Niger J Paed 2016; 43 (1): 20 –25

ORIGINAL

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Ocularhaemodynamics parameters of asymptomatic HAART experienced HIV-infected under-five children

DOI:http://dx.doi.org/10.4314/njp.v43i1.4

Accepted: 3rd August 2015

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Abstract*: Objectives:* Study aimed at evaluating the impacts of HAART on retinal blood flow of asymptomatic HAART-experienced HIV-infected under-five children.
Method: Ethical approval and patient consents were obtained before commencement of the study in the selected hospitals. Thirty asymptomatic HAART-experienced HIV-infected children and three seronegative children aged 0-5 year-old fulfilled conditions for ocular ultrasonography among 60 convenience-sampled under-fives. Ocular ultrasonography was done on the patients in supine position with eyes closed as instructed by the radiologist. Maximum velocity (Vmax), pulsatility index (PI), resistive index (RI), optic nerve diameter, lens thickness and axial diameter were measured. Results of HAART-experienced children were not compared with the control children because of unequal size. Data were analysed by using ANOVA and level of significance was considered at $p<0.05$.
Results: Vmax of blood flow in central retinal artery (CRA) of asymptomatic HAART-experienced HIV-infected children was 12.2cm/s while that of seronegative children was 13.4 cm/s. The PI and RI of blood flow in CRA of asymptomatic HAART-experienced HIV-infected children were 0.8 and 0.5 respectively while those of the seronegative children were 0.6 and 0.4 respectively. Reduced Vmax of blood flow of CRA was significantly associated with both increased PI and RI of asymptomatic HAART-experienced HIV-infected under-five children.
Discussion: Vmax of CRA of asymptomatic HAART-experienced HIV-infected children was reduced because of their increased PI and RI suggesting an increased resistance to blood flow in asymptomatic HAART-experienced HIV-infected children.
Conclusion: Reduced Vmax of blood flow to CRA was significantly associated with increased PI and RI of asymptomatic HAART-experienced HIV-infected children.

Keywords: Ophthalmic artery, Central retina artery, Maximum velocity, Seropositive children, HAART

Introduction

HIV/AIDS is a leading cause of childhood mortality and morbidity in Africa. In under-five children, HIV /AIDS now accounts for 7.7% of mortality worldwide. AIDS already accounts for a 36% rise in under- five's mortality. In a state of declining immunisation, HIV/AIDS threatens recent gains in infant and child survival and health.[1]The increased paediatric HIV infection rate in Africa resulted from both increased HIV infection rate in childbearing women and the competence of Mother to Child transmission (MTCT). Forty million persons were living with HIV in 2003, 70% of them lived in sub-Saharan Africa while 60% of HIV-infected persons in sub-Saharan Africa are women. HIV-infection rates among pregnant women in Africa range from 1% in Senegal to 40% in Botswana. In 2006, World Health Organization (WHO) proposed that 2.3 million children were living with Human Immunodeficiency Virus (HIV) infection mostly acquired through mother to child transmission, about 90% of them live in sub-Saharan Africa[1].

AIDS affects children in many ways in Africa, about 400,000 children below 15 years died of AIDS in 2003. Demographic data from sub-Saharan Africa showed the impact of HIV on childhood mortality. Maternal ill health such as HIV infection has a negative effect on infant survival. Infant and early childhood mortality

among seronegative children of HIV-infected mothers is 2 to 5 times higher than that among seronegative children of HIV-negative mothers.[1]

It is assumed that over 1500 children are infected with HIV every day all over the world. HIV is responsible for 6% of deaths in under-five children in Sub–Saharan Africa. Recent data indicate that 40,000 HIV positive African children received highly active antiretroviral therapy (HAART) in 2005. Nigeria has the highest burden of Mother- to- Child Transmission rates and Paediatric HIV disease in the world. Report on the Global AIDS Epidemic showed that there are an estimated 240,000 HIV-infected children below 15 years old representing 14% of the total African burden.[2] In 2005, the Federal Ministry of Health conducted biennial antenatal clinic sentinel surveys, which showed HIV prevalence of 4.4% and 4.6% in 2007.[3]

The eye had been shown to be an important indicator of the effects of teratogenic compounds, such as thalidomide.[4] Alcohol caused fetal alcohol syndrome which was linked to structural abnormalities of the eye such as microphthalmos, buphthalmos, coloboma, optic nerve hypoplasia and increased tortuosity of the retinal vessels.[5,6]

The WHO commissioned systematic reviews on antiretroviral drug toxicities and laboratory monitoring strategies which include monitoring of potential increased risk of toxicity associated with the long-term use of antiretroviral medicines in pregnancy, breastfeeding mothers andtheir children. It is important to monitor the use of antiretroviral drugs in poor economy countries where toxicities may present a different pattern in association with either environmental or behavioural factors.[7]

This study aimed at evaluating the impacts of HAART on retinal blood flow of 0-5 year-old asymptomatic HIV -infected children on HAART in Southern Nigeria.

