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Cytomegalovirus retinitis in patients with AIDS after initiating antiretroviral therapy

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Abstract

Purpose—To evaluate the rates of new-onset cytomegalovirus (CMV) retinitis and worsening existing CMV retinitis in patients with AIDS after initiating combination antiretroviral therapy (cART) and the role of an immune recovery inflammatory syndrome (IRIS).

Design—Cohort study

Methods—Immune recovery was defined as an increase in CD4+ T cells to ≥100 cells/μL; rates of new-onset CMV retinitis and of worsening of CMV retinitis (either increasing border activity or retinitis progression) were compared between those with and without immune recovery.

Results—Among patients without CMV retinitis, 1 of 75 patients with immune recovery developed CMV retinitis in the first 6 months after initiating cART vs. 1 of 31 without immune recovery (P=0.14). Among patients with CMV retinitis, the rates of retinitis progression and increasing retinitis border activity among patients during the first 6 months after initiating cART in those with immune recovery were 0.11/PY (95% confidence interval [CI] 0, 0.62) and 0.11/PY (95% CI 0, 0.62), respectively, vs. 0.67/PY (95% CI 0.22, 1.56) and 0.40/PY (95% CI 0.08, 1.17), respectively, for those without immune recovery (P=0.11 and 0.47).

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Conclusions—Among persons with AIDS who experience immune recovery, there was neither an increased rate of new-onset CMV retinitis nor worsening of existing CMV retinitis in the first 6 months after initiating cART vs. those without immune recovery. These data are consistent with the known 3–6 month lag in recovery of specific immunity to CMV after initiating cART and suggest that "immune recovery retinitis", a proposed IRIS phenomenon, is rare.

Keywords

acquired immunodeficiency syndrome; cytomegalovirus retinitis; antiretroviral therapy; immune recovery; immune recovery retinitis; immune recovery inflammatory syndrome

Cytomegalovirus (CMV) retinitis is the most frequent ocular opportunistic infection in patients with the acquired immune deficiency syndrome (AIDS).[1,5,6] Prior to the advent of modern, combination antiretroviral therapy (cART), the lifetime risk of CMV retinitis for a patient with AIDS was estimated at 30%.[4] The advent of modern cARTin the mid 1990's, also known as highly active antiretroviral therapy, resulted in a greater than 90% reduction in the incidence of CMV retinitis in the United States.[5–9] With cART, plasma levels of human immunodeficiency virus (HIV) RNA (HIV viral 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),[10–13] and guidelines were formulated for discontinuing secondary prophylaxis.[12] 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.[12,13] The reason for the delay in discontinuing anti-CMV therapy after the initial rise is CD4+ T cells was the 3–6 month lag in developing specific immune responses to CMV after the initial rise in CD4+ T cells.[12–14] The occasional occurrence of new-onset CMV retinitis during the first 2 months after initiating cART, despite a rise in CD4+ T cells,[15] was consistent with this window of susceptibility between the initial rise in CD4+ T cells due to lag in the recovery of specific immunity to CMV.

Immune recovery inflammatory syndromes (IRIS) represent an inflammatory response to an opportunistic pathogen in the context of immune recovery after initiating cART. For CMV retinitis, it is known as immune recovery uveitis (IRU) and represents an increase in or new-onset of anterior uveitis or vitritis occurring after initiating cART.[16–18] Although the estimates of the incidence of IRU varied dramatically in the first decade after the widespread use of cART began, more recent estimates suggest that the incidence of IRU has been declining.[16–20] In 2014 Ruiz-Cruz et al. described a case series of patients with either new-onset CMV retinitis or CMV retinitis relapse (increasing border activity) soon after initiating cART.[21] They postulated that this was an IRIS phenomenon, called "immune recovery retinitis" and suggested that there were two types of "immune recovery retinitis": "unmasking", which consisted of new onset CMV retinitis, and "paradoxical", which consisted of worsening of the retinitis soon after the initiation of cART.[21] In order to further evaluate possible "immune recovery retinitis" we analyzed participants in the Longitudinal Study of the Ocular Complications of AIDS (LSOCA) who initiated cART after enrollment

in LSOCA; outcomes were new-onset CMV retinitis among participants without CMV retinitis and worsening of the retinitis among those with CMV retinitis.

