HIV-Associated Neuroretinal Disorder in Patients With Well-Suppressed HIV-Infection: A Comparative Cohort Study

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See the Appendix for the members of the AGE_hIV Cohort Study Group.

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Purpose. Loss of neuroretinal structure and function, ascribed to a 'HIV-associated Neuroretinal Disorder' (HIV-NRD), in the absence of ocular opportunistic infections, has been reported in HIV-infected individuals treated with combination antiretroviral therapy (cART). Whether HIV-infected individuals with prolonged well-suppressed infection remain at risk for HIV-NRD, is unknown.

Methods. Ninety-two HIV-infected men with suppressed viremia on cART for at least 12 months (HIV+) and 63 HIV-uninfected, highly comparable, male controls (HIV−), aged at least 45 years, underwent functional measurements of spatial (Pelli Robson contrast sensitivity [PR CS]) and temporal contrast sensitivity (TCS) and straylight, as well as spectral-domain optical coherence tomography analysis measured total and individual retinal layer thickness. Mixed-linear regression models were used to assess possible associations between HIV-related and ocular parameters, while accounting for several confounders.

Results. Pelli Robson CS was significantly lower in HIV+ (1.89 vs. 1.93 logCS, P value = 0.001), while TCS values did not differ (2.17 vs. 2.17 logCS; P value = 0.888). Straylight values were higher in HIV+ (1.15 vs. 1.09 log units; P value = 0.026). Peripheral total retinal thickness in the HIV+ group was increased compared with HIV− (+4.6 μm, P value = 0.029), predominantly due to an increase in inner nuclear layer (+1.04 μm, P value = 0.006) and outer plexiform layer (+0.95 μm, P value = 0.006) thickness.

Conclusions. Pelli Robson CS was significantly reduced in HIV-infected individuals, although the loss was one letter and likely not clinically relevant. Instead of an expected neuroretinal thinning, an increase of retinal thickness was detected in the HIV-infected group. These findings should be confirmed and further explored in longitudinal studies. Clinical Trial registered at www.clinicaltrials.gov (identifier: NCT01466582).

Keywords: HIV-NRD, Pelli Robson contrast sensitivity, temporal contrast sensitivity, straylight, optical coherence tomography, retinal layer thickness

The spectrum of HIV-related retinal disease has changed drastically since the introduction of combination antiretroviral therapy (cART), with a major decline in incidence of both opportunistic infections, such as cytomegalovirus (CMV) retinitis, and noninfectious ischemic HIV retinopathy. However, even in cART-treated individuals without ocular opportunistic infections or visible fundus abnormalities, functional and structural retinal changes have been reported, such as a subtle loss of color vision and/or contrast sensitivity,[1–3] visual field deficits,[4–6] and a thinner peripapillary retinal nerve fiber layer (RNFL) thickness.[7–9] These changes are ascribed to a 'HIV-associated Neuroretinal Disorder' (HIV-NRD), and may be mediated by several processes, such as a long-standing microvasculopathy,[10–14] direct damage of neural tissue by HIV and/or

cART,[15–17] or chronic inflammation.[18] HIV-NRD is part of a spectrum of abnormalities in HIV patients considered by some to potentially represent accelerated biological aging associated with HIV infection.[19,20]

The disorder (defined by many studies as having a Pelli Robson contrast sensitivity < 1.5 logCS[21]) is more common among HIV patients with (prior) severe immune-deficiency, with a prevalence reportedly between 3% and 16% and an estimated cumulative incidence at 20 years after AIDS diagnosis as high as 51%.[22] A recent study found that AIDS patients with HIV-NRD have considerably increased risks of bilateral visual impairment and even blindness in the long term versus those without HIV-NRD.[22]

At present however, with the widespread availability of cART, an increasing number of HIV patients will likely never develop AIDS and fewer patients are likely to remain severely immune-deficient for prolonged periods of time. Against this background, whether patients in the current era of cART still remain at risk for HIV-associated neuroretinal degeneration is an outstanding question.

The purpose of the present study was to assess the prevalence and risk factors of retinal structural and functional loss by means of spatial and temporal contrast sensitivity and total and individual retinal layer thickness measurements using spectral domain-optical coherence tomography (SD-OCT) analysis, comparing HIV-infected men with prolonged suppressed viremia on cART with highly comparable HIV-uninfected men, all 45 years or older.

Methods

Study Design and Participants: The AGE_hIV Cohort Study and Neuroretinal Substudy

The AGE_hIV Cohort Study is a prospective comparative cohort study investigating prevalence, incidence, and risk factors of aging-associated comorbidities and organ dysfunction among HIV-1 infected individuals and highly comparable HIV-uninfected controls. Inclusion criteria are 45 years or older and laboratory-confirmed presence, in HIV infected individuals, or absence of HIV-1 infection in the HIV uninfected controls.

