Burden of HIV-Related Cytomegalovirus Retinitis in Resource-Limited Settings: A Systematic Review

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Background. Cytomegalovirus (CMV) is a late-stage opportunistic infection in people living with human immunodeficiency virus (HIV)/AIDS. Lack of ophthalmological diagnostic skills, lack of convenient CMV treatment, and increasing access to antiretroviral therapy have all contributed to an assumption that CMV retinitis is no longer a concern in low- and middle-income settings.

Methods. We conducted a systematic review and meta-analysis of published and unpublished studies reporting prevalence of CMV retinitis in low- and middle-income countries. Eligible studies assessed the occurrence of CMV retinitis by funduscopic examination within a cohort of at least 10 HIV-positive adult patients.

Results. We identified 65 studies from 24 countries, mainly in Asia (39 studies, 12 931 patients) and Africa (18 studies, 4325 patients). By region, the highest prevalence was observed in Asia with a pooled prevalence of 14.0% (11.8%–16.2%). Almost a third (31.6%, 95% confidence interval [CI], 27.6%–35.8%) had vision loss in 1 or both eyes. Few studies reported immune status, but where reported CD4 count at diagnosis of CMV retinitis was <50 cells/μL in 73.4% of cases. There was no clear pattern of prevalence over time, which was similar for the period 1993–2002 (11.8%; 95% CI, 8%–15.7%) and 2009–2013 (17.6%; 95% CI, 12.6%–22.7%).

Conclusions. Prevalence of CMV retinitis in resource low- and middle-income countries, notably Asian countries, remains high, and routine retinal screening of late presenting HIV-positive patients should be considered. HIV programs must ensure capacity to manage the needs of patients who present late for care.

Keywords. cytomegalovirus; HIV; retinitis; resource-limited settings.

Cytomegalovirus (CMV) is responsible for late-stage opportunistic infections in people living with human immunodeficiency virus (HIV)/AIDS (PLHIV) [1]. In persons with prior CMV infection and waning immunity, reactivation of latent virus causes a systemic disease that is characterized by intermittent or constant viremia and seeding with localized infections in 1 or multiple target organs [2]. In PLHIV the most frequent manifestation is retinitis [2], but disseminated CMV infection can also cause extraocular disease and mortality [3, 4].

Before 1995, CMV retinitis occurred in about 1 in 3 PLHIV in Western settings and accounted for >90% of cases of HIV-associated blindness [5, 6]. Incidence of CMV retinitis declined in Western settings from the late 1990s onward as a consequence of early diagnosis of HIV infection and widespread availability and

Received 20 May 2013; accepted 19 July 2013; electronically published 29 July 2013.

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Clinical Infectious Diseases 2013;57(9):1351–61

DOI: 10.1093/cid/cit494

earlier initiation of antiretroviral therapy (ART) [7]. In contrast, in resource-limited settings, ART is less widely available, people continue to present late in their disease progression [8], and access to ophthalmologic services is limited [9]. Reported prevalence of CMV retinitis in PLHIV in resource-limited settings is variable, ranging from <5% in Southern Africa [10] to over 30% in Southeast Asia [11]. The lack of an overall epidemiological picture, limited ophthalmological diagnostic skills or convenient CMV treatment in most settings where ART is provided, increasing provision of ART in middle- and low-income countries over the last decade, and the experience in high-income countries that CMV retinitis virtually disappeared with the introduction of ART have all contributed to an assumption that CMV retinitis is generally no longer a concern in low- and middle-income settings [11].

We conducted this systematic review to gain a better understanding of the prevalence and clinical impact of CMV retinitis in low- and middle-income settings, and how these factors may have changed over the last decade. The review focuses on CMV retinitis because it is typically the only clinical feature of CMV disease that is diagnosed or treated in resource-limited settings.

METHODS

Search Strategy and Selection Criteria

In consultation with clinical experts (D.H., P.S.), we developed a search protocol (Supplementary Appendix 1) to identify studies that reported prevalence of CMV retinitis among PLHIV in low- and middle-income settings. Three databases (PubMed, Embase, and Lilacs) and 3 conferences (Conferences of the International AIDS Society, Conferences on Retroviruses and Opportunistic Infections, and the Annual Meeting of the American Academy of Ophthalmology) were searched for relevant studies published between January 1996 (when triple combination ART first became available) and 1 April 2013. Titles were screened by 1 reviewer (N.F.), and inclusions were verified by a second reviewer (Z.S.). Decisions on final inclusions were made by consensus. Bibliographies of included studies and review articles were hand-searched for potentially eligible studies. Two major HIV treatment providers known to have conducted retinal screening programs (Médicins Sans Frontières and Medical Action Myanmar) were also contacted for unpublished data. No language restriction was applied.

Studies were included if they assessed the occurrence of CMV retinitis by funduscopic examination within a cohort of at least 10 HIV-positive adult patients in low- and middle-income countries, as defined by the World Bank classification [12]. Serological studies and studies diagnosing CMV using polymerase chain reaction (PCR) were excluded, as antibody positivity is consistently high among PLHIV in resource-limited settings [13] and the clinical predictability or correlation of PCR viremia with CMV retinitis, particularly at lower levels, is not well defined [14].