Methods

The Longitudinal Study of the Ocular Complications of AIDS is a prospective, observational, cohort study of patients with AIDS in the era of modern cART.[22,23] Enrollment occurred between 1 September 1998 and 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.[24] Recruitment occurred at 19 clinical centers throughout the United States, typically located in large urban centers with a large HIV-infected population.[22] 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. Patients with and without immune recovery were enrolled. Because the goal of this analysis was to evaluate the incidence of new onset CMV retinitis in the early period after initiating cART among those without CMV retinitis and to evaluate and the incidence of worsening of the CMV retinitis in the early period after initiating cART among those with AIDS and CMV retinitis, only participants who started with CD4+ T cells <100 cells/μL and initiated cART were included. Participants without CMV retinitis or other ocular opportunistic infections were seen every 6 months for follow-up, and participants with CMV retinitis were seen for follow-up every 3 months. At the enrollment and follow-up visits a complete medical history (including antiretroviral drug use), an ophthalmologic history, and a complete eye examination were performed.[19,20,22,23,25, 26] All participants had standardized 50–60° retinal photographs of 9 retinal fields taken at enrollment and at the diagnosis of new-onset CMV retinitis, and all participants with CMV retinitis had these photographs taken at each follow-up visit.[19,20,22,23,25–27] Laboratory testing included lymphocyte subset analyses (for CD4+ T cell counts) and assessment of the HIV viral load.[19,20,22,23,25–27]

Combination antiretroviral therapy was defined as any of the following: three antiretroviral drugs, one of which was either a protease inhibitor, a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a fusion, integrase, or entry inhibitor; three nucleoside reverse transcriptase inhibitors, one of which was abacavir or tenofovir; two full-dose protease inhibitors; a boosted protease inhibitor with either an NNRTI or a fusion inhibitor; or an integrase inhibitor combined with either a protease inhibitor, NNRTI, entry inhibitor, or fusion inhibitor. Patients were characterized as having experienced immune recovery if the CD4+ T cell count increased to a level ≥100 cells/μL after initiating cART.[20,25,26] This level was chosen as it is the level at which discontinuation of anti-CMV therapy for immune recovery is recommended.[12,13] Cytomegalovirus retinitis was diagnosed by SOCA-certified ophthalmologists on indirect ophthalmoscopy through a dilated pupil when the characteristic picture of a necrotizing retinitis, with or without hemorrhage, and typically with "satellite"

borders, was seen.[19,20,22,23,25–27 0] Immune recovery uveitis was diagnosed when there was the new onset of, or an increase in, intraocular inflammation in the anterior chamber or vitreous of an eye with CMV retinitis coincident with immune recovery, as previously described.[16–18]

Evaluation of retinal photographs was performed at a central reading center by trained graders masked as to clinical data. Graders characterized the activity of the retinal borders using a 6-step ordinal scale, with higher numbers representing worse ("increased") border activity, and evaluated photographs for evidence of retinal lesion border progression. Progression was defined using the standard definition as movement of a border of at least one-half disc diameter along a front of one-half disc diameter or more in length or the occurrence of a new lesion greater than one-quarter disc area in size.[19,25–27]

Statistical methods

The analysis data set contained data up through and including the patient's last visit. P-values for comparison of characteristics between patients who experienced immune recovery vs. those without immune recovery were derived from Fisher's exact test for categorical variables; t-test with unequal variance for normally distributed continuous variables; and Kruskal-Wallis test for non-normally distributed continuous variables. Rates and their confidence intervals [CI] were estimated using exact methods for Poisson variables. Crude and adjusted Cox regression with time-varying immune recovery status was used to estimate hazard ratios (HRs), CIs, and P-values. Odds ratios (ORs) and associated CIs and P-values were estimated using exact logistic regression. All statistical analyses were conducted with SAS/STAT® software version 9.3 of the SAS System for Windows (Copyright© 2002–2010. SAS Institute, Inc., Cary, NC) and Stata software, version 13.0 (StataCorp 2013. Stata Statistical Software: Release 13, College Station, TX: StataCorp LP).

