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International consensuses and guidelines on diagnosing and managing cytomegalovirus (CMV) retinitis by the Asia-Pacific Vitreo-retina Society (APVRS), the Asia-Pacific Professors of Ophthalmology (AAPPO) and the Asia-Pacific Society of Ocular Inflammation and Infection (APSOII)

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ABSTRACT

With the paradigm changes in antiviral therapy, there are a myriad of emerging controversies in the management of cytomegalovirus retinitis (CMVR). A certain extent of variability exists in the management of CMVR among clinical practices worldwide. Hence, alignment in the management strategy is important towards optimizing the care of CMVR. An international panel of experts (IPE) formulated consensus statements for CMVR regarding to its 1) diagnosis, 2) screening, 3) treatment, 4) management in special populations and 5) emerging technologies. The clinical diagnosis of CMVR relies on patient's susceptibility due to compromised immune function and characteristic fundus manifestations. Polymerase chain reaction (PCR) of intraocular fluid for detection of CMV is indicated when confirmation is necessary. Oral valganciclovir is the preferred first-line treatment, and intravitreal ganciclovir injection when CMVR threatens to involve the posterior pole. Cessation of maintenance treatment can be considered after 6 months when CMVR remains inactive with immune reconstitution. Immune recovery uveitis (IRU) must be distinguished from CMVR relapse. Screening is recommended for high risk cases. Utilization of telemedicine and artificial intelligence-aided interpretation will help to alleviate the resources required for CMVR screening. Evidence for novel antiviral and immunotherapy have been appraised as second-line treatment options.

1. Introduction

CMVR is a serious, vision threatening ocular infection that primarily affects immunocompromised patients, particularly those infected by human immunodeficiency virus (HIV) with acquired immunodeficiency syndrome (AIDS), organ transplant recipients and those undergoing immunosuppressive therapy. Untreated CMVR causes progressive necrosis of the retina, retinal detachment and permanent vision loss.[1] Even if CMVR is initially controlled with prompt induction of antiviral treatment, it requires ongoing maintenance treatment to prevent disease relapse. Bone marrow suppression and renal function impairment are important potential side effects of antiviral treatment. The cost of long-term antiviral drugs, need for frequent clinic monitoring for disease recurrence, ophthalmic complications and systemic side effects lead to substantial economic and public health burden.[2]

Prior to the widespread use of highly active antiretroviral therapy (HAART), CMVR occurred in 30 % of AIDS patients and was the leading cause of vision impairment.[3] HAART reduced the incidence of CMVR by 80 % due to immune reconstitution.[4] CMVR now occurs in less than 5 % of HIV patients, mostly in late-presenting or ART-nonadherent patients.[4] Despite major advances in antiviral therapy and the introduction of HAART, CMVR continues to present substantial clinical challenges. Delays in diagnosis or suboptimal treatment can lead to rapid progression and irreversible vision loss. While existing diagnostic tools—including fundus examination, polymerase chain reaction (PCR) testing, and advanced retinal imaging—have improved our ability to detect CMVR, there is still significant debate regarding the relative accuracy and practicality of clinical versus laboratory-based diagnostic strategies.[5] Moreover, the evolving diagnostic criteria in the HAART era, compounded by the limitations of PCR reliability in some settings and the emergence of newer imaging modalities, further complicate clinical decision-making.[6]

The therapeutic landscape for CMVR is similarly complex. Systemic antivirals such as ganciclovir, valganciclovir, and foscarnet are commonly employed, either alone or in combination with local (intravitreal) therapy. However, controversies persist around the choice of systemic versus local treatment, the optimal duration of therapy, and the management of drug resistance—particularly in patients undergoing prolonged treatment or those with recurrent disease.[7] In resource-limited settings, these issues are exacerbated by restricted access to medications, laboratory diagnostics, and specialist care, resulting in significant disparities in outcomes.[8] Furthermore, drug resistance to first-line antivirals such as ganciclovir and foscarnet poses additional challenges and necessitates the exploration of novel therapeutic agents.[9]

Screening strategies for CMVR remain another area of ongoing debate. Currently, there is no consensus on who should be screened, how frequently, or by what methods. While regular retinal evaluations are recommended for high-risk groups, such as HIV-infected individuals with CD4 counts below 50 cells/mm^3,[10] resource limitations and lack of trained personnel hinder systematic implementation. Emerging technologies—including portable fundus cameras, widefield imaging, and artificial intelligence–assisted screening tools—offer potential solutions, especially in low-resource settings, but require further validation.

Special consideration is also warranted for paediatric populations, particularly children with congenital CMV or those undergoing immunosuppression for malignancies or transplantation. Diagnostic and therapeutic protocols tailored for paediatric CMVR are scarce, and challenges such as drug dosing, toxicity, and long-term sequelae remain poorly addressed.[11]

Finally, new therapeutic approaches and innovations are emerging.[12,13] The use of letermovir, novel prodrugs, combination regimens, and host-directed therapies is being explored.[14] Artificial intelligence, telemedicine, and digital health platforms may further support early detection, longitudinal monitoring, and clinical decision-making.[15–17] Despite these developments, there remains a lack of globally accepted consensus on the diagnosis, treatment, screening, and monitoring of CMVR across various clinical and geographic settings.

In response to these unmet needs, the Asia-Pacific Vitreo-Retina Society (APVRS), the Academy of Asia-Pacific Professors of Ophthalmology (AAPPO), and the Asia-Pacific Society of Ocular Inflammation and Infection (APSOII) have identified CMVR as a priority topic for their 2025 "Controversies and Consensus Statements" initiative. Recognizing the substantial disease burden, variation in clinical practice, and need for harmonized guidelines, this collaborative effort aims to generate evidence-informed recommendations to standardize the diagnostic and therapeutic approach to CMVR. Two senior authors (YT and DSCL) of this manuscript have been appointed to coordinate the consensus

[1] De-Kuang Hwang and Danny S. C. Ng contributed as co-first authors.

process. Through this initiative, we aim to address current controversies, bridge knowledge gaps, and improve clinical outcomes for patients affected by CMVR worldwide.

