Published in final edited form as:

Ophthalmology. 2015 July ; 122(7): 1452–1463. doi:10.1016/j.ophtha.2015.02.033.

Long-term Outcomes of Cytomegalovirus Retinitis in the Era of Modern Antiretroviral Therapy; Results from a United States Cohort

Douglas A. Jabs, MD, MBA^{1,2,3}, Alka Ahuja, MS³, Mark L. Van Natta, MHS³, Alice T. Lyon, MD⁴, Steven Yeh, MD⁵, Ronald Danis, MD⁶, and the Studies of the Ocular Complications of AIDS Research Group⁷

¹Department of Ophthalmology, the Icahn School of Medicine at Mount Sinai, Madison.

²Department of Medicine, the Icahn School of Medicine at Mount Sinai, Madison.

³Center for Clinical Trials, the Department of Epidemiology, The Johns Hopkins University Bloomberg School of Public Health, Madison.

⁴Department of Ophthalmology, the Northwestern University Feinberg School of Medicine, Madison.

⁵Department of Ophthalmology, the Emory University School of Medicine, Madison.

⁶Department of Ophthalmology, the University of Wisconsin, Madison.

Abstract

Objectives—To describe the long-term outcomes of patients with cytomegalovirus (CMV) retinitis and the acquired immunodeficiency syndrome (AIDS) in the modern era of combination antiretroviral therapy.

Design—Prospective, observational, cohort study

Corresponding author: Douglas A. Jabs, MD, MBA, the Department of Ophthalmology, The Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1183, New York, NY 10029 **Phone:** 212-241-6752 **Fax:** 212-241-5764
douglas.jabs@mssm.edu.

⁷Members of the SOCA Research Group are listed at www.aaojournal@aao.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of Interest: Douglas A. Jabs: Abbott Pharmaceuticals, Applied Genetic Technologies Corporation (AGTC), Alcon Laboratories, Corcept Therapeutics, Genentech, Inc., Genzyme Corporation, GlaxoSmithKline, Novartis Pharmaceutical Corp., Regeneron, and Roche Pharmaceuticals; Alka Ahuja: None; Mark Van Natta: None; Alice T. Lyon: None; Steven Yeh: Clearside Biomedical, Inc., Santen, Bausch and Lomb; Ronald Danis: None.

DISCLOSURE

B) Financial Disclosures: : Douglas A. Jabs: Abbott Pharmaceuticals, Applied Genetic Technologies Corporation (AGTC), Alcon Laboratories, Corcept Therapeutics, Genentech, Inc., Genzyme Corporation, GlaxoSmithKline, Novartis Pharmaceutical Corp., Regeneron, and Roche Pharmaceuticals; Alka Ahuja: None; Mark Van Natta: None; Alice T. Lyon: None; Steven Yeh: Clearside Biomedical, Inc., Santen, Bausch and Lomb; Ronald Danis: None.

C) Contributions to Authors in each of these areas: conception and design (DJ), analysis and interpretation (DJ, AA, MVN), writing the article (DJ), critical revision of the article (DJ, AA, MVN, SY, AL, RD), final approval of the article (DJ, AA, MVN, SY, AL, RD), data collection (SOCA Research Group), provision of materials (SOCA Research Group), statistical expertise (AA, MVN), obtaining funding (DJ, MVN, RD), literature search (DJ), administrative or logistic support (DJ, MVN, RD).

Participants—Patients with AIDS and CMV retinitis

Testing—Immune recovery, defined as a CD4+ T cell count >100 cells/μL for 3 months.

Main outcome measures—Mortality, visual impairment (visual acuity worse than 20/40) and blindness (visual acuity 20/200 or worse) on logarithmic visual acuity charts, loss of visual field on quantitative Goldmann perimetry.

Results—Patients without immune recovery had a mortality of 44.4/100 person years (PY), and a median survival of 13.5 months after the diagnosis of CMV retinitis, whereas those with immune recovery had a mortality of 2.7/100 PY ($P < 0.001$), and an estimated median survival of 27.0 years after the diagnosis of CMV retinitis. The rates of bilateral visual impairment and blindness were 0.9/100 PY and 0.4/100 PY, respectively, and were similar between those with and without immune recovery. Among those with immune recovery, the rate of visual field loss was ~1% of the normal field/year, whereas among those without immune recovery it was ~7% of the normal field/year.

Conclusions—Among persons with CMV retinitis and AIDS, if there is immune recovery, long-term survival is likely, whereas if there is no immune recovery, the mortality rate is substantial. Although higher than the rates seen in the non-HIV-infected population, the rates of bilateral visual impairment and blindness are low, especially when compared to rates seen in the era before modern antiretroviral therapy.

Cytomegalovirus (CMV) retinitis is the most frequently encountered ocular opportunistic infection in patients with the acquired immune deficiency syndrome (AIDS).¹⁻⁷ Prior to the advent of modern, combination antiretroviral therapy, the lifetime risk of CMV retinitis for a patient with AIDS was estimated at 30%,⁶ and CMV retinitis was associated with high rates of visual impairment (up to 98/100 eye-years) and blindness (up to 49/100 eye-years).^{1,2} The advent of modern combination antiretroviral therapy in the mid 1990's, also known as highly active antiretroviral therapy, resulted in a 90% reduction in the incidence of CMV retinitis in the United States.⁷⁻¹⁰ With this approach, human immunodeficiency virus (HIV) RNA circulating in the blood (HIV load) could be suppressed, and immune recovery, manifested as a rise in CD4+ T cells, could occur. Immune recovery enabled the patient to control opportunistic infections without chronic suppressive antimicrobial/antiviral therapy (secondary prophylaxis or “maintenance” therapy),¹¹⁻¹⁷ and guidelines were formulated for discontinuing secondary prophylaxis.¹⁶ In the case of CMV retinitis, a sustained rise in CD4+ T cells to >100 cells/μL for more than 3-6 months was determined to be adequate immune recovery for discontinuing safely CMV “maintenance” therapy.^{16,17} Despite this dramatic decrease in the incidence of CMV retinitis and the improved outcomes due to modern antiretroviral therapy, CMV retinitis and vision loss from CMV retinitis continue to occur.¹⁸⁻²¹ Because antiretroviral-treated, immune-recovered, HIV-infected have an estimated lifespan of >14 years,²² we evaluated the long-term outcomes of patients with AIDS and CMV retinitis enrolled in the Longitudinal Study of the Ocular Complications of AIDS (LSOCA) whose retinitis was diagnosed after the introduction of modern combination antiretroviral therapy.

Methods

The Longitudinal Study of the Ocular Complications of AIDS (LSOCA) is a prospective, observational, cohort study of patients with AIDS in the era of modern combination antiretroviral therapy.^{23,24} Enrollment began on 1 September 1998 and was completed on 31 July 2011; follow-up continued through 31 July 2013. Eligible persons had AIDS diagnosed according to the 1993 Centers for Disease Control and Prevention revised criteria for the diagnosis of AIDS.²⁵ Recruitment occurred at 19 clinical centers throughout the United States, typically located in large urban centers with a high HIV-infected population.²³ Approval for the study and its procedures was obtained from the institutional review boards of the individual participating clinical centers and the three resource centers (chairman's office, coordinating center, and reading center). Written, informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki.

Patients with and without ocular opportunistic infections were recruited. Clinical centers were encouraged to enroll all patients with CMV retinitis seen at their centers. Cytomegalovirus retinitis was diagnosed by a SOCA-certified ophthalmologist when the characteristic picture of a full-thickness necrotizing retinitis was present.¹⁸⁻²⁶ Patients with and without immune recovery were enrolled. Because the goal of this analysis was to evaluate the outcomes of patients diagnosed with CMV retinitis in the era of modern combination antiretroviral therapy, only participants with CMV retinitis diagnosed after 1996 were included in this analysis.

