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Risk of Cataract in Persons with Cytomegalovirus Retinitis and the Acquired Immune Deficiency Syndrome

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Abstract

Objective—To evaluate cataract risk in eyes of patients with AIDS and cytomegalovirus (CMV) retinitis and to identify risk factors.

Design—Prospective cohort study.

Participants—Patients with AIDS and CMV retinitis.

Methods—Patients 13 years of age and older were enrolled between 1998 and 2008. Demographic and clinical characteristics, slit-lamp biomicroscopy findings, and dilated ophthalmoscopy results were documented at quarterly visits. Cataract status was determined at the initial visit (prevalence) and at follow-up visits (incidence).

Main Outcome Measures—For cataract, a high grade of lens opacity by biomicroscopy to which best-corrected visual acuity worse than 20/40 was attributed. Eyes that had undergone cataract surgery before enrollment or between visits also were counted as having cataract.

Results—Seven hundred twenty-nine eyes of 489 patients diagnosed with CMV retinitis were evaluated. Higher prevalence was observed for patients with bilateral versus unilateral CMV retinitis (adjusted odds ratio [aOR], 2.74; 95% confidence interval [CI], 1.76–4.26) and, among unilateral CMV retinitis cases, for eyes with retinitis versus without retinitis (15% vs. 1.4%; $P < 0.0001$). The age-adjusted prevalence of cataract among CMV retinitis cases was higher than

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that in a population-based sample ($P < 0.0001$). Cataract prevalence increased with age (aOR, 11.77; 95% CI, 2.28–60.65 for age ≥ 60 years vs. younger than 40 years) and longer duration of retinitis (aOR, 1.36; 95% CI, 1.20–1.54 per year). Among eyes with CMV retinitis initially free of cataract, the cataract incidence was 8.1%/eye-year (95% CI, 6.7%–10.0%). Prior retinal detachment was associated with higher cataract risk (if repaired with silicone oil: adjusted hazard ratio [aHR], 10.37; 95% CI, 6.51–16.52; otherwise: aHR, 2.90; 95% CI, 1.73–4.87). Large CMV retinitis lesions also were associated with higher risk of cataract (for involvement of 25–49% retinal area: aHR, 2.30; 95% CI, 1.51–3.50; for ≥ 50% involvement: aHR, 3.63; 95% CI, 2.18–6.04), each with respect to ≥ 24% involvement, as were anterior segment inflammation (aHR, 2.27; 95% CI, 1.59–3.25) and contralateral cataract (aHR, 2.52; 95% CI, 1.74–3.66).

Conclusions—Cytomegalovirus retinitis is associated with a high absolute and relative risk of cataract. Among several risk factors, large retinal lesion size and use of silicone oil in retinal detachment repair are potentially modifiable, albeit not in all cases. Cataract is likely to be an increasingly important cause of visual morbidity in this population.

Cytomegalovirus (CMV) retinitis is an important opportunistic complication of human immunodeficiency virus infection^{1–4} and is the leading cause of visual loss in patients with AIDS in the era of highly active antiretroviral therapy (HAART) era,⁵ as it was before the availability of HAART.⁶ The clinical course of CMV retinitis changed dramatically after the clinical application of HAART—with improved visual outcomes⁷ and survival^{8–12}; reduced risks of retinal detachment,^{13,14} retinitis in the second eye,^{14,15} and retinitis progression¹⁶; and the new risk of the immune recovery inflammatory response called immune recovery uveitis.^{17–20} The causes of vision loss in patients with AIDS have evolved with the availability of HAART as well.

In previous investigations, the authors found that, in the era of HAART, cataract was the second leading cause of visual impairment among patients with CMV retinitis^{21,22} and a major source of visual loss among patients with AIDS in general.⁵ To characterize better the risk of cataract among patients with AIDS, this article reports an analysis of the prevalence and incidence of cataract in a large cohort of persons with CMV retinitis observed during the HAART era.

