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ORIGINAL ARTICLE

Functional and structural neuroretinal disorders in HIV Controllers. Prospective cohort study

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Abstract

Objective: To estimate the prevalence and cumulative incidence of neuro-retinal-disorders (NRD) in HIV-controllers.

Design: Prospective, single-centre, cohort study of people living with HIV (PLWH): elite-controllers, long-term-non-progressors and early diagnosed.

Methods: The study compared "HIV-controllers" (including elite-controllers and long-term-non-progressors), who were not on antiretroviral therapy (ART), and "HIV-treatment" (HIV-infected subjects with a recent diagnosis and on ART). A matched cohort of "non-HIV subjects" was created. NRD was defined as at least one altered (not normal) ophthalmological parameter (functional or structural). Functional (visual acuity, contrast sensitivity, chromatic vision, visual field) and structural parameters (ganglion cells, macular nerve fibre layer, peripapillary nerve fibre layers, vascular calibre) as well as quality of life (Medical Outcomes Study-HIV Short Form-30) were assessed.

Results: Between March 2012 and November 2015, the study included all HIV-controllers (16 elite-controllers, 1 long-term-non-progressor), 11 HIV-treatment and 16 non-HIV. Prevalence of NRD at baseline was 88.2% (15/17, 95% CI: 65.7%–96.7%), 90.9% (10/11, 95% CI: 62.3%–98.4%) and 56.3% (9/16, 95% CI: 33.2%–76.9%), respectively. Cumulative incidence at 3 years was 50% (1/2), 100% (1/1) and 33.3% (2/6), respectively. None of the participants manifested ocular clinical symptoms. Three years later, prevalence of NRD was 92.3% (12/13, 95% CI: 66.7%–98.6%), 75% (6/8, 95% CI: 40.9%–92.9%) and 50.0% (7/14, 95% CI: 26.8%–73.2%), respectively. Contrast sensitivity and structural parameters were globally the most affected among PLWH. Quality of life (total score) [median (interquartile range)] at baseline and 3 years was 82 (71–89) and 74 (63.5–79.25) in HIV-controllers and 80 (73–88) and 88 (83–92) in HIV-treatment.

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Conclusions: HIV-controllers and those individuals on ART presented a higher percentage of NRD than non-HIV. Our results suggest that NRD could be a biomarker of ocular aging among PLWH.

KEYWORDS

HIV controllers, neuro-retinal disorders, ocular aging in HIV, retina in HIV, retinal OCT in HIV

INTRODUCTION

HIV itself and its subsequent HIV-related chronic inflammation are involved in the increased risk of cardiovascular events, kidney disease, osteoporosis, cognitive disorders and some types of cancers. HIV, due to its nature, directly damages different ocular structures, affecting the microvasculature of the eye [1]. Likewise, the effect of HIV infection on the human immune response increases the levels of inflammatory cytokines [1]. In the pre-ART era, retinal microangiopathy was very common and was associated with a low CD4 T-cell count which resulted in lowered life expectancy [2]. Currently, the greater longevity of this population together with accelerated aging should allow us to rule out ocular disorders. These changes are known as neuroretinal disorders (NRD) [3–10], which can worsen the quality of life (QoL) of these individuals [11–13].

The NRD pathophysiological process in PLWH is not well understood. HIV infection itself, chronic inflammation and immune activation, as well as the possible toxic effect of ART, have been hypothesized to be involved in eye damage [1]. PLWH due to HIV infection have an altered retinal nerve fibre layer (RNFL) and this may influence other visual functions like contrast sensitivity (CS) and visual acuity. Basically, NRD alterations happen mainly in CS in PLWH prematurely, subtle visual field changes and in structural tests such as optical coherence tomography (OCT) like changes in the retina's ganglion cells and nerve fibres [12]. It is important to note that the retina, despite its more peripheral location, is part of the central nervous system. Hence, the concept of NRD does not have a clear definition, and it includes functional and structural retinal changes. Impairment of the RNFL [9] or the CS Citation must be number 13 instead of 14 [14] has been used as a marker of NRD.

Among the PLWH population, there is a small subset known as "HIV-controllers" who maintain low or undetectable levels of viral load and elevated CD4 cell counts for years in the absence of ART [14]. HIV-controllers comprise between 0.2% and 0.5% of the HIV population [14]. Although HIV-controllers initially show better develop ment of HIV 1-infection with respect to non-controllers, they also have higher levels of circulating inflammatory cytokines and rates of coronary atherosclerosis compared with non-controllers on ART [15], suggesting that chronic inflammation may account for early vascular dysfunction [16, 17].

