Emerging Role of Letermovir, a CMV DNA Terminase Inhibitor, in the Management of Cytomegalovirus Retinitis: Efficacy, Safety, and Treatment Outcomes

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Abstract:

Cytomegalovirus retinitis (CMVR), an eye infection that attacks the retina and, if untreated, can lead to irreversible vision loss. In healthy individuals with a robust immune system, CMV is often asymptomatic; 60% of the immunocompromised population in developed countries are affected while 90% of the immunocompromised population in developing countries are affected. CMVR is a sight-threatening condition resulting from CMV reactivation in immunocompromised individuals, including those with HIV/AIDS and transplant recipients. Conventional antivirals such as ganciclovir, valganciclovir, foscarnet, and cidofovir effectively control CMVR but are limited by toxicities such as myelosuppression and nephrotoxicity, as well as emerging drug resistance. Letermovir, a CMV terminase complex inhibitor, has emerged as a targeted alternative with a favorable safety profile and potential for prophylaxis and treatment. This review examines CMVR epidemiology, risk factors, diagnostic approaches, and current therapeutic strategies, with emphasis on letermovir. Analysis of 23 published case reports shows that combination systemic and intravitreal therapy is the standard of care, with patient outcomes varying from vision improvement to irreversible loss and complications including immune recovery uveitis and retinal detachment. Integrating letermovir into combination regimens represents a promising approach to reduce treatment-related toxicity and resistance. Further clinical trials and long-term follow-up are needed to clarify its role as a therapeutic agent.

Introduction:

Cytomegalovirus (CMV) is a beta-herpesvirus, a subfamily of the herpesvirus that establishes lifelong dormancy within a patient (Griffiths & Reeves, 2021; Zhang et al., 2024). It affects 60% of adults in developed countries and over 90% of adults in developing countries (Jay Narain et al., 2022). In healthy individuals or those with a robust immune system, CMV is often asymptomatic, meaning it presents without noticeable symptoms. However, in patients with a compromised immune system, it can reactivate and cause significant problems when host defenses are unable to suppress it (Griffiths & Reeves, 2021; Jay Narain et al., 2022). CMV is well known to infect populations with impaired immune systems, and primarily infects people in developing countries (Jay Narain et al., 2022; Zhang et al., 2024). Among its common manifestations is CMV retinitis (CMVR), an eye infection that attacks the retina and, if untreated, can lead to irreversible vision loss (Liu et al., 2022; Zhang et al., 2024).

CMVR is a major sight-threatening condition, especially in immunocompromised individuals, like HIV patients and affects non-HIV patients too such as those recovering from a solid organ or hematopoietic stem cell transplantation (Kotton & Kamar, 2023; Zhang et al., 2024). It is mainly found in Asia and is least prevalent in Latin America and Africa (Jay Narain et al., 2022; Zhang et al., 2024). The management of CMVR has historically relied on antiviral treatments, such as ganciclovir, since its approval for use as a treatment option in 1983 (Fan et al., 2018; Ude et al., 2022). While these older antivirals can be effective, they often present issues such as myelosuppression, where bone marrow activity is decreased, and nephrotoxicity, which is kidney damage (Fan et al., 2018; Tasiopoulou et al., 2023). There are also growing cases of resistance to these treatments, especially ganciclovir, leading to attempts to find a new antiviral agent that is just as effective without the drawbacks of complications and resistance (Kotton & Kamar, 2023; Xia et al., 2024).

Recently, letermovir, a CMV terminase complex inhibitor, has emerged as a promising alternative (Limaye et al., 2023; Marty et al., 2017). Letermovir works by precisely targeting CMV and is therefore much more effective than ganciclovir or foscarnet due to its specificity (Kotton & Kamar, 2023; Limaye et al., 2023). Early data suggest that letermovir is safer and can be used as a prophylaxis, a measure taken to prevent a disease, and a treatment option in the future (Ishikawa et al., 2023; Kotton & Kamar, 2023). It also doesn't have to be injected into the eye to be more effective, unlike some older treatment options (Choopong et al., 2016). However, its long-term efficacy in controlling CMVR and preventing resistance to treatments remains under investigation (Kotton & Kamar, 2023; Marty et al., 2017). This paper examines the comparative efficacy, resistance patterns, safety, and modes of delivery of letermovir with traditional antiviral therapies, with a particular focus on its application in various immunosuppressed populations, including HIV-positive patients and transplant recipients.

Methods:

FDA-approved prophylactic drug letermovir for CMVR, was introduced in 2017. For this review, case studies after the introduction of the drug were selected using the NIH database PubMed Central. Use of letermovir is most commonly seen in immunocompromised patients. Search for the relevant articles included HIV-positive as well as HIV-negative individuals. Case studies with HIV-negative individuals were selected to review the difference in the response to the same drug with different HIV status. All papers published between 2017 and 2025 were considered for this review to understand the latest trends in combination therapy that included letermovir. For the purpose of a comparative study, papers related to drugs already in use were selected from the year 2016. The MeSH words that helped in the process of selection were: cytomegalovirus, cytomegalovirus retinitis, HIV-negative, treatment, ganciclovir, foscarnet, valganciclovir, letermovir, combination, patient, patients, case report, case series, case study, recipient, person, child, transplant, CMV DNA terminase.

Overview of CMVR:

CMVR is a severe optical manifestation of CMV and manifests with progressive retinal death, which can lead to irreversible vision loss if left untreated (Liu et al., 2022; Zhang et al., 2024). The disease comes from dormant CMV reactivating in an immunocompromised host, specifically in the eye (Griffiths & Reeves, 2021; Jay Narain et al., 2022). CMVR is indicated by floaters, which are small, dark shapes that drift across the visual field due to debris or inflammation, mild inflammation, and worsening vision, which can progress to retinal detachment, where the retina separates from the underlying tissue, or hemorrhage, a condition where bleeding occurs from a blood vessel, if not treated earlier (Liu et al., 2022; Ude et al., 2022).

Diagnosis of CMVR is made based on clinical examination and patient history. A dilated fundus examination is used to visualize the "pizza pie" retinal lesions and areas of death as shown in Figure 1 (Choopong et al., 2016; Zhang et al., 2024). Optical coherence tomography (OCT) provides cross-sectional imaging of retinal layers, which helps identify early structural changes and movement in parts of the eye, such as the macula (Liu et al., 2022; Xia et al., 2024). Polymerase chain reaction (PCR) testing of fluids in the eye and blood rules out incorrect diagnoses by other DNA viruses such as HZV or VZV, by confirming CMV DNA (Jay Narain et al., 2022; Shapira et al., 2018).

