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Prognostic effect of HIV on visual acuity in ocular syphilis: a systematic review

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BACKGROUND/OBJECTIVES: Ocular syphilis is a vision-threatening disease that can lead to permanent blindness if left untreated. The global re-emergence of syphilis warrants greater investigations into the visual prognosis of eyes affected by this potentially devastating disease. This systematic review investigates the impact of HIV on visual acuity (VA) outcomes in ocular syphilis.

METHODS: A literature search of Medline, PubMed, Embase, Clinicaltrials.gov and Cochrane Reviews was conducted for studies published between 01 January 2011 and 19 March 2022, reporting non-aggregate initial and post-treatment VA data of eyes with ocular syphilis and corresponding HIV status in patients ≥ 18 years.

RESULTS: A total of 95 studies, including 364 patients and 568 eyes, were evaluated. Among people living with HIV with a diagnosis of ocular syphilis, affected eyes were more likely to have optic nerve involvement and panuveitis. However, HIV status, CD4 cell count, and HIV viral load were not predictive of VA outcomes of treated ocular syphilis. Prognostic factors of final VA worse than 1.00 logMAR were female sex, the presence of macular edema, and VA ≥ 1.00 at presentation. The strongest predictor of a worse final VA was VA ≥ 1.00 at presentation.

CONCLUSIONS: This systematic review demonstrates that HIV status, CD4 cell count, and HIV viral load are not significant factors impacting VA outcomes of eyes with ocular syphilis. While visual prognosis is generally good, poor visual outcome is most strongly predicted by poor VA at presentation. This underscores the importance of early recognition and treatment prior to permanent vision loss.

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INTRODUCTION

The incidence of syphilis has increased at an alarming rate over the last two decades, becoming an ever-present threat to global health [1–4]. Caused by the spirochete bacterium, *Treponema pallidum* subspecies *pallidum*, the estimated global incidence of syphilis in 2016 was approximately 6 million cases per year [3], disproportionately affecting high-risk populations such as men who have sex with men (MSM), sex workers, and people living with HIV [5–7].

Ocular syphilis is relatively uncommon, with a prevalence of 2–3% among patients with syphilis [8, 9]. It may occur at any stage of the disease, affecting various structures within the eye and causing a wide range of symptoms, including permanent vision loss [10, 11]. Syphilis and HIV are common co-infections [6, 12] and are known to facilitate the pathogenesis of one another [13]. With appropriate treatment, the visual outcome of ocular syphilis is believed to be in the range of logMAR −0.08 to 0.50 [6, 14–17]. What remains unclear, however, is the effect of HIV on visual acuity in patients with ocular syphilis.

The primary objective of this systematic review is to elucidate the effect of HIV status and related prognostic factors, such as reported CD4 counts and HIV viral load, on the post-treatment visual acuity (VA) of eyes affected by ocular syphilis. Additional objectives include identifying prognostic factors for visual outcomes in ocular syphilis and identifying between-group differences of those with a diagnosis of HIV and those without.

METHODS

A literature search was conducted on 19 March 2022 following a search strategy and methodology developed with guidance from a medical librarian. The search strategy was applied to MEDLINE, PubMed, Embase, ClinicalTrials.gov, and Cochrane Library databases for English language articles published from 01 January 2011 to 19 March 2022, as described in Supplementary Table 1. Manual and computer-assisted reference mining was conducted to ensure completeness [18]. Non-peer reviewed publications, including conference presentations, were excluded. Findings were reported according to MOOSE guidelines [19]. Institutional review board approval was waived by the University of Saskatchewan Research Ethics Board for this systematic review. This systematic review protocol has been registered with PROSPERO (CRD42022304536).

Outcomes

The primary outcome was final VA following treatment for ocular syphilis. Secondary outcomes included pre-treatment VA, laterality of disease, ocular symptoms, associated ocular diagnoses, and all documented treatment.

