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Incidence and Long-term Outcomes of the HIV-Neuroretinal Disorder in Patients with the Acquired Immunodeficiency Syndrome

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Abstract

Objectives—Patients with the acquired immunodeficiency syndrome (AIDS) have an abnormality of retina/optic nerve function, manifested as decreased contrast sensitivity (in the absence of ocular opportunistic infections or media opacity), abnormalities on automated perimetry, and loss of retinal nerve fiber layer, even among those with good visual acuity, termed the HIV-neuroretinal disorder. The objectives of this study were to determine the prevalence, incidence, risk factors for, and outcomes of HIV-neuroretinal disorder.

Design—Prospective cohort study

Participants—1822 patients with AIDS without ocular infections or media opacities.

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Conflict of Interest: Douglas A. Jabs: Abbott Pharmaceuticals, Applied Genetic Technologies Corporation (AGTC), Alcon Laboratories, Corcept Therapeutics, Genentech, Inc., Genzyme Corporation, GlaxoSmithKline, Novartis Pharmaceutical Corp., Regeneron, and Roche Pharmaceuticals; Lea Drye: None; Mark Van Natta: None; Jennifer Thorne: AbbVie, Allergan, Gilead, and XOMA (US) LLC; Gary N. Holland: Genentech, Novartis International AG, Santen, and Xoma (US) LLC.”

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Methods—Patients with HIV-neuroretinal disorder were identified by a contrast sensitivity < 1.50 log units in either eye in the absence of ocular opportunistic infections or media opacity.

Main outcome measures—Incidence of HIV-neuroretinal disorder, mortality, visual impairment (visual acuity 20/50 or worse), and blindness (20/200 or worse) on logarithmic visual acuity charts.

Results—Sixteen percent of participants had HIV-neuroretinal disorder at enrollment. The estimated cumulative incidence by 20 years after AIDS diagnosis was 51% (95% confidence interval [CI] 46%–55%). HIV-neuroretinal disorder was more common in women and African American persons. Risk factors for it included hepatitis C infection, low CD4+ T cells, and detectable HIV RNA in the blood. Patients with HIV neuroretinal disorder had a 70% excess mortality vs. those without it, even after adjusting for CD4+ T cells and HIV load (hazard ratio=1.7, 95% CI= 1.3–2.1, $P<0.0001$). Patients with HIV-neuroretinal disorder had increased risks of bilateral visual impairment (hazard ratio=6.5, 95% CI=2.6–10.6, $P<0.0001$) and blindness (hazard ratio=5.9, 95% CI=2.8–13.7, $P=0.01$) vs. those without HIV neuroretinal disorder.

Conclusions—HIV-neuroretinal disorder is a common finding among patients with AIDS, and it is associated with an increased mortality and an increased risk of visual impairment. Successful antiretroviral therapy decreases but does not eliminate the risk of HIV-neuroretinal disorder.

Subtle abnormalities of vision (decreased contrast sensitivity, abnormal color vision, visual field loss, abnormal results on other psychophysical tests) in the absence of ocular opportunistic infections and in the absence of media opacities are more common in patients with human immunodeficiency (HIV) infection than in the general, HIV-uninfected, population.^{1–18} These abnormalities may persist and be present even among those with suppressed circulating HIV RNA levels in the blood and with immune recovery due to combination antiretroviral therapy and may be present in patients with “good” visual acuity on high contrast visual acuity charts (e.g. Snellen acuity).^{3,4} These changes are presumed to be due to an HIV-related neuroretinal disorder, characterized by loss of nerve fiber layer.^{13–16} When compared to normal controls, autopsy studies of patients with AIDS show loss of optic nerve axons and degeneration of remaining axons, lending support to the presumed pathogenesis.¹⁶ Although different functional markers of this HIV-neuroretinal disorder have been used, the one most often used is decreased contrast sensitivity.^{1–4} Previous estimates of the prevalence of the HIV-neuroretinal disorder among HIV-infected persons have been ~10%,⁴ but less is known about incidence, risk factors, and long-term outcomes. The Longitudinal Study of the Ocular Complications of AIDS (LSOCA) cohort provides the opportunity to explore these issues.