Participants with CMV retinitis were seen for follow-up every 3 months at which time a medical and an ophthalmologic history and a complete eye examination were performed.¹⁸⁻²⁴ Relevant details of the medical history were confirmed from the medical record. The eye examination included measurement of best corrected visual acuity using logarithmic visual acuity charts,^{18,26,27} slit lamp biomicroscopy, and examination of the fundus through a dilated pupil. Visual acuity was recorded as the number of letters read and converted to Snellen equivalents for reporting purposes. In addition proportions with visual impairment (worse than 20/40) and blindness (20/200 or worse) and rates of visual impairment and blindness were reported.²⁸ Standard 60° retinal photographs were taken as previously described and graded at a centralized reading center.^{18-21,26} Modified, standardized, quantitative Goldmann visual fields were performed as previously described.^{18-21,29} The normal quantitative visual field contains 785° of total field.³⁰ Laboratory testing included lymphocyte subset analyses (for CD4+ T cell counts) and assessment of the amount of HIV RNA in plasma (HIV load).^{18-21,23,24} After 2008 follow-up of participants with CMV retinitis was decreased to every 6 months.

Patients were characterized as having experienced immune recovery if the CD4+ T cells were sustained above 100 cells/ μ L for 3 months at any time during follow-up (i.e. two consecutive visits), including the enrollment CD4+ T cell count. This level was chosen as it is the level at which discontinuation of anti-CMV therapy for immune recovery is recommended.^{16,17} Immune recovery uveitis was diagnosed when there was the new onset of or an increase in intraocular inflammation in the anterior chamber or vitreous in either eye

with CMV retinitis in the face of immune recovery, as previously described.^{20,21,31,32} Retinal area affected by CMV retinitis was scored both by the clinician and at the reading center as the percent of normal retina affected by CMV (retina “lost”) and rates were calculated.¹⁸⁻²¹ If a significant difference between those with and without immune recovery was detected for a visual outcome, the rates before and after immune recovery were calculated for the group with immune recovery.

Statistical methods

Patient subgroups of immune recovery versus no immune recovery were compared on enrollment characteristics using the chi-square or Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables.³³ Kaplan-Meier curves³⁴ for time since CMV retinitis diagnosis to patient-specific outcomes were plotted and cumulative incidence with 95% confidence intervals ascertained at the time points of 1, 5, and 10 years after CMV retinitis diagnosis. Event rates were computed as ratios of patient- or eye-specific events to person- or eye-years at risk. For patient-related events (e.g. mortality, 2nd eye involvement by CMV in a patient with unilateral retinitis), rates are reported as events/100 person-years (PY), and for eye-related events (e.g. visual loss) rates are reported as events/100 eye-years (EY).

Cox proportional hazard regression models with staggered entry anchored at the date of CMV retinitis diagnosis were employed to obtain hazard ratios, 95% confidence intervals, and P-values for outcomes pertaining to patients and eyes, as well as for risk factors associated with mortality.³⁵ Both, crude and adjusted models controlling for enrollment differences in years since CMV retinitis, years from AIDS to CMV retinitis diagnosis and enrollment, combination antiretroviral therapy use, and HIV load were constructed. Adjusted models controlled for baseline characteristics significantly different between the two groups and a test for interaction between immune recovery status and duration of CMV retinitis, dichotomized as having been diagnosed with CMV retinitis within 45 days of enrollment (“recently-diagnosed”) or earlier (“previously-diagnosed”). Results for an outcome were stratified by recently or previously diagnosed CMV retinitis patients in light of a statistically significant interaction. Models for eye-level outcomes utilized robust variance estimation to appropriately account for correlation between eyes.³⁶ Regression models which examined risk factors for mortality were restricted to complete cases, excluding missing data for individual predictors, which ranged from 0.2% to 13.0%. In order to evaluate any effect of temporal changes in antiretroviral therapy, subgroup analyses of patients enrolled before and after 1 September 2003 were performed for major patient-related outcomes. The median survival for patients was estimated using Weibull techniques.³⁷

Fixed effects linear regression models,³⁸ clustering on patient and eye, provided estimates of unadjusted and adjusted mean visual field loss and percent of retinal area involved per year. All statistical analyses were conducted with SAS/STAT® version 9.3 (Copyright © 2002-2010. SAS Institute, Inc., Cary, NC) and Stata version 12.0 (StataCorp 2011. Stata Statistical Software: Release 12. College Station, Tx: StataCorp LP) software packages.

Results

Characteristics of the study population

Of the 2392 participants enrolled in LSOCA, 505 had CMV retinitis, and 479 of these 505 were diagnosed with CMV retinitis after 1996. These 479 patients form the study population (table 1). Of these 479 participants, 296 (62%) experienced immune recovery. Of these 296 participants, 205 (69%) were enrolled with apparent immune recovery (an enrollment CD4+ T cells count >100 cells/ μ L), and 91 (31%) were enrolled without apparent immune recovery but experienced immune recovery during follow-up. Enrollment differences between those with immune recovery and those without immune recovery included: a shorter time from AIDS diagnosis to CMV retinitis diagnosis for those with immune recovery (median, 0.9 years) vs. those without (median, 3.9 years, $P<0.0001$); a longer interval from CMV retinitis diagnosis to enrollment (medians, 1.6 vs. 0.07 years, $P<0.0001$); more combination antiretroviral therapy use (84.8% vs. 70.0%, $P<0.0001$); higher CD4+ T cells at enrollment (medians, 178 vs. 17 cells/ μ L, $P<0.001$); a higher nadir CD4+ T cell count (medians, 12 vs. 6 cells/ μ L, $P<0.0001$); and a lower HIV load both at enrollment (median $\log_{10}(\text{copies/mL})$, 2.6 vs. 5.0, $P<0.0001$) and maximum value prior to enrollment (median $\log_{10}(\text{copies/mL})$, 5.5 vs. 5.7, $P<0.0001$). Patients who experienced immune recovery had a greater proportion of patients with bilateral visual impairment at enrollment (8.1% vs. 3.2%, $P=0.03$), consistent with the longer time from CMV retinitis to enrollment in this group. The eyes of patients who experienced immune recovery had a worse distribution of enrollment visual acuities (median 20/25 vs. 20/21, $P=0.0002$) than those without and a greater proportion of eyes with visual impairment (33.1% vs. 20.6%, $P<0.001$) and blindness (15.0% vs. 9.1%, $P=0.02$) than the eyes of patients who did not experience immune recovery. Similarly, the eyes of patients who experienced immune recovery had smaller Goldmann visual fields on enrollment (median 585 degrees vs. 612 degrees, $P=0.01$) than the eyes of those without immune recovery. These results similarly are consistent with the longer duration of CMV retinitis prior to enrollment among the group with immune recovery.

Nearly all patients (98.1%) received antiretroviral therapy at some time, either prior to enrollment or during follow-up (table 1). Those with immune recovery were more likely to receive antiretroviral therapy (100%) vs. those without immune recovery (95.1%, $P=0.0001$). Most antiretroviral therapy use consisted of combination therapy including three or more drugs and at least one potent agent (93.5% of participants) with those who experienced immune recovery being more likely to receive combination therapy (99.0%) vs. those without immune recovery (84.7%, $P<0.0001$). Among those with immune recovery, the mean CD4+ T cell count after immune recovery was identified was 372 cells/ μ L, and the mean never was lower than 340 cells/ μ L (figure 1, available online at www.aaojournal@aao.org). Furthermore, the 95% CI for CD4+ T cells among participants with immune recovery after immune recovery never was lower than 300 cells/ μ L (figure 1). Initial anti-CMV drug regimens differed between those with and without immune recovery in that those with immune recovery were more likely to be enrolled without anti-CMV treatment (24.3% vs. 7.6%) and less likely to be receiving combination systemic and local

(intraocular) anti-CMV therapy (9.1% vs. 20.2%), consistent with the ability to safely discontinue anti-CMV therapy among those with immune recovery.¹⁷

