• Clinical Research •

Syphilitic uveitis in HIV-positive patients: report of a case series, treatment outcomes, and comprehensive review of the literature

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Abstract

● **AIM:** To report the clinical characteristics, treatment and outcomes of active syphilitic uveitis in human immunodeficiency virus (HIV) positive patients and compare them with the previously published data.

● **METHODS:** Retrospective analysis of the case series from an infectious disease center in southern China was conducted. Comprehensive review of previously published cases of HIV positive syphilitic uveitis was conducted using the PubMed and Web of Science databases and the references listed in the identified articles.

● **RESULTS:** Twelve HIV positive patients with active syphilitic uveitis were collected. All were male, with age of 36.3y (range 27 to 53y). Five (41.7%) had a history of syphilis, and three of them had received anti-syphilis treatment. Ocular manifestations included corneal epithelial defect (13%), complicated cataract (17.4%), vitreous opacity (82.6%), optic disc edema (26.1%), macular edema (30.4%), neuro-retinitis (43.5%), and retinal hemorrhage (26.1%). After standardized syphilitic treatment, intraocular inflammation was reduced and vision improved in all cases. The literature review summarizes 105 previously reported cases of HIV positive syphilitic uveitis. High serum rapid plasma regain (RPR) titers may be associated with severe uveitis and poor vision. Treatment with penicillin, ceftriaxone sodium, or penicillin plus benzylpenicillin instead of using benzylpenicillin alone can significantly improve best-corrected visual acuity (BCVA) in HIV positive ocular syphilis patients.

● **CONCLUSION:** For HIV positive syphilitic uveitis patients, prompt diagnosis and appropriate treatment and follow-up are paramount. In our series, the clinical manifestations are diverse. Syphilis patients treated by penicillin G or long-acting penicillin before may still develop syphilitic uveitis. Patients who relapse after long-term penicillin treatment can still benefit from penicillin G.

● **KEYWORDS:** syphilis; uveitis; human immunodeficiency virus; neurosyphilis regimen; literature review

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INTRODUCTION

Syphilis is a sexually and blood borne disease, caused by Treponema pallidum (TP) and may affect various body systems[1]. Syphilis is a rare cause of uveitis and may happen at any stage of disease. It can happen 6wk after infection and could be the initial or only symptom of syphilis[1]. Ocular syphilis could involve most tissue of eye (such as conjunctivitis, scleritis, interstitial keratitis, and uveitis)[2]. Among them, the most common manifestation is uveitis and it may lack of characteristic ocular symptoms in its early stages. Recently the incidence of syphilis with ocular involvement has increased[3-5].

Human immunodeficiency virus (HIV) infection can seriously damage body's immune system, reduce or lose the immune capacity, and lead to complications such as various opportunistic infections. Among HIV infected individuals, syphilis caused ocular infections are common[1,6]. Primary syphilis expanded HIV spread, while HIV may change the natural progress of syphilis and increase neurosyphilis tendency[1]. The proportion of HIV positive ocular syphilis patients is significantly higher than HIV negative cases[7-8]. The ocular manifestations of syphilis appear to be more severe in HIV infected patients[7,9].

Syphilitic uveitis can be treated with appropriate antibiotic[7]. Since ocular is a central nervous system extension, the International Alliance for the Prevention of Sexually Transmitted Infections recommends neurosyphilis regimen for the treatment of ocular syphilis[10-11]. However, for HIV positive ocular syphilis patients, only a few cases have been reported with characteristics and treatment results[7,10-11], especially in Asian patients.

In order to better understand the clinical characteristics, treatment, and outcomes of syphilitic uveitis in HIV positive patients, here we reported a series of cases and conducted a comprehensive review of the literature on active syphilitic uveitis in HIV infected patients to discuss its clinical characteristics and treatment responses.

SUBJECTS AND METHODS

Ethical Approval We obtained approval from Guangzhou No.8 People's Hospital Institutional Ethics Committee (No.202009142) to retrospectively analyze the medical records of HIV positive patients with syphilitic uveitis between April 2014 and April 2019, and waive informed consent. Before analysis, patient information was anonymized.

All patients had a history of acquired immune deficiency syndrome (AIDS). The syphilitic uveitis was diagnosed based on the positive results of specific anti TP serological tests [*i.e.*, positive TP particle agglutination test (TPPA) or TP hemagglutination test and/or positive fluorescent treponema antibody absorption test] in uveitis patients, and excluding other fundus diseases related to AIDS (such as tuberculous uveitis, cytomegalovirus chorioretinitis, toxoplasmosis chorioretinitis, fungal uveitis and acute retinal necrosis). Cerebrospinal fluid or intraocular fluid were further tested to confirm neurosyphilis or syphilis in the eyes.

Anonymized standard entry forms were used to record the following information: sex, age at present in the hospital, eye(s) affected, the time between the beginning of uveitis symptoms and anti-syphilis treatment, laboratory information such as HIV status and serologic tests, cerebrospinal fluid analyses, clinical features, and treatment methods.

All patients underwent ocular assessment including best-corrected visual acuity (BCVA) before and after syphilis treatment, slit-lamp biomicroscopy, and fundus through a dilated pupil. Spectral-domain optical coherence tomography and fundus fluorescein angiography (FFA) were not selectively performed in some patients considering their economic status or the ability to tolerate the tests.

All patients continue with their appropriate anti-HIV treatment. The following anti-syphilis treatment regimens were included: 1) Penicillin G 6 million units intravenously (IV) every 6h, or 18 to 24 million units per day by continuous infusion for 14d; 2) Benzylpenicillin 2.4 million units intramuscularly (IM) every week for 3 to 6wk; 3) Ceftriaxone sodium IV 2 g/d for 14d. Adjunctive corticosteroids treatment (eye drops or systemic), anti-virus (intravitreal injection, or systemic), or anti-tuberculosis drugs were recorded.

Literature Review The review of the literature was performed by searching PubMed database and Web of Science database before September 2022. Search terms included "(((((((((eye) OR (ocular)) OR (iridocyclitis)) OR (chorioretinitis)) OR (uveitis)) OR (retinitis)) OR (optic neuritis)) OR (conjunctivitis)) AND ((HIV) OR (AIDS))) AND ((syphilis) OR (Treponema pallidum))", limiting the language to English. Reference mining was conducted on the identified papers to ensure that all retrospective studies and case reports describe syphilitic uveitis in HIV infected patients were included.