Patients and Methods

The Longitudinal Study of Ocular Complications of AIDS (LSOCA) has been described previously.^{14,16,19,23–27} Persons with AIDS who sought care at 19 AIDS ophthalmology centers in the United States and who were at least 13 years of age were enrolled into this protocol beginning in 1998. Persons with preexisting or newly diagnosed CMV retinitis were oversampled to allow study of their outcomes; these individuals were followed up quarterly after enrollment. The study has been conducted with the annual approval of each participating center's institutional review board for human subject research and has complied with local board requirements.

Data from the time of enrollment evaluated for this report include: demographic information; date of AIDS diagnosis; date of CMV retinitis diagnosis; current (at each visit) and nadir absolute CD4+ T-cell count; current and zenith human immunodeficiency virus load in peripheral blood; presence of anemia (hemoglobin <10 g/dl), diabetes mellitus, hypertension, or hyperlipidemia; Karnofsky score²⁸; the presence of opportunistic complications of AIDS and coinfections; and past and present use of antiretroviral and anti-CMV medications. All data were obtained at the time of enrollment and updated sequentially over the duration of follow-up. Binocular biomicroscopy and dilated binocular ophthalmoscopy were performed by a study-certified ophthalmologist on each eye at each visit. Ophthalmologists recorded the presence of both anterior (including anterior chamber

cells or flare, diagnosis with anterior uveitis or keratitis, presence of posterior synechiae) and posterior segment (including vitreous cells; vitreous haze, diagnosis with pars planitis or intermediate, posterior, or panuveitis or with endophthalmitis; or a combination thereof) inflammatory signs or diagnoses; activity of CMV retinitis; size of CMV retinitis lesions in fraction of retinal area and location with Holland zones²⁹; and the presence of immune recovery uveitis.¹⁹

Slit-lamp biomicroscopy was performed at every visit by study ophthalmologists who did not otherwise receive training in grading cataracts. Lens opacity was graded as: peripheral vacuoles (grade 1), peripheral opacity (grade 2), central opacity (grade 3), central opacity affecting vision (grade 4), less than grade 1, or not applicable (normal or trivial opacities). Study ophthalmologists also were asked what the cause of reduced best-corrected visual acuity was. For purposes of this analysis, cataract was defined as a high grade of lens opacity combined with best-corrected visual acuity worse than 20/40 attributed to cataract in the eye with lens opacity, a definition that allowed comparison with a published population-based prevalence estimate of cataracts among older adults.³⁰ Phakic eyes meeting this definition of cataract at the time of the first visit after the diagnosis of CMV retinitis were considered to have prevalent cataract. Eyes that were pseudophakic or aphakic initially were considered to have had cataract previously. Initially phakic eyes free of cataract at their first visit after the diagnosis of CMV retinitis were considered to have incident cataract if or when they met this definition of cataract or were found to be pseudophakic or aphakic during follow-up.

Sensitivity analyses evaluated whether possible alternative definitions of cataract affected risk estimates and risk factor assessments substantially. Alternative definitions of cataract considered included: (1) indication by the certified ophthalmologist that “based solely on lens status, ... [the eye would] be a candidate for cataract surgery,” (2) diagnosis with a “central [lens] opacity affecting vision,” or both.

Logistic regression models estimated the prevalence of cataract via generalized estimating equations. The incidence rate for cataract is expressed as a rate per 100 person-years. Staggered entry Kaplan-Meier curves were plotted to portray the cumulative probability of incident cataract over time, anchored at the reported date of diagnosis of CMV retinitis. Cox proportional hazards models compared the relative risks of acquiring cataract. Analyses based on complete data at baseline, carrying forward the time-varying covariates and applying multiple imputation for missing values, were conducted as a sensitivity analysis. 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/>, accessed August 19, 2011) statistical packages.

Adjusted odds ratios (ORs) and hazard ratios (HRs) are reported for risk factors for prevalent and incident cataract, respectively. Ninety-five percent confidence intervals (CIs) are given as subscripts, with the boundaries bracketing the risk ratios.

