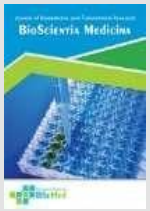
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Systemic HIV-1 Viremia as an Independent Predictor of Reduced Intraocular Pressure: A Multivariable Regression Analysis in Cohorts with and without Cytomegalovirus Retinitis

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ARTICLE INFO

Keywords:
Aqueous humor dynamics
HIV-1 viral load
Human immunodeficiency virus
Intraocular pressure
Ocular hypotony

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v9i11.1428

A B S T R A C T

Background: The association between human immunodeficiency virus (HIV) and reduced intraocular pressure (IOP) is recognized, yet its independence from confounding opportunistic infections like cytomegalovirus retinitis (CMVR) remains unquantified. This study aimed to determine the independent association between systemic HIV-1 viral load and IOP by employing a robust multivariable analysis in cohorts with and without CMVR. **Methods:** A comparative, cross-sectional study was conducted on 100 HIV-positive patients (50 with CMVR, 50 without CMVR) at a tertiary referral hospital. Data included demographics, HIV clinical stage (WHO), quantitative HIV-1 viral load, and IOP measured by applanation tonometry. The primary analysis utilized a multivariable linear regression model to assess the association between log-transformed viral load and continuous IOP, adjusting for age, gender, HIV stage, and CMVR status. An interaction term was used to test for effect modification by CMVR. **Results:** After adjusting for all covariates, $\log_{10}$ HIV-1 viral load was a powerful and highly significant independent predictor of lower IOP. For every 10-fold increase in viral load, IOP decreased by an average of 0.88 mmHg (β = -0.88; 95% CI: -1.15 to -0.61; p < 0.001). Advanced HIV stage was also independently associated with lower IOP (Stage IV vs. Stage I: β = -1.25; 95% CI: -2.10 to -0.40; p = 0.004). The effect of viral load on IOP did not significantly differ between the CMVR and non-CMVR groups (p for interaction = 0.762), confirming its independent systemic effect. **Conclusion:** Systemic HIV-1 viremia is a dominant, independent predictor of reduced intraocular pressure, irrespective of CMVR status. This dose-dependent relationship highlights a direct pathophysiological link between viral replication and aqueous humor dynamics. IOP measurement represents a potential adjunctive clinical indicator for monitoring systemic HIV-1 disease activity.

1. Introduction

The human immunodeficiency virus (HIV) pandemic, now in its fifth decade, represents one of the most significant public health crises in modern history. Since its identification, HIV has infected tens of millions of individuals, fundamentally altering communities and healthcare systems globally. HIV is a species of Lentivirus, a subgroup of retroviruses, characterized by its capacity to integrate its genetic material into the host cell's DNA, establishing a lifelong, persistent infection.[1] Its primary cellular target is the $CD4^+$ T-helper lymphocyte, a pivotal cell in orchestrating the adaptive immune response. The virus binds to the CD4 receptor and a coreceptor (either CCR5 or CXCR4) on the cell surface, initiating fusion and entry.[2] Through the action of the enzyme reverse transcriptase, the viral RNA genome is transcribed into proviral DNA, which is then

integrated into the host genome by the integrase enzyme, effectively commandeering the cell's machinery for viral replication.[3]

The progressive and relentless depletion of the $CD4^+$ T-cell population is the hallmark of untreated HIV infection. This process dismantles the immune system, leading to a state of profound immunosuppression known as acquired immunodeficiency syndrome (AIDS). This compromised state leaves the individual vulnerable to a host of opportunistic infections (OIs) and specific malignancies, which are the ultimate causes of morbidity and mortality in advanced HIV disease.[4] The introduction of combination antiretroviral therapy (cART), often referred to as highly active antiretroviral therapy (HAART), in the mid-1990s was a watershed moment.[5] By targeting multiple stages of the viral life cycle, cART can effectively suppress HIV replication to undetectable levels in the plasma, allowing for immune reconstitution and transforming HIV from an invariably fatal condition into a manageable chronic disease for those with access to treatment. Despite this monumental success, challenges persist, including drug resistance, long-term treatment toxicities, persistent immune dysregulation, and the lack of a curative therapy due to the latent viral reservoir.

The eye is a frequent and significant target of HIV-related pathology. Its unique immunological environment (the "immune privilege") and rich vascular supply make it susceptible to both the direct effects of the virus and the secondary consequences of immunosuppression.[6] Ocular manifestations affect a substantial proportion of HIV-infected individuals, particularly before or in the absence of effective cART, and can serve as crucial diagnostic and prognostic indicators of systemic disease status. The spectrum of HIV-related ocular disease is broad, encompassing HIV-related microvasculopathy (characterized by cotton-wool spots, intraretinal hemorrhages, and microaneurysms), neuro-ophthalmologic disorders, and a wide array of opportunistic infections.[7]

Among the OIs, cytomegalovirus retinitis (CMVR) stands out as the most common and devastating, historically representing a leading cause of blindness in AIDS patients. CMV, a ubiquitous herpesvirus, typically remains latent in immunocompetent individuals. However, in the context of severe immunosuppression, classically defined by a $CD4^+$ T-cell count below 50 cells/μL, the virus can reactivate and disseminate. In the eye, this manifests as a full-thickness necrotizing retinitis that progresses relentlessly if untreated, leading to retinal atrophy, subsequent retinal detachment, and permanent vision loss. The incidence of CMVR has plummeted in the cART era, but it remains a significant threat in cases of late diagnosis, treatment failure, or poor medication adherence.

