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Risk of Cataract among Subjects with the Acquired Immune Deficiency Syndrome Free of Ocular Opportunistic Infections

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Abstract

Purpose—To evaluate the risk of cataract in the setting of AIDS.

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Design—Prospective cohort study.

Participants—Subjects with AIDS free of ocular opportunistic infections throughout catamnesis.

Methods—During 1998–2008 inclusive, subjects ≥13 years of age were enrolled. Demographic characteristics and clinical characteristics were documented at enrollment and semiannually.

Main Outcome Measures—Cataract was defined as high-grade lens opacity observed by biomicroscopy and judged to be the cause of a best-corrected visual acuity worse than 20/40. Eyes that underwent cataract surgery during follow-up were considered to have developed cataract prior to the first visit when pseudophakia or aphakia was observed.

Results—Among 1,606 participants (3,212 eyes), at enrollment 1.9% (95% confidence interval (CI): 1.3%−2.7%) were observed to have cataract or prior cataract surgery. Among the 2,812 eyes initially free of cataract, and followed longitudinally (median follow-up=4.6 years), the incidence of cataract was 0.37%/eye-year (95% CI: 0.26%– 0.53%). In addition to age, significant cataract risk factors included prior cataract in the contralateral eye (adjusted hazard ratio (aHR)=21.6, 95% CI: 10.4–44.8), anterior segment inflammation (aHR=4.40, 95% CI: 1.64–11.9), prior retinal detachment (aHR=4.94, 95% CI: 2.21–11.0), and vitreous inflammation (aHR=7.12, 95% CI: 2.02– 25.0), each studied as a time-updated characteristic. Detectable HIV RNA in peripheral blood was associated with lower risk of cataract at enrollment (adjusted odds ratio=0.32, 95% CI: 0.12–0.80) but not of incident cataract (aHR=1.58, 95% CI: 0.90–2.76). After adjustment for other factors, neither the then current absolute CD4+ T cell count nor antiretroviral therapy status showed consistent association with cataract risk, nor did an additive diagnosis of other other co-morbidities. Compared to the available population-based studies that used similar definitions of cataract, the age-specific prevalence of cataract in our cohort was higher than in one of two such studies, and the age-specific incidence of cataract surgery was higher.

Conclusions—Our results suggest cataract may occur earlier among patients with AIDS free of ocular opportunistic infections than in the general population. Cataract risk was associated most strongly with age and with other ocular morbidity in this population. With improved survival, the burden of cataract likely will increase for persons with HIV/AIDS.

Cataract is the leading cause of visual impairment in the United States[1] and worldwide[2] and is the leading cause of legal blindness among African-Americans.[1] Historically, cataract has not been viewed as one of the significant causes of ocular morbidity in patients with the Acquired Immune Deficiency Syndrome (AIDS), because such morbidity has been dominated by ocular opportunistic complications of immunodeficiency.[3] Furthermore, cataract is typically a disorder of older adults,[4] whereas the AIDS epidemic began predominantly among younger and middle aged adults.[5;6]

In the era of highly active antiretroviral therapy (HAART), the incidence of opportunistic complications of AIDS has declined substantially,[7;8] including the incidence of ocular opportunistic complications.[8–13] Among persons who have a long-term favorable response to HAART, AIDS has evolved into a chronic disease wherein long-term survival is expected. This context provides an opportunity for individuals with AIDS to develop ocular diseases of aging, including cataract. In addition, there are indications that these individuals

may experience accelerated aging,[14;15] of which cataract, and earlier onset of cataract, are potential indicators.[16]

In our investigations of the long-term ocular complications of AIDS, we found that patients with both AIDS and CMV retinitis are at high risk for cataract.[17] We also documented that cataract was the second leading cause of visual impairment in the Longitudinal Study of Ocular Complications of AIDS (LSOCA) cohort among subjects who did not have CMV retinitis at the time of enrollment.[18] To characterize better the risk of cataract among these subjects with AIDS, we report now analyses of the prevalence and incidence of cataract in LSOCA subjects who were free of CMV retinitis and other intraocular opportunistic infections at the time of enrollment.

Methods

The methods of the Longitudinal Study of Ocular Complications of AIDS (LSOCA) have been described extensively.[18–27] Briefly, patients with AIDS ages 13 years and older were enrolled at 19 United States centers specializing in ocular complications of AIDS, beginning in 1998—entirely within the HAART era. The study respects the principles of the Declaration of Helsinki at all centers, operating under the ongoing approval of each site's governing institutional review board.

From the beginning of the study on 2 September, 1998, through 27 March, 2008, the period of the observations reported here, subjects free of intraocular opportunistic infections were evaluated at semiannual study visits. Demographic and clinical data about AIDS diagnosis, current and nadir CD4+ T cell count, current and zenith HIV load in peripheral blood, anemia, the presence systemic opportunistic complications of AIDS, past and present use of medications, and the presence of co-morbidities were obtained at enrollment and updated at each study visit. A complete ophthalmological examination including both binocular biomicroscopy and dilated ophthalmoscopy were performed by a study-certified ophthalmologist at each visit, including grading of lens opacities as: normal or trivial opacities (less than Grade 1); peripheral vacuoles (Grade 1); peripheral opacity (Grade 2); central opacity (Grade 3); central opacity affecting vision (Grade 4); or surgical aphakia or pseudophakia. A total of 158 examiners at 20 clinics evaluated cataract status. The median number of assessments per examiner was 13 (range: 1 to 1670, Interquartile range (IQR)w: 3 to 50). The median number of examiners per clinic was 10 (range: 1 to 23, IQR: 7 to 14). Best-corrected visual acuity with a logarithmic chart was measured at every visit by gold standard methods.[28] For purposes of these analyses, eyes were defined as having a cataract if they met the following three criteria: 1) graded as having a lens opacity; 2) best-corrected visual acuity worse than 20/40; and 3) reduction of best-corrected visual acuity attributed by the examining ophthalmologist to cataract. Eyes that had undergone cataract surgery prior to the first study visit also were considered to have had a cataract. Among phakic eyes free of cataract at the time of enrollment, the incidence of cataract was counted as occurring on the first follow-up visit at which either cataract, pseudophakia, or aphakia was noted. Anterior segment inflammation was defined as present for eyes with anterior chamber cells, anterior chamber flare, a diagnosis of anterior uveitis or keratitis, and/or the presence of posterior synechiae. Posterior segment inflammation was defined as present for eyes with vitreous

cells and/or vitreous haze; eyes with a diagnosis with intermediate uveitis, posterior uveitis, or panuveitis, or endophthalmitis also were considered to have posterior segment inflammation.

