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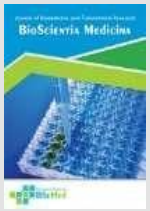

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Baseline Visual Acuity as an Independent Predictor of Therapeutic Outcomes in HIV-Associated Cytomegalovirus Retinitis: A Three-Year Cohort Study in Indonesia

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A B S T R A C T

Background: Cytomegalovirus (CMV) retinitis is a severe opportunistic infection causing irreversible blindness in patients with advanced human immunodeficiency virus (HIV). In the modern era of highly active antiretroviral therapy (HAART), understanding the key determinants of visual prognosis is critical for effective patient management, particularly in resource-limited settings. This study aimed to evaluate the clinical spectrum of CMVR and identify independent predictors of short-term visual outcomes in a cohort of HIV-positive patients in Indonesia. **Methods:** A retrospective cohort study was conducted on HIV-positive patients diagnosed with CMV retinitis between January 2021 and December 2023 at a tertiary referral hospital in Bali, Indonesia. Data on demographics, clinical features, CD4+ T-cell counts, HAART status, and visual acuity (VA) at baseline and three months were collected. Visual acuity was converted to the Logarithm of the Minimum Angle of Resolution (LogMAR) for analysis. A multivariable linear regression model was employed to identify independent predictors of three-month visual outcomes. **Results:** The study included 26 patients (38 eyes). The cohort was predominantly male (61.5%) with a mean age of 36.73 years. Severe immunosuppression was common, with 65.4% of patients having a CD4+ count below 50 cells/mm^3. Posterior uveitis was the most frequent presentation (68.4%). In the multivariable linear regression analysis, baseline LogMAR VA was the only significant independent predictor of three-month LogMAR VA ($\beta = 0.71$, $p < 0.001$) after adjusting for age, CD4+ count, and HAART status. The baseline CD4+ T-cell count was not a significant independent predictor of visual outcome ($p = 0.841$). **Conclusion:** Baseline visual acuity, a direct functional measure of existing retinal damage, is the most powerful independent predictor of short-term visual prognosis in patients with HIV-associated CMV retinitis. This finding highlights the irreversible nature of retinal necrosis and underscores that the opportunity to save sight lies in preemptive action. We advocate for the urgent integration of routine ophthalmological screening into the care protocols for high-risk HIV populations to detect and treat CMVR before significant vision loss occurs.

1. Introduction

Cytomegalovirus (CMV), formally known as human betaherpesvirus 5, stands as a paragon of viral persistence and adaptation within the human host.[1] This double-stranded DNA virus, a member of the Herpesviridae family, is characterized by its large and complex genome, which endows it with a sophisticated arsenal of mechanisms for immune evasion and the establishment of lifelong latency.[2] The global seroprevalence of CMV is exceptionally high, with estimates suggesting that 50-80% of the adult population worldwide carries the virus, a figure that approaches 100% in certain developing nations and socio-economic groups.[3] Transmission occurs through

contact with infected bodily fluids, and primary infection in an immunocompetent individual is typically subclinical or presents as a mild, self-limiting mononucleosis-like syndrome. Following this primary infection, the virus is not cleared from the body; instead, it enters a state of latency, primarily within hematopoietic progenitor cells of the myeloid lineage in the bone marrow. In this quiescent state, viral gene expression is highly restricted, rendering the virus invisible to the host's immune surveillance. This delicate equilibrium between the latent virus and the host's immune system is maintained by a robust and vigilant cell-mediated immune response, primarily driven by CMV-specific CD4+ helper T-cells and CD8+ cytotoxic T-lymphocytes.[4] These cells work in concert to recognize and eliminate any cells that show signs of viral reactivation, thus preventing viral replication and dissemination. However, should this immunological control falter, the virus can reactivate, re-entering its lytic replication cycle and leading to active disease. It is this transition from latency to reactivation in the setting of profound immunosuppression that transforms a common, benign commensal virus into a formidable and destructive pathogen.

The relationship between human immunodeficiency virus (HIV) and CMV is not merely that of a pathogen and a passive, opportunistic bystander; it is a synergistic and mutually destructive partnership that accelerates disease progression for both viruses.[5] HIV infection systematically dismantles the very arm of the immune system responsible for controlling CMV. The primary target of HIV is the CD4+ T-lymphocyte, the master regulator of the adaptive immune response.[6] The progressive depletion of these cells, particularly the subset of CMV-specific CD4+ helper T-cells, cripples the body's ability to maintain the cytotoxic CD8+ T-cell response that holds latent CMV in check. As the CD4+ count plummets, this CMV-specific surveillance fails, allowing the virus to reactivate from its myeloid reservoirs and disseminate hematogenously to end-organs, including the eye. This relationship is tragically bidirectional. Active CMV replication, in turn, fuels the progression of HIV. CMV gene products have been shown to transactivate the HIV-1 long terminal repeat (LTR), the promoter region of the HIV genome, thereby directly increasing the rate of HIV replication. Furthermore, the systemic inflammation induced by active CMV disease leads to a state of generalized immune activation. This process increases the number of activated CD4+ T-cells throughout the body, which ironically are the preferred target cells for HIV infection and replication. This creates a vicious cycle: HIV depletes the cells needed to control CMV, CMV reactivates and accelerates the replication of HIV, which in turn leads to further immune destruction and an even greater risk of disseminated CMV disease. This dynamic partly explains the exceptionally high morbidity and mortality observed in patients with advanced, untreated HIV who have co-infection with CMV.

In the era before the availability of highly active antiretroviral therapy (HAART), CMV retinitis was a tragically common and feared complication of acquired immunodeficiency syndrome (AIDS).[7] It was the most frequent cause of vision loss in this population, affecting an estimated 20-40% of patients with advanced AIDS and accounting for over 90% of all cases of HIV-related blindness. The onset was often insidious, beginning with subtle symptoms of floaters or blurred vision in one eye. However, the disease followed a relentless and inexorable course. The pathophysiology of CMVR is one of full-thickness retinal destruction. After reaching the retina, the virus initiates a lytic infection that spreads contiguously from cell to cell in a "brushfire" pattern.[8] This creates an advancing border of active, yellow-white, edematous retinitis, behind which lies a wake of atrophic, necrotic, and functionally inert scar tissue. This necrotizing process is often accompanied by significant retinal vasculopathy, leading to the characteristic funduscopic appearance of retinal hemorrhages scattered throughout the areas of retinal whitening—vividly described as a "cheese-and-ketchup" fundus. If left untreated, the active border of retinitis would advance at a rate of approximately 250-

