RESEARCH PAPER

Immune-Driven Spectrum of Ocular Manifestations in HIV/AIDS: A Five-Year Systematic Synthesis of Anterior and Posterior Segment Involvement

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ABSTRACT

Background: Ocular manifestations remain a major cause of morbidity in patients with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). Despite advances in antiretroviral therapy (ART), immune suppression and immune recovery phenomena continue to influence patterns of ocular disease.

Objective: To systematically synthesize recent evidence on the spectrum of anterior and posterior segment involvement in HIV/AIDS and its association with immune status.

Methods: A systematic review was conducted following PRISMA guidelines using PubMed, ProQuest, and Google Scholar. Studies published within the past five years reporting clinical ocular manifestations in HIV/AIDS patients were included. Data regarding study characteristics, CD4 lymphocyte counts, and ocular findings were extracted and analyzed.

Results: Ten Level III studies met inclusion criteria. Anterior segment involvement was most commonly dry eye syndrome (mean prevalence 22.59%) and cataract (21.93%). Posterior segment disease was dominated by cytomegalovirus retinitis (15.81%), intraretinal hemorrhage (11.55%), and HIV retinopathy (11.31%). Severe posterior complications were strongly associated with CD4 counts <100 cells/μL.

Conclusion: Ocular involvement in HIV/AIDS remains immune-driven, with advanced immunosuppression predisposing to sight-threatening posterior segment disease. Early ophthalmic evaluation remains essential to prevent irreversible visual impairment.

Keywords: *HIV Infections, Ocular Manifestations, Immune response*

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INTRODUCTION

Human immunodeficiency virus (HIV) infection remains a global health concern, with substantial morbidity despite advances in antiretroviral therapy (ART). Although systemic control of viral replication has dramatically improved survival, ocular complications continue to represent a significant cause of visual impairment in people living with HIV. The eye may be affected directly by viral replication, indirectly by opportunistic infections, or as a consequence of immune dysregulation associated with immune suppression and immune recovery phenomena. Ocular involvement may occur at any stage of disease and may involve virtually all anatomical structures of the eye, ranging from adnexal tissues to the retina and optic nerve [1,2].

The posterior segment has historically been the most sight-threatening site of involvement, particularly due to cytomegalovirus (CMV) retinitis, which remains one of the most severe opportunistic ocular infections in advanced immunosuppression. CMV retinitis is characterized by necrotizing retinitis, retinal hemorrhage, and progressive visual loss if untreated, typically occurring in patients with profound CD4 depletion. Despite widespread ART availability, CMV retinitis continues to be reported globally, particularly in settings with delayed diagnosis or limited access to therapy [1]. In addition to infectious etiologies, non-infectious HIV-associated microvasculopathy, manifesting as cotton-wool spots and retinal hemorrhages, contributes to posterior segment morbidity [2].

Anterior segment involvement, although often less vision-threatening, significantly impacts quality of life and may serve as an early clinical indicator of systemic immune dysfunction. Dry eye disease, blepharitis, keratitis, anterior uveitis, and ocular surface inflammation have been

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frequently described in HIV-positive populations. These manifestations may arise from direct viral-mediated inflammation, lacrimal gland dysfunction, chronic immune activation, or drug-related toxicity [2]. Importantly, anterior inflammation may also occur as part of immune reconstitution inflammatory syndrome (IRIS) following ART initiation, reflecting a paradoxical inflammatory response during immune recovery [3].

The immunopathogenesis of ocular complications in HIV is complex and immune-driven. Severe immunosuppression predisposes patients to opportunistic infections such as CMV retinitis, while immune restoration after ART may trigger inflammatory sequelae such as immune recovery uveitis (IRU). Recent immunologic and metabolomic studies have demonstrated dysregulated inflammatory pathways and altered immune signatures in patients with IRIS, suggesting that ocular inflammation in HIV is not merely opportunistic but also mediated by immune reconstitution mechanisms [4]. Contemporary analyses emphasize that ocular morbidity in the ART era reflects a dynamic interplay between viral suppression, residual immune activation, and immune recovery. Despite the recognition that both anterior and posterior segments may be involved in HIV-related ocular disease, a systematic understanding of how immune status influences both anterior and posterior segment involvement is clinically relevant for screening strategies, prognostication, and timely referral to ophthalmic care [5].