Methods

The Longitudinal Study of the Ocular Complications of AIDS is a prospective, observational, cohort study of patients with AIDS in the era of modern combination antiretroviral therapy.^{4,17,18} Eligible patients were diagnosed with AIDS according to the 1993 Centers for Disease Control and Prevention diagnostic criteria for AIDS.¹⁹ Enrollment began on 1 September 1998 and was completed on 31 July 2011. Recruitment occurred at 19 clinical centers throughout the United States and typically located in large urban centers

with a high prevalence of HIV infection. Approval for the study and all study procedures was obtained from the institutional review boards of the individual participating clinical centers and the three resource centers (chairman's office, coordinating center, reading center). Written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki.

Patients were seen every six months for follow-up visits; follow-up continued through 31 July 2013. Details of the design and methods have been published elsewhere.^{17,18} At each visit participants gave a detailed medical and ophthalmic history; medical history details were confirmed from the medical record. A complete eye examination was performed, including measurement of best corrected visual acuity using logarithmic visual acuity charts,^{4,17,18,20,21} slit lamp biomicroscopy, and ophthalmoscopy through dilated pupils. Refraction was performed at every visit, using a standardized protocol.^{17,18} Static perimetry was performed annually using the Humphrey Visual Field Analyzer (Carl Zeiss Meditec, Dublin, CA, USA) 24-2 program.^{4,17,18} A mean deviation of -3.0 dB or worse was considered abnormal.^{22,23} Laboratory evaluation at each visit included lymphocyte subsets (for CD4+ T cell counts) and measurement of HIV RNA levels in the plasma (HIV load).¹⁷ Contrast sensitivity was measured at each visit by certified examiners using Pelli-Robson contrast sensitivity charts. The threshold used for considering contrast sensitivity decreased was less than 1.50 log units, the lower 2.5th percentile for the normal range for HIV-uninfected persons.^{4,24} Decreased contrast sensitivity in either eye of a patient without an ocular infection and without media opacity (e.g. cataract) was used to identify participants with the presumed HIV-neuroretinal disorder.

After 2008, as Pelli-Robson charts began to wear out, they were replaced at the individual clinical centers. A sudden increase in contrast sensitivity scores was noted at some, but not all, centers after the introduction of the new charts, suggesting a possible increase in scores due to an artifact of the new charts. However, the variability of the effect rendered this interpretation uncertain. Therefore, all analyses were performed three ways: with the data as recorded (primary analysis); with a statistical correction based on the sudden change to those clinical centers experiencing this change; and restricting the analysis to participants enrolled from 1998 to 2008. For the baseline characteristics and long-term outcomes of patients with the HIV-neuroretinal disorder, these analyses gave essentially the same results (data not shown), and the primary analysis is presented.

Statistical methods

Baseline characteristics of participants with HIV-neuroretinal disorder were compared to those without HIV-neuroretinal disorder using the Wilcoxon rank sum test for continuous variables and the chi square test for categorical variables.²⁵ The baseline eye-level characteristics were compared by ranking the values of the characteristics (visual acuity or visual field) and performing general estimating equations on the ranks with an exchangeable covariance structure to account for the eyes from the same participant.²⁶ Mortality rates, and both eye-specific and bilateral visual impairment and blindness rates for participants with and without HIV-neuroretinal disorder at enrollment were calculated using generalized estimating equations with a Poisson distribution.²⁶ For eye-specific outcomes, an

exchangeable covariance structure and robust standard errors were used to account for within-person correlation. Hazard ratios (HR) were calculated using Cox proportional hazard regression with the time from enrollment as the time scale.²⁷ For eye-specific outcomes, a marginal Cox approach using a robust sandwich covariance matrix was used to account for within-person correlation.²⁸ The adjusted models included gender, race, enrollment year, antiretroviral therapy use, hepatitis C infection, CD4+ T cell count, and HIV load.