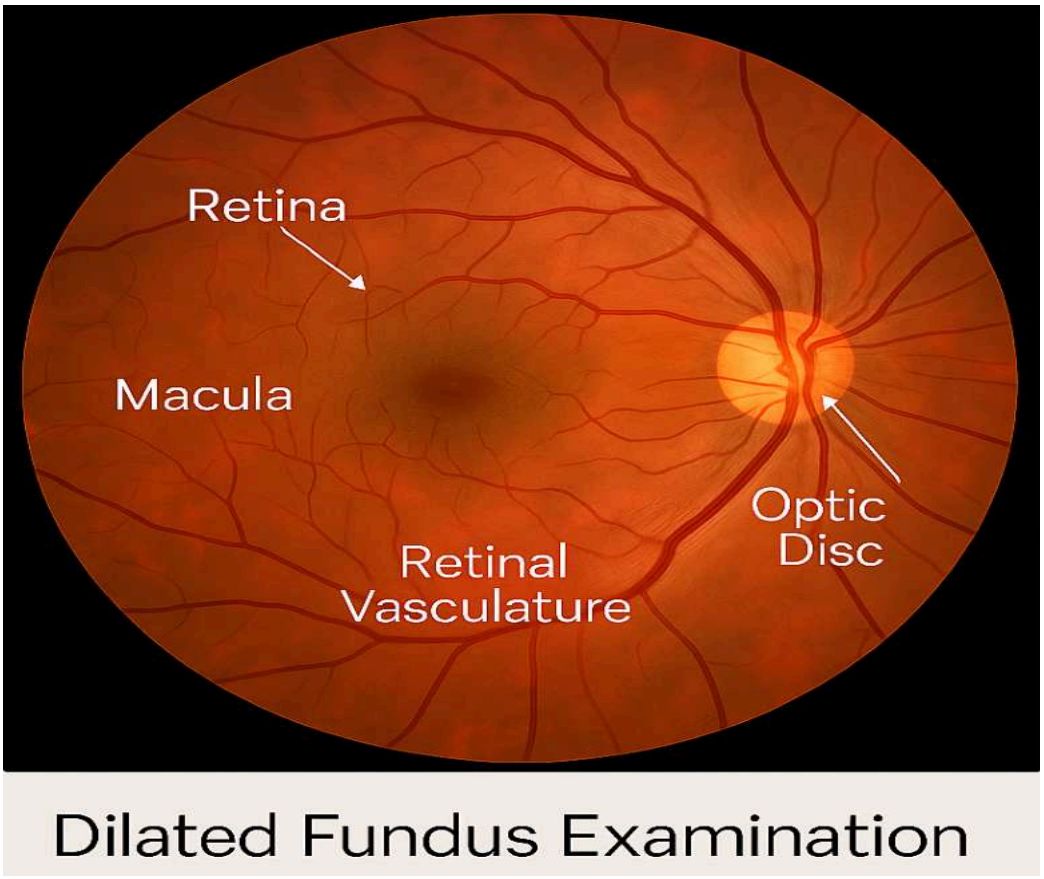

Figure 1*. Color fundus photograph demonstrating a clear view of the retina, macula, optic disc, and retinal vasculature without apparent signs of disease. Image created with ChatGPT (GPT-4) and generated July 25, 2025.*

Treatment standards have mostly been on antivirals that directly suppress CMV replication. First-line antiviral treatments include intravenous or intravitreal ganciclovir and oral valganciclovir (Fan et al., 2018; Tasiopoulou et al., 2023). Foscarnet and cidofovir are alternatives, especially in cases where the patient is resistant or tolerant to the first-line options (Fan et al., 2018; Kotton & Kamar, 2023). However, these treatments have some complications associated with them; ganciclovir and valganciclovir can cause bone marrow suppression, foscarnet is nephrotoxic, and cidofovir can also cause nephrotoxicity and inflammation in the middle layer of the eye, the uvea (Tasiopoulou et al., 2023; Zhang et al., 2024). This can all make long-term management of these treatments complex (Fan et al., 2018; Ude et al., 2022).

Letermovir is a newer antiviral that targets the CMV terminase complex and suppresses viral DNA processing, gaining attention recently as a potential addition to CMV therapies (Limaye et al., 2023; Marty et al., 2017). While it is only currently approved as a prophylaxis for cases of CMV, letermovir has been shown to have a favorable safety profile with minimal toxicity and other complications (Kotton & Kamar, 2023; Limaye et al., 2023). Regardless, its role in active CMVR management is still under evaluation, as clinical trials investigating its efficacy in treating established CMVR and preventing disease progression are limited (Ishikawa et al., 2023; Marty et al., 2017).

CMVR Risk and Protective Factors:

CMVR most commonly affects individuals with severely compromised immune systems, although the disease pattern varies across different patient populations (Jay Narain et al., 2022; Zhang et al., 2024). In people living with HIV, CMVR typically develops when $CD4^+$ T-cell counts fall below 50 cells/μL (Jay Narain et al., 2022; Ude et al., 2022). Patients with underlying conditions like autoimmune diseases or diabetes, as well as those receiving immunosuppressive drugs such as prednisone or abatacept, are at increased risk of CMVR (Shapira et al., 2018; Xia et al., 2024). The mechanisms of CMV itself, such as hiding in $CD34^+$ cells and evading the immune system, increase the likelihood of reactivation when immune defenses are lowered (Griffiths & Reeves, 2021).

CMVR can also infect patients without an impaired immune system. Solid-organ or hematopoietic stem cell transplantation exposes patients to immunosuppressive regimens, which can increase the chances of an infection (Kotton & Kamar, 2023; Limaye et al., 2023). This transplantation also increases the likelihood of an infection as $CD34^+$ cells are introduced during it. Figure 2 illustrates the hematopoietic stem cell transplantation process, providing context for CMVR susceptibility. Specific treatments, like intravitreal corticosteroids, methotrexate, or other transplant-related therapies, increase susceptibility to CMVR (Ude et al., 2022; Xia et al., 2024). Unequal access to healthcare also allows for high CMVR prevalence in regions with less access to treatments and limited screening for the diseases (Jay Narain et al., 2022).