For each patient, uveitis features, laboratory findings, treatment and outcomes were recorded. Patients was grouped based on CD4 cell count (more or less than 200 cells/μL) and rapid plasma regain (RPR) titer (higher or lower than 1:64). Treatment was grouped according to antibiotic. The PNC group were those who received IV or/and IM penicillin (include crystalline penicillin, aqueous penicillin, aqueous penicillin G, and penicillin G). The BPNC group received IV or IM benzylpenicillin (include benzylpenicillin, procaine penicillin G, or penicillin G benzathine). The PNC+BPNC group received IV PNC and IM or IV BPNC. The CRO group received IV ceftriaxone sodium.

To compare visual acuity before and after treatment in different studies, visual acuity records were converted to Early Treatment Diabetic Retinopathy Study (ETDRS) format. IBM SPSS Statistics 24.0 was utilized to analyze the data. A matched samples *t*-test was then employed to contrast the mean and 95% confidence interval (CI) of BCVA between the two groups.

RESULTS

Patient Population Twelve HIV-positive patients were identified coinfected with active syphilitic uveitis and were treated in Guangzhou No.8 People's Hospital between April 2014 and April 2019 (Table 1). This constituted 5.11% of the 235 new diagnosed uveitis patients visited the hospital during the time.

Table 1 Demographics, history of syphilis, and HIV status of patients presenting with syphilitic uveitis

Case	Age/gender	Epidemiological history	History of AIDS	AIDS stage	CD4 count (cells/μL)	Anti-HIV treatment	History of syphilis	Systemic disease
1	35/M	Blood transfusion	21mo	AIDS C3	179	HAART (3TC+TDF+EFV)	2mo, no treatment	-
2	32/M	MSM	1mo	AIDS C3	268	Irregular medication	None	-
3	40/M	Blood transfusion, extramarital sex	2y	AIDS C3	240	HAART	None	Left pneumonia granuloma
4	27/M	MSM	7y	AIDS C3	119	HAART	5y, BPNC twice	-
5	53/M	-	4.5y	AIDS B2	354	HAART	None	-
6	28/M	Extramarital sex	7y	AIDS A2	373	HAART (3TC+TDF+EFV)	1.5y, BPNC	HBV
7	50/M	MSM	1mo	AIDS A2	261	ART	None	-
8	34/M	MSM	10y	AIDS C3	72	HAART (3TC+TDF+EFV)	None	TB
9	27/M	MSM	2y	AIDS C3	402	HAART	1.5y, no treatment	-
10	38/M	-	6mo	AIDS C3	71	HAART (TDF+3TC+RAL)	None	TB, HBV
11	43/M	Extramarital sex	1mo	AIDS C3	39	Irregular medication	7mo, BPNC+ceftriaxone	TB, HBV
12	29/M	MSM	2mo	AIDS C3	21	HAART (TDF+3TC+RAL)	None	TB, lung infection

M: Male; MSM: Men having sex with men; HAART: Highly active anti-retroviral therapy; ART: Anti-retroviral therapy; TC: Lamivudine; TDF: Tenofovir disoproxil fumarate; EFV: Efavirenz; RAL: Raltegravir; BPNC: Benzylpenicillin 2.4 million units intramuscularly once a week for 3-6wk; HBV: Hepatitis B virus; TB: Tuberculosis.

All patients were male. The mean age of patients diagnosed with syphilitic uveitis at admission was 36.3y (range 27 to 53y). According to available data, six patients (50.0%) were homosexual, three (25%) were having extramarital sex, and two (16.7%) had blood transfusion. None of them had ever been involved in intravenous drug abuse. All patients were HIV positive and diagnosed AIDS 2.9y (range 1mo to 10y) prior to their presenting with ocular complaint. Of these, nine patients underwent highly active anti-retroviral therapy, one was on anti-retroviral therapy, two took irregular medication. Six of 12 patients (50.0%) had CD4 counts less than 200 cells/μL. All patients continued their systemic antiviral therapy while ocular syphilitic treatment.

Five (41.7%) patients (Patient 1, 4, 6, 9, and 11) reported a prior history of syphilis. Three of them (Patient 4, 6, and 11) had anti-syphilis treatment before this visit.

Clinical Presentation Of the 12 patients, 23 eyes were involved. Symptoms include decreased vision (100%), redness (26.1%), floating debris (17.4%), ocular pain (13%), visual field defects (8.7%), and headache (8.3%). Symptoms persist from 5d to 12mo. All patients saw an eye care doctor previously, and 9 of them (75%) received topical steroid eye drops for uveitis at the time of visit.

In 11 of the 12 (91.7%) patients, uveitis was bilateral. Of the 23 affected eyes, there were pan-uveitis in 10 eyes (43.5%), posterior uveitis in 6 eyes (26.1%), and anterior/intermediate uveitis in 7 eyes (30.4%). Clinical characteristics were recorded in Table 2 and summarized in Table 3. Protrusive features include optic disc edema (26.1% of the eyes), macular edema (30.4% of eyes), and neuro-retinitis (43.5% of eyes). Figure 1A showed typical macular edema in Patient 5. Other ocular findings included cornea epithelial defect (13% of eyes), complicated cataract (17.4% of eyes), vitreous opacity (82.6% of eyes), and retinal hemorrhage (26.1% of eyes).

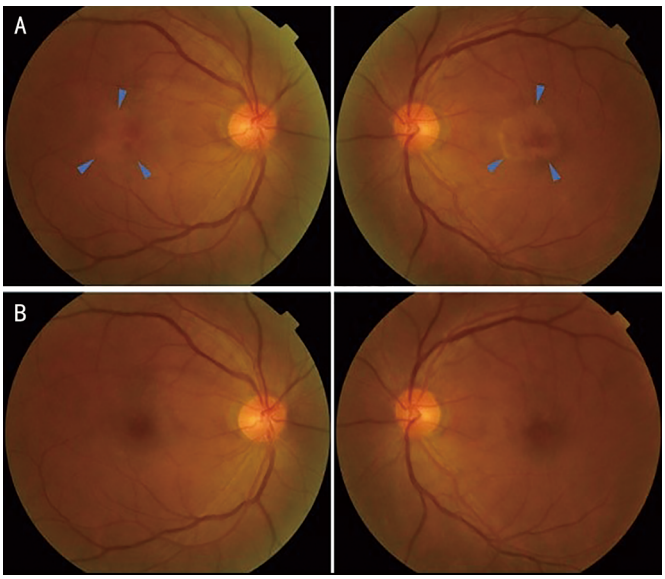

Figure 1 Fundus changes of Patient 5 with macular edema A: Bilateral macular edema before anti-syphilis treatment. Blue arrows indicated macular edema. B: Macular edema reduced after penicillin G intravenous and benzylpenicillin intramuscular treatment.