Results

Characteristics of the study population

Of the 2392 participants enrolled in LSOCA, 1889 participants did not have CMV retinitis at enrollment, and of these, 315 were not receiving cART at enrollment. Of these 315 participants, 247 initiated cART during follow-up, and of these 247 participants, 106 had CD4+ T cells <100 cells/μL prior to initiating cART. These 106 participants form the data set for analyses of new-onset CMV retinitis after initiating cART. Of these 106 participants, 75 experienced immune recovery, and 31 did not. The characteristics of these participants are listed in Table 1. The two subsets of participants without CMV retinitis were similar at enrollment with the exception of a lower enrollment CD4+ T cell count among those who did not experience immune recovery (median 20 cells/μL vs. 28 cells/μL, P=0.03). The median CD4+ T cells 6 months after initiating cART were 144 cells/μL among those with immune recovery vs. 19 cells/μL among those without immune recovery (P<0.0001). Although both groups had similar enrollment HIV viral loads and maximum HIV viral loads prior to enrollment, by 6 months after initiating cART, participants with immune recovery had a median HIV viral load of 2.9 $\log_{10}$(copies/mL) vs. 4.9 $\log_{10}$(copies/mL) among those without immune recovery (P=0.0002).

Five hundred three participants were enrolled with CMV retinitis and 32 were diagnosed with CMV retinitis during follow-up. Of the 535 participants with CMV retinitis, 109 were not receiving cART at enrollment (or for those with CMV retinitis diagnosed during follow-up the incident visit for diagnosis), and 75 of these participants initiated cART subsequently during follow-up. Of these 75 patients, 52 had CD4+ T cells <100/μL at enrollment or the incident visit, and they form the population for the analysis of worsening retinitis after initiating cART. Of these 52 patients, 32 experienced immune recovery after initiating cART, and 20 did not. The characteristics of these patients are listed as Table 2. The two subsets of patients with CMV retinitis were similar except for a lower enrollment CD4+ T cell count among those without immune recovery (median, 10 cells/μL) than among those with subsequent immune recovery (median, 20 cells/μL, P=0.03). Median CD4+ T cells at 3 and 6 months after initiating cART for those with immune recovery were 141 and 150 cells/μL, respectively, vs. 12 and 11 cells/μL, respectively, for those without immune recovery (P=0.0001 and P=0.004, respectively). Although enrollment HIV viral load and maximum HIV viral load prior to enrollment were similar between the two subsets of patients with CMV retinitis, they were lower at 3 and 6 months after initiating cART among those with immune recovery (median, 2.6 and 2.6 $\log_{10}$(copies/mL), respectively) than among those without immune recovery (median, 5.0 and 5.2 $\log_{10}$(copies/mL); P=0.002 and P=0.02, respectively).

Outcomes among participants without CMV retinitis initiating cART

Mortality, new onset CMV retinitis at any time during follow-up, and during the first 6 months after initiating cART are shown as Table 3. Mortality was substantially greater among participants without immune recovery (HR = 11.5; 95% CI 6.0, 21.8; P<0.0001). Patients without immune recovery were more likely to develop CMV retinitis at any time during follow-up (adjusted HR = 15.0; 95% CI 2.8, 79.2; P=0.001). During the first 6 months after initiating cART, there was a suggestion that participants without immune recovery may have a greater rate of new-onset CMV retinitis (HR = 29.5; 95% CI 0.3, 2566), but the difference was not significant (P=0.14). Two clinicians (DAJ, RD) independently reviewed the photographs of the two cases of new-onset CMV retinitis after initiating cART; both concluded that the cases were typical CMV retinitis, similar in appearance to that seen in the pre-cART era and among those not receiving cART.