Mortality

Among those with immune recovery, the mortality rate (table 2 and figure 2) was significantly and substantially lower than among those without immune recovery (2.7/100 PY vs. 44.4/100 PY, $P<0.001$). The adjusted hazard ratio (HR) for mortality for those without immune recovery was 10.5 (95% confidence interval [CI] 7.1-15.4, $P<0.001$). The one-, five-, and 10-year survivals after the diagnosis of CMV retinitis for patients with immune recovery vs. those without immune recovery were 98.0% (95% CI 92.0-99.5%) vs. 54.3% (95% CI 45.3-62.5%), 84.2% (95% CI 78.0-88.8%) vs. 8.5% (95% CI 5.2-12.9%) and 73.8% (95% CI 67.1-79.3%) vs. 3.4% (95% CI 1.6-6.3%), respectively. Median survival among patients with AIDS and CMV retinitis without immune recovery was 13.5 months (1.12 years), whereas for those with immune recovery median survival was estimated at 27.0 years (95% CI 19.2-34.9 years). Mortality results for the enrollment eras are shown as Table 3 (available online at www.aaojournal@aao.org). There was no significant difference in the greater risk of mortality of those without immune recovery between the two enrollment eras (interaction P -value = 0.10). Risk factors for mortality are shown as table 4. In the adjusted model, enrollment CD4+ T cells <50 cells/ μ L was associated with an increased risk of mortality (adjusted HR=4.1, $P<0.001$), whereas nadir CD4+ T cells were not. Enrollment HIV load >2.6 log₁₀(copies/mL) was associated with an increased mortality (adjusted HR=2.8 for HIV load 2.6-5.0 log₁₀(copies/mL), $P<0.001$, and 3.4 for HIV load >5.0, $P<0.001$), whereas maximum HIV load prior to enrollment was not. Bilateral CMV retinitis also was associated with an increased risk of mortality (adjusted HR=1.3, $P=0.05$). In the time-updated model, not using combination antiretroviral therapy, CD4+ T cells <200 cells/ μ L, and HIV load all >2.6 log₁₀(copies/mL) all were associated with an increased risk of mortality. For CD4+ T cells, there was an apparent increasing risk with decreasing CD4+ T cells, with the biggest risk for CD4+ T cells <50 cells/ μ L (adjusted HR vs. >200 cells/ μ L = 12.5, $P<0.001$), whereas for HIV load the risks appeared similar for 2.6-5.0 and >5.0 log₁₀(copies/mL) (adjusted HRs=2.0 and 2.2 vs. <2.6 log₁₀(copies/mL), $P=0.007$ and 0.005, respectively). The time-updated model of mortality without the inclusion of time-varying antiretroviral drug use gave very similar HRs for the effects of CD4+ T cells and HIV load on survival (data not shown), suggesting that the beneficial effect of antiretroviral therapy on survival was not mediated exclusively through these two parameters. In the adjusted model, enrollment era was not associated with any difference in mortality (HR=1.2, 95% CI 0.9, 1.7, $P=0.14$).

Ocular outcomes

Ocular outcomes among patients with CMV retinitis are shown as table 2. Among all patients with unilateral CMV retinitis at presentation, the rate of second eye involvement was 2.1/100 PY. The rates of second eye involvement among patients with unilateral CMV retinitis at enrollment for those patients with immune recovery vs. those without were 1.0/100 PY vs. 6.6/100 PY (crude HR 2.6, $P=0.004$), but the adjusted HR was 1.9 and only of borderline significance ($P=0.09$). Among patients with AIDS and CMV retinitis with immune recovery, the one-, five-, and 10-year cumulative incidences of second eye

involvement after CMV retinitis diagnosis were 4.7% (95% CI 1.5-14.0%), 13.6% (95% CI 7.9-22.7%), and 15.0% (95% CI 9.1-24.1%), respectively.

For the entire population, the rates of bilateral visual impairment and blindness were 0.9/100 PY and 0.4/100 PY, respectively. The rates of bilateral visual impairment and blindness did not differ substantially or significantly by immune recovery status (table 2). The cumulative incidence of bilateral visual impairment (figure 3) at one, five, and 10 years after the diagnosis of CMV retinitis were 5.4% (95% CI 3.0-9.7%), 9.5% (95% CI 6.3-14.3%), and 11.2% (95% CI 7.7-16.2%), respectively. The cumulative incidence of bilateral blindness (figure 3) at one, five, and 10 years after the diagnosis of CMV retinitis were 2.0% (95% CI 0.7-5.4%), 3.2% (95% CI 1.5-6.7%), and 5.7% (95% CI 3.3-9.7%), respectively. Visual impairment and blindness results for the enrollment eras are listed as Table 3 (available online at www.aaojournal@aao.org). There was no significant difference in the risks of bilateral visual impairment, comparing those with immune recovery to those without, between the two enrollment eras (interaction P-value =0.81).

The estimated mean rate of visual field loss on quantitative Goldmann perimetry was 6°/year (95% CI 4-8°/year) for those with immune recovery and 54°/year (95% CI 24-84°/year) for those without immune recovery. Since the normal quantitative Goldmann visual field is ~785° of total field,²⁹ these losses correspond to ~1%/year for those with immune recovery and ~7%/year for those without immune recovery. Loss of visual field was greater among those with retinal detachments than among those without. The respective rates of visual field loss in degrees of field/year (and 95% CIs) are as follows: immune recovered, no retinal detachment, 4.4 (2.5, 6.2); immune recovered, retinal detachment, 15.1 (10.7, 19.5); no immune recovery, no retinal detachment, 33.8 (0.3, 68.0); no immune recovery, retinal detachment 76.0 (52.8, 99.3). These rates correspond to approximately 0.6%, 2%, 4%, and 10% of the normal visual field/year, respectively.

The rate of loss of retinal area from involvement by CMV retinitis was evaluated using both the clinician estimate and the Reading Center grading. The adjusted rates of loss of retinal area using the clinician grading were 0.3% of the retinal area/year for eyes of those with immune recovery, and 5.5%/year for eyes of those without immune recovery (P<0.001). The Reading Center adjusted rates of loss of retinal area were 0.2%/year for eyes of those with immune recovery and 2.2%/year for eyes of those without immune recovery (P<0.01). Among the eyes of patients with immune recovery there was a suggestion that the rate of loss of retinal area declined after immune recovery from 1.4%/year (95% CI 0-3.5%/year) to 0.2%/year (95% CI 0-0.6%/year), using Reading Center grading (adjusted P-value=0.07).

The rate of retinal detachment was significantly affected by whether the CMV retinitis was recently diagnosed (≤ 45 days prior) upon enrollment or was previously diagnosed (>45 days prior to enrollment); the interaction P-value was 0.003. For those with immune recovery, the rates were 1.0/100 EY vs. 1.3/100 EY for eyes of those with recently-diagnosed CMV retinitis vs. eyes of those with previously-diagnosed CMV retinitis. For those without immune recovery, the rates of retinal detachment for patients with recently-diagnosed CMV retinitis and previously-diagnosed CMV retinitis were 8.7/100 EY (adjusted HR vs. those with immune recovery = 6.4, 95% CI 2.2-18.1, P<0.001) and 2.7/100 EY (adjusted HR vs.

those with immune recovery = 0.6, 95% CI 0.2-1.4, $P=0.31$), respectively. Among the eyes of patients with newly-diagnosed CMV retinitis upon enrollment, the large majority (>90%) of detachments occurred within the first 2.5 years after the diagnosis of CMV retinitis.

Immune recovery uveitis

Among patients with AIDS and CMV retinitis with immune recovery, the incidence of immune recovery uveitis was 2.2/100 PY (95% CI 1.7-3.0/100 PY). The rates of bilateral visual impairment and blindness for patients with CMV retinitis, immune recovery, and immune recovery uveitis vs. those of patients with CMV retinitis and immune recovery without immune recovery uveitis were 3.8/100 PY vs. 2.3/100 PY (HR = 1.7, 95% CI 0.8, 3.5, $P=0.12$) and 1.9/100 PY vs. 0.6/100 PY (HR=3.1, 95% CI 1.1, 3.9, $P=0.03$).