Data Extraction

Data were extracted by 2 reviewers (N.F., Z.S.) to assess the proportion of HIV-positive individuals diagnosed with CMV retinitis irrespective of clinical disease stage or ART status but where possible CD4 count at diagnosis was extracted. We also sought information on the proportion of patients who had unilateral or bilateral vision loss due to CMV retinitis according to definitions used by the studies (cases of retinal detachment were considered as cases of blindness because of the complexity of treatment), other organ disease, and mortality among patients with CMV retinitis. We also extracted information on patient and program characteristics, diagnostic approach, definition of CMV retinitis, and indicators of study quality according to a predefined quality scoring table.

Data Analysis

Point estimates and 95% confidence intervals were derived for all outcomes. For prevalence estimates, proportions were stabilized through arcsine square-root transformation [15] and pooled using a DerSimonian-Laird random-effects model [16]. Between-study heterogeneity was estimated using the τ^2 statistic [17]. Prespecified subgroup analyses were carried out to assess the difference in prevalence according to geographical location, clinic setting (primary care center vs hospital), study design, study period, ART use, and patient selection (eg, if patients were selected for screening either by clinical/immunological criteria or after referral following preliminary eye examination). All analyses were conducted using Stata software, version 12 (StataCorp, College Station, Texas), with a P value <.05 considered to be statistically significant.

RESULTS

Study Characteristics

Of 1702 articles and 397 conference abstracts screened, 53 met our inclusion criteria and were taken through for review, comprising 39 published articles and 13 conference abstracts. The full list of inclusions is provided in Supplementary Appendix 2. Data from 13 unpublished cohorts were also included (Figure 1). These 65 studies reported outcomes from funduscopic examinations of 20 280 HIV-positive patients across 24 countries, mainly in Asia (39 studies, 12 931 patients), Africa (18 studies, 4325 patients), and Latin America (5 studies, 2836 patients). The reported age of the patient populations who underwent retinal screening ranged from 22 to 41 years. The majority of studies (50) were carried out in hospital settings. The median date of screening was 2005. Eighteen percent of patients (n = 3626) were screened between 1993 and 2002, 32%