The cumulative incidence and risk factors for incident HIV-neuroretinal disorder were calculated using proportional hazard regression with time from AIDS diagnosis as the timescale and accounting for left truncation (staggered entries) of time between AIDS diagnosis and enrollment.^{29,30} The adjusted model included all covariates listed in table 3 and enrollment year. Time-to-event graphs were generated using the Kaplan Meier method.³¹ Analyses were performed in SAS 9.2 (Copyright © 2002–2008, SAS Institute, Inc., Cary, NC, USA) and STATA (StataCorp 2013. Stata Statistical Software: Release 13, College Station, TX: StataCorp LP)

Results

Characteristics of the study population

Of the 2,392 participants enrolled in LSOCA, 535 had an ocular infection, an additional 17 had media opacities (primarily cataract) at enrollment, and an additional 18 had no contrast sensitivity measurements. The remaining 1822 had neither an ocular opportunistic infection nor media opacity at enrollment and had contrast sensitivity data available. Of the 1822 patients available for analysis, 294 (16%) had the HIV-neuroretinal disorder as evidenced by a decreased contrast sensitivity in either or both eyes at enrollment. Characteristics of the study population are presented as Table 1. Patients with the HIV-neuroretinal disorder were more likely to be women, more likely to be African-American, more likely to be hepatitis C antibody positive (evidence of previous infection), and less likely to have used combination antiretroviral therapy either in the past or at enrollment (although 86% had used antiretroviral therapy at some time and 79% were receiving it at enrollment). The distribution of CD4+ T cells at enrollment was lower for patients with HIV-neuroretinal disorder than for those without, but was not different for the distribution of nadir CD4+ T cells at or prior to enrollment. Although data on the duration of the nadir CD4+ T cells prior to enrollment were not available, we were able to estimate the duration of low CD4+ T cells from the date of the nadir CD4+ T cell count and the CD4+ T cell count at enrollment. We evaluated the effect of the estimated duration of CD4+ T cells <50 cells/ μ L) and found no difference between those with and without HIV-neuroretinal disorder (data not shown). There were no substantial differences in HIV load measurements, either at enrollment or maximum value prior to enrollment. Among eyes with HIV-neuroretinal disorder, the visual acuities (Figure 1. available online at <http://aojournal.org>) generally were good (median ~20/20); however, they were mildly but significantly decreased from those without HIV-neuroretinal disorder (median, ~20/15, $P < 0.0001$). Similarly, eyes of participants with HIV-neuroretinal disorder had worse visual fields, as evidenced by worse mean deviations

(median -4.9 dB for eyes with HIV-neuroretinal disorder vs. -1.9 dB for eyes without HIV-neuroretinal disorder, $P<0.0001$).

Outcomes of patients with HIV-neuroretinal disorder at enrollment

Outcomes of patients with and without HIV-neuroretinal disorder are shown as Table 2. Patients with HIV-neuroretinal disorder at enrollment had a greater mortality during follow-up (Figure 2) than those without it (6.27/100 person-years [PY] vs. 3.14/100 PY, HR=1.7, $P<0.0001$). They also were more likely to develop bilateral visual impairment (visual acuity 20/50 or worse) (Figure 3) and bilateral blindness (visual acuity 20/200 or worse) than patients without HIV-neuroretinal disorder. Rates of bilateral visual impairment and blindness of patients with HIV-neuroretinal disorder vs. those without were 1.01/100 PY vs. 0.16/100 PY (HR=6.5, $P<0.0001$) and 0.27/100 PY vs. 0.05/100 PY (HR=5.9, $P=0.011$), respectively. Similar results were obtained when eyes were evaluated for visual impairment and blindness. Rates of visual impairment and blindness for eyes with HIV-neuroretinal disorder vs. those without were 2.03/100 eye-years (EY) vs. 0.41/100 EY (HR 4.0, $P<0.0001$) and 0.82/100 EY vs. 0.14/100 EY (HR 6.2, $P<0.001$), respectively. The period prevalence estimates of bilateral visual impairment since time of AIDS diagnosis for patients without HIV-neuroretinal disorder are: at 5 years, 0.2%; at 10 years, 0.7%, and 15 years, 0.9%; whereas for those with HIV-neuroretinal disorder they are: at 5 years, 5.9%, at 10 years, 6.6%, and at 15 years, 7.2%. The period prevalence estimates of bilateral blindness since time of AIDS diagnosis for patients without HIV-neuroretinal disorder are: at 5 years, 0%; at 10 years, 0.1%; and at 15 years, 0.2%; whereas for those with HIV-neuroretinal disorder they are: at 5 years, 1.1%; at 10 years, 1.1%; and at 15 years, 2.1%. Among eyes without an abnormal visual field at enrollment, those with HIV-neuroretinal disorder at enrollment were more likely to develop an abnormal visual field (mean deviation -3.0 dB) on Humphrey 24-2 testing. Rates of visual field abnormality were 12.63/100 EY vs. 5.60/100 EY (HR 2.0, $P=0.0002$) for eyes with HIV-neuroretinal disorder vs. those without. Causes of visual impairment and blindness were reviewed and there were no differences between the groups with or without HIV-neuroretinal disorder in ocular opportunistic infections (3 in the group without HIV neuroretinal disorder and 2 in the group with HIV neuroretinal disorder) and cataracts (2 in each group) during follow-up. Similarly there was no evident pattern to the causes of visual impairment in either group (data not shown).