Discussion

Modern antiretroviral therapy has resulted in marked improvements in survival among patients with HIV infection, with median survivals estimated at >14 years from diagnosis of HIV infection.²² Nevertheless, because of late diagnosis of HIV infection or poor control of HIV replication, patients may progress to AIDS and be at risk for opportunistic infections.^{39,40} As such there remains a population in the United States at risk for CMV retinitis, albeit a markedly reduced one, and a commensurate 90% reduction in the incidence of CMV retinitis.⁷ Patients with CMV retinitis, if they experience immune recovery from antiretroviral therapy, are capable of prolonged survival. In this regard, the results in LSOCA are striking. Among participants with CMV retinitis who do not experience immune recovery the median survival is only slightly longer than one year, and less than 10% will be alive five years after the diagnosis of CMV retinitis, whereas among those who experience immune recovery at some time during the course of their disease, the median survival was estimated at 27 years, and nearly 75% will be alive 10 years after the diagnosis of CMV retinitis. The analysis of time-varying risk factors for mortality demonstrated that CD4+ T cells >200 cells/ μ L and HIV load <2.6 log₁₀(copies/mL) were associated with lowest mortality. Mortality was greatest among participants with CD4+ T cells <50 cells/ μ L and intermediate with CD4+ T cells between 50 and 200 cells/ μ L. Although a sustained CD4+ T cell level >100 cells/ μ L is adequate for managing CMV retinitis without anti-CMV drugs and minimizing visual loss among patients with CMV retinitis,^{16,17} these data suggest additional benefit in terms of survival from a higher CD4+ T cell level. Although HIV loads <2.6 log₁₀(copies/mL) were associated with a decreased risk of mortality compared to higher loads, in the time-updated analysis, HIV loads above this threshold appeared to have similar risks, more consistent with a threshold effect than a “dose-response” effect. This apparent threshold level corresponds to 400 copies/mL, the level termed “undetectable” with older HIV assays in use when LSOCA was begun, suggesting that the antiretroviral treatment target for this population also is suppression of HIV replication in the blood. Finally, the magnitude of the benefits of higher CD4+ T cells and lower HIV loads were similar whether or not antiretroviral therapy was included in the model. However, when antiretroviral therapy was included in the model, there appeared to be an additional benefit, not evidently mediated through raising CD4+ T cells or suppressing HIV replication. Similar benefits of combination antiretroviral therapy among patients without immune recovery

were observed early after introduction the introduction of modern combination antiretroviral therapy.^{41,42} However, these earlier studies included patients who were diagnosed with CMV retinitis in the era before modern combination antiretroviral therapy and then experienced a “late” immune recovery,^{41,42} whereas the current study included only patients diagnosed with CMV retinitis after the introduction of modern antiretroviral therapy, and therefore is more relevant to the modern era. As such these data suggest the benefit on survival for antiretroviral therapy even without raising CD4+ T cells or suppressing HIV load still is present today.

Prior to the era of modern antiretroviral therapy, the rates of visual impairment and blindness were substantial, even among those treated with anti-CMV drugs.^{1,2} Cohort studies have demonstrated marked improvements in the visual prognosis of patients with AIDS and CMV retinitis in the era of modern antiretroviral therapy.^{18-21,43,44} Our data suggest that in the modern era the rates of bilateral visual impairment and bilateral blindness are <1%/year and <0.5%/year, respectively. The cumulative incidences of bilateral visual impairment and bilateral blindness at five and 10 years after the diagnosis of CMV retinitis are 9.5% and 3.2%, respectively, at five years and 11.2% and 5.7%, respectively, at ten years. Surprisingly the rates of visual impairment and blindness were similar between those with and without immune recovery, perhaps suggesting the effectiveness of modern anti-CMV management, but also affected by the competing risk of mortality among those without immune recovery. Nevertheless these prevalences of visual impairment and blindness appear greater than those reported in the general non-HIV-infected population, which are estimated at 1.98% and 0.78%, respectively,⁴⁵ suggesting that the adverse effect of CMV retinitis on vision persists in the modern era.

In eyes with CMV retinitis, visual acuity is lost by several mechanisms, including damage to the macula or optic nerve by the infection, retinal detachment, cataract, and among those with immune recovery, macular edema from immune recovery uveitis.⁴⁴ Retinal detachment rates in an eye with CMV retinitis were estimated to be as high as 33%/year in the era before modern antiretroviral therapy,^{1,45} and studies have demonstrated marked reductions in the detachment rates with the advent of modern combination antiretroviral therapy.^{19,20} Our data suggest that the rate of retinal detachment in eyes of patients with CMV retinitis who experience immune recovery is ~1%/year, and it was similar between those participants who enrolled in LSOCA with recently-diagnosed (< 45 days) CMV retinitis and those with more long-standing retinitis on enrollment. However, for participants without immune recovery, the rate was a different between those with previously diagnosed retinitis (2.7/100 EY) and those with recently-diagnosed retinitis (8.7/100 EY). It is possible that these differences represent a survivor bias among those with previously-diagnosed disease -- namely detachments tend to occur early after the diagnosis of CMV retinitis, and these patients had survived without a detachment and were, therefore, less likely to detach. In this regard, most retinal detachments among those with recently-diagnosed CMV retinitis occurred in the first 2.5 years after the diagnosis of CMV retinitis, and the median time from CMV retinitis diagnosis to enrollment among those with previously-diagnosed CMV retinitis was 2.3 years, suggesting that these latter patients largely were past the high risk period for retinal detachment. As such the rate among those participants with recently-diagnosed CMV retinitis may represent a better estimate of what the clinical course will be among patients

with CMV retinitis in the modern era. Although the rates are low among all of these groups and substantially less than the ~33/100 EY in the era before modern combination antiretroviral therapy, they still are greater than the rate in the general, non-HIV-infected population, which is ~1/10,000/year.⁴⁶

Rates of loss of visual field and retinal area from CMV retinitis were low among patients with CMV retinitis and immune recovery, ~1% of the normal visual field/year and <1% of the retinal area/year. They were higher among patients without immune recovery, ~7% of the normal visual field/year and 2-5.5% of the retinal area/year, depending on the methodology used. Differences between the clinician estimate and Reading Center estimate of loss of retinal area probably reflect, in part, the clinician's ability to see the peripheral retina, whereas the Reading Center is limited to the posterior and mid-peripheral areas of the retina accessible to standard 60° photographs.^{23,24,26} Visual field is lost in patients with CMV retinitis due to retinal necrosis from the retinitis and due to retinal detachment. In this regard, there was a greater loss of field among those with detachments, regardless of immune recovery status. However, there still was a loss of field, commensurate to the loss of functioning retina from retinitis, albeit a very small one, among those with immune recovery and no retinal detachment. Nevertheless, both methods demonstrate the benefits of immune recovery on preventing retinal damage and loss of visual function (field).

Immune recovery uveitis is one of the immune recovery inflammatory syndromes (IRIS) seen in patients with AIDS in which there is an inflammatory response to an infectious agent as the immune system recovers. In the case of CMV retinitis, it manifests as a uveitis, typically a vitritis, and may be accompanied by macular edema and decreased vision.^{20, 31,32} Although the rate of immune recovery uveitis in this study is lower than that reported in the era soon after the introduction of modern combination antiretroviral therapy, it is similar to that previously reported for five-year outcomes of the LSOCA CMV retinitis cohort.²⁰ Immune recovery uveitis is associated with an increased risk of visual loss, in this analysis of bilateral blindness. Because the risks of retinal detachments and immune recovery uveitis both are increased by larger CMV retinitis lesions,^{19,20,31} aggressive treatment of all CMV retinitis lesions, including small peripheral CMV lesions in antiretroviral-naïve patients, at least until there is sustained immune recovery,^{16,17} would appear to be appropriate in order to minimize CMV lesion size and the risks of these complications.