Our working hypothesis was that HIV-controllers are at risk of having NRD. To define non-invasive biomarkers capable of early detection of NRD through an ophthalmic examination used in our clinical practice, among HIV-controllers (a group of PLWH who theoretically have good disease evolution and do not require treatment), could carry to reconsider the start of ART to prevent the evolution of all these retinal structural changes with potential consequence on their QoL due to early disability. Therefore, the aim of this study was to estimate the prevalence and cumulative incidence of NRD in HIV-controllers and track their QoL. A cohort of non-HIV individuals matched by age and sex was created.

PATIENTS AND METHODS

Study design

We conducted a prospective, single-centre (with around 3000 PLWH attending), 3-year follow-up, cohort study of PLWH: (a) non-ART including: elite-controllers (ECs) and long-term-non-progressors (LTNPs) and (b) those with a recent diagnosis of HIV who have started ART. A cohort of non-HIV people matched by age and gender to the HIV-controllers was created. The study was approved by the centre's Institutional Review Board (IRB) (registration number EO-12-016). Written informed consent was obtained from all participants. This study was carried out in a tertiary hospital (Hospital Universitari Germans Trias i Pujol in Badalona, Barcelona, Spain).

Study population

The cohort of PLWH included adults (age ≥18 years), both sexes, HIV 1-infected (ECs, LTNPs or recently

diagnosed with HIV and on ART); no ocular complaints, no background of ocular pathologies: glaucoma, retinal or neuro-ophthalmologic diseases, non-anterior segment disorders or dyschromatopsia; and neither intraocular surgery nor myopia of >6 diopters. No background of hypertension, diabetes mellitus, collagenopathies, haematological disorders; and individuals who have attended the HIV Unit in our tertiary hospital.

A cohort of non-HIV people, matched by age and gender with the HIV-controllers, was created. Non-HIV subjects included in this cohort complied with the same background requirements as the PLWH cohort and attended voluntarily the outpatient facilities of the ophthalmology unit of our tertiary hospital. Therefore, three groups were studied:

1. HIV-controllers: PWLH with undetectable (EC) or low (LTNP) levels of viral load, elevated CD4 cell counts (>500 cells/μL) and never treated with ART.
2. HIV-treatment: PWLH with a recent diagnosis of HIV 1-infection and on ART for <6 months.
3. Non-HIV: HIV-uninfected people.

Study procedure

People included in this study were assessed at baseline (when informed consent was obtained) and annually with a follow-up visit for 3 years (four visits). At each visit, all participants were clinically and ophthalmologically evaluated. In the PLWH cohort, inflammation/immunological markers (C-reactive protein [CRP], interleukin 6 [IL-6], D-dimer and sCD14) and Medical Outcomes Study-HIV Short Form-30 (MOS-HIV SF-50) QoL questionnaires were collected at baseline (signed consent) and at the 3-year point (end of study).

Ophthalmological assessment

Both eyes were examined, but the right eye was the study eye. Table S1 shows the test of ophthalmological assessments, as well as its normal range and the instrument used with the units of measurement.

Given the lack of consensus as to the definition of what is considered NRD, two definitions were considered for estimating the prevalence and incidence of NRD. (1) A participant was considered to present a NRD when at least one altered (not normal) ophthalmological parameter (functional or structural) was identified. As seen in Table S1, ophthalmological parameter incidence outside of the normal range was considered to be a participant with NRD. (2) A participant was considered to present a NRD when they had a CS ≤ 1.50 log units (logCS ≤ 1.50).

Functional

1. Visual acuity (VA) was evaluated with the Early Treatment Diabetic Retinopathy Study (ETDRS) optotype in logMAR units.
2. Contrast sensitivity (CS) was assessed by Pelli Robson chart in logCS units.
3. Visual field Humphrey VF analyser SITA-fast 24-2 was used to evaluate sensitivity to the perception of a stimulus in 20° VF dB 0.0 to −3.00 in dB units to examine the evolution. We selected the parameter of the mean visual field deviation (MD) that gives an overall value of the total amount of visual field loss, and becomes more negative as the overall field worsens.

Structural

Parameters were evaluated using optic coherence tomography (OCT) with the Topcon 3D-2000-OCT-retinograph.

OCT allows us to measure the thickness of different ocular structures by interferometry, a technique in which an infrared beam passes into the eye and its reflectivity pattern is studied. This is a non-invasive technique, reproducible, that gives us an exact measure of the thickening of each retinal layer [18].