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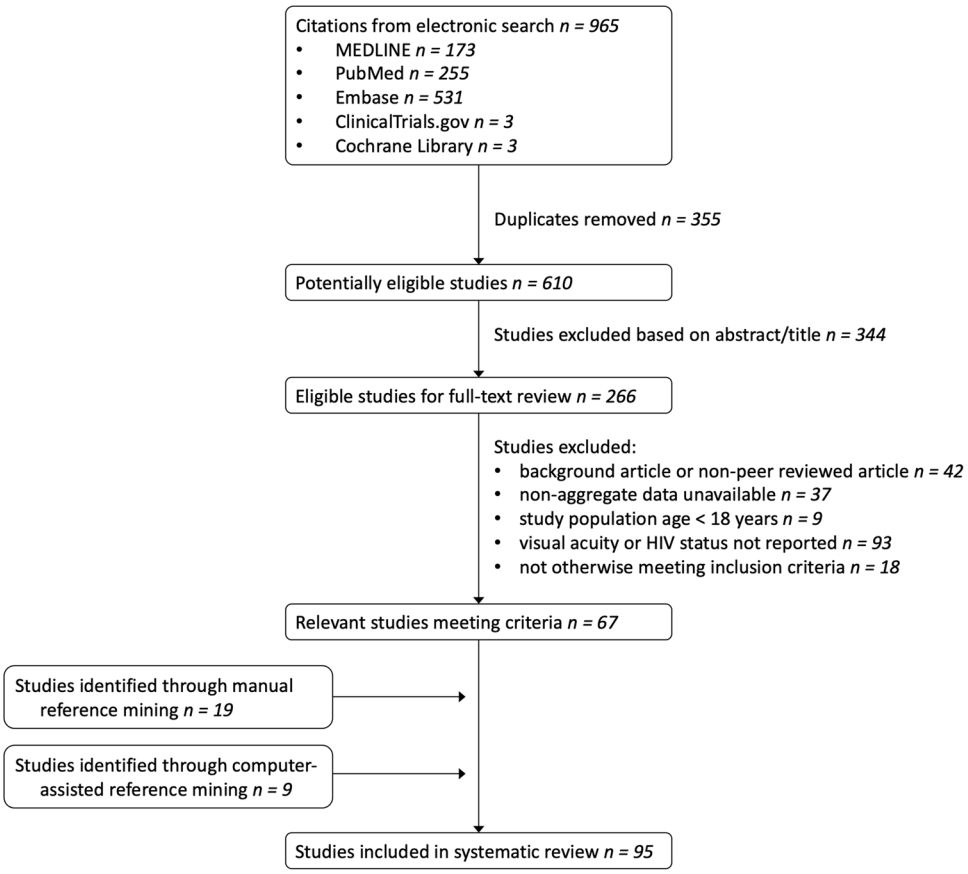

Fig. 1 PRISMA style flow diagram showing selection of eligible studies. Of the 95 studies included in the final analysis, 67 were identified through an electronic database search, 19 through manual reference mining, and 9 through computer-assisted reference mining.

Eligibility criteria

We included studies reporting non-aggregate data for at least one patient diagnosed with ocular syphilis and known HIV status with quantitative VA before and after ocular syphilis treatment. Only patients ≥18 years of age were eligible for inclusion. Additionally, those with a secondary ocular pathology known to significantly impact VA were evaluated by a board-certified ophthalmologist (LB) on a case-by-case basis for exclusion. Patients with congenital syphilis were excluded.

Study selection and data extraction

Two investigators (LZW and TMO) were independently responsible for literature screening, full-text review of screened articles, data extraction, and risk of bias assessment. Literature screening was conducted via Rayyan software [20], and any disagreements were advanced to full-text review until consensus was reached. All eligible articles underwent full-text review for inclusion eligibility. See Fig. 1 for study selection details.

Data extraction was undertaken by reviewers and data for each affected eye was input into a Microsoft Excel file designed to collect outcomes specified by the study protocol. Risk of bias was assessed using the Joanna Briggs Institute critical appraisal tools for case reports, case studies, and cohort studies, as appropriate (Supplementary Table 2) [21–23].

Data elements included study design, patient demographics, HIV status, VA, symptomatology, and laboratory findings. In cases where multiple VAs were reported, only the most recent pre- and post-treatment VA were collected and analysed. Uveitis was classified according to the Standardization of Uveitis Nomenclature (SUN) criteria [24]. Visual acuities measured in Snellen and decimal notation were converted to logMAR format for uniformity. Non-numerical visual acuities were reported according to generally accepted standards [25–28]. Post-treatment VA change was defined as a VA increase or decrease of ≥0.20 logMAR. Post-treatment VA changes <0.20 logMAR were considered stable for the purposes of this study.

Statistical analysis was conducted using SPSS version 28 (IBM SPSS Statistics; Armonk, NY) and SAS software, version 9.4 (SAS Institute Inc. Cary, NC). Patient and eye characteristics were summarized as counts (percent) for categorical data and means (standard deviation (SD)) for continuous data. We investigated between-group differences of patients with and without HIV. Correlations between categorical variables were analyzed using Chi-squared tests or Fisher's exact tests, as appropriate. We used independent *t*-tests and Wilcoxon non-parametric tests to compare normally and non-normally distributed continuous variables, respectively between HIV and non-HIV groups. A multivariable mixed-effects model was used to examine the post-treatment logMAR difference by HIV status. Only significant variables from the univariable analysis were included in the multivariable model. We also investigated the effect of all potential variables on VA using a univariable mixed effects model. Correlations with final VA ≥ 1.00 were investigated using a generalized estimating equation. Subgroup analysis of patients with HIV was conducted to investigate logMAR-reduction differences by CD4 categories as well as correlation between logMAR and log-adjusted HIV viral load. Cases with missing data were excluded from the denominator. A two-sided p-value < .05 was used as the threshold for significance.

RESULTS

An electronic database search yielded 965 citations, of which we included 67 in our final analysis. Manual and computer-assisted reference mining identified a further 28 citations, totalling 95 relevant studies for inclusion [29–123]. See Fig. 1 for PRISMA style flow diagram summarizing results of the literature search. In all cases, study design was descriptive or observational in nature, including 55 case reports, 36 case series, and 4 retrospective cohort studies. Ten eyes were evaluated and excluded because of a clinically significant secondary ocular pathology, three of which were due to secondary infections, likely facilitated by HIV coinfection. Final analysis included 364 patients and 568 eyes. A summary of the characteristics of included studies and quality of evidence are shown in Table 1.

Table 1. Characteristics of eligible studies.