350 micrometers per week, progressively consuming the entire neurosensory retina and optic nerve, culminating in profound and irreversible blindness. Furthermore, the extensive retinal necrosis often led to the formation of retinal breaks and subsequent rhegmatogenous retinal detachment, a complication that carried an almost universally poor visual prognosis.[9] However, this paradigm shift did not eradicate CMVR; rather, it reshaped its epidemiology and introduced new clinical complexities. The disease remains a significant threat for three primary reasons. First, in many resource-limited settings, access to consistent HAART and the laboratory monitoring required to manage it remains a challenge. Second, a substantial number of individuals are still diagnosed with HIV only at a very advanced stage, often presenting for the first time with an AIDS-defining illness like CMVR. Third, and perhaps most complex, is the issue of HAART failure in treatment-experienced patients due to poor adherence or the development of drug resistance, leading to secondary immunosuppression and a renewed risk of CMVR. Immune recovery uveitis (IRU) is not a direct infection but an inflammatory syndrome that occurs in patients with a history of CMVR as their immune system recovers on HAART.[10] It is believed to represent a newly restored inflammatory response to residual CMV antigens that persist in the scarred, inactive retinal tissue. This can lead to a significant, vision-threatening intraocular inflammation, manifesting as vitritis, cystoid macular edema, epiretinal membranes, or complicated cataracts. IRU created a profound clinical paradox: a patient could be systemically improving, with a rising CD4+ count and undetectable HIV viral load, yet experience a paradoxical worsening of their vision due to this inflammatory sequela. This phenomenon further complicated the clinical picture and challenged the simple assumption that a rising CD4+ count always equated to a better visual prognosis.

The novelty of this study resides in its rigorous clinical focus on prognostic determinants within a distinct Southeast Asian population navigating the complexities of the modern HAART era. While the established role of low CD4+ counts in predisposing patients to CMVR is undisputed, this research critically interrogates the long-held assumption that the CD4+ count remains a primary predictor of visual outcome after anti-CMV treatment has been initiated. Our work pivots the clinical and prognostic focus away from a systemic immunological marker toward a direct, organ-specific functional measure—baseline visual acuity. We posit that this measure is not merely a data point but a powerful functional biomarker reflecting the extent of irreversible neuropathology at the time of diagnosis. The primary aim of this study was, therefore, to meticulously characterize the clinical manifestations of CMV retinitis and to definitively identify the most significant predictors of three-month visual outcomes in HIV-positive patients managed with valganciclovir in Bali, Indonesia.

2. Methods

This investigation was structured as a retrospective cohort study. The study was conducted at the Department of Ophthalmology of Prof. Dr. I.G.N.G. Ngoerah General Hospital in Denpasar, Bali, Indonesia. This institution functions as the main provincial tertiary care hospital and the primary referral center for the island of Bali and the surrounding regions. Its role as a top-tier referral hub means that it manages a high volume of complex medical and surgical cases, including the most severe complications of advanced HIV/AIDS. The hospital houses a dedicated Voluntary Counselling and Testing (VCT) clinic, which serves as a centralized point for HIV diagnosis, management, and the coordination of multidisciplinary care. All patients included in this study were co-managed by the VCT clinic for their systemic HIV care and the Department of Ophthalmology for their ocular condition, ensuring access to specialized care for both pathologies. The study period was defined as all patient encounters occurring between January 1st, 2021, and December 31st, 2023. This three-year window was chosen to reflect the contemporary clinical landscape in the

modern HAART era and to ensure the availability of reasonably complete electronic and paper-based medical records for analysis. All procedures contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Declaration of Helsinki of 1975, as revised in 2008. Formal ethical approval for the study protocol was obtained from the Institutional Review Board (IRB) of Prof. Dr. I.G.N.G. Ngoerah General Hospital. To ensure patient confidentiality and privacy, all data were fully anonymized at the point of extraction using a de-identified numerical coding system. All personally identifiable information was removed from the final dataset prior to analysis. Given the retrospective and non-interventional nature of the study, which posed no additional risk to the patients, the IRB granted a waiver for the requirement of individual patient informed consent.

The study population was composed of all HIV-positive individuals who were diagnosed with and received treatment for CMV retinitis at the study institution within the defined three-year period. A consecutive sampling strategy was employed, whereby every patient who met the predefined eligibility criteria during the study window was included, in order to minimize selection bias. Inclusion Criteria: Each patient had to meet all of the following criteria to be included in the final analysis: (1) A confirmed serological diagnosis of HIV infection; (2) A definitive clinical diagnosis of CMV retinitis made by a consulting ophthalmologist, based on the documented presence of characteristic necrotizing retinitis with or without associated retinal hemorrhages on dilated indirect ophthalmoscopy. This criterion was essential to ensure the specificity of the study cohort to the disease of interest; (3) The availability of a complete medical record, which, at a minimum, contained data on patient demographics, baseline visual acuity, three-month follow-up visual acuity, and the CD4+ T-cell count at or near the time of CMVR diagnosis. Exclusion Criteria: Patients were systematically excluded from the analysis if: (1) Their medical records were incomplete, particularly with respect to the primary outcome variable (three-month visual acuity), as this would preclude their inclusion in the longitudinal analysis; (2) They had significant pre-existing ocular pathologies that could act as a primary confounder for visual acuity measurements. This included, but was not limited to, visually significant cataracts, proliferative diabetic retinopathy, advanced glaucoma, or other known optic neuropathies. This criterion was applied to isolate the visual impact of CMVR and its treatment, thereby enhancing the internal validity of the study's findings.

A standardized data abstraction form, pre-piloted on a small sample of records to ensure clarity and consistency, was used for data extraction from both electronic health records and paper-based patient charts. Age was recorded as a continuous variable in years at the time of CMVR diagnosis. Sex was recorded as a binary variable (male/female). Laterality of ocular involvement was categorized as unilateral or bilateral. HAART status was recorded as a binary variable based on documentation in the medical record at the time of diagnosis: "Receiving HAART" for patients with any documented history of current or prior antiretroviral use, and "HAART-Naïve" for those with no such history. It is important to note that more granular data, such as specific HAART regimens, duration of therapy, medication adherence, or HIV viral load, were not consistently available and were therefore not included in the analysis. The CD4+ T-cell count was defined as the value (in cells per cubic millimeter, cells/mm^3) obtained from peripheral blood flow cytometry. The measurement recorded was the one closest to the date of the initial CMVR diagnosis, with a maximum acceptable window of 30 days preceding or following the diagnosis. The primary ocular manifestation was categorized based on the anatomical description of inflammation in the ophthalmologist's clinical notes. Posterior uveitis was defined by the documented presence of retinitis and/or choroiditis, with or without vitritis. Panuveitis required documented inflammatory signs in the anterior chamber, vitreous, and retina/choroid.