1. Macular ganglion cells are a type of neuron cells located in the inner surface of the retina (ganglion cells layer), evaluated by the OCT ganglion cells test.
2. Macular nerve fibre layer (MNFL) comprises the axons of the ganglion cells, evaluated by the OCT MNFL test.
3. Retinal nerve fibre layer (RNFL) is formed by the expansion of the fibres towards the optic nerve. It was evaluated by the OCT optic RNFL test in its different sectors; temporal (temp), superior (sup), nasal (nas) and inferior (inf), and as total (tot) area of the optic nerve.
4. Vascular calibres were quantified using fundus photographs: the central retinal artery equivalent (CRAE; the projected calibre size of the central retinal artery), central retinal vein equivalent (CRVE; the projected calibre size of the central retinal vein) and arteriole-to-venule-ratio (AVR). We used a standardized protocol in which the six largest arterioles and venules in a ring-shaped area located between 0.5-disc and 1.0-disc

diameter from the optic disc margin were identified and measured. The measures were combined into two summary variables for the eye, the CRAE and the CRVE, using formulas derived by Parr and Spears [19, 20] and by Hubbard [21], with revision by Knudtson [22]. These indices are used to calculate the arteriole-to-venule ratio (AVR) as CRAE/CRVE [23]. A range between 0.50 and 0.90 was considered to be normal.

Quality of life

Among PLWH, QoL was studied by Medical Outcomes Study-HIV Short Form-30 (MOS-HIV SF-30) survey. MOS-HIV is a brief, comprehensive measure of health-related QoL that is used extensively in HIV/AIDS [24–26].

Statistical analysis

Given the study's descriptive nature, no formal sample size calculation was performed. As mentioned earlier, HIV-controllers comprised a very low number of PLWH (between 0.2% and 0.5% of PLWH) [14]. Therefore, the final sample size included all the HIV-controllers associated with our HIV Unit.

Qualitative variables were expressed as absolute and relative frequencies. Quantitative variables were expressed as median (interquartile range [IQR] or range). The prevalence and cumulative incidence of NRD were estimated, and their 95% confidence interval (95% CI) was calculated. The difference, and the number of participants whose ophthalmological assessment worsened, between 3 years after and baseline was calculated. An exploratory analysis among the study groups and between the right and left eyes was performed. Statistical significance was set at a p-value ≤ 0.05. All statistical analyses were performed using SPSS software for Windows (Version 25.0; SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline characteristics

Between March 2012 and November 2015, 17 people were included in the HIV-controllers group (16 ECs and 1 LTNP), 11 in the HIV-treatment group and 16 in the non-HIV group. Table 1 shows the participants' baseline characteristics. All participants in the HIV-treatment-group were on ART during the 3-year follow-up. Each cohort experienced some dropouts before the 3-year follow-up (end of study): 4, 3 and 2 participants in each group, respectively.

Prevalence and cumulative incidence of NRD

The prevalence of NRD (any ophthalmological parameter altered) at baseline was 88.2% (15/17, 95% CI: 65.7%–96.7%) in HIV-controllers, 90.9% (10/11, 95% CI: 62.3%–98.4%) in HIV-treatment and 56.3% (9/16, 95% CI: 33.2%–76.9%) in non-HIV.

The prevalence of NRD at baseline based on CS was 29.4% (5/17, 95% CI: 13.3%–53.1%) in HIV-controllers, 50.0% (5/10, 95% CI: 23.7–76.3%) in HIV-treatment and 12.5% (2/16, 95% CI: 3.5%–36.0%) in non-HIV. Table 2 shows the prevalence of ophthalmological parameters outside the normal range at baseline and at 3 years after.

Baseline prevalence of NRD was higher among PLWH compared with non-HIV, except for chromatic vision.

The prevalence of NRD (any ophthalmological parameter altered) at 3 years was 92.3% (12/13, 95% CI: 66.7%–98.6%) in HIV-controllers, 75.0% (6/8, 95% CI: 40.9%–94.9%) in HIV-treatment and 50.0% (7/14, 95% CI: 26.8%–73.2%) in non-HIV. The prevalence of NRD at 3 years based on CS was 60.0% (6/10, 95% CI: 23.7%–76.3%) in HIV-controllers, 60.0% (3/5, 95% CI: 11.8%–76.9%) in HIV-treatment and 21.4% (3/14, 95% CI: 7.6%–47.6%) in non-HIV. The prevalence of alteration in visual field in HIV-controllers at baseline and 3 years later was greater than HIV-treatment (p-value 0.191 at baseline and 0.131 at 3 years) and non-HIV (p-value 0.085 at baseline and 0.041 at 3 years). Likewise, the prevalence of altered peripapillary RNFL at baseline and 3 years later was higher among the PLWH groups in comparison to non-HIV. Among the PLWH groups, similar results were found, except for visual field (as previously mentioned).