Study no.	Method of identification	Study design	Number of participants included	Quality of evidence[a]	Year of publication	Citation
1	MRM	CS	3	4	2015	Afonso et al. [29]
2	ESS	CS	1	4	2018	Agarwal et al. [30]
3	MRM	CS	12	4	2017	Agostini et al. [31]
4	MRM	CR	1	5	2021	Aguilar-Gonzalez et al. [32]
5	ESS	CR	1	5	2011	Albini et al. [33]
6	ESS	CR	1	5	2011	Almekhlafi et al. [34]
7	ESS	CS	7	4	2016	Apinyawasisuk et al. [35]
8	ESS	CR	1	5	2014	Aranda et al. [36]
9	MRM	RC	10	3	2021	Artaechevarria Artieda et al. [37]
10	ESS	CR	1	5	2021	Azar et al. [38]
11	ERM	CR	1	5	2016	Baek et al. [39]
12	ESS	CR	1	5	2017	Bakhsh et al. [40]
13	MRM	CR	1	5	2019	Balci et al. [41]
14	ESS	CS	3	4	2014	Burkholder et al. [42]
15	ESS	RC	4	3	2019	Chen et al. [43]
16	MRM	CR	1	5	2021	Cheng et al. [44]
17	ERM	CR	1	5	2019	Christakopoulos et al. [45]
18	ESS	CR	1	5	2012	Cillino et al. [46]
19	ERM	CS	1	4	2015	Curi et al. [47]
20	MRM	CR	1	5	2019	De Aragao et al. [48]
21	MRM	CR	1	5	2018	De Simone et al. [49]
22	ESS	CS	2	4	2020	Deibert et al. [50]
23	ESS	CS	16	4	2021	DeVience et al. [51]
24	MRM	CR	1	5	2011	Dua et al. [52]
25	ESS	CR	1	5	2016	Eliott et al. [53]
26	MRM	CS	3	4	2019	Etheridge et al. [54]
27	ESS	CR	1	5	2016	Fenolland et al. [55]
28	ESS	CS	9	4	2019	Ghanimi Zamli et al. [56]
29	ESS	CR	1	5	2021	Gonzalez Collazo et al. [57]
30	ESS	CR	1	5	2018	Hamill et al. [58]
31	ESS	CS	2	4	2016	Haug et al. [59]
32	ESS	CR	1	5	2021	Hay et al. [60]
33	ESS	CS	3	4	2020	Herbort et al. [61]
34	ESS	CR	1	5	2018	Horng et al. [62]
35	ESS	CS	2	4	2021	Jahnke et al. [63]
36	ESS	CS	2	4	2015	Ji et al. [64]
37	ESS	CR	1	5	2017	Kansal et al. [65]
38	ESS	CR	1	5	2019	Karti et al. [66]
39	MRM	CS	7	4	2012	Karunaratne et al. [67]
40	ERM	CR	1	5	2020	Khan et al. [68]
41	MRM	CR	1	5	2019	Kim et al. [69]
42	ESS	CS	15	4	2019	Klein et al. [70]
43	ESS	CR	1	5	2021	Kumar et al. [71]
44	ESS	CR	1	5	2014	Kurtz et al. [72]
45	ESS	CR	1	5	2020	Latif et al. [73]
46	ESS	CR	1	5	2013	Lee et al. [74]
47	ESS	CS	14	4	2015	Lee et al. [75]
48	ESS	RC	11	3	2011	Li et al. [76]
49	ESS	CS	3	4	2021	Lim et al. [77]
50	ERM	CS	2	4	2014	Lima et al. [78]
51	ERM	CR	1	5	2016	Loureiro et al. [79]
52	MRM	CR	1	5	2021	Mathews et al. [80]

Table 1. continued

Study no.	Method of identification	Study design	Number of participants included	Quality of evidence[a]	Year of publication	Citation
53	ESS	CR	1	5	2011	Milger et al. [81]
54	ESS	CR	1	5	2015	Mitchell et al. [82]
55	ERM	CR	1	5	2014	Monica et al. [83]
56	ESS	CR	1	5	2020	Morris et al. [84]
57	ESS	CR	1	5	2019	Motlagh et al. [85]
58	ERM	CS	3	4	2018	Mustapha et al. [86]
59	ESS	CR	1	5	2014	Nguyen et al. [87]
60	ESS	CR	1	5	2018	Nolan et al. [88]
61	ESS	RC	19	3	2015	Northey et al. [89]
62	ESS	CS	3	4	2013	Nurfahzura et al. [90]
63	ESS	CS	2	4	2022	Odendaal et al. [91]
64	MRM	CR	1	5	2019	Ormaechea et al. [92]
65	ESS	CR	1	5	2020	.Parija et al. [93]
66	ESS	CR	1	5	2015	Patel et al. [94]
67	ESS	CS	18	4	2014	Pichi et al. [95]
68	ESS	CS	1	4	2019	Pirani et al. [96]
69	ESS	CR	1	5	2019	Ploysangam et al. [97]
70	ESS	CR	1	5	2016	Rishi et al. [98]
71	ESS	CR	1	5	2012	Rodrigues et al. [99]
72	ESS	CS	12	4	2014	Rodrigues et al. [100]
73	ESS	CR	1	5	2013	Rodriguez-Una et al. [101]
74	MRM	CR	1	5	2016	Romao et al. [102]
75	ESS	CS	11	4	2015	Sahin et al. [103]
76	ESS	CR	1	5	2019	Schlaen et al. [104]
77	MRM	CS	4	4	2021	Schulz et al. [105]
78	ESS	CS	9	4	2015	Shen et al. [106]
79	ESS	CR	1	5	2016	Shinha et al. [107]
80	ESS	CR	1	5	2020	Sidiqi et al. [108]
81	MRM	CS	2	4	2020	Silpa-Archa et al. [109]
82	ESS	CR	1	5	2019	Sood et al. [110]
83	ESS	CR	1	5	2021	Świerczyńska et al. [111]
84	ESS	CR	1	5	2020	.Teh et al. [112]
85	ESS	CR	1	5	2021	Tsai et al. [113]
86	ESS	CS	5	4	2017	Tsen et al. [114]
87	ESS	CS	16	4	2016	Tsuboi et al. [115]
88	ESS	CR	1	5	2012	Turchetti et al. [116]
89	ESS	CR	1	5	2020	Vidal-Villegas et al. [117]
90	ERM	CR	1	5	2016	Vignesh et al. [118]
91	MRM	CS	19	4	2012	Yang et al. [119]
92	MRM	CS	10	4	2014	Yap et al. [120]
93	ESS	CR	1	5	2019	Yosar et al. [121]
94	ESS	CS	13	4	2016	Zhang et al. [122]
95	ESS	CS	28	4	2017	Zhu et al. [123]