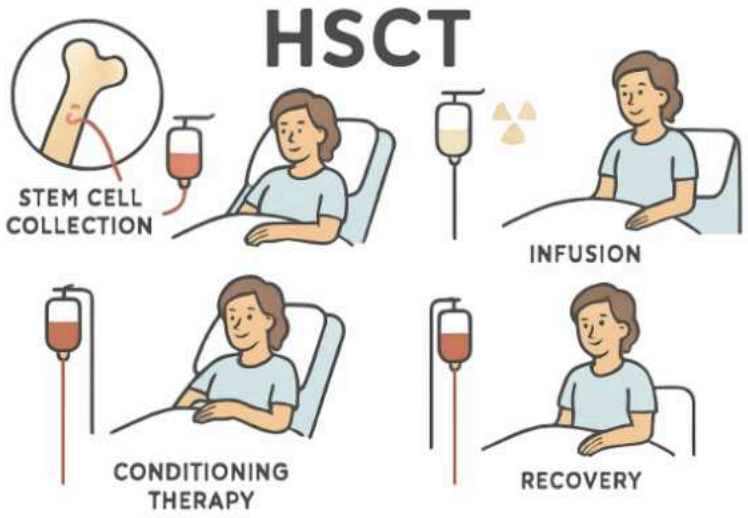

***Figure 2**. Illustration of the hematopoietic stem cell transplantation process. The sequence includes: (1) stem cell collection from bone marrow or peripheral blood; (2) conditioning therapy, typically involving high-dose chemotherapy and/or total body irradiation to eradicate malignant cells and suppress the immune system; (3) infusion of donor or autologous stem cells via intravenous administration; and (4) recovery phase, during which engraftment occurs and hematopoietic and immune function are gradually restored. Image created with ChatGPT (GPT-5) and generated on August 9, 2025 .*

A healthy immune system is crucial for preventing CMV from progressing into retinitis. Natural killer cells and $CD8^+$ T cells, which are cytotoxic, meaning they can kill other cells, are

essential for controlling the reactivation of the virus, limiting its replication, and preventing organ damage (Griffiths & Reeves, 2021). These cells patrol tissues and kill any infected cells before CMVR can develop. $CD4^+$ T cells also help by coordinating cellular responses needed to stop the virus from activating (Griffiths & Reeves, 2021; Ude et al., 2022)).

Limitations of Older Therapies and Emerging Options:

Limitations of Older Therapies

Older antivirals, such as ganciclovir and valganciclovir, are still commonly used as first-line treatments for CMVR (Fan et al., 2018; Ude et al., 2022). These agents are effective in controlling viral replication and saving the vision of many patients (Tasiopoulou et al., 2023; Xia et al., 2024). But they are frequently associated with bone marrow suppression and neutropenia, a condition characterized by low counts of neutrophils, a type of white blood cell (Fan et al., 2018; Tasiopoulou et al., 2023). This typically means that patients, especially those requiring extended treatment, cannot remain on these antivirals for an extended period. Treatment is often more complicated in transplant recipients as well because neutropenia occurs within the first year and increases the risk of graft rejection— a condition where a transplanted organ is attacked by the immune system— and infections (Kotton & Kamar, 2023; Limaye et al., 2023). When resistance appears or toxicity becomes an issue, foscarnet and cidofovir are commonly used as alternatives. These options are beneficial because they are effective against resistant CMV strains (Fan et al., 2018; Zhang et al., 2024). Both treatments have their complications, though, as they can both cause nephrotoxicity and other side effects that make prolonged treatment a difficult task, especially in patients with pre-existing kidney problems (Tasiopoulou et al., 2023; Ude et al., 2022).

Intravitreal therapy, such as intravitreal ganciclovir, is another method for delivering high concentrations of the drug directly to the eye with minimal side effects (Choopong et al., 2016; Fan et al., 2018). The issue with this approach is that the injections are administered on a weekly or bi-weekly basis, which can present challenges for patients and providers, especially in low-income areas where transportation costs can be prohibitive (Jay Narain et al., 2022).

Emerging Option - Letermovir

The CMV terminase complex is an important part of CMV and is responsible for the cleavage and encapsidation of newly replicated viral DNA. After CMV DNA is synthesized as long concatemers, the terminase complex, which is primarily composed of the proteins pUL56, pUL89, and pUL51, recognizes specific packaging signals, cleaves the concatemeric DNA into genome-length units, and translocates them into preformed capsids using ATP hydrolysis as an energy source. Within the complex, pUL56 is the large subunit with ATPase and DNA-binding activity, pUL89 is the small subunit that provides nuclease activity, and pUL51 stabilizes the assembly. Inhibition of this complex disrupts viral growth by preventing DNA packaging, which is a mechanism very different from traditional DNA polymerase inhibitors such as ganciclovir or foscarnet (Ligat et al., 2018)

As shown in Figure 3, letermovir, a newer alternative, targets the CMV terminase complex, a protein complex crucial for CMV replication, rather than the DNA polymerase, a type of enzyme that synthesizes a DNA (Kotton & Kamar, 2023; Limaye et al., 2023). This means that it

has a different mechanism and fewer overlapping resistance issues. Letermovir is non-inferior to valganciclovir in stopping CMV after a kidney transplant and is associated with significantly fewer cases of neutropenia and other toxicities, making it safer for patients who can't tolerate older drugs (Limaye et al., 2023; Marty et al., 2017). It is a promising new alternative for treating CMVR, especially in cases of resistance, despite its continued study as an active treatment option (Ishikawa et al., 2023; Kotton & Kamar, 2023).