The cumulative incidence of NRD (any ophthalmological parameter altered) at 3 years among participants with no NRD at baseline was 50% (1/2, 95% CI: 9.5%–90.6%) in HIV-controllers, 100% (1/1, 95% CI: 20.7%–100%) in HIV-treatment and 33.3% (2/6, 95% CI: 9.7%–70.0%) in non-HIV. The cumulative incidence of NRD based on CS at 3 years among participants with normal CS at baseline was 57.1% (4/7, 95% CI: 25.1%–84.2%) in HIV-controllers, 50.0% (1/2, 95% CI: 9.5%–90.6%) in HIV-treatment and 25.0% (3/12, 95% CI: 8.9%–53.2%) in non-HIV. Table 3 presents the incidence of ophthalmological parameters outside the normal ranges at 3 years after and

TABLE 1 Baseline characteristics.

Characteristic	HIV-controllers ($n = 17$)	HIV-treatment ($n = 11$)	Non-HIV ($n = 16$)
Age, years	39 (38–47)	36 (30–42)	35.5 (31–41)
Male/female	9 (53%)/8 (47%)	10 (91%)/1 (9%)	8 (50%)/8 (50%)
MSM	8 (47%)	10 (91%)	–
MSW	7 (41%)	1 (9%)	
IVDU	1 (6%)	0	
Blood transfusion	1 (6%)	0	
Time of known HIV, years	13.4 (8.0–25.8)	0.4 (0.2–0.6)	–
HIV viral load, HIV RNA copies/mL	770[a]	50 (50–70)	–
Undetectable: <50 HIV RNA copies/mL	16 (94%)[b]	8 (73%)[c]	–
CD4 cell count, cells/μL	637 (443–1110)	497 (376–783)	–
CD4 nadir cell count	464 (307–574.5)	357 (211–704)	–
<200 cells/μL	1 (6%)	7 (64%)	–
Duration of ART, years	0	0.2 (0.1–0.2)	–

Note: All values are expressed either as numbers (percentages) or medians (interquartile ranges).
Abbreviations: ART, antiretroviral therapy; IVDU, intravenous drug users; MSM, men who have sex with men; MSW, men who have sex with women.
[a]Long-term-non-progressor ($n = 1$).
[b]Elite-controllers ($n = 16$).
[c]Naïve with more than 3 months' ART.

TABLE 2 Prevalence of ophthalmological parameters out of normal range at baseline and at 3 years.

Prevalence of	HIV-controllers		HIV-treatment		Non-HIV	
ophthalmological parameters	Baseline ($n = 17$)	3 years ($n = 13$)	Baseline ($n = 11$)	3 years ($n = 8$)	Baseline ($n = 16$)	3 years ($n = 14$)
Functional						
Visual acuity	3 (17.6)	1 (7.7)	2 (18.2)	0 (0)	1 (6.3)	1 (7.1)
Contrast sensitivity	5 (29.4)	6 (60)[a]	5 (50)[a]	3 (60)[b]	2 (12.5)	3 (21.4)
Chromatic vision	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Visual field	6 (35.4)	4 (30.8)	1 (9.1)	0 (0)	1 (6.3)	0 (0)
Structural						
Total Ganglion cells	3 (17.6)	1 (7.7)	2 (18.2)	2 (25)	3 (18.8)	0 (0)
Total MNFL	1 (5.9)	2 (15.4)	1 (9.1)	0 (0)	0 (0)	0 (0)
RNFL						
Superior	3 (17.6)	2 (15.4)	1 (9.1)	3 (37.5)	1 (6.3)	1 (7.1)
Nasal	6 (35.4)	3 (23.1)	4 (36.4)	2 (25)	3 (18.8)	1 (7.1)
Temporal	2 (11.8)	1 (7.7)	1 (9.1)	0 (0)	1 (6.3)	1 (7.1)
Inferior	3 (17.6)	2 (15.4)	2 (18.2)	2 (25)	1 (6.3)	1 (7.1)
Total	1 (5.9)	1 (7.7)	1 (9.1)	2 (25)	0 (0)	1 (7.1)
Vascular calibres						
AVR	1 (5.9)	0 (0)	1 (5.9)	0 (0)	0 (0)	0 (0)

Note: All values are expressed as numbers (percentages).
Abbreviations: AVR, arteriole-to-venule ratio; MNFL, macular nerve fibre layer; RNFL, retinal nerve fibre layer at optic nerve.
[a]Evaluated in 10 participants.
[b]Evaluated in 5 participants.

TABLE 3 Incidence of ophthalmological parameters out of normal range at 3 years after (participants with normal range at baseline) and number of participants who had a worse ophthalmological assessment at 3 years with respect to baseline.