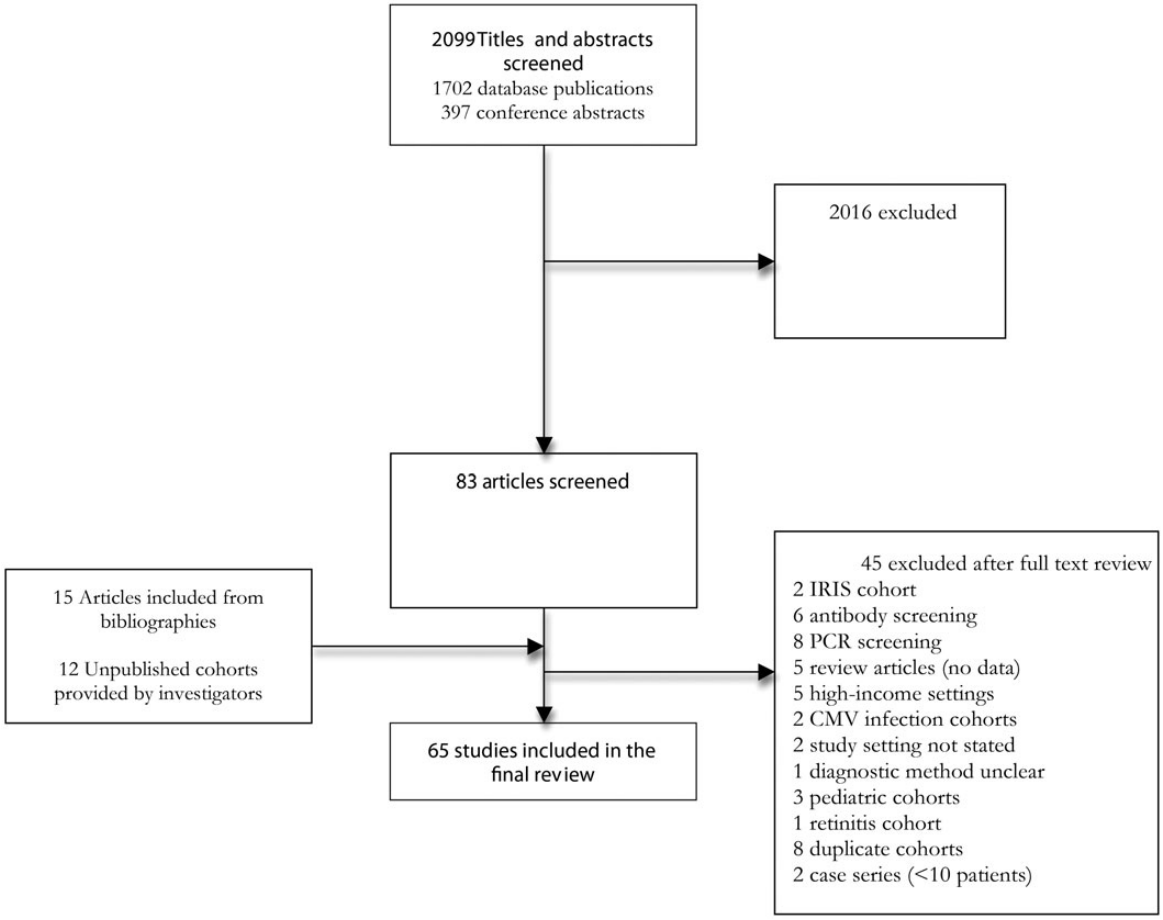

Figure 1. Flow diagram of study selection process. Abbreviations: CMV, cytomegalovirus; IRIS, immune reconstitution inflammatory syndrome; PCR, polymerase chain reaction.

(n = 6473) between 2003 and 2005, 24% (n = 4879) between 2006 and 2008, and 26% (n = 5302) between 2009 and 2013. Study characteristics are summarized in Table 1.

The methodological quality of the studies overall was considered to be low to moderate (Supplementary Table 1). The majority of studies (52) were prospective in design and reported using indirect ophthalmoscopy with pupillary dilation (42 studies), and 30 studies reported that screening was carried out by an ophthalmologist; however, less than half of studies (30) reported outcomes stratified by CD4 count, and only 5 studies verified eye assessments with a second examiner (1 using retinal photography). Most studies undertook funduscopic examination on patients who were selected using clinical/immunological criteria or referred following preliminary eye examination elsewhere (44 studies).

Prevalence and Clinical Characteristics of CMV Retinitis

Overall, there was substantial heterogeneity between studies ($\tau^2 = 0.09$), with prevalence for CMV retinitis ranging from 0.2% in Nigeria (95% confidence interval [CI], .01%–.9%) to 71.5% in Thailand (95% CI, 61.1%–80.9%). By region, the highest prevalence was observed in Asia with 14.0% of patients diagnosed with CMV retinitis (95% CI, 11.8%–16.2%), and the lowest prevalence was seen in Africa, 2.2% (95% CI, 1.3%–3.1%). Prevalence exceeded 5% in 4 countries: Thailand (5 studies, 1397 patients; 24.4% [95% CI, 4.8%–43.9%]), Myanmar (5 studies, 2928 patients; 24.8% [95% CI, 14.6%–35.0%]), China (9 studies, 2357 patients; 15.2% [95% CI, 11.8%–18.7%]), and India (13 studies, 4305 patients; 6.8% [95% CI, 4.8%–8.9%]) (Figure 2).

Nineteen studies reported whether CMV retinitis affected 1 or both eyes, and the raw proportion of bilateral cases of CMV retinitis was 42.9% (95% CI, 38.9%–47.0%). 28 studies reported CMV retinitis cases stratified by CD4 count. Among these, after excluding 8 studies that selected patients using immunological criteria (eg, only considering patients with a CD4 count of <100 cells/μL), CD4 count at diagnosis of CMV retinitis was <50 cells/μL in 73.4% of cases, 50–100 cells/μL in 15.6% of cases, 100–200 cells/μL in 8.3% of cases, and >200 cells/μL in