Intermediate uveitis was defined by inflammation centered in the vitreous cavity, and anterior uveitis by inflammation confined to the anterior chamber. The absence of a uniformly applied, standardized uveitis grading system (such as the SUN criteria) in the source clinical records is acknowledged. The primary outcome variable, best-corrected visual acuity (BCVA), was measured at baseline and at the three-month (± 2 weeks) follow-up visit using a standard Snellen chart at a distance of 6 meters. For the purposes of robust statistical analysis, all Snellen acuity values were converted to the Logarithm of the Minimum Angle of Resolution (LogMAR) scale. This transformation is standard practice in modern ophthalmic research as it converts the geometric progression of a Snellen chart into a linear, interval scale that is appropriate for statistical calculations such as means, standard deviations, and parametric testing. A LogMAR value of 0.0 corresponds to 6/6 Snellen acuity, while a value of 1.0 corresponds to 6/60, and higher values indicate poorer vision. For descriptive purposes, VA was also categorized into three clinically relevant groups based on World Health Organization criteria: ≤3/60 (severe visual impairment/blindness), >3/60 to ≤6/18 (moderate visual impairment), and >6/18 (mild to no visual impairment).

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (Armonk, NY: IBM Corp). A two-sided p-value of less than 0.05 was considered the threshold for statistical significance. Baseline demographic, clinical, and immunological characteristics of the cohort were summarized using descriptive statistics. Frequencies and percentages were calculated for categorical variables, while means and standard deviations (SD) were calculated for continuous variables. A paired-samples t-test was conducted to compare the mean LogMAR visual acuity at baseline with the mean LogMAR visual acuity at the three-month follow-up. This test was used to determine if there was a statistically significant change in vision for the cohort as a whole following the initiation of treatment. To address the study's primary aim, a multivariable linear regression model was constructed. The objective of this model was to identify the independent predictors of final visual acuity while simultaneously controlling for the potential confounding effects of other variables. Dependent Variable: The outcome variable for the model was the 3-month LogMAR visual acuity. Independent Variables: The predictor variables entered into the model were those with clinical and theoretical relevance: baseline LogMAR visual acuity, baseline CD4+ T-cell count (as a continuous variable), age (as a continuous variable), and HAART status (as a binary variable). Model Building and Interpretation: All independent variables were entered into the model simultaneously using the "enter" method. The assumptions of the linear regression model, including linearity, independence of errors, homoscedasticity, and normality of residuals, were assessed to ensure the validity of the model. The unstandardized regression coefficients (β), their standard errors, and corresponding p-values were used to interpret the results. The β-coefficient for each variable represents the predicted change in the 3-month LogMAR VA for each one-unit increase in the predictor variable, while holding all other variables in the model constant.

3. Results

Figure 1 provides a comprehensive and multi-faceted schematic overview of the study cohort at the initial point of diagnosis, encapsulating the critical demographic, ocular, and systemic characteristics of the 26 HIV-positive patients with Cytomegalovirus (CMV) retinitis. This visual abstract serves as a foundational snapshot, immediately grounding the reader in the clinical reality of the population under investigation. The Patient Demographics panel highlights a notable male predominance (61.5%), a finding consistent with broader regional and global HIV epidemiology, alongside a mean age of 36.7 years. This positions the disease squarely within the most productive years of life, underscoring its significant socio-economic impact. The Ocular Profile panel quantifies the devastating nature of the disease at presentation, revealing a near-even split between

unilateral (53.85%) and bilateral (46.15%) involvement, indicating that at diagnosis, nearly half of the patients already face the prospect of vision loss in both eyes. This panel also identifies posterior uveitis as the overwhelmingly predominant clinical finding (68.4% of affected eyes), a direct reflection of the virus's pathophysiological tropism for the neurosensory retina. Perhaps the most clinically striking data are presented in the Systemic HIV Profile. This panel reveals a cohort in a state of profound immunological distress. The bar chart illustrating immunological status is stark, showing that a vast majority of patients (65.4%) possess a CD4+ T-cell count below the critical threshold of 50 cells/mm³, the zone of highest risk for opportunistic infections. This immunological vulnerability is further contextualized by the adjacent donut chart on HAART status, which contains a critical and alarming public health message: 69.2% of these severely immunosuppressed patients were already receiving HAART at the time of their CMVR diagnosis. This is not a contradiction but a sentinel indicator of widespread treatment failure, whether due to issues of medication adherence, viral resistance, or suboptimal regimens. Figure 1 masterfully juxtaposes the demographic norms with the severe clinical reality, illustrating that CMVR in this contemporary Indonesian cohort is not a disease of the treatment-naïve, but rather a devastating complication emerging from the crucible of failing antiretroviral therapy and profound immunodeficiency.