Method

Study design: In order to observe effects of HAART on heamodynamic parameters of the eyes of asymptomatic HAART-experienced HIV-infected under-five children, a quantitative, observational approach was used.

Study setting: Forty (40) HIV-infected children aged 0-5 years old, who had been on HAART for more than a year and 20 seronegative children were recruited for the study in University College Hospital, Ibadan and University of Uyo Teaching Hospital. Consent of caregivers of participants was obtained after ethical approval was received from the study centers.

Study population: Convenience sampling was used to enrol 60 participants aged 0-5 years old who attended either HIV clinic or the general outpatient department.

Inclusion criteria: Selection of participations for the study was based on age 0-5 years, both male and female, asymptomatic HIV-infected children in WHO Stage 1 and seronegative children from seronegative mothers.

Exclusion criteria: Those who were not included in the study were children who were already above five years and HIV-infected children who were not asymptomatic.

Recruitment of participants: Forty (40) HAART-experienced HIV-infected children and 20 seronegative children were enrolled for the study. Thirty (30) HAART-experienced HIV-infected children met the criteria for ultrasonography while 3 seronegative children met the criteria. The children who failed to meet criteria for ocular ultrasonography were due to their age which was slightly below four years and inability to stop blinking the eyes during procedure. The participants were purposefully not sedated for the study.

Data collection: Data were obtained from successful ocular procedures on 30 HAART-experienced under-five HIV-infected children and 3 under-five seronegative children. As a result of unequal size, the result of HAART-experienced HIV-infected children could not be compared with the seronegative children. Hence, the association of hemodynamic parameters such Vmax, PI and RI of the asymptomatic HAART-experienced HIV-infected children was determined.

Ocular Ultrasonography

This investigation was done for the detection of effects of HAART on retinal blood flow of seropositive children. This investigation was performed only on thirty asymptomatic seropositive children who had received HAART for more than a year and three seronegative children who were not on drugs. These children fulfilled criteria for ocular ultrasonography procedures. Maximum velocity (Vmax), pulsatility index (PI) and resistive index (RI) of blood flow in central retinal artery and ophthalmic artery were examined. Optic nerve diameter, axial diameter and lens thickness of the eyes were also examined. Medical personnel in radiology unit of the University College Hospital had software on ultrasonography equipment which could only perform assessment of Vmax, PI, RI and optic nerve diameter while those in University of Uyo Teaching Hospital could only do assessment of axial diameter and lens thickness. In this respect, data from the two centers were analysed separately. Due to failure of majority of the study control participants to meet the criteria for ocular ultrasonography such as keeping the eyes closed during procedure and absence of primary standard parameters in Nigeria and Africa, standard parameters from similar study in USA and Sweden were adopted.

Ocular ultrasonography procedure

The ultrasonography scans were performed with the patient in supine position, eyes closed and directing gaze towards the ceiling. Ultrasound scanners and 5-10MHz linear array transducers were used. Transducers were applied with contact jelly through the closed upper eyelid while the examiner's hand rested upon the orbital margin to minimize the pressure on the globe. Blood flow in the retrobulbar orbit was detected by the production of colour pixel on the visual display unit. The minimum size of sample gate used was 1.2mm X 1.2mm with the Siemens machine. It was directed to a blood

vessel. The spectra analysis of the resultant frequency shift was used to obtain a velocity waveform. The waveform consisted of multiple velocities, the peak velocity values were used in the analyses. In artery, the peak systolic velocity (PSV) and end diastolic velocity (EDV) were used. Since these measures provided no information of the waveform, two indices were used:

Resistive index (Pourcelot's ratio) = $\frac{\text{PSV-EDV}}{\text{PSV.}}$ [8]

Pulsatility index = $\frac{\text{PSV-EDV}}{\text{Tmax.}}$ [9]

NB:

Tmax: Is the time averaged peak velocity

Resistive index is usually quoted from 0-100% (0-1) with 0 representing no resistance and 100 representing high resistance.