Table 1. Study Characteristics

Study	Country	Setting	Period	No.	Design	Age, y	% Female	CD4 at Diagnosis, Cells/μL	On ART Yes/No (%)	Clinical Inclusion Criteria	CMV Therapy
Akinsola	Lagos, Nigeria	Tertiary hospital	2006	108	Prospective cohort	22–67 (range)	46%	NS	NS	Randomly selected HIV patients	NS
Anon	India	Referral center	10/2004–12/2005	100	Prospective cohort	NS	NS	67% <200[a]	Yes	Consecutive patients	NS
Arruda	Sao Paolo, Brazil	Federal university	05/2000–02/2001	200	Retrospective cohort	36	45%	31% <100	NS	Consecutive patients	NS
Assefa	Gondar, Ethiopia	Tertiary university hospital	01/2004–06/2004	125	Cross-sectional study	34	45%	NS	No	None	NS
Ausayakhun 1	Chiang Mai, Thailand	Hospital	03/2000–02/2001	395	Prospective cohort	NS	NS	NS	NS	Newly diagnosed HIV patients	NS
Ausayakhun 2	Chaing Mai, Thailand	Tertiary university hospital	08/2008–04/2009	123	Prospective cohort	37.5	50%	32.5	Yes (90%)	Initial referral to ocular infectious diseases unit	NS
Ayena	Lome, Togo	2 health centers	08/2005–10/2005	422	Prospective cohort	34	67%	64.5% <200	Yes (67%)	None	NS
Balo	Lome, Togo	Hospital ophthalmology service	1999	200	Prospective cohort	NS	59%	NS	NS	AIDS-defining illness	NS
Banker	Western India	Retina clinic and laser center	2008	1286	NS	NS	NS	NS	NS	NS	NS
Beare	Blantyre, Malawi	Central hospital	2002	255	Prospective cohort	32	55%	NS	No	Fever	NS
Biswas[b]	Chennai, India	Hospital	1993–1997	70	Prospective cohort	26	21%	NS	NS	Presented or referred to eye center	Intravitreal/intravenous ganciclovir
Chakravarti	Delhi, India	Tertiary hospital	10/2007–04/2009	70	Prospective cohort	37	29%	100% <100	NS	CD4 <100 cells/μL	NS
Chiou	Taiwan	Taipei veterans general hospital	03/1993–05/1999	89	Prospective cohort	38 (range 18–74)	24%	Median 54	NS	Referral to ophthalmology unit	4 wk ganciclovir
Cochereau	Bujumbura, Burundi	University hospital	1999	154	Prospective cohort	37	35%	75% >100	NS	AIDS	NS
Ebana	Douala, Cameroon	Douala general hospital	04/2004–05/2005	57	Prospective cohort	40	53%	Median 118	NS	Patients with known CD4 count	NS
Emina	Lagos, Nigeria	University hospital	11/2004	40	Prospective cohort	Range 21–50	50%	Median 400–499	Yes (100%)	None	NS
Ganekal	Davangere, India	Tertiary hospital	11/2009–08/2011	100	Prospective cohort	36.4	54%	92.9% <100[a]	Yes (70%)	None	NS
Gharai[c]	Delhi, India	Center for ophthalmic science	09/2004–09/2006	135	Prospective cohort	34	26%	70.3% <200[a]	Yes (62.2%)	None	No
Giorgis	Addis Ababa, Ethiopia	Armed forces teaching general hospital	03/2005–04/2006	186	Prospective cohort	34.3	16%	31.7% <50	No	CD4 <200 cells/μL and excluding those with systemic disease or those on ART	NS

Table 1 continued.

Study	Country	Setting	Period	No.	Design	Age, y	% Female	CD4 at Diagnosis, Cells/μL	On ART Yes/No (%)	Clinical Inclusion Criteria	CMV Therapy
Hakobyan	Armenia	Tuberculosis dispensary	2005–2007	84	Prospective cohort	NS	NS	71% <200	Yes (24%)	HIV/tuberculosis coinfection	NS
Heiden 1	Cape Town, South Africa	Primary care clinic	2006	57	Prospective cohort	NS	NS	NS	NS	Patients with CD4 <50	NS
Heiden 2	Kalasin & Bangkok, Thailand	District hospital and prison hospital	11/2006		Prospective cohort	NS	NS	NS	NS	Patients with CD4 <50	NS
Heiden 3	Kampala, Uganda	District hospital	11/2005	26	Prospective cohort	NS	NS	NS	NS	Patients with CD4 <50	NS
Heiden 4[b]	Yangon, Myanmar	Primary care clinic	11/2006	179	Prospective cohort	NS	NS	NS	NS	Patients with CD4 <100	Intravitreal/intravenous ganciclovir
Heiden 5	Yangon, Myanmar	Primary care clinic	01/2013–02/2013	78	Prospective cohort	NS	NS	NS	Yes (100%)	Patients with CD4 <100	Intravitreal/intravenous ganciclovir
Heiden 6	St Petersberg, Russia	Hospital	06/2012	60	Prospective cohort	NS	NS	NS	NS	Patients with CD4 <100	NS
Huang	Guandong, China	Hospital	2010	762	NS	NS	NS	NS	NS	NS	NS
Janssens	Phnom Penh, Cambodia	2 HIV/AIDS clinics	01/2004–09/2005	352	Prospective cohort	NS	35%	NS	NS	Patients with CD4 <50	NS
Kumarasamy 1	Chennai, India	Tertiary hospital	06/1996–06–2001	609	Prospective cohort	31	NS	NS	Yes (61.3%)	Those who had at least 1 CD4 count	NS
Kumarasamy 2	Chennai, India	Tertiary hospital	2006	1122	Prospective cohort	35	21%	Median 52	Yes (100%)	AIDS defining illness	NS
Lai	Hong Kong	Tertiary Hospital	01/2000–12/2007	151	Retrospective cohort	42	17%	Median 166	Yes (48.3%)	None	Oral valganciclovir, intravenous or intravitreous ganciclovir, intravenous foscarnet, surgery
Lamichhane	Kathmandu, Nepal	Various	01/2007–06/2008	117	Prospective cohort	30	35%	Median 324	Yes (48%)	None	NS
Lin[d]	Taiwan	University hospital	01/1996–01/2006	1185	Retrospective cohort	NS	NS	NS	NS	AIDS	Intravenous, intravitreal, and oral ganciclovir
Loo	Malaysia	3 general hospitals	12/2007–03/2008	202	Prospective cohort	49% 30–39 (median)	25%	76% <200 (those with fundus manifestations)	Yes (47%)	Excluding inpatients, those on HAART <3 mo, previously treated ocular manifestations and critically ill patients	NS
Medical Action Myanmar[b]	Yangon, Myanmar	Primary care clinic	2009–2012	660	Prospective cohort	NS	NS	NS	NS	CD4 <100 (up to 2012) or CD4 <200 (thereafter)	NS
Manosuthi	Bangkok, Thailand	Tertiary hospital	01/2003–12/2004	793	Retrospective cohort	35	44%	Median 26	Yes (100%)	All patients initiating ART, >15 y old and with at least 1 CD4 count	Yes (not described)
Matos	Sao Paolo, Brazil	Tertiary hospital	01/1993–01/1996	1100	Retrospective cohort	NS	21%	NS	NS	NS	NS
Mehta	Mumbai, India	Hospital AIDS clinic	2002	100	Prospective cohort	NS	26%	NS	NS	AIDS-defining illness	NS