We previously have evaluated the roles of different treatment regimens in the era of modern combination antiretroviral therapy.^{17,21} Systemically-administered anti-CMV therapy continues to have a substantial benefit on mortality (50% reduction), second-eye involvement (80% reduction), and in the development of visceral disease (90% reduction) when compared to local therapy only (intravitreal injections or implants).²¹ Furthermore, systemically-administered anti-CMV appeared no worse than and possibly better than repetitive intravitreal injections for controlling the retinitis.²¹ Cytomegalovirus disease is associated with a 60% increase in mortality among persons with AIDS,⁴⁸ likely due to the systemic nature of the infection, CMV's ability to trans-activate HIV, and CMV's own intrinsic immunosuppressive effects.³ Cytomegalovirus DNA can be detected in the blood (CMV "load") of 68% of patients diagnosed with CMV retinitis, and its presence is associated with an increased risk of mortality.⁴⁹ Furthermore, quantitative CMV load

measurements suggest that higher CMV “loads” are associated with greater risks of mortality.⁴⁹ As such, inhibiting CMV replication with systemic therapy might be expected to improve immune function and survival. With sufficient, sustained immune recovery, specific immunity to CMV is restored, and the immune system can control CMV replication, so that anti-CMV therapy no longer is needed.¹⁷ Because CMV load measurements have limited usefulness in managing CMV retinitis,⁴⁹ and most patients are managed primarily with clinical examination, CMV load measurements were not routinely obtained in this study.

Despite the size of the cohort (nearly 500 patients with CMV retinitis diagnosed in the modern era of combination antiretroviral therapy), its prospective nature, and the length of follow-up, there are potential limitations to these data. For some outcomes the number of events and event rates were low, limiting opportunities for further analysis. The SOCA clinical centers were AIDS ophthalmology clinics at academic medical centers, and because of the interest in the outcomes of CMV retinitis, it was oversampled relative to participants without CMV retinitis; as such, the cohort could suffer from referral bias. However, these centers tended to provide primary eye care for large numbers of patients with AIDS, and hence may be generalizable. In this regard, comparison of the LSOCA cohort with national statistics on patients with AIDS suggests that the LSOCA cohort is representative of the AIDS epidemic with the possible exception of under representation of persons whose risk factor for HIV is injection drug use.²³

Participants enrolled with previously-diagnosed CMV retinitis could have a survivor bias, which could lead to an overestimation of our survival data. We sought to minimize this effect by using a staggered entry approach to analysis, which anchors events to the date of CMV retinitis diagnosis, rather than enrollment, and by including duration of AIDS and duration of CMV retinitis in all adjusted analyses. These adjustments minimize any effects of differential duration of CMV retinitis on the comparative data, and in only one instance was there a significant interaction between outcomes comparing those with and without immune recovery and the duration of CMV retinitis at enrollment – namely the interaction between when the CMV retinitis was diagnosed relative to enrollment and the risk of retinal detachment. There was a higher rate of retinal detachment among those with recently-diagnosed CMV retinitis than among those with previously-diagnosed CMV retinitis, as the latter group appeared to be enrolled beyond the high risk period for retinal detachments after diagnosis of CMV retinitis. As such, the risk among those with recently diagnosed CMV retinitis is likely to be the better estimate of the retinal detachment rate among all patients with AIDS and CMV retinitis in the modern era. Nevertheless, the estimates of survival for participants in LSOCA may be longer than those seen in the general population of patients with AIDS and CMV retinitis.

Although dramatic improvements in the survival of patients with CMV retinitis can be expected with immune recovery, those seen in the community at large may not always match the magnitude seen in the LSOCA study for other reasons as well. Participants in LSOCA were motivated to participate in a clinical study and may have been more adherent to their medication regimens. To the extent that antiretroviral regimen adherence is less, the benefits on survival of immune recovery for patients with CMV retinitis may be less,

particularly since our data suggest that the best outcomes are achieved with suppression of HIV replication and recovery of CD4+ T cells to >200 cells/ μ L. Finally, our estimate of the median survival of patients with immune recovery was derived assuming a Weibull distribution, as the Kaplan-Meier median survival was not observed during follow-up. This estimate can be biased if the data do not follow a Weibull functional form. Nevertheless, inspection of the plot of complementary log-log survival function vs. log time supported its use.

In conclusion, our data suggest that in the era of modern combination antiretroviral therapy prolonged survival is possible if there is immune recovery (median survival estimated at 27 years), whereas if there is no immune recovery, the mortality is substantial with a median survival of just over 1 year. Rates of ocular complications, such as retinal detachment, and of visual loss are substantially lower than those observed prior to the modern era, and remain low even past 10 years after CMV retinitis diagnosis. Nevertheless, the rates of complications and visual loss appear to be greater than in the general, non-HIV infected population, testifying to the careful follow-up and management required for these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

A) Funding support: Supported by cooperative agreements from the National Eye Institute, the National Institutes of Health, Bethesda, MD to the Icahn School of Medicine at Mount Sinai, New York, NY (U10 EY 08052); The Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD (U10 EY 08057); and the University of Wisconsin, Madison School of Medicine, Madison, WI (U10 EY 08067).

D) Other Acknowledgements

None

REFERENCES

1. Jabs DA. Ocular manifestations of HIV infection. *Trans Am Ophthalmol Soc.* 1995; 93:623–83. [PubMed: 8719695]
2. Holbrook JT, Jabs DA, Weinberg DV, et al. Visual loss in patients with cytomegalovirus retinitis and acquired immunodeficiency syndrome before the widespread availability of highly active antiretroviral therapy. *Arch Ophthalmol.* 2003; 121:99–107. [PubMed: 12523893]
3. Jabs DA. Cytomegalovirus retinitis and the acquired immune deficiency syndrome: Bench to bedside: LXVII Edward Jackson Memorial Lecture. *Am J Ophthalmol.* 2011; 151:198–216. [PubMed: 21168815]
4. Gallant JE, Moore RD, Richman DD, et al. Incidence and natural history of cytomegalovirus disease in patients with advanced human immunodeficiency virus disease treated with zidovudine. *J Infect Dis.* 1992; 166:1223–7. [PubMed: 1358986]
5. Pertel P, Hirschtick R, Phair J, et al. Risk of developing cytomegalovirus retinitis in persons infected with the human immunodeficiency virus. *J Acquir Immune Defic Syndr.* 1992; 5:1069–74. [PubMed: 1357151]
6. Hoover DR, Peng Y, Saah A, et al. Occurrence of cytomegalovirus retinitis after human immunodeficiency virus immunosuppression. *Arch Ophthalmol.* 1996; 114:821–7. [PubMed: 8660165]