Results

Two thousand one hundred twenty-one persons with AIDS were enrolled and entered into the LSOCA database between September 2, 1998, and March 27, 2008. Twenty-six patients were excluded from these analyses because they had been diagnosed previously with a non-CMV herpetic retinitis, toxoplasmic retinitis, or syphilitic eye disease ($n = 21$), did not complete the enrollment visit ($n = 3$), or had unknown cataract status ($n = 1$) or unknown CMV retinitis status ($n = 1$) at the time of enrollment. Among the remaining 2095 subjects

with completed data on the baseline status of cataract and CMV retinitis, 463 individuals (22%) had CMV retinitis involving 663 eyes at the time of enrollment. During follow-up, an additional 26 subjects developed CMV retinitis affecting 35 eyes (17 unilateral and 9 bilateral), and an additional 31 eyes of persons with initially unilateral CMV retinitis developed retinitis in the second eye. Thus, 729 eyes of 489 subjects were evaluated for the prevalence and incidence of cataract.

Prevalence of Cataract

Characteristics of the population as of the first study visit after diagnosis of CMV retinitis are given in Table 1 (available at <http://aaojournal.org>). At this point, individuals with bilateral CMV retinitis were more than twice as likely to have visually significant cataract (as defined previously) or to have undergone cataract surgery in at least 1 eye than individuals with unilateral CMV retinitis (32% vs. 15%; OR, 1.76^{2.74}_{4.26}). Among the 205 individuals with bilateral CMV retinitis at this point, 139 (68%) had no cataract, 36 (17%) had a cataract in 1 eye, and 30 (15%) had a cataract in each eye. Among the 284 initially unilateral CMV retinitis cases, 242 (85%) had no cataract in either eye, 38 (13%) had cataract only in the eye with CMV retinitis, 4 (1.4%) had bilateral cataract, and none had cataract in the eye free of CMV retinitis. Cataract was approximately 11-fold more frequent among eyes with CMV retinitis than among those free of CMV retinitis (15% vs. 1.4%; $P<0.0001$). For the other 35 individuals with initially unilateral CMV retinitis in whom CMV retinitis developed in the second eye during follow-up, none of the eyes diagnosed during follow-up had cataract at the time of diagnosis, whereas 6 of the contralateral eyes with CMV retinitis had been diagnosed with a cataract (0% vs. 17%; $P=0.041$).

The prevalence of cataract in the LSOCA subjects with CMV retinitis was higher than that of the population-based Proyecto Vision, Evaluation, Research cohort (age-adjusted $P<0.0001$; Table 2), which used a comparable definition of cataract.³⁰ Among subjects clustered by decades of ages 40 to 49 years, 50 to 59 years, and 60 to 69 years—where the age distributions of the 2 cohorts overlapped—the risk was 93-fold, 14-fold, and 5.8-fold higher, respectively, among the LSOCA participants with CMV retinitis. The proportion of individuals with cataract in the Proyecto Vision, Evaluation, Research cohort increased quadratically with age, similar to that reported in a meta-analysis of population-based prevalence studies that had measured cataract based solely on objective findings without reference to visual acuity,³¹ such that the increase with age was even steeper than among LSOCA subjects with CMV retinitis (see below).