ESS electronic search strategy, *MRM* manual reference mining, *ERM* electronic reference mining, *CR* case report, *CS* case series, *RC* retrospective cohort study.
[a]As per the modified Oxford Centre for Evidence-Based Medicine where: 1 = Properly powered and conducted randomized clinical trial; systematic review with meta-analysis, 2 = Well-designed controlled trial without randomization; prospective comparative cohort trial, 3 = Case-control studies; retrospective cohort study, 4 = Case series with or without intervention; cross-sectional study, 5 = Opinion of respected authorities; case reports.

The mean age of patients was 44.9 years (range 18 to 84 years) and 81% of patients were male, of whom 48% were MSM. Median rapid plasma reagin (RPR) titre at baseline was 1:64. Forty-six percent (166/364) of patients included in this study were known to have HIV, among whom the mean HIV viral load was 234,313 copies/mL (SD 760,654) and mean CD4 cell count was 311 cells/mL (SD 226). In the 96 patients whose CD4 cell count was known, 53 (55%) had > 200 cells/mL, 29 (30%) had 101–200 cells/mL, 5 (5%) had 51–100 cells/mL, and 9 (9%) had ≤50 cells/mL. Bilateral disease occurred in 59% (213/362) of patients. In unilateral cases, the right eye was affected 56% of the time and the left eye, 44%. Mean time from ocular symptom development to presentation was 123 days (SD 281). Syphilis was detected in the cerebrospinal fluid (CSF) of 67/138 (49%) patients who had CSF data reported. See Table 2 for participant demographics.

Table 2. Participant demographics.

Variable	All ($n = 364$)	HIV− ($n = 198$)	HIV+ ($n = 166$)	*P* Value
Mean age in years (95% CI)	44.9 (43.6–46.2)	48.6 (46.9–50.3)	40.5 (38.7–42.2)	<0.001
Male sex	295/363 (81.3%)	139/197 (70.6%)	156/166 (94.0%)	<0.001
MSM[a]	68/143 (47.6%)	15/72 (20.8%)	53/71 (74.6%)	<0.001
Median RPR[b]	1:64	1:64	1:256	<0.001
CSF[c] reactive for syphilis	67/138 (48.6%)	25/57 (43.9%)	42/81 (51.9%)	0.355
Mean time to presentation in days (95% CI)	123 (80–167)	200 (110–290)	63 (37–89)	<0.001
Mean time to follow up in days (95% CI)	281 (227–335)	336 (258–413)	206 (137–276)	<0.001
Cases with delayed diagnosis	31/101 (30.7%)	21/59 (35.6%)	10/42 (23.8%)	0.206
Bilateral disease	213/362 (58.8%)	108/197 (54.8%)	105/165 (63.6%)	0.090

[a]*MSM* men who have sex with men.
[b]*RPR* rapid plasma reagin.
[c]*CSF* cerebrospinal fluid.

