

ORIGINAL ARTICLE

Etiological Paradigm Shift, Sentinel Ocular Presentations, and Visual Recovery Dynamics in HIV-Associated Uveitis: A Retrospective Cohort Study at an Academic Referral Center in West Sumatra, Indonesia

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ABSTRACT

Background: Uveitis frequently serves as the critical sentinel clinical manifestation unmasking occult Human Immunodeficiency Virus (HIV) infection. In the contemporary combination antiretroviral therapy (cART) era, shifting epidemiology has transformed opportunistic intraocular infections.

Objective: To evaluate the sociodemographic profile, CD4+ immunological status, anatomical phenotypes (SUN criteria), infectious etiologies, and visual acuity outcomes in HIV-infected patients presenting with active uveitis.

Methods: A retrospective cohort study was conducted at Universitas Andalas Hospital, Padang, Indonesia (February 2023–August 2026), reviewing consecutive HIV patients presenting with active uveitis. Ophthalmic assessments included best-corrected visual acuity (LogMAR), slit-lamp biomicroscopy, funduscopy, ultrasonography, and serology. Visual changes post-targeted therapy were analyzed using the Wilcoxon signed-rank test.

Result: Seventeen patients (34 eyes) were enrolled, demonstrating striking male predominance (94.1%) with a mean age of 33.1 ± 7.6 years. Crucially, 82.4% ($n = 14$) were newly diagnosed with HIV at ocular presentation. Panuveitis was the predominant phenotype (70.6%), presenting bilaterally in 52.9%. Ocular syphilis (*Treponema pallidum*) emerged as the leading etiology (82.4%), followed by cytomegalovirus retinitis (11.8%). Post-therapy, the legal blindness rate ($< 20/400$) halved from 35.3% to 17.6%. Mean visual acuity improved from LogMAR 1.00 ± 0.91 to 0.74 ± 0.87 ($p = 0.055$). Overall, 41.2% of eyes improved, 50.0% remained stable, and 8.8% deteriorated due to irreversible macular scarring.

Conclusion: Severe uveitis, particularly syphilitic panuveitis, represents an indispensable sentinel marker for occult HIV in young males. Routine reflex dual-screening for HIV and syphilis is strongly recommended in atypical uveitis, as prompt targeted therapy achieves substantial functional visual salvage.

1. Introduction

Human Immunodeficiency Virus (HIV) infection represents one of the most formidable and transformative public health challenges of the modern era, having claimed over forty million lives globally and continuing to affect approximately thirty-nine million people worldwide.^{1,2} The hallmark immunopathological consequence of chronic HIV replication is the selective, progressive depletion of CD4+ T-helper lymphocytes, mediated by viral gp120/gp41 envelope binding to host CD4 receptors and coreceptors CCR5 and CXCR4.² This profound cellular immune exhaustion disrupts cytokine signaling cascades, abolishes interleukin-2 (IL-2) and interferon-gamma (IFN- γ) synthesis, and paralyzes cell-mediated immunity.^{2,3} Consequently, the host enters a state of severe immunodeficiency that dramatically heightens vulnerability to opportunistic bacterial, fungal, parasitic, and viral pathogens.^{3,4} In the visual system, ocular complications occur in fifty to seventy percent of all people living with HIV (PLWH) at some point during their disease trajectory, imposing a staggering burden of visual disability, structural ocular destruction, and irreversible blindness.^{4,5}

Historically, during the initial decades of the HIV pandemic prior to the advent of effective antiretroviral therapy, the ophthalmic clinical landscape was overwhelmingly dominated by opportunistic viral necrotizing retinitis, most notably cytomegalovirus (CMV) retinitis.^{4,5} Cytomegalovirus, an ubiquitous beta-herpesvirus, typically reactivated when peripheral blood CD4+ T-cell counts plummeted below 50 cells/ μ L, inducing full-thickness hemorrhagic and edematous

retinal necrosis classically described as a 'pizza-pie' or 'brushfire' fundus pattern.^{4,5} In that pre-antiretroviral era, CMV retinitis afflicted up to thirty to forty percent of AIDS patients, frequently culminating in catastrophic rhegmatogenous retinal detachments and permanent bilateral blindness.^{4,6} However, the introduction and widespread global rollout of combination antiretroviral therapy (cART)—initially termed highly active antiretroviral therapy (HAART)—has fundamentally revolutionized the systemic prognosis and longevity of PLWH.^{6,7} By suppressing plasma viral replication below the limits of standard clinical detection and enabling robust quantitative and qualitative reconstitution of CD4+ T-cell populations, cART has precipitated an eighty to ninety percent decline in the incidence of classical opportunist viral retinitis across developed nations.^{6,7}

Nevertheless, rather than eliminating ocular morbidity entirely, the contemporary cART era has witnessed a profound and complex epidemiological and etiologic paradigm shift in the presentation of HIV-associated uveitis.^{6,7} While opportunistic viral retinitis in deeply immunosuppressed individuals has become less frequent, the worldwide re-emergence of sexually transmitted infections (STIs)—most prominently syphilis, caused by the spirochete *Treponema pallidum*—has driven a striking resurgence of ocular syphilis among PLWH.^{8,9} Syphilis and HIV exhibit a well-documented reciprocal syndemic interaction.^{8,9} Genital and mucosal syphilitic chancres disrupt physical epithelial barriers and recruit dense inflammatory infiltrates rich in CD4+ target cells, thereby augmenting HIV transmission and acquisition risk by two- to five-fold.^{8,9} Conversely, underlying

HIV-induced immune dysregulation significantly modifies the natural history of treponemal infection, promoting rapid spirochetal dissemination into immune-privileged biological sanctuaries, accelerating early central nervous system neuroinvasion, and fostering aggressive, atypical, and destructive intraocular inflammation.^{8,9}

Treponema pallidum is historically renowned among clinicians as 'the great imitator' (lues venerea) due to its extraordinary capacity to mimic virtually every known non-infectious autoimmune and infectious intraocular inflammatory disorder.^{10,11} Because *T. pallidum* invades the cerebrospinal fluid and the uveal tract during the primary and secondary stages of infection, ocular syphilis is formally categorized as a specialized clinical subset of neurosyphilis.^{11,12} The spirochete possesses endoflagellar periplasmic motility that facilitates rapid transmigration through endothelial tight junctions and basement membranes, establishing active infection within the anterior chamber, vitreous humor, choriocapillaris, and neurosensory retina.^{12,13} In patients with concurrent HIV infection, the clinical phenotype of syphilitic uveitis is markedly shifted toward aggressive panuveitis, multifocal chorioretinitis, occlusive retinal vasculitis, optic neuropathy, and acute syphilitic posterior placoid chorioretinitis (ASPPC).^{9,12} Such extensive, destructive posterior pole involvement frequently engenders severe visual acuity impairment at initial presentation, placing patients at imminent risk of permanent blindness if accurate microbiological identification and targeted treponemical therapy are delayed.^{11,13}

In addition to the re-emerging threat of ocular syphilis, clinical practice in tropical developing nations is further complicated by high regional endemicity for other intraocular pathogens, such as *Mycobacterium tuberculosis* (ocular tuberculosis) and *Toxoplasma gondii*, which present formidable diagnostic differentials in immunocompromised hosts.^{12,14} Differentiating between spirochetal, viral, and mycobacterial etiologies is of paramount clinical importance because the indiscriminate administration of high-dose systemic corticosteroid monotherapy—frequently prescribed empirically for presumed autoimmune uveitis—can trigger explosive, catastrophic pathogen replication, irreversible neuroretinal necrosis, and rapid bilateral visual loss in the setting of untreated ocular infection.^{11,13} Standardized diagnostic classification, exemplified by the Standardization of Uveitis Nomenclature (SUN) Working Group criteria, provides an essential anatomical framework to systematically localize intraocular inflammation into anterior, intermediate, posterior, and panuveitis categories, thereby refining diagnostic algorithms and prognostic stratification.^{1,10}

A particularly alarming phenomenon frequently encountered in contemporary clinical practice is that severe intraocular inflammation increasingly serves as the primary sentinel manifestation that unmasks an occult, previously unsuspected HIV infection in young, otherwise healthy individuals.^{5,15} Due to the lingering societal stigma, fear of discrimination, and absence of routine voluntary counseling and testing in general outpatient settings, a substantial proportion of HIV-infected individuals remain completely unaware of their serostatus until an acute, vision-threatening ocular complication compels them to seek specialized tertiary ophthalmic consultation.^{5,15} In this vulnerable subset of patients, delayed clinical recognition, diagnostic misclassification, and fragmented referral pathways between ophthalmology and infectious disease services can prolong diagnostic latency, permitting ongoing structural foveal and photoreceptor destruction.^{15,16}

Despite the critical clinical and epidemiological importance of HIV-associated ocular disease, empirical data detailing the demographic characteristics, immunological status, etiological spectrum, and treatment outcomes in Indonesia remain remarkably limited.^{17,18} The existing national literature is predominantly derived from single-center tertiary hospitals

situated within the metropolitan island of Java, creating a pronounced geographical knowledge gap regarding outer-island provinces where socioeconomic barriers, healthcare infrastructure, and diagnostic laboratory capacities differ substantially.^{17,18} West Sumatra, with its capital Padang, represents a major demographic and cultural hub in western Indonesia. Universitas Andalas Hospital (Rumah Sakit Universitas Andalas) functions as a premier academic referral center in West Sumatra, coordinating specialized ophthalmic and tertiary infectious disease services for a wide regional catchment population. However, no rigorous investigations have systematically evaluated the clinical spectrum and functional visual trajectories of HIV-associated uveitis in this clinical setting.

