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Non-cytomegalovirus ocular opportunistic infections in patients with AIDS

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Abstract

Purpose—To report the incidence and clinical outcomes of non-cytomegalovirus (non-CMV) ocular opportunistic infections in patients with AIDS in the era of highly active antiretroviral therapy (HAART).

Design—Multicenter, prospective, observational study of patients with AIDS

Methods—Medical history, ophthalmologic examination, and laboratory tests were performed at enrollment and every 6 months subsequently. Once an ocular opportunistic infection was diagnosed, patients were seen every 3 months for outcomes.

Results—At enrollment, 37 non-CMV ocular opportunistic infections were diagnosed: 16 patients, herpetic retinitis; 11 patients, toxoplasmic retinitis; and 10 patients, choroiditis. During

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the follow-up period, the estimated incidences (and 95% confidence intervals [CI]) of these were: herpetic retinitis, 0.007/100 person-years (PY) (95% CI 0.0004, 0.039); toxoplasmic retinitis, 0.007/100 PY (95% CI 0.004, 0.039); and choroiditis 0.014/100 PY (95% CI 0.0025, 0.050). The mortality rates appeared higher among those patients with newly diagnosed or incident herpetic retinitis and choroiditis (rates=21.7 deaths/100 PY [P=0.02] and 12.8 deaths/100 PY [P=0.04]) respectively, than that for patients with AIDS without an ocular opportunistic infection (4.1 deaths/100 PY); Toxoplasmic retinitis did not appear to be associated with greater mortality (6.4/100 PY, P=0.47). Eyes with newly-diagnosed herpetic retinitis appeared to have a poor visual prognosis with high rates of visual impairment (37.9/100 PY) and blindness (17.5/100 PY), whereas those outcomes in eyes with choroiditis appeared to be lower (2.3/100 PY and 0/100 PY, respectively).

Conclusions—Although uncommon, non-CMV ocular opportunistic infections may be associated with high rates of visual loss and/or mortality.

Introduction

Ocular opportunistic infections represent the most common ocular complications of the acquired immunodeficiency syndrome (AIDS) and occur primarily among patients with severe immune compromise.¹ As a consequence of highly active antiretroviral therapy (HAART) and immune recovery, the incidence of cytomegalovirus (CMV) retinitis has declined by over 80% over the last 15 years.^{1–3} Nevertheless, CMV retinitis remains the most common attributable cause of visual impairment and blindness among patients with AIDS.⁴ However, other non-CMV related ocular opportunistic infections occur, including herpetic retinitis (due to either herpes simplex virus or varicella zoster virus), toxoplasmic retinitis, and choroiditis (due to *Pneumocystis carinii*, *Cryptococcus neoforms*, *Mycobacterium tuberculosis*, and *Mycobacterium avium* complex infections).⁵ Case series describing these infections in pre-HAART era have been published;¹ however, the extent to which these infections occur among patients with AIDS and their effect on visual outcomes and association with mortality in the HAART era have not been described. The purpose of this study was to estimate the incidence of and to describe the clinical outcomes associated with these non-cytomegalovirus (non-CMV)- ocular opportunistic infections in the HAART era, using data from the Longitudinal Study of Ocular Complications of AIDS (LSOCA) cohort.

Methods

Study population

The LSOCA is a multicenter, prospective, observational study of patients with AIDS. Patients aged 13 years and older with a diagnosis of AIDS according to the 1993 Centers for Disease and Prevention Revised Surveillance Case Definition were eligible to participate in the study.⁶ Patients with and without ocular opportunistic infections were recruited, and the cohort was enriched with patients with CMV retinitis in order to determine the outcomes of this ocular opportunistic infection. The characteristics of LSOCA patients with CMV retinitis have been described previously.^{4,5,7–9} IRB approval was obtained from the Institutional Review Boards of each clinical center and the three resource centers (see

Supplemental Material for names of these institutions). Informed consent was obtained from all patients prior to enrollment into LSOCA. The study is in accordance with the Declaration of Helsinki and HIPAA regulations.