2. Methodology

Further to appointing the two coordinators, the APVRS, AAPPO and APSOII form an international panel of experts (IPE) comprising 21 panelists from 13 countries/territories. A core group of 4 members (DN, DKH, DSCL and YT) selected from the panel was then established to perform an extensive literature search and review on CMVR and prepare the first draft of the consensus statements with explanation and elaboration. Panelists were selected based on their expertise in uveitis, retinal infections, CMVR management, and/or experience in clinical guideline development. Invitations were extended to clinicians, researchers, and public health experts from both academic and high-volume clinical settings.

Databases included PubMed, Embase, Cochrane Library, and ClinicalTrials.gov. Key search terms included 'cytomegalovirus retinitis', 'polymerase chain reaction', 'antiviral treatment', 'complications', and 'immune reconstitution uveitis'. The search was conducted between January 2010 to March 2025, limited to English-language publications, and focused on human studies. Both peer-reviewed articles and relevant grey literature (e.g., guidelines, technical reports) were considered. Databases included PubMed, Embase, Cochrane Library, and ClinicalTrials.gov. Key search terms included 'cytomegalovirus retinitis', 'polymerase chain reaction', 'antiviral treatment', 'complications', and 'immune reconstitution uveitis'.

These statements were organized into five categories: diagnostic controversies, screening controversies, treatment controversies, special population considerations, and emerging controversies. Each panel member independently and anonymously reviewed each statement and provided comments to the core group. The core group then reviewed, evaluated the feedback and comments, revised and sent out the 2nd draft for further opinions. The process was repeated until the statements were finalized. Subsequently, each panel member voted on each statement anonymously for the final draft using a five-point Likert scale, ranging from 'strongly agree', 'agree', 'neutral', 'disagree', to 'strongly disagree'. Consensus was achieved when 75 % of responses were 'strongly agree' or 'Agree'. The consensus-building process followed a modified Delphi methodology, involving iterative rounds of anonymous voting and controlled feedback.[18–20] Different thresholds (60 %, 70 %, 75 %, 80 % or 90 %) for consensus were tested to investigate the robustness of the result for overall consensus.[21] The threshold of 75 % is commonly used in Delphi studies in the context of core outcome set development to ensure that researchers measure and report those outcomes that are most likely to be relevant to users of their research.[22] After due consideration, the threshold of 75 % was chosen as the consensus criterion in which at least 75 % of the experts had voted for "agree" or "strongly agree" to reach a consensus.[23] All panelists were required to disclose potential conflicts of interest prior to participation. Any declared conflicts were documented and managed in accordance with APVRS, AAPPO, and APSOII policies.

3. Controversies and consensus statements

3.1. Diagnostic controversies

The clinical diagnosis of CMVR relies on two fundamental considerations: patient susceptibility and fundus manifestations. Susceptibility is defined by the individual's compromised systemic immune function. Prior to the onset of AIDS epidemic, CMVR was a rare disease seen primarily in patients undergoing organ transplants, attributed by the risk of a CMV seropositive donor organ transplanted into a CMV-seronegative recipient. CMVR is much more common patients with advanced HIV infection and it is an AIDS-defining opportunistic infection.[24] The lifetime risk of developing CMVR after the onset of AIDS was estimated at 30 %.[25] The primary risk factor is low CD4 + T cell count, with the majority of cases occurring among patients with CD4 + T cell counts $\leq$ 50 cells/μL, as CMV- seropositive rates among persons at high risk for HIV infection typically were > 90 %.[26] With the widespread use of HAART, the incidence of CMVR among patients with AIDS has decreased by > 95 %, primarily due to immune recovery and/or restoration of immunity to CMV.[27,28] Patients with other forms of immunosuppression, such as oncology patients who are receiving chemotherapy, patients on long term immunosuppressive following organ or stem cell transplantation, and patients on long term immunosuppression and/or biologic therapy for organ threatening autoimmune disease may develop CMVR.[29] Peripheral blood CD4 cell count is not a reliable risk marker in many of these patients. CMVR in patients have been reported after intravitreal corticosteroid injection or sustained-release corticosteroid implantation, presumably resulting from local, compromised ocular immunity.[30,31]

The cause of immunosuppression directly impacts CMVR treatment strategy and prognosis. There are two major categories to classify the causes of immunosuppression: 1) immunosuppression directly caused by the primary clinical condition or disease such as HIV infection or malignancy and 2) iatrogenic immunosuppression secondary to the use of immunosuppressive drugs. The extent of immunosuppression can be classified to 1) systemic or 2) local (ocular). The management of CMV retinitis is twofold: 1) treating the active viral infection with antiviral medication and 2) addressing the underlying cause of immunosuppression by

reducing immunomodulator/chemotherapy dosage or prescription of HAART for AIDS patients.

