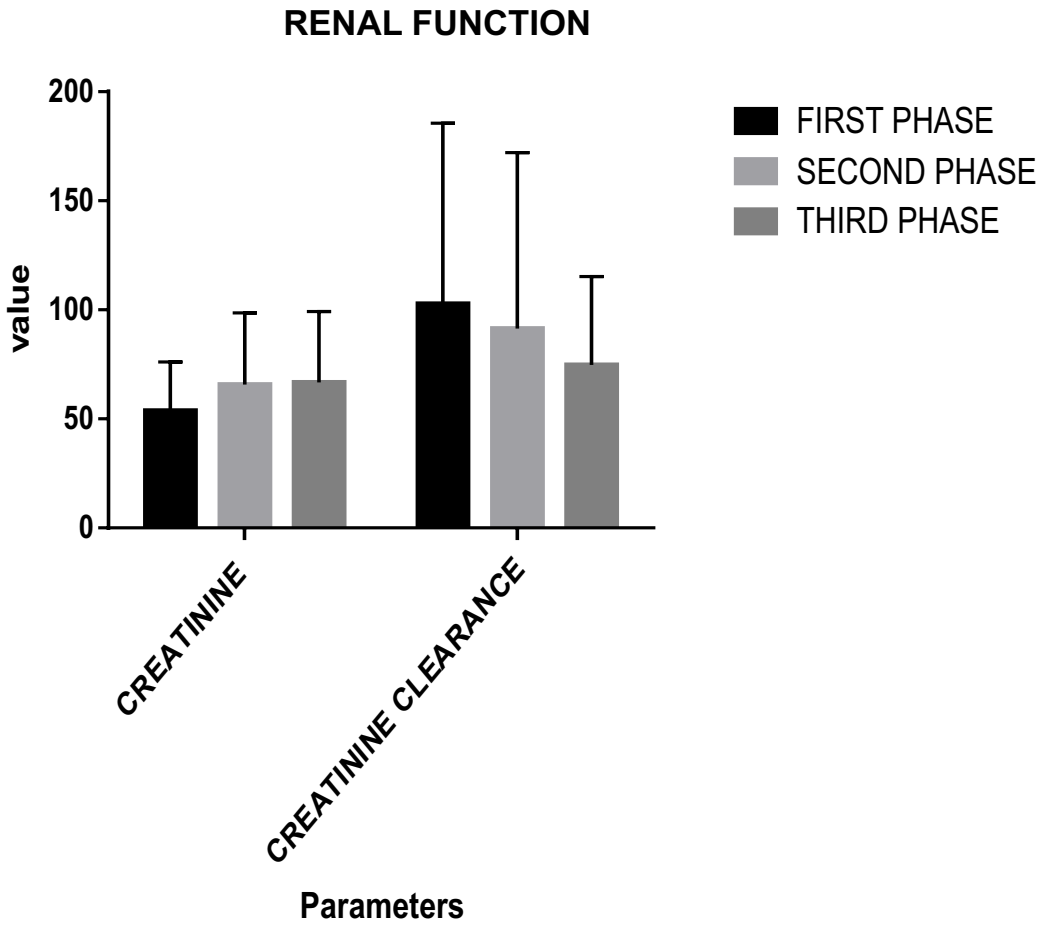

Fig. 4: Comparison of renal function of Group A in Southern Nigeria

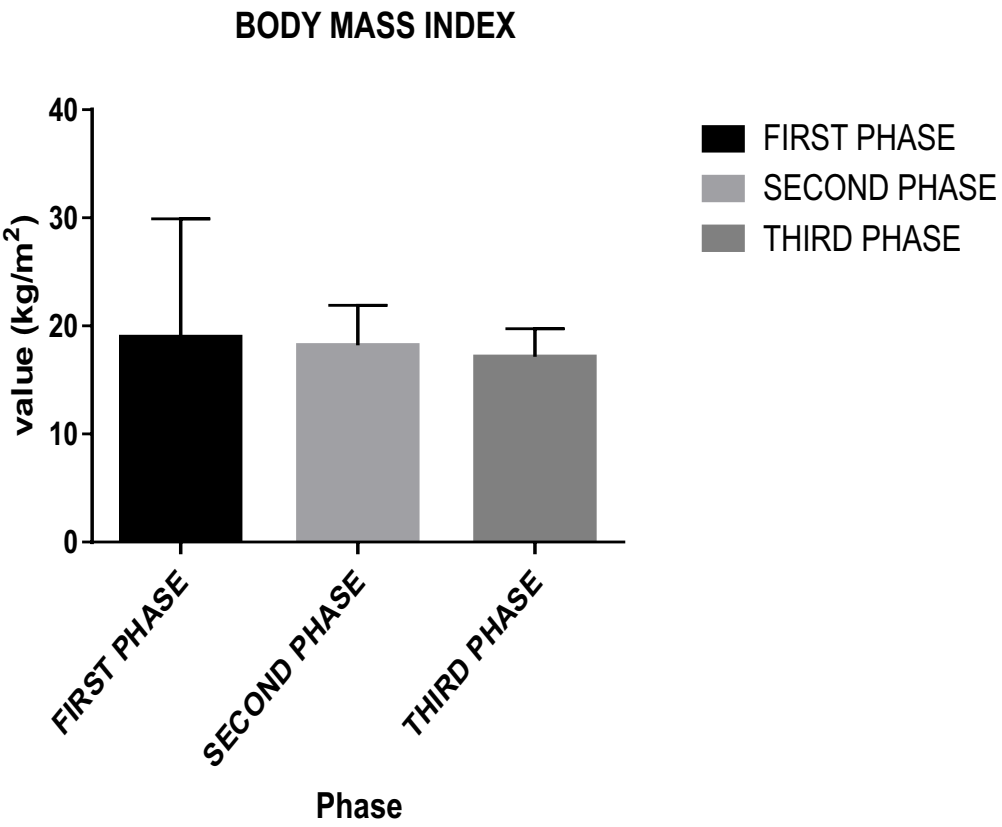

Fig. 5: Comparison of BMI of Group A in Southern Nigeria

DISCUSSION

Effects of HAART on renal function of under-fives

More girls participated in the study in Southern Nigeria which suggested need for improved and expanded facilities for these groups of children through childhood, adolescent and adulthood. HIV-infected children on HAART with higher body mass index (BMI) suggested presence of obesity which could be depended on the combinations of antiretroviral drugs. Previous study had shown that obesity was common among those living with HIV in high income countries while posing new challenge to African health.[8]The mean CD4 cell count for HIV-infected children on HAART was fairly good for healthy children which confirmed that the children were adherent to drug regimen.

Comparison of the BMI of HIV-infected children on HAART based on antiretroviral drug combinations showed that BMI of children on AZT + 3TC + NVP and ABC + 3TC + AZT were higher than the others. These two HAART regimens were associated with increased BMI among HIV-infected children which was higher than that of seronegative children. Other HAART regimens, namely, AZT + 3TC + LPv/rtv, EFV + AZT + 3TC, D4T + 3TC + NVP and ABC + 3TC + LPv/rtv had BMI lower than that of seronegative children. This indicated that these HAART combinations were associated with decreased BMI suggesting lipodystrophy caused by antiretroviral drugs. This supported claims of previous study.[3]

The blood chemistry parameters of all the 6 groups showed that all the groups had normal serum creatinine except HIV-exposed children on nevirapine and those on co-trimoxazole. The lower level of creatinine of exposed children at 6 weeks and 6 months could be due to their low muscle mass and tender organ. Creatinine clearance was higher in HIV-infected children on HAART and seronegative children. This suggested normal renal function of HIV-infected children on HAART. The result supported claims of previous study in adults.[4]HIV-exposed children on co-trimoxazole aged 6 and 18 months respectively had lowest creatinine clearance which suggested low renal function due to effect of co-trimoxazole. The result supported claims of previous study in adult population.[9] Hence, there should be concern for monitoring impact of co-trimoxazole on organs of children receiving prophylactic co-trimoxazole for a long period of time. However, these children stop use of co-trimoxazole after 18 months of life when they are confirmed negative of HIV. The benefits of using co-trimoxazole in resource limited countries outweigh its risks.

Effects of HAART on renal function of under-fives after 6 months of monitoring

