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Choroidal characteristics in HIV infection and their association with disease severity

Neslihan Sevimli[1*], Semiha Çelik Ekinci[2], Meltem Güzin Altınel[1] Berktuğ Öztürk[1]

[1]*Department of Ophthalmology, Fatih Sultan Mehmet Training and Research Hospital, Ataşehir, İstanbul, Türkiye*

[2]*Department of Infectious Diseases and Clinical Microbiology, Fatih Sultan Mehmet Training and Research Hospital, Ataşehir, İstanbul, Türkiye*

ABSTRACT

Aim: To evaluate choroidal characteristics in patients with Human Immunodeficiency Virus (HIV) using spectral-domain optical coherence tomography (SD-OCT), and assess their correlation with disease severity.

Method: Fifty-eight eyes from 29 HIV-positive patients and 62 eyes from 31 age and sex-matched healthy controls were included. Measurements of choroidal thickness (CT), total choroidal area (TCA), stromal area (SA), and luminal area (LA) were obtained via SD-OCT (Maestro, Topcon Co., Tokyo, Japan). The choroidal vascular index (CVI) was calculated using the binarization method. Disease duration, highly active antiretroviral therapy (HAART) duration, HIV-RNA, and CD4 T cell count at diagnosis and at the time of examination, and venereal disease research laboratory (VDRL) test results were recorded. Correlations between SD-OCT results and HIV parameters were analyzed.

Results: No significant differences in age or sex were observed between groups (p=0.988 and p=0.355, respectively). Although the HIV group had lower mean values for CT, TCA, LA, SA, and CVI than controls, these differences were not statistically significant (p=0.344, p=0.054, p=0.075, p=0.865, p=0.313, respectively). SA was inversely correlated with CD4 T cell counts (r = -0.477, p = 0.014). HAART duration was inversely correlated with CT (r=-0.376, p=0.044). VDRL positivity did not affect OCT parameters (p>0.05).

Conclusions: Choroidal structures were thinner in patients who had been on HAART for a longer duration compared to those who were newly diagnosed. Changes in choroidal substructures may be more closely associated with long-term HIV infection or HAART duration rather than HIV-RNA or CD4 T cell counts.

Keywords: Human immunodeficiency virus, optical coherence tomography, choroidal vascular index, choroidal thickness, HAART.

Dr. Neslihan Sevimli *

Department of Ophthalmology, Fatih Sultan Mehmet Training and Research Hospital, Ataşehir, İstanbul, Türkiye

E-mail: neslihandumanli@gmail.com

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1. Introduction

The Human Immunodeficiency Virus (HIV), which emerged around 1890, remains a significant global public health challenge, leading to numerous deaths primarily through the development of Acquired Immunodeficiency Syndrome (AIDS). HIV-induced immune system compromise predisposes individuals to opportunistic infections by reducing CD4 T lymphocyte counts. However, patient outcomes have improved significantly with the advent of highly active antiretroviral therapy (HAART), increasing life expectancy and reducing

morbidity by restoring near-normal immune function [1-4].

Despite the widespread use of HAART, ocular manifestations of HIV continue to affect infected individuals at some point [5]. The posterior segment is affected in a multitude of ways, including retinal microvasculopathy, opportunistic infections such as cytomegalovirus (CMV) retinitis and syphilis, and progressive outer retinal necrosis. These manifestations are particularly prevalent in patients with a CD4 T cell count of less than 200 cells/μL and higher HIV plasma viral loads [1, 6, 7]. Notably, it has been established that HIV retinopathy at baseline represents a significant independent risk factor for mortality [7].

The choroidal tissue, which is the most densely vascularized structure of the eye, plays a vital role in supplying blood to the outer retina, retinal pigment epithelium (RPE), and parts of the optic nerve [8, 9]. HIV has been shown to cause inflammatory ciliochoroidal effusion and impair choroidal perfusion. This process is linked to vascular endothelial dysfunction due to the direct toxic effects of HIV [10, 11]. Compromised choroidal blood flow may significantly contribute to the development of HIV retinopathy by affecting outer retinal oxygenation and thermoregulation, as well as promoting pathological complications such as neovascularization. Furthermore, inflammation in the choroid can lead to photoreceptor loss and potentially cause permanent visual impairment [11].