Table 1 continued.

Study	Country	Setting	Period	No.	Design	Age, y	% Female	CD4 at Diagnosis, Cells/μL	On ART Yes/No (%)	Clinical Inclusion Criteria	CMV Therapy
MSF 1	Nanning, China	Primary HIV clinic and linfectious disease hospital (outpatients and inpatients)	11/2008	91	Retrospective cohort	41	19%	87% <50	Yes (>90%)	Outpatient: CD4 <100 cells/μL at any time during previous 12 mo = 72 Inpatient: consenting, regardless of CD4 count = 19	Intravenous ganciclovir and/or oral valganciclovir, supplemented with intravitreal injections of ganciclovir if necessary
MSF 2[b]	Nanning, China	Primary HIV clinic	11/2008–01/2010	89	Prospective cohort	NS	NS	Median 33	No (most were being worked up for ART)	(i) Current CD4 <100 (ie, proper screening) = 64 (ii) early referrals (ie, <6 mo on ART) = 17 (iii) late referrals (ie, chronic vision loss) = 8	Systemic treatment (mainly valganciclovir) sometimes supplemented with intravitreal ganciclovir (ie, sight-threatening and/or extensive lesions)
MSF 3	Xiangfan, China	Primary HIV clinic	August 2006	45	Retrospective cohort	NS	60%	Median 14	Yes (73.3%)	(i) Current CD4 <50 = 19 (ii) At risk of IRU (ie, started ART when CD4 <100) = 21 (iii) Those with ocular symptoms = 5	Intravitreal ganciclovir
MSF 4	Savannakhet, Laos PDR	District hospital in rural Laos	2007	35	Prospective cohort	NS	NS	100% <50	NS	CD4 <50, unexplained fever, severely ill with dysphagia	Intravitreal injections of ganciclovir
MSF 5	Vientiane, Laos PDR	District hospital in rural Laos	2007	34	Prospective cohort	NS	NS	100% <100	NS	CD4 <100, unexplained fever, severely ill with dysphagia, visual impairment	Intravitreal injections of ganciclovir
MSF 6	Kuchinarai, Thailand	District hospital	2007	49	Prospective cohort	NS	NS	100% <50	NS	CD4 <50 or visual impairment	Intravitreal injections of ganciclovir
MSF 7	Kachin, Myanmar	Primary HIV clinic	2011–2012	913	Prospective cohort	NS	NS	NS	NS	NS	NS
Nirwoth	Northern Tanzania	2 tertiary hospitals	06–12/2008	150	Prospective cohort	38.7	59%	Median 48.5	Yes (38.5%)	CD4 <100 cells/μL	NS
Nwosu	Lagos, Nigeria	University teaching hospital	2008	100	Retrospective cohort	31	49%	NS	NS	NS	NS
Onakoya	Lagos, Nigeria	University teaching hospital	03/2008	400	Prospective cohort	40	70%	NS	Yes (94%)	NS	NS
Osahon	Benin, Nigeria	Benin teaching hospital	09/1997–08/2002	526	Prospective cohort	39.5	52%	NS	NS	None	NS
Otiti-Sengeri	Kampala, Uganda	Teaching hospital	07/2003–08/2004	1012	Prospective cohort	36 (range 18–79)	70%	Median 171	Yes (37%)	Only those with symptoms or decreased visual acuity had detailed ocular examination	NS
Pathai 1	Mumbai, India	ART clinic	08/2008–12/2008	149	Prospective cohort	36	30.2%	Median 180	No	No	NS
Pathai 2	Cape Town, South Africa	HIV/ART clinic	02/2010–04/2010	157	Prospective cohort	34	NS	Median 143	No	No	NS

Table 1 continued.

