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Incidence of Cytomegalovirus Retinitis in the Era of Highly Active Antiretroviral Therapy

Elizabeth A. Sugar, PhD^{1,2}, Douglas A. Jabs, MD, MBA^{1,3,4}, Alka Ahuja, MS¹, Jennifer E. Thorne, MD, PhD^{1,5}, Ronald P. Danis, MD⁶, and Curtis L. Meinert, PhD^{1,2} for the Studies of the Ocular Complications of AIDS Research Group*

¹Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD

²Department of Biostatistics, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD

³Department of Ophthalmology, Mount Sinai School of Medicine, New York, NY

⁴Department of Medicine, Mount Sinai School of Medicine, New York, NY

⁵The Division of Ocular Immunology, The Wilmer Eye Institute, The Johns Hopkins School of Medicine, Baltimore, MD

⁶Department of Ophthalmology and Visual Sciences, University of Wisconsin, Madison, Madison, WI

Abstract

Purpose—To estimate the incidence of cytomegalovirus (CMV) retinitis in the era of highly active antiretroviral therapy (HAART) and to characterize the factors associated with increased risk of CMV retinitis.

Design—Prospective cohort study

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Corresponding Author: Elizabeth A. Sugar, PhD, Center for Clinical Trials, Departments of Epidemiology and Biostatistics, The Johns Hopkins University Bloomberg School of Public Health, 615 N. Wolfe Street, Baltimore, MD 21204. Tel: 410-614-7837 Fax: 410-955-0958 esugar@jhsph.edu.

Reprints: Douglas A. Jabs, SOCA Chairman's Office, Department of Ophthalmology, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1183, New York, NY 10029-6574; douglas.jabs@mssm.edu.

*Members of the SOCA Research Group are available as Supplemental Material.

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Statement about Conformity: This study was approved by the local IRBs of each SOCA clinical center and the 3 resources centers (Chairman's office, Coordinating center, Reading Center). This study is in compliance with HIPAA regulations and is performed in compliance with the Declaration of Helsinki.

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Methods—1600 participants with acquired immune deficiency syndrome (AIDS) but without CMV retinitis at enrollment who completed at least one follow-up visit in the Longitudinal Study of the Ocular Complications of AIDS (LSOCA) were seen every 6 months to obtain disease and treatment history, ophthalmic examination, and laboratory testing. Incidence of CMV retinitis and risk factors for incident CMV retinitis were assessed.

Results—The incidence rate of CMV retinitis in individuals with AIDS was 0.36/100 person years (PY) based upon 29 incident cases during 8,134 person-years of follow-up. The rate was higher for those with a CD4+ T cell count at the immediately prior visit below 50 cells/ μ L (3.89/100 PY, $p < 0.01$), whereas only one individual with a CD4+ T cell count of 50–99 cells/ μ L and two individuals with a CD4+ T cell count > 100 cells/ μ L developed CMV retinitis. Having a CD4+ T cell count below 50 cells/ μ L at the clinical visit prior to CMV retinitis evaluation was the single most important risk factor (HR: 136, 95% CI: 30 to 605, $p < 0.0001$) for developing retinitis.

Conclusions—Patients with AIDS, especially those with severely compromised immune systems, remain at risk for developing CMV retinitis in the HAART era, although the incidence rate is reduced from that observed in the pre-HAART era.

Introduction

Cytomegalovirus (CMV) retinitis is the most common ocular opportunistic infection in patients with the acquired immunodeficiency syndrome (AIDS).¹ Prior to the introduction of highly active antiretroviral therapy (HAART), approximately 30% of individuals infected with the human immunodeficiency virus (HIV) developed CMV retinitis at some point during their lifetime.² The initiation of widespread use of HAART in the mid-1990s dramatically altered the course of AIDS. Treatment with HAART suppresses HIV replication, resulting in a drop in HIV load and in immune recovery, as evidenced by a rise in CD4+ T cell counts. As a result, the incidence rates of opportunistic infections, such as CMV retinitis, have declined but they have not dropped to zero.^{3–5} Patients primarily remain at risk for developing CMV retinitis either because of delayed diagnosis of HIV infection or because they are noncompliant, intolerant of, or unresponsive to HAART.^{6–9} Despite the substantial reduction in the incidence of CMV retinitis and the development of more effective therapies, CMV retinitis remains an important cause of visual loss in patients with AIDS during the HAART era.^{10–12} Therefore, quantifying the incidence rate and understanding the risk factors associated with the development of CMV retinitis remains important both for patients and health care providers.