Most population-based studies of cataract in both the United States and Australia have diagnosed cataract based on masked gradings of lens photographs by a reading center, independent of the effects of any opacities on visual acuity.[29–32] However, slit lamp biomicroscopy-based grading methods comparable to those used here have been applied to estimate the prevalence of cataract in two population-based studies in the United States, each of which studied Hispanics predominantly of Mexican origin.[33;34] One of these, the Los Angeles Latino Eye Study (LALES),[35] provided data on the incidence of individual-level cataract surgery for comparison to the data from LSOCA cohort in this analysis.

Sensitivity analyses were performed to determine whether risk factor associations with incident cataract were consistent across two possible alternative definitions of cataract: 1) presence of a “central opacity affecting vision (grade 4)”; and 2) the ophthalmologist’s indication that “based solely on lens status, …[the eye would] be a candidate for cataract surgery”.

The prevalence of either present or prior cataract was evaluated at the time of enrollment in LSOCA. Logistic regression models were fit via generalized estimating equations to estimate the prevalence of cataract and to compare the prevalence and the four-year incidence in the LSOCA cohort to the population-based studies. Staggered entry Kaplan-Meier curves were constructed to show the cumulative probability of incident cataract over time. Cox proportional hazards models evaluated risk factors for incident cataract. All time-to-event analysis were anchored on age to account for this potent cataract risk factor and clustered by individual to account for inter-eye correlation. Subscripts before and after estimates of adjusted odds ratios (ORs) and hazard ratios (HRs) indicate the upper and lower bounds of 95% confidence intervals. Statistical analyses were performed with SAS software version 9.1 (SAS Inc, Cary, NC), Stata software release 10 (StataCorp, College Station, TX), and R software version 2.11.1 (The R Project for Statistical Computing, http://www.r-project.org/, last accessed April 14, 2014).

Results

Two thousand one hundred twenty-one subjects with AIDS were enrolled into the LSOCA cohort between 2 September 1998 and 28 March 2008. Twenty-six subjects were excluded from the analysis for the following reasons: 1) they had been diagnosed with a non-CMV herpetic retinitis, toxoplasmosis involving the retina, or syphilitic eye disease (n = 21) prior to enrollment or during follow-up; 2) they did not complete the enrollment visit (n = 3); or 3) they had unknown cataract status (1) or unknown CMV retinitis status (1) at the time of enrollment. Among the remaining 2,095 subjects with complete cataract and CMV retinitis data, 1,606 (88%) were free of intraocular opportunistic infections in both eyes at enrollment and did not develop intraocular opportunistic infections during follow-up. The prevalence and incidence of cataract were evaluated in the 3,212 eyes of these 1,606 patients.

Characteristics of the analyzed population at enrollment are given as Table 1, available at http://aaojournal.org. Most patients were young and middle-aged male adults, 46% of whom were white, 36% African-American, 15% Hispanic, and the rest of another race/ethnicity. By inclusion criteria of LSOCA, all met the then current CDC definition of AIDS,[36] 63.2% based on a systemic opportunistic infection and the remainder based on CD4+ T lymphopenia. As of the enrollment visit, the median time since AIDS diagnosis was 4.2 years. Although 84% were receiving HAART, 56% had a detectable HIV load in peripheral blood at enrollment. While for 53% the nadir CD4+ T cell count at or prior to enrollment was less than 50 cells/μL, at enrollment 82% had a CD4+ T cell count of 50 cells/μL or more. A substantial proportion of subjects were ill at enrollment, including about 31.3% with anemia, 9% with diagnosed diabetes mellitus, 20% with systemic hypertension, and 21% with hyperlipidemia; 49% had a Karnofsky score[37] of 80 or less.

Prevalence of Cataract

At enrollment, 30 individuals ($_{1.2}1.9_{2.7}$%) had a visually significant cataract (as defined above) or previously had undergone cataract surgery ("cataract") in at least one eye. Of these, 23 (77%) had cataract in one eye and 7 (23%) had cataract in each eye. In comparison to the population-based studies that assessed cataract prevalence by a comparable method (see Table 2),[33;34] the prevalence of cataract was similar among Proyecto VER participants (Hispanics living in Arizona) and LSOCA participants without CMV retinitis or other ocular opportunistic infections, with the exception that the prevalence of cataract was significantly higher in the 40–49 year old age group in LSOCA (1.6%) than Proyecto VER (0.3%; interaction [age group-study cohort] p=0.042; see Table 2). In contrast, after adjustment for age, the LSOCA cohort had a higher overall prevalence of cataract than the Los Angeles Latino Eye Study (LALES) cohort (adjusted OR (aOR) = $_{1.32}2.15_{3.49}$, p = 0.002, Table 2). Non-Latino population-based studies did not assess cataract in a manner comparable to that in LSOCA.

In the LSOCA cohort, older age was associated with a markedly higher risk of cataract (aOR = $_{1.68}2.61_{4.05}$ per 10-year increase in age) (see Table 3), similar to the pattern universally observed in population studies,[4] including those that evaluated cataract similarly.[33;34] The other factors strongly associated with a greater prevalence of cataract reflected ocular diseases, including a history of retinal detachment (adjusted OR (aOR)=$_{13.8}48.7_{171.4}$) and of anterior segment inflammation (aOR=$_{1.54}5.31_{18.3}$). Detectable HIV in peripheral blood was associated with a reduced prevalence of cataract (aOR=$_{0.12}0.32_{0.80}$), unlike the pattern observed in the incidence analysis (see below). Neither time since diagnosis with AIDS, current CD4+ T cell count, current HIV load in peripheral blood, nor use vs. non-use of highly active antiretroviral therapy (HAART) was associated with altered cataract risk (see Table 4, available at http://aaojournal.org). Subjects diagnosed with diabetes mellitus and hypertension had an increased crude prevalence of cataract, which was attributable to confounding by age. Hepatitis B infection also was associated with increased crude prevalence of cataract, which was attributable to confounding by HIV load.