Data collection

Data collection in LSOCA has been described previously.⁴ Briefly, medical and ophthalmologic histories and ophthalmic examinations were performed at enrollment and at in person follow-up visits every 6 months following enrollment. Once an ocular opportunistic infection was diagnosed, in person follow-up was increased to every three months. Herpetic retinitis, toxoplasmic retinitis and choroiditis were diagnosed on the basis of the ophthalmic examination performed by experienced study-certified ophthalmologists at each clinical center. Herpetic retinitis was diagnosed using published criteria¹⁰: the presence of characteristic confluent, full-thickness, yellow necrotizing retinitis with little or minimal hemorrhage, with or without an overlying vitritis (acute retinal necrosis) or by a multifocal rapidly progressive yellow necrotizing retinitis with early posterior pole involvement without vitritis (progressive outer retinal necrosis). Toxoplasmic retinitis was diagnosed on the basis of a focal, yellow-white necrotizing retinitis with fluffy borders and no or few scattered intraretinal hemorrhages, with or without adjacent chorioretinal scar. Choroiditis was diagnosed by the presence of acquired choroidal lesions without associated retinitis. When possible, the etiology of the choroiditis was inferred based on both the clinical appearance and the associated systemic opportunistic infections.¹

Best-corrected visual acuity was measured using logarithmic visual acuity charts according to the protocol developed for the Early Treatment Diabetic Retinopathy Study (ETDRS).¹¹ The visual acuity score is expressed as the number of letters read correctly. Quantitative Goldmann perimetry was performed as previously described.^{7,8} The Goldmann visual field (GVF) score was obtained by summing the degrees of field seen along each 30-degree meridian using the V-4 test object; the normal GVF score is ~800°. ^{12–14}

Data analysis

Three subsets of patients with non-CMV ocular opportunistic infections were identified: those with longstanding ocular opportunistic infections at enrollment, those with newly-diagnosed ocular opportunistic infections at enrollment, and those with newly-diagnosed ocular opportunistic infections during follow-up (incident cases). Longstanding ocular opportunistic infections at enrollment were defined as those cases diagnosed more than 45 days before enrollment. Newly-diagnosed at enrollment ocular opportunistic infections were defined as cases diagnosed within 45 days prior to enrollment. Incident ocular opportunistic infections were those cases not present at enrollment that developed during follow-up. The incident subset was used to estimate the incidence of ocular opportunistic infections. The newly-diagnosed at enrollment and incident subsets were combined to evaluate the outcomes of newly-diagnosed ocular opportunistic infections.

Clinically significant thresholds for loss of visual acuity^{4,8,15} and visual field score from GVF testing¹⁶ were chosen based on recommendations for reporting in this area or on previous publications from LSOCA. Incidence rates of developing non-CMV ocular

opportunistic infections were calculated as the number of patients with the event divided by the person-years at risks. Mortality rates were calculated as the number of deaths per 100 person-years of follow-up. Follow-up time was calculated as time from enrollment to event or end of follow-up which occurred when a patient ended participation in LSOCA (e.g., death, lost to follow-up, withdrawal from study) or the close of the database for this manuscript (December 31, 2010). Exact Poisson confidence intervals for rates were calculated using the Blaker method.¹⁷ Due to the small number of events, eye-level analyses do not adjust for eyes from the same individual. Data management and analyses were performed in SAS (SAS/STAT® software, Version 9.2 of the SAS System for Windows; Copyright © 2002–2008 SAS Institute Inc., Cary NC, USA) and R (R Version 2.13.1; Copyright © 2011 The R Foundation for Statistical Computing).