Macular and optic Spectral-domain optical coherence tomography was performed in 6 patients. Neuro-retina thickening were found in all 12 eyes (100%), irregular retinal pigment epithelium (RPE) in 12 eyes (100%), optic disc edema in 10 eyes (83.3%), subretinal fluid in 6 eyes (50%), and epiretinal membrane in 2 eyes (16.7%). Figure 2 revealed irregular RPE and subretinal fluid of Patient 1. FFA was performed in 2 patients. The features were optic disc hyper

Table 2 Clinical findings, laboratory findings, and treatment result of syphilitic uveitis in HIV-positive patients

Case	Presenting complaint	Duration	Blood RPR/TPPA	Cerebrospinal fluid RPR/TPPA	Intraocular fluid profile	Ocular preliminary diagnosis	Treatment	Initial BCVA	Final BCVA	Follow-up time
1	OU blurry vision	5mo	1:64/185.5	NA	NA	OU Intermediate-posterior uveitis	PNC+BPNC	0.4/0.08	0.6/0.25	3wk
2	OU shadow float, blurry vision, red eye	10mo	1:128/176.3	NA	NA	OU pan-uveitis	PNC+BPNC	0.02/0.08	0.02/0.4	2wk
3	OU blurry vision, OS red eye	1mo	1:128/214.6	1:4/64.52	NA	OU pan-uveitis	PNC	0.3/FC 10cm	1.0/0.3	3wk
4	OU blurry vision	20d	1:128/119	NA	NA	OU pan-uveitis	PNC+BPNC	0.5/0.4	0.6/0.6	2wk
5	OU blurry vision, visual field defect	1mo	1:128/268.9	-/0.99	NA	OD pan-uveitis, OS posterior uveitis	PNC+BPNC	0.04/0.04	0.4/0.4	2wk
6	OU blurry vision	4mo	1:128/214.9	NA	Aqueous humor: TP (IgG) 0.89 S/C.O., GWc 33.11	OU posterior uveitis	PNC+BPNC	0.08/0.06	0.15/0.15	2wk
7	OU blurry vision, shadow float	6mo	1:128/187.7	1:2/145.8	NA	OU anterior-intermediate uveitis	PNC+BPNC	0.4/0.3	0.8/0.6	3wk
8	OD blurry vision, red eye	2mo	1:128/216.5	1:1/31.87	NA	OD posterior uveitis	PFA, PNC+BPNC	0.5/1.0	1.0/1.0	3wk
9	OD blurry vision, ocular pain, headache	1mo	1:16/NA	NA	NA	OD anterior uveitis	PFA, ceftriaxone+BPNC	FC 50 cm/1.0	0.6/1.0	2wk
10	OU blurry vision, ocular pain	5d	1:1/NA	NA	Vitreous: TP (IgG) 15.3 S/C.O., GWc 26.09	OU pan-uveitis	PFA, PNC+BPNC	0.4/FC 10 cm	0.9/0.5	4wk
11	OU blurry vision	7d	1:16	-/86.41	NA	OU anterior-intermediate uveitis	PNC+BPNC+penicillin eye drop	0.5/0.5	0.8/0.8	3wk
12	OU blurry vision, red eye	12mo	1:128/173.3	1:8/273.6	NA	OU anterior uveitis, OD BRVO	PNC+BPNC	0.5/0.5	0.7/0.7	2wk

OD: Oculus dexter (right eye); OS: Oculus sinister (left eye); OU: Oculus uterque (both eyes); BCVA: Best-corrected visual acuity; TP: Treponema pallidum; GWc: Goldmann-Witmer coefficient; PFA: Trisodium phosphonoformate; BRVO: Branch retinal vein occlusion; FC: Finger counting; PNC: Penicillin G 6 million units intravenously every 6h for 14d; BPNC: Benzylpenicillin 2.4 million units intramuscularly once a week for 3-6wk.

Figure 2 Optical coherence tomography findings of Patient 1
Macular edema, subretinal fluid with structural disturbances in outer layer of the retina.

Table 3 Ocular findings before and after treatment *n* (%)

Parameters	Before treatment	After treatment
BCVA (23 eyes/12 patients)		
>0.4	5 (21.7)	14 (60.9)
0.1-0.4	7 (30.4)	7 (30.4)
LP-0.1	11 (47.8)	1 (4.3)
Cornea (23 eyes/12 patients)		
Epithelial defect	3 (13)	1 (4.3)
Edema	3 (13)	0
KP	12 (52.2)	5 (21.7)
Anterior chamber (23 eyes/12 patients)		
Flare	12 (52.2)	5 (21.7)
Cells	8 (34.8)	3 (13)
Iris (23 eyes/12 patients)		
Iridocyclitis or iritis	3 (13)	1 (4.3)
Lens (23 eyes/12 patients)		
Complicated cataract	4 (17.4)	4 (17.4)
Vitreous (23 eyes/12 patients)		
Opacity	19 (82.6)	13 (56.5)
Cells	4 (17.4)	5 (21.7)
Pigment	2 (8.7)	2 (8.7)
Fundus (23 eyes/12 patients)		
Optic disc edema	6 (26.1)	4 (17.4)
Macular edema	7 (30.4)	3 (13)
Retinal hemorrhage	6 (26.1)	3 (13)
Neuro-retinitis	10 (43.5)	4 (17.4)
Chorioretinitis or chorioretinal scars	13 (56.5)	4 (17.4)
Blurry	7 (30.4)	1 (4.3)
OCT (23 eyes/12 patients)		
Increased thickening of neurosensory retina	12 (100)	0
Epiretinal membrane	2 (16.7)	2 (16.7)
Irregular retinal pigment epithelium	12 (100)	12 (100)
Optic disc edema	10 (83.3)	9 (75)
Subretinal fluid	6 (50)	5 (41.7)
FFA (4 eyes/2 patients)		
Optic disc hyper fluorescence/leakage/staining	4 (100)	NA
Retinal vascular leakage/staining	3 (75)	NA
Retinal staining	4 (100)	NA
Macular edema	2 (50)	NA

BCVA: Best-corrected visual acuity; KP: Keratic precipitate; OCT: Optical coherence tomography; FFA: Fundus fluorescein angiography.

fluorescence/leakage/staining (4 eyes, 100%), retinal vascular leakage/staining (3 eyes, 75%), retinal staining (4 eyes, 100%),

