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Original Article

The Effect of Highly Active Antiretroviral Therapy (HAART) on Accommodative-Convergence Mechanism among HIV/AIDS Patients in North-Western Nigeria

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Abstract

Background: The introduction of Highly Active Anti-Retroviral Therapy (HAART) has led to a dramatic decrease in Human Immune Deficiency Virus (HIV) related morbidity and mortality in the developed as well as developing world. Whilst HAART has been effective in reducing rapidly progressive retinopathies, there are other ocular manifestations of HIV which are yet to be determined, characterised and addressed. The aim of the study was to determine the effect of HAART on Accommodative-Convergence mechanism among HIV/AIDS patients in Northwestern, Nigeria.

Methodology: This was hospital-based cohort study carried out from April 2019 to November 2019. Participants that met the inclusion criteria were recruited and were separated into two groups A and B. Group A were those about to commence HAART referred to as HAART naive, while group B were subdivided into four groups; comprising of B1: those that had been on HAART for 0 - 2½ years, group B2: >2½ - 5 years, group B3: >5 - 7½ years, and group B4: >7½ - 10 years, termed as HAART experience. Information obtained from the patients included sex, age, marital status, Near Point of Convergence (NPC), Amplitude of Accommodation (AA), Presbyopic reading Addition (ADD), CD4+ T cell count, HAART regimen and duration on HAART therapy.

Results: There were 400 participants aged 25 – 55years with a mean age of 37.86 ± 7.5years. The participant's NPC mean was 6.4 ± 1.47cm with a range of 2 – 18cm. Most of the participants 336 (84.0%) had an abnormal Near Point of Convergence compared to 64 (16%) with normal NPC values. The mean AA was 4.18± 1.34DS, ranging from 0.75 to 10.0DS and about 273 (68.2%) of the participant's AA was within 3 to 5DS. The mean presbyopic addition was 1.39± 0.98 DS ranging from 1.00 to 3.50DS whilst majority of the participants, 305 (76.2%) had an abnormal Reading Addition.

Conclusion: The study showed that the HIV/AIDS patients on HAART exhibit an abnormally low AA, receded NPC and High presbyopic reading addition as compared to age matched HAART naïve. There was a statistically significant association between AA and HAART (p = 0.002) and HAART duration (p = 0.00), but there was no association with their CD4+ T cell levels and HAART regimen (p = 0.12, p = 0.08). There was no statistically significant association between Abnormal reading addition and HAART (p= 0.46), CD4+4 T cell levels and HAART regimen (p=0.53 and p= 0.59), but there was a statistically significant association with HAART duration (p= 0.00).

Keywords: HAART; NPC; AA; Reading ADD; HIV/AIDS.

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Introduction

Human Immunodeficiency Virus (HIV) is a retrovirus that primarily infects components of the human immune system such as CD4+ T cells, macrophages and dendritic cells. It directly and indirectly destroys CD4+ T cells[1].acquired immunodeficiency syndrome (AIDS) is defined in terms of either a CD4+ T cell count below 200 cells per µL or the occurrence of specific diseases in association with an HIV infection[2-3]. Highly active antiretroviral therapy (HAART) or Antiretroviral therapy (ART) is the combination of several antiretroviral medicines used to slow the rate at which HIV makes copies of itself (multiplies) in the body. A combination of three or more antiretroviral medicines is more effective than using just one medicine (monotherapy) to treat HIV infection[4].

The goal of antiretroviral combined therapy is to reduce the viral load to a level that can no longer be detected with current blood tests. Evidence indicates that the optimal way to achieve this goal is by initiating combination therapy with two or more antiretroviral agents. HAART provides effective treatment options for treatment-naive and treatment-experienced patients. 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 (INSTIs), Fusion inhibitors (FIs) and Chemokine receptor antagonists (CCR5 antagonists)[5]. Each class targets a different step in the viral life cycle as the virus infects a CD4+ T lymphocyte or other target cell. The use of these agents in clinical practice is largely dictated by their ease or complexity of use, side-effect profile, efficacy based on clinical evidence, practice guidelines, and clinician preference[6].