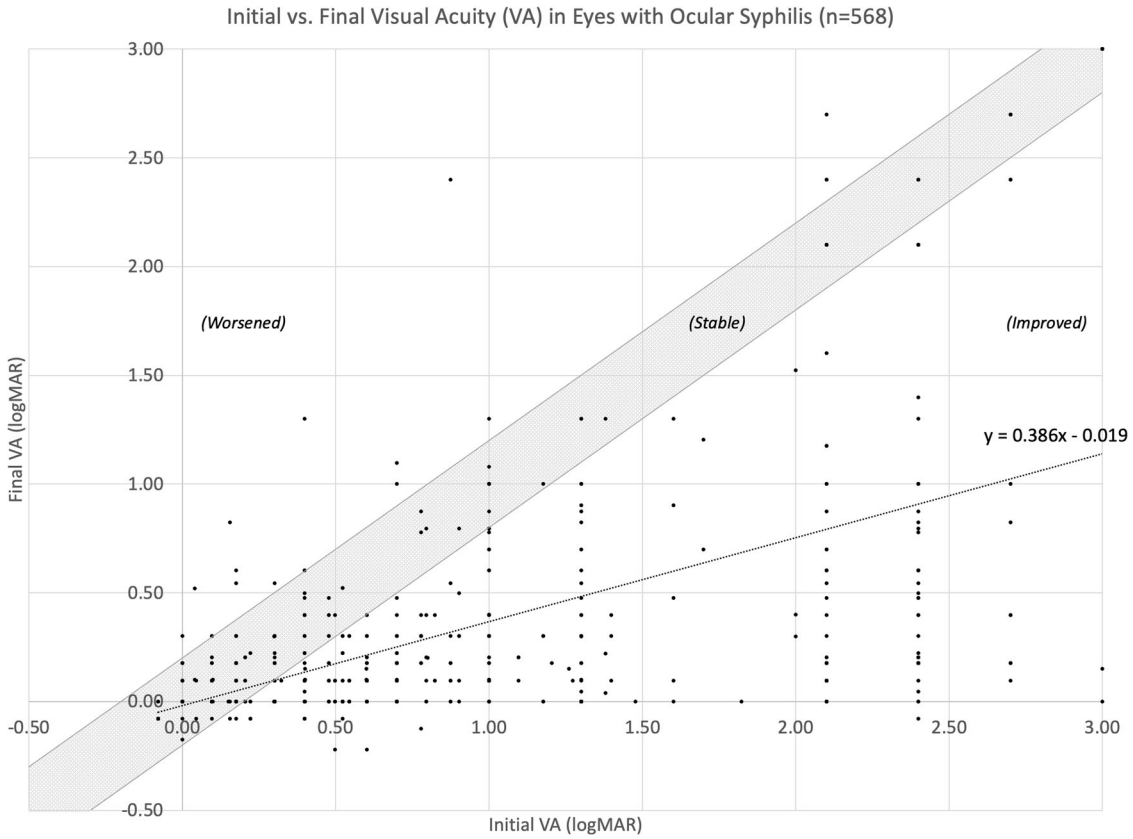

Fig. 2 Initial vs. final visual acuity (VA) in eyes with ocular syphilis. Data points to the right of the shaded region demonstrated improved VA ≥ 0.200 logMAR after treatment. Data points falling in the shaded region demonstrated stable VA with a post-treatment change of <0.200 logMAR. Data points to the left of the shaded region demonstrated worsened VA ≥ 0.200 logMAR after treatment. Counting fingers (CF), hand movements (HM), light perception (LP), and no light perception (NLP) were reported as 2.10, 2.40, 2.70, and 3.00 logMAR, respectively.

The three most common ocular complaints at presentation were VA loss or blurry vision (328/362, 91%), eye pain (49/296, 17%), and red eye (47/296, 16%). Only 16/362 (4%) symptomatic eyes were not associated with any of the above symptoms. Despite being a classic feature of neurosyphilis, Argyll Robertson pupils (bilateral miosis with light-near dissociation) were not reported in any of the eyes included in this review. The most common ocular diagnoses were posterior uveitis (192/515, 37%), anterior uveitis (144/525, 27%), and panuveitis (144/525, 27%). Optic nerve involvement was seen in 197/568 (35%) of eyes. Overall mean VA at presentation was 0.893 (95%CI 0.825–0.961) while mean post-treatment VA was 0.326 (95%CI 0.280–0.373), representing a mean improvement of 0.567 (95%CI 0.510–0.624) or approximately 6 Snellen lines. Mean time to last follow-up was 281 days (SD 485). The majority of eyes, 63%, had improvement of VA after treatment while VA remained stable in 34% and declined in only 3% of eyes.

Initial VA was significantly correlated with final VA ($\beta = 0.386$, $p < 0.001$), as represented in Fig. 2. The overall regression model was: final VA = 0.386 (initial VA)−0.019 ($R^2 = 0.317$, $F(1566) = 262.458$, $p < 0.001$). Prognostic factors of final VA ≥ 1.00 (worse than or equal to Snellen 20/200) included initial VA ≥ 1.00 (OR 5.48, 95%CI

4.17–7.21, $p < 0.001$), macular oedema (OR 4.68, 95%CI 1.54–14.21, $p = 0.006$), and female sex (OR 2.15, 95%CI 1.14–4.05; $p = 0.017$). Females experienced a significantly longer mean time to diagnosis compared to males (female 277 days vs. males 87 days; difference 190; 95%CI 84–296; $p < 0.001$). However, the relationship between female sex and poor final VA was found to occur independently of this delay in diagnosis. Variables significantly predicting final VA included initial VA ≥ 1.00 (mean final VA 0.647 vs. 0.128; difference 0.519, 95%CI 0.433–0.605; $p < 0.001$), female sex (mean final BCVA 0.463 vs. 0.296 for males; difference 0.17, 95%CI 0.046–0.288; $p = 0.003$), and a diagnosis of panuveitis (mean final VA 0.446 vs. 0.275 without panuveitis; difference 0.16, 95%CI 0.059–0.282; $p = 0.017$).