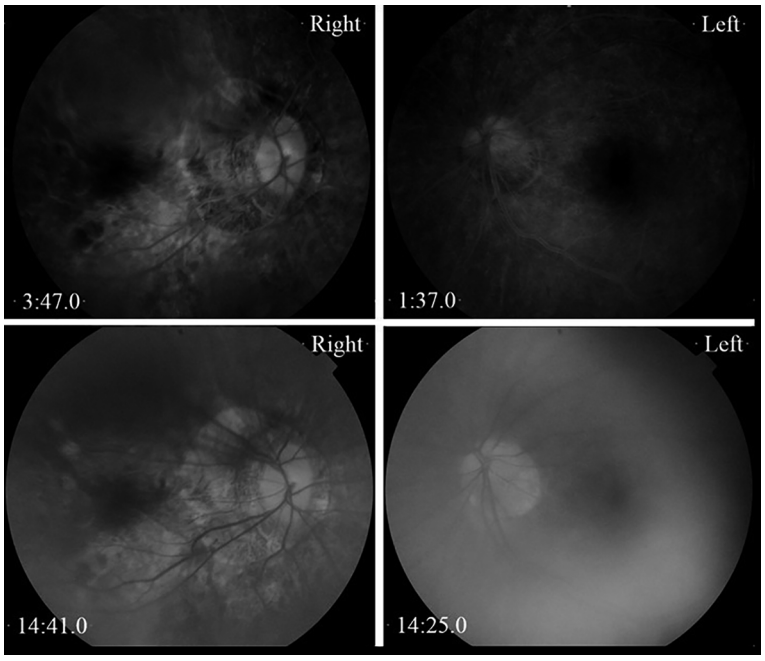

Figure 3 Fundus fluorescein angiography of Patient 2 Fluorescence leakage along the atrophic macula of right optic disc, non-perfusion area and transparent fluorescence on the temporal fundus, and fluorescence leakage in the later stage. The left retinal vein roughness, with punctate fluorescence leakage at posterior pole, and non-perfusion area on the temporal side of the macula.

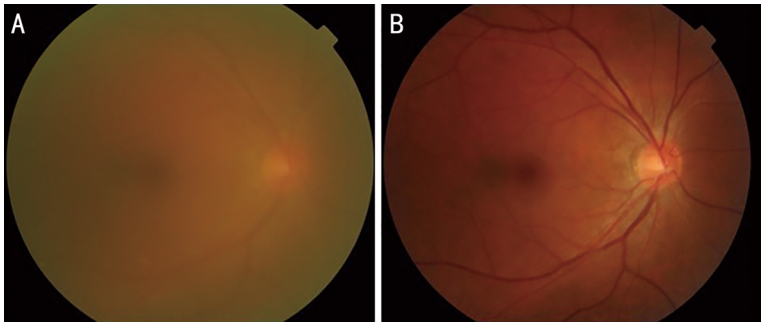

Figure 4 Fundus changes of Patient 8 with posterior uveitis A: Dense vitritis and blurred fundus after phosphonoformate antiviral therapy; B: Improvement of vitritis after switched to penicillin G intravenous follow by benzylpenicillin intramuscular treatment.

and macular edema (2 eyes, 50%). FFA result of Patient 2 showed optic disc fluorescence leakage, non-perfusion area, and retinal vascular leakage (Figure 3).

Laboratory Evaluation Eleven patients showed RPR and TPPA positive. Six patients had lumbar puncture (Table 2), and resulted with four positive RPR and five positive TPPA in cerebrospinal fluid. One patient (Patient 10) with negative RPR and TPPA, underwent vitreous cavity puncture, result with TP IgG 15.3 S/C.O. and Goldmann-Witmer coefficient (GWc) 26.09, which help to confirm the diagnose of syphilitic uveitis. Patient 6 underwent anterior chamber puncture, with TP IgG 0.89 S/C.O., GWc 33.11.

Treatment and Outcomes All patients continue with their appropriate anti-HIV treatment. After diagnosed syphilitic uveitis, seven patients (Patient 1, 2, 5, 6, 7, 11, and 12) were given penicillin G 6 million units IV every 6h for 14d, and then followed with benzylpenicillin 2.4 million units IM every week for 3 to 6wk. Patient 3 was treated with penicillin G IV only, due to benzylpenicillin allergic. Patient 9, who was allergic to penicillin G, took ceftriaxone IV following with benzylpenicillin IM. Patient 11 had long-acting penicillin treatment for syphilitic uveitis 7 months ago, but relapsed this time. Patient 12 adept penicillin G eye drop (5000 units/mL) to relieve syphilitic keratitis as well. Patient 8, 9 and 10 had phosphonoformate antiviral therapy first, but did not show obvious improvement or relieve. At this time, their treatment switched to penicillin G (ceftriaxone) IV follow by benzylpenicillin IM. In addition to anti-syphilis therapy, Patient 12 took blood circulation promoting and neurotrophic drugs to help with his chronic branch retinal vein occlusion (BRVO). Of all patients, the mean follow-up time was 3wk (2-4wk).

After 14d of penicillin G IV treatment, all cases displayed intraocular inflammation decreased (Figures 1, 4, and 5) and better visual acuity. The patient treated with ceftriaxone IV (Patient 10) showed a relief of uveitis and better visual acuity