In sensitivity analyses with the alternative definitions of cataract, results were similar, except that diagnosis with diabetes mellitus remained associated significantly with increased

risk of cataract after adjustment for other variables (aOR=$_{1.03}2.63_{6.70}$) in the analysis defining cataract as a "central opacity affecting vision", but not with the alternative definition (aOR= $_{0.84}2.19_{5.73}$)

Incidence of Cataract

Three thousand one hundred seventy-five phakic eyes (of 1,599 patients) were free of cataract at enrollment. Of these, 2,812 (89%) completed at least one follow-up visit. The median follow-up time was 4.6 years (range: 0.37 – 9.12). Out of 25,377 expected visits over the period of follow-up, 22,251 (88%) study visits were completed. During 12,707 eye-years of risk for cataract, 56 new cataracts were observed (incidence rate = $_{0.26}0.37_{0.53}$/100 eye-years).

Just as for prevalent cataract, the risk of incident cataract increased with age (see Figure), following a trajectory similar to population-based reports, with the higher risk in the group ages 60 years and older.[4;33;34] To account for this known predictive factor, the remaining risk analyses of time-to-cataract are anchored to age; thus, age is not included as a covariate in these models.

As in the prevalence analyses, characteristics (other than age) associated with increased incidence of cataract (see Table 5) were primarily ocular, including a history of cataract in the opposite eye (adjusted hazard ratio (aHR)=$_{10.4}21.6_{44.8}$), anterior segment inflammation (aHR$_{1.64}4.40_{11.9}$), vitreous inflammation (aHR$_{2.02}7.12_{25.0}$), and a history of retinal detachment (aHR$_{2.21}4.94_{11.0}$); all these were measured as time-updated characteristics. Karnofsky score ≤80 and infection with hepatitis B each were associated with marginally significantly increased crude incidence of cataract, but the associations were attributable to confounding by contralateral cataract (see Table 6, available at http://aaojournal.org). Detectable HIV RNA in peripheral blood (aHR=$_{0.90}1.58_{2.76}$), CD4+ T cell count, and use of HAART were not associated significantly with incidence of cataract, although a modest increase in risk with low CD4+ T cell count and with non-use of HAART could not be excluded with the available power. No other demographic and clinical characteristics were associated with altered incidence of cataract.

In the two sensitivity analyses, results were similar, with a few exceptions. For cataract definition 2, vitreous inflammation was not significant in the adjusted model due to confounding with cataract in the fellow eye (aHR= $_{0.57}2.64_{12.2}$). For cataract definition 3, neither anterior inflammation (aHR= $_{0.80}2.88_{10.3}$) nor a history of retinal detachment (aHR= $_{0.89}1.95_{4.25}$) was significant in the adjusted model due to confounding with vitreous inflammation. Hepatitis B infection, which was associated with a non-significant increase in the main model (aHR= $_{0.93}2.36_{5.98}$), passed the threshold of significance with a similar aHR in the two sensitivity analyses. Detectable HIV in peripheral blood was associated with a significantly increased risk under cataract definition 3 (aHR= $_{1.09}1.91_{3.33}$) but not in the main model or the alternative sensitivity analysis.

The incidence of cataract surgery was greater in the LSOCA cohort than the LALES cohort after adjustment for age (aOR=$_{1.006}1.84_{3.36,}$, p = 0.048), the differences being most apparent in the older age groups.

Discussion

In this large cohort of subjects with AIDS who were free of ocular opportunistic infections, age and ocular diseases were the primary drivers of cataract risk. The relationship between cataract risk and age was qualitatively similar to that observed in samples of the general population. However, there appeared to be an increase in cataract prevalence when compared in an age-matched fashion to the HIV-uninfected populations, with higher risk than observed in the LALES cohort, and earlier onset than observed in the Proyecto VER cohort. Also, the age-adjusted risk of cataract surgery was higher in the AIDS subjects compared to a general population sample. While the latter observation could be argued to reflect the more frequent contact between subjects and ophthalmologists[38] mandated in the LSOCA protocol than the in LALES protocol, a similar result was observed in a Danish nationwide hospital registry study, suggesting the result is real.[39] While markers of severity of HIV/AIDS were not statistically significantly associated with cataract risk, association may have been mitigated by competing risk of death in patients with unfavorable markers, and incomplete information regarding patients' entire clinical course. Better current CD4+ T cell count, HIV load and HAART status all tended to be associated with lower risk of cataract, though not to a statistically significant degree. Lower nadir CD4+ T cell count tended to be associated with lower risk of cataract, which also might reflect a survivor bias, whereby otherwise more healthy patients with the same low CD4+ T cell count nadir may have survived to be enrolled and likely would have had lower cataract risk. Thus, the results suggest an overall higher risk of cataract in the setting of AIDS, absent opportunistic ocular complication, otherwise with a pattern of risk factors otherwise similar to that of the general population. This result could be taken as supporting the concept that HIV/AIDS results in faster aging.

Our findings of increased cataract risk and ocular inflammation or prior retinal detachment reflect well-known associations. Many techniques for repair of retinal detachment (e.g., vitrectomy and the injection of vitreous substitutes—particularly silicone oil[40]) increase the risk of cataract, and both ocular inflammation itself and treatment with corticosteroids have been known to contribute to a higher incidence of cataract .[41;42] These associations are not necessarily unique to HIV/AIDS, except that HIV/AIDS, its associated conditions, and the management of these may increase the risk of ocular inflammation[43] and/or retinal detachment.[44] Likewise, genetic and environmental risk factors for cataract are well-known. The strong concordance in cataract risk between eyes of the same patient observed here also may reflect these factors.