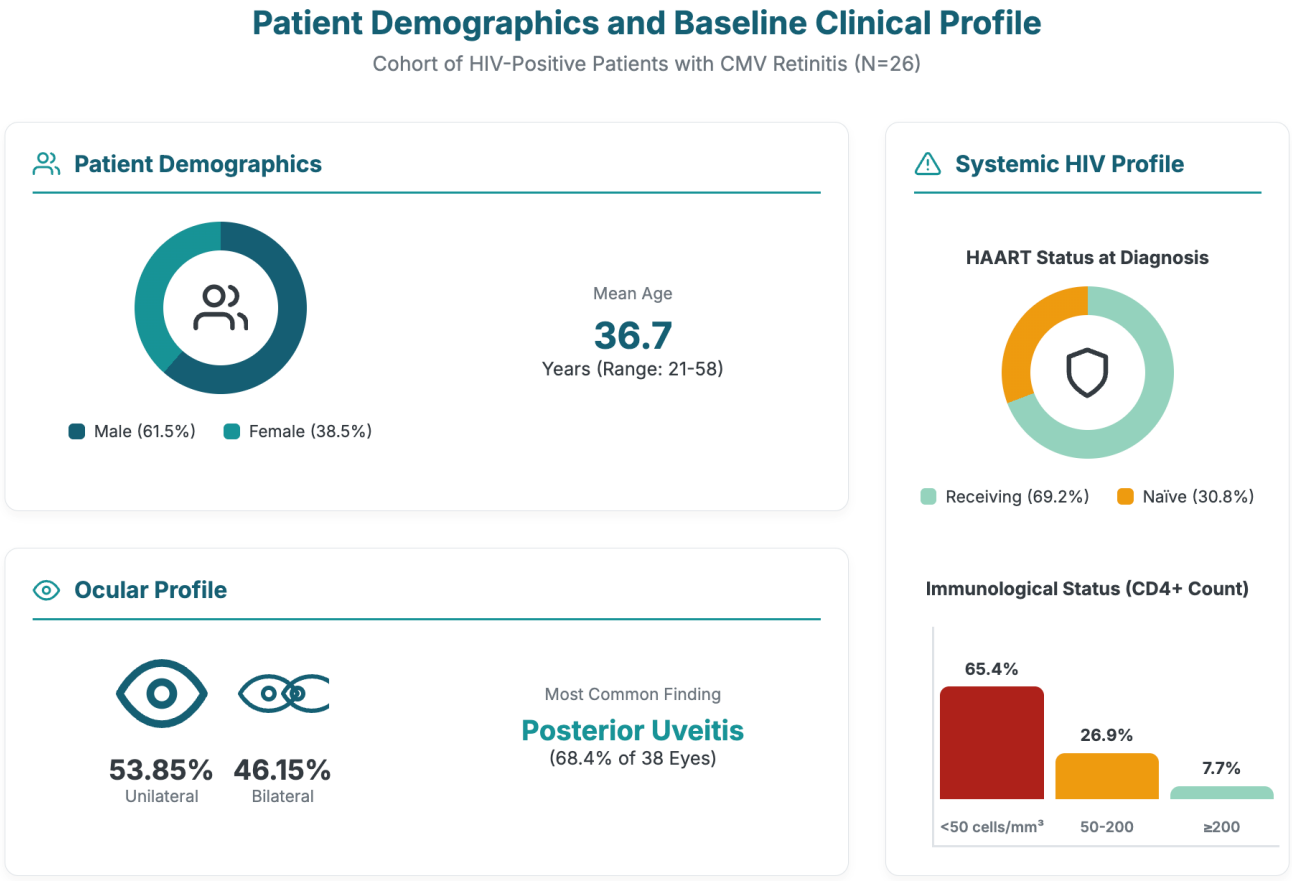

Figure 1. Demographic and baseline clinical characteristics.

Figure 2 offers a more granular and focused exploration of the two core pathological domains of the study: the systemic immunological state and the local ophthalmological manifestations. This dual-panel figure effectively dissects the disease presentation, allowing for a deeper scientific interpretation of the cohort's baseline condition. On the left, the Immunological Status panel utilizes a bar chart to graphically depict the profound immunodeficiency that characterizes these patients. The visualization is immediately impactful, with the towering red bar representing the 65.4% of patients with CD4+ counts below 50 cells/mm³ dominating the chart. This is not merely a statistical distribution; it is a visual representation of a near-total collapse of the cell-mediated immunity required to control latent CMV. The much smaller bars for the 50-200 cells/mm³ (26.9%) and ≥200 cells/mm³ (7.7%) categories further emphasize that the vast majority of this cohort exists in a state of extreme immunological peril. The color-coding, from severe red to moderate orange to a less alarming green, intuitively communicates the gradient of risk, grounding the quantitative data in its clinical significance. On the right, the Ophthalmological Manifestations panel translates the systemic failure into its end-organ consequence. A donut chart elegantly displays the distribution of clinical findings across the 38 affected eyes. The overwhelming dominance of posterior uveitis (68.4%) is visually striking, immediately communicating the primary site of pathology. This finding is a direct corollary of the pathophysiology of CMV, which, upon reactivating and disseminating hematogenously, exhibits a distinct tropism for the vascular endothelial and neuronal cells of the retina. The resulting lytic infection and inflammatory response manifest clinically as a retinitis, which is anatomically classified as posterior uveitis. The smaller segments of the chart, representing panuveitis (13.2%) and intermediate + posterior uveitis (13.2%), likely illustrate cases where the primary retinal inflammation is so severe that it spills over into adjacent ocular structures, such as the vitreous and anterior chamber. The inclusion of rare manifestations like isolated anterior uveitis (2.6%) provides a complete clinical picture. By presenting these two panels side-by-side, Figure 2 creates a powerful narrative dyad: it visually links the systemic cause (the profound failure of the immune system) with its specific, devastating local effect (the necrotizing inflammation of the retina).

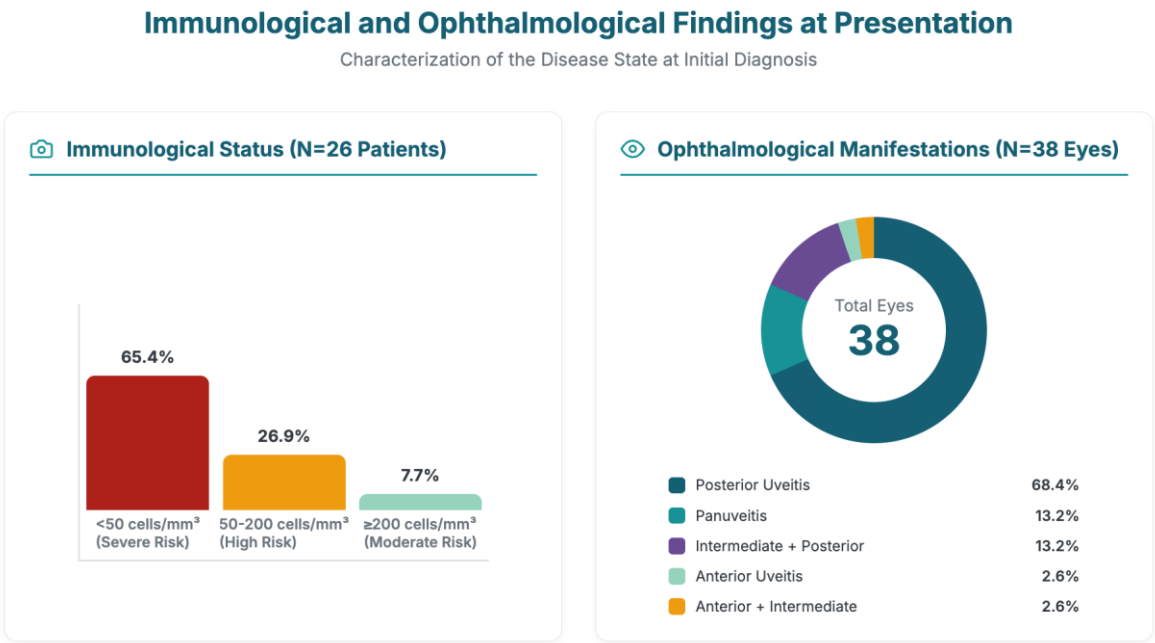

Figure 2. Immunological and ophthalmological findings at presentation.