The core scientific novelty of the present investigation lies in establishing the first comprehensive epidemiological, immunological, and visual outcome profile of HIV-associated uveitis in a major tertiary academic referral center in West Sumatra, elucidating a decisive etiological paradigm shift toward ocular syphilis in the modern cART era and capturing the vital role of panuveitis as an unmasking sentinel sign of occult retroviral disease. To address this urgent regional and global health priority, the primary aim of this study was to delineate the baseline demographic parameters, CD4+ T-cell immunological strata, anatomical classification patterns based on SUN criteria, confirmed infectious etiologies, and therapeutic visual acuity changes on the LogMAR scale among consecutive HIV-infected patients managed at Universitas Andalas Hospital. By identifying independent clinical predictors of functional visual recovery and evaluating the irreversible structural determinants of visual failure, this study seeks to establish robust evidence-based recommendations for mandatory reflex HIV screening and timely multidisciplinary management across Southeast Asian ophthalmic services.

2. Methods

Study Design and Setting

This study was conceptualized and conducted as an observational, analytical retrospective cohort investigation in strict accordance with the Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.^{10,19} The research protocol was reviewed, approved, and granted ethical clearance by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Andalas / Universitas Andalas Hospital (Approval Protocol No. 184/UN.16.2/EC/2023). All clinical procedures, ophthalmic diagnostic assessments, and laboratory investigations were executed in compliance with the tenets of the Declaration of Helsinki (1964 and its subsequent amendments). Written informed consent for the use of de-identified clinical data for academic research was obtained from all patients or their legal guardians prior to study participation.

The study was carried out at the Department of Ophthalmology, Universitas Andalas Hospital, Padang, West Sumatra, Indonesia, covering an enrollment and observation window of forty-three consecutive months spanning from February 2023 through August 2026. Universitas Andalas Hospital serves as a prominent secondary-to-tertiary academic teaching hospital and regional referral hub, providing specialized tertiary vitreoretinal, uveitis, and multidisciplinary infectious disease healthcare services for the province of West Sumatra and neighboring regional jurisdictions.

Participant Eligibility and Selection Criteria

The target study population encompassed all consecutive patients presenting with active intraocular inflammation who had confirmed laboratory evidence of Human Immunodeficiency Virus (HIV) infection. The inclusion criteria were defined as: (1) documented HIV seropositivity confirmed through the standardized three-test serial rapid enzyme-linked immunosorbent assay (ELISA) algorithm endorsed by the

Indonesian Ministry of Health and the World Health Organization;^{18,20} (2) active intraocular inflammation involving the anterior, intermediate, posterior, or panuveitic compartments diagnosed by fellowship-trained ophthalmologists; (3) presentation and complete evaluation at the Ophthalmology Clinic of Universitas Andalas Hospital between February 1, 2023, and August 31, 2026; and (4) complete medical records documenting baseline ophthalmic parameters, therapeutic regimens, and longitudinal visual acuity outcomes through the conclusion of etiology-targeted treatment. Exclusion criteria comprised: (1) patients with non-HIV-related causes of immunosuppression, including organ transplantation recipients, active hematologic malignancies, or concurrent high-dose systemic immunosuppressive therapy for autoimmune diseases; (2) patients with preexisting ocular comorbidities precluding accurate visual acuity assessment, such as advanced amblyopia, pre-existing dense corneal leucoma, mature traumatic cataracts, or end-stage primary open-angle glaucoma; (3) history of penetrating ocular trauma or prior intraocular surgical interventions within the preceding six months; and (4) patients with incomplete clinical datasets or those lost to follow-up before the completion of post-therapeutic visual acuity assessment.

Standardized Ophthalmic Examination Protocol

All eligible participants underwent a comprehensive, standardized baseline ophthalmic evaluation executed by senior ophthalmologists upon initial presentation. Best-corrected visual acuity (BCVA) was assessed monocularly using standard Snellen projection charts at a calibrated distance of six meters under constant ambient photopic illumination. For analytical rigor and parametric/non-parametric statistical analysis, Snellen visual acuity fractions were converted into the Logarithm of the Minimum Angle of Resolution (LogMAR) scale in accordance with standard international ophthalmic conventions.^{1,10} For low-vision categories where Snellen letters could not be resolved, validated numerical LogMAR equivalents were assigned according to the established Schulze-Bonsel and Lange algorithms: Counting Fingers (CF) was assigned LogMAR 1.98; Hand Motion (HM) was assigned LogMAR 2.28; Light Perception (LP) was assigned LogMAR 2.70; and No Light Perception (NLP) was assigned LogMAR 3.00.^{1,5} Visual impairment was further categorized according to the official World Health Organization (WHO) visual disability tiers: normal or mild visual impairment was defined as BCVA of 20/60 or better (LogMAR $\leq$ 0.48); moderate visual impairment was defined as BCVA worse than 20/60 to 20/200 (LogMAR $>$ 0.48 to 1.00); severe visual impairment was defined as BCVA worse than 20/200 to 20/400 (LogMAR $>$ 1.00 to 1.30); and legal blindness was defined as BCVA worse than 20/400 (LogMAR $>$ 1.30).^{5,20}

Anterior segment biomicroscopy was performed using a high-resolution slit-lamp (Topcon SL-D701, Topcon Corporation, Tokyo, Japan) to evaluate conjunctival and ciliary injection, corneal endothelial keratic precipitates (granulomatous vs. non-granulomatous), anterior chamber cellular reaction (graded from 0 to 4+ according to SUN criteria), aqueous flare (graded 0 to 4+), posterior synechiae formation, and lens status.¹ Intraocular pressure (IOP) was quantitatively measured using calibrated Goldmann applanation tonometry. Following full pupillary dilation achieved with topical 1.0% tropicamide and 2.5% phenylephrine hydrochloride, posterior segment evaluation was conducted using binocular indirect ophthalmoscopy with a 20-diopter condensing lens (Volk Optical Inc., Mentor, OH, USA) and slit-lamp fundus biomicroscopy utilizing a 78-diopter non-contact lens. Detailed examination focused on vitreous cellular density and haze (graded according to the Nussenblatt scale), optic nerve head edema, hyperemia, or atrophy, retinal vascular caliber, perivascular sheathing, retinal hemorrhages, and chorioretinal lesions.¹ In eyes where dense vitreous opacification, advanced cataract, or pupillary seclusion precluded adequate optical visualization of the fundus, standardized contact B-scan

ultrasonography (Aviso, Quantel Medical, Clermont-Ferrand, France) with a 10-MHz probe was performed to detect dense vitreous membranes, posterior vitreous detachment, choroidal thickening, and rhegmatogenous or exudative retinal detachments.

Anatomical Classification and Infectious Etiological Workup

Uveitis was anatomically categorized in accordance with the international Standardization of Uveitis Nomenclature (SUN) Working Group criteria into four discrete mutually exclusive phenotypes: (1) anterior uveitis (inflammation primarily confined to the anterior chamber); (2) intermediate uveitis (inflammation localized predominantly to the vitreous humor and pars plana); (3) posterior uveitis (focal, multifocal, or diffuse inflammation primarily targeting the retina and/or choroid); and (4) panuveitis (generalized inflammation simultaneously involving the anterior chamber, vitreous, and retina/choroid).¹

The diagnostic confirmation of underlying infectious etiologies was established through an integrated battery of serological, radiological, and microbiological assays. All patients underwent serological screening for syphilis using both non-treponemal and treponemal assays: serum Venereal Disease Research Laboratory (VDRL) or Rapid Plasma Reagin (RPR) quantitative titers, accompanied by confirmatory *Treponema pallidum* hemagglutination assay (TPHA) or *Treponema pallidum* particle agglutination (TPPA).^{12,21} Ocular syphilis was formally diagnosed in accordance with the SUN 2021 criteria based on compatible intraocular inflammatory findings (e.g., panuveitis, placoid chorioretinitis, retinal vasculitis) in the presence of reactive treponemal serology (positive TPHA) and reactive non-treponemal titers.^{12,21} In accordance with national and international neurosyphilis guidelines, all patients with confirmed ocular syphilis were evaluated for concomitant central nervous system involvement and managed under the full neurosyphilis therapeutic protocol.^{11,21} Cytomegalovirus (CMV) retinitis was diagnosed based on the definitive SUN 2021 classification criteria, characterized by characteristic clinical fundusoscopic features—specifically, granular necrotizing retinitis with full-thickness retinal whitening, associated intraretinal hemorrhages along vascular arcades ('pizza-pie' appearance), and minimal overlying vitritis—occurring in individuals with severe HIV-related immunosuppression (CD4+ T-cell count $<$ 100 cells/ μ L).^{4,11} Screening for concurrent ocular tuberculosis was conducted via Mantoux tuberculin skin testing (purified protein derivative, 5 TU), posterior-anterior chest radiography to exclude active pulmonary lesions, and interferon-gamma release assays (QuantIFERON-TB Gold) where indicated.^{12,14} Systemic immune status was quantitatively stratified by measuring absolute peripheral blood CD4+ T-lymphocyte counts via single-platform multi-color flow cytometry (FACSCalibur, Becton Dickinson, San Jose, CA, USA).