Accommodation refers to a temporary change in the refractive power of the crystalline lens resulting from contraction of the ciliary muscle, thereby altering the location of the point in space optically conjugate with the retina[7]. Accommodation, convergence and myosis are inter-related and they develop together so that a single clear image is appreciated. The ratio of accommoda-tive-convergence (AC) over accom-modation (A) indicates the relation-ship between the amount of con-vergence produced by a stimulus to accommodate and the amount of accommodation which produces that convergence[8]

The introduction of HAART has led to a dramatic decrease in HIV related morbidity and mortality in the developed as well as developing world. Whilst HAART has been effective in reducing rapidly progressive retinopathies, there are other ocular manifestations of HIV which are yet to be determined, characterised and addressed[9]. These include problems of visual dysfunctions [abnormal receded Near Point of Convergence (NPC), low amplitude of accommodation (AA), High presbyopic reading ADD] that can occur in HIV- infected individuals without infectious retinopathies10.The aim of the study was to determine the effect of HAART on Accommodative-Convergence mechanism among HIV/AIDS patients in Northwestern, Nigeria.

Materials and Method

This hospital-based cohort study was carried out from April 2019 to November 2019. The study adhered to the tenets of the Helsinki Declaration and ethical approval was obtained from the Ethics Review Board of Aminu Kano Teaching Hospital, Kano, Nigeria. Participants that met the inclusion criteria were included. Criteria for inclusions were consent to participate, age between 25 – 55years, tested HIV positive on ELISA test, recent CD4+ T cell count result (at least within six months), HAART naïve and had no ocular, medical or therapeutic histories known to affect any of the selected oculo-visual functions. Persons that did not consent, those tested HIV sero-negative, age below 25 or above 55years, without recent or more than six months CD4+ T cell count result, on HAART for more than ten (10) years and have major systemic, medication or vision threatening complications that may affect or preclude testing for the selected oculo-visual functions, were also excluded from the study.

Information obtained from the participants included sex, age, marital status, NPC, AA, presbyopic reading ADD, CD4+ T cell count, HAART regimen and HAART duration. Anterior and posterior segments examination was done using direct Ophthalmoscope and slit lamp biomicroscope. The NPC was measured using accommodative target in Royal Air Force (RAF) meter ruler, AA with the minus-lens to blur method and the presbyopic reading addition (ADD) was obtained by adding plus spherical lenses in +0.25DS steps starting with +1.00DS. The total plus lenses added over the best corrected distance visual acuity (BCDVA) prescription was recorded as the presbyopic reading ADD for each participant respectively.

All the participants that met the inclusion criteria were grouped into two A and B. Group A, were those about to commence HAART referred to as HAART naive, while group B were subdivided into four groups; comprising of B1: those that had been on HAART from zero to two and half years (0 - 2½ years), group B2 were those on HAART from more than two and half years to five years (>2½ - 5 years), group B3 were those on HAART from more than five years to seven and half years (>5 - 7½ years), and group B4 were those on HAART from more than seven and half years to ten years (>7½ - 10 years), termed as HAART experience.

Data Analysis

Data were entered into a Microsoft excel spreadsheet database exported, cleaned and analysed using the Statistical Package for the Social Sciences (SPSS) version 22.0. The Fisher's exact test and Pearson's Chi-Square statistics were used to compare the effect and association of HAART regimen and duration on NPC, AA, Presbyopic reading ADD and CD4+ count. A p value ≤ 0.05 was considered statistically significant.

Results

A total of 400 participants were enrolled. The participants' ages ranged from 25 years to 55 years with a mean age of 37.86 ±7.5years. There were 172 males (43.0%) and 228 females (57.0%). 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.