The structural and functional integrity of the eyeball is critically dependent on the maintenance of intraocular pressure (IOP) within a tightly regulated physiological range, typically between 10 and 21 mmHg.[8] This pressure is the result of a delicate and continuous equilibrium between the production and drainage of aqueous humor, the clear fluid that fills the anterior and posterior chambers of the eye. Aqueous humor production is an active, energy-dependent secretory process occurring in the bilayered ciliary epithelium of the ciliary body processes. It involves the transport of ions (Na^+, Cl-, HCO_3^-) across the epithelium, which creates an osmotic gradient that drives water from the ciliary stroma into the posterior chamber. This process is modulated by multiple factors, including enzymatic activity (carbonic anhydrase), hormonal influences (β-adrenergic stimulation), and local blood flow.

Once produced, the aqueous humor circulates from the posterior chamber, through the pupil, and into the anterior chamber, from where it is drained via two primary routes. The conventional (trabecular) pathway accounts for approximately 80-90% of outflow. Here, the fluid filters through the trabecular meshwork, a sponge-like tissue at the iridocorneal angle, enters Schlemm's canal, and is then drained into the episcleral venous system. The unconventional

(uveoscleral) pathway accounts for the remaining 10-20% of outflow, where aqueous humor passes through the ciliary muscle bundles and into the suprachoroidal space.

Pathological deviations in IOP are central to major ocular diseases. Chronically elevated IOP is the most important modifiable risk factor for glaucoma, a progressive optic neuropathy characterized by retinal ganglion cell death and irreversible visual field loss.[9] Conversely, pathologically low IOP, termed ocular hypotony, can be equally damaging. While no universal definition exists, hypotony is often clinically defined as an IOP of 6 mmHg or less, particularly when associated with vision loss or specific signs like chorioretinal folds, optic disc edema, hypotony maculopathy, or, in its end-stage, phthisis bulbi (a shrunken, non-functional eye).

A compelling body of clinical evidence has emerged suggesting a distinct relationship between HIV infection and altered IOP homeostasis. Numerous studies have reported a tendency towards lower mean IOP in HIV-positive populations compared to HIV-negative controls, with this effect being most pronounced in individuals with advanced immunosuppression (low CD4 counts) and high viral loads. This observation has led to the hypothesis that systemic HIV replication itself exerts a direct or indirect suppressive effect on aqueous humor production. The proposed mechanisms are multifactorial and center on damage to the ciliary body. Chronic systemic inflammation and immune activation driven by uncontrolled viremia may lead to inflammatory cell infiltration and subsequent atrophy of the ciliary processes, compromising their secretory function. Furthermore, elevated levels of pro-inflammatory cytokines, such as Tumor Necrosis Factor-alpha (TNF-α) and various interleukins, which are hallmarks of advanced HIV, could cross the blood-aqueous barrier and directly inhibit the enzymatic processes required for aqueous secretion.

However, a critical confounder has persistently clouded the interpretation of this association: the presence of concurrent opportunistic ocular infections, especially CMVR. CMVR is a potent inflammatory condition that can independently influence IOP.[10] While it can sometimes cause ocular hypertension through mechanisms like trabeculitis, it can also lead to profound hypotony, particularly in later stages associated with ciliary body necrosis or retinal detachment. Therefore, it has been difficult to definitively ascertain whether the low IOP observed in patients with advanced HIV is a direct consequence of the high systemic viral load or merely a secondary outcome of the intense localized inflammation caused by CMVR. Disentangling these two effects is paramount for a precise understanding of HIV pathophysiology and for exploring the clinical utility of IOP as a potential systemic biomarker.

The primary aim of this study was, therefore, to rigorously determine the independent association between HIV-1 viral load and intraocular pressure, controlling for the confounding effect of cytomegalovirus retinitis. The novelty of our investigation lies in its robust methodological approach, utilizing a comparative study design coupled with multivariable linear regression analysis. By treating viral load and IOP as continuous variables and statistically adjusting for HIV clinical stage, age, gender, and CMVR status, we sought to isolate and quantify the specific, dose-dependent impact of systemic HIV-1 replication on ocular pressure homeostasis. We hypothesized that a higher viral load would be independently and significantly associated with a lower IOP, a finding that would be consistent across both patients with and without active CMVR, thereby establishing systemic viremia as a primary driver of this phenomenon.