7. Sugar EA, Jabs DA, Ahuja A, et al. Incidence of cytomegalovirus retinitis in the era of highly active antiretroviral therapy. *Am J Ophthalmol.* 2012; 153:1016–24. [PubMed: 22310076]
8. Palella FJ, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Eng J Med.* 1998; 338:853–60.
9. Holtzer CD, Jacobson MA, Hadley WK, et al. Decline in the rate of specific opportunistic infections at San Francisco General Hospital, 1994–1997. *AIDS.* 1998; 12:1931–3. [PubMed: 9792398]
10. Jacobson MA, Stanley H, Holtzer C, et al. Natural history and outcome of new AIDS-related cytomegalovirus retinitis diagnosed in the era of highly active antiretroviral therapy. *Clin Infect Dis.* 2000; 30:231–3. [PubMed: 10619774]
11. Jabs DA, Bolton G, Dunn JP, Palestine AG. Discontinuing anticytomegalovirus therapy in patients with immune reconstitution after combination antiretroviral therapy. *Am J Ophthalmol.* 1998; 126:817–22. [PubMed: 9860006]
12. Tural C, Romeu J, Sirera G, et al. Long-lasting remission of cytomegalovirus retinitis without maintenance therapy in human immunodeficiency virus-infected patients. *J Infect Dis.* 1998; 177:1080–3. [PubMed: 9534987]
13. Macdonald JC, Torriani FJ, Morse LS, et al. Lack of reactivation of cytomegalovirus (CMV) retinitis after stopping CMV maintenance therapy in AIDS patients with sustained elevations in CD4 T cells in response to highly active antiretroviral therapy. *J Infect Dis.* 1998; 177:1182–7. [PubMed: 9593001]
14. Whitcup SM, Fortin E, Lindblad AS, et al. Discontinuation of anticytomegalovirus therapy in patients with HIV infection and cytomegalovirus retinitis. *JAMA.* 1999; 282:1633–7. [PubMed: 10553789]
15. Kirk O, Reiss P, Uberti-Foppa C, et al. Safe interruption of maintenance therapy against previous infection with four common HIV-associated opportunistic pathogens during potent antiretroviral therapy. *Ann Intern Med.* 2002; 137:239–50. [PubMed: 12186514]
16. Centers for Disease Control and Prevention. Group Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. *Morb Mortal Wkly Rep.* 2009; 58:55–60.
17. Holbrook JT, Colvin R, Van Natta ML, et al. Studies of Ocular Complications of AIDS (SOCA) Research Group. Evaluation of the United States Public Health Service guidelines for discontinuation of anti-cytomegalovirus therapy after immune recovery in patients with cytomegalovirus retinitis. *Am J Ophthalmol.* 2011; 152:628–37. [PubMed: 21742304]
18. Jabs DA, Van Natta ML, Thorne JE, et al. the Studies of Ocular Complications of AIDS Research Group. Course of cytomegalovirus retinitis in the era of highly active antiretroviral therapy: 1. Retinitis progression. *Ophthalmology.* 2004; 111:2224–31. [PubMed: 15582078]
19. Jabs DA, Van Natta ML, Thorne JE, et al. the Studies of Ocular Complications of AIDS Research Group. Course of cytomegalovirus retinitis in the era of highly active antiretroviral therapy: 2. Second eye involvement and retinal detachment. *Ophthalmology.* 2004; 111:2232–9. [PubMed: 15582079]
20. Jabs DA, Ahuja A, Van Natta M, et al. Course of cytomegalovirus retinitis in the era of highly active antiretroviral therapy: five-year outcomes. *Ophthalmology.* 2010; 117:2152–61. [PubMed: 20673591]
21. Jabs DA, Van Natta M, Dunn JP, et al. Comparison of treatment regimens for cytomegalovirus retinitis in patients with AIDS in the era of highly active antiretroviral therapy. *Ophthalmology.* 2013; 120:1262–70. [PubMed: 23419804]
22. Braithwaite RS, Roberts MS, Chang CC, et al. Influence of alternative thresholds for initiating HIV treatment on quality-adjusted life expectancy. *Ann Intern Med.* 2008; 148:178–85. [PubMed: 18252681]
23. Jabs DA, Van Natta ML, Holbrook JT, et al. The Longitudinal Study of the Ocular Complications of AIDS: 1. Ocular diagnoses at enrollment. *Ophthalmology.* 2007; 114:780–6. [PubMed: 17258320]
24. Jabs DA, Van Natta ML, Holbrook JT, et al. The Longitudinal Study of the Ocular Complications of AIDS: 2. Ocular examination results at enrollment. *Ophthalmology.* 2007; 114:787–93. [PubMed: 17210182]

25. Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *Morb Mortal Wkly Rep.* 1992; 41(RR-17):1–19.
26. Studies of the Ocular Complications of AIDS Research Group. The foscarnet ganciclovir cytomegalovirus retinitis treatment trial: 1. Rationale, design, and methods. *Control Clin Trials.* 1992; 13:22–39. [PubMed: 1315661]
27. Ferris FL III, Kassof A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. *Am J Ophthalmol.* 1982; 94:91–6. [PubMed: 7091289]
28. Jabs DA, Rosenbaum JT, Nussenblatt RB, The Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. *Am J Ophthalmol.* 2005; 140:509–16. [PubMed: 16196117]
29. Thorne JE, Van Natta ML, Jabs DA, Duncan JL, Srivastava SK, the Studies of Ocular Complications of AIDS Research Group. Visual field loss in patients with cytomegalovirus retinitis. *Ophthalmology.* 2011; 118:895–901. [PubMed: 21146225]
30. Thorne JE, Jabs DA, Kedhar SR, et al. Loss of visual field among patients with birdshot chorioretinopathy. *Am J Ophthalmol.* 2008; 145:23–8. [PubMed: 17997394]
31. Nguyen QD, Kempen JH, Bolton SG, et al. Immune recovery uveitis in patients with cytomegalovirus retinitis following institution of successful highly active antiretroviral therapy. *Am J Ophthalmol.* 2000; 129:634–9. [PubMed: 10844056]
32. Kempen JH, Min YI, Freeman Wr, et al. the Studies of the Ocular Complications of AIDS Research Group. Risk of immune recovery uveitis in patients with AIDS and cytomegalovirus retinitis. *Ophthalmology.* 2006; 113:684–94. [PubMed: 16581429]
33. Altman, DG. *Practical Statistics for Medical Research.* Chapman and Hall; London: 1991. p. 213-5.p. 241-56.
34. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958; 53:457–81.
35. Tarwater PM, Mellors J, Gore ME, et al. Methods to assess population effectiveness therapies in human immunodeficiency virus incident and prevalent cohorts. *Am J Epidemiol.* 2001; 154:675–81. [PubMed: 11581102]
36. Lin DY. Cox regression analysis of multivariate failure time data: the marginal approach. *Stat Med.* 1994; 13:2233–47. [PubMed: 7846422]
37. Weibull W. A statistical distribution function of wide applicability. *J Appl Mech Trans ASME.* 1951; 18:293–7.
38. *Stata Mixed Effects Reference manual: Release 13.* StataCorp LP; College Station, TX: p. 285-335.
39. Late HIV testing – 34 states, 1996-2005. *Morbidity and Mortality Weekly Report.* 2009; 58:661–5.
40. Edison L, Hughes D, Drenzek C, Kelly J. Prevalence and indicators of viral suppression among persons diagnosed with HIV infection retained in care – Georgia, 2010. *Morbidity and Mortality Weekly Report.* 2014; 63:55–8.
41. Kempen JH, Jabs DA, Wilson LA, et al. Risk of vision loss in patients with cytomegalovirus retinitis and the acquired immunodeficiency syndrome. *Arch Ophthalmol.* 2003; 121:466–76. [PubMed: 12695243]
42. Kempen JH, Jabs DA, Wilson, et al. Mortality risk for patients with cytomegalovirus retinitis and acquired immune deficiency syndrome. *Clin Infect Dis.* 2003; 37:1365–73. [PubMed: 14583871]
43. Thorne JE, Jabs DA, Kempen JH, et al. Incidence of and risk factors for visual acuity loss among patients with AIDS and cytomegalovirus retinitis in the era of highly active antiretroviral therapy. *Ophthalmology.* 2006; 113:1432–40. [PubMed: 16766032]
44. Thorne JE, Jabs DA, Kempen JH, et al. Causes of visual acuity loss among patients with AIDS and cytomegalovirus retinitis in the era of highly active antiretroviral therapy. *Ophthalmology.* 2006; 113:1441–45. [PubMed: 16781775]
45. Congdon N, O'Colmain B, Klaver CC, et al. Causes and prevalence of visual impairment among adults in the United States. *Arch Ophthalmol.* 2004; 122:477–85. [PubMed: 15078664]
46. Studies of Ocular Complications of AIDS (SOCA) Research Group in collaboration with the AIDS Clinical Trials Group (ACTG). Rhegmatogenous retinal detachment in patients with

- cytomegalovirus retinitis: the Foscarnet-Ganciclovir Cytomegalovirus Retinitis Trial. *Am J Ophthalmol.* 1997; 124:61–70. [PubMed: 9222234]
47. Mitry D, Charteris DG, Fleck BW, et al. The epidemiology of rhegmatogenous retinal detachment: geographic variation and clinical associations. *Brit J Ophthalmol.* 2010; 94:678–84. [PubMed: 19515646]
48. Jabs DA, Holbrook JT, Van Natta ML, et al. Risk factors for mortality in patients with AIDS in the era of highly active antiretroviral therapy. *Ophthalmology.* 2005; 112:771–9. [PubMed: 15878056]
49. Jabs DA, Martin BK, Forman MS, Ricks MO for the Cytomegalovirus Retinitis and Viral Resistance Research Group. Cytomegalovirus (CMV) blood DNA load, CMV retinitis progression, and the occurrence of resistant CMV in patients with CMV retinitis. *J Infect Dis.* 2005; 192:640–9. [PubMed: 16028133]

PRECIS

Patients with AIDS and cytomegalovirus retinitis with immune recovery from antiretroviral therapy have an estimated median survival of 27.0 years, whereas those without immune recovery have a median survival of 13.5 months.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 1.
Mean CD4+ T cells among patients with immune recovery after immune recovery. Bars represent 95% confidence intervals.