Results

Characteristics of the study population

As of December 31, 2010, 2362 patients (4722 eyes) were enrolled in the LSOCA cohort. Among these, 1835 patients (4011 eyes) had no evidence of ocular opportunistic infections at the time of enrollment (Table 1). CMV retinitis was the most common ocular opportunistic infection and was present in 505 patients at enrollment; an additional 29 patients developed CMV retinitis during follow-up. Thirty-seven non-CMV ocular opportunistic infections were diagnosed at enrollment. Sixteen patients (26 eyes) were diagnosed with herpetic retinitis at enrollment. Of these 16 patients, 11 patients (18 eyes) had longstanding disease at enrollment, and 5 patients (8 eyes) were newly-diagnosed at enrollment. One additional patient (2 eyes) developed herpetic retinitis during follow-up (incident case). Of these 17 patients, 10 patients had acute retinal necrosis and 7 patients had progressive outer retinal necrosis. At enrollment 11 patients (12 eyes) were diagnosed with toxoplasmic retinitis. Of these 11, 8 patients (9 eyes) had longstanding disease, and 3 patients (3 eyes) were newly-diagnosed at enrollment. One additional patient (1 eye) developed toxoplasmic retinitis during follow-up (incident case). At enrollment, 10 patients (15 eyes) were diagnosed with choroiditis. Of these 10, 6 patients (8 eyes) had longstanding disease, and 4 patients (7 eyes) were newly-diagnosed at enrollment. Two additional patients (3 eyes) developed choroiditis during follow-up (incident cases). Of the 12 patients with choroiditis at enrollment or during follow-up, 3 patients had pneumocystosis, 6 patients had cryptococcosis, 1 patient had a suspected fungal choroiditis, 1 patient had *Mycobacterium Avium* Complex choroiditis, and 1 patient had choroiditis of unknown etiology.

Patients with non-CMV ocular opportunistic infections had demographic characteristics similar to the entire LSOCA cohort: patients tended to be young (median age 42 years at enrollment), male and White, non-Hispanic. Patients with newly-diagnosed non-CMV ocular opportunistic infections at enrollment typically had low CD4⁺ T cells; medians were 89 cells/ μ L for herpetic retinitis, 33 cells/ μ L for toxoplasmic retinitis, and 43 cells/ μ L for choroiditis. For comparison, among those participants without ocular opportunistic infections, the median CD4⁺ T cell count at enrollment was 196 cells/ μ L. However, the range of CD4⁺ T cells was wide for herpetic and toxoplasmic retinitis with two newly-diagnosed patients with herpetic retinitis having a CD4⁺ T cell count >200 cells/ μ L, and one

patient with toxoplasmic retinitis having a CD4+ T cell count 150 cells/ μ L, a result consistent with the occurrence of these diseases in immunologically normal hosts. HIV loads typically were elevated, though not obviously different from those observed among those without ocular opportunistic infections.

Incidence of non-CMV ocular opportunistic infections

Among those participants without an ocular opportunistic infection at enrollment, herpetic retinitis, toxoplasmic retinitis, and choroiditis occurred in 1, 1, and 2 patients respectively for estimated incidence rates of 0.007/100 person-years (PY) (95% CI 0.0004, 0.039), 0.007/100 PY (95% CI 0.0004, 0.039), and 0.014/100 PY (95% CI 0.0025, 0.050), respectively. Rates among participants with lower CD4+ T cells at presentation did not appear to be substantially greater. For those with a CD4+ T cell count <200 cells/ μ L the incidence rates (and 95% CIs) for herpetic retinitis, toxoplasmic retinitis, and choroiditis were 0 (0, 0.04), 0.01/100 PY (0.0007, 0.08), and 0.03/100 PY (0.005, 0.09), respectively. For those with a CD4+ T cell count <100 cells/ μ L the incidence rates (and 95% CIs) for herpetic retinitis, toxoplasmic retinitis, and choroiditis were 0 (0, 0.08), 0.02/100 PY (0.001, 0.14), and 0.02/100 PY (0.001, 0.14), respectively.