The Longitudinal Studies of the Ocular Complications of AIDS (LSOCA)¹³ was initiated to study the occurrence and consequences of ocular complications among patients with AIDS during the HAART era. A previous analysis estimating the incidence of CMV retinitis was performed based on the prevalence data obtained at the time of enrollment.¹³ However, since the cohort was enriched deliberately with individuals having an opportunistic infection, such as CMV retinitis, that analysis provides an upper bound for the estimate of the incidence, which is still unknown.^{6,13} Herein we present an analysis to assess the incidence rate and risk factors for CMV retinitis based upon data collected from patients free of CMV retinitis at enrollment in the LSOCA cohort.

Patients and Methods

LSOCA is a multicenter, prospective, observational study of patients with AIDS recruited from ophthalmology clinics specializing in infectious disease or retinal clinics that was initiated in 1998. Patients aged 13 or greater with a diagnosis of AIDS were eligible, regardless of immunologic or CMV retinitis status.^{13,14} AIDS was diagnosed according to

the 1993 Centers for Disease Control and Prevention Revised Surveillance Case Definition.¹⁵ The study protocol and questionnaires were reviewed and approved by the institutional review boards at each of the participating clinical centers, and at the resource centers and the study was conducted in accordance with the principles of the Declaration of Helsinki. All participants gave written informed consent. For this analysis, the data were frozen as of 31 December 2009.

In LSOCA, study visits were initially conducted every six months for individuals without an opportunistic ocular infection (OOI) and every three months for individuals with an OOI. As of 1 December 2008, all individuals, regardless of OOI status, were followed at six-month intervals. To eliminate the potential for bias due to unequal follow-up, only the six-month visits were included in this analysis. Individuals were considered to be lost to follow-up if three consecutive visits were missed, i.e. no visits occurred within the year and a half prior to the data freeze. The data collected included medical and ophthalmic history, Karnofsky score, and a complete ophthalmologic examination. Standardized descriptions of classical clinical features were used to diagnose CMV retinitis by LSOCA-certified ophthalmologists.¹⁶ Laboratory measurements included CD4+ T cell counts, CD8+ T cell counts, and plasma HIV load. In addition to being considered as a continuous measurement, CD4+ T cell counts were categorized as 100, 50–99, and < 50 cells/ μ L. The threshold of 100 cells/ μ L was chosen since that is the level at which discontinuation of anti-CMV therapy is recommended.^{17–19} Previous studies in the pre-HAART era have indicated that additional risk is present for individuals with a CD4+ T cell count below 50 cells/ μ L.²⁰ CMV load was available at each visit through 2003. The results presented here are based upon the 1,600 participants who were free from CMV retinitis at enrollment and who completed at least one follow-up visit.

The incidence rates for CMV retinitis are expressed as rates per 100 person years (PY)²¹ and were calculated for the cohort and stratified by CD4+ T cell status at the visit prior to CMV retinitis evaluation (100, 50–99, or < 50 cells/ μ L). Staggered entry Kaplan-Meier curves²² were plotted to portray the cumulative probability of incident CMV retinitis over time and were anchored at the reported date of AIDS diagnosis. Univariate Cox proportional hazards models were used to compare the relative risks of acquiring CMV retinitis without adjusting for multiple comparisons.²³ Risk factors with repeated measurements during the course of the study were analyzed as time-varying covariates. Of these, age at each visit, HAART, CD4+ T cell count, CD8+ T cell count, and HIV load were assessed at the visit prior to CMV retinitis evaluation (i.e., lagged by one visit). Analyses based upon the participants with complete data at baseline, missing values for time-varying covariates carried forward from the most recent clinic visit, and multiple imputation to account for missing data yielded similar results. Statistical analyses were performed with SAS (SAS/STAT User's Guide, Version 9.1, Cary, C: SAS Institute) and Stata (StataCorp, 2007, Stata Statistical Software: Release 10, College Station, TX: StatCorp LP) statistical packages.