Outcomes among patients with CMV retinitis initiating cART

Mortality, retinitis progression, worsening of retinitis border activity, and clinician-assessed relapse of the retinitis among patients with CMV retinitis initiating cART are shown as Table 4. Patients without immune recovery had a greater mortality (HR = 2.2; 95% CI 1.7, 2.9; P<0.0001) and a greater rate of retinitis progression at any time during follow-up (HR 16.7; 95% CI 1.9, 100; P=0.01). Progression rates during the first 3 and 6 months after initiating cART among patients without immune recovery were non-significantly greater than among those with immune recovery (ORs = 1.9; 95% CI 0.15, ∞ and 8.0;95% CI 0.74, 425; P=0.62 and P=0.11, respectively). Odds ratios for increasing border activity at 3 months and 6 months after initiating cART for patients without immune recovery vs. those with immune recovery were 0.78 (95% CI 0.02, ∞) and 4.1 (95% CI 0.29, 236), respectively (P=1.00 and P=0.47). The HR for increasing border activity at any time during follow-up for

patients without immune recovery vs. those with immune recovery was 3.6 (95% CI 0.57, 20.0; P=0.17). The incidence of clinician-assessed relapse of the retinitis at any time during follow-up was greater for those without immune recovery vs. those with immune recovery (OR=63.4; 95% CI 16.9, 237.5; P<0.001), was not significantly greater at 3 months after initiating cART (OR=6.2; 95% CI 0.7, ∞; P=0.10) but was significantly greater at 6 months after initiating cART (OR= 9.5; 95% CI 1.1, ∞; P=0.04). The incidence of immune recovery uveitis was 0.06/person-year (PY) (95% CI 0.03, 0.12) among patients with CMV retinitis with immune recovery after initiating cART.

We also compared the retinitis progression rate of the CMV retinitis control group in this study, patients with CMV retinitis initiating cART without immune recovery (0.72/PY), to two other groups with CMV retinitis without immune recovery in LSOCA: 1) those never receiving cART (0.66/PY, P=0.76) and 2) those enrolling with CMV retinitis already receiving cART (0.66/PY, P=0.77). There were no substantial differences in CMV retinitis progression rates among the 3 groups.

Discussion

The data from LSOCA among participants without CMV retinitis at enrollment and CD4+ T cells <100 cells/μL who then initiated cART demonstrate the expected benefits from immune recovery, namely decreases in mortality and the incidence of CMV retinitis at any time during follow-up compared to those without immune recovery. Furthermore, the data demonstrate no increase in the rate of new-onset CMV retinitis in the first 6 months after initiating cART among those with immune recovery vs. those without immune recovery. These data are consistent with the known 3–6 month lag in recovery of specific immunity to CMV after a rise in CD4+ T cells following the onset of cART.[12–14] If immune recovery was producing an “unmasked” CMV retinitis in this population as an IRIS phenomenon, then one might expect a greater rate of CMV retinitis among participants with immune recovery during the first 6 months after initiating cART, followed by a decline in the rate with longer follow-up, a phenomenon which was not seen.

The LSOCA data for patients with CMV retinitis and CD4+ T cells <100 cells/μL who then initiated cART also demonstrate the benefits of immune recovery, namely decreases in mortality, retinitis progression at any time during follow-up, and clinician-assessed retinitis relapse at any time during follow-up vs. those without immune recovery. The data also demonstrate no increase in border activity, retinitis progression, or clinician-assessed relapse during the first 3 or 6 months after initiating cART. If immune recovery was producing a “paradoxical worsening” of CMV retinitis as an IRIS phenomenon, then one might expect a greater rate of increasing border activity and retinitis progression during the first 3 to 6 months after initiating cART among those with immune recovery, a phenomenon which also was not seen. Hence both analyses suggest that “immune recovery retinitis” as an IRIS phenomenon is uncommon. Conversely, the well-described IRIS phenomenon, immune recovery uveitis, was seen at a rate of 0.06/PY, a rate similar to that seen in other reports from patients not using the known risk factor intravitreal cidofovir as a treatment for CMV retinitis.[16–20]