HIV-1–infected participants were recruited at the HIV outpatient clinic of the Academic Medical Center in Amsterdam, The Netherlands, and HIV-uninfected controls from the ongoing Amsterdam Cohort Studies on HIV/AIDS and among persons attending the sexual health clinic of the Public Health Service of Amsterdam (details concerning AGE_hIV Cohort Study have been described in a previous publication).[23]

All eligible participants from the AGE_hIV Cohort were consecutively invited to participate in a nested neuroretinal substudy,[24] assessing the presence of HIV-associated cognitive impairment and subtle brain and eye alterations in patients with well-suppressed HIV infection. Enrollment began in December 2011. Additional eligibility criteria for the substudy were male (as the availability of Dutch-speaking women in the main AGE_hIV Cohort was very limited), and for the HIV-infected group: sustained suppression of HIV viremia on antiretroviral treatment (plasma HIV-RNA < 40 copies/mL) for greater than or equal to 12 months; the presence of so-called viral 'blips' (transient low-level viremia) was not an exclusion-criterion.

Exclusion criteria for the substudy were a history of severe neurologic disorder (e.g., stroke, seizure disorders, multiple sclerosis, dementia [including previous or current diagnosis of HIV-associated dementia (HAD)]), history of traumatic brain injury with loss of consciousness greater than 30 minutes, current/past (HIV-1–associated) central nervous system infection or tumor, current severe psychiatric disorder (e.g., psychosis, major depression), current injecting drug use, daily use of noninjecting recreational drugs (with the exception of daily cannabis use), current excessive alcohol consumption (>48 units of alcohol/week), and/or insufficient command of the Dutch language or mental retardation.

Additional ophthalmic exclusion criteria were high refractive errors (SE $> +5.5$ or > -8.5 diopters [D]), visual acuity below 0.2 logMAR, IOP higher than 22 mm Hg, significant media opacities, and (a history of) ocular opportunistic infections, uveitis, or other retinal disease. Amblyopic eyes were excluded, and we did not use straylight and Pelli Robson data of eyes that did previously have refractive or cataract surgery.[25,26] A total of 103 HIV-infected and 74 HIV-uninfected participants were enrolled into the AGE_hIV neuroretinal substudy; of those individuals, 92 patients and 63 controls were included in the ophthalmic part of the study. The other participants were excluded for varying reasons, including having glaucoma, staphyloma (cataract preventing a reliable OCT examination), toxoplasmosis scars, retinal detachment, and pseudovitelliform macular degeneration.

Standard Protocol Approval, Registration, and Patient Consent

The protocol of the AGE_hIV Cohort Study and the protocol of the substudy were approved by the local ethics committee. Written informed consent was obtained from all participants, separately for the main study and substudy.

Demographic, Clinical, and Laboratory Data Collection

Participants were asked to complete a questionnaire evaluating demographics, (family) medical history, use of medication, substance use, and sexual (risk) behavior. Blood samples were collected for extensive laboratory testing. Markers of inflammation (high-sensitivity C-reactive protein [hsCRP], coagulation [D-dimer]), microbial translocation (soluble CD14 [sCD14]), and monocyte activation (soluble CD163 [sCD163]) were determined for all study participants. Plasma HIV-1 RNA levels were determined in the HIV-infected participants. Detailed information concerning HIV infection and antiretroviral therapy (ART) history was extracted from the Dutch HIV Monitoring Foundation database.[27]

Frailty Assessment

Frailty is increasingly been recognized as a common and important HIV-associated non-AIDS condition.[28] A previous study reported a significant association between positive frailty status and abnormal Pelli Robson CS^2. We estimated the prevalence of (pre)frailty in our study population and examined possible associations with ocular parameters, indicative of neuroretinal degeneration.

The Fried frailty phenotype, as modified by Önen, was assessed in all participants in a standardized manner.[29,30] Presence of at least three of the following five criteria was defined as frailty, presence of one or two was defined as prefrailty and absence of all five factors was considered robust: (1) self-reported unintentional weight loss, (2) low physical activity, (3) exhaustion, (4) weak grip strength, (5) and slow walking time.

AGE Reader

Enhanced accumulation of Advanced Glycation Endproducts (AGE) is associated with a number of (age-related) chronic

