

Understanding the Interplay: A Comprehensive Literature Review on the Correlation of CD4 Counts with Ocular Manifestations in HIV

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Abstract

Human Immunodeficiency Virus (HIV) intricately targets CD4-positive T lymphocytes, compromising the immune system's resilience. While the systemic impact of HIV is well-documented, its influence extends into ocular tissues, giving rise to a diverse array of manifestations reflective of evolving immunological dynamics. This study explores the pivotal correlation between CD4 counts and ocular complications in HIV, unraveling crucial insights into the underlying pathomechanisms. Investigating the intricate interplay between the immune system and ocular health, the study illuminates the role of CD4 counts as vital indicators of susceptibility and disease progression in the realm of HIV-associated ocular manifestations. Navigating this immunological tapestry provides profound implications for diagnosis, treatment, and future research, offering avenues to refine clinical strategies and elevate the quality of care for individuals grappling with both HIV and ocular complications.

Ocular lesions predominantly impact the posterior segment, encompassing conditions like HIV vasculopathy, infectious retinopathy or choroidopathy, and rare neoplasms. In developed nations, HIV vasculopathy or microangiopathy emerges as the predominant AIDS manifestation (40–60%), characterized by retinal hemorrhages, cotton-wool spots, microaneurysms, ischemic maculopathy, and telangiectatic vessels. Conversely, large vessel disease is infrequently observed. Cytomegalovirus (CMV) retinitis, constituting 15–40% of infectious retinopathy in AIDS, leads to complications like immune recovery uveitis (IRU) and retinal detachment, serving as major contributors to visual morbidity. Involvement of the anterior segment is less common, featuring complex cataract, anterior uveitis, fungal keratitis, herpes simplex and zoster keratitis, peripheral ulcerative keratitis, and bacterial keratitis

Keywords: HIV; CD4 counts; Ocular manifestations; HIV vasculopathy; Cytomegalovirus retinitis

1. Introduction

Human Immunodeficiency Virus (HIV) has long been recognized as a formidable adversary to the immune system, particularly targeting CD4-positive T lymphocytes, the architects of a robust immune response. Beyond its systemic effects, HIV weaves a complex narrative within ocular tissues, leading to a spectrum of manifestations that mirrors the evolving immunological landscape. The correlation between CD4 counts and ocular complications in HIV unfolds a critical chapter in understanding the pathomechanisms at play. This exploration delves into the intricate interplay between the immune system and ocular health, shedding light on how CD4 counts serve as sentinel indicators of susceptibility and progression in the realm of HIV-associated ocular manifestations. As we navigate this immunological tapestry, the implications for diagnosis, treatment, and future research become increasingly apparent, offering avenues to refine clinical strategies and enhance the quality of care for individuals facing the dual challenge of HIV and ocular complications.¹

Ocular lesions primarily affect the posterior segment, encompassing conditions such as HIV vasculopathy, infectious retinopathy or choroidopathy, and uncommon neoplasms. In developed countries,

HIV vasculopathy or microangiopathy stands as the predominant AIDS manifestation (40–60%), characterized by retinal hemorrhages, cotton-wool spots, microaneurysms, ischemic maculopathy, and telangiectatic vessels. Conversely, large vessel disease is infrequently observed. Cytomegalovirus (CMV) retinitis, accounting for 15–40% of infectious retinopathy in AIDS, gives rise to complications like immune recovery uveitis (IRU) and retinal detachment, constituting the leading causes of visual morbidity. The involvement of the anterior segment is less frequent, involving complex cataract, anterior uveitis, fungal keratitis, herpes simplex and zoster keratitis, peripheral ulcerative keratitis, and bacterial keratitis.²

2. CD4 Counts in HIV

CD4-positive T cells play a pivotal role in orchestrating the immune response, coordinating defenses against infections and malignancies. HIV, however, selectively invades and destroys these cells, progressively compromising the immune system. Monitoring CD4 counts provides valuable insights into the severity of immune system impairment and aids in guiding clinical decisions. The decline in CD4 counts is closely associated with the progression of HIV. In the early stages of infection, CD4 counts may remain relatively stable, but as the virus replicates and the immune system becomes further compromised, a decline is observed. Lower CD4 counts indicate increased vulnerability to opportunistic infections and signal the need for intervention, such as antiretroviral therapy (ART). Regular monitoring of CD4 counts is integral to the management of HIV. The World Health Organization (WHO) and national health guidelines recommend routine CD4 count assessments to gauge the need for initiating or modifying ART. This personalized approach helps healthcare providers tailor treatment strategies based on individual immune system status. Effective antiretroviral therapy aims not only to suppress viral replication but also to restore and maintain CD4 counts. Successful treatment often results in an increase in CD4 counts, reflecting improved immune function. This serves as a key indicator of treatment efficacy, guiding healthcare professionals in assessing the response to therapy and making informed adjustments when necessary.²

3. Ocular Manifestations in HIV

□ Cytomegalovirus (CMV) Retinitis:

Infectious retinitis, specifically Cytomegalovirus retinitis (CMV retinitis), was prevalent in 30–40% of HIV-infected patients before the advent of Highly Active Antiretroviral Therapy (HAART). Since then, there has been a substantial 75% reduction in infection rates and a 50% decreased risk of retinitis progression. CMV retinitis remains the most common ocular opportunistic infection associated with AIDS. Three prevalent clinical forms include hemorrhagic retinitis with prominent edema, a granular type with satellite lesions, and the less frequent perivascular retinitis. Common symptoms include floaters or a gradual loss of the visual field.³

Clinical examination is pivotal for diagnosing CMV retinitis. Other causes of necrotizing retinitis, such as VZV, HSV, syphilis, toxoplasmosis, and lymphoma, should be ruled out when uncertainty arises. FDA-approved treatments include intravenous ganciclovir, foscarnet, and cidofovir, as well as oral

valganciclovir. Treatment is individualized based on the patient's ocular and systemic disease, side effects, and response to previous treatment. If HAART is not initiated at the time of diagnosis, its commencement should be delayed until the completion of the anti-CMV treatment's induction phase to prevent immune recovery uveitis. However, a delay of more than two weeks has not been shown to yield different results. Maintenance therapy should only be discontinued after 3–6 months of inactive disease, with CD4+ cell counts exceeding 150 cells/ μ L and a reduced HIV viral load observed. If retinitis persists or progresses after six weeks of induction therapy, the virus should be considered resistant, or the initial diagnosis may be incorrect.³

□ Retinal microvasculopathy,

also referred to as HIV retinopathy, was observed in 40–60% of HIV/AIDS patients before the introduction of HAART, and its prevalence has decreased since then. Currently, 45% of patients with CD4+ counts below 50 cells/ μ L exhibit characteristic features of retinal microvasculopathy. The primary manifestation is the presence of cotton-wool spots, although less frequently observed features include intraretinal hemorrhages, microaneurysms, and ischemic maculopathy. Unlike early CMV retinitis, cotton-wool spots in microvasculopathy are not associated with significant contiguous or intralesional hemorrhage, subtle iritis, or mild posterior vitritis. Ischemic maculopathy, occurring in approximately 3% of retinal microvasculopathy cases, may lead to sudden vision loss, characterized by dot and blot hemorrhages and perifoveal cotton-wool spots. These findings are typically transient, except for retinal ischemia. The pathogenesis of retinal microvasculopathy remains unclear, with hypotheses including HIV-induced increase in plasma viscosity, immune complex deposition, direct infection of the endothelium by HIV, and increased rigidity of circulating neutrophils. In most cases, treatment is not warranted; however, in rare instances of macular edema, focal laser photocoagulation may be considered beneficial.⁴

□ Immune recovery uveitis (IRU)

Immune recovery uveitis (IRU) is part of the spectrum of disorders known as immune reconstitution inflammatory syndrome (IRIS), characterized by paradoxical inflammatory responses following robust immune recovery induced by Highly Active Antiretroviral Therapy (HAART). IRIS results from the restoration of immunity to specific antigens, driven by an increase in CD4+ T-lymphocytes, leading to a paradoxical escalation of inflammation. Common primary infections triggering IRIS encompass varicella-zoster, mycobacteria, herpesviruses, and cytomegalovirus. IRU, the intraocular manifestation of IRIS, is frequently observed when immunity is reestablished against CMV. Key findings in IRU include moderate to severe vitritis, cystoid macular edema, optic disc edema, and, less commonly, epiretinal membrane formation, proliferative vitreoretinopathy, and retinal neovascularization. The risk of developing IRU is higher in individuals with a history of CMV retinitis and previous use of cidofovir. IRU is managed with a combination of periocular, topical, or intraocular corticosteroids, as deemed

appropriate. Studies have demonstrated that uveitis can be induced by various drugs used in the treatment of infections associated with HIV/AIDS, including cidofovir and rifabutin.⁴

□ **Toxoplasmosis retinochoroiditis**

Toxoplasmosis retinochoroiditis affects less than 1% of individuals with HIV in the United States; however, regions with higher seroprevalence of *Toxoplasma gondii* show increased rates of toxoplasmic retinochoroiditis. The incidence of ocular toxoplasmosis is lower in HAART-responsive patients, and many discontinue prophylactic treatment as CD4+ cell counts rise. Distinguishing features in HIV-infected patients include moderate to severe vitreous and anterior chamber inflammation, a relatively absence of retinal hemorrhage, and a smooth leading edge instead of a granular one. Multifocal and bilateral disease is more prevalent in HIV-positive individuals. Diagnostic testing involves serology for IgG and IgM toxoplasmosis antibodies, although severely immunosuppressed patients may yield negative results. PCR analysis of intraocular fluids can aid in diagnosis. MRI scanning of the brain is recommended for all HIV patients with suspected toxoplasmic retinochoroiditis, as up to 50% of those with ocular toxoplasmosis may have central nervous system involvement. The common treatment approach involves pyrimethamine in combination with a sulfonamide, oral corticosteroids, and optionally clindamycin (300 mg PO four times a day for three or more weeks). Patients with persistent severe immune deficiency often require repeated therapy. Significantly reducing recurrences is achieved with one tablet of 160 mg of trimethoprim and 800 mg of sulfamethoxazole (Bactrim) every three days.⁴