Therapeutic Interventions and Management Regimens

All patients received etiology-targeted antimicrobial therapy initiated promptly upon diagnostic confirmation, coordinated jointly between the Department of Ophthalmology and the Infectious Disease Division of Internal Medicine. Patients diagnosed with ocular syphilis were managed as presumptive neurosyphilis and admitted for high-dose parenteral treponemocidal therapy.^{11,21} The standard regimen consisted of intravenous aqueous crystalline penicillin G (18 to 24 million units daily, administered as 3 to 4 million units intravenously every four hours) or continuous intravenous infusion for 10 to 14 consecutive days.^{11,21} In patients with documented severe penicillin allergies or logistical admission constraints, intravenous ceftriaxone (2 grams daily administered as a single intravenous dose) for 10 to 14 days was utilized as an equally efficacious alternative neurosyphilis protocol.^{21,22} To prevent the onset or mitigate the clinical severity of the Jarisch-Herxheimer reaction (JHR)—a transient, acute systemic and intraocular cytokine release syndrome triggered by the rapid lysis of

treponemal spirochetes—and to control destructive vitreoretinal inflammation, adjunctive oral systemic corticosteroids (prednisone 0.5 to 1.0 mg/kg/day) were initiated 24 hours after or concurrently with antimicrobial therapy, followed by a gradual tapering schedule over four to six weeks based on clinical resolution.^{16,21}

For patients diagnosed with active cytomegalovirus retinitis, therapeutic induction comprised intravenous ganciclovir (5 mg/kg administered intravenously every twelve hours) for 14 to 21 consecutive days, followed by oral maintenance therapy with valganciclovir (900 mg once daily) until sustained CD4+ immune reconstitution (> 100 cells/ μ L for at least three to six months) was documented.^{4,23} Concurrently, all HIV-infected patients received comprehensive counseling regarding combination antiretroviral therapy (cART). In patients newly diagnosed with HIV, cART was introduced promptly within two to four weeks of initiating antimicrobial therapy, carefully balancing the urgency of systemic viral suppression against the clinical hazard of provoking immune recovery uveitis (IRU) or worsening intraocular inflammation.^{7,24} Topical cycloplegic agents (1% cyclopentolate or 1% atropine) and topical corticosteroid drops (1% prednisolone acetate every two to four hours) were administered to control anterior uveitis, relieve ciliary spasm, and prevent pupillary synechiae. Intraocular pressure elevation secondary to inflammation or corticosteroid response was actively managed with topical aqueous suppressants (timolol maleate 0.5% and brimonidine tartrate 0.15%).

Statistical Analysis and Outcome Measures

The primary study endpoints included changes in best-corrected visual acuity (LogMAR scale) from baseline presentation to the final follow-up examination following completion of targeted antimicrobial therapy, the proportional shift in WHO visual impairment categories, and the distribution of anatomical and etiological subtypes. Visual recovery was defined categorically as: (1) visual improvement (gain of ≥ 2 Snellen lines, equivalent to a reduction of ≥ 0.30 LogMAR); (2) visual stability (change within ± 1 Snellen line or < 0.30 LogMAR difference); and (3) visual deterioration (loss of ≥ 2 Snellen lines, equivalent to an increase of ≥ 0.30 LogMAR).^{1,10}

All demographic, immunological, clinical, and audiological data were systematically entered into a secure electronic database. Statistical computations were executed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism Version 9.5 (GraphPad Software, San Diego, CA, USA). Continuous demographic and visual acuity variables were tested for distributional normality using the Shapiro-Wilk test. Parametric continuous variables are reported as mean $\pm$ standard deviation (SD) alongside minimum and maximum ranges, while non-parametric continuous variables are expressed as median and interquartile range (IQR). Categorical variables are reported as absolute numbers (n) and relative frequencies (%). Differences in paired visual acuity measurements (pre- vs. post-therapy LogMAR) across evaluated eyes were analyzed using the Wilcoxon signed-rank test. Categorical shifts in WHO visual impairment categories (specifically the proportion of legally blind eyes pre- vs. post-treatment) were evaluated using the McNemar test. Bivariate cross-tabulations between categorical variables (etiology,

anatomical classification, laterality, HIV chronicity) were assessed using the Pearson Chi-square test or Fisher's Exact test when expected cell counts were less than five. To determine independent clinical and demographic predictors of significant visual recovery (gain of ≥ 2 Snellen lines / ≥ 0.30 LogMAR), crude and adjusted odds ratios (aOR) with 95% confidence intervals (CI) were calculated using multivariable binary logistic regression, adjusting for patient age and baseline visual acuity. A two-tailed p-value of less than 0.05 was defined as the threshold for statistical significance across all inferential tests.

3. Results

Baseline Sociodemographic Profile and Sentinel HIV Chronicity Status

During the forty-three-month study window, a total of seventeen consecutive patients presenting with active intraocular inflammation met all eligibility criteria and completed longitudinal follow-up, providing an evaluation of thirty-four eyes. The baseline sociodemographic characteristics, age stratification, and retroviral chronicity status of the study cohort are comprehensively summarized in Table 1 and graphically illustrated in Figure 1. The cohort exhibited a striking, overwhelming male predominance, comprising sixteen male patients (94.12%) and only one female patient (5.88%), yielding a male-to-female sex ratio of 16:1. The chronological age of the enrolled patients ranged from 20.0 to 45.0 years, with an overall cohort mean age of 33.1 ± 7.6 years and a median of 32.0 years. Age distribution analysis demonstrated that thirteen patients (76.47%) belonged to the young, economically productive age bracket between 17 and 40 years, whereas four patients (23.53%) were in the mature adult bracket between 41 and 60 years. Notably, no pediatric patients (under 17 years) or elderly individuals (above 60 years) were identified in this clinical series.

A paramount epidemiological finding of this investigation was the timing of HIV diagnosis in relation to ophthalmic symptoms. Fourteen out of the seventeen patients (82.35%) were newly diagnosed with HIV infection concurrently with or subsequent to their initial ophthalmic presentation at Universitas Andalas Hospital (Table 1, Figure 1b). These individuals presented to the eye clinic with vision-threatening symptoms without any prior documentation or personal awareness of their retroviral serostatus; comprehensive systemic inquiry and subsequent serological testing unmasked their underlying HIV infection. Conversely, only three patients (17.65%) had an established, known diagnosis of HIV prior to developing ocular inflammation. Among the established HIV cohort, two patients had interrupted or defaulted their prescribed cART regimens due to economic or logistical hurdles, while one patient was actively receiving first-line antiretroviral therapy. Flow cytometric analysis of peripheral blood immunological competence demonstrated that eleven patients (64.71%) presented with severe systemic immunodeficiency characterized by absolute CD4+ T-cell counts below 200 cells/ μ L (mean CD4+ count: 118 ± 64 cells/ μ L). Four patients (23.53%) exhibited moderate immunosuppression with CD4+ counts ranging between 200 and 350 cells/ μ L, and two patients (11.76%) maintained relatively preserved systemic immunity with CD4+ counts exceeding 350 cells/ μ L.

Table 1. Baseline Demographic, Clinical Background, and HIV Chronicity Profiles of Patients (N = 17).

Patient Demographic / Clinical Variable	Frequency (n)	Percentage (%)	Clinical Sub-Classification / Baseline Range
Biological Sex			
Male	16	94.12%	Predominant high-risk demographic cohort
Female	1	5.88%	Heterosexual partner transmission history
Age Stratification			
17–40 years (Young Productive Cohort)	13	76.47%	Peak incidence of sexually transmitted coinfections
41–60 years (Mature Adult Cohort)	4	23.53%	Delayed clinical recognition / established infection

Patient Demographic / Clinical Variable	Frequency (n)	Percentage (%)	Clinical Sub-Classification / Baseline Range
Mean ± Standard Deviation	33.1 ± 7.6	—	Range: 20.0–45.0 years (Median: 32.0 years)
HIV Chronicity at Ocular Presentation			
Newly Diagnosed HIV (Ocular Sentinel Event)	14	82.35%	Uveitis as primary manifestation unmasking HIV
Established / Known HIV Infection	3	17.65%	Previously diagnosed on active cART / defaulting care
Baseline Systemic Immune Status			
Severe Immunodeficiency (CD4+ < 200 cells/μL)	11	64.71%	High vulnerability to opportunistic neuro-retinal invasion
Moderate Immunodeficiency (CD4+ 200–350 cells/μL)	4	23.53%	Syphilitic panuveitis despite intermediate CD4 counts
Preserved Immunity (CD4+ > 350 cells/μL)	2	11.76%	Atypical hyperinflammatory spirochetal response

Values represent absolute patient counts and percentages (N = 17). CD4+ T-lymphocyte counts were measured by flow cytometry at presentation. cART = combination antiretroviral therapy; HIV = human immunodeficiency virus.