Visualizing the choroid is challenging due to its location between the light-absorbing RPE and the optically opaque sclera. However, spectral domain optical coherence tomography (SD-OCT) offers a high-definition view of the various layers of the retina, enhancing our understanding of the choroid's role in eye health. Although choroidal thickness (CT) measurement provides indirect insights into choroidal blood flow, it does not reveal detailed choroidal structure [12]. Agrawal et al. introduced the choroidal vascularity index (CVI), a novel OCT parameter that quantifies structural changes in the choroid by calculating the ratio of the luminal area (LA) to the total choroidal area (TCA) [13]. CVI has been utilized to examine different conditions affecting choroidal circulation.

The objective of this study was to evaluate the impact of HIV infection on the structure of the choroid, excluding the presence of infectious retinitis. Secondary objectives included assessing choroidal structural changes and correlating these findings with disease severity. We compared choroidal structures in HIV-infected patients with healthy controls to describe the patterns and risk factors of ocular manifestations of HIV in the HAART era, focusing on their correlation with CD4 T cell counts and other clinical and demographic characteristics within a cohort of HIV-infected individuals in Western Türkiye.

2. Materials and methods

2.1. Study population and design

This prospective cross-sectional study was conducted at the Department of Ophthalmology and the Department of Infectious Diseases and Clinical Microbiology at Fatih Sultan Mehmet Training and Research Hospital from February 2023 to August 2023. The study received approval from the Ethics Committee (FSMEAH-KAEK 2022/118) and adhered to the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all participants and documented.

We evaluated 29 patients diagnosed with HIV either newly or through ongoing follow-up at the Department of Infectious Diseases and Clinical Microbiology. The ophthalmological assessment was conducted at the Department of

Ophthalmology to identify ocular findings. The study also included a control group of 31 healthy volunteers, matched for age and gender. These controls were predominantly subjects who attended the clinic for routine ocular examinations, such as spectacle prescriptions.

2.2. Inclusion and exclusion criteria

Presence of ocular diseases affecting the ocular media (e.g., cataracts), retinal conditions influencing OCT measurements (e.g., age-related macula degeneration, diabetic retinopathy), History of ocular surgery, any ocular or head trauma within the last 3 months, best corrected visual acuity (BCVA) worse than 0.1 logMAR, refractive error of ≥ ±3.00 D to minimize axial length effects on the choroid, Intraocular pressure (IOP) greater than 21 mmHg, diabetes mellitus (DM), systemic hypertension (HT), metabolic syndrome or history of cerebrovascular disease were excluded from the study.

A diagnosis of HIV-related retinopathy was made when clinically detectable cotton-wool spots, intraretinal hemorrhages, microaneurysms, and telangiectasia were observed and excluded.

2.3. Examination procedures

A comprehensive ocular examination was performed on all participants, comprising the measurement of best corrected visual acuity (BCVA) using Snellen charts, with values subsequently transformed to the Logarithm of the Minimum Angle of Resolution (LogMAR) scale. Intraocular pressure (IOP) was determined through the utilization of non-contact pneumatic tonometry (RK-1a Auto Ref/Keratometer, Nidek, Japan), while an assessment of the anterior segment was conducted through slit-lamp biomicroscopy. A subsequent posterior segment examination was conducted with pupil dilation achieved through the administration of 1% tropicamide and the utilization of a 90D lens. CT and CVI values were assessed using SD-OCT (Maestro, Topcon Co., Tokyo, Japan) with a scanning speed of 50,000 A-scans/sec with high resolution (HR) mode using 1:2 pixel scale. Each eye was evaluated independently, but for analysis purposes, correlations were calculated by averaging the two eyes.