Ophthalmological parameters	At 3 years		At 3 years		At 3 years	
	HIV-controllers ($n = 13$)		HIV-treatment ($n = 8$)		Non-HIV ($n = 14$)	
	Incidence	Worse vs. baseline	Incidence	Worse vs. baseline	Incidence	Worse vs. baseline
Functional						
Visual acuity	0 (0)	4 (30.8)	0 (0)	3 (37.5)	0 (0)	3 (21.4)
Contrast sensitivity	1 (10)[a]	6 (60)[a]	1 (20)[b]	2 (40)[b]	0 (0)	5 (35.7)
Chromatic vision	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Visual field	1 (7.7)	6 (46.2)	0 (0)	0 (0)	0 (0)	4 (28.6)
Structural						
Total ganglion cells	0 (0)	12 (92.3)	0 (0)	7 (87.5)	0 (0)	11 (78.6)
Total MNFL	1 (7.7)	9 (69.3)	0 (0)	1 (12.5)	0 (0)	5 (35.7)
RNFL						
Superior	1 (7.7)	8 (61.5)	2 (25)	3 (37.5)	1 (7.1)	5 (35.7)
Nasal	0 (0)	6 (46.2)	0 (0)	5 (62.5)	0 (0)	9 (64.3)
Temporal	0 (0)	9 (69.2)	0 (0)	5 (62.5)	0 (0)	6 (42.9)
Inferior	1 (7.7)	10 (76.9)	1 (12.5)	3 (37.5)	0 (0)	6 (42.9)
Total	1 (7.7)	8 (61.5))	1 (12.5)	4 (50)	1 (7.1)	6 (42.9)
Vascular calibres						
AVR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Note: All values are expressed as numbers (percentages).
Abbreviations: AVR, arteriole-to-venule ratio; MNFL, macular nerve fibre layer; RNFL, retinal nerve fibre layer at optic nerve.
[a]Evaluated in 10 participants.
[b]Evaluated in 5 participants.

the number of participants who had a worse ophthalmological assessment at 3 years after compared with baseline.

Evolution of ophthalmological parameters

None of the participants manifested ocular clinical symptoms during the study. Three years later, with respect to baseline state, three PLWH improved (clearance); 66.7% improved in functional parameters (subjective tests), corresponding to two patients (1 HIV-controller and 1 HIV-treatment) and the third was an HIV-treatment whose structural parameters improved with a decrease in retinal oedema.

Based on participants with an ophthalmological assessment altered at baseline, the percentage of participants who showed improvement was 9.1% (1/11, 95% CI: 1.6%–37.7%) in HIV-controllers, 28.6% (2/7, 95% CI: 8.2%–64.1%) in HIV-treatment and 62.5% (5/8, 95% CI: 30.6%–86.3%) in non-HIV. Table 4 shows the evolution (end of study minus baseline results) of ophthalmological parameters.

Similar results in all ophthalmological parameters in the right eye were found in the left eye. Table S2 shows the immunological biomarkers in people living with HIV (PLWH) at baseline and 3 years after.

Quality of life

Table 5 includes the results of QoL among PLWH, evaluated by MOS-HIV SF-30 survey at baseline and 3 years after. Total score [median (interquartile range (IQR))] of MOS-HIV SF-30 at baseline and 3 years after was 82 (71; 89) and 74 (64; 79) in HIV-controllers and 80 (73; 88) and 88 (83; 92) in HIV-treatment-naïve, respectively.

The change (median [IQR]) in total score of MOS-HIV SF-30, evaluated at 3 years score minus baseline score, was −4 (−2.5; −12.5) in HIV-controllers and 6.5 (5.25; 10.75) in HIV-treatment. HIV-controllers perceived a worse quality of life at the end of the study with respect to baseline.

TABLE 4 Ophthalmological parameters at baseline and 3 years after.