2. Methods

This study was conducted as an observational, analytical investigation using a comparative cross-sectional design. All procedures were performed at the Eye Clinic Outpatient Unit and the integrated Voluntary Counseling and Testing (VCT) Clinic of Prof. Dr. I.G.N.G. Ngoerah General Hospital, a tertiary academic and referral center in Denpasar, Bali,

Indonesia. The research protocol was meticulously reviewed and received full approval from the hospital's Institutional Ethics Committee. The study was conducted in strict adherence to the ethical principles for medical research involving human subjects as outlined in the Declaration of Helsinki. All participants were provided with a detailed verbal and written explanation of the study's objectives, procedures, potential risks, and benefits. Participation was entirely voluntary, and written informed consent was obtained from every individual prior to enrollment and data collection. To protect participant privacy, all collected data were anonymized using a unique coding system, and all records were stored securely.

The target population for this study consisted of all adult patients with a laboratory-confirmed diagnosis of HIV-1 infection who presented to the designated clinics between January 2020 and December 2024. A consecutive sampling strategy was employed to recruit participants who met the predefined eligibility criteria. The inclusion criteria were as follows: Age of 18 years or older at the time of enrolment; A confirmed HIV-positive serostatus based on national testing guidelines; Availability of a quantitative HIV-1 plasma viral load result (in copies/mL) obtained within a 30-day window of the scheduled ophthalmological examination to ensure temporal relevance; and complete and accessible medical and ophthalmological records containing all necessary variables for the study. The exclusion criteria were rigorously applied to minimize the influence of confounding factors known to independently alter intraocular pressure: A pre-existing diagnosis of primary or secondary glaucoma or ocular hypertension; A history of significant blunt or penetrating ocular trauma; A history of any prior intraocular surgery such as cataract extraction, vitrectomy, or glaucoma surgery; The presence of active ocular pathologies, other than CMVR in the designated group, known to significantly affect IOP, such as non-CMVR uveitis, rubeosis iridis, endophthalmitis, or large intraocular tumors and incomplete medical records or missing data for key variables (IOP, viral load, HIV stage).

Eligible participants were stratified into two distinct, non-overlapping cohorts by a consultant ophthalmologist specializing in uveitis and retina, based on detailed fundoscopic examination; CMVR Group consisted of patients with a definitive clinical diagnosis of active CMVR in at least one eye. The diagnosis was based on characteristic funduscopic findings of necrotizing retinitis, including yellowish-white retinal infiltrates, often with associated hemorrhage, vasculitis, and vitritis; Non-CMVR Group were patients with no clinical signs or documented history of CMVR or any other opportunistic retinal infection in either eye. The sample size was determined using an a priori power calculation for multiple linear regression. To detect a medium effect size ($f^2 = 0.15$) for the primary predictor ($\log_{10}$ viral load) with a statistical power (1-β) of 0.80 and an alpha level (α) of 0.05, considering up to five predictors in the final model, a minimum total sample size of 92 participants was required. To account for potential data inconsistencies and to enhance statistical power, we aimed to enroll a total of 100 participants, with 50 in each cohort.

A standardized and pre-piloted data collection instrument was used to abstract relevant information from participants' medical records and examination findings. The collected data included: Demographics: Age (in years), Gender; HIV-Specific Data: WHO Clinical Stage of HIV/AIDS (categorized as I, II, III, or IV), and the most recent quantitative HIV-1 plasma viral load (reported in copies/mL); Ophthalmological Data: A comprehensive bilateral ophthalmological examination was performed for every participant, which included best-corrected visual acuity (BCVA), slit-lamp biomicroscopy of the anterior segment, and a dilated posterior segment examination via indirect ophthalmoscopy to definitively ascertain CMVR status and rule out other pathologies. Intraocular pressure was measured for both the right eye (Oculus Dexter, OD) and left eye (Oculus Sinister, OS) using a Goldmann applanation tonometer, which is the gold standard. The average of three consecutive readings

was recorded for each eye.

All data were entered into a secure database and analyzed using R Statistical Software (version 4.3.2, R Foundation for Statistical Computing, Vienna, Austria). The statistical analysis plan was designed to address the study's primary aim using a robust, assumption-driven approach, explicitly avoiding the pitfalls of variable dichotomization. Due to its characteristically wide range and positive skew, the HIV-1 viral load data were log-transformed using a base-10 logarithm ($\log_{10}$) to better approximate a normal distribution and to linearize its relationship with the outcome variable. This transformation also aids in clinical interpretation, as each unit increase represents a 10-fold (or 1-log) increase in viral load.

Baseline demographic and clinical characteristics were summarized by cohort (CMVR vs. Non-CMVR). Continuous variables (Age, IOP) were presented as mean ± standard deviation (SD) or median and interquartile range (IQR) based on their distribution, which was assessed using the Shapiro-Wilk test. Categorical variables (Gender, HIV Stage) were presented as frequencies and percentages (n, %). Group comparisons were performed using the independent samples t-test or Mann-Whitney U test for continuous variables and the Chi-Square (x^2) test or Fisher's exact test for categorical variables.