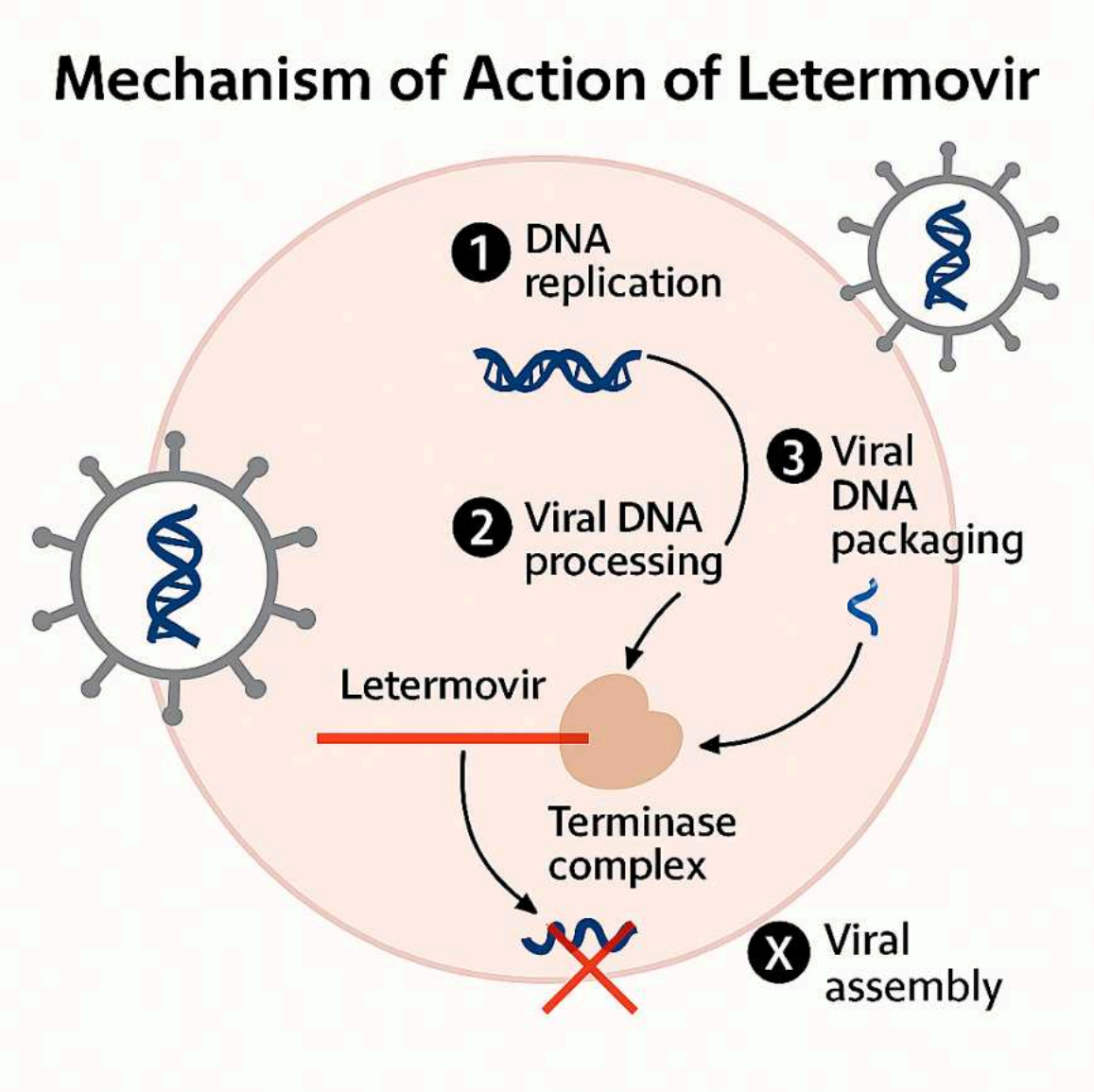

Figure 3. *Mechanism of action of letermovir in CMV replication.*

CMV, a double-stranded DNA virus, replicates its genome within the host cell nucleus, followed by processing, packaging of viral DNA into capsids, and assembly of infectious virions. (1) Viral DNA replication produces long concatemeric DNA strands. (2) The viral terminase complex cleaves and processes these concatemeric DNA molecules into unit-length genomes. (3) The processed DNA is then packaged into preformed viral capsids. (4) Viral assembly occurs as the DNA-filled capsids acquire their tegument and envelope, resulting in infectious virions, though letermovir stops this. It specifically inhibits the viral terminase complex,

preventing DNA processing and packaging, which halts successful viral maturation. Image created with ChatGPT (GPT-5) and generated on October 4, 2025.

Analysis of case studies:

There have also been a diverse number of case studies on CMVR that detail outlier cases in terms of diagnosis, treatment, and appearance.

CMVR can appear in patients with HIV or even without HIV. One case study showed that patients with blood cancers, such as myelodysplastic syndrome, after hematopoietic stem cell transplantation, can develop CMVR made worse by resistance to treatments and complications in the eye (Lee & Kim, 2025). Another case study showed that patients on belatacept-based immunosuppression after a solid-organ transplant have experienced CMVR that required combination antiviral therapy due to resistance (Deliège et al., 2020). Patients receiving new immunomodulatory drugs, such as upadacitinib for autoimmune diseases, have been affected. Survivors of lymphoma, a cancer of the immune system, as well as those with congenital immunodeficiencies like severe combined immunodeficiency, are also vulnerable (Hirai et al., 2023; Vassallo et al., 2020).

Pediatric cases include premature infants with congenital CMV infection and children undergoing chemotherapy for acute lymphoblastic leukemia, a fast-growing cancer of the blood and bone marrow that affects immature white blood cells called lymphoblasts (Li et al., 2025; Mandura et al., 2021), who often experience atypical progression and prolonged treatment courses. The coexistence of CMVR with ocular tumors such as retinoblastoma complicates both diagnosis and management (Meller et al., 2024).

Diagnosis is challenging, especially when other infections are present. Coinfections with ocular tuberculosis and toxoplasmosis, a disease caused by the parasite *Toxoplasma gondii*, which can affect the eyes and other organs, can mimic or occur alongside CMVR, complicating clinical assessment in immunocompromised patients (Sudharshan et al., 2020). Similar retinal inflammation from other causes increases the risk of misdiagnosis.

Immune recovery inflammatory phenomena, where inflammation occurs due to a trigger causing the immune system to attack the body, have also been observed in both HIV-positive and non-HIV patients. Conditions such as immune recovery uveitis and immune reconstitution inflammatory syndrome, which develop after antiviral therapy, can worsen retinal inflammation and injury to the circulatory system (Park et al., 2022). The use of local corticosteroids, including intravitreal or subtenon triamcinolone, for complications such as cystoid macular edema, where fluid enters the macula, requires caution to avoid viral reactivation and tissue damage (Lee & Kim, 2025).

Visual results in cases differ among patients. Some experience good recovery after systemic and intravitreal antiviral treatments, while others progress to vision loss due to retinal ischemia, neovascular glaucoma, or retinal detachment despite therapy (Jeong, 2024; Park et al., 2022; Sudharshan et al., 2020). Reports of neovascular glaucoma, a type of glaucoma caused by new, abnormal blood vessels growing on the eye's drainage channels, which block fluid outflow and increase eye pressure, and iris neovascularization, the growth of new, abnormal blood vessels on the iris, often related to poor blood flow or inflammation, have increased, even in patients without HIV, usually linked to retinal ischemia, a condition where the retina doesn't get enough blood and oxygen, leading to tissue damage and vision problems, and immune-related vascular damage (Jeong, 2024; Park et al., 2022; Sudharshan et al., 2020). Table 1 provides an

overview of the various treatment types employed, the range of visual outcomes observed, and the complications that arose during follow-up. (Alhoumaily & Dheyab, 2025; Benyahia et al., 2025; Deliège et al., 2020; Garg et al., 2022; Hirai et al., 2023; Jeong, 2024; Kao et al., 2021; Lee & Kim, 2025; Li et al., 2025; Mandura et al., 2021; Meller et al., 2024; Park et al., 2022; P. N. Patel et al., 2023; S. Patel & Robin, 2020; Qian et al., 2022; Saban et al., 2023; Serris et al., 2024; Shukla et al., 2023; Silva et al., 2022; Stoicescu et al., 2024; Sudharshan et al., 2020; Vassallo et al., 2020; Zemba et al., 2021)

***Table 1**. Summary of patient characteristics, clinical outcomes, treatment strategies, drug resistance, and complications reported across 23 published case reports of CMVR.*