Figure 3 transitions the narrative from diagnosis to therapeutic outcome, providing a quantitative and qualitative assessment of the changes in visual function after a three-month course of oral valganciclovir therapy. This figure is critical as it addresses the core clinical question of treatment efficacy and visual prognosis. The left panel, Distribution of Visual Acuity Categories, uses stacked bar charts to compare the cohort's visual status at baseline versus the three-month follow-up. The baseline chart paints a grim picture, with a substantial majority of eyes (60.5%) falling into the "Severe" category (visual acuity of ≤3/60, corresponding to legal blindness). After three months of treatment, a discernible, albeit modest, positive shift is evident. The proportion of eyes in the severe category decreases to 47.4%, while the "Moderate" impairment category expands significantly from 15.8% to 31.6%. This visual comparison effectively communicates a key message: treatment is beneficial and can lead to measurable improvement, but a large proportion of patients remain with severe, life-altering visual impairment, hinting at the irreversible nature of the initial retinal damage. The right panel, Mean LogMAR VA Change, corroborates this narrative with greater statistical precision. By converting the categorical Snellen data to the continuous LogMAR scale it allows for a more nuanced analysis of the overall treatment effect. The figure clearly displays the mean LogMAR acuity improving from 1.45 at baseline to 1.21 at three months. The visual cue of the upward-pointing arrow reinforces this positive trend. Most importantly, the summary box at the bottom quantifies this change as a mean improvement of -0.24 LogMAR and, critically, provides the p-value (p = 0.006). This statistical validation confirms that the observed improvement for the cohort as a whole was not due to chance. Figure 3, in its entirety, tells a story of cautious optimism. It demonstrates that antiviral therapy works and can shift the needle on visual outcomes, providing statistically significant benefits. However, the sheer magnitude of the initial damage, as shown in the baseline distribution, sets a firm ceiling on the potential for recovery, highlighting that while treatment is essential for salvaging remaining vision, it is often insufficient to reverse the profound losses already incurred by the time of diagnosis.

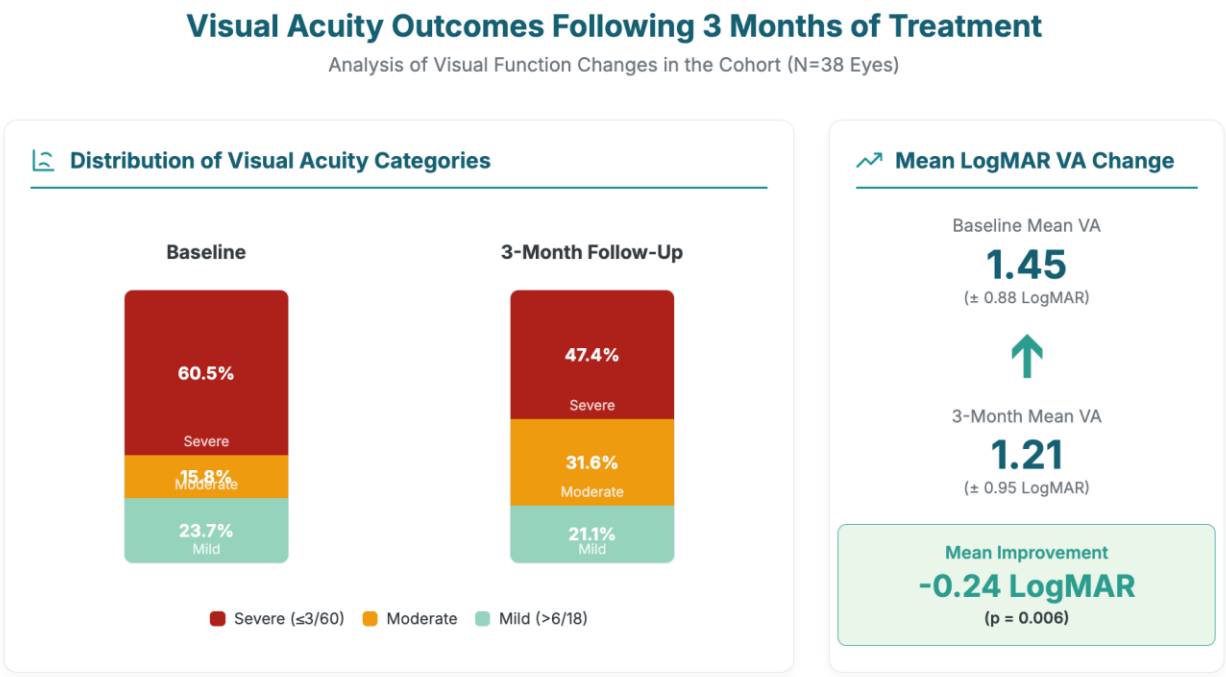

Figure 3. Visual acuity outcomes following 3 months of treatment.

Figure 4 represents the analytical apex of the manuscript, moving beyond descriptive statistics to the realm of predictive modeling. This schematic visually dissects the results of the multivariable linear regression analysis, a sophisticated statistical method designed to isolate the independent impact of several variables on a single outcome—in this case, the 3-month LogMAR visual acuity. The bar for Baseline VA extends across the entire width of the container and is colored in a vibrant, significant green. This immediately communicates its overwhelming importance. The accompanying statistics provide the quantitative proof: a large beta coefficient (β = 0.71) indicates a strong effect size, and a highly significant p-value ($p < 0.001$) confirms this relationship is not due to random chance. This finding establishes that baseline visual acuity is not just correlated with the final outcome; it is a powerful, independent predictor.

In stark contrast, the bars for the other variables—CD4+ Count, Age, and HAART Status—are diminutive and colored in a muted, insignificant grey. Their corresponding beta coefficients are close to zero, and their p-values are high, indicating a lack of any statistically significant independent predictive power. The visual disparity between the bar for Baseline VA and the others is the core message of the entire study, powerfully rendered. This figure does more than present data; it tells a compelling scientific story. It demonstrates that in the complex clinical equation of CMV retinitis, the patient's systemic immune status, age, or treatment history, while clinically important, are statistically eclipsed by one dominant factor: the amount of irreversible retinal damage that has already occurred at the moment of diagnosis, as functionally measured by their initial visual acuity.