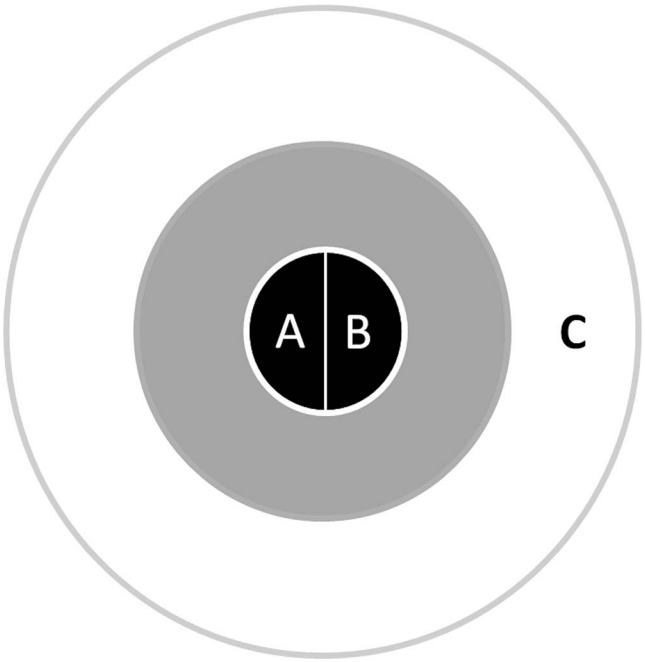

FIGURE 1. Stimulus layout for straylight and temporal contrast sensitivity measurements with the C-Quant device. The stimulus consists of a circular test area, radius 1.6°, divided in two halves (**A**, **B**), surrounded by a ring-shaped light (**C**) that flickers as the glare source, during the straylight measurement and illuminates constantly during the temporal contrast sensitivity test.

diseases, and has also been implicated in retinal aging and disease.[31] In our study, we assessed whether higher skin AGE levels were associated with retinal parameters of aging/neurodegeneration. AGE levels were noninvasively measured by autofluorescence using the AGE Reader (Diagnoptics Technologies B.V., Groningen, The Netherlands). This device uses characteristic fluorescent properties of certain AGE to estimate skin AGE-accumulation. This method has been validated and strongly correlates with AGE-accumulation measured in skin biopsies.[32,33]

Ophthalmic Examination

Visual acuity was measured using a modified Early Treatment Diabetic Retinopathy Study (ETDRS) chart with Sloan letters (Lighthouse, NY, USA) at 4 m. Visual acuity (VA) was recorded in logMar units. Intraocular pressure was measured by air-puff tonometry (computerized tonometer, CT80; Topcon Medical Systems, Inc., Oakland, NJ, USA). All subjects underwent pupil dilation (0.5% Tropicamide and 5% Phenylephrine) and a standard ophthalmic examination, including slit-lamp biomicroscopy with a handheld lens, as well as fundus photography.

Straylight Measurement (C-Quant)

Intraocular straylight was measured with the C-Quant straylight meter (Oculus GmbH, Germany), according to the manufacturer's instructions.[34] The measurement is based on the compensation comparison method and has proven to give reliable and objective measurements of intraocular straylight. Briefly, the test field consisted of a dark circle divided into two halves (left and right), surrounded by a ring-shaped flickering light, which served as the glare source (Fig. 1). Light emitted from the ring was scattered in the eye, resulting in the perception that the test field was flickering. A counter phase compensation light was then presented in one of the semicircles. The participants had to choose the side that flickered more intensely.

Temporal Contrast (Flicker) Sensitivity (C-Quant)

Temporal contrast sensitivity (TCS) was measured with the same C-Quant device, using custom written software (Matlab; Mathworks, Natick, MA, USA). Testing procedures were similar to those for straylight measurement, but with a ring of constant luminance- instead of a flickering ring- surrounding the semicircles (Fig. 1). Randomly in one-half, flicker was presented and the subject had to decide which half was flickering. The method is described more in detail in a previous report.[35]

Both straylight and TCS were measured twice per eye and the mean of the two measurements per eye was used for statistical analysis.

Pelli Robson Contrast Sensitivity

Spatial contrast sensitivity was determined using Pelli Robson contrast sensitivity charts (Haag-Streit, Essex, UK) at a distance of 1 m with chart background luminance within the range recommended by the manufacturer (60–120 cd/m^2). The logCS score was calculated as the total number of letters read correctly minus 3, then multiplied by 0.05.[36] Our protocol does not permit confusion between "C" and "O," which is consistent with the technique described by Myers and associates.[36] A different chart was used per eye.

SD-OCT and Retinal Layer Segmentation

Optical coherence tomography images of the subjects were obtained with SD-OCT (Topcon 3D OCT-1000; Topcon Inc., Paramus, NJ, USA) using the three-dimensional (3D) macular and disc volume scan protocols. From each 3D macular volume, individual retinal layers were segmented automatically by the publicly available and extensively validated Iowa Reference Algorithm.[37,38] The Iowa Reference Algorithm[37,38] allows for the calculation of the thickness of all individual retinal layers (Fig. 2A) for each of the nine ETDRS-grid defined regions. We selected on the foveal, pericentral, and peripheral ETDRS rings (Figs. 2B–E), as we have done in previous studies.[39–42]

In addition, peripapillary RNFL thickness measurements (average and quadrantal) were acquired from the 3D optic nerve head OCT's using the same Iowa Reference Algorithm.[37,38] The peripapillary ring was centered manually with the center of the ring coinciding with the center of the optic disc.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics software version 21 and SAS software version 9.3 (Cary, NC, USA). Demographic/clinical characteristics were compared between the two groups using the Student's *t*-test, the Mann-Whitney *U* test, or the χ^2 test, as appropriate. Mixed-linear regression models with a compound symmetry covariance structure were used to explore associations between HIV-status and ocular variables in all study participants, while taking the correlation between both eyes of an individual into account. All models were adjusted for age (as well as spherical equivalent and OCT Quality Factor in the OCT analyses).