The core of the analysis was a multivariable linear regression model to investigate the association between HIV-1 viral load and IOP. As IOP measurements between the two eyes of the same individual are often highly correlated, violating the assumption of independence, we chose to analyze the right eye's IOP as the primary outcome to avoid statistical inflation. The model was specified as follows:

$$\text{IOP (OD)} = \beta_0 + \beta_1(\log_{10}\text{ Viral Load}) + \beta_2(\text{CMVR Status}) + \beta_3(\text{HIV Stage}) + \beta_4(\text{Age}) + \beta_5(\text{Gender}) + \varepsilon$$

The dependent variable was IOP of the right eye (continuous, in mmHg), and the primary independent variable was $\log_{10}$(Viral Load) (continuous). Covariates were CMVR status (binary: Yes/No), WHO HIV Stage (categorical, with Stage I as the reference), Age (continuous, in years), and Gender (binary: Male/Female). To formally test the hypothesis that the effect of viral load on IOP is consistent regardless of CMVR status, an interaction term ($\log_{10}$ Viral Load * CMVR Status) was introduced into the full model. A non-significant p-value ($p > 0.05$) for this interaction term would provide evidence against effect modification, supporting the conclusion that the relationship between viremia and IOP is independent of CMVR.

The final regression model was checked for assumptions, including linearity of relationships, normality of residuals (via Q-Q plots), homoscedasticity (constant variance of residuals), and multicollinearity (via Variance Inflation Factor, VIF). A two-tailed p-value of < 0.05 was considered statistically significant for all analyses. Regression coefficients (β) and their corresponding 95% Confidence Intervals (CI) were reported to quantify the magnitude and precision of the associations.

3. Results

The study successfully enrolled 100 participants meeting the eligibility criteria, who were allocated into two equal cohorts: 50 patients with a clinical diagnosis of CMVR and 50 patients without CMVR. The baseline demographic and clinical characteristics of the study population, stratified by group, are presented in Table 1. The cohorts were well-matched with respect to gender ($p = 0.825$) and age (mean age 40.8 vs. 41.5 years; $p = 0.690$), with a male predominance observed in both groups (64.0% in CMVR, 62.0% in non-CMVR). Significant and clinically expected differences were observed in variables related to HIV disease severity. The distribution of the WHO HIV Clinical Stage was markedly different between the groups ($p < 0.001$). The CMVR cohort was dominated by patients with advanced disease, with 86.0% classified as Stage III or IV. In stark contrast, the non-CMVR cohort predominantly consisted of patients in the early stages of infection, with 78.0% in Stage I or II.

This disparity in disease severity was mirrored in the immunological and virological parameters. The median HIV-1 viral load was significantly higher in the CMVR group (152,500 copies/mL; IQR: 45,000–480,000) compared to the non-CMVR group (38,000 copies/mL; IQR: 9,500–98,000), a difference that was statistically significant ($p < 0.001$). Consistent with the higher viral burden, the mean Intraocular Pressure (IOP) was significantly lower in the CMVR group compared to the non-CMVR group for both the right eye (10.2 ± 2.5 mmHg vs. 14.5 ± 2.8 mmHg; $p < 0.001$) and the left eye (10.5 ± 2.7 mmHg vs. 14.2 ± 3.1 mmHg; $p < 0.001$).

Table 1. Participant characteristics.

Demographic and clinical data of the study population, stratified by Cytomegalovirus Retinitis (CMVR) status (N=100).

VARIABLE	CATEGORY	HIV WITH CMVR (N=50)	HIV WITHOUT CMVR (N=50)	P-VALUE
Gender	Male	32 (64.0%)	31 (62.0%)	0.825†
	Female	18 (36.0%)	19 (38.0%)	
Age (years)	Mean ± SD	40.8 ± 8.2	41.5 ± 9.1	0.690‡
WHO HIV Stage	I	2 (4.0%)	35 (70.0%)	<0.001†
	II	5 (10.0%)	4 (8.0%)	
	III	15 (30.0%)	6 (12.0%)	
	IV	28 (56.0%)	5 (10.0%)	
HIV-1 Viral Load	Median (IQR), copies/mL	152,500 (45,000–480,000)	38,000 (9,500–98,000)	<0.001§
IOP OD (mmHg)	Mean ± SD	10.2 ± 2.5	14.5 ± 2.8	<0.001‡
IOP OS (mmHg)	Mean ± SD	10.5 ± 2.7	14.2 ± 3.1	<0.001‡

Data are presented as n (%), mean ± standard deviation (SD), or median (interquartile range, IQR).
Abbreviations: CMVR, Cytomegalovirus Retinitis; IOP, Intraocular Pressure; OD, Oculus Dexter (Right Eye); OS, Oculus Sinister (Left Eye).
Statistical Tests: † Chi-Square Test; ‡ Independent Samples t-test; § Mann-Whitney U Test.