Risk factors for cataract at the time of presentation with CMV retinitis (including prevalent pseudophakia or aphakia) are summarized in Table 3. Iterative statistical analyses indicated that prior retinal detachment and a larger fraction of the retinal area involved by CMV retinitis (adjusted OR [aOR] for lesions 25%–49%, 3.30^{6.52}_{12.88}; aOR for lesions 50%, 3.91^{8.53}_{18.60}) were the predominant risk factors for prevalent cataract in this cohort. Prior retinal detachment was associated much more strongly with cataract if silicone oil had been used in the repair (aOR, 7.47^{19.73}_{52.07}) than if not (aOR, 0.83^{2.32}_{6.47}); there was an overall 4.12^{8.25}_{16.50}-fold increased odds of cataract for eyes with history of retinal detachment. In addition, higher age (particularly among those 60 years of age or older relative to those younger than 40 years: aOR, 2.28^{1.77}_{60.65}), longer duration of CMV retinitis (aOR, 1.22^{1.39}_{1.59} per year), and the presence of anterior segment inflammatory signs (aOR, 1.29^{2.46}_{4.67}) were associated with increased odds of having cataract at presentation. A currently active CMV retinitis border was associated with decreased odds of cataract at presentation (aOR, 0.07^{0.26}_{0.93}).

Several factors associated with cataract in bivariate analysis did not show significant association after adjustment for other factors (see Table 4, available at <http://aaojournal.org>).

Factors associated with higher crude risk before adjustment for confounders (with the primary confounder(s) given in parentheses) were: prevalent immune recovery uveitis (anterior inflammation); involvement of zone 1 with CMV retinitis (area of involvement); hyperlipidemia, time since AIDS diagnosis, and history of ganciclovir implant therapy (retinal detachment); history of use of intravenous or intravitreal cidofovir (duration of CMV retinitis and age); and history of use of foscarnet (duration of CMV retinitis and age). Factors associated with lower crude risk of cataract before adjustment for confounders were: black race, anemia, current absolute CD4+ T-cell count less than 50 cells/ μ l, log (human immunodeficiency virus load) -2.6 , vitreous inflammatory signs, and use of valganciclovir; these variables generally were confounded by multiple other variables. In addition, nadir CD4+ T-cell count of 50 cells/ μ l or more, hepatitis B infection, and involvement of zone 3 with CMV retinitis were not associated with altered crude odds of having cataract at presentation, but were associated with increased risk after adjusting for the variables included in the final multiple regression model.

Incidence of Cataract

Five hundred ninety-one (81%) phakic eyes (of 419 patients) were free of cataract at the time of the first visit after the diagnosis of CMV retinitis. Of these, 521 (88%) completed at least 1 follow-up visit. The median follow-up time was 1.99 eye-years (range, 0.15–9.36 eye-years). From 5961 expected visits during this period, 5148 (86%) were completed. Of 1566 eye-years at risk of cataract, 145 cataracts were observed (rate, 6.78.1_{10.0} per 100 eye-years).

Over the limited follow-up time of cases free of cataract at the initial visit with CMV retinitis, risk factors for incident cataract were less numerous than in the prevalence analysis, but similar patterns were observed (summarized in Table 5). Longer follow-up time after the diagnosis of CMV retinitis was associated with increasing risk of cataract (Fig 1); therefore, evaluation of time-to-cataract was anchored to the time from diagnosis of CMV retinitis. Because time-updated age and time since AIDS diagnosis in the incidence model were correlated strongly with time since CMV retinitis diagnosis, the former variables were omitted from the incidence analysis. Prior retinal detachment, both without (adjusted HR [aHR], 1.73_{2.90}_{4.87}) or with (aHR, 6.51_{10.37}_{16.52}) silicone oil repair, was associated with an increased risk of development of cataract, with an overall 3.45_{5.04}_{7.37}-fold overall increase for eyes with retinal detachment. Larger CMV retinitis lesion sizes (aHR for lesions 25%–49%, 1.51_{2.30}_{3.50}; aHR for lesions $\geq$ 50%, 2.18_{3.63}_{6.04}) were associated with progressively increased risk of cataract. Anterior chamber inflammatory signs were associated with approximately a 2-fold higher risk of cataract (aHR, 1.59_{2.27}_{3.25}), a stronger association than was observed with diagnosis of either immune recovery uveitis or vitreous inflammatory signs. Presence of cataract in the contralateral eye also was associated with a higher risk of incident cataract (aHR, 1.74_{2.52}_{3.66}).