Figure 2. Kaplan Meier estimates of survival of patients with AIDS and cytomegalovirus retinitis after the diagnosis of cytomegalovirus retinitis, for patients with and without immune recovery. Shaded areas represent 95% confidence intervals.

Figure 3. Cumulative probability of: a) bilateral visual impairment (worse than 20/40); and b) bilateral blindness (20/200 or worse) among patients with cytomegalovirus retinitis after the diagnosis of cytomegalovirus retinitis. Shaded areas represent 95% confidence intervals.

Table 1

Characteristics of the Study Population

Characteristic at Enrollment	Overall Population	Immune recovery	No immune recovery	P-value
Number of patients	479	296	183	
Age at enrollment (years)				0.0004
Median	40	42	39	
Interquartile range	35, 46	36, 47	34, 33	
Gender (%)				0.72
Men	80.4	79.7	81.4	
Women	19.6	20.3	18.6	
Race and ethnicity (%)				0.036
White, non-Hispanic	44.0	42.2	47.0	
African-American, non-Hispanic	33.2	30.7	37.2	
Hispanic	18.2	22.0	12.0	
Other	4.6	5.1	3.8	
HIV risk factor (%)				0.72
Men having sex with men (MSM)	52.6	51.4	54.6	
Injection drug use (IDU)	2.1	2.4	1.6	
Both MSM and IDU	2.7	2.4	3.3	
Heterosexual contact	24.6	24.3	25.1	
Other	18.0	19.6	15.3	
Interval from AIDS to cytomegalovirus retinitis diagnoses (years)				<0.0001
Median	1.6	0.9	3.9	
Interquartile range	0.3, 4.8	0.1, 3.2	1.0, 6.8	
Interval from cytomegalovirus retinitis diagnosis to enrollment (years)				<0.0001
Median	0.5	1.6	0.07	
Interquartile range	0.04, 2.8	0.1, 3.0	0.01, 0.9	
Interval from AIDS diagnosis to enrollment (years)				0.002
Median	4.0	3.7	4.6	
Interquartile range	1.2, 6.7	0.9, 5.8	2.1, 7.6	
Enrollment era (%)				0.46
9/1/1998 through 8/31/2003	71.2	69.9	73.2	
9/1/2003 through 7/31/2011	28.8	30.1	26.8	
Combination antiretroviral therapy (%)				
Ever used prior to enrollment	79.1	84.8	70.0	<0.0001
Receiving at enrollment	77.9	83.4	68.8	0.0002
Received during follow-up	93.5	99.0	84.7	<0.0001
Any antiretroviral therapy prior to or at enrollment or during follow-up	98.1	100	95.1	0.0001

Characteristic at Enrollment	Overall Population	Immune recovery	No immune recovery	P-value
CD4+ T cells (cells/ μ L)				
Median, enrollment	84	178	17	<0.0001
Interquartile range, enrollment	20, 257	76, 364	7, 39	
Median, nadir	10	12	6	<0.0001
Interquartile range, nadir	4, 22	5, 30	3, 18	
HIV load ($\log_{10}$ (copies/mL))				
Median, enrollment	3.8	2.6	5.0	<0.0001
Interquartile range, enrollment	2.5, 5.1	1.8, 4.1	4.5, 5.6	
Median, maximum prior to enrollment	5.6	5.5	5.7	<0.0001
Interquartile range, maximum	5.1, 5.8	5.0, 5.8	5.4, 5.8	
Cytomegalovirus retinitis				
Bilateral disease (%)	39.0	39.5	38.2	0.34
Zone 1 * disease either eye (%)	44.0	44.3	43.7	0.92
Area retina involved >25% either eye (%)	28.4	29.7	26.2	0.46
Bilateral V _A worse than 20/40 (%)	6.3	8.1	3.2	0.03
Bilateral V _A 20/200 or worse (%)	1.0	1.4	0.6	0.65
Enrollment/initial cytomegalovirus retinitis treatment †				<0.0001
Systemic only	47.4	43.2	54.1	
Local only	21.3	23.3	18.0	
Systemic and local	13.4	9.1	20.2	
None	18.0	24.3	7.6	
<i>Eye specific characteristics in eyes with cytomegalovirus retinitis</i>				
Number eyes	667	414	253	
Zone 1 * involvement (%)	39.0	39.4	38.3	0.80
Are retina involved >25% (% eyes)	25.5	27.0	22.9	0.29
Visual acuity				
Median (letters)	81	80	84	0.0002
Snellen equivalent	20/24	20/25	20/21	
Interquartile range (letters)	64, 87	59, 86	75, 88	
Visual acuity worse than 20/40 (%)	28.3	33.1	20.6	<0.001
Visual acuity 20/200 or worse (%)	12.7	15.0	9.1	0.02
Quantitative Goldmann visual field score				
Median	598	585	612	0.01
Interquartile range	427, 702	403, 695	467, 712	

* Zone 1 encompasses an area within 3000 μ m from the center of the fovea and 1500 μ m for the edge of the optic nerve.

† Systemic therapy includes intravenous ganciclovir, intravenous foscarnet, intravenous cidofovir, oral ganciclovir, and valganciclovir. Local therapy includes intravitreal injections of ganciclovir or foscarnet and the ganciclovir implant.

Table 2

Outcomes of Patients with AIDS and Cytomegalovirus Retinitis

Outcome	Overall Population	Immune recovery	No immune recovery
Mortality			
Patients at risk	479	296	183
Events	229	69	160
Person-years	2836	2476	360
Rate (/100 person-years)	8.0	2.7	44.4
Crude hazard ratio		Reference	11.5
95% confidence interval			8.4, 15.8
P-value			<0.0001
Adjusted hazard ratio *		Reference	10.5
95% confidence interval			7.1, 15.4
P-value			<0.001
2 nd eye involvement in patients with unilateral retinitis			
Patients at risk	281	170	111
Events	39	15	24
Person-years	1776	1416	360
Rate (/100 person-years)	2.1	1.0	6.6
Crude hazard ratio		Reference	2.6
95% confidence interval			1.3, 5.1
P-value			0.004
Adjusted hazard ratio *		Reference	1.9
95% confidence interval			0.8, 4.2
P-value			0.09
Immune recovery uveitis in either eye			Not applicable
Patients at risk		268	
Events		45	
Person-years		1973	
Rate (/100 person-years)		2.2	
95% CI * (/100 person-years)		1.7, 3.0	
Bilateral visual acuity worse than 20/40			
Patients at risk	413	246	167
Events	26	17	9
Person-years	2673	2025	647
Rate (/100 person-years)	0.9	0.8	1.3
Crude hazard ratio		Reference	0.8
95% confidence interval			0.3, 1.8
P-value			0.61