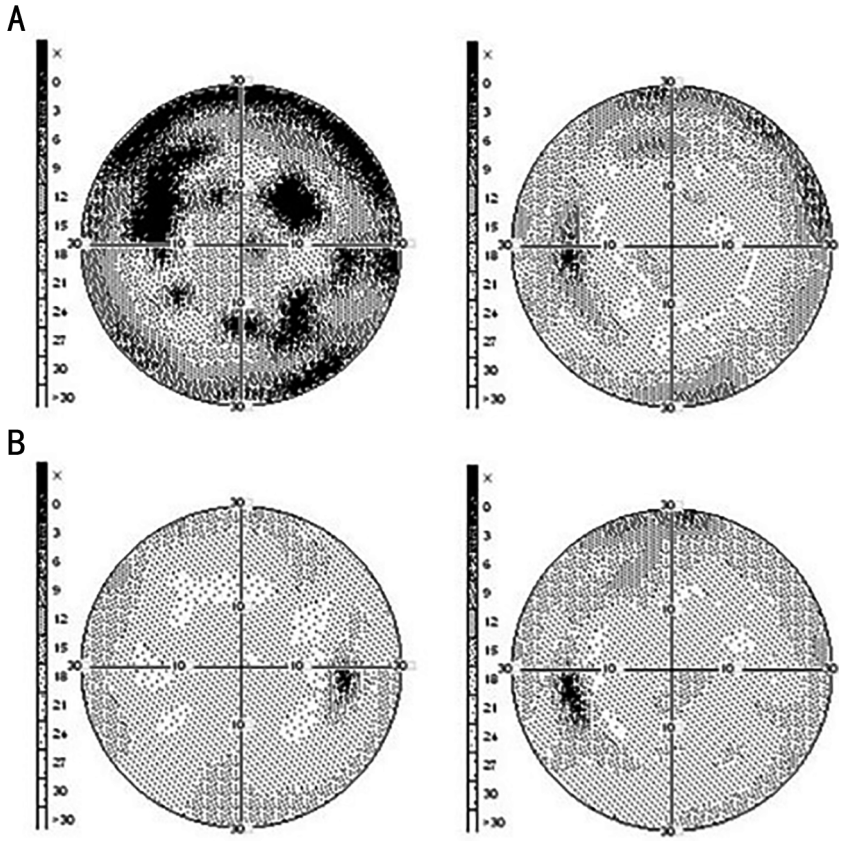

Figure 5 Visual field changes of Patient 7 with anterior-intermediate uveitis A: Visual sensitivity decline at presentation; B: Visual field recovered after penicillin G intravenous follow by benzylpenicillin intramuscular treatment.

as well. Of all 23 affected eyes, the proportion of eyes with 0.4 or better, worse than 0.4 but better than 0.1, and 0.1 or worse were 21.7%, 30.4%, and 47.8%. At the last visit, the proportion was 60.9%, 30.4%, and 4.3%, respectively. The 95.7% of the affected eyes had improved vision, 4.3% remained stable, and none of the eyes deteriorated. After treatment, the patients also showed resolution of cornea epithelial defect, anterior chamber flare or cells, vitreous opacity, optic disc edema, macular edema, and neuro-retinitis (Table 3).

Literature Review A total of 174 original records of HIV-positive patients with syphilitic uveitis were identified. Among them, one hundred and five patients have clear antibiotic treatment, vision outcomes and follow-up time record. These cases were described in 9 retrospective studies (62 patients, 107 eyes) and 35 case reports (43 patients, 78 eyes).

Seventy-nine eyes of 46 patients were presented as posterior uveitis (42.7%). Other presentations include pan-uveitis in 65 eyes of 39 patients (35.1%), anterior/intermediate uveitis in 29 eyes of 19 patients (15.7%) and unclassified uveitis in 12 eyes of 7 patients (6.5%). In terms of uveitis subtype, initial BCVA, or final BCVA, there was no significant difference between the CD4 cell count more than 200 cells/μL group and the group with less than 200 cells/L. Initial BCVA, but not final BCVA, of patients with serum RPR titer lower than 1:64 was significantly better than patients with RPR titer higher than 1:64 group (P=0.013). After antibiotic treatment, higher RPR titer group showed more BCVA improvements than lower RPR titer group (P=0.026; Table 4).

The patients received various treatment strategies. Most patients treated by neurosyphilis regimen with intravenous penicillin for at least 10d (46.7%, n=49) or daily intramuscular penicillin injections for the same time (9.5%, n=10). The patients' treatment outcomes were recorded, but their follow-up periods varied. Ten patients (9.5%) were followed for less than a month, 54 patients (51.4%) were followed for one to six months, 20 patients (19%) were followed for six months to one year, and 21 patients (20%) were followed for more than a year.

Among all treatment groups, PNC group had largest patient number and longest follow-up period. Visual acuity improved in 76.4% of eyes after PNC treatment, remained stable in 15.7% eyes, and decreased in 7.9%. After receiving PNC, CRO, or PNC+BPNC treatment, the final BCVA significantly improved (P<0.001, P=0.004, P=0.005 respectively). But BCVA of BPNC group did not show significantly improved (P=0.084). Details of antibiotic treatments and their outcomes were summarized in Table 5.

DISCUSSION

Ocular Syphilis and Diagnosis Recent years, ocular syphilis incidence rate is increasing[4,12]. It may be the only present of

Table 4 Anatomical classification, vision outcomes before and after treatment according to CD4 cell count and RPR titer in 44 published studies

Parameters	Anatomical classification (eyes)				BCVA (ETDRS), mean±SD (95%CI)		
	Pos.	Pan.	An./In.	Un.	Initial	Final	Improvement
CD4 count (cells/μL)							
≥200 (92 eyes/54 patients)	52	26	8	4	48.2±31.4 (41.7, 54.8)	73.2±18.1 (69.4, 76.9)	24.9±28.2
<200 (44 eyes/26 patients)	16	21	5	2	43.2±31.1 (33.8, 52.7)	66.9±24.5 (59.4, 74.3)	23.6±27.1
P					0.305	0.235	0.922
Serum RPR titer							
≤1:64 (16 eyes/9 patients)	11	3	0	2	61.2±27.6 (46.6, 75.9)	71.4±13.1 (64.5, 78.4)	10.2±20.1
>1:64 (66 eyes/40 patients)	24	31	10	1	40.8±31.1 (33.1, 48.4)	68.7±20.9 (63.6, 73.8)	27.9±21.9
P					0.013	0.785	0.026

RPR: Rapid plasma regain; BCVA: Best-corrected visual acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; SD: Standard deviation; CI: Confidence interval; Pos.: Posterior uveitis; Pan.: Pan-uveitis; An./In.: Anterior/intermediate uveitis; Un.: Unclassified uveitis.

Table 5 Vision outcomes before and after different antibiotic treatment in 44 published studies

Antibiotic groups	Follow-up time (d)		Initial BCVA (ETDRS)		Final BCVA (ETDRS)		*P*
	Mean±SD	Range	Mean±SD	95%CI	Mean±SD	95%CI	
PNC (127 eyes/72 patients)	316.0±543.8	3271.0	44.0±32.0	38.4, 49.7	70.3±21.8	66.5, 74.1	<0.001
CRO (13 eyes/9 patients)	44.7±50.9	159.0	58.6±25.5	43.2, 74.1	81.3±4.4	78.7, 84.0	0.004
PNC+BPNC (18 eyes/10 patients)	259.0±244.7	690.0	43.7±40.7	23.4, 63.9	65.3±27.3	51.7, 78.8	0.005
BPNC (7 eyes/4 patients)	62.0±25.9	62.0	48.6±39.1	12.4, 84.8	79.3±4.2	75.4, 83.1	0.084

BCVA: Best-corrected visual acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; PNC: Penicillin; CRO: Ceftriaxone; BPNC: Benzathine penicillin; SD: Standard deviation; CI: Confidence interval.

system syphilis, and can occur six weeks or many years after transmission[2]. Except eyelid and conjunctiva involvement, ocular syphilis is uncommon in the first stage. Ocular manifestations like keratitis, iris nodules, iridocyclitis, and scleritis may occur in the second stage.