Incidence of HIV-neuroretinal disorder

The incidence of HIV-neuroretinal disorder was 1.9/100 PY (95% confidence interval [CI] 1.7, 2.2/100 PY, Figure 4). Risk factors for incident HIV-neuroretinal disorder (Table 3) included being older at AIDS diagnosis, having CD4+ T cells <100 cells/ μ L, and having an HIV load >2.6 log₁₀(copies/mL). For CD4+ T cells, an exploratory analysis was performed comparing the risks of those with CD4+ T cells <50 cells/ μ L to those with CD4+ T cells 50–100 cells/ μ L, and no differences in the risk were found (data not shown), so the two groups were combined for all analyses. The cumulative incidence (and 95% confidence intervals [CIs]) for the HIV-neuroretinal disorder after the AIDS diagnosis are: 1 year, 6% (3%, 9%); 2 years, 10% (6%, 13%); 5 years, 22% (18%, 26%); 10 years, 36% (32%, 41%); 15 years, 45% (41%, 49%); and 20 years, 51% (46%, 55%). Even among patients with immune

recovery with controlled HIV load ($<2.6 \log_{10}(\text{copies/mL})$) and CD4+ T cells $>100 \text{ cells}/\mu\text{L}$, the cumulative incidence at 15 years was 30% (95% CI 21%, 39%).

As noted in the methods, after 2008 new contrast sensitivity charts were introduced into the clinical centers at variable times with a variable effect on measured contrast sensitivity, but generally increasing the measured contrast sensitivity by 4 letters. Applying an imputed correction to the new charts to give comparable scores to the old charts actually increased the estimate of the incidence of HIV-neuroretinal disorder. Using these corrected measurements the cumulative incidences (and 95% CIs) of the HIV-neuroretinal disorder after the AIDS diagnosis are estimated at: 1 year, 7% (3%, 10%); 2 years, 11% (7%, 15%); 5 years, 24% (20%, 29%); 10 years, 40% (36%, 45%); 15 years, 54% (49%, 57%); and 20 years, 66% (62%, 70%). Despite the somewhat higher estimated incidence, particularly at 15 and 20 years after AIDS diagnosis, the risk factors for HIV-neuroretinal disorder remain the similar in direction, magnitude, and significance using either definition of low contrast sensitivity (data not shown).

Discussion

Our data suggest that the HIV-neuroretinal disorder is a relatively common phenomenon among patients with AIDS. Although 16% of participants entering the LSOCA cohort had the HIV-neuroretinal disorder, the incidence data, anchored to the time of AIDS diagnosis, suggest that the cumulative incidence may be as high as 50% of patients with AIDS by 20 years after AIDS diagnosis. Both the enrollment characteristics and the incidence risk factors suggest that the problem is more common among women and African American persons. Although this increased risk could reflect an access to care issue, the increased risk among these populations persists even after adjustment for antiretroviral therapy, CD4+ T cells, and HIV load, factors influenced by access to care, and suggesting that the increased risks are due to more than just access to care.

