

Original Research Article

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Heterophoria analysis of HIV/AIDS patients on highly active antiretroviral therapy in Northwestern Nigeria

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ABSTRACT

Background: Despite the efficacy of highly active antiretroviral therapy (HAART) on HIV, there are other ocular side effects of HAART which are yet to be determined and characterized. The aim of the study was to determine and characterize the pattern of latent deviation of eyes among HIV/AIDS patients.

Methods: Consenting patients were recruited and grouped into two groups A and B. Group A were HAART naive, while group B were HAART experienced. These were further subdivided into four groups; comprising of B1: on HAART from 0>2½ years, B2: 2½>5 years, B3: 5>7½ years, and B4: 7½>10 years.

Results: There were 400 participants aged 25-55 years with a mean age of 37.86±7.5 years. About 135 (33.8%) and 129 (32.3%) were Orthophoric for habitual phoria at near and far (HPN and HPF), while 207 (51.7%) and 218 (54.5%) were also Orthophoric for induced phoria at far and near (IPN and IPF) respectively. There was a statistically significant association between effect and HAART duration with induced lateral phorias at both distances ($p=0.01$), no association with CD4+ T-cells count, HAART Regimen and habitual lateral phorias at both distances ($p=0.06$ and $p=0.95$).

Conclusions: HIV/AIDS patients on HAART exhibit either convergence excess or divergence insufficiency as a binocular vision syndrome depending on the degree of deviation both at far and near distances. The effect and duration of HAART are statistically significant with induced lateral phorias at both distances ($p=0.01$).

Keywords: HAART, HIV/AIDS, Heterophoria, Divergence insufficiency and convergence excess

INTRODUCTION

Human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) is a spectrum caused by infection with the human immunodeficiency virus¹. Once exposed to the infection, the person may not show any symptoms or may experience a brief period of influenza-like illness which is typically followed by a prolonged period with no symptoms.²

HIV is a retrovirus that mainly attacks components of the human immune system such as CD4+ T cells, macrophages and dendritic cells³. It directly and indirectly destroys CD4+ T cells.³⁻⁴ acquired immunodeficiency syndrome (AIDS) is referred in terms of either a CD4+ T cell count below 200 cells per μ l or the occurrence of specific diseases in association with an HIV infection.⁴⁻⁶

Highly active antiretroviral therapy (HAART) or Antiretroviral therapy (ART) is the combination of several antiretroviral drugs used to slow the rate at which HIV multiplies in the body.⁵ A combination of three or more antiretroviral medications is more effective than using just one medication to manage HIV infection.^{5,6}

The goal of antiretroviral combined therapy is to reduce the viral load to an undetectable level within the blood stream of which current blood tests will not indicate the virus.³ Clinical evidence shows that the optimal way to achieve this goal is by starting combination therapy with two or more antiretroviral agents.^{3,4} HAART provides effective treatment options for treatment-naïve and treatment-experienced patients.⁴ Six classes of antiretroviral agents currently exist, as follows: Nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), Protease inhibitors (PIs), Integrase inhibitors (TIs), Fusion inhibitors (FIs) and Chemokine receptor antagonists (CCR5 antagonists).^{1,3,4,5,7}

Each class targets a different step or stage in the viral life cycle as the virus attacks the CD4⁺ T lymphocyte or other target cell.¹⁻⁵ The application of these agents in clinical practice is largely based by their ease or complexity of use, side-effect profile, efficacy based on clinical evidence, practice guidelines, and clinician preference.¹⁻⁸

Heterophoria is the tendency for one or both eyes to move away from the position where both eyes are fixating together in the same direction latently.⁷ Esophoria means a tendency for the eye to deviate inwards (towards the nose), and exophoria means a tendency for the eye to deviate outwards (towards the ear)⁹. Heterophoria and fusional vergence range tests are essential components of standard optometric binocular vision assessment.^{7,10}

Binocular vision requires that the eyes move together so that the visual axes intersect at the object of regard.⁷ The eyes are held in alignment by a combination of the sensory and motor fusion mechanisms.¹⁰ If sensory fusion is abolished by any clinical means, only the motor fusion mechanism is operational and a misalignment or deviation of the visual axes will occur in many patients.⁷ This misalignment is sometimes referred to as a latent deviation but is more commonly known as a heterophoria.¹⁰ Heterophoria can be defined in terms of the direction of the misalignment when the sensory fusion is prevented esophoria is the convergence of the visual axes while Exophoria is the divergence of the visual axes.^{7,10,11}