In ocular inflammation patient, syphilis should be considered when making a diagnosis[13]. Serological tests, such as specific treponema tests like fluorescent treponema antibody absorption test or TPPA, as well as nonspecific tests like venereal disease research laboratory (VDRL) tests and RPR, should be taken as part of the diagnostic process. RPR cannot be used as the only test because it may become negative with prolonged infection[14]. If necessary, an additional investigation such as TPPA should be considered. Screening by RPR test will miss 11% of ocular syphilis patients. Therefore, for patients suspected of syphilitic uveitis, a specific TP test needs to be used for screening[15].

High serum RPR titer is related to severe uveitis and poor vision. After treatment with antibacterial drugs, the RPR titer can decrease or even turn negative, which can be used to evaluate the therapeutic effect of antibacterial treatment. As optic nerve is a continuation of the central nervous system, ocular syphilis may be a result of spread of neurosyphilis. High rate of cerebrospinal fluid abnormal was found in patients with syphilitic uveitis[16]. For ocular syphilis patients, lumbar puncture cerebrospinal fluid examination should be considered for help diagnose neurosyphilis[17].

Aqueous humor and vitreous fluid analysis is also important for the diagnosis of syphilitic uveitis, especially for those with highly suspected clinical symptoms while with negative RPR and TPPA[2]. In our study, one patient confirmed the diagnose of syphilitic uveitis through vitreous fluid test. The GWc is the ratio of specific IgG levels in ocular fluid and serum of a specific pathogen, which currently commonly used in diagnosis of infectious uveitis. In our series, two patients underwent intraocular fluid test and showed GWc positive.

Clinical Manifestations of Ocular Syphilis Ocular syphilis can occur in one or both eyes, with pan-uveitis and posterior uveitis are the most common manifestations[18]. Optic neuropathy, interstitial keratitis, anterior uveitis, retinal vasculitis, and syphilitic meningitis are additional manifestations.

The incidence of syphilis infection in the anterior segment is relatively low, and can be manifested as superficial scleritis, scleritis, scleral keratitis, and iridocyclitis. Simple anterior uveitis is relatively rare, while total uveitis with anterior uveitis inflammation is more common. The clinical manifestations of anterior segment inflammation caused by syphilis are redness, eye pain, and diminished visual acuity. Conjunctival and limbal congestion, anterior chamber inflammatory cells, and anterior chamber flicker are the physical symptoms. In severe cases, posterior iris adhesion and anterior chamber pus can occur[19]. Intermediate uveitis caused by syphilis is also rare, and may manifest as peripheral retinal vasculitis[20].

Posterior uveoretinal involvement is the most common form of syphilitic uveitis, which can manifest as simple posterior uveitis or pan-uveitis. It can be manifested as choroiditis, diffuse or multifocal chorioretinitis, retinitis, retinal vasculitis, RPE inflammation, optic discitis, and neuroretinitis[21]. Neuroretinitis with vitreous opacity is the main type of uveitis in patients with a shorter course of disease, and diffuse chorioretinitis is the most common type of uveitis in patients with a longer course of disease. Common complications include vitreous opacity, retinal hemorrhage, retinal vascular occlusion, retinal detachment, proliferative vitreoretinopathy, retinal surface deposits, yellow-white nodular changes in the retina, rigid exudation of the retina, optic nerve atrophy, cystoid macular edema, and anterior macular membrane[22]. Among them, retinal surface deposits are characteristic manifestations that contribute to the rapid diagnosis of syphilitic uveitis[23]. In our series, posterior and pan-uveitis were 69.6%, and mainly showed as chorioretinitis, neuro-retinitis and macular edema.

The typical manifestation of chorioretinitis is a grayish yellow lesion in the posterior pole and middle circumference, which is initially small, about 1/2 to 1 optic papilla diameter, but can fuse into a larger lesion, accompanied by retinal vasculitis, optic papilla edema, and serous retinal detachment[24]. Retinal vasculitis caused by syphilis can involve retinal arteries, arterioles, capillaries, and veins[25]. FFA shows vascular wall staining, leakage, and vascular obstruction; Focal retinal vasculitis can manifest as BRVO. In our series, one patient (Patient 12) had BRVO in his right eye. Syphilis can also be manifested as middle and peripheral necrotizing retinitis, which can fuse with vasculitis and vascular obstruction, similar to acute retinal necrosis, but progress is relatively slow, and treatment with penicillin is expected to have a good visual outcome.

Ocular Syphilis Coinfect with HIV HIV co-infection is strong related to syphilitic uveitis. HIV-positive patients now have a longer life expectancy due to HAART therapy. With the shift in perception of AIDS as a disease that can be controlled and the rise in unprotected sex, the global incidence rate of syphilis has increased. This is especially in homosexual men with HIV. Before developing ocular syphilis, all 12 patients in our study were HIV positive. Among them, six (50.0%) were homosexual, three (25%) had extramarital sex, and two (16.7%) had blood transfusion. This emphasized the likelihood of co-infection with sexually and blood transmitted diseases. In HIV infected patients the present of ocular syphilis might be 10% higher[26].

By altering the immune response to TP, HIV can change the natural progress of syphilis, and increase the risk of neurosyphilis and ocular syphilis, shown as an increased risk of abnormalities in cerebrospinal fluid testing[8]. This type of patient is prone to bilateral morbidity, rapid progression, more complications, and higher risk of disease recurrence. In our series, of all twelve patients, eleven had ocular syphilis in both eyes. Taking HAART has little effect on the epidemiology and clinical manifestation of ocular syphilis[27]. Syphilitic uveitis were more likely to show as posterior uveitis or pan-uveitis in HIV-positive patients[28-30]. Necrotizing retinitis, posterior squamous chorioretinitis, serous retinal detachment may occur. HIV infection making the diagnosis of syphilis uveitis more difficult[9]. AIDS and other comorbidities that are related to fundus lesions must be excluded. Sometimes, it is hard to determine whether the uveitis is caused by AIDS or syphilis. Eye changes of AIDS mostly happen in the posterior segment of eye, including AIDS retinopathy, opportunistic infection, rare tumors, and neuro-ophthalmic diseases. Among them, retinal microvascular disease is the most common ocular symptom of AIDS, with the main manifestations of retinal soft exudates or hemorrhage. In our study, AIDS related fundus diseases were excluded. In the case series, four patients had tuberculosis history, and three had hepatitis B virus infection before. These indicated that HIV-positive patients should be carefully diagnosed with syphilitic uveitis. The treatment effect also reflects the correct direction of diagnosis. Medical history, symptoms, examinations, laboratory tests and treatment effects should be considered together. A positive effect of anti-syphilis treatment may also verify the diagnosis.