HIV status ($p = 0.289$), HIV viral load ($p = 0.144$), and CD4 cell count ≤200 cells/mL ($p = 0.962$), ≤100 cells/mL ($p = 0.965$), and ≤50 cells/mL ($p = 0.653$) were not predictive of visual outcome. Final VA was not significantly associated with age ($p = 0.06$), RPR titre ($p = 0.273$), delayed diagnosis ($p = 0.847$), initial corticosteroid therapy ($p = 0.261$), bilaterality ($p = 0.814$), or optic nerve involvement ($p = 0.537$).

All 281 patients whose treatment status was described received systemic treatment for ocular syphilis: 85% received IV penicillin G, 17% IM penicillin G, and 12% IV ceftriaxone. Notably, 31% (31/101) of patients were initially misdiagnosed, and 27% (20/74) of those for whom data were available were initiated on systemic corticosteroid therapy before anti-syphilis treatment was given. In cases which were initially misdiagnosed and data were available, 80% (16/20) were treated with corticosteroids prior to antibiotic therapy. Overall, 5 cases of Jarisch-Herxheimer reaction were reported, none of which occurred in those patients who received systemic corticosteroids.

Patients with HIV were significantly more likely to be younger (mean 40.5 vs. 48.6 years; difference 8.1, 95%CI 5.72–10.57; $p < 0.001$), male (OR 6.51, 95%CI 3.20–13.23, $p < 0.001$), and have higher RPR at the time of diagnosis (median 1:256 vs. 1:64, $p < 0.001$) despite presenting to care earlier (mean 63 vs. 200 days; difference 137, 95%CI 53–222; $p < 0.001$). Amongst male patients with ocular syphilis, those with HIV were more likely to be MSM (OR 11.19, 95% CI 5.13–24.42, $p < 0.001$). No significant relationship was found between being infected with HIV and likelihood of positive syphilis serology in the CSF ($p = 0.355$), bilaterality of ocular syphilis ($p = 0.090$), or side of the eye affected ($p = 0.688$). HIV status was not significantly correlated with any presenting clinical symptom. However, infection with HIV was associated with panuveitis (OR 2.19, 95%CI 1.48–3.26, $p < 0.001$) and optic nerve involvement (OR 1.60, 95%CI 1.13–2.27, $p = 0.009$), described variably as optic neuritis, papillitis, optic nerve atrophy, and optic nerve oedema. HIV status was not significantly associated with presenting VA ($p = 0.342$) and there was no association with the likelihood of VA improvement ($p = 0.795$), stability ($p = 0.722$), and decline ($p = 0.808$), final VA ($p = 0.773$), or VA change from pre- to post-treatment ($p = 0.499$). See Table 3 for eye characteristics by HIV status.

DISCUSSION

To our knowledge, this is the largest systematic review of visual acuity outcomes in ocular syphilis to date. Commonly known as "the great masquerader" for its many manifestations, syphilis has a unique ability to present in myriad ways. The diagnosis of syphilis involves treponemal and non-treponemal tests, which can cross-react, be serofast, or produce false positive or negative results [124, 125]. Ocular syphilis in particular, can pose a diagnostic challenge due to its variable presentation and lack of pathognomonic features [48, 56, 67, 126]. Therefore, a diagnosis of ocular syphilis is often presumptive, and a strong index of suspicion is key [126, 127]. Our systematic review reveals the typical clinical presentations of ocular syphilis to aid the clinician in their diagnostic accuracy.

The predominance of ocular syphilis in males, especially MSM, and middle-aged patient groups has been well-established [128, 129] and is consistent with the demographic findings of this study. At presentation, bilateral disease was more common than unilateral disease, and there was a similar distribution of ocular syphilis affecting the left and right eyes. VA loss or blurry vision, eye pain, and red eye were the most common ocular complaints at presentation with a combined sensitivity of 96%. The most common of these symptoms was VA loss or blurry vision, with a prevalence of 91%. Therefore, in patients with syphilis, the lack of VA loss or blurry vision reduces the likelihood of ocular involvement. The most common ocular diagnoses were posterior uveitis, panuveitis, and anterior uveitis, occurring in 38%, 27%, and 27% of patients, respectively. The morbidity of ocular syphilis stems largely from the inflammation rather than the infection itself. If a patient with an extremely suppressed immune system was unable to mount an immune response, they may have no visual symptoms or signs at all, hampering the ability to establish a diagnosis of ocular syphilis. Despite treatment guidelines by the Centers for Disease Control and Prevention and Public Health Agency of Canada for routine CSF analysis in ocular syphilis [130, 131], CSF data were only available for approximately one-third of all patients and detected syphilis in 49%. At presentation, the mean VA was 0.893 (Snellen equivalent 20/156) and median VA was 0.602 (20/80). VA improved to a mean of 0.326 (20/42) and median 0.097 (20/25) with treatment, highlighting the good prognosis of ocular syphilis with appropriate management.

Nearly one-third of patients were initially misdiagnosed, among whom 80% were initiated on systemic corticosteroid therapy. Of note, there was a large number of missing values regarding diagnostic accuracy. The role of systemic corticosteroids in ocular syphilis has been controversial, with some reporting it to cause clinical worsening while others suggest it as a valuable adjunct to antibiotic therapy [30, 132–135]. In our analysis, patients who received initial corticosteroid therapy prior to antibiotics were not found to have poorer visual outcomes, but the limited sample size limits the conclusions that can be drawn from this finding. Our study indicates the importance of future prospective work to explore and address the timing of steroids in ocular syphilis.