In these subjects without ocular opportunistic infections, most indicators of HIV disease status did not predict cataract, including current and previous absolute CD4+ T cell count and HIV load in peripheral blood. The exception was that detectable HIV in peripheral blood was associated with a significantly lower risk of cataract in the prevalence, but not the incidence, analysis, in which the risk pattern tended in the opposite direction. This inconsistency might be explained because viremic subjects may have been more likely to be referred to the participating ophthalmology centers for CMV retinitis screening, whereas others may have been less likely referred unless they had visual complaints (in some cases due to cataract), which may have led to differential enrollment that balanced out over

follow-up time (affecting prevalence more than incidence). Use of HAART tended to be associated with a lower risk of cataract but not to a statistically significant level with the available power; a 1/2- to 1/3-fold difference in risk associated with HAART could not be excluded with the available information. Conditions such as diabetes and hyperlipidemia—the risks and severities of which may be influenced by some HIV-related treatments—were not associated with large differences in the risk of cataract in this analysis. However, diabetes is a well-established risk factor for cataract,[45;46] which could be relevant in the setting of HIV/AIDS given the higher risk of diabetes that has been associated with at least some forms of antiretroviral therapy and with AIDS.[47]

Limitations of these analyses include the possibility that the risk of cataract in the LSOCA cohort could be overestimated because subjects were recruited when they presented for eye care, a limitation that would have affected prevalence more than incidence. Likewise, because several participating clinics are centers also focusing on the care of uveitis, ocular inflammation may be over-represented in the cohort, although some have proposed a higher incidence of uveitis in cases of HIV/AIDS.[43] While incidence is a methodologically superior measurement than prevalence for evaluating possibly associated risk factors, the moderate duration of follow-up for a long-term outcome like cataract provides limitations on the power of our incidence study to detect associations, even though the scale of this study was large. Thus, additional data would be needed to identify factors associated with mild to moderately increased risk of cataract. The lack of an internal non-AIDS comparison group also is a limitation, which we attempted to overcome here by comparing results to well-established population-based samples that had used similar methods of cataract ascertainment and documentation. Hispanic population studies were the only US studies available that had used similar cataract definitions; whether the risk of cataract differs among Hispanics from other racial/ethnic groups is uncertain but possible.[48] However, the risk of cataract within the LSOCA cohort did not differ by racial/ethnic status. Standardization of cataract grading across sites was not feasible, which is a limitation, but the outcome observed was supported across two sensitivity analyses.

Strengths of the study include: 1) considerably greater study power to address the question of cataract risk with AIDS than previously was available; 2) reliable information regarding diagnosis of AIDS and its associated clinical status and complications; and 3) the estimation of prevalence and incidence under a common protocol that was enforced and monitored rigorously across all participating centers. The LSOCA cohort also is similar in its distribution of demographic characteristics to the general population of individuals with AIDS in the United States.

In summary, our data suggest that the risk of cataract among subjects with AIDS free of intraocular opportunistic infection may be higher than that observed in the general population, consistent with the hypothesis of accelerated aging in the setting of AIDS. Among our patients with AIDS, immunologic and virologic factors were not clearly associated with altered risk of cataract, although a modest protective effect of HAART could not be excluded. Cataract risk was affected by age and ocular disease (retinal detachment and inflammation). Given the greatly increased survival of persons with AIDS in an era of frequently effective antiretroviral therapy, the burden of cataract among these individuals

likely will increase substantially over time. Additional research, especially with a longer period of surveillance, would strengthen our understanding regarding whether modest but potentially important increases in the risk of cataract exist among patients with AIDS free of ocular opportunistic complications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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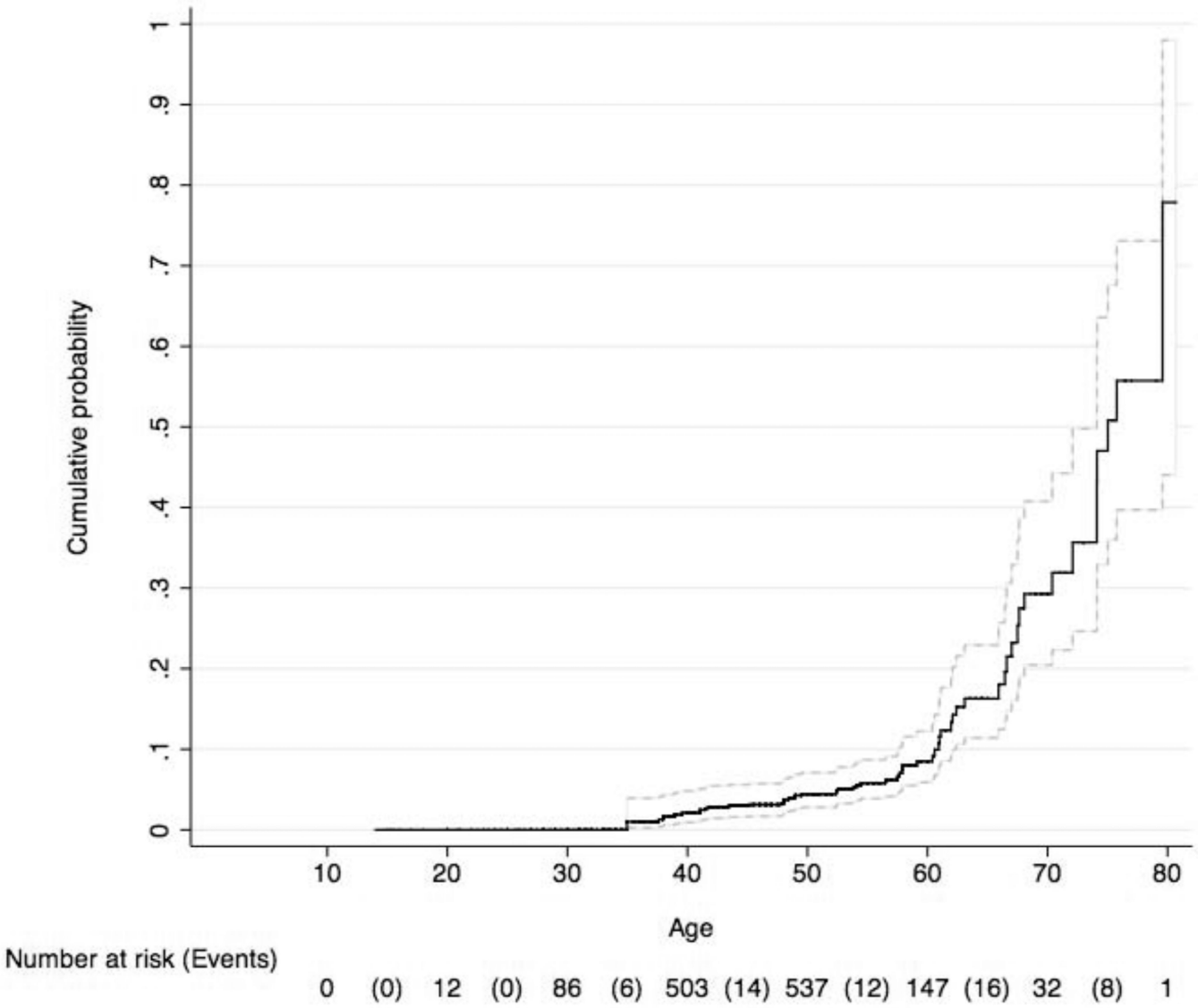

Figure.