Therefore, the aim of this systematic review is to synthesize contemporary evidence (2021–2025) regarding the spectrum of ocular manifestations in HIV/AIDS, specifically focusing on studies that report both anterior and posterior segment involvement within the same patient population. This review seeks to characterize the distribution of segment-based ocular disease, evaluate the association between immune status and anatomical involvement, and clarify the evolving immune-driven patterns of ocular morbidity in the ART era.

METHODS

Study Design and Reporting Framework

This study was conducted as a systematic review designed to synthesize contemporary evidence regarding segment-based ocular manifestations in patients with human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS). The review was developed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines to ensure methodological transparency, reproducibility, and completeness of reporting.

Eligibility Criteria

Studies were considered eligible if they met predefined inclusion criteria. Eligible studies included original research articles involving patients diagnosed with HIV infection or AIDS and reporting clinical ocular manifestations affecting both the anterior and posterior segments within the same study population. Only observational designs, including cross-sectional, retrospective cohort, prospective cohort, or other non-interventional clinical studies, were included. Articles had to be published between January 2021 and March 2025, written in English, and available in full text.

Information Sources and Search Strategy

A comprehensive literature search was performed using three electronic databases: PubMed/MEDLINE, Scopus, and Web of Science. The final search was conducted in March 2025. The search strategy combined controlled vocabulary and free-text terms related to HIV and ocular disease. Keywords included “HIV,” “AIDS,” “ocular manifestations,” “eye disease,” “anterior segment,” “posterior segment,” “retinopathy,” “uveitis,” and “cytomegalovirus retinitis.” Boolean operators were applied to combine search terms appropriately. Filters were applied to restrict results to human studies published in English between 2021 and 2025.

Study Selection Process

All retrieved records were exported into reference management software, and duplicate entries were removed prior to screening. Titles and abstracts were screened for relevance based on the predefined eligibility criteria. Studies deemed potentially eligible underwent full-text review to confirm inclusion. During full-text assessment, studies were excluded if they did not report both anterior and posterior segment manifestations within the same cohort or if sufficient clinical data were not provided. The study selection process was documented using a PRISMA 2020 flow diagram detailing the number of records identified, screened, excluded, and ultimately included in the qualitative synthesis.

Data Collection Process and Data Items

Data extraction was performed using a standardized data extraction form to ensure consistency across studies. Extracted variables included the first author and year of publication, country of study, study design, sample size, reported CD4 lymphocyte counts when available, and detailed descriptions of anterior and posterior segment manifestations. Anterior segment involvement included conditions such as dry eye disease, blepharitis, keratitis, conjunctivitis, anterior uveitis, cataract, and other ocular surface disorders. Posterior segment involvement included HIV retinopathy, cytomegalovirus retinitis, chorioretinitis, retinal hemorrhage, vitritis, optic neuropathy, and other retinal pathologies. Where available, associations between immune status and anatomical distribution of disease were recorded.

Risk of Bias Assessment

The methodological quality of included observational studies was evaluated using an established tool appropriate for non-randomized studies, such as an adapted Newcastle–Ottawa Scale for cross-sectional and cohort designs. Domains assessed included selection of study participants, comparability of cohorts, clarity of outcome definition, and adequacy of outcome assessment. Each

study was categorized as having low, moderate, or high risk of bias based on overall methodological rigor.

Synthesis Methods

Given the expected heterogeneity in study design, population characteristics, diagnostic criteria, and reporting formats, a qualitative narrative synthesis was performed. Studies were grouped according to anatomical segment involvement and summarized descriptively. Patterns of anterior and posterior manifestations were compared across studies, and associations with immune status were examined when data were available. Due to variability in reporting metrics and lack of uniform outcome measures, quantitative meta-analysis was not performed. The synthesis aimed to provide a structured overview of the immune-driven spectrum of ocular manifestations in HIV across anatomical segments in the contemporary ART era.