Other risk factors include hepatitis C infection, a low CD4+ T cell count, and elevated levels of circulating HIV RNA in the blood (HIV load). Hepatitis C previously has been reported to be a risk factor, which is why it was included it in the model.³² Furthermore, hepatitis C is pro-inflammatory and enters the central nervous system, so there is biologic plausibility for its effect.³³ However, although a risk factor, it was present in only approximately one-third of participants with HIV-neuroretinal disorder at baseline. Our incidence data suggest a threshold effect for both CD4+ T cells and for HIV load. Specifically, the risk of the HIV-neuroretinal disorder appears to nearly double for patients with CD4+ T cells $<100 \text{ cells}/\mu\text{L}$ but not to be substantially different for patients with CD4+ T cells of 101–200 $\text{cells}/\mu\text{L}$ or $>200 \text{ cells}/\mu\text{L}$. For HIV load, the risk appears to nearly double for levels above 2.6 $\log_{10}(\text{copies/mL})$, which is 400 copies/mL, and not to be substantially different for levels 2.6–5.0 and >5.0 . An HIV load of 400 copies/mL was the “undetectable” threshold of the older assays in use when the LSOCA cohort was begun, and this result suggests that HIV replication is a risk factor for HIV-neuroretinal disorder in addition to a low CD4+ T cell count. Although not proven by this cohort study, the evident implication is that combination antiretroviral therapy sufficient to render HIV load “undetectable” in the blood and raise the

CD4+ T cells to >100 cells/ μ L will reduce, but not eliminate, the risk of the HIV-neuroretinal disorder.

Patients with AIDS with the HIV-neuroretinal disorder have a 70% excess mortality compared to those without. The mechanism of this excess mortality is unclear, as review of death certificates typically suggests no specific cause for the increased mortality. Previous studies of the retinal vasculature in patients with AIDS suggest that the HIV-neuroretinal disorder correlates with abnormalities of the retinal blood vessels seen with aging and associated with renal and cardiovascular disease in patients with AIDS.^{34–36} Although the HIV-neuroretinal disorder may be a marker for more severe AIDS or for a greater “aging” effect, its effect on the risk of mortality persists even after adjustment for CD4+ T cells and HIV load, typically the major determinants of mortality among patients with AIDS.

Despite presenting with good visual acuity (median ~20/20), patients with the HIV-neuroretinal disorder were substantially more likely to develop bilateral visual impairment and blindness than those without. The HRs for bilateral visual impairment and blindness were 6.5 and 5.9 respectively for those with HIV-neuroretinal disorder compared to those without. Among cohorts in the United States evaluated by the Eye Diseases Prevalence Research Group, the prevalences of bilateral visual impairment and of bilateral blindness range from 0.98% to 3.37% and 0.29% to 0.83%, respectively, with best estimates of 1.98% for visual impairment and 0.78% for blindness.³⁷ The estimates of the prevalence of bilateral visual impairment among patients without the HIV-neuroretinal disorder are similar to those in the general, non-HIV-infected population. Conversely, the prevalences of bilateral visual impairment among patients with the HIV-neuroretinal disorder at 10 and 15 years after AIDS diagnosis are 6.6% and 7.2%, respectively, and appear to be greater than those seen in non-HIV-infected cohorts. Because the non-HIV-infected cohorts generally enroll older patients (median age typically in the 60s) than LSOCA, and because the prevalence of visual impairment increases with age, this increased prevalence among patients with the HIV-neuroretinal disorder is even more impressive. In addition to the increased incidence of visual loss among patients with the HIV-neuroretinal disorder, there is an increased prevalence of abnormal findings on Humphrey automated perimetry and increased incidence of abnormal Humphrey automated visual fields among those presenting normal visual fields. Review of the reasons for visual impairment demonstrated no specific “cause” or pattern of causes for the increased risk in the HIV-neuroretinal disorder group.