Cumulative incidence of cataract as a function of age of diagnosis among participants with AIDS enrolled in the Longitudinal Study of Ocular Complications of AIDS (95% confidence interval indicated by hatched lines).

Table 1

Characteristics of individuals and eyes at enrollment for individuals in the Longitudinal Study of Ocular Complications of AIDS without cytomegalovirus retinitis.

Characteristics of patients at enrollment	Participants (N = 1606)	
Demographic characteristics		
Age at enrollment, years		
Median (interquartile range)	43	(38 , 49)
Gender		
Female	317	(20%)
Male	1289	(80%)
Race/Ethnicity		
White	739	(46%)
Black	577	(36%)
Hispanic	236	(15%)
Other	54	(3%)
Education		
High school or less	652	(41%)
Some college	490	(31%)
College graduate	460	(29%)
Missing, N(%)	4	(0%)
Associated morbidities		
Karnofsky score		
90–100	826	(52%)
≤ 80	779	(49%)
Missing, N(%)	1	(0%)
Anemia		
No	1104	(69%)
Yes	492	(31%)
Missing, N(%)	10	(1%)
Diabetes		
No	1462	(91%)
Yes	144	(9%)
Hypertension		
No	1282	(80%)
Yes	323	(20%)
Missing, N(%)	1	(0%)
Hyperlipidemia		
No	1256	(78%)
Yes	346	(22%)
Missing, N(%)	4	(0%)
Human Immunodeficiency Virus (HIV)/Acquired Immune Deficiency Syndrome (AIDS) History		
Years since AIDS diagnosis (years)		

Characteristics of patients at enrollment	**Participants (N = 1606)**	
Median (interquartile range)	4.2	(1.6 , 7.1)
Absolute CD4+ T cell count, cells/μL		
Median (interquartile range)	189	(78 , 338)
Cells/uL, N(%)		
≥ 50 cells/uL	1306	(82%)
< 50 cells/uL	283	(18%)
Missing, N(%)	17	(1%)
Nadir CD4+ T cells (cells/uL)		
≥ 50 cells/uL	742	(47%)
< 50 cells/uL	839	(53%)
Missing, N(%)	25	(2%)
(HIV) viral load, $\log_{10}$(copies/mL)		
Median (interquartile range)		2.9 (2.0, 4.7)
Log $_{10}$ (copies/mL)		
< 2.6 (undetectable)	677	(44%)
2.6 or higher	848	(56%)
Missing, N(%)	81	(5%)
Highly active antiretroviral therapy		
No	261	(16%)
Yes	1344	(84%)
Missing, N(%)	1	(0%)
Co-infections		
Cerebral toxoplasmosis		
No	1593	(99%)
Yes	13	(1%)
Hepatitis B		
No	1488	(93%)
Yes	117	(7%)
Missing, N(%)	1	(0%)
Hepatitis C		
No	1487	(93%)
Yes	118	(7%)
Missing, N(%)	1	(0%)
Ocular characteristics	**Eyes (E = 3212)**	
Anterior inflammation*		
No	3121	(97%)
Yes	91	(3%)
Vitreous inflammation†		
No	3151	(98%)
Yes	61	(2%)

Characteristics of patients at enrollment	Participants (N = 1606)	
History of retinal detachment‡		
No	3188	(99%)
Yes	24	(1%)

*Anterior chamber cells or flare, diagnosis with anterior uveitis or keratitis, presence of posterior synechiae, or a combination thereof.

†Vitreous haze, anterior vitreous cells, intermediate uveitis, endophthalmitis.

‡Retinal detachment includes individuals with a documented history of retinal detachment and/or the presence of silicone oil.

Table 2

Comparison of the prevalence of at least one eye with a cataract in individuals from the ProyectoVER, LSOCA (patients without CMV retinitis or other ocular opportunistic infections), and LALES cohorts.*

Age category	Proyecto VER Cohort			LSOCA Cohort No CMV Retinitis			LALES Cohort		
	N	%	(95% CI)	N	%	(95% CI)	N	%	(95% CI)
< 40	0	n/a		518	0.6%	(0.1% – 1.7%)	0	n/a	
40–49	1594	0.3%	(0.06% – 6.5%)	736	1.6%**	(0.8% – 2.9%)	2364	0.9%	(0.6% – 1.4%)
50–59	1362	2.0%	(1.3% – 28.8%)	313	2.2%	(0.9% – 4.6%)	1853	1.8%	(1.3%–2.6%)
60–69	984	8.6%	(6.9% – 10.6%)	63	9.5%	(3.5% – 19.6%)	1195	7.3%	(5.9% – 8.9%)
70–79	636	23.3%	(20.0% – 26.8%)	10	20.0%	(2.5% – 55.7%)	584	24.1%	(20.7% – 27.8%)
80+	196	58.2%	(50.9% – 65.2%)	0	n/a		146	52.1%	(43.6% – 60.4%)

* N = number of individuals; % = percent; 95% CI = exact binomial 95% confidence interval LSOCA = Longitudinal study of the ocular complications of AIDS; CMV = cytomegalovirus; LALES = Los Angeles Latino Eye Study; Proyecto VER data derive from reference 28, and LALES data from reference 29.

** The prevalence of 1.6% in the LSOCA Cohort 40–49 year-old age category was statistically significantly different than the same age group in the Proyecto VER Cohort (age-group/study cohort interaction p=0.042). No other statistically significant age-group/study cohort interactions were observed.