The participant's mean NPC was 6.4 ± 1.47cm with a range of 2 – 18cm. Most of the participants 336 (84.0%) had an abnormal NPC compared to 64 (16%) with normal NPC values (Table 1). Pearson's Chi-Square showed that there was no correlation or association of HAART on NPC with chi square (x2) of 3.911 and p value of 0.06.

Table 1: Near Point of Convergence of HAART naïve and HAART experience participants

NPC (cm)	HAART naïve	HAART experience				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 NPC ±SD	6.21± 0.8	6.72 ± 1.8	6.19± 1.1	6.3± 1.2	6.6± 2.0	6.4± 1.5
Normal	7 (8.8%)	19 (23.8%)	11 (13.8%)	12 (15.0%)	15 (18.8%)	64 (16.0%)
Abnormal	73 (91.2%)	61 (76.2%)	69 (86.2%)	68 (85.0%)	65 (81.2%)	336 (84.0%)

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).

The mean Amplitude of Accommodation was 4.18± 1.34DS, ranging from 0.75 to 10.0DS and 273 (68.2%) of the participant's Amplitude of Accommodation was within 3 to 5DS. (Table 2). It also showed a decreased order of amplitude of accommodation as compared with HAART naïve and experience based on their various durations on HAART and was statistically significant with amplitude of accommodation (P= 0.002).

Table 2: Amplitude of Accommodation of HAART naïve and HAART experience participants

Amplitude of Accommodation (DS)	HAART naïve	HAART experience				Total (n=400)	Test Statistics (Fisher's Exact Test)
	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 AA ± SD	5.04 ± 1.6	4.90 ± 1.7	4.25 ± 1.2	3.8±1.1	3.9 ± 1.3	4.18± 1.34	
Normal	2 (2.5%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.0%)	
Abnormal	78(97.5%)	79(98.8%)	80(100%)	80(98.8%)	80(100%)	397(99.0%)	*P*=0.002

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).

The mean presbyopic power of all the participants was 1.39± 0.98 DS ranging from 1.00 to 3.50DS whilst majority of the participants had an abnormal Reading addition 305 (76.2%) and 95 (23.8%) had averagely normal respectively (Table 3). Pearson's Chi-Square showed that there was no correlation or association of HAART on Presbyopic reading addition with chi square (x2) of 0.777 and P value of 0.46.

Table 3: Mean Presbyopic Power of HAART naïve and HAART experience participants

Presbyopic Power (Reading Add)	HAART naïve	HAART experience				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 ADD±SD	1.27± 0.97	0.95± 0.87	1.27± 1.05	1.55± 0.95	1.92± 0.76	1.39 ± 0.98
Normal	22 (27.5%)	31 (38.8%)	27 (33.8%)	13 (16.2%)	2 (2.5%)	95 (23.8%)
Abnormal	58 (72.5%)	49 (61.2%)	53 (66.2%)	67 (83.8%)	78 (97.5%)	305(76.2%)

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).

The above table showed a high increase of their abnormal reading addition within the duration groups of HAART experience as compared with HAART naïve.

Table 4: Relationship between CD4+ and Near Point of Convergence, Amplitude of Accommodation and Presbyopic Reading ADD

Oculo-Visual functions	CD4+ <199cells/mm^3 n (%)	CD4+ 200-349cells/mm^3 n (%)	CD4+ 350-499cells/mm^3 n (%)	CD4+4 >500cells/mm^3 n (%)	Test Statistic (χ^2)	P – Value
NPC (cm)					Fisher exact Test	0.175
Normal	5 (7.8)	14 (21.9)	13 (20.3)	32 (50.0)		
Abnormal	42 (12.5)	78 (23.2)	96 (28.6)	120 (35.7)		
AA (D)					6.768	0.054
Normal	47 (11.9)	89 (22.5)	108 (27.3)	152 (38.4)		
Abnormal	0 (0.0)	3 (75.0)	1 (25.0)	0 (0.0)		
ADD					Fisher exact Test	0.374
Normal	15 (15.8)	21 (22.1)	21 (22.1)	38 (40.0)		
Abnormal	32 (10.5)	71 (23.3)	88 (28.9)	114 (37.4)		

Test statistics using Fisher's exact test showed no relationship between the NPC, AA, ADD, and CD4+ T-cells (Table 4).