4. Correlation of CD4 with ocular HIV

The correlation of CD4 count with ocular manifestations in HIV patients is a significant aspect of understanding the impact of the virus on the eyes. CD4 cells, also known as T-helper cells, play a crucial role in regulating the immune system. In individuals with HIV, the virus specifically targets and damages these CD4 cells, leading to a decline in their count. The CD4 count is often used as an indicator of the immune status of an individual with HIV.⁵

In the context of ocular manifestations in HIV, there is a strong correlation between the severity of these manifestations and the CD4 count. A lower CD4 count is generally associated with a higher likelihood and increased severity of ocular complications. The CD4 count serves as a marker for the overall immunocompetence of the individual, and a decline in CD4 count suggests a weakened immune system, making the individual more susceptible to opportunistic infections⁵

Common ocular manifestations in HIV patients include conditions like HIV retinopathy, cytomegalovirus (CMV) retinitis, and other infections or inflammations that affect different parts of the eye. The severity and type of ocular complications may vary based on the CD4 count, and monitoring CD4 levels is essential in assessing the risk and progression of ocular manifestations.⁵

Patients with lower CD4 counts are more prone to severe ocular conditions, such as CMV retinitis, which can lead to visual impairment if not addressed promptly. Conversely, individuals with higher CD4 counts may have a lower risk of developing severe ocular complications.⁶

The Immune System in HIV:

Human Immunodeficiency Virus (HIV) orchestrates its deleterious effects primarily on the immune system, and CD4-positive T lymphocytes play a pivotal role in the immune response. These cells are crucial for coordinating defenses against various pathogens, maintaining immune balance, and orchestrating immune memory. As HIV selectively targets and infects CD4 cells, the progressive depletion of these cells weakens the immune system, leaving the body susceptible to opportunistic infections.⁷

Pathomechanism of Ocular Manifestations in HIV:⁷

□ Impact on Retinal Cells:

In the context of ocular manifestations, the virus can directly infect retinal cells, leading to conditions such as cytomegalovirus (CMV) retinitis. CMV, a common opportunistic pathogen, takes advantage of the weakened immune system to cause inflammation and damage to the retina.

□ Immune Dysregulation:

The decline in CD4 counts signals a breakdown in immune regulation. The loss of regulatory control can result in heightened inflammation within ocular tissues, contributing to various manifestations such as uveitis and conjunctivitis.

□ Opportunistic Infections:

With lowered CD4 counts, the immune system's ability to ward off opportunistic infections diminishes. Ocular tissues become susceptible to infections that would typically be kept in check by a healthy immune response. This vulnerability contributes to the development of conditions like HIV-related optic neuropathy.

□ Role of Systemic Inflammation:

HIV triggers a systemic inflammatory response that can extend to ocular tissues. Chronic inflammation may exacerbate pre-existing ocular conditions or induce new pathologies, further complicating the clinical landscape.

Correlation with CD4 Counts:

A notable association was observed between the severity of posterior segment lesions and a decline in the CD4+ count ($P < 0.0001$). In the study, 47% of patients exhibiting ocular manifestations had CD4+ counts ranging from 51 to 200, while 13% had CD4+ counts exceeding 500. Among cases with CD4+ counts below 50, three presented with CMV retinitis and HIV retinopathy. Previous research by Sudharshan et al. indicated that a CD4+ count limit of 200 showed a stronger clinical correlation with HAART and the occurrence of ocular lesions. In their investigation, 47.7% of patients were not undergoing HAART at the time of ocular lesion diagnosis, and 69% of them had CD4+ counts below 200. Similarly, in the study by Gogri et al., a

majority of patients with posterior segment lesions had CD4+ counts below 200. Narasimhaiah et al. found that the majority of patients with ocular manifestations had CD4+ counts ranging from 51 to 199 (less than 200). A significant correlation was identified between the severity of ocular manifestations, particularly posterior segment findings and opportunistic infections, which escalated with a decrease in CD4+ count ($P < 0.001$).⁵⁻⁷

5. Conclusion

In conclusion, our investigation into the correlation of CD4 counts with ocular manifestations in HIV has illuminated the intricate relationship between immunological status and ocular health. The significant association between lower CD4 counts and the severity of posterior segment lesions underscores the pivotal role of CD4-positive T lymphocytes in influencing the ocular landscape in HIV-infected individuals. As we navigate the complexities of HIV-associated ocular complications, our findings emphasize the importance of CD4 counts as valuable indicators for both susceptibility and progression of ocular manifestations. The identified patterns, such as the prevalence of HIV vasculopathy and CMV retinitis, provide clinicians with crucial insights for early detection and management. The implications extend beyond diagnosis, influencing treatment decisions and highlighting the need for vigilant ocular monitoring in individuals with varying CD4 counts.

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