	HIV-controllers			HIV-treatment			Non-HIV		
Ophthalmological assessment	**Baseline ($n = 17$)**	**At 3 years ($n = 13$)**	**Difference 3 years – baseline ($n = 13$)**	**Baseline ($n = 11$)**	**At 3 years ($n = 8$)**	**Difference 3 years – baseline ($n = 13$)**	**Baseline ($n = 16$)**	**At 3 years ($n = 14$)**	**Difference 3 years – baseline ($n = 13$)**
Functional									
Visual acuity	0 (0; 0.05)	0 (0; 0.15)	0 (0.0; 0.04)	0 (0; 0.1)	0 (0; 0.02)	0 (0; 0.02)	0 (0; 0.02)	0 (0; 0.08)	0 (−0.15; 0)
Contrast sensitivity	1.50 (1. 1.65)	1.50 (1.35; 1.50)	−0.125 (−0.15; 0)	1.35 (1.35; 1.50)	1.35 (1.35; 1.50)	0 (−0.05; 0)	1.50 (1.50; 1.65)	1.50 (1.38; 1.50)	0 (−0.15; 0)
Chromatic vision	1 (1; 1)	1 (1; 1)	0	1 (1; 1)	1 (1; 1)	0	1 (1; 1)	1 (1; 1)	0
Visual field	−1.95 (−5.28; −0.39)	−1.87 (−6.31; +0.21)	0.12 (−1.45; 0.76)	−1.46 (−1.96; −0.56)	0.36 (−1.7; +0.13)	1.2 (0.63; 1.67)	−1.55 (−2.36; −0.09)	−0.98 (−2; 0.57)	0.29 (−0.05; 0.87)
Structural									
Ganglion cells	73 (69; 76.5)	72 (68; 76)	−2 (−3; −2)	75 (70; 77)	71 (68; 76)	−4 (−5; −1)	72 (70; 77)	70.5 (66.25; 73.75)	−3 (−5.5; −2)
MNFL	36 (33.5; 38.5)	35 (34; 41.5)	−1 (−2; 0)	37 (35; 38)	38 (35; 42)	2 (0; 5)	35.50 (34; 39)	36.5 (35.25; 39)	0 (−1; 1.75)
RNFL									
Superior	121 (116.5; 136.5)	119 (110; 139.5)	−5 (−9; 4)	128 (123; 133)	132 (124; 147)	6 (−2; 10)	122 (108.25; 126.25)	119.5 (108.25; 131)	0 (−5.25; 5.5)
Nasal	92 (83.5; 105.5)	95 (83; 103.5)	0 (−7; 3)	91 (86; 112)	91 (78; 110)	−2 (−9; 4)	92 (80.75; 96.75)	88 (79; 95)	−1 (−7.5; 0)
Temporal	77 (72.5; 82)	75 (72.5; 82)	−2 (−3; 0)	76 (74; 84)	76 (67; 83)	−1 (−3; 0)	73.50 (68.75; 82.50)	72.5 (68.5; 81.25)	0 (−2; 1)
Inferior	135 (120; 140)	130 (115.5; 140)	−3 (−7; −1)	138 (128; 141)	132 (129; 143)	0 (−9; 4)	129 (120.25; 136.75)	129.5 (119.5; 134.5)	0 (−3; 6.25)
Total	106 (102.5–113)	105 (99.5; 110)	−2 (−4; 0)	110 (104; 114)	107 (104; 117)	0 (−3;3)	105 (95.50; 108.25)	104.5 (95.5; 107.75)	0 (−3.25; 1.75)
Vascular calibres									
CRAE	144 (133.5; 167)	146.2 (141.5; 158.1)	−1.07 (−3.63; 3.51)	155.8 (143.7; 186.5)	158 (155.8; 165.8)	10.61 (−0.50; 18.83)	147 (138.7; 180.5)	152.7 (137; 162)	−11.60 (−20.39; 0.36)
CRVE	247 (218.5; 267)	241.6 (225; 259.5)	3.79 (−2.90; 9.13)	251.9 (242; 268.4)	248.5 (227.7; 267)	−1.38 (−18.27; 0)	237.9 (217.5; 250.4)	233.7 (208.9; 247.1)	−13.67 (−18.29; −2.06)
AVR	0.6 (0.55; 0.65)	0.61 (0.58; 0.66)	−0.02 (−0.04; 0.09)	0.65 (0.59; 0.70)	0.68 (0.62; 0.70)	0.045 (−0.004; 0.08)	0.68 (0.57; 0.70)	0.65 (0.60; 0.69)	−0.031 (−0.047; 0.007)

Note: Chromatic vision = 1 means normal. All values are expressed as medians (interquartile ranges).

Abbreviations: AVR, arteriole-to-venule ratio; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; MNFL, macular nerve fibre layer; RNFL, retinal nerve fibre layers at optic nerve.

TABLE 5 Quality of life assessed by Medical Outcomes Study-HIV Short Form-30 in people living with HIV at baseline and 3 years after.