Data management and analysis: Data was stored using Microsoft Office 2008. Data was analysed by using descriptive statistics and analysis of variance (ANOVA). Statistical significance was considered at level $p < 0.05$. Statistical Package for the Social Sciences (SPSS) software version 20.0 (SPSS Inc. Chicago, III, USA) was used for the analysis.

Results

Ocular ultrasonography measurement

The mean age of study participants was 4.71±0.59 years, 15 (45.45%) boys and 18 (54.55%) girls successfully performed ocular ultrasonography (Table 1).

Table 1: Demographic characteristics of participants

s/n	Character	Frequency
i	Age (years)	4.71±0.59
ii	Male	15 (45.45%)
iii	Female	18 (54.55%)
	Total	33

The ocular ultrasonography measurements of asymptomatic seropositive children on HAART in UCH showed that the mean of maximum velocity (Vmax) of blood flow in Central retinal artery (CRA) of eyewas12.2 cm/s while that of seronegative children was 13.4 cm/s (Fig. 1). The pulsatility index (PI) of blood flow in CRA of eye of asymptomatic HIV-infected children on HAART was 0.8while that of the seronegative children was 0.6. The Resistive index (RI) of blood flow in CRA of eyeof asymptomatic HIV-infected children on HAART was 0.5while that of the seronegative children was 0.4 (Table 2).

The Vmax of blood flow in ophthalmic artery of eye of asymptomatic seropositive children on HAART was 23.6 cm/s while that of the seronegative children was 33.8 cm/s (Fig. 2). PI of blood flow in ophthalmic artery of eye of asymptomatic HIV-infected children on HAART was 1.4 while that of seronegative children was 0.8. RI of blood flow in ophthalmic artery of eye of asymptomatic seropositive children on HAART was0.7 while that of the seronegative children was 0.4. The optic nerve diameter of the right eye of asymptomatic seropositive children on HAART was 0.5 cm while that of seronegative children was 0.4 cm (Fig. 3), (Table 2).

The ocular ultrasonography measurements of asymptomatic seropositive children on HAART in UUTH showed that the mean of axial diameter of right eye was 2.2 cm while that of the left eye was 2.3 cm (Fig. 4). Lens thickness of right eye of seropositive children on HAART was 0.1 cm (Fig. 5) and that of the left eye was 0.1 cm (Table 2).

Fig 1: Comparison of blood flow in central retinal artery of children on HAART and seronegative children (control)

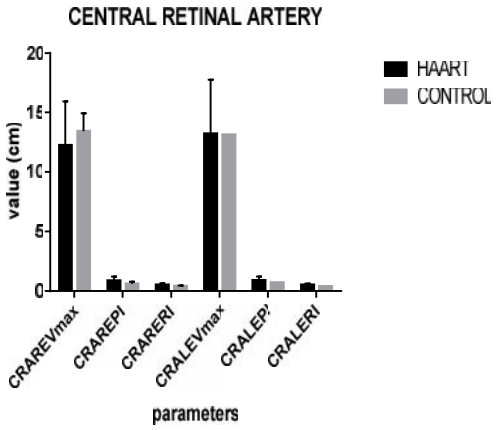
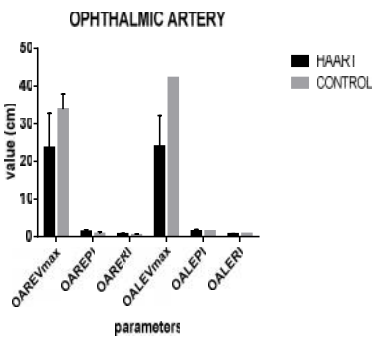