The typical fundus manifestation in CMVR varies from granular retinitis (Figs. 1 and 2), wedge-shaped retinitis (Fig. 3) and the hemorrhagic (fulminant) form (Fig. 4) of retinitis[32] Granular retinitis appears in the peripheral retina as punctate lesions with varied shapes, sometimes devoid of hemorrhage. Wedge-shaped retinitis encompasses one retinal quadrant, with lesions forming a 'wedge' pointing to the optic disc. In hemorrhagic retinitis, more extensive areas of hemorrhages, admixed with areas of retinal edema and necrosis that often involve the posterior pole are present. There is a zone of satellite lesions at the borders of CMV lesions that can be up to ½ a disc diameter wide. The coexistence of retinal necrosis and intraretinal hemorrhages is often referred to as the 'cottage cheese and ketchup' or 'pizza pie' or 'bush fire' appearances. Patients with CMVR typically have relatively small amounts of anterior chamber and vitreous inflammation at presentation plausibly due to the failure to mount an effective immune reaction. If untreated, the end result of CMVR is full-thickness retinal necrosis leaving a thin, atrophic (Fig. 4), and gliotic scar. Retinal detachment used to be a frequent complication of CMVR, due to multiple retinal tears and/or atrophic retinal holes, typically at the border of normal retina and the atrophic scar. The incidence of retinal detachment is related to the extent of retina involved by CMVR and its incidence has declined with the widespread use of HAART.[33,34]

The diagnosis of CMVR may be confused with infectious necrotizing retinitis by other herpesvirus and toxoplasma. Acute retinal necrosis (ARN) may have relatively well demarcated borders with marked vitreous and anterior chamber inflammation. Progressive outer retinal necrosis (PORN) involves multiple deep, sharply demarcated white retinal lesions with early optic nerve involvement and minimal vitreous infiltration.[35] In immunocompromised hosts, toxoplasma retinitis can present as one or mare lesions of extensive retinitis without adjacent scars that are difficult to distinguish from CMVR.[36] Other differential diagnosis of CMVR include infectious posterior/panuveitis from syphilis or tuberculosis (TB). Syphilitic retinitis typically has a characteristic diaphanous or ground-glass retinitis often with creamy yellow superficial retinal precipitates.[37] Syphilitic retinitis can easily be misdiagnosed as viral retinitis. The diagnosis of syphilis is made by serological testing.[38] Mycobacterium TB is another common opportunistic

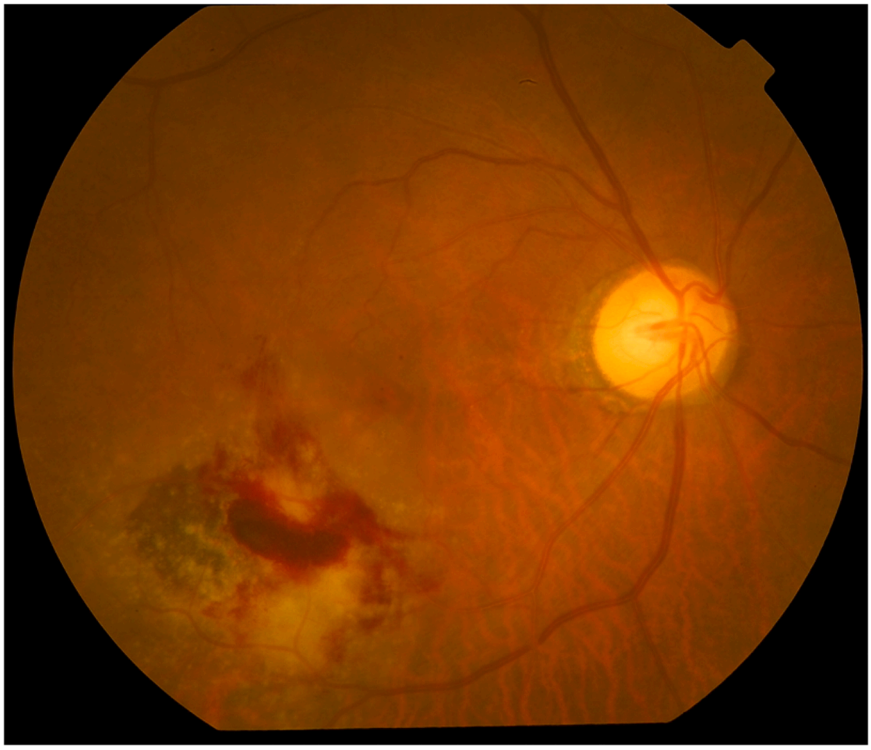

Fig. 1. This picture showed the presence of a typical cytomegalovirus retinitis (CMVR) lesion close to the macula with classic hemorrhage and infiltrate resembling the "cheese-on-ketchup appearance." The absence of media haze also signified absence of vitritis. The lesion might threaten the fovea with Snellen visual acuity still preserved at 20/20. (Fig. 1 is contributed by IW, original author).