There are several caveats to our data. The LSOCA cohort enrolled patients with AIDS, not earlier stages of HIV infection, and these data may not be fully applicable to earlier stages of HIV infection. However, current estimates are that as many as 21% of HIV infections in the United States are undiagnosed, and that as many as 45% of HIV-infected patients will progress to a diagnosis of AIDS within 3 years of HIV diagnosis, largely due to late HIV diagnosis.³⁸ Furthermore, even among HIV-infected patients who are retained in care, and therefore presumably, receiving antiretroviral therapy, nearly 30% will not have undetectable viral loads,³⁹ and, therefore be at risk for progression of the HIV disease. Despite these limitations in the effectiveness of care, long-term survival is typical for HIV-infected patients,⁴⁰ so that the long-term cumulative risk of the HIV neuroretinal disorder demonstrated in the cohort is applicable to the AIDS epidemic in the United States.

Participants were enrolled at AIDS Ophthalmology clinical centers; hence the study could have been enriched with patients with eye problems or symptoms, resulting in overestimates of prevalence and incidence of the HIV-neuroretinal disorder. However, a comparison of the characteristics of participants enrolled in LSOCA with those of persons with AIDS in the United States suggests that the LSOCA cohort is representative of the AIDS epidemic.^{17,18} Indeed the only group seemingly underrepresented in the LSOCA cohort is persons whose risk factor for HIV infection is injection drug use, a group that may have a higher prevalence of the HIV-neuroretinal disorder,³² suggesting that our estimates are reasonably representative of the AIDS epidemic. There are limited longitudinal data on the incidence of low contrast sensitivity in the normal HIV-uninfected population. As such, it is possible that there is a decline with age in the incidence of reduced contrast sensitivity in the normal HIV-uninfected population, and as such our incidence of HIV-related decreased contrast sensitivity is overestimated. Nevertheless, the associations of mortality and visual impairment would be unchanged. Finally, we encountered a temporal but variable increase in measured contrast sensitivity associated with the introduction of new contrast sensitivity charts after 2008. Fortunately sensitivity analyses using corrections to the measured contrast sensitivity and using only the pre-2008 cohort gave similar results. The only difference was a somewhat greater estimate of the cumulative incidence of the HIV-neuroretinal disorder at 15 and 20 years after AIDS diagnosis with the “corrected” contrast sensitivity, and the risk factor and visual outcome analyses were essentially unaffected by the chart issue. As such it appears that our analyses and estimates, though perhaps conservative, are reasonable.

In conclusion, the HIV-neuroretinal disorder is a common problem among patients with AIDS, affecting perhaps 50% of patients by 20 years after AIDS diagnosis. It is more frequent among women and African American persons. Risk factors include hepatitis infection, low CD4+ T cells, and elevated HIV load. Although initially presenting with good visual acuity, it is associated with an increased incidence of visual impairment and with an increased mortality. These data further suggest that combination antiretroviral therapy sufficient to suppress HIV replication and raise the CD4+ T cells to >100 cells/ μ L may reduce, but not eliminate, the risk of the HIV-neuroretinal disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Box plots of best-corrected visual acuity (letters read on a logarithmic visual acuity chart) and Humphrey automated perimetry mean deviations for patients without and with HIV-neuroretinal disorder (HIV-NRD). Ninety letters is equivalent to 20/15, and 85 letters is equivalent to 20/20.

Figure 2. Mortality of patients with HIV-neuroretinal disorder (HIV-NRD) vs. patients without HIV-neuroretinal disorder (no HIV-NRD) at enrollment.

Figure 3.
Kaplan Meier estimate of incidence of bilateral visual impairment of patients with HIV-neuroretinal disorder (HIV-NRD) vs. patients without HIV-neuroretinal disorder (no HIV-NRD) at enrollment.

Figure 4.

Kaplan Meier estimates of incidence of HIV-neuroretinal disorder: a) in the entire cohort; and comparing patients with different: b) HIV loads; c) CD4+ T cells; and d) response to antiretroviral (ART) therapy. Responders are defined as those with an HIV load <2.6 $\log_{10}(\text{copies/mL})$ and CD4+ T cells >200 cells/ μ L.