Visual acuity outcomes were not found to be worse in eyes affected by bilateral ocular syphilis and, contrary to previous reports [136, 137], optic nerve involvement was not a predictor of final VA in our analysis. Reporting on other measures of visual function, such as visual field defects and colour vision, was generally lacking in the studies included in this systematic review. This would be a useful outcome to investigate in future research as these are valuable measures of visual function. Prognostic factors for post-treatment VA ≥ 1.00 included VA ≥ 1.00 at presentation, female sex, and presence of macular oedema. Although females also experienced a significantly longer time to diagnosis than males, female sex was found to be a predictor of poor visual outcome independent of the delay in diagnosis. Similarly, the presence of macular oedema was significantly associated with poor visual outcome. However, we lack the long-term data to assess whether macular oedema was reversible with treatment or if these cases were associated with poor final VA even if macular oedema resolved. Of all the variables significantly associated with final VA, VA ≥ 1.00 at presentation was the strongest predictor of a worse final VA. Therefore, detection of ocular syphilis before severe VA loss is critical in achieving good visual outcomes for patients. Patients with syphilis complaining of visual acuity loss should be promptly referred to ophthalmology.

Given the relative rarity of ocular syphilis, its relationship with HIV is not well understood. This study contributes to a better understanding of the interaction between the two diseases. HIV subgroup analysis revealed that patients who were coinfected with HIV were younger, more likely to be male, and had higher

Table 3. Characteristics of eyes by HIV status.

Variable	All ($n = 568$)	HIV− ($n = 300$)	HIV+ ($n = 268$)	*P* Value
Right eye affected	285/568 (51.8%)	150/294 (51.0%)	135/256 (52.7%)	0.688
Visual acuity				
Mean initial VA[a] (logMAR) (95% CI)	0.893 (0.825–0.961)	0.837 (0.750–0.924)	0.956 (0.849–1.062)	0.342
Mean final VA[a] (logMAR) (95% CI)	0.326 (0.280–0.373)	0.318 (0.255–0.380)	0.336 (0.265–0.406)	0.773
Mean VA[a] (logMAR) change (95% CI)	0.567 (0.510–0.624)	0.519 (0.446–0.592)	0.620 (0.531–0.709)	0.499
Symptoms				
Visual acuity loss or blurry vision	328/362 (90.6%)	178/195 (91.3%)	150/167 (89.8%)	0.635
Eye pain	49/296 (16.6%)	26/148 (17.6%)	23/148 (15.5%)	0.639
Red eye	47/296 (15.6%)	19/148 (12.8%)	28/148 (18.9%)	0.152
Floaters	46/296 (15.5%)	19/148 (12.8%)	27/148 (18.2%)	0.199
Scotoma	38/306 (12.4%)	17/148 (11.5%)	21/158 (13.3%)	0.632
Visual field defect	32/315 (9.4%)	17/176 (9.7%)	15/165 (9.1%)	0.857
Photophobia	27/296 (9.1%)	10/148 (6.8%)	17/148 (11.5%)	0.158
Headache	17/315 (5.4%)	9/165 (5.5%)	8/150 (5.3%)	0.962
Dyschromatopsia	15/296 (5.1%)	9/148 (6.1%)	6/148 (4.1%)	0.427
Macular edema	17/515 (3.3%)	15/259 (5.8%)	2/256 (0.8%)	0.001
RAPD	16/515 (3.1%)	9/259 (3.5%)	7/256 (2.7%)	0.628
Photopsia	8/296 (2.7%)	5/148 (3.4%)	3/148 (2.0%)	0.473
Diagnoses				
Keratitis	88/515 (17.1%)	45/259 (17.4%)	43/256 (16.8%)	0.862
Scleritis	12/515 (2.3%)	5/259 (1.9%)	7/256 (2.7%)	0.545
Vasculitis	37/501 (7.4%)	21/249 (8.4%)	16/252 (6.3%)	0.372
Anterior uveitis	144/525 (27.4%)	72/259 (27.8%)	72/266 (27.1%)	0.851
Intermediate uveitis	126/525 (24.5%)	62/259 (23.9%)	64/256 (25.0%)	0.779
Posterior uveitis	192/515 (37.3%)	102/259 (39.4%)	90/256 (35.2%)	0.321
Panuveitis	144/525 (27.4%)	51/259 (19.7%)	93/266 (35.0%)	<0.001
Optic nerve involvement[b]	197/568 (34.7%)	89/300 (29.7%)	108/268 (40.3%)	0.009
Retinal detachment	18/501 (3.6%)	6/249 (2.4%)	12/252 (4.8%)	0.157
Jarisch-Herxheimer reaction	5/220 (2.3%)	2/89 (2.2%)	3/131 (2.3%)	0.983

[a]*VA* visual acuity.
[b]optic nerve involvement includes optic neuritis, papillitis, optic nerve atrophy, and optic nerve edema.