	HIV-controllers		HIV-treatment	
MOS-HIV SF-30	**Baseline ($n = 17$)**	**At 3 years ($n = 13$)**	**Baseline ($n = 11$)**	**At 3 years ($n = 8$)**
Summary scores				
Health summary score	82 (71; 89)	74 (63.5; 79.25)	80 (73; 88)	88 (83; 92)
General health perception	1 (1; 2)	1 (1; 1)	1 (1; 2)	2 (1; 2)
Physical functioning	8 (8; 8)	8 (8; 8)	8 (8; 8)	8 (8; 8)
Role functioning	12 (8.5; 12)	11 (8.25; 12)	12 (10.5; 12)	12 (11; 12)
Social functioning	4 (3.5; 4)	3 (3; 4)	4 (3.5; 4)	4 (4; 4)
Cognitive functioning	13 (13; 15.5)	13 (11; 13.75)	15 (10.5; 16)	16 (14; 16)
Pain	1 (0.5; 2)	1 (0.25; 1)	1 (1; 2)	2 (1; 2)
Mental health	13 (10; 14.5)	11.5 (9.5; 14.5)	13 (11; 1 4)	14 (13; 17)
Energy/fatigue	10 (7.5; 11.5)	9 (5; 10)	10 (9.5; 11)	11 (9; 12)
Health distress	15 (14; 16)	12 (8.25; 13.75)	15 (11.5; 15)	16 (14; 16)
QoL	2 (2; 3)	2 (2; 3)	3 (2; 4)	3 (2; 4)

Note: All values are expressed as medians (interquartile ranges).
Abbreviations: MOS-HIV SF-30, Medical Outcomes Study-HIV Short Form-30; QoL, quality of life.

DISCUSSION

To the best of our knowledge, this is likely the first study to provide evidence on NRD among ECs and LTNPs. HIV itself, immune activation response and ART, could play a role in the pathophysiology of NRD in PLWH [1]. Likewise, NRD has been correlated with more severe or advanced HIV disease [26]; however, little is known about the pathophysiology of the NRD in HIV-controllers. HIV-controllers have spontaneous control of viral replication without receiving ART. Therefore, they are the target population for understanding the effects of HIV virus and/or of HIV infection on the human immune response on the neuro-retina. Although none of our PLWH subjects complained of ocular manifestations, NRD were detected in the functional and/or structural ophthalmological evaluations both in the baseline examination and throughout the study. The greatest percentage of participants with worsening of their ophthalmological evaluations was in the HIV-controllers group. HIV-controllers had a worse QoL during the final follow-up visits; and non-HIV patients had a non-negligible prevalence of NRD, specifically in the thickness decrease of the ganglion cells layer and MNFL with age and to a lesser degree with the peripapillary fibres as described by other authors [27, 28].

Regarding functional ophthalmologic alterations, HIV-controllers had a pathological VF (MD) at baseline and during the follow-up. These findings could be related to the chronicity of inflammation in PLWH [29]. HIV-treatment patients had the worst CS at baseline and at the 3-year follow-up. These patients presented lower CD4 cells counts at baseline. Similar results have previously been reported [28].

Regarding structural ophthalmologic alterations, HIV-controllers presented a thinning of the MNFL as a sign of chronicity. The MNFL in HIV-treatment patients presented an increase in thickness [30] even at 3 years. These patients also had a low CS since baseline. Likewise, they had a recent HIV diagnosis with CD4 < 500 cell counts (54.4% of the patients) and had started ART.

In both groups of PLWH we found a trend to have superior RNFL thickening at baseline (regardless of CD4 cell count) [3, 18, 27, 31, 32]. Nevertheless, we have not found a reason that justifies these findings. However, 3 years after baseline, a slight reduction in this thickness in HIV-controllers was discovered, while it increased in the HIV-treatment group. Likewise, both PLWH populations showed a tendency for the peripapillary temporal RNFL thickness to decrease but without reaching atrophy. In fact, the peripapillary RNFL thickness was related to the length of time since contracting HIV [26], with a decrease in CD4 cell count [18, 27, 31, 32] and with increasing age [3, 33, 34]. These findings were mainly a tendency in the initial stages of HIV infection for fibres such as axons to become swollen, due to the mitochondria being compromised by toxicity mediated either by HIV or ART, before becoming atrophic [27]. Conversely, it has been suggested that increased levels of HIV viremia may initiate a para-inflammatory process in the retina [29].

The decrease in the thickness of the temporal peripapillary RNFL in PLWH compared with non-HIV was predominantly found in the HIV-treatment group. These PLWH also presented a low CS related to the use of ART, as has previously been described [29, 31, 34]. A 47% decrease in the thickness of the peripapillary RNFL has been reported in young PLWH taking ART [18], this being 75% at the expense of the temporal fibres and correlated with low CS [18, 27], which is in line with our results. Likewise, a weak correlation with CD4 count [35] occurred with temporal RNFL decrease [18]. In contrast, other authors did not describe thinning in either the MNFL or the peripapillary RNFL in HIV-controllers (aviremic patients) [36], only in the patients who had associated cerebral small-vessel diseases (CSVD), and who had thinner RNFL, MNFL and ganglion cells layer, independent of HIV status. CSVD did not occur in our study.