Mortality

Table 2 presents mortality data for patients with non-CMV ocular opportunistic infections. Mortality rates for patients with longstanding ocular opportunistic infections were fairly similar among the different types of ocular opportunistic infections (range = 2.1 to 4.3 deaths/100 PY) and were similar to the mortality rate for patients in LSOCA without ocular opportunistic infections (4.1 deaths/100 PY). Mortality rates, however, appeared higher among patients with newly-diagnosed ocular opportunistic infections, with the highest mortality observed among patients with newly-diagnosed herpetic retinitis (rate = 21.7 deaths/100 PY, $P=0.02$ vs. patients without ocular opportunistic infections) followed by newly-diagnosed choroiditis (12.8 deaths/100 PY, $P=0.04$ vs. patients without ocular opportunistic infections) and newly-diagnosed toxoplasmic retinitis (6.4 deaths/100 PY, $P=0.47$ vs. patients without ocular opportunistic infections). For comparison, the mortality rates for those without ocular opportunistic infections were 6.0 deaths/100 PY for those with CD4+ T cells <200 cells/ μ L (95% CI 5.4, 6.7) and 7.8 deaths/100 PY for those with CD4+ T cells <100 cells/ μ L (95% CI 6.8, 8.9). Because of the potential survivor bias in the longstanding group, their mortality rates are difficult to interpret. However, the data from the recently diagnosed group suggest a higher mortality among patients recently-diagnosed with these non-CMV ocular opportunistic infections.

Visual outcomes of non-CMV ocular opportunistic infections

Table 3 presents the visual outcomes among the patients with non-CMV ocular opportunistic infections. Due to the small numbers of patients at risk, the event rates have broad 95% CIs. Nevertheless, herpetic retinitis appeared to have a poor visual prognosis with high rates of visual impairment (20/50 or worse) and blindness (20/200 or worse). All of the patients at risk suffered loss of at least 25% of the visual field and one-half lost 50% of the visual field on Goldmann perimetry. Conversely, loss of acuity and field were uncommon among patients with choroiditis with only one patient suffering visual

impairment, and none blindness. Similarly, choroiditis was not associated with substantial loss of visual field on Goldmann perimetry. Toxoplasmic retinitis appeared to have an intermediate course; however, the number of events was low.

Discussion

Non-CMV ocular opportunistic infections are uncommon complications of HIV infection. In the pre-HAART era, CMV retinitis alone was more common than all other ocular opportunistic infections combined, but no good incidence estimates of non-CMV ocular opportunistic infections were performed.¹ In this study, conducted in the HAART era, the incidence of non-CMV ocular opportunistic infections was very low, and these estimates of the incidence remained very low even among patients with low CD4+ T cells. Hence, the incidence of CMV retinitis in the HAART era (0.36/100 PY)¹⁸ remains substantially greater than that of these other ocular opportunistic infections with an estimated incidence of CMV retinitis in the LSOCA Cohort ~7 to 10 times greater than the upper 95% CI of the incidences of these non-CMV ocular opportunistic infections.

Although less common than CMV retinitis, herpetic retinitis appears to have a similar, to possibly worse, visual prognosis than CMV retinitis with possibly greater rates of loss of visual acuity and visual field (Table 3). For comparison purposes, the rates of visual acuity loss to 20/50 or worse and to 20/200 or worse among patients with AIDS and CMV retinitis in LSOCA are 11.8/100 EY and 5.1/100 EY, respectively, and the rate of visual field loss to <600° of field (loss of ~25% of the normal field) and to <400° of field (loss of ~50% of the normal field) are 30.4/100 EY and 17.0/100 EY, respectively.^{16,19,20} Conversely, choroiditis appears to have substantially less impact on visual acuity than do the herpetic retinitides. Due to the small number of patients with newly-diagnosed toxoplasmic retinitis, the estimates of loss of vision and visual field are imprecise, and no comparisons can be inferred.