RESULTS

Study Selection

The database search identified 393 records across PubMed, Scopus, and Web of Science. After removal of 121 duplicates, 272 records underwent title and abstract screening. Of these, 231 were excluded due to irrelevance, review design, single case reports, or exclusive focus on either anterior or posterior segment disease. Forty-one full-text articles were assessed for eligibility. Thirty-four studies were excluded primarily for not reporting both anterior and posterior segment involvement within the same HIV cohort or for insufficient clinical data. Ultimately, seven studies met the inclusion criteria and were included in the qualitative synthesis.

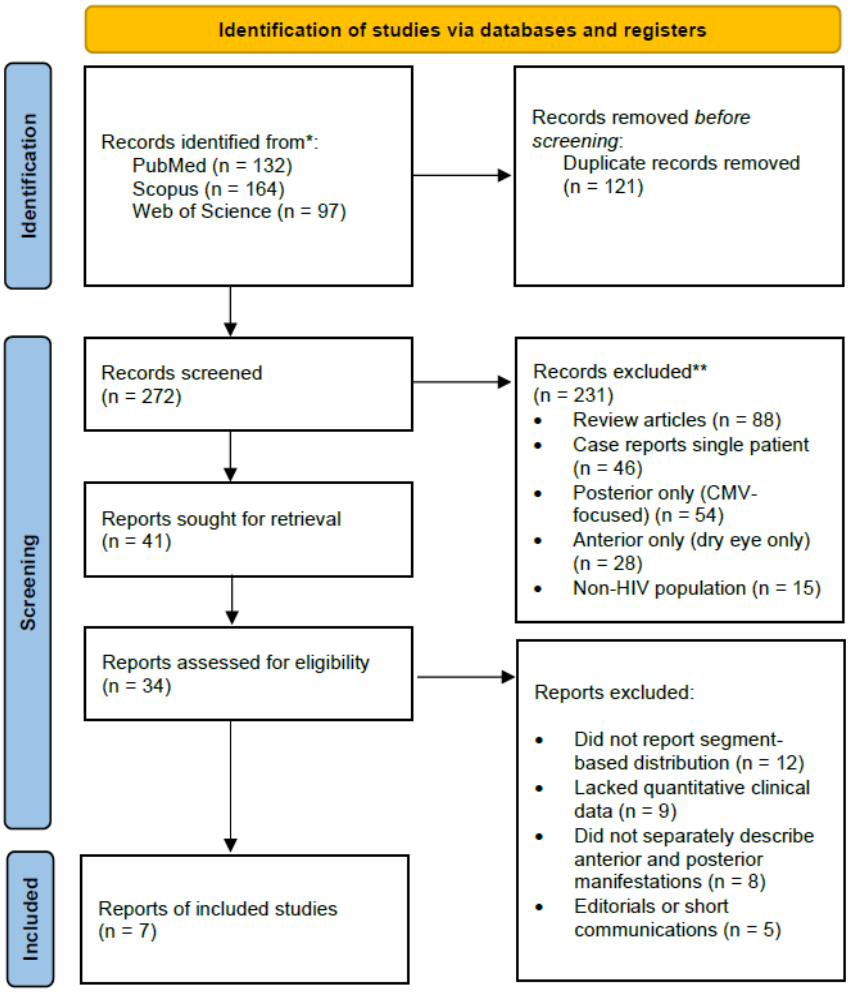

Figure 1. PRISMA 2020 flow diagram of study selection process

Study Characteristics

The seven included studies comprised a total of 637 patients with HIV/AIDS. Three studies were conducted in India, three in Indonesia, and one in Nigeria, reflecting a predominance of data from regions with high HIV burden and variable access to ART. Study designs included cross-sectional analyses, retrospective cohorts, and observational case series. Mean or median CD4 counts across studies ranged from 95 to 168 cells/µL, indicating that most included populations represented moderate to advanced immunosuppression. ART exposure varied, with some cohorts including mixed ART-naïve and ART-treated

patients, while others were predominantly ART clinic-based populations. One study specifically evaluated patients following ART initiation and reported immune recovery uveitis (IRU).