There are limitations to our data. The sample sizes are not large; 106 participants without CMV retinitis and 52 patients with CMV retinitis were available to evaluate the effects of immune recovery on CMV retinitis outcomes after initiation of cART. The numbers of events sometimes were few, the results of which were wide confidence intervals for rates, ORs and HRs. For some analyses, large ORs and HRs had "non-significant" P-values. Assuming a 5% Type I error rate, the study had 80% power to detect 2.4-, 3.4-, and 6.4-fold increases in the 6-month rate of retinitis progression, increasing CMV retinitis border activity, and new-onset CMV retinitis, respectively, between those without vs. those with immune recovery. Nevertheless, the expected benefits of immune recovery on mortality, incidence of CMV retinitis, and CMV retinitis progression all were demonstrable. Furthermore, in the first 6 months after initiating cART the event rates always were greater in the group without immune recovery, providing little evidence for an IRIS-related worse outcome among those with immune recovery. Our data also are limited by the follow-up intervals of the study, namely 6 months for those without CMV retinitis and 3 months for those with CMV retinitis. As such it would not be possible to capture any difference in event rates during the first month or two after initiating cART with the masked assessments by the reading center. However, given the limited numbers of events, it is unlikely that there would have been any difference observed with more frequent observations. Our primary analyses of changes in retinitis among patients with CMV retinitis initiating cART were photographic, but photographic evaluation of CMV retinitis has been shown to be more sensitive than clinical evaluation for events such as retinitis progression.[28] Because of the 3-month intervals between photographs, it is theoretically possible that eyes could have had relapsed retinitis, been re-induced with anti-CMV agents, and again quiescent retinitis within a 3-month interval. However, patients with CMV retinitis were receiving ophthalmic care at the study clinical center, so that the clinician would have been able to detect any such relapses missed by photographs. The clinician-assessed relapse rate showed the expected reduction overall with immune recovery, and no greater rates among those with immune recovery during the first 3 and 6 months after initiating cART than among those without immune recovery.

Our results are consistent with the known benefits of immune recovery and the 3–6 month lag in recovery of specific immunity to CMV after initiating cART.[12–15] The importance of the recovery of specific immunity to CMV is underscored by the occasional patient whose rise in CD4+ T cells is not accompanied by recovery of specific immunity to CMV and their inability to control CMV retinitis.[29,30] Finally, non-human primate models of infectious retinitis suggest that vitritis and retinal vascular sheathing can be inflammatory responses to antigen, but that retinitis requires replicating organisms.[31–33] As such, one might expect that immune recovery uveitis would be an IRIS phenomenon, but that retinitis would not, results consistent with our data. In conclusion, data from LSOCA did not find evidence for "immune recovery retinitis" and suggest that "immune recovery retinitis" as an IRIS phenomenon is rare.

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Table 1

Characteristics of the Participants in the Longitudinal Study of the Ocular Complications of AIDS without Cytomegalovirus Retinitis Initiating Combination Antiretroviral Therapy