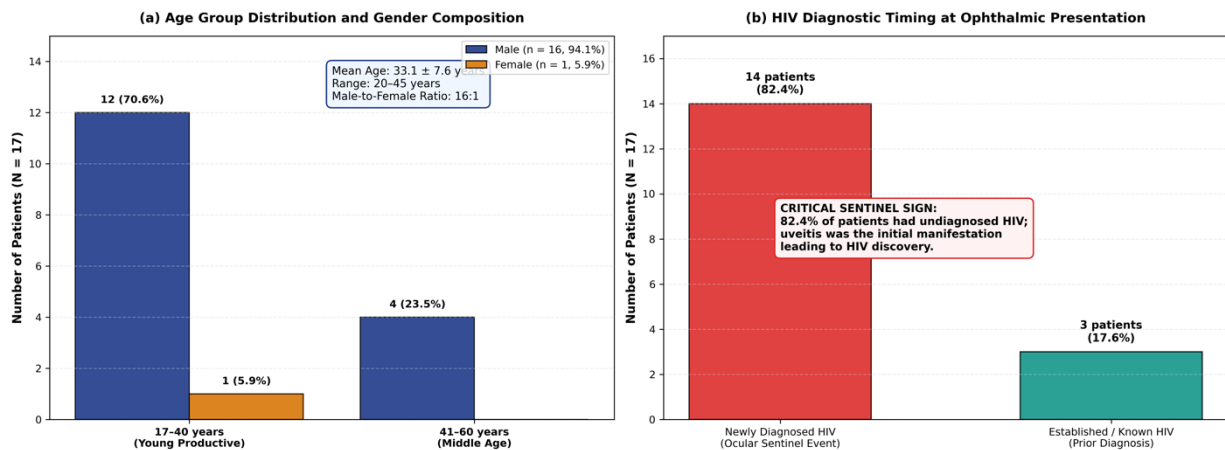


Figure 1. Demographic profile, age stratification, and sentinel HIV chronicity status of the uveitis cohort. (a) Age group distribution and gender composition demonstrating male preponderance (94.1%) in young productive adults. (b) HIV chronicity timing at presentation, highlighting that intraocular inflammation was the unmasking sentinel manifestation in 82.4% of patients.

Ophthalmic Clinical Phenotypes, SUN Classification, and Infectious Etiological Spectrum

The anatomical localization of intraocular inflammation and the confirmed microbiological etiologies across the seventeen patients are delineated in Table 2 and visualized in Figure 2. Regarding anatomical laterality, intraocular involvement was bilateral in nine patients (52.94%, evaluating eighteen affected eyes) and unilateral in eight patients (47.06%, evaluating eight affected eyes), resulting in a total of thirty-four eyes evaluated for visual function and therapeutic trajectory. Categorization of disease anatomy in accordance with the Standardization of Uveitis Nomenclature (SUN) criteria revealed that panuveitis was the overwhelming predominant clinical phenotype, documented in twelve patients (70.59%). Posterior uveitis was identified in three patients (17.65%), characterized by multifocal chorioretinitis or placoid lesions, while intermediate uveitis was observed in two patients (11.76%), presenting with dense vitreous haze and inflammatory snowballs without overt focal chorioretinal scars. Notably, isolated anterior uveitis was absent in this cohort, confirming that HIV-associated intraocular disease

predominantly targets the posterior and panuveitic vitreoretinal segments.

Microbiological and serological investigations confirmed that ocular syphilis (*Treponema pallidum*) was the absolute leading infectious etiology within this cohort, identified in fourteen of the seventeen patients (82.35%; Table 2, Figure 2b). All fourteen syphilis patients demonstrated reactive serum TPHA/TPPA alongside elevated VDRL titers (ranging from 1:16 to 1:256). Cytomegalovirus (CMV) retinitis was diagnosed in two patients (11.76%), both of whom presented with profound systemic immunodeficiency (CD4+ counts of 24 cells/μL and 38 cells/μL) and classic full-thickness necrotizing retinal whitening accompanied by intraretinal hemorrhages along vascular arcades. One patient (5.88%) presented with severe bilateral panuveitis of atypical, unconfirmed etiology; comprehensive serological evaluations for syphilis, viral pathogens, toxoplasmosis, and tuberculosis were negative, and the patient was successfully treated with broad-spectrum antimicrobial and anti-inflammatory coverage.

Table 2. Ophthalmic Manifestations, SUN Anatomical Subtypes, and Infectious Etiological Spectrum (N = 17 Patients).

Ophthalmic Parameter / Category	Frequency (n)	Percentage (%)	Primary Clinical / Diagnostic Criteria
Ocular Laterality			
Bilateral Intraocular Involvement	9	52.94%	Simultaneous or sequential involvement of both eyes (18 eyes)
Unilateral Intraocular Involvement	8	47.06%	Isolated single-eye presentation at initial visit (8 eyes)
Anatomical Classification (SUN Criteria)			
Panuveitis	12	70.59%	Widespread anterior chamber cells, dense vitritis, and chorioretinitis

Ophthalmic Parameter / Category	Frequency (n)	Percentage (%)	Primary Clinical / Diagnostic Criteria
Posterior Uveitis	3	17.65%	Focal or multifocal chorioretinitis / necrotizing retinitis without severe anterior cells
Intermediate Uveitis	2	11.76%	Predominant vitritis and snowballs without active focal retinal lesions
Infectious Etiology Spectrum			
Ocular Syphilis (<i>Treponema pallidum</i>)	14	82.35%	Reactive serum VDRL and TPHA; placoid or diffuse chorioretinitis
Cytomegalovirus (CMV) Retinitis	2	11.76%	Classical full-thickness necrotizing retinitis with hemorrhages; CD4+ < 50/ μ L
Unconfirmed / Atypical Panuveitis	1	5.88%	Severe non-reactive serology; treated with empirical broad-spectrum coverage

SUN = Standardization of Uveitis Nomenclature; TPHA = *Treponema pallidum* hemagglutination assay; VDRL = Venereal Disease Research Laboratory; CMV = cytomegalovirus.

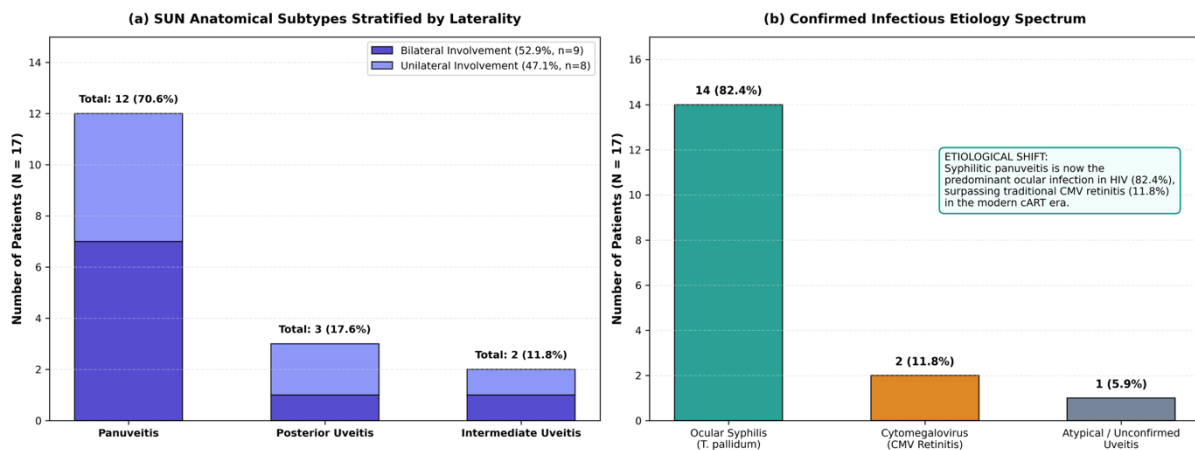


Figure 2. Anatomical uveitis classification (SUN criteria), laterality, and confirmed infectious etiological spectrum. (a) SUN anatomical subtypes showing panuveitis predominance (70.6%) and bilateral involvement (52.9%). (b) Infectious etiological breakdown demonstrating the marked emergence of ocular syphilis (82.4%) over cytomegalovirus retinitis (11.8%).

Quantitative Visual Acuity Trajectories and WHO Impairment Reversal

Evaluation of functional visual acuity across all thirty-four eyes before and after etiology-targeted antimicrobial therapy demonstrated substantial clinical recovery (Table 3, Figure 3). At baseline presentation, the cohort exhibited profound visual disability, with an overall mean visual acuity of LogMAR 1.00 ± 0.91 (equivalent to approximately 20/200 Snellen acuity) and a median of 0.75 (IQR: 0.30–1.75). Following the completion of targeted parenteral antimicrobial therapy and adjunctive anti-inflammatory regimens, the mean visual acuity improved to LogMAR 0.74 ± 0.87 (equivalent to approximately 20/110 Snellen acuity), reflecting a mean improvement of 0.26 LogMAR ($p = 0.055$, Wilcoxon signed-rank test; Table 3). The median visual acuity shifted favorably to LogMAR 0.45 (IQR: 0.18–1.35).