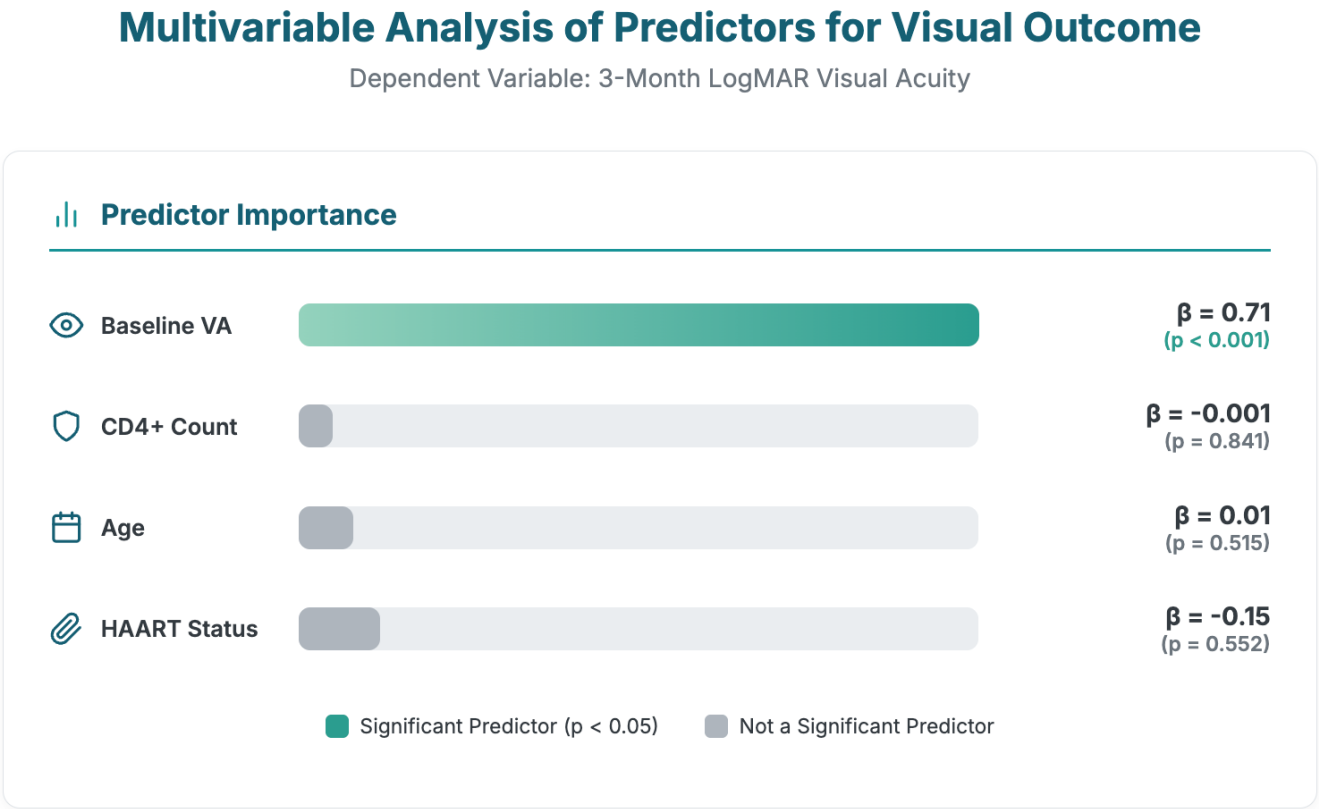

Figure 4. Multivariable analysis of predictors for visual outcome.

4. Discussion

Before delving into the prognostic factors, it is imperative to address the most urgent finding from our cohort: nearly 70% of patients who developed this devastating, AIDS-defining illness were already documented as receiving HAART.[11] This is not merely a data point; it is a stark clinical signal of a significant public health challenge. This observation suggests a troubling gap between the prescription of antiretroviral medications and the achievement of effective, sustained immune reconstitution necessary to protect against opportunistic infections. CMVR in a patient on HAART is a sentinel event, indicating profound immunological failure.[12] This failure can stem from a multitude of factors prevalent in resource-limited settings. Poor adherence due to medication fatigue, lack of social support, or socio-economic barriers is a primary driver. Furthermore, the development of drug resistance is a major concern, particularly if patients remain on failing first-line regimens without access to routine HIV viral load monitoring or resistance testing. The high prevalence of CMVR in this "treatment-experienced" group underscores that simply being on HAART is not a sufficient safeguard. This finding carries an urgent message for clinicians and health systems: patients on HAART, especially those with historically low CD4+ nadirs or inconsistent follow-up, remain a high-risk population. Integrated care, with close collaboration between HIV specialists and ophthalmologists, is essential for monitoring these vulnerable patients.[13] This study, therefore, highlights an immediate need to strengthen HIV treatment programs, focusing on adherence counseling, accessible virological monitoring, and proactive screening for opportunistic infections in patients with evidence of treatment failure.

Figure 5 presents a detailed conceptual schematic that synthesizes the core findings of this study into a cohesive pathophysiological narrative. The schematic begins by establishing the foundational prerequisite for CMV reactivation: a catastrophic failure of the host's immune system. The first stage, labeled "Systemic Cause: Immune Collapse," represents the systemic landscape of a patient with advanced HIV infection. The central tenet of this stage is the profound depletion of CD4+ T-lymphocytes, the master regulators of cell-mediated immunity.[14] This is not a gradual decline but a collapse below a critical threshold, as evidenced by the study's finding that the vast majority of the cohort (65.4%) had CD4+ counts below 50 cells/mm³. This state of profound immunodeficiency is graphically represented by a shield icon with a breach, symbolizing the failure of the immune system's protective barrier. This immunological collapse is the "key" that unlocks the door to opportunistic disease. It dismantles the CMV-specific T-cell surveillance mechanisms that are essential for holding the latent virus in a quiescent state within myeloid progenitor cells. Without this constant immunological pressure, the virus is free to reactivate, enter its lytic replication cycle, and disseminate hematogenously throughout the body, ultimately seeding distant end-organs, most notably the retina. This stage underscores that the CD4+ count is a critical factor in pathogenesis—it creates the permissive state required for the disease process to begin.[15] The second stage of the model, "Local Pathology," represents the pivotal event where the systemic failure translates into organ-specific, localized damage. This stage is depicted as the central hub of the schematic, signifying its critical importance as the primary determinant of the final outcome. Once CMV reaches the retina—an immune-privileged site where inflammatory responses are naturally downregulated—it initiates a direct, lytic infection of the neurosensory tissue. The virus spreads contiguously from cell to cell, resulting in full-thickness necrotizing retinitis. This process is not a benign inflammation; it is a destructive wave that permanently annihilates the highly specialized, post-mitotic neurons of the retina, including photoreceptors and ganglion cells.