Table 3

Risk factors for Cataract (or Prior Cataract Surgery) at the Time of Cohort Entry in Eyes without an Opportunistic Ocular Infection during follow-up in the Longitudinal Studies of the Complications of AIDS, Final Logistic Regression Model

Characteristics*	No Cataract	Cataract	Unadjusted Odds Ratio (95% Confidence Interval)	Unadjusted P-value	Adjusted Odds Ratio (95% Confidence Interval)	Adjusted P-value
Age (per 10 years)	NA	NA	2.83 (1.88, 4.25)	< 0.0001	2.61 (1.68, 4.05)	< 0.0001
HIV viral load [Log10(copies/mL)]						
< 2.6 (undetectable)	1329 (98%)	25 (2%)	1.00		1.00	
2.6 or higher	1686 (99%)	10 (1%)	0.32 (0.13, 0.72)	0.0061	0.32 (0.12, 0.80)	0.0141
Anterior inflammation**						
No	3088 (99%)	33 (1%)	1.00		1.00	
Yes	87 (96%)	4 (4%)	5.99 (2.1, 17.03)	0.0008	5.31 (1.54, 18.24)	0.0079
History of retinal detachment***						
No	3158 (99%)	30 (1%)	1.00		1.00	
Yes	17 (71%)	7 (29%)	28.08 (6.89, 1114.29)	< 0.0001	48.66 (13.81, 171.40)	< 0.0001

HIV = human immunodeficiency virus; NA = not applicable (age is a numerical variable).

* The following characteristics were evaluated but not included in the final logistic regression model (summarized in Table 4, available at: http://aaojournal.org) since they were not significantly associated with cataract at the time of cohort entry: gender, race/ethnicity, education, Karnofsky score, anemia, hyperlipidemia, time since AIDS diagnosis, current CD4+ T-cell count, nadir CD4+ T-cell count, current use of highly active antiretroviral therapy, and hepatitis C. African American race and vitreous inflammation had no crude association with cataract at the time of cohort entry, but were associated after adjustment for the factors above. Hepatitis B, diabetes, and hypertension were associated with increased risk of prevalent cataract that was attributable to counfounding by the variables included in the final multiple logistic regression model above.

** Anterior chamber cells or flare, diagnosis with anterior uveitis or keratitis, presence of posterior synechiae, or a combination thereof.

*** Retinal detachment includes individuals with a documented history of retinal detachment and/or the presence of silicone oil.

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Table 4

Risk factors for Cataract (or Prior Cataract Surgery) at the Time of Cohort Entry in Eyes without an Opportunistic Ocular Infection during follow-up in the Longitudinal Study of Ocular Complications of AIDS

Characteristics	No Cataract	Cataract	Unadjusted Odds Ratio (95% Confidence Interval)	Unadjusted P-value	Adjusted Odds Ratio (95% Confidence Interval)	Adjusted P-value
Demographic characteristics						
Age (per 10 years)	NA	NA	2.83 (1.88, 4.25)	< 0.0001	2.61 (1.68, 4.05)	< 0.0001
Gender						
Female	623 (98%)	11 (2%)	1.00		1.00	
Male	2552 (99%)	26 (1%)	0.58 (0.24, 1.37)	0.2104	0.52 (0.19, 1.41)	0.1939
Race/Ethnicity						
Not black	2040 (99%)	18 (1%)	1.00		1.00	
Black	1135 (98%)	19 (2%)	1.9 (0.88, 4.06)	0.0982	2.97 (1.41, 6.22)	0.0039
Education						
High school or less	1291 (99%)	13 (1%)	1.00		1.00	
Some college	967 (99%)	13 (1%)	1.34 (0.53, 3.31)	0.5327	1.18 (0.46, 3.01)	0.7330
College graduate	909 (99%)	11 (1%)	1.2 (0.48, 2.98)	0.6910	0.77 (0.29, 1.96)	0.5777
Missing	8 (100%)					
Associated morbidities						
Karnofsky score (at enrollment)						
90–100	1639 (99%)	13 (1%)	1.00		1.00	
≤ 80	1534 (98%)	24 (2%)	1.97 (0.89, 4.33)	0.0900	1.79 (0.8, 3.99)	0.1546
Missing	2 (100%)					
Anemia						
No	2179 (99%)	29 (1%)	1.00		1.00	
Yes	976 (99%)	8 (1%)	0.62 (0.23, 1.6)	0.3176	0.78 (0.24, 2.47)	0.6779
Missing	20 (100%)					
Diabetes						
No	2897 (99%)	27 (1%)	1.00		1.00	
Yes	278 (97%)	10 (3%)	3.86 (1.56, 9.53)	0.0034	2.92 (0.96, 8.85)	0.0582
Hypertension						
No	2543 (99%)	21 (1%)	1.00		1.00	

Characteristics	No Cataract	Cataract	Unadjusted Odds Ratio (95% Confidence Interval)	Unadjusted P-value	Adjusted Odds Ratio (95% Confidence Interval)	Adjusted P-value
Yes	630 (98%)	16 (2%)	3.08 (1.41, 6.69)	0.0045	1.92 (0.86, 4.25)	0.1086
Missing	2 (100%)					
Hyperlipidemia						
No	2482 (99%)	30 (1%)	1.00		1.00	
Yes	685 (99%)	7 (1%)	0.85 (0.32, 2.18)	0.7271	0.39 (0.14, 1.05)	0.0603
Missing	8 (100%)					
Human Immunodeficiency Virus (HIV)/Acquired Immune Deficiency Syndrome (AIDS) History						
Time since AIDS diagnosis (years)						
< 2 years	906 (99%)	10 (1%)	1.00		1.00	
2–4 years	593 (99%)	5 (1%)	0.76 (0.2, 2.82)	0.6856	0.53 (0.13, 2.11)	0.3668
4–6 years	570 (99%)	8 (1%)	1.27 (0.42, 3.85)	0.6703	1.08 (0.32, 3.62)	0.8974
≥6 years	1058 (99%)	14 (1%)	1.2 (0.44, 3.22)	0.7188	0.79 (0.25, 2.45)	0.6788
Missing	48 (100%)					
CD4+ T cells, N(%)						
≥ 50 cells/uL	2580 (99%)	32 (1%)	1.00		1.00	
< 50 cells/uL	563 (99%)	3 (1%)	0.43 (0.12, 1.44)	0.1686	0.80 (0.28, 2.03)	0.6807
Missing	32 (94%)	2 (6%)				
Nadir CD4+ T cells (cells/uL)						
≥50 cells/uL	1465 (99%)	19 (1%)	1.00		1.00	
< 50 cells/uL	1661 (99%)	17 (1%)	0.79 (0.36, 1.71)	0.5480	1.01 (0.45, 2.22)	0.9848
Missing	49 (98%)	1 (2%)				
HIV viral load [Log10(copies/mL)]						
< 2.6 (undetectable)	1329 (98%)	25 (2%)	1.00		1.00	
2.6 or higher	1686 (99%)	10 (1%)	0.32 (0.13, 0.72)	0.0061	0.32 (0.12, 0.80)	0.0141
Missing	160 (99%)	2 (1%)				
Highly active antiretroviral therapy						
No	515 (99%)	7 (1%)	1.00		1.00	
Yes	2658 (99%)	30 (1%)	0.83 (0.29, 2.31)	0.7212	0.43 (0.12, 1.41)	0.1605
Missing	2 (100%)					
Co-infections						
Hepatitis B						