Subsequently, within the HIV-positive group, we investigated potential associations between visual function/OCT parameters and (1) HIV/cART-related factors (prior AIDS diagnosis, nadir CD4 counts [$\leq$ and $\geq$ 100 cells/μl], mean CD4 and CD8

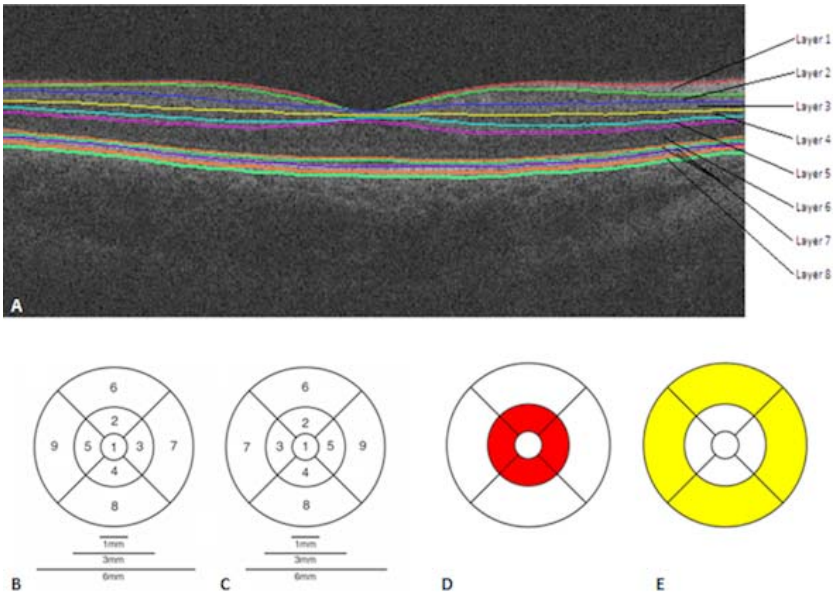

FIGURE 2. (**A**) Macular SD-OCT B-scan with intraretinal surfaces as indicated by the *colored lines* and segmented using the Iowa Reference Algorithm.[37,38] In this study, the highly reflective layer between inner and outer segments, and the outer segments up to the retinal pigment layer were taken together as one layer, the outer segment layer (OSL), ignoring the line ascribed to the cone outer segments.[48] Corresponding retinal layers: (1) RNFL, (2) ganglion cell layer, (3) inner plexiform layer, (4) inner nuclear layer, (5) outer plexiform layer, (6) outer nuclear layer + inner segments (photoreceptors), (7) outer segments (photoreceptors), and (8) retinal pigment epithelium. (**B**–**E**) Early Treatment Diabetic Retinopathy Study grid. Nine subfields of the nine ETDRS regions in each eye. (**B**) Right eye. (**C**) Left eye. For each retinal layer, three areas were defined using this ETDRS grid: the fovea, the central circle with a diameter of 1 mm (depicted as 1 in Figs. 1B, 1C); the pericentral ring, a donut-shaped ring centered on the fovea with an inner diameter of 1 mm and an outer diameter of 3 mm (Fig. 1D); and the peripheral ring, with an inner diameter of 3 mm and outer diameter of 6 mm (Fig. 1E). Thickness measurements of the pericentral and peripheral rings were estimated by averaging the thickness measurements of the four corresponding quadrant areas (segments 2–5 for the pericentral ring and segments 6–9 for the peripheral ring).

counts during the year prior to study enrollment, mean $\log^{10}$ plasma HIV-1 RNA load in 12 months prior to enrollment and before start of ART, the years since start first ART) and (2) other (risk) factors possibly involved in the pathophysiology of HIV-NRD (including markers of inflammation and innate immune activation, frailty status, and AGE-reader measurement). With respect to OCT parameters, we focused in particular on the retinal layers known to change with increasing age[40] (to test the hypothesis of accelerated/accentuated aging in HIV) as well as the inner retinal layers (to assess possible neuroretinal degeneration[42]) instead of exploring all individual layers, to reduce the chance of type I errors. Because of the exploratory nature of this study and established a priori hypotheses, adjustment for multiple comparisons was not performed. Statistical significance was set at a two-sided *P* value of 0.05.

RESULTS

Subject Characteristics

Table 1 shows the baseline characteristics of all study participants; the two groups were comparable in terms of age, nationality, sexual orientation, comorbidities, and frailty status. However, HIV-infected individuals had higher plasma levels of inflammation markers as well as a higher AGE-reader measurement and were more likely to be ever-smokers, whereas ecstasy use was more prevalent among controls. On average, HIV-infected individuals were known to be infected for a prolonged period of time and approximately 32% had previously been diagnosed with AIDS. Most men used cART for many years, 99% had an undetectable viral load and the majority had experienced immune recovery on treatment, with a median nadir CD4 count of 180 cells/μL and current median CD4 count of 595 cells/μl.