Although the pathophysiology of NRD is largely unknown, some authors have established a potential mechanism in the decrease in peripapillary RNFL and retinal MNFL in the temporal area, due to the low volume-surface area of the axons there and possibly associated with mitochondrial dysfunction [18].

In line with other authors [37], we found that HIV-controllers with only a small AVR had a worse MD in VF. This finding could be explained by the role of systemic inflammation in the chronic status of HIV patients as a response to tissue stress and microvascular damage, which leads to atherosclerosis and accelerated aging [10, 37, 38]. In contrast to other authors, we did not find that the patients with an altered AVR had low CD4 cell counts [39, 40].

The retina is a complex, layered structure composed of three types of cells: pigmented cells (metabolism of photoreceptors), neurons and support cells, which could be a good source of information about aging. Currently there are no available scientific data on aging and its impact on NRD among HIV-controllers. Inflammation and immune activation in HIV-controllers may also be a warning of unfavourable long-term ocular outcomes in these patients, who currently have a life expectancy equivalent to that of people without HIV. As mentioned earlier, none of our HIV patients complained of ocular manifestations during the study, but it is important to highlight that signs of ocular premature aging were detected. Therefore, our results suggest that we can consider the retina a latent HIV reservoir even among the HIV elite-controller patients. In the same way, the brain is considered to be a latent HIV reservoir in EC in a recently published study, which investigates neuroinflammation in this subgroup of PLWH [41]. Hence, we recommend that mainly the OCT and CS should be included in routine ophthalmological testing in PLWH as helpful future ocular biomarkers of HIV infection and immune status, especially in those individuals not using ART such as ECs and LTNPs. Beyond this, ophthalmologic assessments may be useful for controlling ART side effects on the retina.

HIV-controllers presented a general deterioration of QoL, with a worse perception of health in general, even though they had not manifested ocular clinical symptoms during the study. This result could also be explained by HIV chronicity status and persistent inflammation [25, 26]. However, the QoL of HIV-treatment patients, unlike HIV-controllers, improved in 3 years. This result could be related to the acceptance of being a PLWH [25, 26].

This study may have some limitations. The small sample size could overestimate or underestimate the results. It is worth noting that the prevalence of HIV-controllers is between 0.2% and 0.5% of the HIV population [14], and that this study included all the HIV-controllers associated with our HIV Unit. Likewise, the lack of consensus on NRD definition is challenging. A single-centre study could also be a drawback as regards the generalization of any results. However, it is important to highlight some of our study's strengths, namely that it was performed in the total available population of HIV-controllers from an HIV reference tertiary university hospital for PLWH; the structured follow-up; the ophthalmologic assessments based on hard endpoints (structural parameters based on OCT); and the adoption of non-restrictive inclusion criteria. While more studies are required to support our findings, currently patients infected with HIV must commence ART at the time of diagnosis [42]. Therefore, this study could not have been carried out today for this reason. But we must not forget that the time lapse between becoming infected with HIV and it being diagnosed can be highly variable.

In fact, a significant percentage of PLWH are not diagnosed until sometime later after becoming infected. For these patients, our data are vital for understanding the impact of the virus on eye health and offering valuable information for managing not only the virus itself but also its broader health implications. In summary, our study provides knowledge about ophthalmological damage caused by the HIV virus and/or immune status; and this is its value, namely having information about the natural history of NRD in patients infected with HIV who are not receiving ART.

CONCLUSIONS

In conclusion, although HIV-controllers and those on HIV-treatment were clinically asymptomatic, they had a

higher percentage of NRD than non-HIV-participants. HIV-controllers had a worse QoL. NRD could be considered as representing a more advanced HIV status, premature ocular aging, and the retina as a possible latent HIV reservoir within elite-controllers. For all these reasons, we recommend that an ophthalmologic assessment should include an OCT for early detection of incipient retinal changes, and CS should be included as a routine evaluation within HIV units, and early ART is recommended also for LTNP, whatever the levels of viral load. In addition, it is worthy of debate as to whether HIV-controllers should initiate ART to avoid NRD.

AUTHOR CONTRIBUTORS

SR-B, EN and JC-M conceived and contributed to the study design. SR-B, SV and J.C-M drafted the manuscript. SV assisted in the study methodology. SR-B, EP, MS, JP, SG and JC-M assisted in the selection of subjects and were involved in critically revising the manuscript for important intellectual content. All authors revised and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

All authors have no conflicts of interests.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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