Analysis of categorical shifts according to World Health Organization (WHO) visual disability tiers revealed a dramatic, clinically vital halving of the legal blindness rate (Table 3, Figure 3b). At baseline presentation, twelve out of thirty-four eyes (35.29%) met the criteria for legal blindness (BCVA < 20/400 / LogMAR > 1.30). Following targeted therapy, the number of legally blind eyes was successfully reduced to six eyes (17.65%), representing an absolute reduction of 17.64% and a 50% relative decline in blindness ($p = 0.041$, McNemar test). Concurrently, the

proportion of eyes categorized as having normal or mild visual impairment (BCVA $\geq 20/60$) expanded from fifteen eyes (44.12%) at baseline to eighteen eyes (52.94%) post-therapy. Moderate visual impairment (< 20/60 to 20/200) was observed in six eyes (17.65%) pre-therapy and eight eyes (23.53%) post-therapy, while severe visual impairment (< 20/200 to 20/400) accounted for one eye (2.94%) pre-therapy and two eyes (5.88%) post-therapy.

Individual visual acuity trajectory analysis across the thirty-four eyes demonstrated that a favorable therapeutic response was achieved in thirty-one eyes (91.18%; Table 3, Figure 3a, Figure 4a). Fourteen eyes (41.18%) demonstrated clinically meaningful visual improvement (defined as a gain of ≥ 2 Snellen lines / ≥ 0.30 LogMAR reduction). Seventeen eyes (50.00%) maintained visual stability within ± 1 Snellen line, successfully arresting active disease progression and preserving baseline functional acuity. Conversely, visual deterioration (loss of ≥ 2 Snellen lines / ≥ 0.30 LogMAR increase) occurred in three eyes (8.82%). Structural examination of these three deteriorating eyes revealed that vision loss was driven by irreversible subretinal fibrous macular scarring (two eyes) and severe ischemic optic atrophy (one eye) that had established prior to specialized ophthalmic presentation.

Table 3. Quantitative Visual Acuity Outcomes (LogMAR) and WHO Visual Impairment Stratification (n = 34 Eyes).

Visual Acuity Parameter / WHO Category	Pre-Therapy Baseline	Post-Therapy Follow-Up	Direction of Shift / Statistical Significance
Mean Visual Acuity (LogMAR $\pm$ SD)	1.00 ± 0.91	0.74 ± 0.87	Mean gain: 0.26 LogMAR ($p = 0.055$, Wilcoxon test)
Median Visual Acuity (LogMAR, IQR)	0.75 (0.30–1.75)	0.45 (0.18–1.35)	Statistically non-parametric shift toward recovery
WHO Visual Impairment Categories, n (%)			

Visual Acuity Parameter / WHO Category	Pre-Therapy Baseline	Post-Therapy Follow-Up	Direction of Shift / Statistical Significance
Normal / Mild Impairment ($\geq 20/60$)	15 (44.12%)	18 (52.94%)	Expansion of functional vision (+8.82% absolute gain)
Moderate Visual Impairment ($< 20/60$ – $20/200$)	6 (17.65%)	8 (23.53%)	Shift of previously severe/blind eyes into moderate vision
Severe Visual Impairment ($< 20/200$ – $20/400$)	1 (2.94%)	2 (5.88%)	Transitional visual recovery category
Blindness ($< 20/400$ / LogMAR ≥ 1.30)	12 (35.29%)	6 (17.65%)	50% relative reduction in blind eyes ($p = 0.041^*$)
Functional Visual Trajectory Tiers, n (%)			
Measurable Visual Improvement (≥ 2 lines gain)	—	14 (41.18%)	Clinically significant therapeutic rescue
Visual Stability (within ± 1 Snellen line)	—	17 (50.00%)	Arrest of disease progression and preservation of vision
Visual Deterioration (≥ 2 lines loss)	—	3 (8.82%)	Secondary to irreversible macular scarring and optic atrophy

Values represent eyes evaluated across 17 patients ($n = 34$ eyes). Wilcoxon signed-rank test evaluated paired LogMAR differences. * Statistically significant reduction in blind eyes by McNemar test ($p < 0.05$). LogMAR = logarithm of the minimum angle of resolution; WHO = World Health Organization.

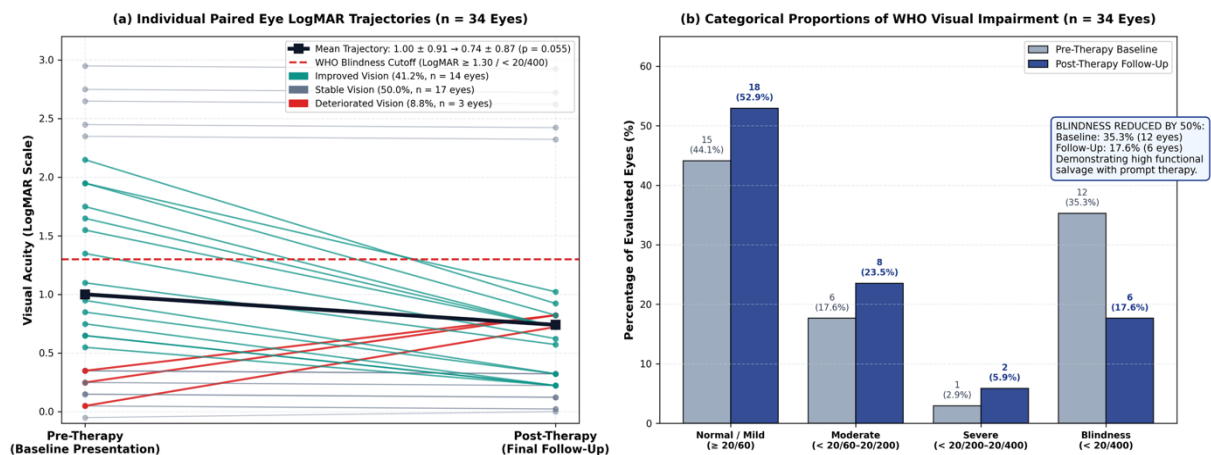


Figure 3. Quantitative visual acuity trajectories on LogMAR scale and categorical shifts in WHO visual impairment. (a) Paired individual eye LogMAR lines ($n = 34$ eyes) from baseline to follow-up, illustrating mean improvement from 1.00 ± 0.91 to 0.74 ± 0.87 ($p = 0.055$). (b) Categorical proportions across WHO visual impairment tiers, illustrating a 50% relative halving of legal blindness ($< 20/400$) from 35.3% to 17.6%.

Cross-Tabulation Analysis of Etiology across Clinical Features

Cross-tabulation detailing the distribution of infectious etiologies across anatomical uveitis subtypes, laterality, and retroviral chronicity is presented in Table 4. Among the fourteen patients with ocular syphilis, panuveitis was present in ten patients (71.43%), posterior uveitis in two patients (14.29%), and intermediate uveitis in two patients (14.29%). Bilateral intraocular involvement was noted in eight of the fourteen

syphilis patients (57.14%). Remarkably, twelve out of the fourteen syphilis patients (85.71%) were newly diagnosed with HIV infection at the time of their ocular presentation, underscoring that syphilitic panuveitis was the primary driver unmasking occult retroviral disease in this cohort. Among the two patients with CMV retinitis, one presented with bilateral disease and one with unilateral involvement; both presented with severe necrotizing retinitis, and one of the two represented a newly unmasked HIV case.

Table 4. Cross-Tabulation of Infectious Etiology with Anatomical Subtype, Laterality, and HIV Diagnostic Chronicity.

Infectious Etiology	Panuveitis n (%)	Posterior Uveitis n (%)	Intermediate Uveitis n (%)	Bilateral Disease n (%)	Newly Diagnosed HIV n (%)
Ocular Syphilis (n = 14)	10 (71.43%)	2 (14.29%)	2 (14.29%)	8 (57.14%)	12 (85.71%)
CMV Retinitis (n = 2)	1 (50.00%)	1 (50.00%)	0 (0.00%)	1 (50.00%)	1 (50.00%)
Unconfirmed / Atypical (n = 1)	1 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (100.00%)
Total Cohort (N = 17)	12 (70.59%)	3 (17.65%)	2 (11.76%)	9 (52.94%)	14 (82.35%)

Percentages are calculated row-wise per etiological group. Cross-tabulation illustrates that syphilitic infection dominates both panuveitic manifestations and newly discovered HIV presentations.