Table 2: Ocular ultrasonography measurement

S/n	Region		Eye	Pars	Mean Children on HAART (cm)	Control (cm)
1	UCH	Central retinal Artery	Right	Vmax	12.2±3.6	13.4±1.5
				PI	0.8±0.3	0.6±0.1
				RI	0.5±0.1	0.4±0.0
			Left	Vmax	13.2±4.5	13.1±0.0
				PI	0.8±0.3	0.7±0.0
				RI	0.5±0.1	0.3±0.0
		Oph-thalmic artery	Right	Vmax	23.6±9.1	33.8±4.0
				PI	1.4±0.4	0.8±0.5
				RI	0.7±0.1	0.4±0.2
			Left	Vmax	24.0±8.1	42.1±0.0
				PI	1.5±0.4	1.5±0.0
				RI	0.7±0.0	0.7±0.0
		Optic nerve	Right	Diameter	0.5±0.1	0.4±0.1
			Left	Diameter	0.5±0.1	0.6±0.0
2	UUTH	axis	Right	Diameter	2.2±0.0	2.2±0.1[1]
			Left	Diameter	2.3±0.0	2.2±0.1[1]
		Lens	Right	Thickness	0.1±0.0	0.3±0.1[2]
			Left	Thickness	0.1±0.0	0.30.1[2]

Obtained from Swedish study.[14,15]
Obtained from United States study.[18]
Vmax- maximum velocity, PI- pulsatility index, RI- resistive index

Fig 2: Comparison of blood flow in ophthalmic artery of children on HAART and seronegative children (control)



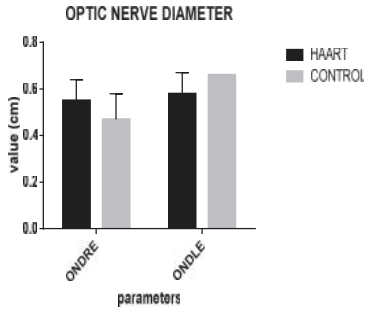


Fig 3: Comparison of optic nerve diameter between children on HAART and seronegative (control) children

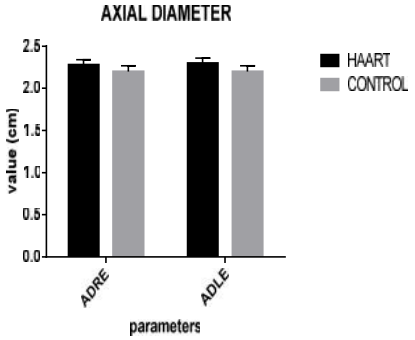


Fig 4: Comparison of axial diameter of children on HAART and control children

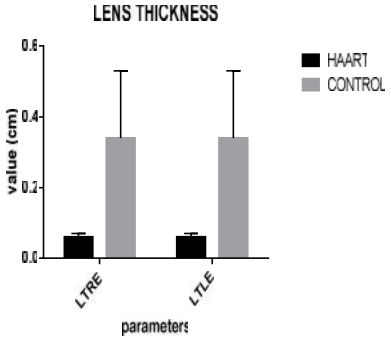


Fig 5: Comparison of lens thickness of children on HAART and control children

Maximum velocity (Vmax) of blood flow of both central retinal artery and ophthalmic artery was compared with both pulsatility index (PI) and resistive index (RI) in eyes of asymptomatic seropositive children on HAART. Axial diameter was compared with lens thickness in eyes of asymptomatic seropositive children on HAART. The results were significant (Table 3).

Table 3: Comparison of ocular parameters of children on HAART

Ocular parameters				p-value
Central retina artery	Right eye	Vmax	PI	P<0.001
			RI	P<0.001
	Left eye	Vmax	PI	P<0.001
			RI	P<0.001
Ophthalmic artery	Right eye	Vmax	PI	P<0.001
			RI	P<0.001
	Left eye	Vmax	PI	P<0.001
			RI	P<0.001
Axial diameter	Right eye	Axial diameter	Lens thickness	P<0.001
	Left eye	Axial diameter	Lens thickness	P<0.001

Vmax- maximum velocity, PI- pulsatility index, RI- resistive index

Discussion

Maximum velocity of central retina artery (CRA) of the eye of seropositive children on HAART was reduced because of their increased pulsatility index (PI) and resistive index (RI). This possibly suggested that increased pulsatility index indicated an increased resistance to ocular blood flow in children receiving HAART. This finding in asymptomatic HAART-experienced HIV-infected under-fives supports the claims of previous studies.[9,10] Williamson had documented in their study that reduced velocity was detected in the central retinal artery of patients with progressive non-arteritic ischemic optic neuropathy when compared with unaffected contralateral eyes. The central retinal artery velocity was increased while the pulsatility index in the posterior ciliary arteries was reduced after optic nerve sheath decompression following an immediate postoperative period. Observation of patients with chronic papilledema from pseudotumor cerebri indicated reduced velocities in the central retinal and posterior ciliary arteries with an increased pulsatility index in the central retinal artery when compared to controls. Following optic nerve sheath decompression after 48 hours, an increase in the blood velocities was observed in patients with improved vision which was due to increased perfusion of the blood vessels.[9]