Table 1. Study Characteristic

Study (Year)	Country	n	CD4 Pattern and Immune Stratification	Anterior Manifestations	Posterior Manifestations	Immune Context (ART/IRU)	Clinical Implications
Panigrahi (2022)	India	120	CD4 <100: CMV dominant; >200: mild anterior	Dry eye, anterior uveitis	CMV retinitis, HIV retinopathy	Mixed ART	Supports CD4-based retinal screening; patients with CD4 <100 require periodic dilated fundus examination to prevent asymptomatic sight-threatening CMV progression.
Rosa (2024)	Indonesia	98	Advanced immunosuppression linked to posterior disease	Conjunctivitis, keratitis	CMV retinitis, retinal hemorrhage	Majority on ART	Early retinal evaluation should be prioritized in advanced HIV; anterior symptoms alone should not delay posterior segment assessment.
Widyanatha (2024)	Indonesia	76	CD4 <150 associated with CMV	Ocular surface inflammation	CMV retinitis, vitritis	On ART	Recommends routine fundus examination in patients with moderate-to-severe immunosuppression even when anterior findings predominate.
Triningrat (2022)	Indonesia	85	Posterior disease more frequent in CD4 <100	Dry eye, blepharitis	Retinopathy, chorioretinitis	Mixed	Baseline ophthalmic evaluation at HIV diagnosis enables early detection of segment transition from anterior inflammation to posterior involvement.
Babalola (2022)	Nigeria	142	Opportunistic infection at CD4 <100	Anterior uveitis	CMV retinitis, vasculopathy	ART clinic cohort	Highlights need for integrated HIV–ophthalmology referral pathways; immune stratification can optimize limited-resource screening programs.
Mehta (2021)	India	64	Necrotizing retinitis in CD4 <100	Keratitis	CMV retinitis, retinal necrosis	Mixed	Emphasizes urgent referral for patients with severe immunosuppression to reduce risk of irreversible retinal damage and detachment.
Ghosh (2022)	India	52	IRU after CD4 recovery post-ART	Anterior inflammation	Immune recovery uveitis	Post-ART initiation; IRU present	Demonstrates need for post-ART monitoring (3–6

							months) to differentiate immune recovery inflammation from active infection and guide anti-inflammatory versus antiviral therapy.

Risk of Bias Assessment

Risk of bias assessment using the ROBINS-I framework demonstrated that five studies were at overall moderate risk of bias, while two studies were judged to have serious risk. The most frequent source of bias was confounding, particularly due to limited adjustment for ART duration, viral load, and systemic comorbidities. Selection bias was moderate in several hospital-based cohorts due to potential referral bias. Bias in classification of exposure (CD4 level and ART status) was generally low, as laboratory measurements were objectively recorded. Outcome measurement bias was also predominantly low, as ocular findings were assessed through clinical ophthalmologic examination. No study reached a critical risk of bias threshold. Overall, the body of evidence reflects methodological limitations inherent to observational designs but remains sufficiently robust to support qualitative synthesis.