Contrast Sensitivity and Straylight Measurements

Pelli Robson contrast sensitivity was significantly lower in the HIV-infected group, although the difference was only one letter (1.89 vs. 1.93 logCS, *P* value = 0.001), while temporal contrast sensitivity values did not differ significantly among the two groups (2.17 vs. 2.17 logCS; *P* value = 0.888). Straylight values were slightly higher among the HIV-infected individuals (1.15 vs. 1.09 log units; *P* value = 0.026; Table 2). Of the HIV-infected patients, only one patient (1.3%) had a PR contrast sensitivity below 1.5 and six patients (7.7%) had a PR contrast sensitivity below 1.65 logCS (these cut-off values were used by previous studies to denote 'poor CS'[1–3]), respectively, while none of the HIV-uninfected participants had PR scores below 1.7 logCS.

Thickness of Retinal Layers

Mean layer thickness measurements (individual retinal layers, peripapillary RNFL, and total retinal thickness) adjusted for age, OCT quality factor, and spherical equivalent for patients and controls are shown in Table 3. The two groups had comparable retinal thicknesses regarding most layers; the most notable difference was a significantly increased total peripheral retinal thickness in the HIV-infected group (+4.6 μm, *P* value = 0.029), predominantly due to an increase in inner nuclear layer (+1.04 μm, *P* value = 0.006), and outer plexiform layer (+0.95 μm, *P* value = 0.006) thickness. Peripapillary RNFL thickness was not significantly different among the two groups.

Multivariable Analyses Within the HIV-Infected Group

Exploring potential risk factors of retinal structural and functional changes within the HIV-infected group, we did not

Table 1. Participant Characteristics

Sociodemographic Characteristics	HIV-Infected Participants ($n = 92$)	HIV-Uninfected Participants ($n = 63$)	*P* Value
Age (y)	53.5 (45–76)	52 (45–80)	0.940*
Male sex	100%	100%	–
Nationality, Dutch	88%	85%	0.587†
MSM	94.5%	88%	0.164†
Smoking			
Current	28.2%	16.7%	0.100†
Ever smoked	76.1%	56.7%	**0.012**†
Pack of smoking, y	20.3 (0.2–90)	9 (0–74.3)	**0.013***
Heavy daily drinker	5.4%	8.3%	0.517‡
Recreational drug use, d–mo			
Cannabis	15.2%	15.0%	1.000‡
Cocaine	3.3%	5%	0.681‡
XTC	2.2%	13.3%	**0.014**‡
Comorbidities			
DM type II; (using medication)	2.2% (0)	0 (0)	0.517‡
Hypertension; (using medication)	29.3% (63.0%)	29.5% (44.4%)	0.983[b]
HIV- and cART-related characteristics			
Years known to be HIV positive	14.5 (1–27)	–	–
Prior clinical AIDS	32.6%	–	–
CD4 cell count, cells/μl			
Current	595 (320–1110)	–	–
In year prior to enrollment	620.8 (216–1130)	–	–
Nadir	180 (0–620)	–	–
Cumulative duration of CD4 cell count			–
< 200 cells/μL; mo	0.78 (0–96.8)	–	–
< 100 cells/μl; mo	0 (0–66.5)	–	–
CD8 cell count, cells/μl			
Current	860 (190–1620)	–	–
In year prior to enrollment	890 (162–1992)	–	–
CD4/8 ratio	0.75 (0.29–4.13)	–	–
Plasma viral load			
Prior start ART	4.9 (3.4–6.7)		
Current	1.6 (1.6–1.94)	–	–
In year prior to enrollment	1.6 (1.6–2.73)	–	–
Undetectable during year before enrollment	98.9%	–	–
Cumulative duration of undetectability; y	10.2 (0–15.1)	–	–
Years since start of first ART	12 (1–21)	–	–
Naïve at start of first cART	81.5%	–	–
ART naïve at enrollment	0%	–	–
Markers of systemic inflammation			
High sensitivity C-reactive protein (CRP), mg/L	1.5 (0–60.4)	0.9 (0.3–8.3)	**0.011***
D-dimer, mg/L	0.2 (0.2–1.59)	0.27 (0.2–2.3)	0.061*
Soluble CD14, ng/mL	1565 (726–3886)	1200 (569–3316)	**<0.001***
Soluble CD163, ng/mL	268 (81–1146)	250 (111–783)	0.307*
Frailty status (presence of 0–5 criteria)			
Not frail (0)	68.5%	70%	0.203†
Prefrail (1–2)	29.3%	30%	
Frail (≥3)	2.2%	0%	
AGE-reader measurement, AU	2.3 (0–4.7)	2 (1.5–2.7)	**<0.001***
AGE-reader measurement higher compared with reference value (> +1SD)	20%	1.7%	0.001‡

Data are presented as median (range) or percentage. *n*, number of patients.
* Mann–Whitney *U* test.
† χ^2 test.
‡ Fisher's exact test.