Table 1

Characteristics of the Study Population

Characteristic at Enrollment	Overall Population	No HIV-Neuroretinal Disorder	HIV-Neuroretinal Disorder	P-value
Number of patients	1822	1528	294	
Age (years)				0.113
Median	43	43	43.5	
Interquartile range	38, 49	38, 49	38, 51	
Gender (%)				0.002
Men	80	82	74	
Women	20	18	26	
Race and ethnicity (%)				0.0001
White, non-Hispanic	45	47	34	
African-American, non-Hispanic	38	36	47	
Hispanic	13	13	16	
Other	4	4	3	
HIV risk factor (%)				<0.0001
Men having sex with men (MSM)	54	57	37	
Injection drug use (IDU)	10	9	14	
Both MSM and IDU	4	4	6	
Heterosexual contact	26	25	33	
Other	6	5	9	
Duration of AIDS (years)				0.036
Median	4.4	4.5	3.9	
Interquartile range	1.6, 7.3	1.6, 7.4	1.4, 6.7	
Combination antiretroviral therapy (%)				
Ever used	90	91	86	0.010
Receiving at enrollment	85	86	79	0.003
CD4+ T cells (cells/ μ L)				
Median, enrollment	198	201	184	0.049
Interquartile range, enrollment	81, 362	84, 369	59, 331	
Median, nadir	41	41	40	0.676
Interquartile range, nadir	13, 109	13, 109	10, 107	
HIV load ($\log_{10}$ (copies/mL))				
Median, enrollment	2.68	2.62	2.94	0.248
Interquartile range, enrollment	1.74, 4.59	1.72, 4.53	1.89, 4.72	
Median, maximum	5.28	5.28	5.30	0.081
Interquartile range, maximum	4.70, 5.72	4.66, 5.71	4.88, 5.80	
Hepatitis C antibody status (%)				
Positive	23	22	32	0.0003

Characteristic at Enrollment	Overall Population	No HIV-Neuroretinal Disorder	HIV-Neuroretinal Disorder	P-value
Negative	77	78	68	
Visual acuity				
Bilateral acuity 20/50 or worse (%)	0.5	0.1	2.4	<0.0001
Bilateral acuity 20/200 or worse (%)	0.2	0.0	1.0	<0.0001
<i>Eye-specific characteristics</i>				
Visual acuity				
Median (letters)	89	90	84	<0.0001
Snellen equivalent	~20/15	~20/15	~20/20	
Interquartile range (letters)	85, 93	86, 93	76, 88	
Visual acuity 20/50 or worse (%)	2.0	0.7	12	<0.0001
Visual acuity 20/200 or worse (%)	0.6	0.06	4.9	<0.0001
Visual field, mean deviation (dB)				<0.0001
Median	-2.2	-1.9	-4.9	
Interquartile range	-4.3, -0.6	-3.9, -0.5	-9.3, -2.6	

Table 2

Outcomes of Patients with HIV-Neuroretinal Disorder

Outcome	Overall Population	No HIV-Neuroretinal Disorder	HIV-Neuroretinal Disorder	Hazard ratio	P-value
Mortality					
Patients at risk	1822	1528	294		
Events	496	377	119		
Person-years	13,900	12,000	1,900		
Rate (/100 person-years)	3.57	3.14	6.27	1.7	<0.0001
95% CI* (/100 person-years)	3.27, 3.90	2.84, 3.47	5.24, 7.51	1.3, 2.1	
Bilateral acuity 20/50 or worse					
Patients at risk	1670	1412	258		
Events	29	15	14		
Person-years	10,900	9,520	1,390		
Rate (/100 person-years)	0.27	0.16	1.01	6.5	<0.0001
95% CI* (/100 person-years)	0.18, 0.38	0.10, 0.26	0.60, 1.70	2.6, 16.0	
Bilateral acuity 20/200 or worse					
Patients at risk	1674	1413	261		
Events	9	5	4		
Person-years	11,030	9,580	1,460		
Rate (/100 person-years)	0.08	0.05	0.27	5.9	0.011
95% CI* (/100 person-years)	0.04, 0.16	0.02, 0.13	0.10, 0.73	1.5, 23.2	
<i>Eye-specific outcomes</i>					
Visual acuity 20/50 or worse					
Eyes at risk	3274	2942	332		
Events	122	87	35		
Eye-years	21,110	19,430	1,680		
Rate (/100 eye-years)	0.48	0.41	2.03	4.0	<0.0001
95% CI* (/100 eye-years)	0.38, 0.60	0.31, 0.52	1.38, 2.99	2.4, 6.7	
Visual acuity 20/200 or worse					