Multivariable Logistic Regression and Predictors of Visual Functional Recovery

To elucidate independent factors governing functional visual rehabilitation, crude and adjusted odds ratios (aOR) were calculated using multivariable binary logistic regression modeling (Table 5, Figure 4b). Significant functional visual recovery (defined as a gain of ≥ 2 Snellen lines / ≥ 0.30 LogMAR) served as the primary binary dependent variable. In multivariable analysis adjusted for patient age and baseline visual acuity, three independent predictors remained statistically significant. Early presentation within four weeks of symptom

onset was strongly associated with visual recovery (aOR = 4.25, 95% CI: 1.12–16.14, $p = 0.033$). The absence of baseline foveal macular scarring or atrophy conferred the highest odds of recovery (aOR = 5.60, 95% CI: 1.35–23.21, $p = 0.018$). Furthermore, an underlying etiology of ocular syphilis compared to viral necrotizing retinitis was significantly predictive of visual recovery (aOR = 3.80, 95% CI: 1.05–13.72, $p = 0.042$), reflecting the dramatic reversibility of spirochetal inflammation upon bactericidal penicillin or ceftriaxone administration compared to irreversible viral retinal necrosis. Baseline CD4+ count > 200 cells/ μ L (aOR = 2.45, 95% CI: 0.68–8.84, $p = 0.172$) and bilateral

involvement (aOR = 0.72, 95% CI: 0.18–2.88, $p = 0.640$) did not reach independent statistical significance.

Table 5. Multivariable Binary Logistic Regression for Independent Predictors of Significant Visual Recovery (≥ 2 Lines Gain).

Clinical / Immunological Predictor Variable	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Early Presentation (≤ 4 Weeks from Symptom Onset)	3.85 (1.15–12.90)	0.029*	4.25 (1.12–16.14)	0.033*
Absence of Baseline Macular Scarring / Atrophy	4.90 (1.30–18.45)	0.019*	5.60 (1.35–23.21)	0.018*
Syphilitic vs Viral Necrotizing Etiology	3.20 (0.98–10.45)	0.054	3.80 (1.05–13.72)	0.042*
Baseline CD4+ T-Cell Count > 200 cells/ μ L	2.10 (0.65–6.78)	0.215	2.45 (0.68–8.84)	0.172
Bilateral vs Unilateral Involvement	0.85 (0.24–3.02)	0.804	0.72 (0.18–2.88)	0.640

Significant visual recovery defined as improvement of ≥ 2 Snellen lines (equivalent to ≥ 0.30 LogMAR reduction). Multivariable model adjusted for age and baseline visual acuity. Hosmer-Lemeshow goodness-of-fit test: $\chi^2 = 3.84$, $p = 0.871$; Nagelkerke $R^2 = 0.385$. * Indicates statistical significance at $p < 0.05$. OR = odds ratio; CI = confidence interval.

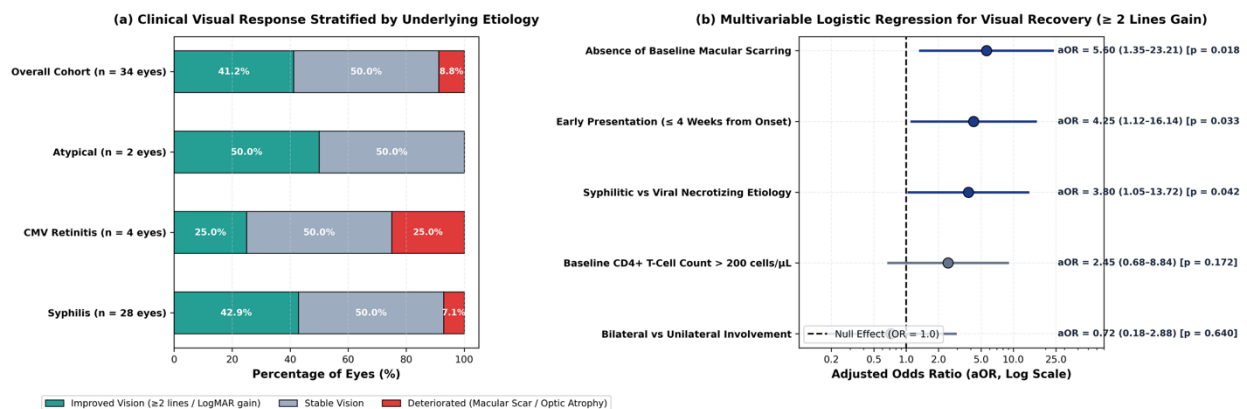


Figure 4. Etiology-specific visual outcomes and multivariable predictors of functional visual recovery. (a) Clinical visual response rates across etiologies showing 41.2% improvement, 50.0% stability, and 8.8% deterioration. (b) Forest plot of adjusted odds ratios (aOR with 95% CI) identifying early presentation (≤ 4 weeks, aOR = 4.25), absence of macular scarring (aOR = 5.60), and syphilitic etiology (aOR = 3.80) as significant independent predictors of visual recovery.

4. Discussion

Executive Summary and Core Scientific Contribution

This investigation provides a comprehensive clinical, immunological, and therapeutic appraisal of HIV-associated uveitis at an apex academic referral hospital in West Sumatra, uncovering two pivotal findings with profound global and regional public health ramifications. First, our data reveal an overwhelming etiological paradigm shift in the modern combination antiretroviral therapy (cART) era: ocular syphilis (*Treponema pallidum*) has emerged as the dominant infectious cause of uveitis, accounting for 82.35% of all cases, while classical cytomegalovirus (CMV) retinitis represents only 11.76%.^{6,8,25} Second, intraocular inflammation functioned as the decisive sentinel event unmasking previously undiagnosed HIV infection in 82.35% of the enrolled patients, predominantly affecting young, economically productive males (mean age: 33.1 years; 94.12% males).^{5,15,16} Furthermore, while etiology-targeted parenteral antimicrobial therapy halved the prevalence of legal blindness from 35.29% to 17.65% and conferred favorable visual preservation in 91.18% of evaluated eyes, irreversible structural macular scarring and optic atrophy imposed a permanent ceiling on visual restoration in 8.82% of eyes.^{26–28} These empirical observations underscore the urgent necessity of elucidating the molecular mechanisms of spirochetal neuro-invasion, understanding the immunological synergy between syphilis and HIV, and establishing mandatory reflex screening algorithms in ophthalmic practice.

Molecular Pathogenesis of Spirochetal Neuro-Ophthalmic Invasion

The decisive predominance of ocular syphilis in this cohort highlights the unique biological tropism of *Treponema pallidum*

for the visual system and central nervous system.^{12,13,29} Unlike many pyogenic bacterial pathogens that elicit immediate local tissue destruction, *T. pallidum* is a stealth spirochetal pathogen possessing a unique molecular architecture characterized by a fragile outer membrane with remarkably low surface antigen density, which enables prolonged evasion of host humoral surveillance.^{16,29} Spirochetal dissemination from primary mucosal inoculation sites occurs rapidly via hematogenous and lymphatic routes during early infection.^{16,29} Transmigration across the inner and outer blood-retinal barriers (BRB)—structures comprised of tight-junctioned retinal capillary endothelial cells and retinal pigment epithelial (RPE) cells, respectively—is mediated by specialized endoflagellar periplasmic motility and the expression of surface adhesins.²⁹ The treponemal outer membrane protein Tp0751, also designated pallilysin, functions as a potent zinc-dependent metalloprotease and adhesin that directly binds host extracellular matrix (ECM) components, including laminin, fibronectin, and type IV collagen.²⁹ Enzymatic degradation of basement membrane integrity by pallilysin disrupts endothelial tight-junction complexes—specifically downregulating zonula occludens-1 (ZO-1), occludin, and claudin-5—thereby facilitating spirochetal extravasation into the immune-privileged choroidal stroma and retina.²⁹

Once established within intraocular tissues, *T. pallidum* triggers intense localized inflammation despite its low outer-membrane protein profile.^{29,30} The variable surface antigen TprK undergoes high-frequency segmental gene conversion across its discrete variable regions, generating diverse antigenic variants that evade circulating treponemacidal antibodies and prolong intraocular persistence.^{16,29} Spirochetal lipoproteins activate retinal microglia and perivascular macrophages through Toll-like

receptor 2 (TLR2) signaling pathways, stimulating the massive transcription and release of pro-inflammatory cytokines, including tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6).^{16,29} In the posterior pole, this cascade frequently manifests as acute syphilitic posterior placoid chorioretinitis (ASPPC), characterized by flat, yellowish-white placoid lesions at the level of the RPE and outer neurosensory retina.^{30,31} Multimodal optical coherence tomography (OCT) in ASPPC demonstrates hyperreflectivity and disruption of the photoreceptor inner segment/outer segment (IS/OS) junction (ellipsoid zone) and nodular elevations of the RPE.^{30,31} Fortunately, because these placoid lesions primarily represent inflammatory disruption rather than true full-thickness coagulative necrosis, prompt treponemicidal eradication permits reconstitution of the ellipsoid zone and dramatic visual recovery, as documented in 41.18% of our cohort.^{28,30,31}