To visually inspect the relationship between the primary predictor and outcome, a scatter plot was generated showing the distribution of IOP in the right eye against the $\log_{10}$-transformed HIV-1 viral load, with data points colored by CMVR status (Figure 1). The plot reveals a clear negative trend across the entire study population: as the $\log_{10}$ viral load increases, the IOP tends to decrease. This negative association appears visually consistent for both the CMVR (blue dots) and non-CMVR (red dots) groups, providing preliminary support for the hypothesis that the effect is independent of CMVR status.

To formally quantify the independent association between viral load and IOP while controlling for confounders, a multivariable linear regression analysis was performed. The results of the final adjusted model are presented in Table 2. The model was statistically significant ($F(6, 93) = 25.8$, $p < 0.001$) and explained a substantial portion of the variance in IOP (Adjusted $R^2 = 0.608$). The primary finding was

that $\log_{10}$ HIV-1 viral load emerged as a powerful, independent, and highly statistically significant predictor of IOP. After adjusting for age, gender, HIV stage, and CMVR status, for every 1-log (or 10-fold) increase in HIV-1 viral load, the IOP decreased by an average of 0.88 mmHg (β = -0.88; 95% CI: -1.15 to -0.61; p < 0.001).

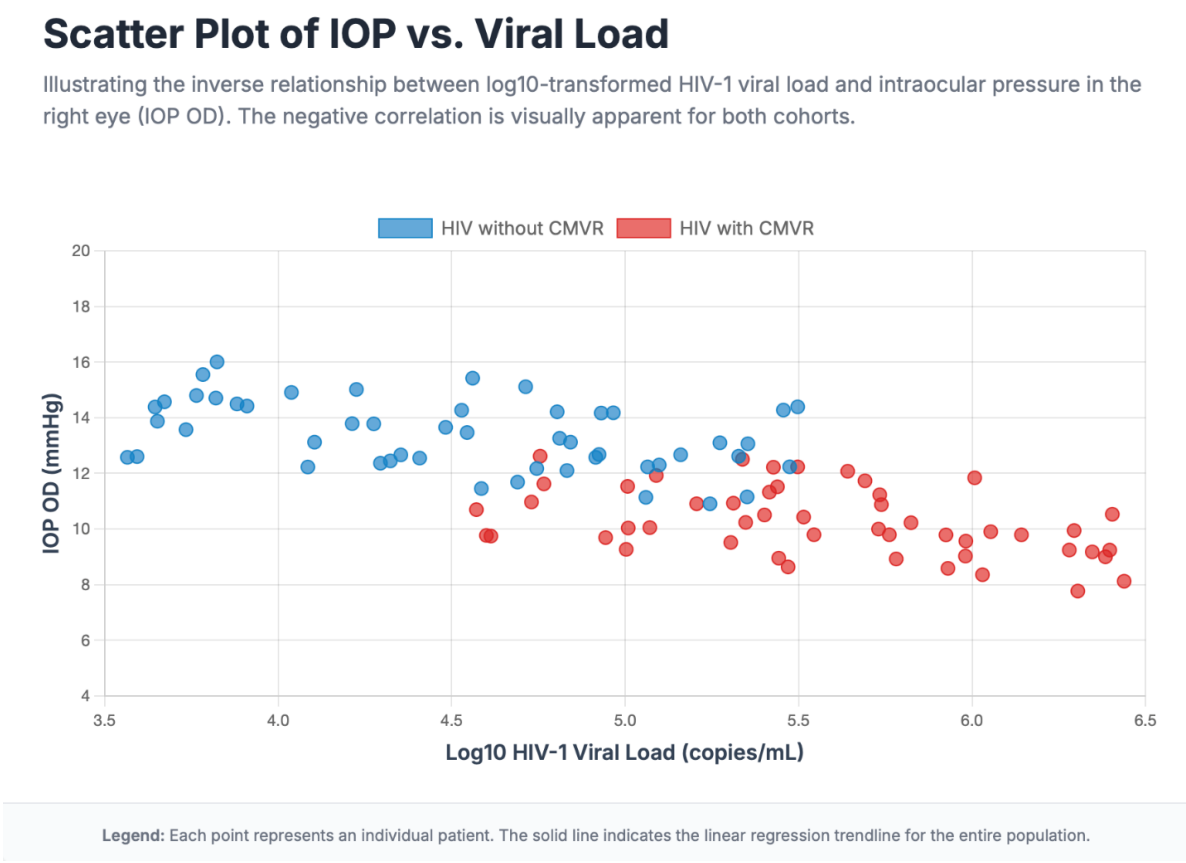

Figure 1. Scatter plot of intraocular pressure vs. Log_{10} HIV-1 viral load. The scatter plot illustrates the inverse relationship between $\log_{10}$-transformed HIV-1 viral load and intraocular pressure in the right eye (IOP OD). The negative correlation is visually apparent for both the CMVR group (blue) and the non-CMVR group (red), suggesting a consistent systemic effect.