The distribution of distance heterophoria and near heterophoria have been well documented in literature.^{12,13} There exists a high incidence of exophoria ranging from 0 to 0.5 prism diopters at distance and exophoria of about 0 to 6 prism diopters at near viewing distance as a normal range of heterophoria in healthy individuals. Heterophoria seems to vary with different viewing distances.^{7,10-13} Distance phoria was claimed to be different from tonic vergence due to accommodative divergence.¹⁴⁻¹⁶

A normal visual acuity does not preclude the possibility of visual function deficits as some sero-positive patients have been found to have deficits in visual function (binocular anomaly e.g. Heterophoria), whilst visual acuity remains normal and CD4 counts relatively high.^{2,3,17}

The aim of the study was to determine and characterize the pattern of latent deviation of eyes among HIV/AIDS Patients in Northwestern Nigeria.

METHODS

The study adhered to the tenets of the Helsinki Declaration and ethical approval was obtained from the Ethical Review Board of Aminu Kano Teaching Hospital, Kano. This prospective comparative randomized cross-sectional hospital-based study was carried out with a sample size of 400 participants from May 2019 to December 2019, obtained with Dobson's Formula for cross-sectional studies.

Participants that consented and fulfilled the inclusion criteria were recruited, criteria for inclusions were consent to participate, age between 25-55 years, testing HIV positive on ELISA test, recent CD4⁺ T cell count result (at least within 6 months), HAART naïve and had no ocular, medical or therapeutic histories known to affect lateral phoria.

Participants who refused to give consent, tested HIV sero-negative, less than 25 or above 55 years, without recent or more than 6 months CD4⁺ T cell count result, on HAART for more than ten (10) years and have major systemic, medication or vision threatening ocular complication that may affect or preclude testing for the selected oculo-visual function (lateral phoria at near and far distances) were excluded from the study.

Anterior and posterior segments examination were done using direct ophthalmoscope and slit lamp biomicroscope. Information obtained from the patients were gender, age, marital status, Lateral Phoria tests at far and near, CD4⁺ T cell count, HAART regimen and HAART duration. Distance and near lateral phoria were measured with a Phoropter, with the participant's best corrected distance visual acuity (BCDVA) prescription, visual acuity was tested with illuminated Snellen's visual acuity chart at a distance of 6 meters and 35 cm at near respectively. The habitual and induced lateral phorias at far and near measurements were obtained with the von Graefe technique.^{9,10}

All the 400 participants were grouped into two groups A and B. Group A, were those that were about to commence HAART referred to as HAART naïve, while group B were those that were on HAART termed as HAART experienced and were subdivided into four groups; comprising of B₁: those that have been on HAART from zero to two and half years (0>2½ years), group B₂: those on HAART from two and half years to five years (2½>5 years), group B₃ were those on HAART from five years to

seven and half years ($5>7\frac{1}{2}$ years), and group B₄ were those on HAART from seven and half years to ten years ($7\frac{1}{2}>10$ years).

Data analysis

Data was entered into a Microsoft excel spreadsheet database before being exported, cleaned and analysed in SPSS 22.0 version. The patients' socio-demographic characteristics and measurement results were evaluated using descriptive statistics to show the frequency of occurrence and percentage of distribution of age range. The Fisher's exact test and Pearson's Chi-Square statistics was also used to analyse and compare the effect and association of HAART regimen and duration on distance and near lateral phorias and CD4+ count. All statistical significance was evaluated with 95% confidence level, where $p\leq 0.05$ was considered statistically significant.

RESULTS

A total of 400 participants were enrolled. The participant's age ranged from 25 years to 55 years with a mean age of 37.86 ± 7.5 years. There were 172 males (43.0%) and 228 females (57.0%) with M:F ratio of 1:1.3. Most of the participants 224 (56.0%) were married, 61 (15.3%) were divorced, 54 (13.4%) were widow/widower and 61 (15.3%) were single.