As in the prevalence analysis, several factors significant in the crude analysis did not show statistically significant association with incident cataract after adjustment for other factors (see Table 6, available at <http://aojournal.org>). Factors associated with higher risk of cataract only before adjustment (with their primary confounder(s) in parentheses) included: lower absolute CD4+ T-cell count (several factors), zone 1 involvement (lesion size), prior ganciclovir implant therapy (retinal detachment), systemic foscarnet or valganciclovir therapy (age and duration of CMV retinitis), and diagnosis with CMV retinitis in the contralateral eye (cataract in the contralateral eye). As in the prevalence analysis, immune recovery uveitis and prior use of cidofovir had no significant crude association with cataract. Also, in contrast to the prevalence analysis results, a currently active border to the CMV retinitis was associated with increased crude risk of cataract in the incidence analysis, but with no significant difference in risk after adjusting for other factors.

A sensitivity analysis, imputing rather than omitting missing values, yielded similar results to those described above. Sensitivity analyses using the alternative cataract definitions also yielded similar results.

Discussion

These results indicate that CMV retinitis profoundly increases the risk of cataract in patients with AIDS, as demonstrated by the observations that: (1) among unilateral CMV retinitis cases, cataract risk is several-fold higher in the eye with retinitis; (2) patients with bilateral retinitis have proportionately higher risk of cataract than patients with unilateral retinitis; and (3) the risk of cataract among patients with AIDS and CMV retinitis is several-fold higher than that in persons in a general population sample of comparable ages. The observations—specifically that (1) eyes diagnosed with retinitis during follow-up did not have cataracts and (2) the risk increased progressively over time after CMV retinitis diagnosis—suggest that the effects of CMV retinitis (or the associated inflammatory response, no matter how modulated by the underlying immunodeficiency) on the lens are not instantaneous, but rather accumulate over time. After adjusting for other factors, retinitis activity was associated neither with increased nor with decreased incidence of cataract, suggesting that control of retinitis is not sufficient to prevent cataract during this period. Nonetheless, the strong association between larger size of the CMV retinitis lesion and cataract suggests that early detection of retinitis and suppression of the progression of retinitis may reduce the risk of cataract formation or progression over a longer period.

Consistent with previous reports^{21,22} from an earlier stage of enrollment and follow-up of this HAART-era cohort, cataract was found to be an important cause of visual loss among patients with CMV retinitis from the perspective of both absolute risk and relative risk. In the present analysis, approximately one-fifth of subjects had cataract at or before their enrollment into the LSOCA, and those initially free of cataract demonstrated cataract at a rate of 8.1 per 100 eye-years during follow-up.

A large area of retinitis involvement was associated with a many-fold higher risk of cataract, a stronger relationship than was expected. Adjustment for therapy with ganciclovir implants or cidofovir did not eliminate the association; neither of the latter factors proved to have a major impact on cataract risk after adjustment for confounding factors. Inflammatory signs in the anterior chamber were associated with a modest increase in cataract risk, which may have resulted from the inflammation itself, use of therapeutic topical corticosteroids, or both. However, the magnitude of the association of cataract with large lesion size was much stronger than the association with inflammation, and that association persisted after adjustment for observed inflammatory findings and diagnosis with immune recovery uveitis. Neither immune recovery uveitis nor observed posterior segment inflammatory signs was associated strongly with cataract in this cohort. However, given that it is difficult to quantify and to adjust for inflammation when the documented observations are limited to quarterly visits and that clinical examination may capture imperfectly the extent of inflammation occurring in these eyes (either from the primary opportunistic retinal infection or from the immune recovery inflammatory responses), additional cumulative inflammation missed under the study protocol might have contributed to the association between large lesion size and cataract risk. Cytomegalovirus also has been known to infect other parts of the eye, such as the iris³²; it is conceivable that such involvement is more widespread than clinically appreciated and may alter or enhance cataract risk.