2.4. OCT measurements

OCT scans were performed without pupil dilation, at a fixed time between 9:00 and 11:00 a.m., to minimize the impact of daily fluctuations in CVI and CT. All measurements and calculations were performed three times by an experienced ophthalmologist (MGA), and the average of these three measurements was reported.

An internal fixation target was employed to optimize image quality, and only images with a quality score exceeding 45 were included in the subsequent analysis.

The CT was quantified utilizing the manual caliper apparatus provided by the OCT software. The assessment was undertaken from an area extending vertically from the outer edge of the retinal pigment epithelium (RPE) to the border between the choroid and sclera.

CVI was calculated using gray-scale images of the choroid, which were processed using the ImageJ 1.53e software (National Institutes of Health, Bethesda, MD, USA; http://imagej.nih.gov/ij/). Initially, the ImageJ line tool was employed to establish the scale by calibrating the pixel length of the image. Subsequently, the OCT scan image was converted to 8-bit format. Subsequently, the image was binarised through the application of both the auto-local and Niblack threshold settings. The region of interest (ROI), representing the total choroidal area, was selected using the polygon tool and added to the ROI manager. The region of interest (ROI) was delineated from the choroid-RPE intersection

(upper edge) to the choroid-sclera intersection (lower edge). The image was converted to RGB format, and the color threshold settings were adjusted (first bar to zero and second bar to 250) in the brightness section. The measurements were added to the ROI manager. The composite area was measured by merging the initial and secondary measurements using the AND tool in the ROI manager. (Figure 1). The Luminal Area (LA) and Total Choroidal Area (TCA) were determined by the ROI manager. CVI was calculated as the ratio of LA to TCA (Figure 2).

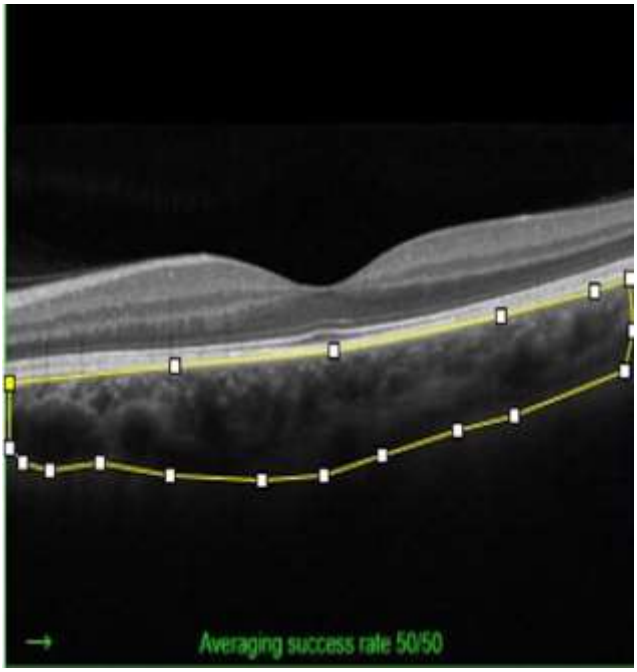

Figure 1. An original SD-OCT image, extending vertically from the outer edge of the RPE to the boundary between the choroid and the sclera.
SD-OCT; Spectral-domain optical coherence tomography, RPE; retinal pigment epithelium.

2.5. Assessment of HIV

HIV-RNA levels and CD4 T lymphocyte count test results were recorded at the time of HIV diagnosis and during the eye examination. VDRL (Venereal Disease Research Laboratory) positivity was recorded. Additionally, information was collected regarding the antiretroviral medications used by the patients, including the specific drugs and their duration. Patients with a history of active opportunistic infections, such as CMV, were excluded from the study.

Figure 2. Segmented SD-OCT image for calculating the choroidal vascularity index using the binarization method.
SD-OCT; Spectral-domain optical coherence tomography, CVI; choroidal vascularity index.