Table 1: Socio-demographic characteristics of HAART naïve and experience participants by gender and marital status.

Socio-demographic characteristics	HAART naïve N (%)		HAART experience N (%)				Total (n=400)
	Group A (n=80)	Group B ₁ (n=80)	Group B ₂ (n=80)	Group B ₃ (n=80)	Group B ₄ (n=80)		
Gender							
Male	36 (45.0)	31 (38.8)	36 (45.0)	32 (40.0)	37 (46.2)	172 (43.0)	
Female	44 (55.0)	49 (61.2)	44 (55.0)	48 (60.0)	43 (53.8)	228 (57.0)	
Marital status							
Single	12 (15.0)	19 (23.8)	13 (16.2)	12 (15.0)	5 (6.3)	61 (15.3)	
Married	46 (57.5)	52 (65.0)	39 (48.8)	38 (47.4)	49 (61.1)	224 (56.0)	
Widow(er)	12 (15.0)	6 (7.5)	12 (15.0)	15 (18.8)	9 (11.3)	54 (13.4)	
Divorced	10 (12.5)	3 (3.8)	16 (20.0)	15 (18.8)	17 (21.3)	61 (15.3)	

Note: Data presented as frequencies and percentages. Key group A- HAART naïve; group B- HAART experience (B₁ are those on HAART from 0-2½ years; B₂ on HAART from 2½-5 years; B₃ on HAART from 5-7½ years and group B₄ on HAART from 7½-10 years).

Table 2: Socio-demographic characteristics of HAART naïve and experience participants by age.

Age (years)	HAART naïve		HAART naïve				Total (n=400)
	Group A (n=80)	Group B ₁ (n=80)	Group B ₂ (n=80)	Group B ₃ (n=80)	Group B ₄ (n=80)		
Mean age \pm SD	36.40 \pm 7.4	35.11 \pm 6.9	36.96 \pm 7.5	39.19 \pm 7.6	41.65 \pm 6.3	37.86 \pm 7.5	
25-34	38 (47.5)	36 (45.0)	33 (41.2)	24 (30.0)	12 (15.0)	143 (35.8)	
35-44	29 (36.2)	36 (45.0)	35 (43.8)	33 (41.3)	40 (50.0)	173 (43.2)	
45-54	11 (13.8)	7 (8.8)	10 (12.5)	21 (26.2)	26 (32.5)	75 (18.8)	
55-64	2 (2.5)	1 (1.2)	2 (2.5)	2 (2.5)	2 (2.5)	9 (2.2)	

Note: Data presented as frequencies and percentages. Key group A- HAART naïve; group B- HAART experience (B₁ are those on HAART from 0-2½ years; B₂ on HAART from 2½-5 years; B₃ on HAART from 5-7½ years and group B₄ on HAART from 7½-10 years).

Table 3: Lateral phoria at far and near distance of HAART naïve and HAART experience participants.

Lateral phoria at far and near distance	HAART naïve N (%)		HAART experience N (%)				Total (N=400) N (%)
	Group A (n=80)	Group B ₁ (n=80)	Group B ₂ (n=80)	Group B ₃ (n=80)	Group B ₄ (n=80)		
Habitual phoria at near (HPN)							
Phoria position	Orthophoria 36 (45.0)	Orthophoria 30 (37.5)	Esophoria 38 (47.5)	Orthophoria 46 (57.5)	Esophoria 32 (40.0)	Orthophoria 182 (45.5)	
Other positions	Exo/esophoria 44 (55.0)	Exo/eso 50 (62.5)	Ortho/exo 42 (52.5)	Exo/eso 34 (42.5)	Ortho/exo 48 (60.0)	Exo/eso 218 (54.5)	
Habitual phoria at far (HPF)							
Phoria position	Esophoria 31 (38.8)	Orthophoria 28 (35.0)	Orthophoria 31 (38.8)	Orthophoria 34 (42.5)	Esophoria 30 (37.5)	Orthophoria 154 (37.5)	
Other positions	Ortho/Exo 49 (61.2)	Exo/Eso 52 (65.0)	Exo/Eso 49 (61.2)	Exo/Eso 46 (57.5)	Ortho/Exo 50 (62.5)	Exo/Eso 246 (62.5)	
Induced phoria at near (IPN)							
Phoria position	Orthophoria 44 (55.0)	Orthophoria 46 (57.5)	Orthophoria 38 (47.5)	Orthophoria 39 (48.8)	Orthophoria 40 (50.0)	Orthophoria 207 (51.7)	
Other positions	Exo/Eso 36 (45.0)	Exo/Eso 34 (42.5)	Exo/Eso 42 (52.5)	Exo/Eso 41 (51.2)	Exo/Eso 40 (50.0)	Exo/Eso 193 (48.3)	
Induced phoria at far (IPF)							
Phoria position	Orthophoria 48 (60.0)	Orthophoria 44 (55.0)	Orthophoria 51 (63.7)	Orthophoria 35 (43.8)	Orthophoria 40 (50.0)	Orthophoria 218 (54.5)	
Other positions	Exo/esophoria 32 (40.0)	Exo/eso 36 (45.0)	Exo/eso 29 (36.3)	Exo/eso 45 (56.2)	Exo/eso 40 (50.0)	Exo/eso 182 (45.5)	