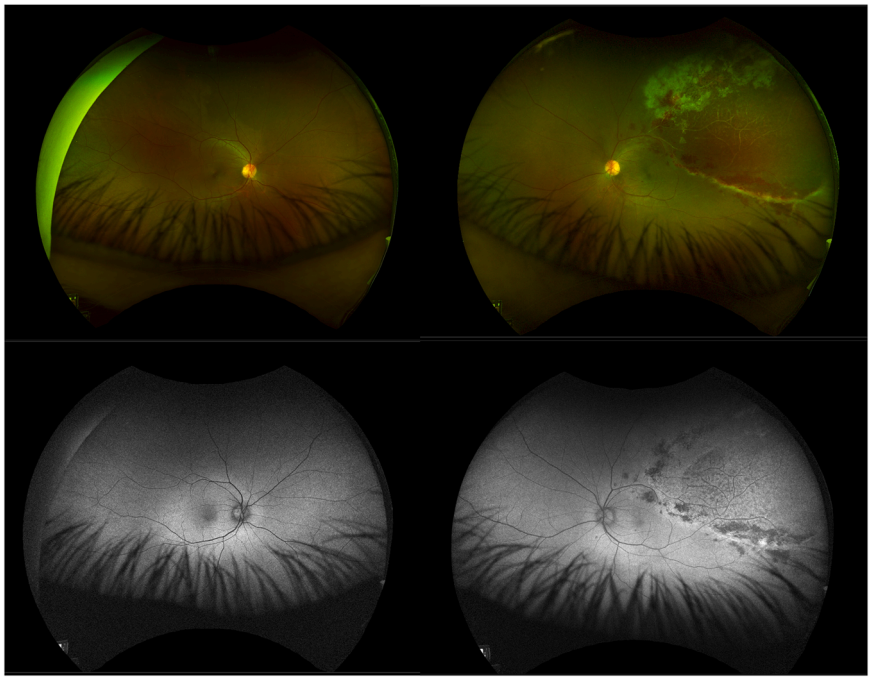

Fig. 2. Ultra-widefield fundus and autofluorescence (FAF) images of a 46-year-old male with acquired immunodeficiency syndrome (AIDS) since 2008 (CD4 + T-cell count 28 cells/μL), on long-term anti-retroviral therapy, who presented with 3 months of blurred vision, floaters, photopsia, and inferior visual field blurring.
(TOP LEFT and BOTTOM LEFT) Right eye showed preserved fovea and disc, no evidence of active retinitis, with corresponding FAF showing normal macular autofluorescence.
(TOP RIGHT and BOTTOM RIGHT) Left eye revealed extensive superior necrotizing cytomegalovirus retinitis (CMVR) with retinal whitening, hemorrhages, and vascular involvement. The retinitis displayed the classic "bushfire" advancing front, with granular borders spreading along the superior retina, explaining the inferior visual field loss. FAF highlighted hypoautofluorescence in necrotic/atrophic retina and hyperautofluorescence at the active leading edge, delineating the progression of the disease. (Fig. 2 is contributed by RLDN, original author)

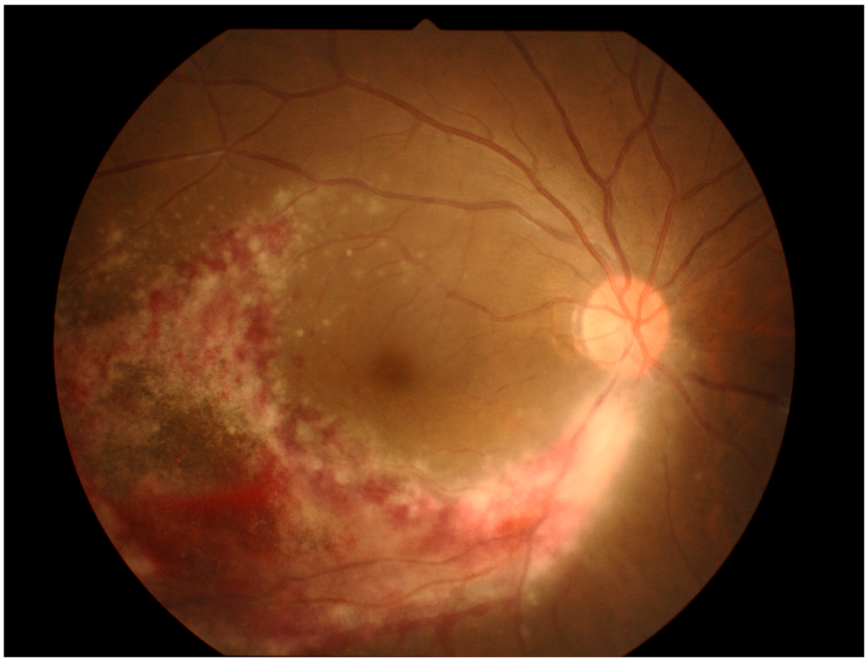

Fig. 3. Active cytomegalovirus retinitis (CMVR) presented as "wedge-shaped" retinitis that encompassed the inferior temporal quadrant, with lesion forming a 'wedge' pointing to the optic disc. There are satellite lesions and involvement of zone 1. (Fig. 3 is contributed by PC, original author).