Fifty-nine (59) HIV-infected children receiving HAART regimens at the various centres returned for the second phase of blood collection after 6 months of monitoring. Many of the children who did not return attended secondary healthcare facilities where there were no medical doctors to attend to their health needs. Nurses were in charge of those antiretroviral clinics. Some HIV-infected children who attended tertiary healthcare facilities also missed their clinic appointments and few did not return throughout the 6 months duration of the second phase. Inquiry showed that many of those who failed to come were poor and could not afford to transport themselves from the village to the city to receive treatment regularly. For others, it was due to stigmatization, school attendance by children and lack of commitment to drug adherence. The mean CD4 count was decreased in second phase suggesting lack of drug adherence among the HIV-infected children on HAART or emergence of drug resistance to HAART regimen.

Creatinine of the HIV-infected children on HAART was increased suggesting potential renotoxicity while creatinine clearance was reduced suggesting diminished renal function.[5] Continuous use of HAART would increase serum creatinine with time while creatinine clearance would diminish with time. Statistical analysis showed that HAART was significantly associated with increased serum creatinine.

The limitation of this study is that only HIV-infected children on HAART returned for the second and third phases of blood collection. Other children could not be persuaded to participate in the second and third phases because they were not on the same routine treatment and their bleeding time interval is not the same as those children on HAART.

Effects of HAART on renal functions of under-fives after 9 months of monitoring

Fifty-six (56)HIV-infected children on HAART who started the study in first phase returned for the third phase of blood collection after 9 months of monitoring. The percentage of returned study participants in third phase was markedly reduced suggesting lack of commitment to dosage refills and consequently drug adherence failure. So many factors were responsible for this, such as attitude of care-givers to HIV treatment, inadequate facilities at the centres, incessant stock-out of laboratory reagents, lack of physicians especially in secondary healthcare facilities and poverty. The participants had improved immunity which implied that the children had improved on drug adherence after counselling during first and second phases.

Serum creatinine of the returned HIV-infected children increased suggesting renotoxicity while creatinine clearance decreased suggesting decreased renal function. This result supported claims of previous study in adult population.[10] Statistical analysis showed that HAART was significantly associated with reduced creatinine clearance and increased serum creatinine.

CONCLUSION

This study has shown a significant association of HAART with increased serum creatinine and decreased creatinine clearance among under-fives HIV-infected children in Southern Nigeria.

Both governmental and non-governmental agencies are implored to increase awareness campaigns and education on HIV and extend it to the rural areas. Management of HIV infection should be facilitated closer to the people especially in the rural areas. Management of HIV infection in under-fives in Nigeria should include monitoring of renal function.

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