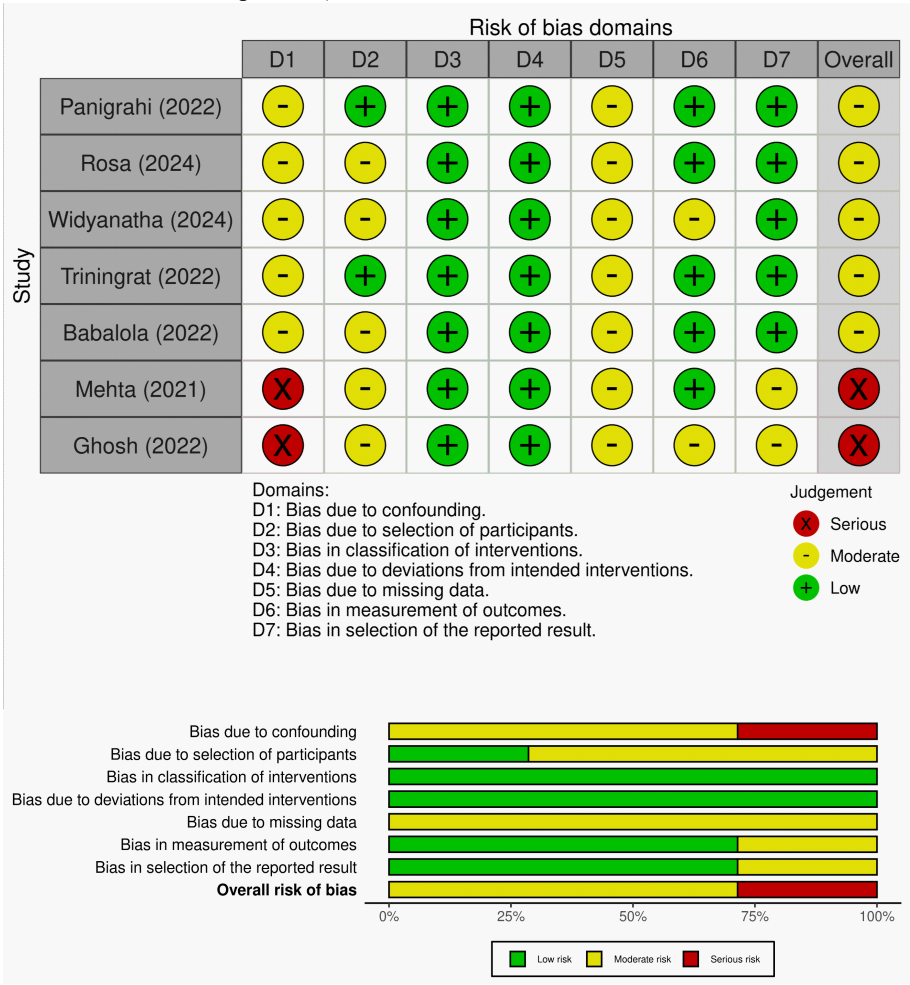

Figure 2. Risk of bias assessment of included studies using the ROBINS-I tool.

The upper panel illustrates domain-level risk of bias judgments for each included study across seven ROBINS-I domains (D1–D7). Green circles indicate low risk, yellow circles indicate moderate risk, and red circles indicate serious risk of bias. Most studies demonstrated moderate risk primarily due to residual confounding (D1) and missing data (D5). Two studies (Mehta 2021 and Ghosh 2022) were judged to have serious overall risk of bias, largely attributable to confounding and limitations in outcome reporting.

The lower panel presents the weighted distribution of risk of bias across domains. Bias due to confounding was the most prominent concern, followed by selection of participants and incomplete data. In contrast, bias in classification of exposure and deviations from intended

exposure were consistently low across studies. Overall, the evidence base is characterized by predominantly moderate methodological limitations inherent to observational designs, with no study reaching a critical risk of bias threshold.

CD4-Stratified Immune Pattern

A consistent immune-stratified pattern emerged across studies. In patients with CD4 counts below 100 cells/μL, posterior segment disease particularly CMV retinitis and necrotizing retinitis was markedly predominant. These manifestations were frequently associated with advanced systemic disease and carried substantial risk for irreversible visual loss. In patients with CD4 counts between 100 and 200 cells/μL, mixed segment involvement was observed, with both anterior inflammatory conditions and posterior microvasculopathy reported. Although opportunistic infections remained possible in this group, they were less frequent than in those with CD4 <100 cells/μL. In patients with CD4 counts above 200 cells/μL, anterior segment manifestations such as dry eye disease and mild inflammatory conditions were more common, while severe posterior opportunistic infections were rarely reported. This gradient supports the concept of an immune-driven anatomical spectrum in which the severity and localization of ocular disease correspond to the degree of immunosuppression.