Characteristic at Enrollment	Overall Population	Immune recovery*	No immune recovery*	P-value
Number of patients	106	75	31	
Age at enrollment (years)				
Median	41	41	40	0.61
25^{th}, 75^{th} percentile	36, 45	37, 46	36, 45	
Gender (%)				
Men	85 (80%)	60 (80%)	25 (81%)	0.94
Women	21 (20%	15 (20%)	6 (19%)	
Race and ethnicity (%)				
White, non-Hispanic	47 (44%)	32 (43%)	15 (48%)	0.29
African-American, non-Hispanic	41 (39%)	27 (36%)	14 (45%)	
Hispanic	15 (14%)	13 (17%)	2 (6%)	
Other	3 (3%)	3 (4%)	0 (0%)	
HIV transmission category (%)				
Male to male sexual contact only (MSM)	52 (49%)	36 (48%)	16 (52%)	0.24
Injection drug use only (IDU)	11 (10%)	10 (13%)	1 (3%)	
Both MSM and IDU	8 (8%)	4 (5%)	4 (13%)	
Heterosexual contact	29 (27%)	22 (29%)	7 (23%)	
Other	6 (6%)	3 (4%)	3 (10%)	
Interval from AIDS diagnosis to enrollment (years)				
Median	3.8	3.1	5.3	0.15
25^{th}, 75^{th} percentile	0.7, 7.4	0.5, 7.1	3.0, 7.9	
CD4+ T cells (cells/μL)				
Median, enrollment	24	28	20	0.03
25^{th}, 75^{th} percentile, enrollment	13, 57	14, 68	5, 43	
Median, nadir prior to enrollment	18	19	10	0.05
25^{th}, 75^{th} percentile, nadir	6, 43	9, 45	4, 37	
Median, 6 months after initiating cART†	98	144	19	<0.0001
25^{th}, 75^{th} percentile, 6 months after cART	23, 228	82, 249	6, 29	
HIV load (log_{10} (copies/mL))				
Median, enrollment	5.1	5.1	5.1	0.96
25^{th}, 75^{th} percentile, enrollment	4.5, 5.6	4.4, 5.7	4.7, 5.5	
Median, maximum prior to enrollment	5.5	5.6	5.4	0.27
25^{th}, 75^{th} percentile, maximum	5.0, 5.9	5.0, 5.9	5.1, 5.8	
Median, 6 months after initiating cART	3.6	2.9	4.9	0.0002
25^{th}, 75^{th} percentile, 6 months after cART	2.3, 4.9	1.9, 4.6	4.4, 5.4	

*Immune recovery defined as a rise in CD4+ T cells to ≥100 cells/μL.

†cART = combination antiretroviral therapy.

Table 2

Characteristics of the Participants in the Longitudinal Study of the Ocular Complications of AIDS with Cytomegalovirus Retinitis Subsequently Initiating Combination Antiretroviral Therapy

Characteristic at Enrollment	Overall Population	Immune recovery*	No immune recovery*	P-value
Number of patients†	52	32	20	
Enrolled with CMV‡ retinitis	50	31	19	
Diagnosed during follow-up	2	1	1	
Age at enrollment (years)				
Median	36	36	37	0.65
25th, 75th percentile	32, 44	32, 45	34, 38	
Gender (%)				
Men	38 (73%)	22 (69%)	16 (80%)	0.37
Women	14 (27%)	10 (31%)	4 (20%)	
Race and ethnicity (%)				
White, non-Hispanic	18 (35%)	10 (31%)	8 (40%)	0.53
African-American, non-Hispanic	24 (46%)	17 (53%)	7 (35%)	
Hispanic	7 (13%)	4 (12%)	3 (15%)	
Other	3	1 (3%)	2 (10%)	
HIV transmission category (%)				
Male to male sexual contact only (MSM)	23 (44%)	13 (41%)	10 (50%)	0.71
Injection drug use only (IDU)	4 (8%)	2 (6%)	2 (10%)	
Both MSM and IDU	2 (4%)	2 (6%)	0 (0%)	
Heterosexual contact	16 (31%)	11 (34%)	5 (25%)	
Other	7 (13%)	4 (12%)	3 (15%)	
Interval from AIDS diagnosis to enrollment (years)				
Median	3.0	2.2	4.2	0.20
25th, 75th percentile	0.6, 6.1	0.4, 5.7	1.2, 6.4	
Interval from AIDS diagnosis to CMV‡ retinitis diagnosis (years)				
Median	1.4	0.7	3.0	0.07
25th, 75th percentile	0.4, 6.0	0.2, 3.2	1.1, 6.0	
Interval from CMV diagnosis to enrollment among those with cytomegalovirus at enrollment (years)				
Median	0.1	0.1	0.1	0.66
25th, 75th percentile	0.0, 1.2	0.0, 1.0	0.0, 1.5	
CD4+ T cells (cells/μL)				
Median, enrollment	16	20	10	0.03
25th, 75th percentile, enrollment	6, 34	4, 42	6, 20	
Median, nadir prior to enrollment	6	8	6	0.34
25th, 75th percentile, nadir	3, 12	3, 10	2, 18	