Study	Country	Setting	Period	No.	Design	Age, y	% Female	CD4 at Diagnosis, Cells/μL	On ART Yes/No (%)	Clinical Inclusion Criteria	CMV Therapy
Ruiz-Cruz	Mexico City, Mexico	Referral AIDS clinic	2008	515	Retrospective and prospective cohort	35	10%	Median 98	Yes (80%)	AIDS-defining illness	NS
Sahoo	Dar-el-Salaam, Tanzania	Tertiary hospital	03/2005–08/2005	150	Prospective cohort	34	54%	Median 190	NS	Diagnosed cases of HIV referred to ophthalmology dept	NS
Saranchuk	Kunming, China	Hospital	01/2013	33	Prospective cohort	NS	NS	NS	NS	<100	NS
Shah	Mumbai, India	Tertiary hospital	04–06/2008	112	Prospective cohort	39	32%	Median 122	Yes (100%)	<200	NS
Sharma	India	Tertiary hospital	2011	100	Prospective cohort	NS	NS	NS	Yes (100%)	None	NS
Shi[b]	Shanghai, China	Tertiary hospital	10/2005–12/2007	303	Retrospective cohort	42	17%	Median 32	No	WHO stage 3 or 4	Ganciclovir (5 mg/kg) administered twice a day then once a day (maintenance)
Tabarsi	Iran	Pulmonary disease referral center	01/2002–01/2005	44	Prospective cohort	38	7%	Median 155	Yes (25%)	Patients referred to pulmonary disease referral center	NS
Tao	Peking, China	Hospital	2008	96	NS	NS	NS	NS	NS	AIDS-defining illness	NS
Tokunaga	Sao Paolo, Brazil	University hospital	2002	200	Prospective cohort	NS	NS	NS	Yes	Patients with AIDS	NS
Tun	Yangon Division, Shan State, Kachin State and Rahkine State, Myanmar	HIV clinics	11/2006–07/2009	891	Prospective cohort	32	36%	Median 38	NS	CD4 count <100 cells/μL; broad clinical criteria if CD4 >100	intraocular ganciclovir (2.5 mg ganciclovir in 0.05 mL of solution) followed by weekly injections for as long as clinically required
Wang	Shanghai, China	Shanghai public health clinical center	08/2009–07–2010	787	Prospective study	41	16.5%	Median 43[a]	Yes (87.5%)	None	Ganciclovir 5 mg/kg twice daily for 2–3 wks (33.7% of patients)
Wijeyasangary	Tamil Nadu, India	Secondary level hospital	2006	352	Prospective cohort	NS	28%	NS	Yes (57%)	None	NS
Yanez	Lima, Peru	Hospital	04/2004–07/2006	821	Prospective cohort	36	26%	57% <200	Yes (14%)	None	NS

The reference list for included studies can be found in Supplementary Appendix 2.

Abbreviations: ART, antiretroviral therapy; CMV, cytomegalovirus; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IRU, ; MSF, Médicins Sans Frontières; NS, not stated; WHO, World Health Organization.

[a] Patients with ocular complications.

[b] These studies provided data on mortality among patients with CMV retinitis.

[c] Full paper reports 100 patients; additional patient data reported in conference abstract.

[d] Data reported from 1995.

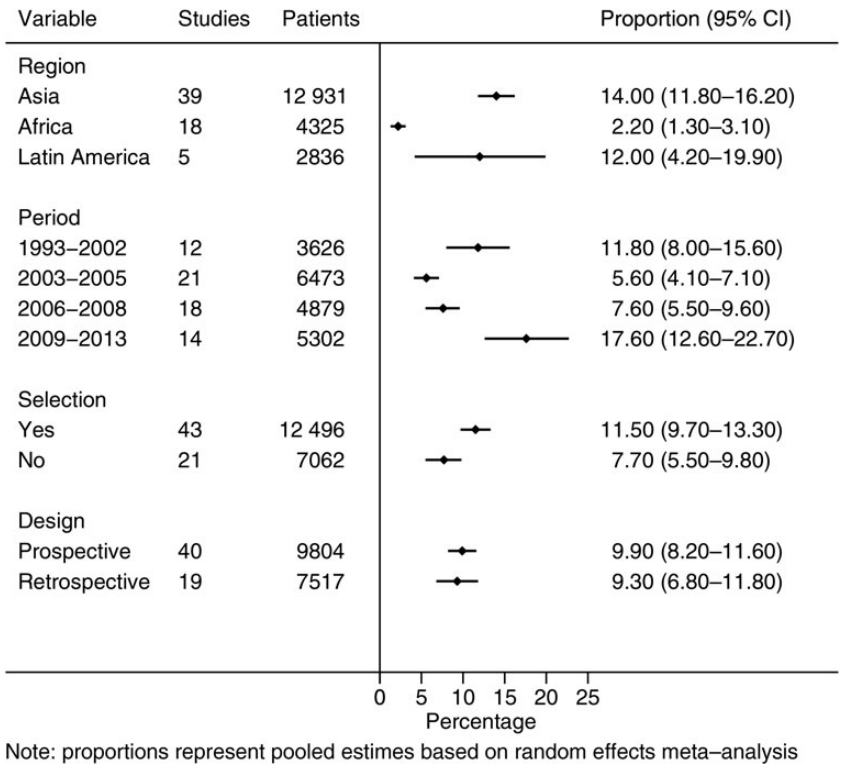

Figure 2. Prevalence of cytomegalovirus retinitis. Abbreviation: CI, confidence interval.

2.7% of cases. Nadir CD4 cell count among these patients was not reported. Too few studies reported ART status to allow this subgroup analysis to be conducted.