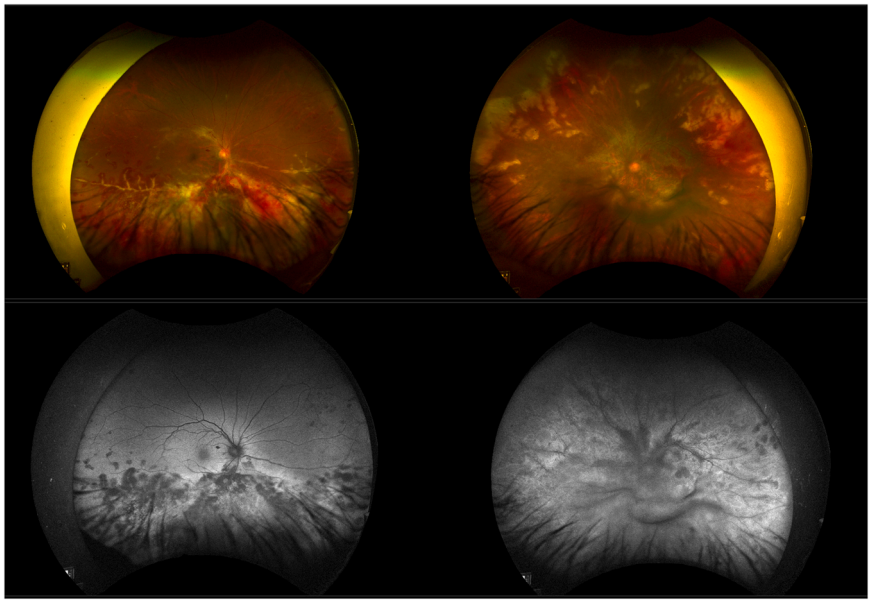

Fig. 4. Ultra-widefield fundus photography and fundus autofluorescence (FAF) of a 35 year-old male with recently diagnosed HIV infection (CD4 + T-cell count 79 cells/μL), on tenofovir, lamivudine, and dolutegravir (TLD) and anti-tuberculosis treatment for 2 months. The patient reported sudden blurred vision in the left eye 5 months earlier and in the right eye 1 month earlier; the presenting visual acuity of right eye was 6/10 and left eye had no light perception.
(**TOP LEFT**) The right eye showed more recent and active disease, characterized by retinal whitening, blot hemorrhages, edema, and perivascular sheathing consistent with frosted branch angiitis.
(**TOP RIGHT**) The left eye showed extensive necrotizing retinitis with broad areas of scarring, pigmentary changes, intraretinal hemorrhages, and retinal atrophy, consistent with advanced, chronic cytomegalovirus retinitis (CMVR) after multiple intravitreal foscarnet injections. Autofluorescence demonstrated mottled hypo-autofluorescence (scarring/atrophy) interspersed with granular hyperautofluorescence at lesion borders, reflecting a mixture of inactive and residual activity.
(**BOTTOM LEFT & RIGHT**) FAF highlighted linear hyperautofluorescence along the lesion edges (activity) and patchy hypoautofluorescence in necrotic areas.
Overall, these findings were consistent with bilateral, advanced CMVR, with the left eye showing end-stage disease and the right eye displaying active retinitis with frosted branch angiitis. (Fig. 4 is contributed by RLDN, original author)

infections associated with AIDS, and although ocular TB is uncommon, it remains an important differential diagnosis in developing countries.[39] TB retinitis is common in TB-associated intraocular inflammation which involves vitreous opacification, gray-white retinal lesions, and focal retinal vasculitis.[40] Due to the nonspecific ocular signs and potentially low pathogen load, diagnosing tuberculosis usually requires tuberculin skin tests (TST), chest x-ray, and QuantiFERON-TB Gold blood as an alternative to TST that is not affected by prior BCG vaccination.

Intraocular lymphoma may appear with yellow-white deep retinal lesions, sparse superficial retinal hemorrhages and perivascular exudates that mimics CMVR and is another differential diagnosis.[41]

Polymerase Chain Reaction (PCR) is a highly sensitive and specific molecular technique that can be used to detect CMV DNA in ocular fluids, aiding in the diagnosis of CMVR particularly in immunocompromised patients with atypical and minimal clinical manifestations.[42] With weakened immune systems, these patients are vulnerable to the other aforementioned infectious uveitis and reliance solely on clinical findings may lead to misdiagnosis in these cases. Anterior chamber paracentesis or vitreous tap are invasive techniques required for obtaining intraocular fluids for PCR detection of CMV. The invasive nature and the high cost of laboratory setup preclude the routine indication of CMV PCR in some clinical settings. Furthermore, false negative result is possible if sampling is inadequate or when the viral load is low. Hence, treatment should not be delayed while awaiting for the availability of PCR results. Intraocular fluid CMV DNA load correlates positively with CMVR lesion area; in early-stage or CMVR eyes with very small lesions, quantitative CMV DNA results may yield false-negative results.[43] Early CMVR lesions are often misdiagnosed as other conditions due to lacking typical features, especially CMVR initially presenting in the macula. For immunosuppressed patients highly suspected of having CMVR, particularly those with zone 1 involvement, more aggressive intervention should be considered, including initiating empirical systemic anti-CMV treatment with adjuvant intravitreal ganciclovir injections. Zone 1 is defined as a circle with a radius of 1500 microns from the edge of the optic disc or 3000 microns from the fovea.[32]

Detection of CMV antigenemia (pp65) in serum and urine as well as quantitative peripheral blood CMV PCR viral load are alternative diagnostic tests. CMV viremia is intermittent, and a study found no significant difference in subsequent CMVR development between patients with or without detectable viremia.[44]

A CMV-positive PCR result does not differentiate between active infection and latent virus. This can lead to the detection of CMV DNA in individuals who are not actively experiencing CMVR, but may have been previously infected or are carrying the virus without symptoms.[45] Even when CMV DNA is detected, there is no universally agreed-upon viral load threshold to distinguish between active disease and asymptomatic carriage. Different studies and clinical settings may use varying thresholds, leading to inconsistent interpretations. Factors such as the type of sample (e.g., vitreous, aqueous humor, blood) and the patient's immune status can influence the significance of a given viral load.[46] Ultimately, the diagnosis of CMVR relies on a combination of clinical, laboratory, and imaging data. There is a need to develop more standardized PCR assays and to better define the clinical significance of different viral load levels.

Studies have employed fluorescein angiography (FA), optical coherence tomography (OCT), and optical coherence tomography angiography (OCTA) to evaluate CMVR. FA reveals leakage and non-perfusion in affected areas.[47] Several reports described "subclinical CMVR" manifesting as progressive vascular occlusion, with some cases even developing neovascular glaucoma due to large areas of non--perfusion.[48,49] It is recommended that, for populations where immune status is unlikely to improve rapidly, regular (ultra-widefield) FA can be applied to monitor for the development of retinal non-perfusion areas.[50]

OCT assesses destruction of retinal nerve fiber layers, multiple cystic spaces, and loss of inner segment/outer segment junction of the photoreceptors.[47] (Fig. 5) OCT in AIDS patients with CMVR has been categorized into typical and atypical presentations. In the active phase, the typical presentation is characterized by significant thickening of the retina with hyperreflective lesions and destruction of all layers of the retinal structure with vascular enlargement, while the atypical type shows the destruction of all layers of the retina as well, but without thickening or much thinning. The choroid, vitreous, and retinal vessels are not involved. While in the healing stage, the retina is thinner and both types of retinal layers are disrupted.[51] OCT helps in diagnosis, management, and prediction of CMVR outcomes, and can be used as an effective test for CMVR management.[52] However, current evidence does not substantiate routine diagnostic or monitoring value from these modalities for CMVR.