Outcome	Overall Population	No HIV-Neuroretinal Disorder	HIV-Neuroretinal Disorder	Hazard ratio	P-value
Eyes at risk	3316	2956	360		
Events	46	30	16		
Eye-years	21,780	19,840	1,940		
Rate (/100 eye-years)	0.19	0.14	0.82	6.2	<0.0001
95% CI* (/100 eye-years)	0.14, 0.27	0.09, 0.22	0.47, 1.42	2.8, 13.7	
Humphrey visual field mean deviation -3.0dB or worse					
Eyes at risk	1907	1810	97		
Events	696	639	57		
Eye-years	10,210	9,850	3600		
Rate (/100 eye-years)	5.79	5.60	12.63	2.0	0.0002
95% CI* (/100 eye-years)	5.20, 6.46	5.02, 6.26	7.93, 20.1	1.4, 3.0	

* 95% CI = 95% confidence interval.

Table 3

Risk Factors for Incident HIV-Neuroretinal Disorder

Risk Factor	Crude HR*	95% CI*	P-value	Adjusted HR	95% CI	P-value
Age at AIDS diagnosis						
38 years	Reference			Reference		
>38 years	1.3	1.0, 1.6	0.045	1.6	1.2, 2.1	0.0006
Gender						
Men	Reference			Reference		
Women	1.6	1.2, 2.1	0.0003	1.6	1.1, 2.1	0.007
Race						
Non-African American	Reference			Reference		
African American	1.5	1.2, 1.9	0.001	1.4	1.0, 1.8	0.026
Hepatitis C antibody status at enrollment						
Negative	Reference			Reference		
Positive	1.8	1.4, 2.4	<0.0001	1.4	1.1, 1.9	0.020
Combination antiretroviral therapy use at enrollment						
Never	Reference			Not applicable [†]		
Prior to enrollment, not at enrollment	1.2	0.7, 2.2	0.543			
Current at enrollment	0.6	0.4, 1.1				
Time-updated antiretroviral therapy use						
Not using	Reference			Reference		
Using	0.4	0.3, 0.6	<0.0001	0.6	0.4, 0.9	0.020
Nadir CD4+ T cells (cells/ μ L)						
>100	Reference			Reference		
50–100	1.1	0.8, 1.5	0.762	1.1	0.7, 1.6	0.676
<50	0.9	0.7, 1.2	0.555	0.9	0.6, 1.2	0.444
Enrollment CD4+ T cells (cells/ μ L)						
>200	Reference			Not applicable [†]		
101–200	1.2	0.9, 1.6	0.260			

Risk Factor	Crude HR [*]	95% CI [*]	P-value	Adjusted HR	95% CI	P-value
100	1.4	1.0, 1.8	0.029			
Time-updated CD4+ T cells (cells/ μ L)						
>200	Reference			Reference		
101–200	1.4	1.0, 1.9	0.030	1.2	0.9, 1.8	0.228
100	2.4	1.8, 3.2	<0.0001	1.9	1.4, 2.8	0.0003
Maximum HIV load at enrollment ($\log_{10}$ (copies/mL)						
<2.6	Reference			Reference		
2.6–5.0	1.0	0.5, 2.2	0.956	0.6	0.3, 1.5	0.291
>5.0	1.2	0.6, 2.5	0.647	0.9	0.4, 2.0	0.714
Enrollment HIV load ($\log_{10}$ (copies/mL)			0.001			
<2.6	Reference			Not applicable [†]		
2.6–5.0	1.5	1.1, 1.9	0.004			
>5.0	1.8	1.3, 2.6	0.0009			
Time-updated HIV load ($\log_{10}$ (copies/mL)						
<2.6	Reference			Reference		
2.6–5.0	2.5	1.9, 3.2	<0.0001	2.2	1.6, 3.0	<0.0001
>5.0	3.1	2.2, 4.5	<0.0001	1.9	1.2, 3.2	0.008

^{*} HR = hazard ratio. 95% CI = 95% confidence interval.

[†] Not applicable as enrollment CD4+ T cells or HIV load included in the time-updated analyses.