Category	Number of Cases that underwent Treatment(s) in the Category	Percentage of Cases that underwent Treatment(s) in the Category	Citations
Gender			
Male	15	61%	(Alhoumaily & Dheyab, 2025; Deliège et al., 2020; Jeong, 2024; Lee & Kim, 2025; Mandura et al., 2021; Meller et al., 2024; Park et al., 2022; S. Patel & Robin, 2020; Qian et al., 2022; Saban et al., 2023; Shukla et al., 2023; Silva et al., 2022; Stoicescu et al., 2024; Sudharshan et al., 2020; Vassallo et al., 2020)
Female	8	35%	(Benyahia et al., 2025; Garg et al., 2022; Hirai et al., 2023; Kao et al., 2021; Li et al., 2025; P. N. Patel et al., 2023; Serris et al., 2024; Zemba et al., 2021)
Age			
0-18 year old*	4	17%	(Garg et al., 2022; Li et al., 2025; Mandura et al., 2021; Meller et al., 2024)
19-64 year old*	15	61%	(Alhoumaily & Dheyab,

			2025; Benyahia et al., 2025; Lee & Kim, 2025; Park et al., 2022; P. N. Patel et al., 2023; S. Patel & Robin, 2020; Qian et al., 2022; Saban et al., 2023; Serris et al., 2024; Shukla et al., 2023; Stoicescu et al., 2024; Sudharshan et al., 2020; Vassallo et al., 2020; Zemba et al., 2021)
65+ year old*	5	22%	(Deliège et al., 2020; Hirai et al., 2023; Jeong, 2024; Kao et al., 2021; Silva et al., 2022)
Region			
Europe	5	22%	(Deliège et al., 2020; Serris et al., 2024; Stoicescu et al., 2024; Vassallo et al., 2020; Zemba et al., 2021)
Asia	12	52%	(Alhoumaily & Dheyab, 2025; Hirai et al., 2023; Jeong, 2024; Kao et al., 2021; Lee & Kim, 2025; Li et al., 2025; Mandura et al., 2021; Park et al., 2022; Qian et al., 2022; Saban et al., 2023; Shukla et al., 2023; Sudharshan et al., 2020)
North America	5	22%	(Benyahia et al., 2025; Garg et al., 2022; Meller et al., 2024; P. N. Patel et al., 2023; S. Patel & Robin, 2020)
South America	1	4%	(Silva et al., 2022)
Patient Characteristics			

HIV-positive	5	22%	(Alhoumaily & Dheyab, 2025; Qian et al., 2022; Serris et al., 2024; Stoicescu et al., 2024; Sudharshan et al., 2020)
HIV-negative	18	78%	(Benyahia et al., 2025; Deliège et al., 2020; Garg et al., 2022; Hirai et al., 2023; Jeong, 2024; Kao et al., 2021; Lee & Kim, 2025; Li et al., 2025; Mandura et al., 2021; Meller et al., 2024; Park et al., 2022; P. N. Patel et al., 2023; S. Patel & Robin, 2020; Saban et al., 2023; Shukla et al., 2023; Silva et al., 2022; Vassallo et al., 2020; Zemba et al., 2021)
Clinical Outcomes			
Vision Improvement*	14	61%	(Alhoumaily & Dheyab, 2025; Deliège et al., 2020; Hirai et al., 2023; Kao et al., 2021; Mandura et al., 2021; S. Patel & Robin, 2020; Qian et al., 2022; Saban et al., 2023; Shukla et al., 2023; Silva et al., 2022; Vassallo et al., 2020; Zemba et al., 2021)
Vision Stabilization	4	17%	(Garg et al., 2022; Park et al., 2022; P. N. Patel et al., 2023; Serris et al., 2024)
Vision worsening/blindness	6	26%	(Benyahia et al., 2025; Jeong, 2024; Meller et al., 2024; Qian et al., 2022; Stoicescu et al., 2024; Sudharshan et al., 2020)

Unknown/Unspecified	2	9%	(Lee & Kim, 2025; Li et al., 2025)
Treatment Types			
Systemic antiviral treatment**	20	87%	(Alhoumaily & Dheyab, 2025; Benyahia et al., 2025; Deliège et al., 2020; Garg et al., 2022; Hirai et al., 2023; Jeong, 2024; Kao et al., 2021; Mandura et al., 2021; Meller et al., 2024; Park et al., 2022; P. N. Patel et al., 2023; S. Patel & Robin, 2020; Qian et al., 2022; Saban et al., 2023; Serris et al., 2024; Shukla et al., 2023; Silva et al., 2022; Stoicescu et al., 2024; Sudharshan et al., 2020; Vassallo et al., 2020; Zemba et al., 2021)
Intravitreal antiviral injections**	12	52%	(Alhoumaily & Dheyab, 2025; Benyahia et al., 2025; Deliège et al., 2020; Garg et al., 2022; Hirai et al., 2023; Jeong, 2024; Lee & Kim, 2025; Li et al., 2025; Park et al., 2022; S. Patel & Robin, 2020; Qian et al., 2022; Saban et al., 2023; Serris et al., 2024; Vassallo et al., 2020)
Newer antivirals (letermovir, maribavir)**	3	13%	(Benyahia et al., 2025; Deliège et al., 2020; Serris et al., 2024)
Drug Resistance and Failure			
Drug resistance	5	22%	(Benyahia et al., 2025;

reported			Deliège et al., 2020; Garg et al., 2022; Saban et al., 2023; Serris et al., 2024)
Prophylaxis failure cases	4	17%	(Benyahia et al., 2025; Deliège et al., 2020; Garg et al., 2022; Serris et al., 2024)
Complications			
Retinal detachment	6	26%	(Benyahia et al., 2025; Hirai et al., 2023; Meller et al., 2024; P. N. Patel et al., 2023; Qian et al., 2022; Stoicescu et al., 2024)
Macular edema	6	26%	(Garg et al., 2022; Lee & Kim, 2025; Mandura et al., 2021; Shukla et al., 2023; Vassallo et al., 2020; Zemba et al., 2021)

* = *There were multiple patients in some case reports*
** = *Multiple treatments were used*

Treatment approaches in these cases often combine systemic valganciclovir with intravitreal injections of ganciclovir or foscarnet, alongside laser photocoagulation. This medical treatment utilizes laser light to create small burns in the retina, sealing or destroying abnormal blood vessels or tissue to control ischemic complications (Mandura et al., 2021; Vassallo et al., 2020). Local corticosteroids are used cautiously for inflammatory complications such as cystoid macular edema, with antiviral coverage to prevent reactivation (Lee & Kim, 2025).

Outcomes of Letermovir Treatment:

Recently, letermovir has been gaining attention because it can treat patients with CMVR strains that are resistant to first-line treatments such as ganciclovir or valganciclovir (Kotton & Kamar, 2023; Limaye et al., 2023). In certain case studies, such as the one shown in Table 2, patients treated with letermovir were able to control ganciclovir-resistant CMV retinitis without any significant side effects, including nephrotoxicity or myelosuppression (Ishikawa et al., 2023; Marty et al., 2017; Turner et al., 2019). This could be useful in patients who are unable to take older antivirals or require treatments for longer durations (Kotton & Kamar, 2023; Xia et al., 2024). Letermovir has been shown to have a more favorable profile and also doesn't require as many dose adjustments as ganciclovir or valganciclovir, making it a good alternative under challenging cases (Limaye et al., 2023; Tasiopoulou et al., 2023).