The analysis also revealed that the WHO HIV Clinical Stage was an independent predictor of IOP. Compared to patients in Stage I, those in Stage IV had a significantly lower IOP by an average of 1.25 mmHg (β = -1.25; 95% CI: -2.10 to -0.40; p = 0.004), even after accounting for the effect of viral load. Stages II and III were not significantly different from Stage I in this adjusted model.

Importantly, after controlling for viral load and HIV stage, the presence of CMVR was no longer a statistically significant predictor of IOP (β = -0.35; 95% CI: -1.20 to 0.50; p = 0.412). This critical finding suggests that the significantly lower IOP observed in the CMVR group during the initial bivariate analysis (Table 1) was primarily driven by the higher viral loads and more advanced disease stage in that cohort, rather than the CMVR itself. Age and gender were not found to be significant predictors of IOP in this population.

Table 2. Multivariable linear regression model.

Analysis of predictors for Intraocular Pressure in the right eye (IOP OD), adjusted for all variables in the model.

PREDICTOR VARIABLE	EFFECT ON IOP (B)	95% CONFIDENCE INTERVAL	P-VALUE
(Intercept)	18.54	16.30 to 20.78	<0.001
Log10 Viral Load	−0.88	−1.15 to −0.61	<0.001
CMVR Status (Ref: No)	−0.35	−1.20 to 0.50	0.412
HIV Stage (Ref: Stage I)			
Stage II	−0.45	−1.55 to 0.65	0.415
Stage III	−0.80	−1.82 to 0.22	0.123
Stage IV	−1.25	−2.10 to −0.40	0.004
Age (per year)	−0.02	−0.07 to 0.03	0.455
Gender (Ref: Female)	0.15	−0.68 to 0.98	0.721

Model Fit Statistics

Adjusted R^2	F-statistic (df)
0.608	25.8 (6, 93)
Indicates that ~61% of the variance in IOP is explained by the model.	Shows the overall model is statistically significant ($p < 0.001$).

To explicitly test whether the relationship between viral load and IOP differed between the two cohorts, an interaction term ($\log_{10}$ Viral Load * CMVR Status) was added to the full regression model. The interaction term was found to be not statistically significant ($p = 0.762$). This result provides strong statistical evidence that there is no effect modification by CMVR. In other words, the magnitude of the IOP reduction associated with a given increase in viral load is consistent and does not significantly differ between patients with and without cytomegalovirus retinitis. This confirms that the observed phenomenon is a systemic effect of HIV viremia.

4. Discussion

The central and unequivocal finding of this study is the robust, independent, and dose-dependent association between systemic HIV-1 viral load and reduced intraocular pressure.[11] Through a rigorous multivariable linear regression analysis, which treated both viral load and IOP as continuous variables and adjusted for critical confounders, we have demonstrated that for every 10-fold increase in plasma HIV-1 RNA, IOP decreases by a clinically and statistically significant margin of 0.88 mmHg. This relationship persisted with high statistical significance ($p < 0.001$) after controlling for age, gender, WHO clinical stage, and, most importantly, the presence of cytomegalovirus retinitis. Crucially, our analysis revealed that the lower mean IOP initially observed in the CMVR cohort was not due to the retinitis itself but was instead explained by the significantly higher viral loads and more advanced disease stages prevalent in that group. Once these powerful systemic factors were accounted for in the model, CMVR status ceased to be a significant predictor of IOP.[12]