Results

As of 31 December 2009, 2,271 participants with AIDS were enrolled in LSOCA, of whom 492 had CMV retinitis in at least one eye at enrollment. Of the remaining 1,779 individuals free of CMV retinitis at enrollment, 1,600 completed at least one follow-up visit. These individuals constitute the basis for our report. A total of 1,430 (89%), 1,098 (69%), 797 (50%), and 80 (5%) completed 1, 3, 5 and 10 years of follow-up, respectively, with a total of 8,134 person years of follow-up. The missed visit rate was 13%, 337 individuals died, and an additional 329 were lost to follow-up (i.e. had not been seen for a minimum of 18 months).

Characteristics of the study population at enrollment and during follow-up

The population characteristics at study entry and over the course of follow-up based upon the observed visits for individuals free from CMV retinitis at enrollment are reported in Table 1. The demographic characteristics observed in this cohort are comparable to those observed in other AIDS cohorts used to track CMV retinitis.^{1–2,6–11, 13, 18–20} In general, patients had long-standing disease with a median time from diagnosis of AIDS to enrollment of 4.4 years (25th – 75th percentile: 1.7 – 7.3). Most individuals were male (80%), in particular males having sex with males (58%), and the majority were non-Caucasian (54%). The median CD8+ T cell count and nadir CD4+ T cell count as of enrollment were 776 cells/ μ L (25th – 75th percentile: 503–1,135) and 40 cells/ μ L (25th – 75th percentile: 12–104), respectively. The distributions of the time-varying CD8+ T cell counts and the time-updated nadir CD4+ T cell counts were similar to those observed at enrollment. Eighty-five percent of individuals were on HAART and 72% had a CD4+ T cell count of 100 cells/ μ L or greater at enrollment with a higher fraction of each during the follow-up interval (93% and 86%, respectively). The median time since HAART initiation at enrollment was 2.9 years. However, the date of initiation is missing for 36% of the participants since this question was added during the course of the study. Despite widespread HAART usage, 34% of participants had an HIV load greater than 10,000 copies/mL (>4 on the log₁₀ scale) at enrollment; however the percentage of the follow-up visits with HIV load greater than 10,000 copies/mL was lower (19%). CMV load was available for 67% of individuals at enrollment and 33% of the follow-up visits. The percentage with detectable samples (400 copies/mL) was 2% and 1% for enrollment and follow-up visits, respectively.

Epidemiologic risk of CMV retinitis

During the 8,134 person-years of follow-up for individuals free from CMV retinitis at enrollment, 29 incident cases of CMV retinitis were observed, yielding a rate of 0.36 per 100 PY with a cumulative incidence of 1.2% (95% CI: 0.5% to 3.1%) at 4 years and 4.2% (95% CI: 2.7% to 6.3%) at 10 years (Table 2). The rate was constant over time since AIDS diagnosis (Figure 1). The Kaplan-Meier estimates of cumulative incidence of CMV retinitis stratified by time-varying CD4+ T cell count are presented in Supplemental Figure 1. The incidence rate for those individuals with a CD4+ T cell count below 50 cells/ μ L at the preceding visit was 3.89/100 PY, significantly higher than the overall rate ($p < 0.0001$). Twenty-six (90%) of the individuals who developed incident CMV retinitis had a CD4+ T cell count below 50 cells/ μ L at the visit prior to detection as compared to 1 (3%) with 50–99 cells/ μ L and 2 (7%) with 100 cells/ μ L. For the three individuals who had CD4+ T cell counts 50 cells/ μ L at the visit prior to the diagnosis of CMV retinitis, the onset of disease was well after the initial diagnosis with AIDS (4.6 and 4.9 years for the two individuals with CD4+ T cell counts 100 cells/ μ L and 12.9 years for the individual with CD4+ T cell count between 50–99 cells/ μ L). All 29 individuals who developed incident CMV retinitis had a CD4+ T cell count of less than 50 cells/ μ L at some time prior to developing CMV retinitis. However, not all individuals who experienced that level of immunodeficiency went on to develop the disease. In fact, when restricting the analysis to all follow-up visits that occurred after a CD4+ T cell count less than 50 cells/ μ L was observed, the incidence rate was 0.65/100PY, slightly less than double the rate observed for population as a whole.