Characteristics	No Cataract	Cataract	Unadjusted Odds Ratio (95% Confidence Interval)	Unadjusted P-value	Adjusted Odds Ratio (95% Confidence Interval)	Adjusted P-value
No	2947 (99%)	29 (1%)	1.00		1.00	
Yes	226 (97%)	8 (3%)	3.6 (1.38, 9.37)	0.0088	1.63 (0.62, 4.27)	0.3199
Missing	2 (100%)					
Hepatitis C						
No	2939 (99%)	35 (1%)	1.00		1.00	
Yes	234 (99%)	2 (1%)	0.72 (0.16, 3.04)	0.6518	0.60 (0.14, 2.54)	0.4846
Missing	2 (100%)					
Ocular characteristics						
Anterior inflammation*						
No	3088 (99%)	33 (1%)	1.00		1.00	
Yes	87 (96%)	4 (4%)	5.99 (2.1, 17.03)	0.0008	5.31 (1.54, 18.24)	0.0079
Vitreous inflammation**						
No	3116 (99%)	35 (1%)	1.00		1.00	
Yes	59 (97%)	2 (3%)	2.13 (0.63, 7.08)	0.2183	0.10 (0.03, 0.32)	0.0001
History of retinal detachment***						
No	3158 (99%)	30 (1%)	1.00		1.00	
Yes	17 (71%)	7 (29%)	28.08 (6.89, 1114.29)	< 0.0001	48.66 (13.81, 171.40)	< 0.0001

*Anterior chamber cells or flare, diagnosis with anterior uveitis or keratitis, presence of posterior synechiae, or a combination thereof.

**Vitreous haze, anterior vitreous cells, intermediate uveitis, endophthalmitis.

***Retinal detachment includes individuals with a documented history of retinal detachment and/or the presence of silicone oil.

Table 5

Assessment of Risk Factors for Incident Cataract in Eyes without an Opportunistic Ocular Infection (participants in the Longitudinal Study of Ocular Complications of AIDS), Final Cox Regression Model.

Characteristics*	Rate per 100 Eye-years	Count of Cataracts per Eye-year at Risk	Unadjusted Hazard Ratio (95% Confidence Interval [CI])	Unadjusted P-value	Adjusted Hazard Ratio (95% CI)	Adjusted P-value
Human Immunodeficiency Virus (HIV)/Acquired Immune Deficiency Syndrome (AIDS) History						
CD4+ T cells (time-varying)						
≥50 cells/uL	0.43	(50 / 11633)	1.00		1.00	
< 50 cells/uL	0.55	(6 / 1091.3)	2.16 (0.88, 5.25)	0.090	1.64 (0.77, 3.45)	0.19
	0	(0 / 135.7)				
Nadir CD4+ T cells (at enrollment)						
≥50 cells/uL	0.64	(39 / 6132.4)	1.00		1.00	
< 50 cells/uL	0.26	(17 / 6458.2)	0.62 (0.33, 1.16)	0.13	0.55 (0.31, 0.95)	0.031
	0	(0 / 111.6)				
HIV viral load (time-varying)						
< 2.6 (undetectable)	0.45	(35 / 7764.9)	1.00		1.00	
2.6 or higher	0.43	(21 / 4849.8)	1.58 (0.9, 2.76)	0.11	1.51 (0.86, 2.64)	0.1485
Highly active antiretroviral therapy (time-varying)						
No	0.81	(8 / 982.8)	1.00		1.00	
Yes	0.41	(48 / 11743.6)	0.5 (0.22, 1.1)	0.082	0.54 (0.26, 1.11)	0.093
Ocular Characteristics						
History of cataract in contralateral eye						
No	0.27	34 / 12570.3	1.00		1.00	
Yes	14.1	22 / 156	21.16 (10.05, 44.53)	< 0.0001	21.58 (10.39, 44.81)	< 0.0001
Anterior inflammation (time-varying)†						
No	0.4	50 / 12570.3	1.00		1.00	
Yes	3.85	6 / 156	6 (1.67, 21.52)	0.0060	4.40 (1.64, 11.78)	0.0032
Vitreous inflammation (time-varying)‡						
No	0.41	52 / 12661.8	1.00		1.00	
Yes	6.2	4 / 64.5	11.31 (3.6, 35.52)	< 0.0001	7.12 (2.02, 25.02)	0.0022
History of retinal detachment§						

Characteristics*	Rate per 100 Eye-years	Count of Cataracts per Eye-year at Risk	Unadjusted Hazard Ratio (95% Confidence Interval [CI])	Unadjusted P-value	Adjusted Hazard Ratio (95% CI)	Adjusted P-value
No	0.39	48 / 12387.4	1.00		1.00	
Yes	2.36	8 / 338.9	5.30 (2.51, 11.16)	< 0.0001	4.94 (2.21, 11.02)	< 0.0001

*Additional variables that were not associated with increased incidence of cataract included: gender, race, education, anemia (time-varying), diabetes, hypertension, hyperlipidemia, current CD4+ T-cells, current human immunodeficiency virus load, current use of highly active antiretroviral therapy, and hepatitis C. Nadir CD4+ T-cell count had no crude association with incident cataract, but was associated with incident cataract after adjustment for the factors above. Several variables were associated significantly with incident cataract in the crude analysis, but were omitted from the adjusted analysis because they were confounded by 1 or more of the variables in the final model and were not associated with incident cataract after adjustment. These include: Karnofsky score and hepatitis B.

†Anterior chamber cells or flare, diagnosis with anterior uveitis or keratitis, presence of posterior synechiae, or a combination thereof.

‡Vitreous haze, anterior vitreous cells, intermediate uveitis, endophthalmitis.

§Retinal detachment includes individuals with a documented history of retinal detachment and/or the presence of silicone oil.