Note: Data presented as frequencies and percentages. Key group A- HAART naïve; group B- HAART experience (B₁ are those on HAART from 0-2½ years; B₂ on HAART from 2½-5 years; B₃ on HAART from 5-7½ years and group B₄ on HAART from 7½-10 years). P value=0.01 for both IPN and IPF when HAART experience were compared with HAART naïve using Chi square.

Table 4: Association between CD4+ and habitual/induced lateral phorias.

Oculo-visual functions	CD4+ <199 cells/mm ³ N (%)	CD4+ 200-349 cells/mm ³ N (%)	CD4+ 350-499 cells/mm ³ N (%)	CD4+ >500 cells/mm ³ N (%)	Test statistic (χ^2)	P value
HPN (ΔD)					Fisher exact test	0.489
Esophoria	22 (10.2)	50 (23.1)	60 (27.8)	84 (38.9)		
Orthophoria	22 (16.3)	29 (21.5)	33 (24.4)	51 (37.8)		
Exophoria	3 (6.1)	13 (26.5)	16 (32.7)	17 (34.7)		
HPF (ΔD)					Fisher exact test	0.842
Esophoria	23 (10.3)	52 (23.2)	63 (24.8)	86 (38.4)		
Orthophoria	20 (15.5)	29 (22.5)	32 (24.8)	48 (37.2)		
Exophoria	4 (8.5)	11 (23.4)	14 (29.8)	18 (38.3)		
IPN (ΔD)					Fisher exact test	0.748
Esophoria	15 (10.3)	38 (26.0)	43 (29.5)	50 (34.2)		
Orthophoria	28 (13.5)	43 (20.8)	53 (25.6)	83 (40.1)		
Exophoria	4 (8.5)	11 (23.4)	13 (27.7)	19 (40.4)		
IPF (ΔD)					2.235	0.900
Esophoria	13 (9.2)	36 (25.4)	41 (28.9)	52 (36.6)		
Orthophoria	29 (13.3)	48 (22.0)	57 (26.1)	84 (38.5)		
Exophoria	5 (12.5)	8 (20.0)	11 (27.5)	16 (40.0)		

Note: Data presented as frequencies and percentages. Key: CD+4<199cells/mm³ (those with CD+4 less than 199), CD+4 200-349 cells/mm³ (those with CD+4 200-349), CD+4 350-500 cells/mm³ (those with CD+4 350-500 cell/mm³), CD+4 >500+ cells/mm³ (those with CD+4 of 500 cells/mm³ and above). There was no statistically significant association between CD+4 T cell count and habitual/induced lateral phorias both at far and near distances (P value=0.489, 0.842, 0.748, 0.900).

Table 5: Association between HAART regimen and habitual/induced lateral phorias.