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Table 2. Visual Function Test Results in HIV Patients and Controls

Ocular Parameters/Visual Function	HIV-Infected Participants, $n = 92$				HIV-Uninfected Participants, $n = 63$					P
	Eyes	Mean	SD	Range	Eyes	Mean	SD	Range	Coefficient	Value
Spherical equivalent refraction, D	161	−0.6	2.2	−7.5 to 4.8	111	−1.4	2.2	−8.0 to 3.5	0.721	**0.046**
IOP, mm Hg	161	14.4	2.7	7 to 21	111	13.8	3.2	7 to 22	0.546	0.250
Visual acuity, logMar	161	−0.01	0.08	−0.2 to 0.2	111	−0.03	0.07	−0.2 to 0.18	0.016	0.160
Pelli Robson CS; logCS	155	1.89	0.10	1.45 to 2.05	113	1.93	0.04	1.70 to 2.05	−0.040	**0.001**
Temporal CS; logCS	172	2.17	0.17	1.55 to 2.50	121	2.17	0.17	1.73 to 2.52	−0.004	0.888
Straylight; log units	161	1.15	0.19	0.75 to 1.79	113	1.09	0.16	0.79 to 1.64	0.060	**0.026**

P values derived from linear mixed-models; adjusted for age at assessment. *P* values in bold are $P < 0.05$. CS, contrast sensitivity.

detect significant associations between indicators of (past) HIV disease severity (nadir or current CD4 counts, CD8 counts, prior AIDS diagnosis, and pre-ART plasma VL) and any of the visual function/OCT parameters tested.

We did observe significant associations between other explanatory variables and retinal measures: central outer segment layer thickness was negatively associated with ART duration (–0.141 μm/year; *P* value: 0.048) and positively associated with soluble CD163 levels (+0.63 microns per 100 ng/mL, *P* value: 0.009). Central retinal pigment epithelium thickness was positively associated with prefrailty (+1.075 μm; *P* value 0.012) and peripheral ganglion cell layer thickness was negatively associated with a higher AGE-reader measurement (–1.28 μm/AU, *P* value 0.012).

Discussion

In this study assessing HIV-related neuroretinal degeneration, we found only minimal changes in contrast sensitivity and no decrease in (neuro)retinal and peripapillary RNFL thickness when comparing HIV-infected men with prolonged suppressed viremia on cART to a highly similar group of HIV-negative men, all aged 45 years or above.

HIV-infected patients scored only one letter less on the Pelli Robson (PR) contrast sensitivity chart, while having comparable temporal contrast sensitivity outcomes. Two recent comparable studies on contrast sensitivity and RNFL thickness in cART-treated HIV-infected patients without opportunistic ocular infections, reported similar subtle differences in PR contrast sensitivity between HIV-infected individuals and HIV-negative controls: Kalyani et al.[1] measured a median PR score of 1.90 logCS in a group of 57 HIV-infected individuals (89% with a prior diagnosis of AIDS), with only 2.9% of eyes having abnormal contrast sensitivity (<1.5 logCS; based on CS values of a control group described by Myers et al.[36]). Pathai et al.[2] reported a mean difference of 0.06 logCS (~1 letter) between a group of 225 HIV-infected subjects (72% with WHO stage III/IV HIV) and 203 HIV-negative controls, while the percentage of subjects with 'poor' CS (<1.65 logCS) was 43.5% in the HIV-infected group and 31.8% in the control group. Pathai[2] also detected an association between poor CS and positive frailty status and HIV viral load greater than 2 log copies/ml.

In our study, only one (1.3%) and six patients (7.7%) had a PR contrast sensitivity of 1.5 and 1.65 logCS, respectively. We couldn't confirm the findings of Pathai[2] and did not find an association between PR contrast sensitivity and either frailty status nor HIV viral load. However, compared with the previous two studies, our HIV-infected cohort has a better immunologic and clinical status, with only 33% having been previously diagnosed with AIDS and 99% having had undetectable viremia, and were treated for many years. These differences could explain the better contrast sensitivity outcomes of our patients and the lack of correlation detected between frailty status and contrast sensitivity.

In addition to measuring spatial contrast sensitivity, we also assessed temporal contrast sensitivity (TCS), using an adaptation of the C-Quant, and we found no significant differences between patients and controls. Because we are the first group evaluating TCS in HIV-infected patients in the cART era, we cannot compare our results with other studies. The discrepancy in PR CS scores and TCS values in the present study might be ascribed to the fact that PR outcome is influenced by both optical and retinal components, while TCS assesses purely retinal function,[35] although PR CS remained significantly lower in the patient group, after adjusting for straylight in the statistical analysis (data not shown). However, straylight is known to influence spatial CS only very weakly[43] and while we did not test PR CS of participants with a history of refractive/cataract surgery, other optical factors, such as higher order aberrations, might have affected the PR outcomes.