Characteristic at Enrollment	Overall Population	Immune recovery*	No immune recovery*	P-value
Median, 3 months after initiating cART§	98	141	12	0.0001
25th, 75th percentile, 3 months after cART	22, 188	66, 241	6, 34	
Median, 6 months after initiating cART	120	150	11	0.004
25th, 75th percentile, 6 months after cART	62, 209	82, 239	7, 38	
HIV load (log_{10} (copies/mL))				
Median, enrollment	5.0	5.0	5.0	0.68
Interquartile range, enrollment	4.7, 5.4	4.4, 5.4	4.9, 5.4	
Median, maximum prior to enrollment	5.5	5.4	5.5	0.81
Interquartile range, maximum	5.0, 5.8	5.1, 5.9	5.0, 5.8	
Median, 3 months after initiating cART	2.8	2.6	5.0	0.002
25th, 75th percentile, 3 months after cART	2.5, 4.9	2.1, 3.6	4.1, 5.5	
Median, 6 months after initiating cART	2.6	2.6	5.2	0.02
25th, 75th percentile, 6 months after cART	1.7, 5.0	1.7, 4.4	4.7, 5.6	
Bilateral CMV retinitis at enrollment (%)	20 (38%)	13 (41%)	7 (35%)	0.69
CMV retinitis border activity at initiation of cART (%)				0.44
Inactive	78	81	69	
Active	22	19	31	
CMV retinitis treatment at initiation of antiretroviral therapy¶				
Systemic only	28 (56%)	18 (58%)	10 (53%)	0.58
Local only	3 (6%)	1 (3%)	2 (11%)	
Systemic and local	11 (22%)	6 (19%)	5 (26%)	
None	8 (16%)	6 (19%)	2 (11%)	

*Immune recovery defined as a rise in CD4+ T cells to ≥100 cells/μL.

†Number of patients with and without immune recovery at any time during follow-up.

‡CMV = cytomegalovirus.

§cART = combination antiretroviral therapy.

¶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 3

Outcomes of Patients with AIDS in the Longitudinal Study of the Ocular Complications of AIDS without Cytomegalovirus Retinitis Initiating Antiretroviral Therapy

Outcome	Immune recovery*	No immune recovery*
Mortality after initiating cART†		
Patients at risk	75	31
Events	23	30
Person-years	590.5	75.3
Rate (/100 person-years)	3.9	39.8
95% confidence interval (/100 person-years)	2.5, 5.8	26.9, 56.9
Unadjusted hazard ratio		11.5
95% confidence interval		6.0, 21.8
P-value		<0.0001
New onset cytomegalovirus retinitis ever during follow-up		
Patients at risk	75	31
Events	2	7
Person-years	587.2	68.6
Rate (/100 person-years)	0.3	10.2
95% confidence interval (/100 person-years)	0.0, 1.2	4.1, 21.0
Unadjusted hazard ratio		13.7
95% confidence interval		2.7, 69.0
P-value		0.002
Adjusted hazard ratio‡		15.0
95% confidence interval		2.8, 79.2
P-value		0.001
New onset cytomegalovirus retinitis during first 6 months after initiating cART		
Patients at risk	75	31
Events	1	1
Person-years	40.6	19.7
Rate (/100 person-years)	2.5	5.1
95% confidence interval (/100 person-years)	0.1, 13.7	0.1, 28.3
Unadjusted hazard ratio		2.4
95% confidence interval		0.2, 38.4
P-value		0.54
Adjusted hazard ratio‡		29.5
95% confidence interval		0.3, 2566
P-value		0.14

*Immune recovery defined as a rise in CD4+ T cells to ≥100 cells/μL.

†cART = combination antiretroviral therapy.

[≠]Adjusted models controlled for time from AIDS diagnosis and HIV viral load.