Distribution of Anterior and Posterior Segment Manifestations

Across all included studies, both anterior and posterior segment manifestations were reported within the same patient populations, supporting a true spectrum of ocular involvement. Anterior segment manifestations most frequently included dry eye disease, blepharitis, conjunctivitis, keratitis, and anterior uveitis. These findings were generally observed across a broad CD4 range but were more prevalent among patients with relatively preserved immune function compared to those with severe immunosuppression. Posterior segment manifestations were dominated by cytomegalovirus (CMV) retinitis, HIV-associated retinopathy, retinal hemorrhage, vasculopathy, chorioretinitis, and, in severe cases, necrotizing retinitis. CMV retinitis was consistently the most frequently reported sight-threatening posterior pathology across studies. The data demonstrate a distinct anatomical shift in disease burden according to immune status, with posterior opportunistic infections predominating in advanced immunosuppression.

Summary of Immune-Driven Spectrum

The included studies demonstrate a consistent pattern in which ocular manifestations in HIV/AIDS follow an immune-stratified distribution. Severe immunosuppression (CD4 <100 cells/μL) is strongly associated with sight-threatening posterior segment opportunistic infections, particularly CMV retinitis. As immune function improves, the burden shifts toward anterior segment inflammatory and ocular surface disorders. Additionally, ART initiation introduces a second immune-mediated phase characterized by inflammatory sequelae such as IRU. These findings substantiate the concept of an immune-driven spectrum of ocular involvement spanning anatomical segments and clinical severity in the contemporary ART era.

DISCUSSION

The present synthesis confirms that ocular manifestations in HIV/AIDS demonstrate a reproducible immune-stratified anatomical gradient across diverse geographic settings. The included core studies from India, Indonesia, and Nigeria consistently showed that posterior segment disease predominates in patients with CD4 counts below 100 cells/μL, particularly CMV retinitis and necrotizing retinitis [6–12]. Panigrahi and colleagues reported a clear CD4 threshold effect, whereas Babalola's ART clinic cohort observed a similar posterior dominance despite ART exposure [6,10]. In contrast, Triningrat and Rosa described mixed segment involvement in moderate immunosuppression, suggesting a transitional immunologic phase rather than abrupt anatomical shift [7,9]. These inter-study comparisons indicate that the immune gradient is not binary but progressive, reinforcing the immune-driven model of ocular disease distribution.

The predominance of CMV retinitis in severe immunosuppression aligns with contemporary virologic and retinal imaging analyses demonstrating persistent opportunistic vulnerability in patients with advanced CD4 depletion [13,14]. Zhang and Kobayashi emphasized that CMV-related retinal necrosis remains biologically linked to cytotoxic T-cell deficiency [13,14]. Widyanatha's findings mirror this pathophysiologic mechanism, showing high CMV frequency in CD4 <150 populations [8]. However, compared to earlier pre-ART cohorts, recent data suggest reduced fulminant presentations, possibly reflecting earlier ART initiation [15]. This shift supports the notion that ART modifies but does not abolish the posterior disease burden.

Anterior segment manifestations displayed greater variability across studies, with dry eye, blepharitis, and anterior uveitis reported even in patients with CD4 counts above 200 cells/μL [7,9]. Yang and Smith highlighted chronic immune activation and ocular surface dysregulation as mechanisms underlying anterior disease in virologically suppressed patients [16,17]. Compared with posterior infections, anterior manifestations appear less directly tied to profound immunodeficiency and may represent immune dysregulation rather than pure immune failure [17]. This distinction underscores that anterior involvement is not simply "milder disease," but may reflect different immunopathogenic pathways.

The immune reconstitution phenomenon introduces a second mechanistic dimension to the spectrum. Ghosh documented immune recovery uveitis (IRU) following ART initiation, characterized by posterior inflammation with anterior spillover [12]. Alves and Duraikkannu corroborate this by demonstrating inflammatory cytokine dysregulation during IRIS-related ocular events [18,19].