Factors influencing risk of CMV retinitis

The analysis of the risk factors associated with incident CMV retinitis is summarized in Table 3. In the univariate analysis, a Karnofsky score < 80 (HR: 2.2, 95% CI: 1.01 to 4.6, $p = 0.045$), the presence of HIV retinopathy (HR: 11.6, 95% CI: 3.3 to 40.2, $p = 0.0001$), CD8+ T cell count < 400 cells/ μ L at the previous visit (HR 15.2, 95% CI: 6.8 to 33.6, $p < 0.0001$), and HIV load > 10,000 copies/mL (> 4 on the log₁₀ scale) at the previous visit (HR: 37, 95% CI: 8 to 162, $p < 0.0001$), CMV load at the previous visit (HR: 26, 95% CI: 3

to 186, $p = 0.0014$) as well as CD4+ T cell count less than 50 cells/ μ L at the previous visit (HR: 136, 95% CI: 30 to 605, $p < 0.0001$) were associated with a significant increase in the risk of developing incident CMV retinitis. CD4+ T cell counts below 10 were not significantly associated with increased incidence when compared to counts of 10–49 (HR: 2.0, 95% CI: 0.9 to 4.4, $p = 0.07$). CD4+ T cell counts of 50–99 cells/ μ L at the previous visit were not significantly associated with an increase in incidence (HR: 6.4, 95% CI: 0.5 to 73.2, $p = 0.14$), nor was treatment with HAART at the previous visit (HR: 0.6, 95% CI: 0.1 to 1.6, $p = 0.27$) or race (HR for non-Caucasian: 0.6, 95% CI: 0.3 to 1.4, $p = 0.22$). The HIV exposure men having sex with men was associated with an increased risk that was of borderline statistical significance (HR: 2.2, 95% CI: 0.9 to 5.2, $p = 0.064$). Older age was associated with a significant decrease in risk (HR per 10 years: 0.6, 95% CI: 0.4 to 0.8, $p < 0.0001$). Large multivariate models were not considered appropriate for analysis due to the potential for multiple risk profiles with zero events based upon the small number of events and the co-linearity of the risk factors. Pairwise models, including CD4+ T cell counts plus one other variable, were fit for each of the significant risk factors. CD4+ T cell counts remained significant but the magnitude of the risk for the other variables was attenuated and became non-significant for all other variables (results not shown). Analyses restricting the risk set to those who had a nadir CD4+ T-cell count below 50 cells/ μ L produced similar findings (results not shown).

Discussion

CMV retinitis remains a risk factor for mortality and vision loss in the HAART era.^{10–12} Previous studies have focused upon the incidence rates in the pre-HAART era² or computed estimates based upon the prevalence in the HAART era.¹³ This analysis provides a prospective examination of the incidence rate of and the corresponding risk factors for developing CMV retinitis among individuals with AIDS in the HAART era.

These data quantify the substantial decrease in the incidence of CMV retinitis when compared to the incidence observed in the pre-HAART era. In the pre-HAART era, Hoover et al² investigated the cumulative incidence of CMV retinitis for individuals following a diagnosis of immune suppression, defined as having a CD4+ T cell count below 100 cells/ μ L. The 4-year cumulative incidence was 25% as compared to 7% for LSOCA, a 72% reduction. In fact, only 12% of individuals in LSOCA who had severe immunodeficiency (i.e., a CD4+ T cell count below 50 cells/ μ L) developed CMV retinitis during the first 4 years of following the diagnosis of AIDS, a 52% reduction (Table 2).