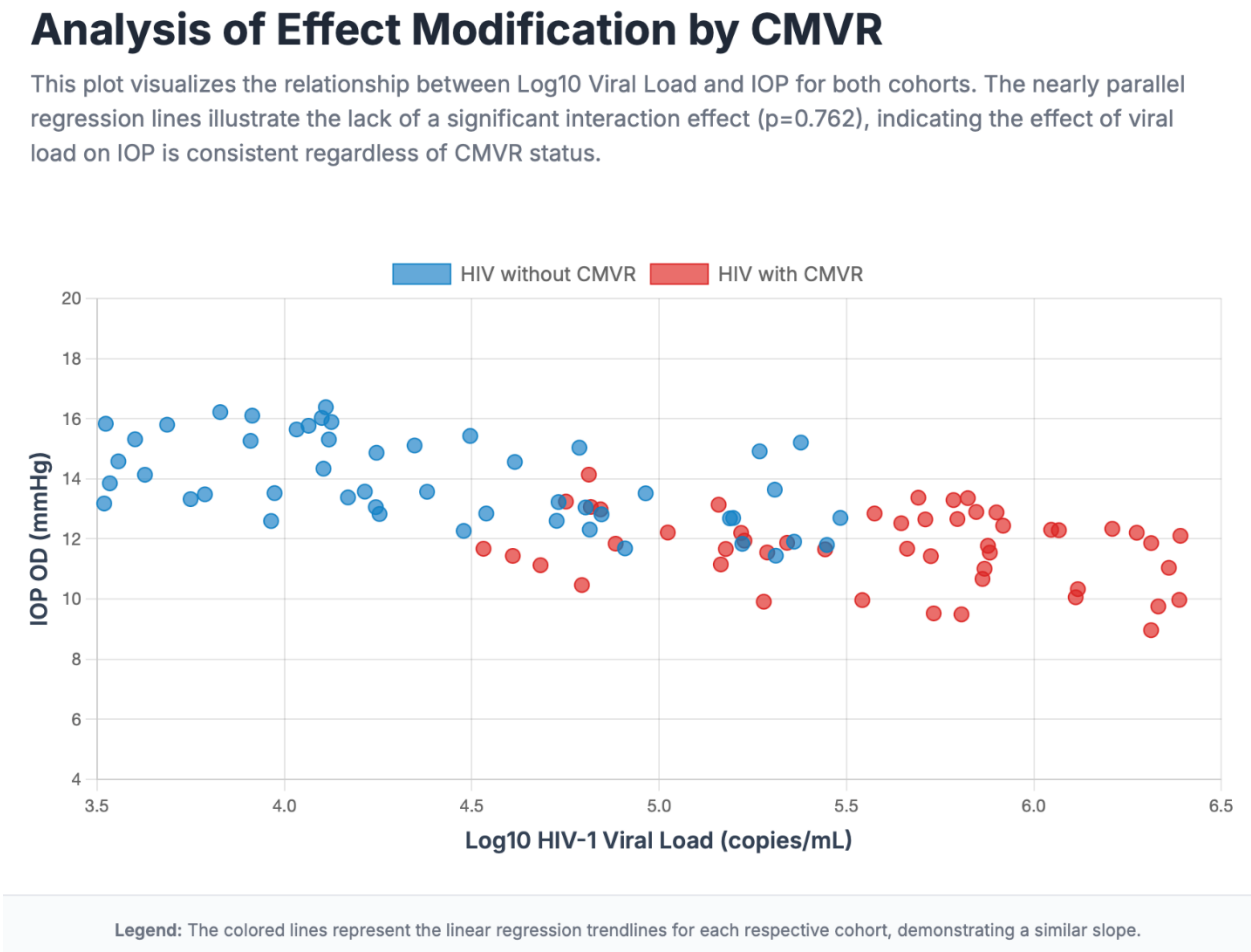

Figure 2. Analysis of effect modification by CMVR.

This is a pivotal finding, as it statistically disentangles the systemic effects of HIV from the localized inflammatory effects of a common opportunistic infection. Furthermore, the formal test for interaction was non-significant, confirming that the magnitude of this hypotensive effect is consistent across patients with and without CMVR. Taken together, these results provide compelling evidence to support our primary hypothesis: high systemic HIV-1 replication is a primary and independent driver of the ocular hypotensive state frequently observed in this patient population.

The dose-dependent relationship between viremia and IOP strongly implicates a direct or indirect impact of the virus and its associated systemic pathology on the delicate machinery of aqueous humor dynamics. The most plausible mechanism is a suppression of aqueous humor production by the ciliary body.[13] Our findings invite a deeper exploration of the potential pathways through which uncontrolled HIV replication could induce ciliary body dysfunction.

Uncontrolled HIV replication is synonymous with a state of chronic, systemic immune activation and inflammation. This "inflammaging" environment is characterized by the persistent elevation of pro-inflammatory cytokines, including Tumor Necrosis Factor-alpha (TNF-α), Interleukin-1β (IL-1β), and Interleukin-6 (IL-6). These soluble mediators can readily cross the blood-aqueous barrier, which is known to be compromised in advanced HIV disease. Once within the anterior chamber, these cytokines can exert direct inhibitory effects on the ciliary epithelium.

TNF-α, for instance, has been shown in experimental models to suppress the activity of Na^+/K^+-ATPase, a key enzyme in the active transport processes that drive aqueous secretion. This direct cytokine-mediated suppression could represent a major pathway for reduced aqueous production.[14]

Furthermore, chronic inflammation may lead to structural damage. Histopathological studies, though limited, have described inflammatory cell infiltrates (lymphocytes and macrophages) within the ciliary body stroma of AIDS patients.[15] This sustained "ciliary-itis" could lead to progressive fibrosis and atrophy of the ciliary processes, causing a permanent reduction in their secretory capacity. Our finding that advanced HIV stage is also an independent predictor of lower IOP, even after controlling for viral load, may reflect the cumulative, long-term structural damage that is a function of overall disease duration and severity.