***Table 2**. The table showcases the clinical outcomes of patients A, B, C, D after the treatment of letermovir (with a daily minimal dosage of 720 mg). Adapted from another case study* (Turner et al., 2019).

	Patient A	Patient B	Patient C	Patient D
Age/Gender	66-year-old male	50-year-old male	46-year-old male	66-year-old male
Plasma CMV DNA at start of letermovir	342 IU/mL	1416 IU/mL	745 IU/mL	<137 IU/mL
Prior CMV Prophylaxis	Valganciclovir	Valganciclovir	Valganciclovir	Valganciclovir
Known CMV mutations before using letermovir	UL97	UL54	UL97, UL54	UL97, UL54
Letermovir dose (mg daily)	720	720	720 → 960*	720
Follow-up duration (weeks)	38	39	32	34
Clinical Outcome	Improved on retinal exam	Improved on retinal exam	Improved on retinal exam	Improved on retinal exam

** = Patient was started on 720 mg letermovir daily, but the condition wasn't improving, so dosage was increased to 960 mg daily with no harmful side effects noted.*

While all these benefits exist, letermovir also has its issues. CMVR can still become resistant to letermovir through the UL56 gene, which can disrupt letermovir's ability to target the terminase complex (Limaye et al., 2023; Marty et al., 2017). CMVR patients with high CMV loads, prolonged exposure to antivirals, or incomplete immune recovery may allow the virus to adapt and change, thereby resisting letermovir (Kotton & Kamar, 2023; Ude et al., 2022). To combat this, it is necessary to keep monitoring the patient even after the letermovir regimens are complete and to follow up on their immune status just in case (Ishikawa et al., 2023).

Another issue is that letermovir has limited penetration into the eye and central nervous system, which could explain why patients experience relapse or even progression of retinitis even when actively receiving the drug (Limaye et al., 2023; Zhang et al., 2024). In some series, relapses occurred months after the initial disease was controlled, meaning that letermovir by itself might not be able to suppress CMVR (Marty et al., 2017; Xia et al., 2024). Due to this, letermovir is currently used in conjunction with other treatments or as a maintenance option after the initial disease is controlled, rather than as a stand-alone treatment (Kotton & Kamar, 2023; Tasiopoulou et al., 2023).

Discussion:

CMVR is described as a sight-threatening infection that appears in immunocompromised hosts, such as those with HIV/AIDS or patients who are taking immunosuppressive therapies after a solid organ or hematopoietic stem cell transplantation (Jay Narain et al., 2022; Kotton & Kamar, 2023). It works by reactivating when the immune system becomes impaired and leads to progressive retinal death, hemorrhage, and possibly irreversible vision loss if left untreated (Ude et al., 2022; Zhang et al., 2024). Diagnosis is achieved through tools like a dilated fundus exam, optical coherence tomography, and polymerase chain reaction testing (Choopong et al., 2016; Shapira et al., 2018). Management of CMVR has relied chiefly on first-line treatments such as ganciclovir and valganciclovir despite their side effects, such as myelosuppression and toxicity with prolonged use (Fan et al., 2018; Tasiopoulou et al., 2023). Alternatives, such as foscarnet and cidofovir, exist and are used in cases of resistance; however, they also have complications, including nephrotoxicity and other risks (Liu et al., 2022; Zhang et al., 2024). Recently, letermovir has emerged and can be used adjunctively or as maintenance therapy for CMVR, which may be more effective due to its specific mechanism of action and fewer complications (Kotton & Kamar, 2023; Limaye et al., 2023).

In Table 1, which mentions the study of the 23 case reports, the majority were HIV-positive (65%), consistent with the known epidemiology of the disease. Clinical outcomes revealed that while 35% of patients experienced vision improvement and 43% achieved stabilization, a notable 22% suffered from worsening or progression to blindness, highlighting the persistent risk of severe visual impairment despite treatment. Systemic antiviral therapy was the mainstay of treatment, utilized in 87% of cases, often supplemented with intravitreal antiviral injections (52%), showcasing the current combination treatment approaches. Drug resistance and prophylaxis failure were observed in 17% and 22% of cases, respectively, showing how antiviral resistance is a sizable problem when it comes to CMVR. Common complications included immune recovery uveitis (26%) and retinal detachment (17%), which continue to impact clinical outcomes and patient quality of life (Alhoumaily & Dheyab, 2025; Benyahia et al., 2025, 2025; Deliège et al., 2020; Garg et al., 2022; Hirai et al., 2023; Jeong, 2024; Kao et al., 2021, 2021; Lee & Kim, 2025; Li et al., 2025; Mandura et al., 2021; Meller et al., 2024; Park et al., 2022; P. N. Patel et al., 2023; S. Patel & Robin, 2020; Qian et al., 2022; Saban et al., 2023; Serris et al., 2024; Shukla et al., 2023; Silva et al., 2022; Stoicescu et al., 2024; Sudharshan et al., 2020; Vassallo et al., 2020; Zemba et al., 2021).

These developments in treatment demonstrate how CMVR management has evolved from older, broader antivirals to newer, more targeted treatments that are significantly safer (Ishikawa et al., 2023; Marty et al., 2017). Letermovir has explicitly been documented to benefit patients with resistance to ganciclovir greatly and allows for initial control over CMVR (Kotton & Kamar, 2023; Tasiopoulou et al., 2023). It also has almost no reported toxicities and a noticeably reduced risk of myelosuppression compared to valganciclovir (Limaye et al., 2023; Xia et al., 2024). Letermovir is still not a complete replacement for older therapies though. It is unable to penetrate the retina well and therefore can lead to relapses (Marty et al., 2017; Zhang et al., 2024). A mutation of the UL56 gene can also create resistance to letermovir, especially in patients with high viral loads or incomplete immune recovery (Kotton & Kamar, 2023; Ude et al., 2022).

Conclusion:

Future directions in CMVR management will likely focus on integrating newer antivirals such as letermovir into combination regimens to reduce the risk of resistance and toxicity. More clinical trials and continued follow-ups past a patient's treatment regimen are necessary to learn more about letermovir's role as a prophylactic and therapeutic agent. As more evidence emerges, it appears increasingly likely that virus-specific agents will replace traditional antivirals, marking a step toward a more efficient way of treating CMVR.