Outcome	Overall Population	Immune recovery	No immune recovery
Adjusted hazard ratio *		Reference	0.3
95% confidence interval			0.1, 1.0
P-value			0.06
Bilateral visual acuity 20/200 or worse			
Patients at risk	464	284	180
Events	13	8	5
Person-years	3063	2360	703
Rate (/100 person-years)	0.4	0.3	0.7
Crude hazard ratio		Reference	1.2
95% confidence interval			0.3, 3.9
P-value			0.75
Adjusted hazard ratio *		Reference	0.5
95% confidence interval			0.1, 1.9
P-value			0.32
<i>Eye-specific outcomes in eyes with cytomegalovirus retinitis</i>			
Visual acuity worse than 20/40			
Eyes at risk	474	277	197
Events	160	105	55
Eye-years	2427	1740	687
Rate (/100 eye-years)	6.5	6.0	8.0
Crude hazard ratio		Reference	0.9
95% confidence interval			0.6, 1.3
P-value			0.73
Adjusted hazard ratio *		Reference	0.7
95% confidence interval			0.4, 1.1
P-value			0.14
Visual acuity 20/200 or worse			
Eyes at risk	579	352	227
Events	93	62	31
Eye-years	3439	2582	857
Rate (/100 eye-years)	2.7	2.4	3.6
Crude hazard ratio		Reference	1.0
95% confidence interval			0.6, 1.8
P-value			0.73
Adjusted hazard ratio *		Reference	0.7
95% confidence interval			0.4, 1.2
P-value			0.28
Visual field loss on Goldmann Perimetry			

Outcome	Overall Population	Immune recovery	No immune recovery
Unadjusted rate (°/year)		6	54
95% confidence interval		4, 8	24, 84
P-value			<0.01
Adjusted rate (°/year) *		6	53
95% confidence interval		4, 8	23, 84
P-value			<0.01
Retinal area affected by retinitis (% retina)			
<i>Clinical grading</i>			
Unadjusted rate (% retina/year)		0.3	5.3
95% confidence interval		−0.1, 0.7	4.3, 6.3
P-value			<0.001
Adjusted rate (% retina/year) *		0.3	5.5
95% confidence interval		−0.1, 0.8	4.4, 6.6
P-value			<0.001
<i>Reading center grading</i>			
Unadjusted rate (% retina/year)		0.1	2.6
95% confidence interval		−0.07, 0.4	1.7, 3.4
P-value			<0.01
Adjusted rate (% retina/year) *		0.2	2.2
95% confidence interval		−0.02, 0.5	1.3, 3.1
P-value			<0.01

* Adjusted models controlled for the following enrollment characteristics: time from cytomegalovirus retinitis diagnosis, time from AIDS diagnosis , time from AIDS diagnosis to cytomegalovirus retinitis diagnosis, combination antiretroviral drug use, and HIV load.

Table 3

Outcomes of Patients with AIDS and Cytomegalovirus Retinitis by Enrollment Era

Outcome	Immune recovery	No immune recovery
<i>Mortality</i>		
Enrolled 9/1/1998 through 8/31/2003		
Patients at risk	207	134
Number of events	59	122
Person-years	2011	283
Rate (/100 person-years)	2.9	43.0
Hazard ratio	Reference	9.8
95% confidence interval		6.9, 14.1
P-value immune recovery vs. no immune recovery		<0.001
Enrolled 9/1/2003 through 7/31/2011		
Patients at risk	89	49
Number of events	10	38
Person-years	465	77
Rate (/100 person-years)	2.1	49.6
Hazard ratio	Reference	19.4
95% confidence interval		9.0, 41.7
P-value immune recovery vs. no immune recovery		<0.001
Interaction P-value for enrollment era	0.10	
<i>Bilateral visual acuity worse than 20/40</i>		
Enrolled 9/1/1998 through 8/31/2003		
Patients at risk	169	125
Number of events	12	8
Person-years	1637	577
Rate (/100 person-years)	0.7	1.3
Hazard ratio	Reference	0.8
95% confidence interval		0.3, 2.1
P-value immune recovery vs. no immune recovery		0.74
Enrolled 9/1/2003 through 7/31/2011		
Patients at risk	77	42
Number of events	5	1
Person-years	388	70.5
Rate (/100 person-years)	1.2	1.4
Hazard ratio	Reference	0.4
95% confidence interval		0.05, 4.3
P-value immune recovery vs. no immune recovery		0.52
Interaction P-value for enrollment era	0.81	
<i>Bilateral visual acuity 20/200 or worse</i>		

Outcome	Immune recovery	No immune recovery
Enrolled 9/1/1998 through 8/31/2003		
Patients at risk	197	132
Number of events	6	5
Person-years	1912	618
Rate (/100 person-years)	0.3	0.8
Hazard ratio	Reference	1.2
95% confidence interval		0.3, 4.5
P-value immune recovery vs. no immune recovery		0.72
Enrolled 9/1/2003 through 7/31/2011		
Patients at risk	87	48
Number of events	2	0
Person-years	448	85
Rate (/100 person-years)	0.4	0
Hazard ratio	Reference	Not calculable
95% confidence interval		Not calculable
P-value immune recovery vs. no immune recovery		Not calculable
Interaction P-value for enrollment era	Not calculable	

Table 4

Risk Factors for Mortality among Patients with Cytomegalovirus Retinitis

Risk Factor	Crude			Adjusted		
	HR *	95% CI †	P-value	HR	95% CI	P-value
Combination antiretroviral therapy at enrollment						
Yes	Reference			Reference		
No	2.1	1.5, 2.8	<0.001	1.1	0.8, 1.6	0.34
Enrollment CD4+ T cells (cells/μL)						
>200	Reference			Reference		
101-200	1.4	0.8, 2.5	0.20	1.3	0.7, 2.3	0.35
50-100	1.1	0.6, 2.2	0.61	0.9	0.5, 1.8	0.92
<50	5.2	3.4, 8.0	<0.001	4.1	2.4, 7.0	<0.001
Nadir CD4+ T cells (cells/μL)						
>100	Reference			Reference		
50-100	1.5	0.5, 4.2	0.40	1.6	0.5, 4.6	0.36
<50	1.9	0.8, 4.8	0.13	0.8	0.3, 2.1	0.68
Enrollment HIV load (log ₁₀ (copies/mL))						
<2.6	Reference			Reference		
2.6-5.0	3.4	2.0, 5.9	<0.001	2.8	1.6, 4.9	<0.001
>5.0	6.8	4.0, 11.7	<0.001	3.4	1.9, 6.2	<0.001
Maximum HIV load prior to enrollment (log ₁₀ (copies/mL))						
<5.0	Reference			Reference		
>5.0	1.4	0.9, 2.0	0.06	0.9	0.6, 1.4	0.84
Bilateral cytomegalovirus retinitis at enrollment						
No	Reference			Reference		
Yes	1.2	0.9, 1.6	0.09	1.3	0.9, 1.7	0.05
<i>Time-updated risk factors</i>						
Combination antiretroviral therapy						
Yes	Reference			Reference		
No	3.3	2.4, 4.5	<0.001	2.4	1.7, 3.4	<0.001
CD4+ T cells (cells/μL)						
>200	Reference			Reference		
101-200	4.1	2.4, 7.0	<0.001	3.3	1.8, 5.8	<0.001
50-100	4.7	2.4, 9.1	<0.001	4.1	2.0, 8.3	<0.001
<50	19.6	12.7, 30.3	<0.001	12.5	7.5, 20.9	<0.001
HIV load (log ₁₀ (copies/mL)						
<2.6	Reference			Reference		
2.6-5.0	4.3	2.7, 6.8	<0.001	2.0	1.2, 3.3	0.007
>5.0	9.8	6.0, 15.8	<0.001	2.2	1.2, 3.8	0.005

	Crude			Adjusted		
Risk Factor	HR [*]	95% CI [†]	P-value	HR	95% CI	P-value
Enrollment era						
On/after 1 September 2003	Reference			Reference		
Before 1 September 2003	1.4	1.09, 1.9	0.01	1.2	0.9, 1.7	0.14

* HR = hazard ratio.

† 95% CI = 95% confidence interval.