We did not find any significant differences in peripapillary RNFL thickness between HIV-infected individuals and HIV-negative controls. This is largely in accordance with the findings of Kalyani et al.[1] and Pathai et al.[2] reported a similar average RNFL thickness between patients and controls, while only 8.8% of the HIV-infected group examined by Kalyani et al.[1] had a thinner RNFL than average. Other studies assessing peripapillary RNFL thickness in HIV-infected patients, reported a decrease in RNFL thickness particularly in patients with low (<100 cells/μL) nadir CD4 counts for at least 6 months, compared with patients with nadir CD4 counts higher than 100 cells/μL and HIV-uninfected controls.[5,7,8] In our HIV-infected group, 30% had nadir CD4 counts less than 100 cells/μL, for a short mean cumulative duration of 0.2 years, and no associations between (duration of) nadir CD4 counts and peripapillary RNFL thickness were detected.

Subsequently, we segmented and analyzed total and individual retinal layer thickness in the central, pericentral, and peripheral ETDRS areas, using the extensively validated Iowa Reference Algorithm. As it is hypothesized that damage (caused by HIV and/or other factors) to the optic nerve leads to thinning of the peripapillary RNFL in HIV, a decrease in ganglion cell layer thickness (and possibly other inner retinal layers) would also be expected, considering that the axons of the ganglion cell layer make up the optic nerve for a large part. Parallel to the peripapillary RNFL thickness in our study population however, we did not detect thinner inner retinal layers in the HIV-infected group versus the controls. In addition, the retinal layers known to change with increasing age,[40] were not significantly thinner in the HIV-infected individuals, providing no support for the hypothesis of accelerated retinal aging in HIV. We also did not find an association of retinal thickness with monocyte activation markers sCD14/sCD163 in the HIV-infected group, which are considered to be implicated in HIV-related neurodegeneration and neurocognitive deficits.[44]

Table 3. OCT Retinal Layer Thicknesses in HIV Patients and Controls

	HIV-Infected Participants, $n = 92$				HIV-Uninfected Participants, $n = 63$					
Macular Layer Thickness, µm	**Eyes**	**Mean**	**SD**	**Range**	**Eyes**	**Mean**	**SD**	**Range**	**Coefficient**	***P* Value**
RNFL										
Fovea	167	8.08	3.2	1.6–19.6	120	7.8	3.1	2.3–18.5	0.646	0.215
Pericentral ring	167	24.4	2.3	18.3–32.2	120	24.4	2.1	19.7–28.9	0.310	0.374
Peripheral ring	167	36.6	4.7	26.3–53.6	120	36.1	3.9	26.8–48.1	1.045	0.135
GCL										
Fovea	167	12.8	5.4	1.9–29.9	120	12.4	5.6	3.7–35.2	0.615	0.503
Pericentral ring	167	48.3	6.7	27.9–65.3	120	47.3	7.4	24.2–63.2	1.222	0.301
Peripheral ring	167	28.0	3.3	19.2–36.7	120	26.9	4.0	17.6–34.8	0.792	0.193
IPL										
Fovea	167	30.6	5.3	16.2–46.2	120	30.9	5.2	10.6–44.4	0.095	0.915
Pericentral ring	167	42.6	3.8	34.2–59.4	120	42.5	3.7	33.3–55.0	0.303	0.634
Peripheral ring	167	38.6	2.2	33.2–48.8	120	38.3	2.7	31.9–47.9	0.401	0.329
INL										
Fovea	167	18.2	5.4	5.8–34.8	120	17.2	6.1	3.2–37.8	1.054	0.285
Pericentral ring	167	37.8	3.3	29.2–47.0	120	36.4	3.6	24.9–46.7	1.433	**0.019**
Peripheral ring	167	28.9	2.1	23.8–33.8	120	27.7	2.5	20.8–32.8	1.035	**0.006**
OPL										
Fovea	167	23.2	4.3	14.2–35.6	120	23.5	4.2	13.0–36.2	0.251	0.694
Pericentral ring	167	31.5	3.6	25.2–43.3	120	31.0	4.0	26.1–43.6	0.718	0.214
Peripheral ring	167	28.3	1.9	24.1–33.3	120	27.5	2.5	23.2–34.7	0.950	**0.006**
ONL + IS										
Fovea	167	123.8	9.9	90.1–151.6	120	120.7	9.5	100.1–151.4	2.026	0.222
Pericentral ring	167	97.2	7.8	75.9–114.9	120	94.8	7.9	75.1–111.3	1.604	0.224
Peripheral ring	167	78.9	6.8	59.5–95.7	120	77.6	6.1	63.6–91.4	0.658	0.542
OSL										
Fovea	167	48.5	3.7	36.7–58.2	120	49.0	3.8	27.6–55.2	−1.040	0.086
Pericentral ring	167	43.3	2.4	36.5–48.7	120	43.3	2.3	35.6–48.7	−0.276	0.465
Peripheral ring	167	40.5	2.9	30.4–47.8	120	40.3	2.5	34.5–45.5	−0.014	0.977
RPE										
Fovea	167	18.5	1.9	13.1–22.4	120	17.9	2.0	13.8–22.1	0.664	**0.029**
Pericentral ring	167	17.9	1.8	12.9–21.3	120	17.5	1.9	13.5–21.4	0.333	0.259
Peripheral ring	167	18.1	1.5	14.4–21.4	120	18.2	1.8	14.1–21.2	−0.086	0.758
Total foveal RT	167	265.2	22.6	214.2–317.6	120	261.6	21.7	208.4–326.0	3.556	0.367
Total pericentral RT	167	325.0	15.2	293.7–365.7	120	319.6	15.1	285.0–354.1	4.872	0.065
Total peripheral RT	167	279.8	12.5	249.2–310.4	120	274.4	12.0	249.5–308.1	4.575	**0.029**
Peripapillary RNFL, µm										
Average	168	102.0	11.3	73.3–132.7	120	100.0	10.1	74.3–124.8	1.170	0.520
Superior	168	125.5	20.2	35.8–178.4	120	125.4	17.3	82.8–160.4	−0.345	0.916
Inferior	168	131.1	16.8	78.9–172.8	120	128.1	15.8	86.5–161.1	2.138	0.413
Temporal	168	72.9	13.5	43.2–115.9	120	72.4	12.5	50.5–127.5	0.729	0.732
Nasal	168	78.5	15.3	31.3–132.1	120	74.2	16.0	38.5–123.5	2.190	0.370