Table 5: Relationship between HAART Regimen and Near Point of Convergence, Amplitude of Accommodation, Reading ADD

Oculo-visual functions	1st Line Regimen n (%)	2nd Line Regimen n (%)	3rd Line Regimen n (%)	Test Statistic (χ^2)	P – Value
NPC (cm)				Fisher's Exact Test	0.64
Normal	54 (94.7)	2 (3.2)	1 (1.8)		
Abnormal	242 (92.0)	17 (6.5)	4 (1.5)		
AA (D)				Fisher's Exact Test	0.08
Normal	52 (94.7)	7 (11.5)	2 (3.3)		
Abnormal	98 (93.4)	12 (5.7)	2 (0.9)		
ADD				Fisher's Exact Test	0.59
Normal	67 (1.8)	4 (5.5)	2 (2.7)		
Abnormal	229 (92.7)	15 (6.1)	3 (1.2)		

1st Line Regimen (which comprised of Efavirenz, Lamivudine, Tenofovir, Zidovudine, and Nevirapine), 2nd Line Regimen (Atazanavir, Lopinavir, Ritonavir, and Zidovudine), 3rd Line Regimen (Ritonavir, Zidovudine, Lamivudine).

Table 5 showed that there is no relationship between the HAART regimen and the presbyopic reading ADD, amplitude of accommodation and Near Point of Convergence.

Table 6: Relationship between HAART Duration and Near Point of Convergence, Amplitude of Accommodation, Reading Addition (ADD)

HAART Duration	Group B_1 n (%)	Group B_2 n (%)	Group B_3 n (%)	Group B_4 n (%)	Test Statistic (χ^2)	P– Value
NPC (cm)					3.764	0.29
Normal	19 (33.3)	12 (21.1)	12 (21.1)	14 (24.6)		
Abnormal	62 (23.6)	85 (32.3)	52 (19.8)	64(24.3)		
AA (D)				Fisher's Exact Test		0.00
Normal	11 (18.0)	15 (24.6)	14 (23.0)	11(34.4)		
Abnormal	43 (20.0)	72 (31.0)	47(22.0)	60(27.0)		
ADD					34.661	0.00
Normal	31 (42.5)	30 (41.1)	10 (13.7)	2 (2.7)		
Abnormal	50 (20.2)	67 (27.1)	54 (21.9)	76(30.8)		

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 6 showed that HAART duration has an association that is statistically significant with amplitude of accommodation and the reading addition (P=0.00) while insignificantly related to the near point of convergence (P=0.29).

Discussions

This study indicated the accommodative-convergence mechanism (receded NPC, low AA and abnormal presbyopic reading ADD) failure among HIV positive population on HAART therapy attending SS Wali ART clinic of Aminu Kano Teaching Hospital Kano, Nigeria. The strength of this study was the large number of the study participants (n = 400) compared to previous studies of accommodation failure in HIV positive patients[14-17]. The results of this study would add to the body of knowledge on accommodative-convergence mechanism failure among HIV positive patients on HAART.

Assessing the NPC showed that majority of the participants 336 (84.0%) had an abnormal or receded NPC compared to the 64 (16%) with normal NPC values. Furthermore, HIV- positive patients on HAART had receded NPC with mean of 6.4± 1.47cm and a range of 2 – 18cm. This result also indicates that there is a tendency of them having convergence insufficiency. Similar findings were also reported by Rouse et al[11]. Large number of the participants with an abnormal or receded NPC in this study could account for the age range (25 -55 years) of the study population where some of them are either within the age of none-presbyopia, onset- presbyopia or full presbyopia and may not necessarily be the effect of HAART or their HIV- sero positive status. Table 1 showed that there was no association between HAART and NPC among HIV-sero positive patients (p = 1.00) and Tables 4, 5 and 6 also showed that there was no relationship between NPC and CD4+ T cell levels, HAART regimen or duration.