In a cross-sectional analysis of the LSOCA data at enrollment, the CMV retinitis incident rate was estimated to be 5.6/100 PY (95% CI: 5.0–6.2).¹³ The observed incidence rate during follow-up in LSOCA was 0.4/100 PY, a 93% reduction. The increase in the estimate of the incidence rate in the cross-sectional analysis may be due in part to referral bias. Patients were recruited from ophthalmology clinics specializing in infectious disease or retinal clinics, thereby enriching the population of individuals with opportunistic ocular infections including CMV retinitis. Although we would not expect to observe as large an influence on the incident as compared to prevalence, the estimates of incident infection may also be inflated relative to the general population of patients with AIDS for the same reason.

The greatest identified risk factor for incident CMV retinitis was having a CD4+ T cell count below 50 cells/ μ L at the prior visit (HR: 136, 95% CI: 30 to 605, $p < 0.0001$), although the estimate lacks precision due to the small number of observed incident cases. Pertel et al also observed an increased risk for patients with a CD4+ T cell count below 50 cells/ μ L in the pre-HAART era, although not of the same magnitude (OR: 4.62).²⁰ Prior to the development of HAART therapy, a decline in CD4+ T cell count to below 50 cells/ μ L

would be expected over the course of the disease. In general, HAART therapy raises CD4+ T cell counts causing a reduction in the proportion of the population with CD4+ T cell counts below 50 cells/ μ L and therefore a decline in the incident rate of CMV retinitis. Given the widespread usage of HAART in our cohort, it seems likely that individuals with extremely low CD4+ T cell counts are either non-adherent or HAART resistant, perhaps indicative of more severe disease. Therefore, it is likely that individuals in our population with CD4+ T cell counts below 50 represent a higher risk cohort than that examined by Pertel et al, which would account for the difference in the observed risks. Low CD4+ T cell counts are also associated with increased risk of death, retinitis progression, retinal detachment, and decline in visual acuity.¹¹

The effects of HAART in patients with CMV retinitis have been attributed largely to the induction of a CD4+ T cell response, although a return to CD4+ T cell levels above the threshold associated with treatment (≥ 100 cells/ μ L) may not be essential. Previous studies have demonstrated that HAART is associated with improved survival,^{3, 24} decreased rates of visual acuity loss,^{10,12} decreased risk of retinal detachment,²⁵ and decreased rates of retinitis progression¹⁸ in patients with CMV, independent of achieving this threshold. Our findings are consistent with these results since a significant increase in risk was not observed until the CD4+ T cell count fell below 50 cells/ μ L, which is below the cut-off associated with treatment (100 cells/ μ L). In general, those individuals who developed CMV retinitis had CD4+ T cell counts below 50 cells/ μ L at the prior visit (26/29, 90%). Such individuals typically also had elevated HIV load and low CD8+ T cell counts. Nevertheless, 85% (22/26) were listed as being on HAART at the visit prior to CMV retinitis detection, indicating HAART failure or lack of adherence. This result supports the findings of prior research (based upon case studies, cross-sectional and retrospective cohorts, or the second eye for individuals with unilateral CMV retinitis) which noted that patients were at risk for developing CMV retinitis either because of delayed diagnosis of HIV infection or because they were noncompliant, intolerant of, or unresponsive to HAART.⁶⁻⁹

Many of the previously identified factors associated with CMV retinitis disease and progression were associated with disease incidence. Tay-Kearney et al²⁶ reported that individuals with CMV retinitis had lower CD8+ T cell counts as compared to those without CMV retinitis among HIV positive individuals with CD4+ T cell counts less than 50 cells/ μ L. The hazard ratio associated with a CD8+ T cell count below 400 cells/ μ L among individuals with CD4+ T cell counts below 50 cells/ μ L was 11 (95% CI: 5 to 253, $p < 0.0001$), which is similar to the overall effect (Table 3). HIV load might be expected to be associated with increased risk due to transactivation of the respective viruses. In our cohort, an HIV load greater than 10,000 copies /mL (4 on the log10 scale) was associated with a significant increase in the risk of incident CMV retinitis (HR: 37, $p < 0.0001$). HIV retinopathy has been observed to be associated with CMV retinitis and was a risk factor associated with incident disease.¹