2.5. Statistical analysis

The data obtained from this study were analyzed using IBM SPSS Statistics for MacOS, version 29.0 (IBM Corp., Armonk, NY). The descriptive statistics employed included frequency and percentage for categorical variables, and median, along with the 25th and 75th percentiles for continuous variables. The Mann-Whitney U test was employed to compare the differences between the groups. The Fisher's Exact Test was used to analyze categorical variables, while the Spearman's Correlation Analysis was used for continuous variables. The threshold for statistical significance was set at a p-value of less than 0.05.

3. Results

The mean age of HIV patients was 34.31 ± 8.46 years, while the mean age of the control subjects was 34.42 ± 8.40 years. In the HIV group, there were 28 males (96.55%) and 1 female (3.45%), compared to 27 males (87.1%) and 4 females (12.9%) in the control group. There were no statistically significant differences

Table 1. Distribution of demographic and clinical findings of patients according to HIV diagnosis.

Variables	**Total**	**HIV negatif (n=31)**	**HIV Positive (n=29)**	***p*-value**
Age (year)	n=60	n=31	n=29	0.988*
Mean ± SD	34.37±8.36	34.42±8.40	34.31±8.46	
Median (Q25-Q75)	33 (28-41)	32 (28-41)	33 (28-40)	
Gender, n (%)				0.355^{X}
Female	5 (8.33)	4 (12.9)	1 (3.45)	
Male	55 (91.67)	27 (87.1)	28 (96.55)	
HIV-RNA Count x10^3 copies/mL (Diagnosis)	n=23		n=23	NA
Mean ± SD	1757.90±5019.00	-	1757.90±5019.00	
Median (Q25-Q75)	299.15 (45.00-843.42)	-	299.15 (45.00-843.42)	
CD4 Count (cell/µL) (Diagnosis)	n=22		n=22	NA
Mean ± SD	350.05±173.72	-	350.05±173.72	
Median (Q25-Q75)	359.5 (258-462)	-	359.5 (258-462)	
VDRL, n (%)	n=29		n=29	NA
Negative	21 (72.41)	-	21 (72.41)	
Positive	8 (27.59)	-	8 (27.59)	
HAART Duration (months)	n=29		n=29	NA
Mean ± SD	28.97±43.54	-	28.97±43.54	
Median (Q25-Q75)	4 (0-49)	-	4 (0-49)	
HIV-RNA Count copies/mL (Examination)	n=29		n=29	NA
Mean ± SD	667751.59±1613765.93	-	667751.59±1613765.93	
Median (Q25-Q75)	256 (0-573740)	-	256 (0-573740)	
CD4 Count (cell/µL) **(Examination)**	n=29		n=29	NA
Mean ± SD	529.45±289.7	-	529.45±289.7	
Median (Q25-Q75)	529 (359-719)	-	529 (359-719)	

*HIV; Human Immunodeficiency Virus, VDRL; Venereal Disease Research Laboratory, HAART; Highly active antiretroviral therapy. *: Mann Whitney U-Test. X: Fisher's Exact Test.*

in age or sex between the two groups (p = 0.988 and p = 0.355, respectively). Table 1 provides the distribution of patients' demographic and clinical findings according to their HIV diagnosis.

Among the cohort of patients diagnosed with HIV, the most commonly prescribed antiretroviral medication was a single-tablet formulation containing "bictegravir, emtricitabine, and tenofovir alafenamide fumarate," which was administered to 13 patients. The second most common regimen was a two-tablet regimen comprising “emtricitabine and tenofovir disoproxil fumarate” in conjunction with “dolutegravir,” which was prescribed to 5 patients. Three patients were administered a single-tablet regimen containing “elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide fumarate.” The remaining three patients received one of the following regimens: “abacavir, lamivudine, and dolutegravir”; “lamivudine and dolutegravir”; or “raltegravir, emtricitabine, and tenofovir disoproxil fumarate”. The mean duration of HAART use was 28.97 ± 43.54 months. While the mean CT, TCA, LA, SA, and CVI were lower in the HIV group compared to controls, these differences were not statistically significant (p = 0.344, p = 0.054, p = 0.075, p = 0.865, p = 0.313, respectively). Table 2 details the distribution of SD-OCT findings according to HIV diagnosis.