Consensus Statement 1.1: *The clinical diagnosis of CMVR relies on patient's susceptibility due to compromised immune function and characteristic fundus manifestations of granular, wedge-shaped or hemorrhagic retinitis. (Consensus score: 100 % [strongly agree: 83.33 %; agree: 16.67 %; neutral: 0 %; disagree: 0 %; strongly disagree: 0 %])*

Consensus Statement 1.2: *The differential diagnosis of CMVR include other infectious retinitis, such as ARN, active ocular toxoplasmosis in immunocompromised patients, syphilis and TB may sometimes be difficult to distinguish from CMVR. (Consensus score: 91.66 % [strongly agree: 58.33 %; agree: 33.33 %; neutral: 0 %; disagree: 8.33 %; strongly disagree: 0 %])*

Consensus Statement 1.3: *PCR for detection of CMV in intraocular fluid is preferred to confirm the diagnosis of CMVR. It requires an invasive procedure, and the high cost of laboratory setup precludes its routine indication in low resource environments. Furthermore, a positive PCR result cannot distinguish between active or old infection. Clinical correlation with investigation findings is always necessary. (Consensus score: 91.66 % [strongly agree: 58.33 %; agree: 33.33 %; neutral: 0 %; disagree: 8.33 %; strongly disagree 0 %])*

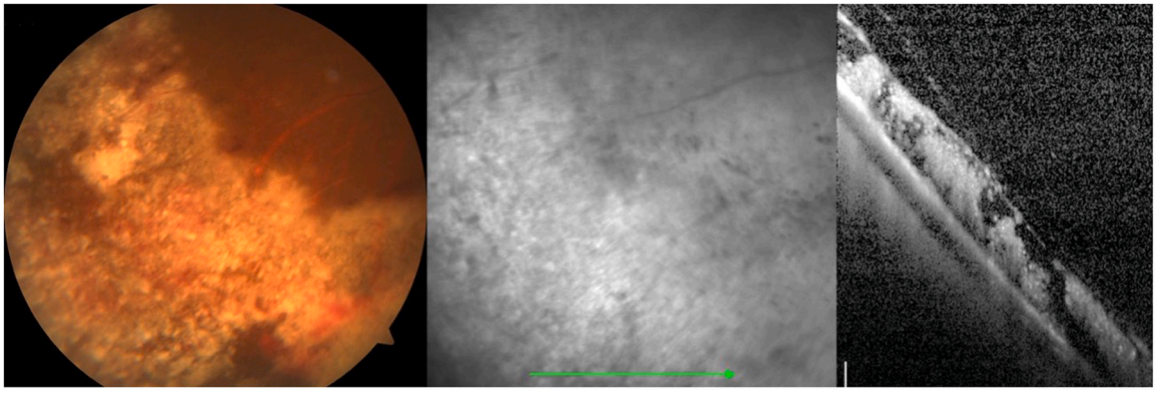

Fig. 5. A 54 year-old female had history of peripheral T-cell lymphoma on chemotherapy presented with both eyes blurring of vison for 1 month. Cytomegalovirus retinitis (CMVR) was confirmed with polymerase chain reaction (PCR) positive for CMV DNA. (**LEFT**) Fundoscopy exam revealed diffuse retinal necrosis and intraretinal hemorrhages. (**MIDDLE**) The appearance of retinitis on red free fundus photograph that corresponded to the areas of intraretinal hemorrhages and necrosis in the inferior part of the retina. (**RIGHT**) OCT showed the CMVR involved area was thinned and the boundaries between all the layers were no longer distinguishable. (Fig. 5 is contributed by YT, original author).

Consensus Statement 1.4: *For immunosuppressed patients highly suspected of having CMVR, particularly those with macular involvement*, more aggressive intervention should be considered, including potentially initiating empiric anti-CMV treatment. (Consensus score: 100 % [strongly agree: 91.67 %; agree: 8.33 %; neutral: 0 %; disagree: 0 %; strongly disagree: 0 %])*

**Macular involvement is defined by zone 1 disease as a circle with a radius of 1500 microns (or 1.5 mm) from the edge of the optic disc or 3000 microns (3 mm) from the fovea.*[32]

Consensus Statement 1.5: *Imaging modalities (FA, OCT, OCTA) do not add additional diagnostic or monitoring value. (Consensus score: 66.67 % [strongly agree: 25 %; agree: 41.67 %; neutral: 16.67 %; disagree: 8.33 %; strongly disagree: 8.33 %])*

3.2. Screening controversies

CMVR is a serious opportunistic infection affecting immunocompromised patients, particularly those with advanced AIDS (CD4 + T-cell count <50 cells/μL) and transplant recipients. While ocular symptoms like blurred vision or floaters can be present, they aren't always reliable indicators. CMVR screening involves an ophthalmologic examination, typically including pupil dilation and ophthalmoscopy, to visualize the retina for signs of the infection. Screening for CMVR has been a topic of debate due to evolving treatment paradigms, cost-effectiveness concerns, and changes in at-risk populations.[53]

With widespread HARRT use, the incidence of CMVR in HIV patients has drastically declined. Some argue that routine screening is no longer cost-effective in well-managed HIV populations. However, certain high-risk groups, such as those with poor HAART adherence, late HIV diagnosis, or resistant virus may still benefit from screening. Older guidelines recommended regular ophthalmologic screening for patients with CD4 + T-cell < 50.[54] Whereas newer guidelines suggest symptom-based screening rather than routine exams due to low incidence.[55]

CMVR is increasingly seen in non-HIV immunocompromised patients, such as those with post-organ transplant or on long-term biologics. There is no consensus on screening protocols for CMVR in these patients. The risk of CMVR is high in CMV-seronegative recipients with a seropositive donor, hematopoietic stem cell transplant patients with acute graft versus host disease (GVHD) or requiring prolonged immunosuppression. Delayed onset CMVR can occur many months to years post-transplant. In some clinical protocols there is routine CMV blood monitoring by serology or PCR because detection or increase viremia may precede retinitis.[56] The cost-effectiveness for routine CMVR screening is not yet determined. Patients who are on valganciclovir prophylaxis have lower risk of CMVR and reduces the need for screening.[57] Risk stratified screening is advocated for patients with known CMV viremia, those who are on high-dose immunosuppression therapy, and those who have symptoms of seeing increased floaters and blurring of vision. Regular screening is scheduled at every 3–6 months.