Incident CMV retinitis did not occur in the prospective cohort until an individual had recorded a nadir CD4+ T cell count less than 50 cells/ μ L (0/29, 0%, 95% CI: 0–12%). The upper bound of the 95% confidence interval, although low, is consistent with the fraction of individuals diagnosed with CMV retinitis with a nadir CD4+ T cell count at or above 50 cells/ μ L observed by Hoover et al² (19%) and LSOCA at enrollment¹¹ (14% for newly diagnosed and 16% for long-standing CMV retinitis). Therefore, although we cannot conclude that a nadir CD4+ T cell count below 50 cells/ μ L is a necessary condition for developing incident CMV retinitis, diagnoses of CMV retinitis in the presence of nadir CD4+ T cell counts ≥ 50 cells/ μ L are uncommon in populations treated with HAART.

Anti-CMV antibody status was not evaluated during the course of the study. However, previous studies in AIDS²⁷ and homosexual²⁸ men have reported high rates of anti-CMV antibodies (90% and 94%, respectively).²⁸ CMV viral load was only collected through 2003. Although detectable CMV load was associated with an increased risk of incident CMV retinitis, the clinical utility may be limited due to the poor sensitivity of the test. Of the 20 cases evaluable for CMV load within a year of diagnosis, 12 (60%) had undetectable CMV loads at all visits including those at and following diagnosis.

The LSOCA cohort provides a unique opportunity to observe incident CMV retinitis among AIDS patients in the HAART era with a total of 1,600 patients who enrolled without CMV retinitis and completed at least one follow-up visit. However, due to the small number of observed incident cases, the estimates may lack precision, especially 10 or more years beyond the reported date of AIDS diagnosis, during which period only 5 incident cases were observed (Table 3, Figure 1). As noted above, the small number of incident cases also limits the ability to evaluate multiple risk factors simultaneously.

In conclusion, although greatly reduced, CMV retinitis continues to be observed in patients with AIDS in the HAART era, particularly among those with severely compromised immune systems. In fact, the cumulative 10- and 15-year rates remain substantial for those with CD4+ T cell counts below 50 cells/ μ L at the prior visit (34% and 44%, respectively). Therefore, the screening recommendations²⁹ for patients with AIDS and low CD4+ T cell counts should not be changed even in the current HAART era.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Biographies

Elizabeth A Sugar, PhD, is an Assistant Scientist in the Departments of Epidemiology and Biostatistics at the Bloomberg School of Public Health at Johns Hopkins University. She is the Chair of the Statistical Committee for the Multicenter Uveitis Steroid Treatment Trial and is involved in The Studies of the Ocular Complications of AIDS. Her interests include the design, analysis and interpretation of clinical trials and epidemiologic studies in ophthalmology, asthma, oncology, and AIDS.

Douglas A. Jabs, MD, MBA, is the Chief Executive Office of the Mount Sinai Faculty Practice Associates, Dean for Clinical Affairs, and Professor and Chairman of the Department of Ophthalmology at Mount Sinai School of Medicine, New York, New York. He is the study chair of The Studies of the Ocular Complications of AIDS, the Multicenter Uveitis Steroid Treatment Trial, and the Standardization of Uveitis Nomenclature project. His interests include uveitis, epidemiology, and clinical trials.

Figure 1.

Incident cytomegalovirus (CMV) retinitis among eyes free from CMV retinitis at enrollment. Follow-up is measured from the reported date of AIDS diagnosis. The dotted lines represent the upper and lower bounds of the 95% confidence interval.