Figure 5. The pathophysiological basis of visual outcomes.

The key event in this stage is the "Initial Retinal Damage," the extent of which is established at or before the time of clinical presentation.[16] Crucially, at this stage, the patient's clinical course diverges into two distinct, prognostically critical paths, as illustrated by the branching schematic. Clinical Path

A: Macula Spared. In this more fortunate scenario, the necrotizing lesion is confined to the peripheral retina. While this still represents significant pathology, it spares the macula—the small, central area of the retina responsible for high-acuity, detailed, and color vision. As a result, the patient's central vision remains intact, and they present with a Good Baseline Visual Acuity. Clinical Path B: Macula Involved, In this devastating scenario, the wave of retinal necrosis has already encroached upon or completely destroyed the macula by the time of diagnosis. This catastrophic event obliterates the patient's central vision, leaving them with only peripheral sight. Consequently, they present with a poor baseline visual acuity. This divergence is the core of the study's findings. The baseline visual acuity is not merely a symptom; it is a direct functional measurement—a real-time biomarker—that precisely quantifies which of these two paths the patient is on. It is a direct reflection of the location and severity of the irreversible damage that has already occurred. The final stage, "Final Visual Outcome," illustrates the consequences of the preceding events following therapeutic intervention. Patients are treated with a dual approach: systemic anti-CMV therapy (oral valganciclovir) to halt viral replication, and HAART to restore systemic immunity. This treatment is highly effective at what it is designed to do: it stops the progression of the necrotizing border, effectively "putting out the fire." However, the schematic emphasizes the critical limitation of this therapy: it cannot regenerate the neural tissue that has already been destroyed. The necrotic retina is replaced by a non-functional glial scar, and the vision lost is permanent.[17] Therefore, the final visual outcome is irrevocably tethered to the state of the retina at the beginning of treatment. A patient who began on Clinical Path A, with a spared macula and good baseline vision, will have that good vision preserved. A patient who began on Clinical Path B, with a destroyed macula and poor baseline vision, will have that poor vision locked in permanently. The prognosis is, therefore, determined by the baseline state. Baseline Visual Acuity is the Key Predictor because it is a direct functional measurement of the irreversible damage that has occurred in Stage 2. It accurately reflects which clinical path (A or B) the patient is on and is therefore a powerful and independent predictor of the final outcome in Stage 3. CD4+ Count is Not a Predictor of the final visual outcome because its primary role is as the systemic trigger that initiates the entire cascade in Stage 1. It creates the conditions for the disease but does not measure the location or severity of the subsequent local retinal damage. Therefore, it has no independent power to predict the final visual state.

The central conclusion from our multivariable analysis is that baseline visual acuity is the most powerful independent predictor of three-month visual outcome. This relationship is not merely a statistical artifact; it is profoundly rooted in the neurobiology of the retina. The retina is an extension of the central nervous system, composed of post-mitotic neurons with virtually no capacity for regeneration.[18] CMV causes a direct, lytic infection of these cells, leading to full-thickness retinal necrosis—a process of complete and utter tissue destruction. The necrotic tissue is eventually replaced by a non-functional glial scar. Visual acuity is our most precise clinical measure of the functional integrity of the macula, the small central area of the retina responsible for all detailed vision. Therefore, a poor baseline VA is not just a symptom; it is a direct, real-time functional biomarker that quantifies the extent of irreversible damage to the most critical retinal real estate. Our regression model shows that even after accounting for a patient's age, immune status, and treatment history, the amount of vision they have at the start is the overwhelming determinant of the vision they will have at the end. Anti-CMV therapy with valganciclovir is effective at halting viral replication and preventing the necrotic border from expanding, but it cannot resurrect dead neural tissue.[19] This explains why the therapeutic effect, while statistically significant, was modest in our cohort; treatment primarily stabilizes the disease and prevents further loss, but it cannot restore what has already been destroyed. One of the key unmeasured

confounders in this study is the anatomical location of the lesion. A CMVR lesion in Zone 1 (involving the macula or optic nerve) will inherently produce a poor baseline VA and a poor final VA. It is likely that baseline VA in our model is acting, in part, as a strong proxy for macular involvement. This does not diminish the findings' clinical utility; it reinforces it. Whether we measure the damage by its location (Zone 1) or its functional consequence (poor VA), the message is the same: once the central retina is destroyed, the prognosis is grim.[20]

One of the most intriguing findings, confirmed by our multivariable analysis, is the striking lack of an independent predictive relationship between the baseline CD4+ T-cell count and the final visual outcome. This challenges the simplistic notion that a better systemic immune status should translate to better ocular healing. The explanation is multifactorial. First, there is likely a "floor effect." CMVR is an opportunistic infection that reactivates when CMV-specific T-cell surveillance fails, an event that typically occurs when the CD4+ count drops below a critical threshold of 50-100 cells/mm³. Most of our patients were well below this floor. It is biologically plausible that once immunosuppression is this severe, the precise number of circulating CD4+ cells (be it 10 or 40) becomes irrelevant to the local retinal pathology. The immunological "permission" for viral replication has already been granted. Second, the peripheral CD4+ count is a poor proxy for the unique immunological environment of the eye, an immune-privileged site. The patient's visual prognosis is determined by the local battle between the virus and the retina, a process influenced more by the direct cytopathic effect of the virus than by the number of T-cells in an arm vein. The CD4+ count is the key that unlocks the door for CMV to enter the retina. But once the virus is inside, the extent of the destruction it causes—functionally measured by visual acuity—becomes the sole determinant of the outcome. Finally, the phenomenon of Immune Recovery Uveitis (IRU) further complicates the relationship. In some patients, a rising CD4+ count due to effective HAART can trigger a paradoxical inflammatory response to lingering CMV antigens in the eye, leading to vision-threatening complications like macular edema. In such cases, an improving systemic marker can be associated with a worsening ocular outcome, further decoupling the two variables and explaining the lack of a simple positive correlation.