References:

1. Alhoumaily, A. Y., & Dheyab, A. M. (2025). Combined Cytomegalovirus Retinitis and Vitreous Hemorrhage in an Immunocompromised Patient. *Case Reports in Ophthalmological Medicine*, *2025*(1), 5510040. https://doi.org/10.1155/crop/5510040
2. Benyahia, S. A., Kahlon, S., Paul, S., Abdoul-Nasr, Y., Harvey, K., Patel, M., Shah, S., & Abdallah, E. (2025). Navigating Cytomegalovirus Retinitis in a Patient With Myelodysplastic Syndromes Transitioning to Acute Myeloid Leukemia Post Transplant: A Case Study. *Cureus*. https://doi.org/10.7759/cureus.78491
3. Choopong, P., Vivittaworn, K., Konlakij, D., Thoongsuwan, S., Pituksung, A., & Tesavibul, N. (2016). Treatment outcomes of reduced-dose intravitreal ganciclovir for cytomegalovirus retinitis. *BMC Infectious Diseases*, *16*(1), 164. https://doi.org/10.1186/s12879-016-1490-6
4. Deliège, P.-G., Bastien, J., Mokri, L., Guyot-Colosio, C., Arndt, C., & Rieu, P. (2020). Belatacept associated - cytomegalovirus retinitis in a kidney transplant recipient: A case report and review of the literature. *BMC Ophthalmology*, *20*(1), 468. https://doi.org/10.1186/s12886-020-01741-1
5. Fan, J.-J., Tao, Y., & Hwang, D.-K. (2018). Comparison of intravitreal ganciclovir monotherapy and combination with foscarnet as initial therapy for cytomegalovirus retinitis. *International Journal of Ophthalmology*, *11*(10), 1638–1642. https://doi.org/10.18240/ijo.2018.10.10
6. Garg, A., McKay, B. R., Francisconi, C. L. M., & Muni, R. H. (2022). Toxoplasmosis chorioretinitis mimicking cytomegalovirus retinitis in an immunocompromised pediatric

patient following bone marrow transplantation [Text/html]. *GMS Ophthalmology Cases*, *12*. https://doi.org/10.3205/OC000201

7. Griffiths, P., & Reeves, M. (2021). Pathogenesis of human cytomegalovirus in the immunocompromised host. *Nature Reviews. Microbiology*, *19*(12), 759–773. https://doi.org/10.1038/s41579-021-00582-z
8. Hirai, H., Akai, Y., Ogata, N., & Ueda, T. (2023). Cytomegalovirus Retinitis in a Patient Taking Upadacitinib: A Case Report. *Cureus*. https://doi.org/10.7759/cureus.48337
9. Ishikawa, S., Tasaki, M., Saito, K., Nakagawa, Y., Ikeda, M., Takahashi, K., & Tomita, Y. (2023). Long-term CMV monitoring and chronic rejection in renal transplant recipients. *Frontiers in Cellular and Infection Microbiology*, *13*, 1190794. https://doi.org/10.3389/fcimb.2023.1190794
10. Jay Narain, S., Visser, L., & Sibanda, W. (2022). Cytomegalovirus retinitis and antiretroviral treatment: A fifteen year experience. *Southern African Journal of HIV Medicine*, *23*(1). https://doi.org/10.4102/sajhivmed.v23i1.1322
11. Jeong, S. (2024). Cytomegalovirus retinitis with panretinal occlusive vasculopathy concealed by hypertensive uveitis: A case report. *Journal of Yeungnam Medical Science*, *41*(4), 300–305. https://doi.org/10.12701/jyms.2024.00584
12. Kao, C.-C., Hsu, S.-L., & Sheu, S.-J. (2021). Presumed cytomegalovirus retinitis in a non-immune compromised patient with breast carcinoma during treatment: A case report. *American Journal of Ophthalmology Case Reports*, *23*, 101161. https://doi.org/10.1016/j.ajoc.2021.101161
13. Kotton, C. N., & Kamar, N. (2023). New Insights on CMV Management in Solid Organ Transplant Patients: Prevention, Treatment, and Management of Resistant/Refractory

Disease. *Infectious Diseases and Therapy*, *12*(2), 333–342. https://doi.org/10.1007/s40121-022-00746-1

14. Lee, J. Y., & Kim, M. S. (2025). Treatment with Subtenon and Intravitreal Triamcinolone Acetonide for Cystoid Macular Edema after Cytomegalovirus Retinitis: A Case Report. *Korean Journal of Ophthalmology*, *39*(2), 192–194. https://doi.org/10.3341/kjo.2024.0086
15. Li, Y., Sun, W., Jin, X., Zhao, L., & Zhu, X. (2025). Congenital cytomegalovirus retinitis of prematurity: A case report and literature review. *Frontiers in Pediatrics*, *13*, 1558820. https://doi.org/10.3389/fped.2025.1558820
16. Ligat, G., Cazal, R., Hantz, S., & Alain, S. (2018). The human cytomegalovirus terminase complex as an antiviral target: A close-up view. *FEMS Microbiology Reviews*, *42*(2), 137–145. https://doi.org/10.1093/femsre/fuy004
17. Limaye, A. P., Budde, K., Humar, A., Vincenti, F., Kuypers, D. R. J., Carroll, R. P., Stauffer, N., Murata, Y., Strizki, J. M., Teal, V. L., Gilbert, C. L., & Haber, B. A. (2023). Letermovir vs Valganciclovir for Prophylaxis of Cytomegalovirus in High-Risk Kidney Transplant Recipients: A Randomized Clinical Trial. *JAMA*, *330*(1), 33–42. https://doi.org/10.1001/jama.2023.9106
18. Liu, M., He, H., Lu, Q., & Zhang, J. (2022). CMV retinitis and subsequent acute cystoid macular oedema after treatment with vitreous ganciclovir injection: A case report. *BMC Ophthalmology*, *22*(1), 284. https://doi.org/10.1186/s12886-022-02500-0
19. Mandura, R. A., Talat, K., & Jastaniah, W. (2021). Unilateral Cytomegalovirus Retinitis in a Child With Acute Lymphoblastic Leukemia While on Maintenance Chemotherapy. *Cureus*. https://doi.org/10.7759/cureus.15246