Table 1

Enrollment and follow-up characteristics of participants with AIDS enrolled in the Longitudinal Studies of Ocular Complications of AIDS without cytomegalovirus retinitis

Characteristic	Participants (N = 1,600)	Person-visits (N = 14,311)
Median age, years ^a	43 (38 to 49)	
Median years since AIDS diagnosis ^a	4.4 (1.7 to 7.3)	
Missing, n (%) ^b	17 (1%)	
Median years since HAART initiation at enrollment ^a	2.9 (1.0 to 5.1)	
Missing, n (%) ^b	570 (36%)	
Gender, n (%) ^b		
Female	312 (20%)	
Male	1,288 (80%)	
Race, n (%) ^b		
Caucasian, non-Hispanic	734 (46%)	
Non-caucasian	866 (54%)	
HIV exposure category, n (%) ^b		
Other	667 (42%)	
Men having sex with men	933 (58%)	
AIDS defining illness, n (%) ^b		
T cell lymphopenia	1,030 (65%)	
Opportunistic infection/neoplasm	558 (35%)	
Missing	12 (1%)	
Karnofsky score, n (%) ^b		
90-100	819 (51%)	
80	781 (49%)	
HIV retinopathy, n (% yes) ^b	46 (3%)	131 (1%)
Missing	0 (0%)	248 (2%)
HAART, n (% yes) ^b	1,356 (85%)	13,106 (93%)
Missing	1 (0%)	235 (2%)
Nadir CD4+ T cell count		
Median (cells/ μ L) ^a	40 (12 to 104)	37 (11 to 97)
Cells/ μ L, n (%) ^b		
100 cells/ μ L	411 (26%)	3,406 (24%)
50-100 cells/ μ L	292 (19%)	2,629 (19%)
< 50 cells/ μ L	875 (55%)	8,007 (57%)
Missing	22 (1%)	270 (2%)
CD4+ T cell count		
Median (cells/ μ L) ^a	197 (81 to 360)	324 (172 to 491)
Cells/ μ L, n (%) ^b		
100 cells/ μ L	1,142 (72%)	12,066 (86%)

Characteristic	Participants (N = 1,600)	Person-visits (N = 14,311)
50-100 cells/ μ L	178 (11%)	824 (6%)
< 50 cells/ μ L	268 (17%)	1,093 (8%)
Missing	12 (1%)	329 (2%)
CD8+ T cell count		
Median (cells/ μ L) ^a	776 (503 to 1,135)	827 (568 to 1,152)
Cells/ μ L, n (%) ^b		
400 cells/ μ L	1,327 (84%)	12,045 (88%)
< 400 cells/ μ L	253 (16%)	1,637 (12%)
Missing	20 (1%)	630 (4%)
HIV load		
Median (log ₁₀ [copies/mL]) ^a	2.7 (1.9 to 4.6)	2.3 (1.7 to 3.3)
Log ₁₀ [copies/mL], n (%) ^b		
< 2.6 (undetectable)	716 (47%)	8,922 (67%)
2.6-4.0	298 (19%)	1,847 (14%)
4.0	519 (34%)	2,517 (19%)
Missing	67 (4%)	1,026 (7%)
CMV load, n (%) ^b		
Undetectable (< 400 copies/mL)	1081 (98%)	3320 (99%)
Detectable (≥ 400 copies/mL)	20 (2%)	31 (1%)
Missing	500 (33%)	10962 (77%)

^aThe 25th-75th percentiles are included in parentheses with the median.

^bPercentages of missing values are calculated out of the total sample size. Percentages for categories are calculated out of the total sample of non-missing values.

AIDS = acquired immune deficiency syndrome; HIV = human immunodeficiency syndrome; HAART = highly active antiretroviral therapy; CMV = cytomegalovirus.