Correlation analysis revealed an inverse relationship between CT and both the duration of HAART use (p = 0.044, r = -0.376) and the CD4 T cell count at the time of examination (p = *0.006*, r = -0.495). Additionally, an inverse relationship was observed between SA and the CD4 T cell count at examination (p = 0.014, r = -0.477). Table 3 presents the results of the correlation analysis evaluating the relationships between HIV findings and OCT measurements in HIV-positive patients.

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Table 2. Comparison of the different choroidal parameters between the groups.

SD-OCT measurements	**HIV negative (n=62 eyes)**	**HIV positive (n=58 eyes)**	***p*-value***
CT (µm)	n=59	n=54	0.344
Mean ± SD	298.78±41.58	291.72±36.90	
TCA (mm^2)	n=59	n=54	0.054
Mean ± SD	1.64±0.19	1.57±0.17	
LA (mm^2)	n=56	n=53	0.075
Mean ± SD	1.24±0.15	1.19±0.13	
SA (mm^2)	n=56	n=53	0.865
Mean ± SD	0.4±0.07	0.39±0.06	
CVI (%)	n=56	n=53	0.313
Mean ± SD	75.52±3.36	75.21±2.87	

*HIV; Human Immunodeficiency Virus, SD-OCT; Spectral-domain optical coherence tomography, CT; Choroidal thickness, TCA; Total choroidal area, LA; Luminal area, SA; stromal area, CVI; choroidal vascular index. *: Mann Whitney U-Test.*

between HIV findings and OCT measurements in HIV-positive patients.

Eight patients in the HIV group had positive VDRL, and no statistically significant differences in OCT findings were observed between groups with different VDRL test results. Table 4 shows the distribution of SD-OCT findings based on VDRL test results.

4. Discussion

Chronic HIV infection often leads to non-infectious vision loss, making it crucial to study its impact on retinal and choroidal structures. This study employed SD-OCT to examine these structures in HIV patients without opportunistic infections or retinopathy, comparing them to

Table 3. Correlation between the choroidal structural parameters and the HIV parameters.

Variables		**CT**	**TCA**	**LA**	**SA**	**CVI**
HIV-RNA Count	**r**	-0.001	0.130	0.014	0.235	-0.125
	p	0.996	0.554	0.950	0.293	0.580
HAART Duration	**r**	**-0.376**	-0.094	-0.024	-0.046	0.145
	p	**0.044**	0.629	0.908	0.822	0.480
CD4 Count	**r**	**-0.495**	-0.211	-0.052	**-0.477**	0.375
	p	**0.006**	0.271	0.802	**0.014**	0.059

*HIV; Human Immunodeficiency Virus, SD-OCT; Spectral-domain optical coherence tomography, CT; Choroidal thickness, TCA; Total choroidal area, LA; Luminal area, SA; stromal area, CVI; choroidal vascular index, HAART; Highly active antiretroviral therapy. *Spearman's Correlation Analysis.*

Table 4. Comparison of the areas of different structures of the choroid and CVI based on VDRL results in HIV patients.

SD-OCT Measurements	**VDRL (-) (n=21)**	**VDRL (+) (n=8)**	***p*-value***
CT (µm)	n=21	n=8	0.318
Mean ± SD	295.88±33.18	281.94±32.57	
TCA (mm^2)	n=21	n=8	0.605
Mean ± SD	1.59±0.14	1.56±0.14	
LA (mm^2)	n=19	n=7	0.860
ean ± SD	1.19±0.11	1.19±0.12	
SA (mm^2)	n=19	n=7	0.063
Mean ± SD	0.41±0.05	0.36±0.05	
CVI (%)	n=19	n=7	0.094
Mean ± SD	74.63±2.64	76.66±2.48	

*HIV; Human Immunodeficiency Virus, SD-OCT; Spectral-domain optical coherence tomography, VDRL; Venereal Disease Research Laboratory, CT; Choroidal thickness, TCA; Total choroidal area, LA; Luminal area, SA; stromal area, CVI; choroidal vascular index. *: Mann Whitney U-Test.*

healthy controls. To our knowledge, this is the first study to compare CVI values between HIV patients and healthy controls using SD-OCT, while also binarizing SA, LA, and TCA to assess correlations with HIV disease severity.