Moreover, NPC and AA are linked with the relationship between Accommodation and Convergence known as AC/A ratio. The coupling of accommodation and convergence allows clear stable single binocular vision across a range of viewing distances. A change in accommodation (A) is usually accompanied by a change in convergence known as accommodative convergence (AC). When accommodation is exerted, the eyes are induced to converge. The amount of accommodative convergence in prism evoked by 1D of accommodation is known as AC/A ratio[13.] The AC/A ratio is a useful measure in the diagnosis and management of binocular vision problems like convergence insufficiency[12.]

The findings of this study also proved that HIV- sero positive patients on HAART demonstrated failed or poor accommodation with a mean Amplitude of Accommodation of 4.18± 1.3DS, ranging from 0.75 to 10.0DS. Table 2 showed that 318 (80.3%) participants that had abnormal amplitude of accommodation were on HAART whereas about 78 (19.7%) were not on HAART.

The mean presbyopic reading ADD was 1.39 ± 0.98, where 305 (76.2%) had an abnormal presbyopic ADD more than their expected age range when compared with 95 (23.8%) of those with normal ADD. The study also demonstrated that there was a statistically insignificant association between presbyopic reading ADD of HIV-sero positive patients on HAART and HAART (p= 0.46) and there was no association with CD4+4 T cell levels and HAART regimen (p=0.53 and p= 0.59) but statistically significant association to HAART duration (p= 0.00). It has been reported that HIV-sero positive patients' exhibit failed accommodation. Thierfelder et al[14], reported that reduced amplitude of accommodation is an early ophthalmological symptom of HIV infected patients. They stated that the possible causes may be either direct neuronal infection by HIV 1, pathologic changes of the lens or the ciliary body. But they failed to find any relationship between accommodative failure and CD4+ count[14].

Neeta and Radhakrishnan in their study[15], identified accommodative failure in a significant proportion of HIV-positive patients on ART aged between 35 and 45years. They also discovered that this problem may be under-recognized and need for near correction for the pre presbyopic age is often overlooked. According to them, Accommodation failure was not related to CD4 count or current ART regimen being used[15]. In contrast, this study found low amplitude of accommodation in HIV-sero positive patients on HAART between the ages of 25 -55 years with a total sample size of 400, as compared with the studies of Wu et al23, Thierfelder et al[14], and Westcott et al[16], that have smaller sample sizes. Accommodation failure was recorded both in HAART experience and HAART naïve, Amplitude of accommodation was found to have statistically significant association with HAART (p = 0.002) and no association with their CD4+ T cell levels and HAART regimen (p = 0.12, p = 0.08), but statistically significant association with HAART duration (p = 0.00). Findings here are similar with those of Neeta and Radhakrishnan[15].

The accommodation failure among HIV- sero positive on HAART may occur due to either direct neuronal infection by HIV 1, pathologic changes of the lens or the ciliary body or adverse effects of some individual drugs among the HAART regimen on the cranial nerves such as oculomotor nerve which play vital roles in the mechanism of accommodation and convergence. Majority of the participants in this study were on first- and second-line HAART regimens which contain

Zidovudine, Efavirenz and Lamivudine, Tenofovir and Atazanavir. This may account for the low amplitude of accommodation, near point of convergence and high presbyopic ADD found in this study.

As Westcott et al[16] discussed, it remains a possibility that accommodative impairment in HIV positive patients may arise secondary to changes in the lens resistance to deformation, as a consequence of either age-accelerated changes or pathological change. They also reported that in normal subjects there is evidence that the decline in ciliary body contractility is only minimal before the age of 45-50 years. In HIV-positive patients it is possible that impairment of the ciliary body muscle occurs, as a consequence of either direct changes to the muscle or parasympathetic neuropathy. The causal role of a parasympathetic neuropathy is a possibility as several studies have shown that autonomic neuropathy is frequently found early in the course of HIV infection[16].