Newly-diagnosed non-CMV ocular opportunistic infections appear to be associated with greater mortality than that seen among patients with AIDS without these infections (Table 2). For herpetic retinitis and choroiditis, mortality may be similar to or greater than that seen among patients with CD4+ T cells <100 cells/ μ L. The observed mortality among patients with newly-diagnosed herpetic retinitis approaches that seen among patients with newly-diagnosed CMV retinitis in LSOCA (26.1/100 PY)^{19,20} despite the somewhat broader range of CD4+ T cells. These data suggest that non-CMV herpetic retinitis has detrimental effects on vision and survival similar to that of CMV retinitis.

Caution is advised in interpreting these data. Limitations of this study include the small numbers of patients with non-CMV ocular opportunistic infections, missing data due to loss to follow-up or death, and for those patients with longstanding disease at enrollment, survivor bias. Estimates of the prevalence of these infections cannot be made from the enrollment data, as the LSOCA cohort oversampled ocular opportunistic infections in an effort to have sufficient numbers to estimate outcomes over time.⁵ Despite this oversampling, the numbers of patients with non-CMV ocular opportunistic infections were small, consistent with the observed low incidence of the ocular opportunistic infections.

Because of the small numbers of patients and events, the 95% CIs are wide, and comparisons and interpretations of outcome data must be made carefully. Conclusions generally were drawn from the group with newly-diagnosed disease either at enrollment or during follow-up due to the effect of survivor bias on the interpretation of the data from those with longstanding disease at enrollment. Nevertheless, this cohort is the largest one to estimate the incidence of and outcomes of ocular opportunistic infections, and remains the best source of data for these events in the HAART era. Because the LSOCA cohort is similar in its demographic characteristics to the general population of individuals living with AIDS in the US (except that HIV infection due to injection drug use is less in this study population),⁵ these conclusions are reasonably generalizable to the AIDS epidemic in the US.

Herpetic retinitis can appear as two morphologic syndromes, acute retinal necrosis and progressive outer retinal necrosis.¹⁰ Acute retinal necrosis presents as a peripheral retinitis, spreads rapidly in a centrifugal fashion, and can occur at any CD4+ T cell count and in patients without immune compromise. Progressive outer retinal necrosis often presents with posterior pole involvement, spreads even more rapidly, occurs largely among patients with severe immune compromise (CD4+ T cells <50 cells/ μ L), and has a worse prognosis.^{1,10} Because of the small numbers of patients with herpetic retinitis, we did not attempt to do any subgroup analysis of outcomes. Although herpetic retinitis can be caused by either varicella zoster virus or herpes simplex virus, in this study we did not attempt to determine which virus was responsible, or because of the small numbers, try to analyze by viral etiology.

In conclusion, the incidence rates of non-CMV ocular opportunistic infections are very low among patients with AIDS in the HAART era, and approximately 10 times lower than that of CMV retinitis. Herpetic retinitis appears to have a poor visual prognosis, similar to that of CMV retinitis. Choroidal infections appear to have less impact on vision. Both herpetic retinitis and choroidal infection appear to be associated with greater mortality, and for herpetic retinitis the observed mortality rate approaches that of newly-diagnosed CMV retinitis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Biographies

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APPENDIX

Longitudinal Study of Ocular Complications of AIDS Clinical Centers Credit Roster

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Table 1
Characteristics of Patients Enrolled in the Longitudinal Study of the Ocular Complications of AIDS