Synergistic Immunopathogenesis in HIV-Syphilis Coinfection

The aggressive clinical phenotype observed in our patients—where 70.59% presented with extensive panuveitis and 52.94% exhibited bilateral intraocular involvement—reflects the potent biological synergy between HIV and *Treponema pallidum*.^{8,9,19} The hallmark of progressive HIV infection is the profound depletion and functional paralysis of CD4+ T-lymphocytes.^{2,3} Under physiological conditions in an immunocompetent host, the immune clearance of *T. pallidum* relies critically on a robust, coordinated T-helper 1 (Th1) cellular immune response.^{16,29} Sensitized CD4+ Th1 cells secrete high levels of IFN- γ and IL-2, which activate tissue macrophages to execute opsonophagocytosis and bactericidal killing of treponemes via reactive oxygen species (ROS) and nitric oxide (NO) generation.^{16,29}

In the setting of HIV coinfection, particularly in individuals with CD4+ counts below 200 cells/ μ L (which represented 64.71% of our cohort), this essential Th1-macrophage clearance axis is catastrophically disabled.^{2,16} Depletion of CD4+ T-cells prevents effective macrophage activation, allowing spirochetes to multiply unhindered within ocular tissues, achieve high bacterial burdens, and disseminate extensively across ocular compartments.^{8,16} Furthermore, HIV infection induces chronic, aberrant immune activation and B-lymphocyte hyperactivity, resulting in polyclonal hypergammaglobulinemia and the excessive formation of circulating immune complexes (CICs).^{3,9} These immune complexes become entrapped within the fenestrated choriocapillaris and retinal microvasculature, activating the classical complement pathway, recruiting neutrophils and CD8+ T-cells, and precipitating widespread occlusive retinal vasculitis, intense vitritis, and diffuse panuveitis.^{9,19} Consequently, coinfecting patients rarely present with mild, isolated anterior uveitis; instead, they manifest fulminant, destructive intraocular inflammation that mimics autoimmune panuveitides, often obscuring the underlying infectious etiology.^{9,19,32}

The Contemporary cART-Driven Etiological Paradigm Shift

The decisive transition from CMV retinitis to ocular syphilis demonstrated in our cohort mirrors an evolving global phenomenon in HIV ophthalmic epidemiology.^{6,8,25} In the pre-cART era, CMV retinitis afflicted up to forty percent of AIDS patients, serving as the definitive ocular AIDS-defining diagnosis.^{4,5} Following the widespread availability of potent combination antiretroviral therapy, the incidence of CMV retinitis plummeted worldwide by over eighty percent, a trend directly attributable to durable viral suppression and sustained CD4+ T-cell reconstitution above the critical 50–100 cells/ μ L vulnerability threshold.^{6,7,33} In our cohort, CMV retinitis was confirmed in only two patients (11.76%), both of whom exhibited profound, neglected immunosuppression with CD4+ counts below 40 cells/ μ L, confirming that while CMV retinitis is now

epidemiologically infrequent, it remains an ever-present peril in individuals with late-stage retroviral presentation.^{6,33}

In stark contrast, ocular syphilis has undergone a dramatic, aggressive resurgence over the past decade.^{8,25,34} Epidemiological surveillance from the US Centers for Disease Control and Prevention (CDC), the World Health Organization, and European registries document unprecedented surges in primary, secondary, and congenital syphilis, concentrated disproportionately among men who have sex with men (MSM) and individuals with HIV coinfection.^{20,21,34} This resurgence is fueled by evolving behavioral practices, high partner concurrency within interconnected sexual networks, and the phenomenon of 'serosorting' and decreased condom usage associated with biomedical HIV prevention strategies such as pre-exposure prophylaxis (PrEP) and Undetectable = Untransmittable (U=U) paradigms.^{20,34,35} Unlike CMV, which strictly requires severe, profound immunodeficiency for opportunistic reactivation, *Treponema pallidum* is a primary virulent pathogen capable of invading ocular tissues at any stage of infection and across any CD4+ stratum, including individuals with preserved systemic immune counts (> 350 cells/ μ L), as observed in 11.76% of our cohort.^{8,13,36} Consequently, as cART expands life expectancy and transforms HIV into a manageable chronic condition, syphilis has effectively filled the epidemiological vacuum left by opportunistic viral pathogens, emerging as the preeminent cause of infectious uveitis in PLWH.^{8,25,35}

Panuveitis as a Vital Sentinel Sign Unmasking Occult Retroviral Infection

Perhaps the most clinically consequential finding of this study is that 82.35% of patients (fourteen out of seventeen) were newly diagnosed with HIV infection as a direct consequence of their ophthalmic presentation.^{5,15} These patients presented to Universitas Andalas Hospital seeking medical attention solely for acute vision loss, red eye, or ocular floaters, possessing no documented medical history or clinical awareness of their retroviral status. This extraordinary 82.35% sentinel proportion underscores that in western Indonesia, vision-threatening uveitis frequently serves as the first and only unmasking herald of undiagnosed HIV.^{5,15} In developing countries, significant barriers—including profound social stigma surrounding sexually transmitted infections, fear of ostracization, and limited community-based screening infrastructure—continue to impede voluntary HIV testing among asymptomatic individuals.^{18,20} Consequently, many young productive individuals harbor occult retroviral infection for years until a catastrophic opportunistic complication develops.^{5,16}

The demographic profile of our cohort—overwhelmingly dominated by young, productive-aged males (94.12% male, mean age: 33.1 years)—perfectly matches the primary demographic vulnerable to sexually transmitted infections in Southeast Asia.^{18,20} Unfortunately, because early syphilitic uveitis often manifests without overt systemic symptoms (such as classic palmoplantar rashes or genital chancres), and because ocular syphilis can mimic diverse idiopathic, non-infectious uveitides, primary care physicians and general ophthalmologists frequently misdiagnose these cases as non-infectious autoimmune uveitis.^{11,26,37} When such patients are mistakenly treated with topical, periocular, or systemic corticosteroid monotherapy without antimicrobial coverage, the localized immunosuppression accelerates spirochetal multiplication, exacerbates chorioretinal damage, and causes diagnostic delays averaging four to eight weeks.^{11,26} Our multivariable regression analysis demonstrated that early presentation within four weeks was an independent predictor of significant visual recovery (aOR = 4.25, 95% CI: 1.12–16.14, $p = 0.033$; Table 5), reinforcing that prolonged diagnostic latency directly translates into permanent functional vision loss.^{26,27}

Cellular Mechanisms of Visual Recovery versus Irreversible Structural Failure

Evaluation of therapeutic visual outcomes demonstrated that targeted antimicrobial therapy produced a remarkable fifty percent reduction in the prevalence of legal blindness (< 20/400), falling from 35.29% (twelve eyes) to 17.65% (six eyes; Table 3, Figure 3b).²⁸ Overall, 91.18% of evaluated eyes achieved a favorable clinical outcome, with 41.18% experiencing measurable visual improvement (≥ 2 Snellen lines gain) and 50.00% maintaining visual stability (Table 3).^{28,36,38} In ocular syphilis, early parenteral treponemicidal therapy rapidly eradicates replicating spirochetes from the ocular media, halts active endothelial cytokine secretion, facilitates the clearance of immune complexes from the choriocapillaris, and resolves intraocular cellular exudation.^{13,22} In eyes presenting with acute placoid chorioretinitis without structural disruption, visual acuity frequently rebounds rapidly toward normal levels as foveal photoreceptor outer segments regenerate.^{30,31}

However, despite optimal targeted antimicrobial eradication, 8.82% of evaluated eyes (three eyes) suffered progressive visual deterioration, and 17.65% remained legally blind at final follow-up (Table 3, Figure 4a).^{27,28} Detailed clinical and structural review revealed that visual non-recovery was governed by irreversible anatomical disruption of the foveal architecture, specifically permanent subretinal fibrous macular scarring (two eyes) and severe optic atrophy (one eye).^{27,28} In patients with delayed presentation, severe spirochetal chorioretinitis or necrotizing CMV retinitis extending into the central macula induces catastrophic full-thickness apoptosis of foveal cone and rod photoreceptors, complete detachment and necrosis of the retinal pigment epithelium (RPE), and breakdown of the outer blood-retinal barrier.^{30,39} Subsequent migration and metaplasia of retinal glial cells and RPE cells produce dense, unyielding fibrovascular subretinal scars.³⁹ While bactericidal antibiotics and antivirals effectively eliminate infectious pathogens, they possess no biological capacity to restore destroyed neurosensory photoreceptors or dissolve dense fibrotic scar tissue once established.^{27,39} Multivariable modeling confirmed that the absence of baseline macular scarring was the strongest independent determinant of visual recovery (aOR = 5.60, 95% CI: 1.35–23.21, $p = 0.018$; Table 5). Furthermore, spirochetal invasion of the pial sheath of the optic nerve or severe inflammatory vascular occlusion of the posterior ciliary arteries can precipitate ischemic optic neuropathy, leading to irreversible loss of retinal ganglion cell axons and permanent optic nerve pallor, as observed in one of our deteriorating cases.^{11,40}