Table 6

Assessment of Risk Factors for Incident Cataract in Eyes without an Opportunistic Ocular Infection (participants in the Longitudinal Study of Ocular Complications of AIDS)

Characteristics*	Rate per 100 Eye-years	Count of Cataracts per Eye-years at Risk	Ratio (95% Confi-	Unadjusted P-value	Adjusted Hazard Ratio (95% CI)	Adjusted P-value
Demographic characteristics						
Gender						
Female	0.49	(12 / 2438.4)	1.00		1.00	
Male	0.43	(44 / 10288)	0.86 (0.45, 1.65)	0.6538	0.98 (0.5, 1.92)	0.9535
Race/Ethnicity						
Not black	0.44	(37 / 8366)	1.00		1.00	
Black	0.44	(19 / 4360.3)	1.43 (0.78, 2.61)	0.2468	1.20 (0.71, 2.05)	0.4898
	4.15	(1 / 24.1)				
Education (at enrollment)						
High school or less	0.45	(21 / 4646.8)	1.00		1.00	
Some college	0.25	(10 / 3926.3)	0.54 (0.25, 1.14)	0.1025	0.72 (0.34, 1.52)	0.3891
College graduate	0.58	(24 / 4129.1)	0.82 (0.43, 1.53)	0.5269	1.03 (0.57, 1.84)	0.9300
Associated morbidities						
Karnofsky score (at enrollment)						
90–100	0.36	(26 / 7285.9)	1.00		1.00	
<80	0.55	(30 / 5440.4)	1.73 (1.01, 2.96)	0.0457	1.43 (0.85, 2.39)	0.1740
	0	(0 / 3.8)				
Anemia (time-varying)						
No	0.43	(37 / 8645.3)	1.00		1.00	
Yes	0.47	(19 / 4077.3)	1.37 (0.77, 2.42)	0.2819	1.35 (0.82, 2.21)	0.2378
Diabetes (at enrollment)						
No	0.44	(51 / 11664.1)	1.00		1.00	
Yes	0.47	(5 / 1062.2)	0.89 (0.35, 2.21)	0.7940	0.91 (0.35, 2.35)	0.8484
Hypertension (at enrollment)						
No	0.37	(39 / 10408.6)	1.00		1.00	
Yes	0.73	(17 / 2317.7)	1.36 (0.77, 2.39)	0.2815	1.41 (0.77, 2.57)	0.2604

Characteristics*	Rate per 100 Eye-years	Count of Cataracts per Eye-years at Risk	Ratio (95% Confi-	Unadjusted P-value	Adjusted Hazard Ratio (95% CI)	Adjusted P-value
	0	(0 / 10.3)				
Hyperlipidemia (at enrollment)						
No	0.41	(40 / 9757.9)	1.00		1.00	
Yes	0.54	(16 / 2958.1)	1.12 (0.61, 2.04)	0.7202	1.16 (0.6, 2.22)	0.6494
Human Immunodeficiency Virus (HIV)/Acquired Immune Deficiency Syndrome (AIDS) History						
CD4+ T cells (time-varying)						
≥50 cells/uL	0.43	(50 / 11633)	1.00		1.00	
< 50 cells/uL	0.55	(6 / 1091.3)	2.16 (0.88, 5.25)	0.0896	1.64 (0.77, 3.45)	0.1925
	0	(0 / 135.7)				
Nadir CD4+ T cells (at enrollment)						
≥50 cells/uL	0.64	(39 / 6132.4)	1.00		1.00	
< 50 cells/uL	0.26	(17 / 6458.2)	0.62 (0.33, 1.16)	0.1312	0.55 (0.31, 0.95)	0.0307
	0	(0 / 111.6)				
HIV viral load (time-varying) [Log10(copies/mL)]						
< 2.6 (undetectable)	0.45	(35 / 7764.9)	1.00		1.00	
2.6 or higher	0.43	(21 / 4849.8)	1.58 (0.9, 2.76)	0.1050	1.51 (0.86, 2.64)	0.1485
Highly active antiretroviral therapy (time-varying)						
No	0.81	(8 / 982.8)	1.00		1.00	
Yes	0.41	(48 / 11743.6)	0.5 (0.22, 1.1)	0.0819	0.54 (0.26, 1.11)	0.0930
Co-infections						
Hepatitis B (at enrollment)						
No	0.42	(51 / 12206.9)	1.00		1.00	
Yes	0.97	(5 / 516.3)	2.7 (1.04, 7.01)	0.0406	2.36 (0.93, 5.98)	0.0705
	0	(0 / 3.1)				
Hepatitis C (at enrollment)						
No	0.45	(55 / 12171.1)	1.00		1.00	
Yes	0.18	(1 / 552.1)	0.45 (0.06, 3.28)	0.4306	0.56 (0.08, 3.95)	0.5640
Ocular characteristics						
History of cataract in contralateral eye						
No	0.27	(34 / 12570.3)	1.00		1.00	

Characteristics*	Rate per 100 Eye-years	Count of Cataracts per Eye-years at Risk	Ratio (95% Confi-	Unadjusted P-value	Adjusted Hazard Ratio (95% CI)	Adjusted P-value
Yes	14.1	(22 / 156)	21.16 (10.05, 44.53)	< 0.0001	21.58 (10.39, 44.81)	< 0.0001
Anterior inflammation (time-varying)†						
No	0.4	(50 / 12570.3)	1.00		1.00	
Yes	3.85	(6 / 156)	6 (1.67, 21.52)	0.0060	4.40 (1.64, 11.78)	0.0032
Vitreous inflammation (time-varying)‡						
No	0.41	(52 / 12661.8)	1.00		1.00	
Yes	6.2	(4 / 64.5)	11.31 (3.6, 35.52)	< 0.0001	7.12 (2.02, 25.02)	0.0022
History of retinal detachment§						
No	0.39	(48 / 12387.4)	1.00		1.00	
Yes	2.36	(8 / 338.9)	5.30 (2.51, 11.16)	< 0.0001	4.94 (2.21, 11.02)	< 0.0001

†Anterior chamber cells or flare, diagnosis with anterior uveitis or keratitis, presence of posterior synechiae, or a combination thereof.

‡Vitreous haze, anterior vitreous cells, intermediate uveitis, endophthalmitis.

§Retinal detachment includes individuals with a documented history of retinal detachment and/or the presence of silicone oil.

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