Antibiotic Treatment Syphilis is a curable disease. Early diagnosis and correct treatment are crucial. For ocular syphilis with active clinical manifestations, antibiotic treatment should be carried out according to the neurosyphilis treatment plan, with penicillin G being the first choice. A drop of more than four times of the non-syphilitic spirochete test titer is considered a response to treatment.

In HIV positive patients, syphilis is related with higher plasma HIV viral load and lower CD4 cell counts. Therefore, treatment of syphilis is important for helping control the HIV infection. Penicillin is the main treatment for syphilis of HIV-positive patients[11]. After receiving penicillin, no clinical relapse was observed in a large randomized study[31]. Tetracyclines, cephalosporins, or macrolides are options if patients were allergic to penicillin. Neurosyphilis is more common in HIV-positive individuals[26-27], which can happen even after penicillin treatment. The treatment strategy for neurosyphilis should be chosen at this point, with intravenous injections of 18-24 million units of penicillin per day. The suggested treatment for ocular syphilis depends on a neurosyphilis routine, even with a negative cerebrospinal fluid test, as aqueous penicillin G 3 to 4 million units IV 6 times a day for 10 to 14d, then followed by 2.4 million units of benzylpenicillin IM each week for 3 to 6wk[32]. Penicillin G benzathine treatment cannot

completely control the progression of syphilis in HIV infected patients, and may develop to neurosyphilis[33]. Additionally, the literature review reveals that PNC, CRO, or PNC+BPNC treatment can significantly improve BCVA. However, vision may not be significantly improved by BPNC alone.

The results of our series supported the guidelines of ocular syphilis treatment. Most patients were cured after appropriate penicillin treatment. For those who took antiviral therapy or long-acting penicillin first, but did not show much improvement or relapse, when switched to penicillin G IV follow by benzylpenicillin IM regimen, they all showed an improved BCVA after treatment. In our case series, all cases treated with IV penicillin G or ceftriaxone showed either reduction or resolution of uveitis. Aqueous penicillin G regimen is more effective than long-acting penicillin for neurosyphilis in patients with HIV. Patient HIV status or CD4 count did not influence the treatment response.

Our study supported the neurosyphilis regimen for ocular syphilis in HIV infected patients. After appropriate penicillin treatment, most patients recovered. For those who took antiviral therapy or long-acting penicillin first, but did not show much improvement or relapse, when switched to penicillin G IV follow by benzylpenicillin IM regimen, they all showed an improved BCVA after treatment. In our case series, all cases treated with IV penicillin G or ceftriaxone demonstrated either reduction or resolution of their uveitis. In HIV-positive patients, the aqueous penicillin G regimen is more effective than long-acting penicillin for neurosyphilis. The patient's HIV status or CD4 count did not appear to affect treatment outcomes. It also supported by literature review that CD4 cell counts did not affect syphilis uveitis subtype and BCVA before or after treatment. Even though HIV co-infection could lead to a more severe ocular symptom, our series demonstrated that aggressive treatment can still get an excellent prognosis and most patients remain good visual acuity. These finding were consistent with other series[30,34-36].

Patients with ocular syphilis might encounter treatment failure. There are instances of recurrent or persistent infection in HIV-positive patients even after appropriate antibiotic treatment[37]. In order to detect recurrence or reinfection, continue monitoring after treatment is necessary. Although there has been no recurrence and improved vision in our case series due to the short time of follow-up, the long-term prognosis must be taken to caution. Our case series have limitations due to its retrospective design, including non-standardized collection of data, variable duration of follow-up, and assessments performed at different intervals. The sample size was relatively small; thus, selection bias may have been present. Despite this, the study's findings still contribute to better understanding of treatment for HIV-positive syphilitic uveitis patients.

In conclusion, we described the clinical features of ocular syphilis in HIV-positive patients. For ocular syphilis, neurosyphilis intravenous penicillin regimen is required following diagnosis, and it improved the visual prognosis. Literature review indicated that higher serum RPR titer may correlated with sever uveitis and poor vision. PNC, CRO, or PNC+BPNC treatment, but not BPNC alone, could significantly increase BCVA in HIV-positive patients. Because HIV-positive patients may relapse despite penicillin treatment, long-term follow-up is important. For those who relapse after long-acting penicillin treatment, still can benefit from penicillin G IV follow by benzylpenicillin IM regimen. These clinical manifestations, serological features, and treatment outcomes data may help better understanding and treatment of ocular syphilis patients coinfect with HIV.

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REFERENCES

1 Dutta Majumder P, Chen EJ, Shah J, Ching Wen Ho D, Biswas J, Yin LS, Gupta V, Pavesio C, Agrawal R. Ocular syphilis: an update. *Ocul Immunol Inflamm* 2019;27(1):117-125.

2 Tsan GL, Claiborne RT. Ocular syphilis. *Clin Exp Optom* 2021;104(7): 756-759.

3 Tsuboi M, Nishijima T, Yashiro S, Teruya K, Kikuchi Y, Katai N, Oka S, Gatanaga H. Prognosis of ocular syphilis in patients infected with HIV in the antiretroviral therapy era. *Sex Transm Infect* 2016;92(8):605-610.

4 Fonollosa A, Martinez-Indart L, Artaraz J, *et al*. Clinical manifestations and outcomes of syphilis-associated uveitis in northern Spain. *Ocul Immunol Inflamm* 2016;24(2):147-152.

5 Ramchandani MS, Cannon CA, Marra CM. Syphilis: a modern resurgence. *Infect Dis Clin North Am* 2023;37(2):195-222.

6 Wu LZ, Orlowski TM, Karunatilake M, Lee S, Mondal P, Kogilwaimath S, Bursztyn LLCD. Prognostic effect of HIV on visual acuity in ocular syphilis: a systematic review. *Eye (Lond)* 2023. Epub ahead of print.

7 Nurfahzura MJ, Hanizasurana H, Zunaina E, Adil H. Successful treatment of syphilitic uveitis in HIV-positive patients. *Clin Ophthalmol* 2013;7:1651-1654.

8 Lee SY, Cheng V, Rodger D, Rao N. Clinical and laboratory characteristics of ocular syphilis: a new face in the era of HIV co-infection. *J Ophthalmic Inflamm Infect* 2015;5(1):56.

9 Yang M, Kamoi K, Zong Y, Zhang J, Ohno-Matsui K. Human immunodeficiency virus and uveitis. *Viruses* 2023;15(2):444.

10 Sood AB, Pearce WA, Workowski KA, Lockwood J, Yeh S. Combined intravitreal and systemic antibiotic therapy in a patient with syphilitic

uveitis. *Ocul Immunol Inflamm* 2019;27(1):131-133.