Previous studies have confirmed subtle macular changes in HIV patients without ocular opportunistic infections [3, 14-16]. HIV affects the retina and choroid through several mechanisms, including increased phagocytic activity, immune complex deposition, elevated fibrinogen levels, and direct toxic effects on the retinal vessel endothelium. These mechanisms lead to endothelial dysfunction, microvasculopathy, focal ischemia, and hypoxia, contributing to retinopathy and choroidopathy [1, 5, 7, 17-19].

Several studies using optical coherence tomography angiography (OCTA) have reported decreased vessel flow density (VFD) in HIV patients compared with healthy controls [5, 7, 14, 20-22]. However, the literature on the effect of HIV on macular and choroidal layer thickness is contradictory [3, 4, 11]. Differences in findings may be due to variations in CD4 T cell counts, viral load, disease duration, and treatment, as well as the level of infection suppression in HIV-infected individuals.

Some reports, similar to our findings, show that patients being followed up for HIV exhibit abnormal choroidal structural alterations, with thinner CT. These studies suggest that viral particles may trigger autoimmune reactions, leading to thinning of the macula and choroid. Additionally, decreased choroidal blood flow due to microvasculopathy may cause choroidal atrophy and reduced CT in chronic HIV [4]. Other reports indicate that choroidal layers, including the retinal nerve fiber layer (RNFL), may be thinner due to HIV-associated neuroretinal disorders [3, 11, 14, 21-25]. Demirkaya et al. proposed that, given the choroid's high vascularity, mitochondrial dysfunction might play a role in HIV-related ocular neuroretinal disorders and thinning as a result [24].

Conversely, some studies report increased CT due to HIV-associated choroidal vascular dysfunction. Agarwal et al. [11] found that patients with detectable HIV microangiopathy, indicative of higher viral load and poor disease control, had increased CT compared to those without microangiopathy. They attributed this to impaired choroidal circulation caused by the virus's toxic effects. Another study suggested that HIV-related choroidal dysfunction could result from uveal effusion, inflammation, increased vascular permeability, and endothelial cell activation, and this may cause thickening of the CT [10]. Also, several studies showed that the inner choroidal vasculature appeared to be mostly unaffected in HIV [3, 7].

Viral load and CD4 T cell count are critical markers in HIV research. Many studies have shown that increasing viral load negatively affects retinal and choroidal layers and endothelial function [3, 5, 7, 19, 26, 27]. Çetin et al. reported a negative correlation between HIV-RNA and choroidal thickness ($r = -0.435$, $P = 0.003$) [3]. We did not detect a direct effect of HIV-RNA on choroidal layers.

Newly diagnosed HIV patients have low CD4 T cells and high HIV-RNA counts. In our study, HAART was initiated immediately upon HIV diagnosis, making the duration of HIV and HAART use duration almost equivalent. Several studies reported a negative association between retinal and choroidal layer thickness and choroidal microvascular circulation, and both HIV diagnosis duration and HAART use duration suggested degenerative tendencies [3, 14, 20, 28]. We observed a negative correlation between CT and HAART usage duration. In contrast to our findings, Cetin et al. reported

thinner CT in newly diagnosed patients compared to those on treatment [3]. Conversely, other studies have found no significant correlation between HIV infection duration and retinal and choroidal layers or VFD [5, 22]. Although drugs such as protease inhibitors have been reported to disrupt the vascular endothelium of the choroid [29], none of our patients were using these drugs.