That a longer time since diagnosis of CMV retinitis is associated with progressively increasing risk of cataract probably reflects similar inflammatory issues. Although longer duration of retinitis is associated with larger lesion size, each factor remained significantly

and strongly associated with higher cataract risk after adjusting for the other. It is likely that the various problems set in motion by CMV retinitis have a cumulative impact over time. Thus, although early detection and effective treatment may reduce the cataract incidence rate somewhat by limiting the extent (area) of retinal damage by CMV retinitis, cataract likely will become increasingly prevalent with improving survival in the HAART era because the clinical course of CMV retinitis is prolonged.

The observation that retinal detachment is associated strongly with increased cataract risk is not surprising, given that repair typically involves vitrectomy surgery,³³ which itself is an established risk factor for cataract,³⁴ particularly if silicone oil is used,³⁵ as was recommended in the pre-HAART era,³⁶ and sometimes is required in the HAART era as well. Likewise, age is an established risk factor for cataract, and the increasing risk of cataract with age seen in the LSOCA CMV retinitis participants is seen in each successive decade group older than 40 to 49 years in population-based prevalence studies as well.³¹

Regarding the effect of anti-CMV therapies on the risk of cataract, after adjusting for the several confounding factors, these analyses suggest that the treatment selection has little influence. This conclusion held even for treatments that were expected to be cataractogenic, including cidofovir (well known to induce uveitis and hypotony) and ganciclovir implants (implantation of which involves manipulation or removal, or both, of vitreous adjacent to the lens and sometimes direct mechanical injury to the lens, particularly when the implant strut is left long).

Many other factors had a crude association with increased cataract risk, which seemed to be attributable to confounding by CMV lesion size, retinal detachment, and age. Patients with poor general health characteristics tended to have altered risk of cataract, as suggested by crude risk ratios, but these analyses suggest that the mechanisms from which their risks derive were related to the confounding factors (e.g., shorter survival leading to less cataract risk).

This study has several limitations, including use of a less rigorous (but not unprecedented³⁰) definition of cataract than that typically used in population-based epidemiologic studies. However, given that the same general trends of association were observed across a range of visually relevant alternative cataract definitions and that the strength of the associations observed tended to be large, it is unlikely that substantially different results would have been found if a photographic reading center-based approach to cataract definition had been used. In addition, many of the CMV retinitis cases were prevalent rather than incident at the time of enrollment, potentially leading to prevalence-incidence bias. To limit the effects of such bias, the incidence analysis was anchored at the date of CMV retinitis diagnosis; both prevalence and incidence analyses confirmed the major associations. The quarterly visit frequency in this study also might have restricted detection of the full effects that inflammation might have had on cataract risk, thus limiting the ability to evaluate the extent to which inflammation was a mechanism of cataractogenesis in eyes more severely affected by CMV retinitis. Strengths of the study include cross-sectional and prospective data collection under a common protocol, enforced by data auditing and site visiting, in a large CMV retinitis cohort with demographic characteristics resembling those of the population of patients with AIDS in the United States.

In summary, subjects with AIDS and CMV retinitis had both a high absolute and a high relative risk of cataract compared both with fellow eyes free of CMV retinitis and with the general population. Risk factor analyses suggest that the involvement of a large portion of the retina with retinitis and the use of silicone oil for retinal detachment repair are the most important potentially modifiable risk factors for cataract formation, although these factors

are not modifiable in all cases, because CMV retinitis cannot always be controlled, and sometimes silicone oil is required to reattach a retina successfully. Also, longer duration of CMV retinitis and increasing age are major factors associated with increasing risk; the presence of inflammation affecting the anterior segment has a more modest effect. With ever-improving survival, cataract is likely to be an increasingly important cause of visual morbidity among people with AIDS and CMV retinitis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Graph showing the risk of cataract after diagnosis of cytomeg-avirus retinitis (CMVR) among affected eyes of patients with AIDS.