Prevalence was higher in those studies that selected patients for eye exam either by clinical/immunological criteria (AIDS-defining illness or CD4 count) or via referral (11.5% [95% CI, 9.7%–13.3%]) but was still high in those that did not select patients prior to retinal examination (7.6% [95% CI, 5.5%–9.8%]). There was no clear pattern of prevalence over time, which was similar for the reporting period 1993–2002 (11.8% [95% CI, 8%–15.7%]) and 2009–2013 (17.6% [95% CI, 12.6%–22.7%]). No difference in prevalence was observed according to study design, ART status, publication status, or whether screening was performed by an ophthalmologist or an HIV clinician trained in retinal examination.

Twenty-five studies provided sufficient information to estimate the proportion of cases of CMV retinitis that resulted in some degree of vision loss: this ranged from 0% [18, 19] to 75% [20], with an overall raw proportion of 31.6% (27.6%–35.8%). In over a quarter of cases (27.6% [95% CI, 20.9%–35.1%]) vision loss was bilateral.

Mortality was reported by 8 studies, with data disaggregated by CMV status in 5 studies. Overall, 22% of patients with CMV retinitis were known to have died, but none of these studies provided autopsy data on cause of death or time of death in relation to diagnosis of CMV retinitis.

DISCUSSION

The prevalence of CMV retinitis in high-income settings has declined significantly over the last 15 years as ART has become more widely available and the immune status of patients at ART initiation has progressively improved [21]. In contrast, this review found that the prevalence of CMV retinitis in resource-limited settings, notably Asian countries, remains high. Part of the explanation for the enduring high prevalence of CMV retinitis in Asia can be found in the fact that, despite considerable progress in scaling up access to ART, the proportion of patients who present late for HIV care remains high, with around 1 in 5 patients presenting with a CD4 count of <100 cells/μL [22], and median CD4 at ART initiation appears to be lower in Asian settings compared to African settings [23].

This review indicates an important clinical burden of CMV retinitis, predominantly in patients with a CD4 count of <100 cells/μL, and suggests that the disease is commonly bilateral and commonly associated with vision loss. The proportion of

individuals with CMV retinitis who have bilateral involvement and the proportion who have CD4 counts >50 cells/μL suggests that infection is being diagnosed after a substantial period of delay from the initial development of retinal lesions. Studies from the United States found that CMV retinitis was bilateral in only 28% of newly diagnosed cases in the era before use of ART, and in only 26% of newly diagnosed cases after the introduction of ART. Furthermore, among the latter group, involvement was only 9% among ART-naive patients, suggesting that second eye involvement is a late occurrence in the course of CMV retinitis [24]. In the same study, approximately 20% of patients with newly diagnosed CMV retinitis had CD4 counts >50 cells/μL, but nearly all of those individuals had just started ART or had evidence of ART failure. Active CMV retinitis can be seen in the early stages of ART, before immune recovery is achieved [24]. That over a quarter of individuals with CMV retinitis in this review had CD4 counts >50 cells/μL likely reflect diagnoses made after CD4 counts begin to rise with the start of ART. Taken together, these observations suggest missed opportunities for earlier diagnoses of CMV retinitis, with the potential for preservation of vision.

Consistent with expectations, prevalence was higher in programs that selected patients at higher risk (ie, those presenting with low baseline CD4 count and/or AIDS-defining illness), underscoring the importance of routine funduscopic examination for "late presenters." This review also confirms prior reports that prevalence of CMV retinitis is generally higher in Asia than in Africa [10, 11]; this finding is despite a high rate of prior exposure to CMV [25] and presence of end-organ CMV disease in autopsy studies in PLHIV in sub-Saharan Africa [26]. Explanations put forward for this difference include virus or host genetic differences [27] and competing mortality risks [28]. Antiretroviral coverage is, on average, lower in Southeast Asia compared to Africa (39% vs 49%) [29]. Nevertheless, the higher HIV prevalence in sub-Saharan Africa means that the absolute number of CMV cases may also be high.

Very little information was reported regarding extraocular CMV disease. Diagnosis of CMV retinitis can be established on physical examination, but diagnosis of other forms of end-organ CMV disease such as esophagitis, hepatitis, colitis, and pneumonia requires confirmation by biopsy, fulfillment of specific histopathologic and virologic criteria, and exclusion of other diseases, all of which are challenging in resource-limited settings. A large multicenter prospective cohort study from Europe reported that among 707 patients with documented end-organ CMV disease, 64% had CMV retinitis, 27% had extraocular CMV disease, and 8% had both [6]. Autopsy studies from high-income settings in the pre-ART era found disseminated CMV infection in up to 60% of patients [3, 4], and CMV pneumonitis has been identified among the main pathological findings in up to 50% of deaths among people living with HIV and having pulmonary infections in sub-Saharan Africa [26]. Moreover, the presence of CMV retinitis predicts mortality [30], systemic anti-CMV treatment reduces mortality in patients with CMV retinitis [31], and high CMV viremia has been found to be independently associated with a higher risk of mortality in both Asian [32] and African [33] settings.