Despite many studies indicating that decreased CD4 T cell counts are associated with retinal and choroidal thinning and microvasculopathy, especially in those with opportunistic infections [1, 5, 7, 25], several studies suggested that persistent viremia might play a more significant role in choroidal and vascular injury than CD4 T cell count alone [3, 4, 24]. Increased CD4 T cell counts over time are associated with reduced viral load. We found a negative correlation between CD4 T cell count and SA and CT, but we could not determine the relationship between HIV-RNA count and choroidal structures. The cell destruction, most likely caused by CD4 to combat the viral load, supports the hypothesis that it causes thinning through apoptotic effects, especially in the choroidal stroma. Also, we did not include patients with opportunistic infections or HIV retinopathy, which could affect our results.

Du et al. found that CVI was lower in HIV patients, and those with HIV-related microvasculopathy is automatically calculated in the OCTA device, suggesting that HIV-RNA impacts microvasculopathy more than choroidal stroma [14]. While the increase in CD4 T cell count was significantly inversely correlated with SA, there was also a non-significant inverse association with LA. This may have led to the CVI not changing significantly.

Ocular syphilis is an often underestimated manifestation of syphilis, and its prevalence has notably increased among HIV-positive patients [30]. In patients with syphilis, inflammatory choriocapillaris non-perfusion can lead to ischemic damage to the outer retina, which is a hallmark of syphilitic posterior placoid chorioretinitis [31]. Our study identified 8 HIV-positive patients with a positive VDRL test, which raises concerns about the potential impact of syphilis on choroidal dysfunction. Despite the known association between syphilis and retinal/choroidal changes, our analysis revealed no significant effect of VDRL positivity on OCT parameters ($p > 0.05$).

Our study's strength lies in standardized imaging and quantitative measurements, facilitating objective analysis. Despite the heterogeneity in the HIV cohort and varying disease durations, our longitudinal study design allows us to assess the impact of disease progression on choroidal anatomy.

In our study, we employed ImageJ software to analyze choroidal structural areas, a methodological approach that distinguishes our research from other studies in the literature. Unlike traditional measurements of CT, which provide data on a localized choroidal area, our approach involved calculating the total choroidal area TCA and the SA and LA through image binarization. This method allowed us to assess the entire choroidal area and derive the CVI by calculating the ratio of LA to TCA.

4.1. Limitations

It should be noted that the present study is subject to several limitations. Primarily, the sample size was relatively small and had a very low number of female participants, which may limit the generalisability of the findings. Although imaging was conducted at the same time of day to minimize diurnal variations in choroidal thickness, potential confounding factors of drug use, heavy coffee consumption (defined as more than two and a half cups per day), and heavy smoking (defined as more than

20 cigarettes per day) were not assessed. Similarly, alcohol consumption was not taken into account.

The lack of data on the axial length of the subjects and controls may have influenced the accuracy of CT measurements. Additionally, the present study did not encompass the evaluation of visual function, encompassing aspects such as color perception, contrast sensitivity, multifocal electroretinography, or visual field assessment. The absence of significant differences in choroidal measurements between HIV-infected patients and control subjects may be attributed to the high CD4 T cell counts and effective treatment in the majority of our HIV-infected cohort.

4.2. Conclusion

Our findings indicate that a reduction in viral load and an increase in CD4 T cell count over time are associated with changes in choroidal structures. The duration of exposure to viral load or HAART use may have a significant impact on choroidal measurements. Analyzing choroidal structures in HIV patients may offer a valuable objective and quantitative biomarker for assessing the severity of retinal and choroidal involvement. Additionally, an increase in CD4 T lymphocytes over time may lead to choroidal thinning by reducing both viral load and inflammation by increasing apoptosis. Our findings suggest that chronic HIV infection, particularly when well-controlled, may not exacerbate choroidal damage as significantly as previously thought. Further prospective studies with larger sample sizes are needed to explore these relationships more comprehensively and to determine if choroidal structures could be used to monitor treatment response effectively.

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