5. Conclusion

This study, conducted in a real-world clinical setting in Indonesia, provides robust evidence that refines our understanding of prognostic indicators in HIV-associated CMV retinitis. In the modern era of potent antiviral and antiretroviral therapies, the primary determinant of a patient's visual destiny is the functional integrity of their retina at the moment of diagnosis. Our analysis demonstrates that baseline visual acuity is the single most powerful and significant independent predictor of post-treatment visual outcomes, serving as a direct proxy for the extent of irreversible neuropathological damage. Conversely, the peripheral CD4+ T-cell count, while critical for assessing systemic risk, is not an independent predictor of visual recovery. This emphasizes a crucial pathophysiological principle: while a competent immune system is required to control the infection, it cannot regenerate lost neural tissue. The opportunity to save sight in CMVR lies in preemptive action. Therefore, our findings constitute an urgent call for the universal integration of routine ophthalmological screening into the standard care protocols for all high-risk individuals living with HIV, particularly those with low CD4+ counts or evidence of HAART failure. Early detection of asymptomatic, peripheral lesions is the only meaningful strategy to alter the course of this devastating disease and prevent the tragedy of irreversible blindness.

6. References

1. Zemba M, Rogoz R-E, Zaharia AC, Dimirache AE, Dumitrescu O-M, Dărăbuş D-M. Challenges in HIV-negative cytomegalovirus

retinitis - case report. Rom J Ophthalmol. 2021; 65(3): 247–54.
2. Edwin CP, Hassan S, Ebisike PI, Habib SG, Amole TG, Bakare RA. Human cytomegalovirus infection, viraemia and retinitis among people living with HIV/AIDS in Kano, North-Western Nigeria. Int J Res Med Sci. 2021; 9(8): 2191.
3. Qian Z, Fan H, Chen X, Tao Y. The predictive value of interleukin-8 in the development of Cytomegalovirus retinitis in HIV-negative patients. Ophthalmic Res. 2022; 65(3): 287–92.
4. Shi Y-H, Wang H, Kang H, Feng J, Hu X-F, Li Y, et al. Risk factors for the long-term prognosis and recurrence of HIV-negative cytomegalovirus retinitis in North China. Int J Ophthalmol. 2022; 15(10): 1634–40.
5. Tungsattayathitthan U, Singcanvanit R, Choopong P, Jaru-Ampornpan P, Tesavibul N, Sopitviriyaporn W, et al. Predictors for recurrence of Cytomegalovirus retinitis in HIV-negative patients. Ocul Immunol Inflamm. 2024; 32(5): 493–500.
6. Cai J, Xie Z-K, Tang D-Y, Zuo H-Y, Liang H. Investigation of the infection route of HIV-associated cytomegalovirus retinitis. Int J Ophthalmol. 2025; 18(3): 478–86.
7. Kasimova RI, Musabaeva NE, Pulatova RZ. The role of cytomegalovirus infection in the development of the nervous system lesions and retinitis in people living with HIV. HIV Infect Immunosuppr Disord. 2020; 12(2): 89–96.
8. Jay Narain S, Visser L, Sibanda W. Cytomegalovirus retinitis and antiretroviral treatment: a fifteen year experience. South Afr J HIV Med. 2022; 23(1): 1322.
9. Jabs DA, Van Natta ML, Holland GN, Danis R, Studies of the Ocular Complications of AIDS Research Group. Cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome after initiating antiretroviral therapy. Am J Ophthalmol. 2017; 174: 23–32.
10. Holland GN, Van Natta ML, Goldenberg DT, Ritts R Jr, Danis RP, Jabs DA, et al. Relationship between opacity of Cytomegalovirus retinitis lesion borders and severity of immunodeficiency among people with AIDS. Invest Ophthalmol Vis Sci. 2019; 60(6): 1853–62.
11. Ahmad S, Keat G, Subramaniam S, Ghani S, Samsudin A. Cytomegalovirus retinitis associated with high CD4 counts and DHEA abuse. Indian J Sex Transm Dis AIDS. 2020; 41(1): 119.
12. Bogoni G, Lucas Júnior RM, Reis Schneider GA, Castanheira de Souza NF, Carvalho MK, Marcusso RM, et al. Cytomegalovirus retinitis in hospitalized people living with HIV in the late antiretroviral therapy era in São Paulo, Brazil. Int J STD AIDS. 2023; 34(1): 48–53.
13. Liang X, An H, He H, Shen B, Ou Z, Li L. Comparison of two different intravitreal treatment regimens combined with systemic antiviral therapy for cytomegalovirus retinitis in patients with AIDS. AIDS Res Ther. 2023; 20(1): 46.
14. Samlali F, Bahari F, Hamouche A, Bentouhami R, Mchachi YHA, Benhmidoun L, et al. A retrospective study on AIDS related ocular complications particularly Cytomegalovirus retinitis in 100 AIDS patients. Asian J Res Rep Ophthalmol. 2025; 8(1): 66–73.
15. Yanagihara RT, Mustafi D, Huang LC. Cytomegalovirus retinitis response in a child treated with systemic maribavir. Ophthalmology. 2025; 132(7): e126.
16. Kikuchi T, Watanabe M, Tsukada N, Matsumoto C, Nomura-Yogo M, Kunisada K, et al. Cytomegalovirus retinitis during idecabtagene vicleucel therapy in patients with relapsed/refractory multiple myeloma. Transpl Infect Dis. 2025; 27(4): e70040.

17. Cochran-Perez MR, Sharma P, Delisle J-S, Schlesinger M, Rao H, Trias J, et al. Bispecific antibody therapy-associated opportunistic infections: cytomegalovirus retinitis and chronic salmonellosis in a non-HIV patient. Haematologica. 2025.
18. Wongwian T, Hemapanpairoa J, Kulthanachairojana N. Cost-utility and budget impact analyses of valganciclovir for cytomegalovirus retinitis in patients with human immunodeficiency virus in Thailand. J Pharm Policy Pract. 2025; 18(1): 2529472.
19. Li CY, Massa A, Krisch M, Gupta N, Raval N, Nanda T, et al. Utility of screening examination for Cytomegalovirus retinitis among patients with Cytomegalovirus viremia. Am J Ophthalmol. 2025; 277: 230–41.
20. Lo Cascio A, Bures Jelstrup A. Cytomegalovirus necrotizing retinitis in an immunocompetent patient: a case report. Arch Soc Esp Oftalmol (Engl Ed). 2025.