We used a broad search strategy that was able to include a large number of published and unpublished reports from a wide range of countries and program settings. By definition, publication bias exists in HIV treatment programs as the majority of treatment programs in low-income settings do not present or publish details on their cohorts. To compensate for this, we applied a random-effects analysis and present it with uncertainty intervals. The included studies should therefore be interpreted as a sample of all possible cohorts. We undertook subgroup analyses to explain some of the variation in prevalence. These analyses were limited to covariates reported by the studies, but other explanations may exist. The majority of programs undertook eye examinations using the commonly accepted "gold standard" for diagnosis of CMV retinitis, which is dilated examination of the entire retina with an indirect ophthalmoscope by a trained clinician. Although this provides confidence in the data, it limits the generalizability of the findings as patients presenting to centers that are able to do funduscopy are not representative of the broader patient population. Patients included in this review were mostly severely immunocompromised, and some had been referred for ophthalmologic examination, and the results should be interpreted in this light. Another important limitation was that reporting of important covariates was inconsistent, with few studies reporting nadir CD4 count, timing of ART initiation and associated complications, extent of vision loss, type and outcomes of treatment provided, cause of mortality, and extraocular CMV disease. Our inclusion criteria resulted in a few studies being included from the pre-ART era. We explored the potential influence of these studies in a sensitivity analysis that removed all studies reporting data prior to 2000; this did not significantly change the regional prevalence estimates. There was also a lack of high-quality studies, in particular longitudinal studies with adequate follow-up. Information about duration of disease is lacking, especially as it relates to vision loss, and reports of CMV retinitis early in the course of disease will lead to underestimates of vision loss as, in general, CMV progresses slowly but without treatment will invariably result in blindness. Finally, underdiagnosis of CMV retinitis may result from the fact that approximately 20% of patients who first present for HIV care in resource-limited settings are lost to follow-up within a year of starting ART [34], and around half of these individuals will have died [35]. Although many of these patients will have received ART, CMV retinitis can still develop after start of ART, during the first 3- to 6-month period before immune recovery occurs [24].

Our review has several potential implications for policy and practice. We found no difference in the proportion of patients identified with CMV retinitis when screening was done by trained HIV clinicians compared to ophthalmologists. From an operational perspective this is encouraging and points toward the potential for integrating routine retinal examination as part of basic care for all late presenters, especially those with CD4 <100 cells/μL, which may also allow for the diagnosis of other HIV-related conditions such as disseminated tuberculosis [36]. The fact that our review found a high prevalence of CMV retinitis in some primary care settings underscores the value of such capacity building.

This review highlights the need for improved detection of patients infected with CMV retinitis and clearly defined, standardized diagnostic criteria that can be applied easily in areas where experience with CMV retinitis has been limited. CMV retinitis is a disease mainly occurring among people who are severely immunocompromised. Recent studies have shown that with effective ART, even people starting ART with a very low CD4 cell count can expect to live several decades [37], but quality of life will be severely compromised by loss of vision. Routine retinal screening by indirect ophthalmoscopy of all late presenters with CD4 <100 cells/μL should be considered. There is also a need to define optimal screening approaches to identify patients who would benefit from systemic treatment for extraocular CMV disease. Consideration should also be given to oral systemic prophylaxis in high-risk patients with HIV, as this approach was demonstrated to halve end-organ disease in HIV patients in the pre-ART era [38], may protect against posterior pole disease [24], and is a widely accepted method to reduce CMV disease and associated mortality in patients undergoing solid organ transplant [39]. Future research is encouraged to further document the burden of CMV disease in resource-limited settings, define simple approaches to introducing eye examination as part of the basic care package for patients presenting late for ART care, and assess the feasibility of treating CMV retinitis in nonspecialized settings.

Given that CMV is a systemic infection and a potential cause of a spectrum of morbidity and mortality, improving access to oral systemic treatment with valganciclovir is a priority: access to oral therapy particularly needs to improve in resource-limited settings where lack of specialists limits capacity to administer intraocular injections. In addition, the cost of CMV treatment in developing countries is currently too expensive in high-burden settings, and where it is provided represents a substantial part of overall treatment costs for PLHIV [40]. Improving access to convenient oral therapy would stimulate HIV programs to introduce retinal screening—an incentive that has been missing for the last 20 years in resource-limited settings due to the lack of any convenient and affordable treatment option. To date, the demand for valganciclovir to treat CMV has been very limited, which has provided insufficient incentive for manufacturers to develop quality-assured and affordable treatment for CMV infections.

Finally, the enduring burden of CMV retinitis and associated vision loss points to an urgent need to improve and sustain efforts to identify people who are HIV-positive, ensuring that they are enrolled into care earlier in their disease progression. At the same time, national HIV programs should ensure capacity to manage late presenters, including early diagnosis and treatment of CMV retinitis where prevalence is high, to reduce the risk of blindness and, potentially, other CMV-related morbidity and CMV-associated mortality.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Acknowledgments. This research was partially supported by the Medicines Patent Pool.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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