RPR at diagnosis. As previously reported, MSM were at an increased risk of being coinfected with HIV and ocular syphilis [129]. Our work indicates the importance of ensuring routine syphilis testing in HIV care. Time to presentation of ocular symptoms in those patients with HIV was significantly earlier than those who tested negative for HIV. This may be, in part, due to the regular monitoring that occurs as part of routine HIV care. All patients included in this study were treated promptly with antibiotics once the diagnosis was established. Patients with HIV presented for care earlier than those without HIV, and therefore received earlier treatment, but delay in diagnosis was not found to affect visual outcome. It is possible that HIV coinfection may result in a more severe and rapid disease course, and this risk was offset by earlier treatment, but firm conclusions cannot be drawn without an untreated control arm. There could be a bias in the reported literature reflecting outcomes of patients being treated at academic centres, and rural communities may face more barriers in reaching the same level of engagement as their urban counterparts [138, 139]. While previous studies have demonstrated a propensity for bilateral disease in patients with HIV [14, 140], our systematic review did not confirm this relationship. Among those with unilateral ocular syphilis, we found a similar distribution between left and right eyes, contradicting a previously reported increased risk of left eye disease [128]. Although HIV status was not associated with any presenting symptom, patients with HIV were more likely to be diagnosed with panuveitis and demonstrate optic nerve involvement. Our study agrees with previous literature that HIV positive and negative patients appear to present with different forms of ocular inflammation (anterior, posterior, optic nerve, panuveitis), but this was not found to be a significant predictor of final visual acuity [141].

Ultimately, HIV status, CD4 cell count, and HIV viral load was not found to impact the visual prognosis of eyes with ocular syphilis. Subgroup analysis of patients with CD4 cell counts ≤200 cells/mL, ≤100 cells/mL, and ≤50 cells/mL also did not suggest a relationship to visual outcome. It has been hypothesized that immunosuppression by HIV puts patients with syphilis at risk for developing ocular involvement [142, 143]. However, HIV has never been implicated in the visual prognosis of patients with ocular syphilis [14, 128]. Our analysis relies on the data made available through the global literature, among which there are limited reports of severe immunosuppression available for analysis. While all 364 patients in our systematic review had known HIV status, CD4 cell count was reported in only 96 and HIV viral load was reported in 59. Furthermore, there were few cases of low CD4 cell count ≤100 cells/mL available for analysis, possibly due to the widespread prevalence of antiretroviral therapy for HIV in the modern era. The limited number of patients with severe

immunosuppression limits our ability to draw definitive conclusions in these individuals. Future studies evaluating patients with ocular syphilis and HIV should be designed to include important variables that reflect disease activity and immune status, such as viral load and CD4 + counts.

Data used in the composition of this systematic review were primarily sourced from case reports and series. There exists a possible sampling bias as typically only unique or extraordinary cases are published. We are unable to verify or standardize the methods and techniques used to measure outcomes in each study, including VA, due to the retrospective nature of a systematic review. Finally, as discussed above, the diagnosis of ocular syphilis can be challenging and requires interpretation within a clinical context and, thus, we rely on the judgement of the studies' authors to confirm the diagnosis in each eye analysed.

In this systematic review, post-treatment visual acuity in eyes affected by ocular syphilis was not impacted by HIV status, CD4 cell count, or HIV viral load. While visual prognosis was generally good, factors significantly associated with final VA ≥ 1.00 included initial VA ≥ 1.00, female sex, and presence of macular oedema. VA ≥ 1.00 at presentation was the strongest predictor of worse final VA. This finding highlights the importance of prompt referral of ocular syphilis to allow early diagnosis and management in preserving visual acuity.

Summary

What was known before

- Ocular syphilis is a rare but increasingly prevalent vision-threatening disease, often occurring in patients with HIV.
- Symptoms typically improve with appropriate antibiotic treatment, but no prognostic factors have been identified in determining the visual outcome of ocular syphilis.

What this study adds

- HIV status, CD4 cell count, and HIV viral load were not found to impact the post-treatment visual acuity (VA) of eyes with ocular syphilis.
- Factors significantly correlated with post-treatment VA worse than 1.00 logMAR included female sex, presence of macular edema, and VA worse than 1.00 logMAR at presentation.
- Visual prognosis for eyes with ocular syphilis is generally good with antibiotic treatment, particularly if treatment is initiated before significant loss of visual acuity occurs.

DATA AVAILABILITY

The datasets analysed in this work are available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

LZW was responsible for study concept and design, study design registration with PROSPERO, article screening and full-text review, risk of bias assessment, acquisition and interpretation of data, statistical analysis, manuscript drafting, updating reference lists, and creating tables and figures. TMO was responsible for article screening and full-text review, risk of bias assessment, acquisition and interpretation of data, manuscript drafting, updating reference lists. MK was responsible for analysis and interpretation of data, manuscript drafting, technical/administrative support. SL was responsible for analysis and interpretation of data, manuscript revision, technical/administrative support, and study supervision. PM was responsible for statistical analysis, analysis and interpretation of data, technical/administrative support, and manuscript revision. SK was responsible for analysis and interpretation of data, technical/administrative support, manuscript revision, and study supervision. LB was responsible for analysis and interpretation of data, technical/administrative support, manuscript drafting and revision, and study supervision.

COMPETING INTERESTS

The authors declare no competing interests.

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