The approach to CMVR screening is varied in lower-income countries, where late presentation and postponed diagnosis of CMVR are more frequent. Early detection and treatment initiation can forestall lesion expansion of CMVR and preserve vision Due to the lack of accessibility to trained specialists in ophthalmology, the use of telemedicine and artificial intelligence (AI) are potentially useful tools for CMVR screening. Data from developing regions suggest that portable fundus camera and AI interpretation have been utilized. Studies show deep learning and AI can detect CMVR from retinal images with > 90 % accuracy.[58–60] However, there are barriers for the implementation of AI, including the requirement for high quality imaging and non-standardized imaging acquisition techniques.

The optimal screening method for CMVR should be discussed. The commonly accepted screening method of CMVR is dilated examination of the entire retina with an indirect ophthalmoscopy.[61] A standard retinal camera with nine overlapping 45° fields is another tool for traditional screening. Wide-field imaging is now available many clinics for screening due to its broad field of view, mydriasis-free operation, and time-saving advantages.[62] The effectiveness and necessity of telemedicine should also be evaluated, given the heavy burden of HIV infection and the limited in-person care in developing countries and remote areas.

Consensus Statement 2.1: *HIV patients with CD4 + T-cell counts below 50 cells/μL should undergo monthly fundoscopic screening, while those with counts below 100 cells/μL require quarterly screening. (Consensus score: 75 % [strongly agree: 41.67 %; agree: 33.33 %; neutral: 16.67 %; disagree: 8.33 %; strongly disagree: 0 %])*

Consensus Statement 2.2: *The indication for CMVR screening is risk stratified for non-HIV immunocompromised patients. Patients with known CMV viremia and those who are on high-dose immunosuppression therapy are indicated for screening. (Consensus score: 100 % [strongly agree: 50 %; agree: 50 %; neutral: 0 %; disagree: 0 %; strongly disagree: 0 %])*

Consensus Statement 2.3: *Increase uptake of CMVR screening is recommended in low-income countries due to higher frequency of visual comorbidities. The use of telemedicine and artificial intelligence for interpretation of fundal images potentially reduces the demand for manpower and resources for CMVR screening. (Consensus score: 91.66 % [strongly agree: 58.33 %; agree: 33.33 %; neutral: 0 %; disagree: 8.33 %; strongly disagree: 0 %])*

3.3. Treatment controversies

The general principle of therapy involves an induction phase with higher or more frequent doses of drug followed by the maintenance phase with lower or less frequent chronic suppressive doses to prevent relapse. Systemic anti-viral therapy is the first-line treatment of CMVR due to its efficacy, reduction of overall morbidity and prevention of disease in the uninvolved fellow eye. Valganciclovir, an oral prodrug converted to ganciclovir, is the preferred drug because it offers improved pharmacokinetics for convenient dosing to enhance patient compliance. It is prescribed as a twice daily dose of 900 mg of oral valganciclovir for induction therapy for 3 weeks followed by the maintenance phase of 900 mg daily. It has an efficacy and safety profile comparable to that of intravenous ganciclovir including the risks of neutropenia, anemia, and thrombocytopenia but without intravenous (IV) catheter-related complications.[63] Ganciclovir is renally excreted, and the systemic dose of ganciclovir must be reduced in patients with impaired renal function to minimize toxicity and side effects.[64]

Ganciclovir has various administration routes including oral, intravenous, intravitreal, and intraocular implants.[65] While the drug acquisition cost of valganciclovir is significantly higher than intravenous ganciclovir, it avoids the costs associated with hospitalization and intravenous administration.[66] It precludes the risk of catheter line-associated complications such as sepsis, thrombophlebitis and catheter occlusion. Even in health economic models where valganciclovir has a higher total cost, the improvement in quality of life due to oral administration is significant.[67] Nonetheless, the cost-influencing factors vary by regions and healthcare systems, and sensitivity analyses are required to determine how they affect the cost-effectiveness outcomes.[68]

Although ganciclovir has low oral bioavailability, for patients requiring systemic anti-CMV therapy, considering economic factors and accessibility, high-dose oral ganciclovir (>2 g/day) may still serve as a treatment option when valganciclovir is not available, weighing the potential adverse event of ganciclovir-induced bone marrow suppression.