Table 2

Comparison of the Prevalence of Cataract for Proyecto Vision, Evaluation, Research (VER) Participants and the Subset of Longitudinal Study of the Ocular Complications of AIDS Participants with Cytomegalovirus Retinitis in at Least 1 Eye at Enrollment, Stratified by Age

Age Range (yrs)	<u>Proyecto VER Cohort: All Participants</u>			<u>Longitudinal Study of the Ocular Complications of AIDS Cohort: Participants with Cytomegalovirus Retinitis</u>		
	<i>No.</i>	<i>%</i>	<i>95% Confidence Interval</i>	<i>No.</i>	<i>%</i>	<i>95% Confidence Interval</i>
<40	0	NA		185	15.7	10.7–21.8
40–49	1594	0.3	0.06–6.5	205	27.8	21.7–34.5
50–59	1362	2.0	1.30–2.9	63	27.0	16.5–39.7
60–69	984	8.6	6.90–10.6	10	50.0	18.7–81.3
70–79	636	23.3	20.0–26.8	0	NA	
80+	196	58.2	50.9–65.2	0	NA	

NA = not applicable.

Table 3

Risk Factors for Cataract (or Prior Cataract Surgery) at the Time of Cohort Entry in Eyes with Cytomegalovirus Retinitis at the First Visit after Cytomegalovirus Retinitis Diagnosis for Each Eye, 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 (yrs)						
39 or younger	253 (87%)	37 (13%)	1.00		1.00	
40–49	255 (78%)	73 (22%)	2.01 (1.22–3.30)	0.006	2.76 (1.25–6.09)	0.012
50–59	73 (77%)	22 (23%)	2.04 (1.04–4.00)	0.037	2.52 (0.94–6.75)	0.065
60 or older	10 (63%)	6 (38%)	4.00 (1.32–12.05)	0.014	11.77 (2.28–60.65)	0.003
Anterior inflammation [†]						
No	395 (87%)	59 (13%)	1.00		1.00	
Yes	196 (71%)	79 (29%)	2.52 (1.63–3.87)	<0.0001	2.46 (1.29–4.67)	0.006
History of retinal detachment						
No	550 (89%)	70 (11%)	1.00		1.00	
Yes, repair without silicone oil	28 (64%)	16 (36%)	3.84 (1.52–9.66)	0.004	2.32 (0.83–6.47)	0.11
Yes, repair with silicone oil	13 (20%)	52 (80%)	19.90 (9.00–43.97)	<0.0001	19.73 (7.47–52.07)	<0.0001
Time since CMV retinitis diagnosis (per yr)	NA	NA	1.50 (1.03–1.65)	<0.0001	1.39 (1.22–1.59)	<0.0001
Activity at the border of CMV retinitis lesion(s)						
No	362 (76%)	117 (24%)	1.00		1.00	
Yes	214 (98%)	5 (2%)	0.10 (0.04–0.25)	<0.0001	0.26 (0.07–0.93)	0.037
Percent of retina involved by CMV retinitis						
<25	418 (94%)	26 (6%)	1.00		1.00	
25–49	116 (69%)	53 (31%)	6.69 (4.05–11.03)	<0.0001	6.52 (3.30–12.88)	<0.0001
50	45 (51%)	43 (49%)	11.68 (6.36–21.42)	<0.0001	8.53 (3.91–18.60)	<0.0001
Missing	12 (43%)	16 (57%)				

CMV = cytomegalovirus; NA = not applicable.