Oculo-visual functions	1 st line regimen N (%)	2 nd line regimen (%)	N	3 rd line regimen N (%)	Test statistic (χ^2)	P value
HPN (ΔD)				Fisher's exact test	0.47	0.47
Esophoria	163 (90.6)	14 (7.8)		3 (1.7)		
Orthophoria	95 (96.0)	3 (3.0)		1 (1.0)		
Exophoria	38 (92.7)	2 (4.9)		1 (2.4)		
HPF (ΔD)				Fisher's exact test	5.59	5.59
Esophoria	17 (93.4)	10 (5.5)		2 (1.1)		
Orthophoria	91 (91.0)	7 (7.0)		2 (2.0)		
Exophoria	34 (91.9)	2 (5.4)		1 (2.7)		
IPN (ΔD)				Fisher's exact test	0.79	0.79
Esophoria	116 (92.1)	8 (6.3)		2 (91.6)		
Orthophoria	152 (93.3)	9 (5.5)		2 (1.2)		
Exophoria	28 (90.3)	2 (6.5)		1 (3.2)		
IPF (ΔD)				Fisher's exact test		0.55
Esophoria	117 (94.4)	6 (4.8)		1 (0.8)		
Orthophoria	156 (91.8)	11 (6.5)		3 (1.8)		
Exophoria	296 (92.5)	19 (5.9)		5 (1.6)		

Note: Data presented as frequencies and percentages. Key 1st line regimen (which comprised efavirenz, lamivudine, tenofovir, zidovudine, and nevirapine), 2nd line regimen (it comprised atazanavir, lopinavir, ritonavir, and zidovudine), 3rd line regimen (ritonavir, zidovudine, lamivudine). There was no statistically significant association between HAART regimen and habitual/induced lateral phorias both at far and near distances (p value=0.47, 5.59, 0.79, 0.55).

Table 6: Association between HAART regimen and habitual/induced lateral phorias.

HAART duration	Group B ₁ n (%)	Group B ₂ n (%)	Group B ₃ n (%)	Group B ₄ n (%)	Test statistic (χ^2)	P value
HPN (ΔD)					22.475	0.00
Esophoria	37(20.6)	53(29.4)	34(18.9)	56(31.1)		
Orthophoria	37(37.4)	24(24.2)	21(21.2)	17(17.2)		
Exophoria	7(17.1)	20(48.8)	9(22.0)	5(12.2)		
HPF (ΔD)					9.294	0.16
Esophoria	46(25.1)	47(25.7)	37(20.2)	53(29.0)		
Orthophoria	29(29.0)	35(35.0)	18(18.0)	18(18.0)		
Exophoria	6(16.2)	15(40.5)	9(18.9)	7(18.9)		
IPN (ΔD)					13.717	0.03
Esophoria	29(23.0)	35(27.8)	24(19.0)	38(30.2)		
Orthophoria	47(28.8)	46(28.2)	32(19.6)	38(23.3)		
Exophoria	5(16.1)	16(51.6)	8(25.8)	2(6.5)		
IPF (ΔD)					17.788	0.01
Esophoria	32(25.8)	25(20.2)	29(23.4)	38(30.6)		
Orthophoria	45(26.5)	60(35.3)	27(15.9)	38(22.4)		
Exophoria	4(15.4)	12(46.2)	8(30.8)	2(7.7)		

Note: Data presented as frequencies and percentages. Key 1st line regimen (which comprised efavirenz, lamivudine, tenofovir, zidovudine, and nevirapine), 2nd line regimen (it comprised atazanavir, lopinavir, ritonavir, and zidovudine), 3rd line regimen (ritonavir, zidovudine, lamivudine). There was a statistically significant association between HAART duration and habitual/induced lateral phorias both at far and near distances (p value=0.00, 0.03, 0.01), but statistically insignificant with habitual phoria at far (p value=0.16).

DISCUSSION

This study reports the patterns of latent deviations of eyes among HIV positive population on HAART therapy attending ART clinic of Aminu Kano Teaching Hospital Kano (one of the major referral centers in the Northwestern Nigeria). The results of this study significantly contributes to the growing literature on binocular anomalies among HIV positive patients in this HAART era. The key strength

of this study was the large number of the study participants compared to previous studies of oculo-visual functions in HIV positive patients.^{17,18,20}

Determination of the distribution pattern of the lateral heterophoria among HIV-sero positive patients on HAART indicates an increase in the mean induced lateral phoria at far and near as compared with the mean habitual phoria at far and near. Majority of the patients had

Orthophoria followed with Esophoria both at far and near distances for habitual and induced phoria respectively. About one-third of the patients are Orthophoric for habitual phoria at near and far (HPN and HPF), while over half of the patients are also Orthophoric for induced phoria at far and near (IPN and IPF).