11 Green MB, Agranat JS, Davoudi S, Sanayei N, Ness S. Penicillin responsive presumed seronegative ocular syphilis in a patient with human immunodeficiency virus: a case report and review of the literature. *Ocul Immunol Inflamm* 2023:1-8.

12 Oliver SE, Aubin M, Atwell L, *et al*. Ocular syphilis——eight jurisdictions, United States, 2014-2015. *MMWR Morb Mortal Wkly Rep* 2016;65(43):1185-1188.

13 Ly V, Elhusseiny AM, Sallam AB. Syphilis-related ocular inflammation in HIV-positive and HIV-negative patients. *Ocul Immunol Inflamm* 2023;31(5):1035-1040.

14 Motlagh MN, Javid CG. Presentation of ocular syphilis in a HIV-positive patient with false-negative serologic screening. *Case Rep Infect Dis* 2019;2019: 8191724.

15 Nair N, Sudharshan S, Anand AR, Biswas J, Therese KL. Utility of treponemal testing from aqueous fluid in the diagnosis of ocular syphilis in patients with HIV/AIDS. *Ocul Immunol Inflamm* 2022;30(2):444-450.

16 Kesserwani H. De complexifying serum and cerebrospinal fluid (CSF) serologic testing of neurosyphilis: a case report of ocular syphilis and highlights of the principles of serologic testing. *Cureus* 2020;12(11):e11533.

17 Bazewicz M, Lhoir S, Makhoul D, Libois A, Van den Wijngaert S, Caspers L, Willermain F. Neurosyphilis cerebrospinal fluid findings in patients with ocular syphilis. *Ocul Immunol Inflamm* 2021;29(1):95-101.

18 Moradi A, Salek S, Daniel E, *et al*. Clinical features and incidence rates of ocular complications in patients with ocular syphilis. *Am J Ophthalmol* 2015;159(2):334-343.e1.

19 Yap SC, Tan YL, Chio MT, Teoh SC. Syphilitic uveitis in a Singaporean population. *Ocul Immunol Inflamm* 2014;22(1):9-14.

20 Sahin O, Ziaei A. Clinical and laboratory characteristics of ocular syphilis, co-infection, and therapy response. *Clin Ophthalmol* 2015;10:13-28.

21 Weng CY, Albini TA. Syphilitic posterior uveitis. *JAMA Ophthalmol* 2015;133(4):e144630.

22 Park JH, Joe SG, Yoon YH. Delayed diagnosis of ocular syphilis that manifested as retinal vasculitis and acute posterior multifocal placoid epitheliopathy. *Indian J Ophthalmol* 2013;61(11):676-678.

23 Browning DJ. Posterior segment manifestations of active ocular syphilis, their response to a neurosyphilis regimen of penicillin therapy, and the influence of human immunodeficiency virus status on response. *Ophthalmology* 2000;107(11):2015-2023.

24 Kelgaonkar A, Patel A, Tyagi M, Padhi TR, Basu S, McCluskey P. Beaded Pearls Appearance in Syphilitic Chorioretinitis. *Ocul Immunol Inflamm* 2023:1-5. Epub ahead of print.

25 Kaburaki T, Fukunaga H, Tanaka R, *et al*. Retinal vascular inflammatory and occlusive changes in infectious and non-infectious uveitis. *Jpn J Ophthalmol* 2020;64(2):150-159.

26 Chen C, Du KF, Xie LY, Jiang TY, Kong WJ, Dong HW, Guo CG, Li XN, Wei WB. Clinical features of ocular pathology in patients with acquired immunodeficiency syndrome and syphilis. *Adv Ther* 2021;38(6):3362-3372.

27 Kunkel J, Schürmann D, Pleyer U, Rüther K, Kneifel C, Krause L, Reichert M, Ignatius R, Schneider T. Ocular syphilis–indicator of previously unknown HIV-infection. *J Infect* 2009;58(1):32-36.

28 Schlaen A, Aquino MP, Ormaechea MS, Couto C, Saravia M. Spectral optical coherence tomography findings in an adult patient with syphilitic bilateral posterior uveitis and unilateral punctate inner retinitis. *Am J Ophthalmol Case Rep* 2019;15:100489.

29 Dutta Majumder P, Mayilvakanam L, Palker AH, Sridharan S, Biswas J. Intravitreal sustained-release dexamethasone implant for the treatment of persistent cystoid macular edema in ocular syphilis. *Indian J Ophthalmol* 2019;67(9):1487-1490.

30 Mohd Fadzil NI, Abd Hamid A, Muhammed J, Hashim H. Ocular syphilis: our experience in Selayang Hospital, Malaysia. *Cureus* 2022;14(7):e26655.

31 Rolfs RT, Joesoef MR, Hendershot EF, *et al*. A randomized trial of enhanced therapy for early syphilis in patients with and without human immunodeficiency virus infection. The Syphilis and HIV Study Group. *N Engl J Med* 1997;337(5):307-314.

32 Tuddenham S, Ghanem KG. Management of adult syphilis: key questions to inform the 2021 centers for disease control and prevention sexually transmitted infections treatment guidelines. *Clin Infect Dis* 2022;74(Suppl_2):S127-S133.

33 Antonio MB, Cuba GT, Vasconcelos RP, *et al*. Natural experiment of syphilis treatment with doxycycline or benzathine penicillin in HIV-infected patients. *AIDS* 2019;33(1):77-81.

34 Hughes EH, Guzowski M, Simunovic MP, Hunyor AP, McCluskey P. Syphilitic retinitis and uveitis in HIV-positive adults. *Clin Exp Ophthalmol* 2010;38(9):851-856.

35 Pipitò L, Medaglia AA, Trizzino M, Bonura S, Gioè C, Di Carlo P, Colomba C, Cascio A. A case of syphilis associated with immune reconstitution inflammatory syndrome and review of the literature. *AIDS Res Ther* 2023;20(1):28.

36 Vadboncoeur J, Labbé AC, Fortin C, Serhir B, Rabia Y, Najem K, Jaworski L, Aubin MJ. Ocular syphilis: case series (2000–2015) from 2 tertiary care centres in Montreal, Canada. *Can J Ophthalmol* 2020;55(1):30-37.

37 Tran TH, Cassoux N, Bodaghi B, Fardeau C, Caumes E, Lehoang P. Syphilitic uveitis in patients infected with human immunodeficiency virus. *Graefes Arch Clin Exp Ophthalmol* 2005;243(9):863-869.