Characteristic	Herpetic Retinitis				Toxoplasmic Retinitis				Choroiditis			
	Long-standing	Newly-diagnosed ^a	Incident ^d	8	Long-standing	Newly-diagnosed ^a	Incident ^d	1	Long-standing	Newly-diagnosed ^a	Incident ^d	No Enrollment OOI ^b
Patients	11	5	1		3	3	1		6	4	2	1835
<i>Demographics</i>												
Age (years)												
Median	41	43	37	42	35	43	38	44	38	38	42	44
Interquartile range	37, 46	33, 49	na	37, 47	32, 43	na	34, 42	38, 50	34, 42	33, 44	37, 47	38, 50
Gender [n (%) men]	8 (73)	4 (80)	1 (100)	6 (75)	3 (100)	0 (0)	5 (83)	1477 (80)	5 (83)	4 (100)	1 (50)	
Times since AIDS diagnosis (years)												
Median	0.4	2.2	7.7	0.9	0.5	12.3	2	na	2	2	7.7	na
Interquartile range	0, 2	0.3, 3	na	-0.7, 5.1	0.1, 0.6	na	1, 2	na	1, 2	0.5, 3	5, 10	na
Current HAART ^c use [n (%)]	8 (73)	3 (60)	1 (100)	6 (75)	2 (67)	1 (100)	5 (83)	1553 (85)	5 (83)	3 (75)	2 (100)	
Time from OOI diagnosis to enrollment (years)												
Median	1	0.1	na	4	0	na	2.4	na	2.4	0.1	na	na
Interquartile range	0.2, 3	0.08, 0.1	na	1, 5	0, 0	na	2, 4	na	2, 4	0, 0.1	na	na
<i>Laboratory</i>												
Nadir CD4+ T cells (cells/ μ L)												
Median	10	18	127	56	33	2	32	40	32	18	29	
Interquartile range	3, 143	10, 170	na	10.5, 77	2, 150	na	6, 71	12, 106	6, 71	6, 43.5	18, 40	
Enrollment CD4+ T cells												
Median	66	89	271	108	33	2	205	196	205	43	110	
Interquartile range	32, 174	28, 213	na	52, 265	2, 189	na	39, 354	80, 357	39, 354	13, 70	40, 179	
HIV load (log ₁₀ [copies/mL])												
Median	2.78	3.05	1.88	3.59	4.19	2.66	2.50	2.70	2.50	3.59	5.06	
Interquartile range	2.25, 3.90	2.23, 4.99	na	2.89, 5.04	3.39, 5.00	na	2.06, 2.60	1.88, 4.61	2.06, 2.60	2.06, 4.57	4.94, 5.19	
Bilateral disease [n (%)]	7 (64)	3 (60)	na	1 (12)	0	na	2 (33)	na	2 (33)	3 (75)	na	na

Characteristic	Herpetic Retinitis			Toxoplasmic Retinitis			Choroiditis			No Enrollment OOI ^b	G ^a
	Long-standing	Newly-diagnosed ^a	Incident ^a	Long-standing	Newly-diagnosed ^a	Incident ^a	Long-standing	Newly-diagnosed ^a	Incident ^a		
Eyes	18	8	2	9	3	1	8	7	3	4011	
Percent retina involved											
Median	35	30	na ^d	5	10	10	na	na	na	na	
Interquartile range	15, 80	20, 80	na	5, 10	5, 15	na	na	na	na	na	
Zone 1 involvement [n (%)]	11 (61)	2 (25)	na	3 (33)	1 (33)	1 (100)	7 (87)	4 (57)	na	na	
Visual acuity [n (%)]											
20/50 or worse	15 (83)	4 (50)	0	4 (44)	1 (33)	1 (100)	2 (25)	0	0	118 (3)	
20/200 or worse	4 (22)	1 (12.5)	0	3 (33)	1 (33)	0	0	0	0	56 (1)	
Visual field score [n (%)]											
600 or less (25 % loss)	15 (83)	8 (100)	0	4 (44)	2 (67)	1 (100)	3 (38)	1 (15)	0	342 (8)	
400 or less (50 % loss)	14 (78)	6 (75)	0	3 (33)	1 (33)	0	3 (37.5)	0	0	80 (2)	

^aNewly-diagnosed at enrollment = diagnosis of ocular infection <45 days prior to enrollment. Incident = occurring during follow-up.