* The following characteristics were evaluated but not included in the final logistic regression model (summarized in Table 4, available at: <http://aaojournal.org>): gender, level of education, Karnofsky score, diabetes, hypertension, current use of highly active antiretroviral therapy, hepatitis C infection, cerebral toxoplasmosis, and CMV retinitis in the contralateral eye. These were not associated significantly with cataract at the time of cohort entry. Nadir CD4+ T-cell count, hepatitis B infection, and zone 3 involvement³¹ by CMV retinitis had no crude association with cataract at the time of cohort entry, but were associated after adjustment for the factors above. Nonblack race or ethnicity, anemia (hemoglobin <12.0 g/dl in women and <13.0 g/dl in men), hyperlipidemia, longer time since AIDS diagnosis, higher baseline CD4+ T-cell count, undetectable human immunodeficiency virus load, lack of vitreous inflammation, zone 1 involvement,³¹ diagnosis with immune recovery uveitis, treatment with systemic ganciclovir, treatment with ganciclovir implant, treatment with cidofovir, treatment with systemic foscarnet, and lack of treatment with systemic valganciclovir were associated with increased risk of cataract that was attributable to confounding by the variables included in the final multiple regression model above.

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

Table 5

Assessment of Risk Factors for Incident Cataract in Eyes with Cytomegalovirus Retinitis, Final Cox Regression Model^{*}

Characteristics	Rate per 100 Eye-Years	No. of Cataracts per No. of Eye-Years at Risk	Unadjusted Hazard Ratio (95% Confidence Interval)	Unadjusted P Value	Adjusted Hazard Ratio (95% Confidence Interval)	Adjusted P Value
History of retinal detachment						
No	6.62	92/1389	1.00		1.00	
Yes, repair without silicone oil	24.49	21/86	3.80 (2.37–6.06)	<0.0001	2.90 (1.73–4.87)	<0.0001
Yes, repair with silicone oil	107.6	32/30	17.40 (12.06–25.09)	<0.0001	10.37 (6.51–16.52)	<0.0001
Anterior inflammation (time varying)						
No	6.23	78/1252	1.00		1.00	
Yes	26.54	67/252	4.29 (3.11–5.90)	<0.0001	2.27 (1.59–3.25)	<0.0001
Percent retinal involvement (time-varying)						
<25	5.4	62/1149	1.00		1.00	
25–49	16.63	49/295	3.14 (2.14–4.60)	<0.0001	2.30 (1.51–3.50)	<0.0001
50	57.36	29/51	10.89 (6.95–17.05)	<0.0001	3.63 (2.18–6.04)	<0.0001
History of cataract in contralateral eye						
No	7.29	94/1290	1.00		1.00	
Yes	23.81	51/214	3.74 (2.63–5.30)	<0.0001	2.52 (1.74–3.66)	<0.0001

Additional variables that were not associated with increased incidence of cataract included: gender, race or ethnicity, level of education, Karnofsky score, anemia (hemoglobin <12.0 g/dl in women and <13.0 g/dl in men, time-updated), diabetes at enrollment, hypertension at enrollment, hyperlipidemia at enrollment, nadir CD4+ T-cell count at enrollment, human immunodeficiency virus load (time-updated), use of highly active antiretroviral therapy (time-updated), cerebral toxoplasmosis, hepatitis B infection, hepatitis C infection, vitreous inflammation, involvement of zone 3 with cytomegalovirus retinitis, diagnosis with immune recovery uveitis, and history of intravenous or intravitreal cidofovir therapy.

Several variables were associated significantly with cataract in the crude analysis, but were omitted from the adjusted analysis because they were confounded by 1 or more of the variables included in the final adjusted analysis and were not associated with cataract after adjustment. These were omitted from the adjusted model so as to avoid including more variables in the model than the number of events observed could support. These variables included: lower current (time-updated) CD4+ T-cell count, involvement of zone 1 with cytomegalovirus retinitis, currently active cytomegalovirus retinitis, history of ganciclovir implant therapy, history of systemic foscarnet therapy, history of systemic valganciclovir therapy, and history of cytomegalovirus retinitis in the contralateral eye.

For additional details regarding the crude association between these variables and the incidence of cataract, see Table 6, available at <http://aaojournal.org>.

* Analysis is anchored in time from cytomegalovirus retinitis diagnosis. Because time-updated age and time since AIDS diagnosis are highly correlated with time from cytomegalovirus retinitis diagnosis, these variables are omitted from the model.