P values derived from linear mixed-models and adjusted for age at assessment, OCT quality factor and spherical equivalent. *P* values in bold are $P < 0.05$. GCL, ganglion cell layer; IPL, inner plexiform layer; OPL, outer plexiform layer; ONL-IS, outer nuclear layer-inner segments; RPE, retinal pigment epithelium; RT, retinal thickness.

In contrast, we observed a significant increase in retinal thickness in HIV-infected individuals compared with the control group. At present, only one other study, by Arcinue et al.,[45] has measured individual retinal layer thickness in HIV-infected patients and they described an increase in retinal thickness as well, in particular the inner retinal layers, in a group of 10 HIV-positive patients compared with 10 HIV-negative controls. In our study, the increase in total retinal thickness was predominantly due to thicker inner nuclear and outer plexiform layers. A good comparison of our results with those of Arcinue et al.[45] is difficult, considering the very small sample size of their study, different segmentation algorithm used (applied on only 3 B-scans), lack of correction for important confounders in the analyses and inclusion of patients with a history of more severe immune-deficiency. An increased volume of inner nuclear (and outer plexiform[46]) layer[46,47] has also been reported by recent studies assessing retinal layer thickness in multiple sclerosis, a disease characterized by neuro-inflammation and degeneration, processes both regarded important in HIV-associated neurocognitive and

retinal changes as well. The authors speculated that these changes might reflect low grade inflammatory activity, which could also be relevant in the HIV-infected population. Furthermore in these studies, correlations were detected between inner plexiform layer (INL) thickening and inflammatory magnetic resonance imaging (MRI) activity and cerebrospinal fluid findings.[46,47]

Similar (longitudinal) research combining OCT, MRI, and laboratory parameters would provide more insight in the potential role of (neuro)inflammation in HIV-associated neuroretinal changes.

Multivariable analyses within the HIV-infected group showed no consistent (e.g., the significant associations were not found in multiple retinal layers or regions) associations between predictive variables and retinal parameters. Considering the high number of *P* values generated, it is likely that the significant associations we detected were due to type I errors.

Strengths of our study are the inclusion of a highly similar control group, and the adjustment for relevant confounding factors (e.g., age, OCT quality factor, spherical equivalent) in our statistical analyses. Furthermore, we introduced a novel, more accurate method[35] for assessing retinal function, instead of the standard Pelli Robson chart used by most studies, which is also confounded by the optics of the eye.

The relatively small sample size of the study may have hampered the detection of some potential associations, but the detection of some small statistical differences, that cannot be considered clinically relevant, makes it unlikely we missed important associations. Ongoing longitudinal follow-up of the AGE_hIV neuroretinal study will provide more information on retinal changes in this group of middle-aged HIV-infected and HIV-uninfected individuals.

In summary, this is the first study in a group of patients with prolonged well-suppressed HIV-infection on cART, assessing the neuroretina by means of both spatial and temporal contrast sensitivity as well as individual retinal layer thickness measurements. Our results provide little evidence for neuroretinal loss in individuals with well-suppressed HIV-infection, compared with HIV-uninfected controls, with no clinically relevant reduction in PR CS and absence of neuroretinal atrophy.

The significantly increased retinal thickness we detected in the HIV-infected group was unexpected and should be confirmed and further explored by larger longitudinal studies. The long-term effects of HIV-infection on the retina are still unknown, and as life expectancy of HIV-infected patients is increasing with the global roll-out of cART, vision loss might become more prevalent and symptomatic with time.

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