20. Marty, F. M., Ljungman, P., Chemaly, R. F., Maertens, J., Dadwal, S. S., Duarte, R. F., Haider, S., Ullmann, A. J., Katayama, Y., Brown, J., Mullane, K. M., Boeckh, M., Blumberg, E. A., Einsele, H., Snydman, D. R., Kanda, Y., DiNubile, M. J., Teal, V. L., Wan, H., … Badshah, C. (2017). Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation. *New England Journal of Medicine*, *377*(25), 2433–2444. https://doi.org/10.1056/NEJMoa1706640
21. Meller, L., Jagadeesh, V., Oca, M., Wilson, K., Zuraski, C., Koretz, Z. A., Chevez-Barrios, P., Liu, C., Berry, J. L., & Scott, N. L. (2024). Cytomegalovirus Retinitis in an Eye with Unilateral Retinoblastoma: A Case Report. *Case Reports in Ophthalmology*, *15*(1), 483–489. https://doi.org/10.1159/000538738
22. Park, S. H., Cho, H., Seong, M., Kang, M. H., & Shin, Y. U. (2022). Rapidly Progressive Neovascular Glaucoma Associated with Atypical Cytomegalovirus Retinitis: A Case Report. *Korean Journal of Ophthalmology*, *36*(2), 171–179. https://doi.org/10.3341/kjo.2021.0185
23. Patel, P. N., Alkaliby, A. M., Mehta, M. C., & Wang, A. L. (2023). CMV retinitis in patients on mycophenolate immunosuppression: A report of two cases. *Allergy, Asthma, and Clinical Immunology: Official Journal of the Canadian Society of Allergy and Clinical Immunology*, *19*(1), 72. https://doi.org/10.1186/s13223-023-00817-z
24. Patel, S., & Robin, A. (2020). Cytomegalovirus Retinitis in a Patient on Long-term Mycophenolate Mofetil Treatment for Myasthenia Gravis. *Journal of Ophthalmic and Vision Research*, *15*(3), 428–431. https://doi.org/10.18502/jovr.v15i3.7463
25. Qian, Y., Wang, L., Jiang, J., Suo, J., Weng, H., Che, X., Lu, H., & Wang, Z. (2022). Cytomegalovirus-Immune Recovery Retinitis After Initiation of Highly Active Antiretroviral

Therapy: A Case Series. *Frontiers in Medicine*, *9*, 807013. https://doi.org/10.3389/fmed.2022.807013

26. Saban, T., Shargian, L., Eiger-Moscovitch, M., Prockop, S., Doubrovina, E., Yeshurun, M., & Kramer, M. (2023). Case Report: Cytomegalovirus-specific T-lymphocyte infusion for resistant cytomegalovirus retinitis. *Frontiers in Ophthalmology*, *3*, 1131674. https://doi.org/10.3389/fopht.2023.1131674
27. Serris, A., Rahi, M., Rioux, C., Fidouh, N., Joly, V., & Boutolleau, D. (2024). Refractory anti-viral resistant CMV retinitis in an immunological nonresponder person living with HIV. *International Journal of Infectious Diseases: IJID: Official Publication of the International Society for Infectious Diseases*, *148*, 107229. https://doi.org/10.1016/j.ijid.2024.107229
28. Shapira, Y., Mimouni, M., & Vishnevskia-Dai, V. (2018). Cytomegalovirus retinitis in HIV-negative patients – associated conditions, clinical presentation, diagnostic methods and treatment strategy. *Acta Ophthalmologica*, *96*(7). https://doi.org/10.1111/aos.13553
29. Shukla, R., Mishra, A. K., Verma, A., Garg, P., & Lnu, S. (2023). A Rare Case of Cytomegalovirus Retinitis in a Young Immunocompetent Patient. *Cureus*. https://doi.org/10.7759/cureus.44948
30. Silva, F., Ficher, K. N., Viana, L., Coelho, I., Rezende, J. T., Wagner, D., Vaz, M. L., Foresto, R., Silva Junior, H. T., & Pestana, J. M. (2022). Presumed cytomegalovirus retinitis late after kidney transplant. *Brazilian Journal of Nephrology*, *44*(3), 457–461. https://doi.org/10.1590/2175-8239-jbn-2020-0254
31. Stoicescu, E. R., Ghenciu, L. A., Iacob, R., Ardelean, A. I., Dăescu, E., Hațegan, O. A., Manolescu, D., Tudorache, E., Boru, C., & Dima, M. (2024). CMV Retinitis in the Context

of SARS-CoV-2 Infection: A Case Study and Comprehensive Review of Viral Interactions. *Pathogens (Basel, Switzerland)*, *13*(11), 938. https://doi.org/10.3390/pathogens13110938

32. Sudharshan, S., Babu, R., Nair, N., & Biswas, J. (2020). Combined infection of ocular tuberculoma and cytomegalovirus retinitis in the same eye of a patient with human immunodeficiency virus. *Indian Journal of Ophthalmology*, *68*(9), 1965. https://doi.org/10.4103/ijo.IJO_1321_20
33. Tasiopoulou, A., Urzua, C. A., & Lightman, S. (2023). Successful treatment of cytomegalovirus retinitis with oral/intravitreal antivirals in HIV-negative patients with lymphoma. *Eye (London, England)*, *37*(9), 1895–1903. https://doi.org/10.1038/s41433-022-02267-0
34. Turner, N., Strand, A., Grewal, D. S., Cox, G., Arif, S., Baker, A. W., Maziarz, E. K., Saullo, J. H., & Wolfe, C. R. (2019). Use of Letermovir as Salvage Therapy for Drug-Resistant Cytomegalovirus Retinitis. *Antimicrobial Agents and Chemotherapy*, *63*(3), e02337-18. https://doi.org/10.1128/AAC.02337-18
35. Ude, I. N., Yeh, S., & Shantha, J. G. (2022). Cytomegalovirus retinitis in the highly active anti-retroviral therapy era. *Annals of Eye Science*, *7*, 5. https://doi.org/10.21037/aes-21-18
36. Vassallo, F., Nuzzi, R., Cattani, I., Dellacasa, C., Giaccone, L., De Rosa, F. G., Cavallo, R., Iovino, G., Brunello, L., Bruno, B., & Busca, A. (2020). CMV retinitis in a stem cell transplant recipient treated with foscarnet intravitreal injection and CMV specific immunoglobulins. *Therapeutic Advances in Hematology*, *11*, 2040620720975651. https://doi.org/10.1177/2040620720975651

37. Xia, J., Kantipudi, S., Striebich, C. C., Henao-Martinez, A. F., Manoharan, N., Palestine, A. G., & Reddy, A. K. (2024). Cytomegalovirus chronic retinal necrosis with ganciclovir resistance: A case report. *Journal of Ophthalmic Inflammation and Infection*, *14*(1), 50. https://doi.org/10.1186/s12348-024-00434-w
38. Zemba, M., Rogoz, R.-E., Zaharia, A. C., Dimirache, A. E., Dumitrescu, O.-M., & Dărăbuş, D.-M. (2021). Challenges in HIV-Negative Cytomegalovirus Retinitis – case report. *Romanian Journal of Ophthalmology*, *65*(3). https://doi.org/10.22336/rjo.2021.49
39. Zhang, J., Kamoi, K., Zong, Y., Yang, M., Zou, Y., Miyagaki, M., & Ohno-Matsui, K. (2024). Cytomegalovirus Retinitis: Clinical Manifestations, Diagnosis and Treatment. *Viruses*, *16*(9), 1427. https://doi.org/10.3390/v16091427