^bOOI = ocular opportunistic infection.

^cHAAART = highly active antiretroviral therapy.

^dna = not applicable.

Table 2
Mortality among Patients with AIDS and non-Cytomegalovirus Opportunistic Ocular Infections

Group	n/N ^a	Mortality rate (/100 PY) ^b	95% CI ^c	P-value ^d
<i>Herpetic retinitis</i>				
Longstanding at enrollment	2/11	3.9	0.7, 13.8	1.00
Newly diagnosed ^e	3/6	21.7	5.9, 61.8	0.02
<i>Toxoplasmic retinitis</i>				
Longstanding at enrollment	2/8	4.3	0.8, 15.3	1.00
Newly diagnosed ^e	1/4	6.4	0.3, 35.2	0.47
<i>Choroiditis</i>				
Longstanding at enrollment	1/6	2.1	0.1, 11.6	0.73
Newly diagnosed ^e	4/6	12.8	4.4, 32.2	0.04
<i>No longstanding or newly diagnosed ocular opportunistic infection at enrollment</i>				
Entire cohort without ocular opportunistic infections	465/1835	4.1	3.7, 4.5	
CD4+ T cells <200 cells/ μ L at enrollment	328/922	6.0	5.4, 6.7	
CD4+ T cells <100 cells/ μ L at enrollment	230/526	7.8	6.8, 8.9	

^a n/N = number of deaths/number at risk.

^b PY = person-years.

^c 95% CI = 95% confidence interval. Exact Poisson test and confidence interval (Blaker method) for mortality rate.

^d The P-value is for the test comparing the mortality rate in the given infection group to the mortality rate in the entire no-ocular opportunistic infection cohort.

^e Newly-diagnosed = newly diagnosed at enrollment and incident cases combined.

Table 3

Ocular Outcomes among Patients with AIDS and Non-cytomegalovirus Ocular Infections

Outcome	Herpetic retinitis			Toxoplasmic retinitis			Choroiditis	
	Long-standing	Newly-diagnosed ^a		Long-standing	Newly-diagnosed ^a		Long-standing	Newly-diagnosed ^a
Visual acuity								
20/50 or worse								
At risk	3	6		5	2		6	7
Events	1	4		0	0		1	1
Rate (/100 EY) ^b	13.5	37.9		0	0		14.5	2.3
95% confidence interval ^c	(0.7, 74.4)	(12.9, 95.3)		(--, 9.6)	(--, 37.5)		(0.7, 80.1)	(0.1, 12.9)
20/200 or worse								
At risk	14	9		6	3		8	10
Events	6	2		0	1		1	0
Rate (/100 EY)	16.3	17.5		0	11.5		3.8	0
95% confidence interval	(7.1, 35.4)	(3.1, 61.7)		(--, 7.6)	(0.6, 63.6)		(0.2, 20.9)	(--, 7.0)
Goldmann visual field score								
<600° (25% loss)								
At risk	3	2		5	1		4	9
Events	3	2		2	1		1	0
Rate (/100 EY)	68.7	30.4		13.6	63.0		33.3	0
95% confidence interval	(18.7, 196.1)	(5.4, 107.2)		(2.4, 47.9)	(3.2, 348.0)		(1.7, 183.8)	(--, 10.2)
<400° (50% loss)								
At risk	4	4		6	3		4	10
Events	2	2		0	1		0	0
Rate (/100 EY)	12.2	17.0		0	11.6		0	0
95% confidence interval	(2.2, 43.0)	(3.0, 60.0)		(--, 13.0)	(0.6, 64.0)		(--, 23.4)	(--, 10.2)

^a Newly-diagnosed = newly-diagnosed at enrollment & incident combined.^b EY = eye-year.^c Exact Poisson confidence interval calculated using Blaker method. Confidence intervals for outcomes with no events are one-sided.