Pei's metabolomic profiling further supports the biological plausibility of immune restoration–mediated inflammation [20]. Compared with CMV-driven necrosis in CD4 <100, IRU reflects paradoxical inflammation after CD4 recovery, illustrating that ocular disease in HIV spans both deficiency and hyperactivation states.

Geographic comparisons also reveal contextual variability. Indonesian cohorts reported mixed segment patterns during moderate immunosuppression [7–9], whereas the Nigerian ART-based cohort showed stronger posterior predominance [10]. Resource availability, timing of diagnosis, and ART penetration likely influence these differences [21]. Screening studies demonstrate that structured retinal programs significantly improve early detection rates in high-risk populations [22]. Therefore, variations between cohorts likely reflect systemic healthcare factors rather than biological inconsistency.

Imaging-based analyses add further nuance. Advances in retinal imaging reveal microvascular changes even in patients without overt CMV infection, suggesting chronic subclinical retinal involvement [23,24]. Li and Roberts reported biomarkers associated with inflammatory retinal changes independent of active infection [23,25]. These findings suggest that the immune-driven spectrum includes subtle microvascular pathology beyond clinically obvious retinitis.

Across studies, the most consistent predictor of sight-threatening posterior disease remains CD4 <100 cells/μL [6,8,10,13]. However, Mehta's cohort demonstrated necrotizing retinitis even in patients with slightly higher counts, emphasizing that CD4 threshold alone is insufficient without considering ART duration and viral load [11]. Von Hofsten and Asadi similarly note that immune metrics must be interpreted within broader clinical context [26,27]. Thus, while CD4 stratification is clinically useful, it should be integrated with systemic assessment.

Importantly, the transition toward ART-modified disease patterns does not eliminate risk. Kuo's national cohort analysis and Mwangi's regional data demonstrate that posterior complications persist even in modern ART programs [28,29]. Alberta and Triningrat report ongoing retinal impairment and microvascular changes despite therapy [9,30]. These findings collectively indicate that immune restoration shifts disease phenotype but does not normalize ocular risk.

The comparison across the seven core studies and supporting literature demonstrates a coherent pattern that severe immunosuppression drives posterior opportunistic infection, moderate immunosuppression yields mixed segment disease, immune recovery introduces inflammatory sequelae, and preserved immunity favors anterior surface involvement. This gradient supports the conceptual integrity of an immune-driven spectrum rather than isolated ophthalmic conditions. Ocular disease in HIV/AIDS is not random it reflects the patient's immunologic state. CD4-guided, segment-based ophthalmic screening and structured post-ART monitoring are essential to prevent avoidable visual morbidity in the contemporary ART era.

CONCLUSION

This systematic synthesis demonstrates that ocular manifestations in HIV/AIDS follow a reproducible immune-stratified anatomical continuum. Posterior segment opportunistic infections, particularly CMV retinitis, dominate in advanced immunosuppression, while anterior inflammatory and ocular surface disorders become more prevalent with partial immune preservation. ART modifies disease expression by reducing fulminant opportunistic infection yet introducing immune recovery–related inflammation such as IRU. Across diverse geographic settings, CD4 level remains the most consistent predictor of anatomical distribution, though ART dynamics and systemic context modify risk.

Ethical Approval

This study was conducted as a systematic review of previously published literature. No human participants were directly involved, and no new patient data were collected. Therefore, institutional ethical approval and informed consent were not required.

Consent for Publication

Not applicable.

Competing Interests

The authors declare that they have no competing interests related to this work.

Availability of Data and Materials

All data analyzed in this study were derived from publicly available published articles. Extracted data supporting the findings of this review are available from the corresponding author upon reasonable request.

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Authors' Contributions

Conceptualization: RM, HE, SST

Literature search and screening: RM

Data extraction and analysis: RM, HE

Risk of bias assessment: RM, SST

Manuscript drafting: RM

Critical revision and final approval: HE, SST

All authors have read and approved the final manuscript.

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