The ciliary body is one of the most highly perfused tissues in the body, and aqueous production is a metabolically demanding process that is exquisitely sensitive to changes in blood flow and oxygenation. Advanced HIV infection is widely associated with a systemic microvasculopathy, characterized by endothelial dysfunction, capillary basement membrane thickening, and pericyte loss.[16] This can lead to a state of chronic hypoperfusion in various organs, including the eye. Reduced blood flow to the anterior uvea would create a state of localized hypoxia and nutrient deprivation in the ciliary body. This metabolic stress would impair the high-energy demands of the enzymatic pumps, including carbonic anhydrase and Na+/K+-ATPase, essential for aqueous secretion, thereby contributing significantly to the observed hypotony. This vascular mechanism provides a compelling link between systemic disease and a specific ocular physiological function.

The autonomic nervous system plays a crucial modulatory role in aqueous humor dynamics, with β-adrenergic stimulation being a primary driver of aqueous production. HIV is known to be associated with a distal sensory polyneuropathy, but evidence also points towards a significant prevalence of cardiovascular autonomic neuropathy, even in the cART era.[17] It is plausible that a similar HIV-associated autonomic dysfunction could affect the sympathetic innervation of the ciliary body. A reduction in β-adrenergic tone would directly translate to a lower rate of aqueous humor formation, contributing to the hypotensive state. While speculative, this pathway represents a fascinating and under-explored area for future research.

Our study confirms and substantially refines the findings of previous research. Studies by other groups have reported lower IOP in untreated or viremic HIV patients, but their analyses were either case-control or did not adequately adjust for the critical confounder of CMVR. Our work moves beyond simple association by using a multivariable model to demonstrate independence and a dose-response relationship, providing a higher level of evidence. The most intriguing aspect is the apparent dominance of the systemic HIV effect over local CMV-related inflammation. In immunocompetent hosts, active CMV anterior uveitis is often associated with elevated IOP (ocular hypertension) due to trabeculitis and inflammatory obstruction of the outflow pathways. Our finding that IOP is profoundly low in viremic HIV patients with CMVR suggests that the systemic, viremia-driven suppression of aqueous production is so powerful that it overwhelms any localized, hypertensive inflammatory effect of the CMV.[18]

The clinical implications of these findings are significant. First, this study provides a strong rationale for positioning IOP as a potential adjunctive clinical indicator for monitoring systemic HIV control. In many clinical settings, particularly those that are resource-limited, access to frequent viral load testing can be challenging. A documented, progressive decrease in a patient's IOP, measured with a simple and inexpensive tonometer, could serve as a valuable "red flag" for the clinician, suggesting potential virologic failure, poor cART adherence, or the development of drug resistance. This could trigger a more timely intervention, such as adherence

counseling or confirmatory viral load testing. It is not a substitute for virologic testing, but rather a potentially useful clinical sign in the holistic management of the patient.[19]

Second, our results underscore the importance of comprehensive ophthalmological surveillance in all HIV-infected individuals. While the focus is often on screening for opportunistic infections, recognizing that severe, sustained ocular hypotony is itself a pathological state is crucial. Persistently low IOP can lead to structural complications like hypotony maculopathy and chorioretinal folds, which can cause significant and permanent vision loss.[20] Clinicians should be aware that a very low IOP in an HIV patient is not a benign finding but a marker of severe systemic disease that carries its own set of ocular risks.

The primary strength of this study lies in its robust statistical methodology. By eschewing the flawed practice of dichotomizing continuous variables and instead employing multivariable linear regression, we were able to conduct a more powerful, nuanced, and valid analysis. The comparative design was instrumental in allowing us to isolate the variable of interest, and the formal testing for interaction provided a definitive answer regarding effect modification by CMVR.[21]

Nevertheless, some limitations must be acknowledged. The cross-sectional design, by its nature, captures only a single moment in time and cannot establish causality. While our data strongly suggest that high viral load leads to low IOP, we cannot rule out a more complex bidirectional relationship or the influence of unmeasured variables. A prospective, longitudinal study that tracks IOP and viral load over time in patients initiating or changing cART would be the definitive next step to confirm a causal link. Secondly, the study was conducted at a single tertiary referral center, which may limit the generalizability of our findings. Patients at such centers may have more complex or severe disease profiles than the broader HIV population. Finally, while we controlled for major confounders, we did not have data on the specific cART regimens or duration of therapy, which could potentially influence IOP. Future studies should aim to incorporate these variables into their models.

5. Conclusion

This study provides compelling and statistically robust evidence that systemic HIV-1 viremia is a powerful and independent predictor of decreased intraocular pressure. This dose-dependent association persists after controlling for advanced disease stage and is not modified by the presence of cytomegalovirus retinitis, firmly establishing it as a systemic phenomenon directly linked to the level of viral replication. The findings point towards a pathophysiology rooted in viremia-induced ciliary body dysfunction, likely mediated by chronic inflammation and microvascular compromise. From a clinical perspective, this work elevates intraocular pressure from a simple ocular measurement to a potential, non-invasive adjunctive indicator of systemic HIV-1 disease activity, offering a valuable tool in the comprehensive management of people living with HIV.

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