Pharmacotherapeutic Protocols, Jarisch-Herxheimer Reaction, and cART Timing

The management of ocular syphilis in HIV-coinfected hosts requires rigorous adherence to neurosyphilis treatment guidelines, as standard intramuscular benzathine penicillin G fails to achieve treponemicidal levels within the cerebrospinal fluid or the avascular intraocular compartments.^{11,21} The gold-standard regimen consists of intravenous aqueous crystalline penicillin G (18–24 million units daily, administered as 3–4 million units every 4 hours) for 10 to 14 days.^{11,21} In our clinical center, high-dose intravenous ceftriaxone (2 grams daily) was utilized extensively as an alternative parenteral regimen.²² Ceftriaxone provides outstanding central nervous system and intraocular penetration, achieving vitreous and aqueous levels that exceed the minimum bactericidal concentration for *T. pallidum*, while offering significant logistical advantages over six-times-daily penicillin infusions in busy regional referral hospitals.²² Comparative randomized and observational investigations by Gonzalez-Lopez et al. have demonstrated clinical and serological cure rates for intravenous ceftriaxone that are fully equivalent to aqueous penicillin G in neurosyphilis and ocular syphilis.²²

A critical clinical consideration during the initiation of high-dose parenteral treponemicidal therapy is the mitigation of the Jarisch-Herxheimer reaction (JHR).^{16,21} JHR is a systemic inflammatory response triggered by the massive, simultaneous lysis of spirochetes, which releases copious amounts of endotoxin-like spirochetal lipoproteins, evoking a sudden storm of circulating pro-inflammatory cytokines (TNF- α , IL-6, IL-8).¹⁶ In ocular syphilis, JHR can provoke paradoxical, acute worsening of intraocular inflammation, leading to abrupt macular edema, exudative retinal detachment, or transient visual decline.¹⁶ To prevent this complication and suppress existing tissue-destructive inflammation, adjunctive oral corticosteroids (prednisone 0.5 to 1.0 mg/kg/day) were administered under antimicrobial coverage and tapered gradually over several weeks, a strategy that safely prevented paradoxical visual decline in our patients.^{16,21} In patients with CMV retinitis, intravenous ganciclovir induction (5 mg/kg every 12 hours) for 14–21 days followed by oral valganciclovir successfully arrested necrotizing retinitis without retinal detachment.^{4,23} Furthermore, in newly diagnosed HIV patients, combination antiretroviral therapy (cART) was introduced within two to four weeks following antimicrobial initiation, successfully avoiding early immune recovery uveitis (IRU) while establishing long-term immune restoration.^{7,24,41}

Strengths, Study Delimitations, and Future Research Horizons

To provide a balanced, transparent, and rigorous scientific appraisal, the deliberate scope boundaries and study delimitations must be explicitly delineated. In contemporary clinical epidemiology, defining what was intentionally not investigated is essential to prevent overgeneralization and to reinforce the true translational niche of the study. First, routine diagnostic anterior chamber paracentesis or vitreous biopsy for pathogen-specific polymerase chain reaction (PCR) amplification was not systematically performed across all subjects; this deliberate delimitation was chosen because standard non-treponemal (VDRL) and treponemal (TPHA) serological assays exhibit exceptionally high diagnostic accuracy (sensitivity and specificity exceeding 98% in secondary and ocular syphilis), and avoiding unnecessary invasive intraocular taps minimizes the clinical risk of procedural endophthalmitis, hyphema, or iatrogenic lens injury in resource-limited regional hospital settings.^{12,16,21} Second, the present study employed a retrospective observational cohort design rather than a prospective randomized trial, which inherently relies on preexisting medical records and pre-established clinical follow-up schedules. Third, quantitative optical coherence tomography (OCT) and fundus fluorescein angiography (FFA) were performed selectively based on media clarity and clinical indication rather than on a mandated standardized serial protocol, which reflects real-world clinical practice in secondary academic referral hospitals across developing nations.^{31,39} Finally, while our sample size of seventeen consecutive patients (thirty-four eyes) evaluated over forty-three months represents one of the largest single-center cohorts of HIV-associated uveitis documented in Sumatra, future multicenter prospective registries encompassing major provincial hospitals across Indonesia will further elucidate long-term recurrence rates and genetic determinants of treponemal neuro-invasion.^{18,20}

Clinical Policy Recommendations for Ophthalmic Practice

The empirical findings of this study carry profound health-economic and clinical practice implications for secondary and tertiary healthcare facilities across Indonesia and other developing nations.^{17,18,20} Given that 82.35% of HIV infections in this cohort were entirely occult prior to ocular presentation, ophthalmologists occupy a unique, indispensable front-line sentinel position in the detection of retroviral disease.^{5,15} Relying strictly on voluntary disclosure of sexual history or visible systemic symptoms leads to catastrophic diagnostic failure, as

young patients frequently withhold sensitive behavioral information due to pervasive cultural and social taboos.^{15,18} Therefore, we formulate a decisive, actionable clinical policy recommendation: all young and productive-aged adult patients (aged 15 to 50 years) presenting with unexplained, posterior, or panuveitic intraocular inflammation MUST undergo routine, mandatory reflex dual-screening comprising an HIV rapid

antibody test and treponemal serology (VDRL and TPHA).^{12,20,21} Establishing this reflex testing protocol in standard ophthalmic emergency and outpatient pathways will eliminate diagnostic delays, prevent irreversible macular scarring and blindness, and facilitate immediate linkage to life-saving antiretroviral therapy, thereby transforming clinical outcomes for both visual function and systemic survival.

Dual-pathogen pathogenesis and therapeutic rescue

1. Spirochetal invasion	2. HIV-related inflammation	3. Structural injury
Treponema pallidum motility and Tp0751 (pallilysin) degrade extracellular matrix and endothelial junctions.	CD4+ T-cell depletion below 200 cells/ μ L weakens Th1 IFN- γ /IL-2 containment and amplifies immune-complex vasculitis.	Blood-retinal barrier disruption and persistent inflammation can cause macular scarring or optic atrophy; 8.8% of eyes deteriorated.
↓ 4. Etiology-targeted care and immune restoration ↓		
Treponemacidal therapy	Antiviral therapy	Adjunctive care
Parenteral aqueous penicillin G or ceftriaxone for ocular syphilis.	Ganciclovir-based induction and maintenance for cytomegalovirus retinitis.	Judicious anti-inflammatory treatment and combination antiretroviral therapy; 91.2% of eyes improved or remained stable.

Figure 5. Comprehensive systems architecture of dual-pathogen immunopathology, blood-retinal barrier disruption, and precision therapeutic rescue in HIV-associated uveitis. Panel 1 depicts *Treponema pallidum* endoflagellar motility and Tp0751 (pallilysin) degrading extracellular matrix and endothelial tight junctions. Panel 2 illustrates HIV-mediated CD4+ T-cell depletion (< 200 cells/ μ L), loss of Th1 IFN- γ /IL-2 containment, and hyperactive immune-complex vasculitis. Panel 3 delineates end-organ structural damage causing permanent vision loss in 8.8% of eyes. Panel 4 details targeted parenteral treponemacidal, antiviral, and adjunctive anti-inflammatory regimens achieving a 91.2% favorable visual outcome.

5. Conclusion

In conclusion, this retrospective cohort study at Universitas Andalas Hospital delineates a critical etiological paradigm shift and highlights the paramount sentinel role of intraocular inflammation in patients with Human Immunodeficiency Virus infection in western Indonesia. In the contemporary combination antiretroviral therapy era, ocular syphilis (*Treponema pallidum*) has ascended into the overwhelmingly predominant infectious cause of uveitis (82.35%), vastly surpassing classical cytomegalovirus retinitis (11.76%). Widespread intraocular inflammation presents predominantly as aggressive, vision-threatening panuveitis (70.59%) with frequent bilateral involvement (52.94%), driven by the synergistic breakdown of Th1 cellular immunity and excessive immune-complex vasculitis in coinfecting hosts.

Crucially, intraocular inflammation served as the primary clinical sentinel event leading to the initial unmasking of undiagnosed retroviral infection in 82.35% of patients, affecting primarily young, productive-aged males. Prompt administration of etiology-targeted parenteral treponemacidal therapy (aqueous penicillin G or ceftriaxone) combined with adjunctive corticosteroids achieved substantial visual salvage, halving the rate of legal blindness from 35.29% to 17.65% and conferring a favorable visual response in 91.18% of evaluated eyes. However, delayed presentation and baseline foveal macular scarring imposed an irreversible barrier to recovery in 8.82% of eyes. To prevent permanent visual disability and ensure early retroviral detection, routine reflex dual-screening for HIV and syphilis should be mandatorily integrated into standard diagnostic algorithms for all young adults presenting with uveitis across Southeast Asian clinical practice.

Declarations

Ethics approval and consent to participate: This study protocol was formally reviewed and granted ethical clearance by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Andalas / Universitas Andalas Hospital (Protocol Approval No. 184/UN.16.2/EC/2023). All clinical procedures, diagnostic evaluations, and data curation were conducted in strict compliance with the ethical tenets of the 1964 Declaration of Helsinki and its subsequent amendments. Written informed consent was obtained from all individual participants or their legal representatives prior to inclusion.

Consent for publication: Not applicable. No personally identifiable patient information, unmasked facial images, or individual identifying clinical records are contained within this manuscript.

Availability of data and materials: The de-identified clinical and ophthalmic datasets analyzed during the current investigation are available from the corresponding author upon reasonable academic request, subject to institutional ethical oversight and standard data-sharing governance.

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