According to Grosvenor, esophoria means a tendency for the eye to deviate inwards (towards the nose), and exophoria means a tendency for the eye to deviate outwards (towards the ear). Heterophoria and fusional vergence range tests are essential components of standard optometric binocular vision assessment.^{9,10}

Sweeney et al observed that seropositive patients demonstrated disturbances in pursuit ocular movements that were correlated with extent of immunosuppression.¹⁸⁻²⁴ They noted that oculomotor disturbances are present in HIV-1 seropositive individuals before the manifestation of marked AIDS dementia complex.¹⁹ For this reason, and because more severe ocular movement impairments have been observed in patients with AIDS, quantitative ocular movement studies may provide a useful neurobehavioral procedure for characterizing and monitoring progression of CNS involvement associated with HIV-1 infection early in the course of the disease.¹⁹⁻²⁵

Espana-Gregori et al reported that the horizontal latent ocular deviation at near and distance in advanced AIDS patients indicated lower values than the expected and lower AC/A relationship.²⁶ They reported that AIDS patients suffer a divergence insufficiency, which could add to other visual complaints such as blurred vision, photophobia, Nyctalopia and reading difficulty at near.²⁵ They also conclude that there is a variation of the deviation angles in AIDS patients, leading to lower values at near and at distance with regards to that expected, due to a possible oculomotor nerve alteration produced in relation to the degree of HIV affection.²⁰⁻²⁶

In concordance with their findings, this study also found that the lateral latent ocular deviation for habitual and induced phoria at far and near distances in HIV- sero positive population on HAART were abnormal compared with expected normal range.²³⁻²⁶

Majority of our patients had esophoria at far and near distances for habitual phoria while Orthophoric at far and near distances for induced phoria. Orthophoria was greater among the HAART naïve for habitual and induced phoria at both distances as compared with esophoria while esophoria was also greater among HAART experienced for habitual and induced phoria at both distances, with statistically significant differences between HAART naïve and HAART experienced for induced phoria at both distances ($p=0.01$) and no statistically significant association between HAART naïve and experienced for habitual phoria at both distances ($p=0.95$).

It was determined that there was no significant association between lateral heterophoria among HIV- sero positive population and their CD4+ T cell levels and HAART regimen but there was a significant association to the HAART duration ($p=0.001$). As reported by Espana-Gregori et al the results from this study indicated that HIV-sero positive patients on HAART exhibits either divergence insufficient or convergence excess depending on the visual distances, which could add to other visual complaints such as blurred vision, photophobia, frontal headache, diplopia (especially while reading and watching television at closed range, etc) and difficulty reading tiny prints at near.²⁶

The results also confirmed the different deviation angles that is subtended by their visual axes, and the etiology of these binocular vision anomalies among the HIV-sero positive patients on HAART may be due to their receded near point of convergence, low amplitude of accommodation with high presbyopic reading ADD, autonomic dysfunction associated with the innervation of the accommodative-convergence mechanism and pathological changings due HIV virus, HAART effect or duration.^{6,7}

Limitations

Limitations of this study are the absence or inability to use HIV/AIDS seropositive patients who are HAART naïve with a known CD4 count and follow up to 5-10 years post-HAART exposures due to time constrain.

Another is the lack of comparison with an age matched control group who are HIV sero-negative, tested under the same conditions as in this study.

There are no clinical means to investigate whether these HIV/AIDS seropositive patients on HAART were predisposed to these abnormal binocular visual functions before HIV-infection, exposure to any of the opportunistic infections and commencement of the HAART therapy.

CONCLUSION

HIV positive patients on HAART exhibit either Convergence Excess or Divergence Insufficiency as a binocular vision syndrome depending on the degree of deviation both at far and near distances, in that majority of them are Orthophoric with Esophoria at far and near distances. HAART effect was associated with Induced lateral phoria. There was an association between HAART duration and lateral phorias, however, there was no association between CD4+T cells count, HAART regimen and lateral (habitual and induced) phorias.

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