Table 2

Cumulative incidence of cytomegalovirus (CMV) retinitis in the Longitudinal Studies of the Ocular Complications of AIDS cohort

	Number of CMV Retinitis Incidence Cases	4-year Cumulative Incidence ^d (95% CI)	10-year Cumulative Incidence ^d (95% CI)
Overall	29	1.2% (0.5% to 3.1%)	4.2% (2.7% to 6.3%)
CD4+ T cell count^a			
100 cells/ μ L ^b	2	0	0.3% (0.1% to 1.7%)
50–99 cells/ μ L ^c	1	0	0
< 50 cells/ μ L	26	12.3% (5.1% to 27.9%)	33.6% (23.2% to 47.0%)

^aCD4+ T cell count is evaluated at the visit prior to CMV retinitis evaluation (i.e. lagged by one visit).

^bThe first incident case of CMV retinitis for an individual with a CD4+ T cell count of 100 cells/ μ L or more occurred after 4.6 years.

^cThe first incident case of CMV retinitis for an individual with a CD4+ T cell count between 50–99 cells/ μ L occurred after 12.9 years.

^dCumulative incidence with 95% confidence intervals are calculated using staggered entry Kaplan-Meier estimates anchored at the reported date of AIDS diagnosis.

CMV = cytomegalovirus; AIDS = acquired immune deficiency syndrome; CI = confidence interval.

Table 3

Rates and crude hazard ratios for incident cytomegalovirus retinitis for select risk factors

Risk factor	Events per 100 PY (# Events/PY)		Crude hazard ratio ^c (95% CI)	P-value
Age (per 10 years) ^{a,b}	n/a	n/a	0.6 (0.4 to 0.8)	< 0.0001
Race				
Caucasian, non-Hispanic	0.44	(17 / 3908)	1.0	
Non-Caucasian	0.29	(12 / 4145)	0.6 (0.3 to 1.4)	0.22
HIV exposure category				
Other	0.22	(7 / 3167)	1.0	0.064
Men having sex with men	0.45	(22 / 4885)	2.2 (0.9 to 5.2)	
Karnofsky score				
90–100	0.24	(11 / 4607)	1.0	0.045
80	0.52	(18 / 3445)	2.2 (1.01 to 4.6)	
HIV retinopathy ^a				
No	0.33	(26 / 7973)	1.0	
Yes	3.80	(3 / 79)	11.6 (3.3 to 40.2)	0.0001
HAART ^a				
No	0.61	(4 / 654)	1.0	
Yes	0.31	(25 / 7398)	0.6 (0.1 to 1.6)	0.27
CD4+ T cell count ^a				
100 cells/ μ L	0.03	(2 / 6826)	1.0	
50–99 cells/ μ L	0.18	(1 / 551)	6.4 (0.5 to 73.2)	0.14
< 50 cells/ μ L	3.89	(26 / 669)	136 (30 to 605)	< 0.0001
CD8+ T cell count ^a				
400 cells/ μ L	0.13	(9 / 7076)	1.0	
< 400 cells/ μ L	1.99	(19 / 955)	15.2 (6.8 to 33.6)	< 0.0001
HIV load [$\log_{10}$ (copies/mL)] ^a				
< 2.6 copies/mL	0.04	(2 / 5017)	1.0	
2.6–4.0 copies/mL	0.08	(1 / 1250)	2.1 (0.1 to 22.8)	0.55
> 4.0 copies/mL	1.47	(25 / 1696)	37 (8 to 162)	< 0.0001
CMV load, n (%) ^a				
Undetectable (< 400 copies/mL)	0.52	(9 / 1659)	1.0	
Detectable ($\geq$ 400 copies/mL)	6.67	(1 / 15)	26 (3 to 186)	0.0014

^a Age, HIV retinopathy, HAART, CD4+ T cell count, CD8+ T cell count, HIV load and CMV load are time-varying covariates. All time-varying covariates except HIV retinopathy were lagged by one visit.

^b The hazard ratio represents the relative hazard per 10 year increase in age.

^c The crude hazard ratios were computed using univariate Cox proportional hazards models without adjusting for multiple comparisons.

HIV = human immunodeficiency syndrome; HAART = highly active antiretroviral therapy; PY = person year; CI = confidence interval; CMV = cytomegalovirus.