However, the combined individual adverse drug reaction of HAART among the regimen may have also contributed in the reported failed or poor amplitude of accommodation, abnormal high presbyopic reading ADD and abnormal receded near point of convergence in HIV/AIDS patients on HAART. Maschke et al[17] reported that the currently used HAART for the treatment of HIV infection is associated with long term side effects. In addition, Nucleoside reverse transcriptase inhibitors (NRTIs) may cause mitochondrial toxicity, leading to distal symmetric polyneuropathy (DSP). They reported that nearly one-third of the patients treated with Nucleoside reverse transcriptase inhibitors (NRTIs) experience peripheral neuropathic side effect[17]. The works of Mackey[18] and Shaikh et al[19] as reported by Sui-Yi et al[20] also supported that drug resistance, adverse side effect and drug-drug interaction have been universal problem with the application of HAART for HIV infected patients. They stated that the toxicity of nucleoside reverse transcriptase inhibitor (NRTIs) therapy e.g., Zidovudine, may cause potential inhibition of host mitochondrial DNA polymerase and the long-time use of Zidovudine may also account for the late complication of optic neuropathy[18-20].

Brinkman et al[21]supported this by concluding that Mitochondrial toxicity is a clearly recognized adverse effect of NRTI and that the clinical features of this toxicity, which can be both reversible and irreversible, vary inter-individually and between several tissues. Moreover, they also discovered that Zidovudine and protease inhibitors (Is) used alone can induced endothelial cell proliferation, causing a dysregulation of angiogenesis, which makes HIV- positive patients more prone to hemangiomas[20].

The results of this study also correlated with their findings, in that majority of the participants on HAART regimen, especially first and second line regimens had an abnormal near point of convergence, amplitude of accommodation and high presbyopic reading ADD, which may be related to the neuropathies of the cranial nerves such as optic nerve, oculomotor nerve and abducent nerve etc. These cranial nerves play an important role in the innervation of the muscles responsible for accommodative-convergence mechanism.

Another adverse drug reaction of the HAART regimen is myopathy and myositis as reported by Nikhil and Santosh[22]. Myopathy is one of the neurological manifestations of HIV which can be caused by complication of HIV itself or may also result from the medicines used to control HIV (HAART). They discovered that Zidovudine (ZDV), a nucleoside reverse transcriptase inhibitor is known to cause mitochondrial toxicity which leads to various side effects including myopathy. This may also account for the majority of the participants who had abnormal amplitude of accommodation 98(93.4%), highly presbyopic ADD 229(92.7%) and poor receded near point of convergence 242(92.0%), were found to be on the first line regimen, which contains Zidovudine followed with second line of regimen[22].

Therefore, the abnormalities of NPC, AA and reading ADD may occur due to neural myopathy as a result of mitochondrial toxicity, which may lead to loss of muscle tone known as muscles sclerosis. The sclerosis of the ciliary muscles and the suspensory ligament (that play a vital role in the process of accommodation and accommodative-convergence mechanism) of the eye, may have contributed to the poor AA, receded NPC and high presbyopic reading ADD as observed in this study. Thus, leading to the accommodative-convergence mechanism failure observed among the HIV/AIDS patients on HAART, as shown in the study.

Conclusion

The study showed that the HIV/AIDS patients on HAART exhibit abnormally low amplitude of accommodation (AA), receded Near Point of Convergence (NPC) and High presbyopic reading ADD as compared to age matched HAART naïve. AA was found to have statistically significant association with HAART ($p = 0.002$) and HAART duration ($p = 0.00$), but no association to their CD4+ T cell levels and HAART regimen ($p = 0.12$, $p = 0.08$). There was no association

between Abnormal reading ADD and HAART (p= 0.46), CD4+4 T cell levels and HAART regimen (p=0.53 and p= 0.59), but there was a statistically significant association to HAART duration (p= 0.00).

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