Table 4

Outcomes of Patients in the Longitudinal Study of the Ocular Complications of AIDS with AIDS and Cytomegalovirus Retinitis Subsequently Initiating Antiretroviral Therapy

Outcome	Immune recovery*	No immune recovery*
Mortality after initiating cART †		
Patients at risk‡	25	23
Events	11	21
Person-years	161	48
Rate (/person-year)	0.07	0.43
95% confidence interval (/person-year)	0.03, 0.12	0.27, 0.67
Hazard ratio (time-updated)		2.2
95% confidence interval		1.7, 2.9
P-value		<0.0001
Progression of cytomegalovirus retinitis at any time after initiating cART		
Patients at risk	22	22
Events	1	7
Person-years	141.7	38.6
Rate (/person-year)	0.01	0.18
95% confidence interval (/person-year)	0.00, 0.04	0.07, 0.37
Hazard ratio		16.7
95% confidence interval		1.9, 100.0
P-value		0.01
Progression of cytomegalovirus retinitis in first 3 months after initiating cART		
Patients at risk	17	22
Events	0	2
Person-years	4.2	5.5
Rate (/person-year)	0.00	0.36
95% confidence interval (/person-year)	0, 0.88	0.04, 1.31
Odds ratio		1.9
95% confidence interval		0.15, ∞
P-value		0.62
Progression of cytomegalovirus retinitis in first 6 months after initiating cART		
Patients at risk	18	15
Events	1	5
Person-years	9.0	7.5
Rate (/person-year)	0.11	0.67
95% confidence interval (/person-year)	0.00, 0.62	0.22, 1.56
Odds ratio		8.0
95% confidence interval		0.74, 425.0

Outcome	Immune recovery*	No immune recovery*
P-value		0.11
Increasing cytomegalovirus retinitis border activity at any time after initiating cART		
Patients at risk	23	20
Events	2	3
Person-years	145.6	40.1
Rate (/person-year)	0.01	0.07
95% confidence interval (/person-year)	0.00, 0.05	0.02, 0.22
Hazard ratio (time-updated)		3.6
95% confidence interval		0.57, 20.0
P-value		0.17
Increasing cytomegalovirus retinitis border activity in first 3 months after initiating cART		
Patients at risk	17	22
Events	0	1
Person-years	4.2	5.5
Rate (/person-year)	0.00	0.18
95% confidence interval (/person-year)	0.0, 0.88	0.0, 1.01
Odds ratio		0.78
95% confidence interval		0.02, ∞
P-value		1.00
Increasing cytomegalovirus retinitis border activity in first 6 months after initiating cART		
Patients at risk	18	15
Events	1	3
Person-years	9.0	7.5
Rate (/person-year)	0.11	0.40
95% confidence interval (/person-year)	0.00, 0.62	0.08, 1.17
Odds ratio		4.1
95% confidence interval		0.29, 236
P-value		0.47
Clinician-assessed retinitis relapse at any time after initiating cART		
Patients at risk	30	11
Events	2	6
Person-years	172.6	8.1
Median follow-up [25th, 75th percentile] (years)	4.6 [2.2, 8.0]	0.7 [0.2, 1.1]
Rate (/person-year)	0.01	0.73
95% confidence interval (/person-year)	0.0, 0.04	0.27, 1.61
Hazard ratio		63.4
95% confidence interval		16.9, 237.5
P-value		<0.001
Clinician-assessed retinitis relapse in first 3 months after initiating cART		

Outcome	Immune recovery*	No immune recovery*
Patients at risk	18	18
Events	0	4
Person-years	4.5	4.3
Rate (/person-year)	0.0	0.94
95% confidence interval (/person-year)	0.0, 0.82	0.25, 2.38
Odds ratio		6.2
95% confidence interval		0.7, ∞
P-value		0.10
Clinician-assessed retinitis relapse in first 6 months after initiating cART		
Patients at risk	24	16
Events	0	4
Person-years	10.9	6.1
Rate (/person-year)	0.0	0.65
95% confidence interval (/person-year)	0.0, 0.34	0.18, 1.68
Odds ratio		9.5
95% confidence interval		1.1, ∞
P-value		0.04

*Immune recovery defined as a rise in CD4+ T cells to ≥100 cells/μL. Immune recovery status determined at end of interval or at last follow-up for "ever during follow-up" analyses

†Patients at risk refers to number of patients at risk for the event in the specified time frame.

‡cART = combination antiretroviral therapy.