Maximum velocity of ophthalmic artery (OA) of the eye of asymptomatic seropositive children on HAART was reduced because of their increased PI and RI. The increased PI and RI possibly suggested an increased resistance to blood flow. This finding in asymptomatic HAART-experienced HIV-infected under-fives supports claim of previous study.[9,10] Williamson in their study affirmed that both pulsatility and resistive indices provide an indication of the effects of resistance on blood flow in the retinal blood vessels.[9]

Increased optic nerve diameter of the eye was observed among asymptomatic seropositive children on HAART regimens which may suggest effect of HAART. Earlier study showed that increased optic nerve diameter was associated with elevated cerebrospinal fluid pressure and intracranial pressure.[11,12,13]Ballantyne in their study explained that the optic nerve diameter in children below 1 year is indicated to have normal values from 0.21-0.40cm and for children above 1 year of age is 0.24-0.43cm. The normal range of values for children of age 1-15 years is close to the normal values of optic nerve diameter in adult. An optic nerve diameter greater than 0.4cm in infants less than 1 year of age, while 0.45 cm or greater in older children are considered as abnormal. Increasedoptic nerve sheath diameter was indicated in patients suffering from intracranial hypertension which returned to normal values after surgical or medical treatment. An increased optic nerve diameter was also indicated in elevated cerebrospinal fluid pressure and intracranial pressure.[11]However, there is a need to determine normal values of ocular hemodynamic parameters for under-fives in Nigeria.

In absence of control group and lack of normal data,

axial diameter of the eye of asymptomatic seropositive children on HAART was compared with a Swedish normal value for age 3-5 years (2.07-2.34 cm). Comparing the mean, it could be suggested that the axial diameter of children on HAART was normal.[14,15]

In spite of all the differences in ocular parameters between the asymptomatic seropositive children on HAART and control children, there was no physical observation of abnormality in the vision of the asymptomatic seropositive children on HAART. This observation was in support of findings obtained by Ogunbosi et al., in their study on clinical pattern of HIV-infection among children at the same site of this study. In their study, there was no indication of cytomegalovirus infection and any other ocular diseases among clinical pattern of HIV infection illustrated in children with advanced stage of AIDS[3].Similar observation was made by Fetuga et al in their ten year review of paediatric HIV/AIDS among hospitalized children in another study site in Southwest Nigeria.[16]This obviously rules out involvement of HIV infection in reduced blood velocity of ophthalmic artery and central retinal artery. Yung et al., observed that adult HIV positive patients with AIDS showed a statistically significant reduction of perifoveal capillary blood flow velocity in a study performed in United States of America.[17]In this study, asymptomatic HAART-experienced HIV-infected under-five children were involved. Therefore, HIV infection appears not to have been the cause of reduced blood velocity in both ophthalmic and central retinal arteries. However, the observed differences could have serious implication in the future of these children.

The association of reduced maximum velocity (Vmax) with pulsatility index (PI) and resistive index (RI) of both central retinal artery and ophthalmic artery of the eyes of asymptomatic seropositive children on HAART were statistically significant. Similarly, there was significant association between lens thickness and axial diameter of the eyes of asymptomatic seropositive children who were on HAART.

Conclusion

This study has shown significant association between reduced maximum velocity of blood flow in both ophthalmic artery and central retinal artery with increased pulsatility and resistive indices of the eyes of asymptomatic seropositive children on HAART. Similarly, lens thickness was significantly linked to the axial diameter of the eyes of 0-5year old asymptomatic seropositive children on HAART.

Recommendation

Vision test should be incorporated in the monitoring of adverse events in under-five children on HAART. More studies involving a large number of HIV-infected children on HAART should be done to evaluate impacts on ocular hemodynamic parameters.

Authors' contribution
AMO designed the study, performed field work, wrote manuscript, OMK and MJO participated in designing the study, supervised work and edited the manuscript; OBA took care of technical aspect of the study and edited the manuscript.
Conflict of interest: None
Funding : None

Acknowledgement

The supports of staff of radiology department and HIV centres were appreciated.

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