Repeated intravitreal injections of ganciclovir, although time-consuming and labor intensive, have proven to be very effective, relatively safe, and affordable.[69] For retinitis that involves the posterior pole at the time of diagnosis adjuvant treatment with intravitreal injections or intraocular implants of slow-release ganciclovir reservoirs are considered.[70] During the induction phase, typically it takes 2–4 weeks to control CMVR. In that time CMVR lesions may progress up to a disc diameter and intravitreal treatment is indicated to control the retinitis as

rapidly as possible if perimcular or peripapillary retina is involved. Furthermore, it is indicated for patients who develop dose limiting side effects from systemic antiviral drugs or have pre-existing cytopenia.[71] Intravitreal ganciclovir should not be sole therapy as it provides no protection against contralateral or extraocular CMV infection. For CMVR secondary to local ocular immunosuppression such as post-intravitreal injection of triamcinolone acetonide or intravitreal corticosteroid implants, intravitreal ganciclovir has been an effective treatment.[43,72,73]

Chronic maintenance therapy with an anti-CMV agent is required to prevent reactivation of the disease, as previous studies reported that the time to retinitis progression after stopping therapy has been typically 6–8 weeks.[74,75] With the introduction of HAART, there have been several reports of patients with AIDS-related CMVR who experience immune recovery, as evidenced by a sustained increase in CD4 + T-cell counts to more than 100 cells/uL, reporting that they can discontinue maintenance therapy without reactivation of CMVR.[76,77] There are no long-term, prospective studies comparing survival and vision loss in patients discontinuing treatment to those continuing treatment after immune recovery.[78] Based on the case reports of successful discontinuation of treatment without disease reactivation, the United States Public Health Service (USPHS) guidelines for secondary prophylaxis were revised in 1999 to suggest discontinuing anti-CMV therapy once patients with quiescent retinitis achieve sustained immune recovery.[79] Continued close follow-up by an ophthalmologist is recommended since reactivation of retinitis and vision loss due CMVR may occur among patients with CD4 + T-cell counts higher than 200 cells/uL, albeit at much reduced rates.[80] Specifically, treatment can be considered for discontinuation after at least 3–6 months of CMV treatment, inactive lesions, and a CD4 + T-cell count consistently above 100 cells/mm^3 due to HAART. While CMV viral load by PCR of intraocular fluid is not the primary indicator for stopping treatment, it can be useful for monitoring the response to antiviral therapy to aide in making the decision for treatment cessation. The decision to stop treatment should be individualized, taking into account factors like the location of the lesions, vision in the other eye, the accessibility of regular clinical monitoring and cost.

In HIV infection, the virus directly depletes the CD4 + T-cells, and successful antiretroviral therapy allows the repopulation of CD4 + T-cells. Hence, the CD4 + T-cells count is sensitive to the amount of immune reconstitution in AIDS patients. However, CD4 + T-cells count alone is not appropriate for assessing immune reconstitution after solid organ or hematopoietic stem cell transplant. Immune reconstitution after transplant is a complex process which involves various pathways. Even if the CD4 + T-cell count appears normal, but the functions of these cells may often be dysregulated and lacking in repertoire (the ability to recognize a wide arrange of pathogens.) [81] The thymus may become impaired and produces sick T-cells. [82] Long-term use of immunosuppressive drugs that prevent rejection or GVHD by deliberately inhibiting T-cell activation and proliferation, and such that low CD4 + T-cell count cannot be a surrogate for poor immune reconstitution. [83] CMV-specific T-cell function assays are designed to measure the strength and quality of the T-cell response specifically targeted against CMV. They measure the frequency and functionality (e.g., IFN-γ production) of CD4 + and CD8 + T-cells that recognize CMV antigens. There is evidence that CMV-specific T-cell response is strongly correlated with protection against CMV viremia and disease in transplant recipients.[84]

Peripheral blood CD4 + T-Cell function tests assess the overall functional capacity of the immune system.[81,85] The most common and clinically validated test is CD4 + T-cell lymphoproliferative responses to mitogens.[86] It measures the ability of a patient's lymphocytes, particularly CD4 + T-cells, to proliferate in response to non-specific stimulants. This is a holistic test of whether the entire T-cell arm of the immune system is functionally intact. However, it cannot tell if a patient is protected against CMV or any specific pathogen. A patient can have a good mitogen response but still lack CMV-specific cells and be at risk for CMV.

Regular ophthalmic monitoring at 3-month intervals is recommended after stopping treatment. The clinical features of treated retinitis are sharp demarcation between necrotic and uninvolved retina, variable pigmentation of necrotic retina, and lipid or calcification may be present but should not be confused with active retinitis. Clinical features of relapse or progression include increased border opacification ("smoldering retinitis"), new border satellite lesions, expansion of previously inactive border of retinitis, and appearance of new lesions in same or fellow eye. Careful monitoring of retinitis with serial retinal photographs is an effective mean of determining active versus inactive disease.

The assessment for the underlying causes for recurrent or refractory CMVR should focus on the evaluation of following: 1) patient's immune status, 2) anti-CMV treatment factors and 3) patient's general medical history. One of the most common causes of CMVR recurrence is delayed immune reconstitution which may associate with a persistently low CD4 + T-cell count (< 50–100 cells/μL). This could be failure of HAART in HIV patients due to non-compliance or the use of prolonged immunosuppression medication in non-HIV patients. CMVR reactivation may still occur in HIV patients with a CD4 + count > 100 cells/μL due to a CMV-specific adaptive immune deficiency, where the overall immune system has recovered but the response to the CMV virus itself is insufficient.[87]

Anti-CMV treatment failure can be associated with poor drug bioavailability or infection by genotypic resistance CMV. UL97 mutations in CMV have been reported in low-grade ganciclovir resistance. Ganciclovir requires phosphorylation by the CMV's own UL97 protein kinase to become active. The phosphorylated form of ganciclovir then inhibits the CMV DNA polymerase, which is essential for viral DNA replication. Mutations in the UL97 gene alter the kinase's structure, making it unable to effectively recognize and phosphorylate ganciclovir.[88] Patients infected by UL97 mutations in CMV usually respond to cidofovir or foscarnet as neither antiviral drug requires phosphorylation by viral enzymes. The UL54 gene encodes the CMV DNA polymerase, which is essential for viral replication. UL54 mutation leads to high-grade ganciclovir resistance due to the failure to impair CMV DNA polymerase, which often also causes resistance to cidofovir.[89] Mutations causing foscarnet resistance are less well studied and more difficult to identify. When resistance is uncertain, PCR testing for antiviral resistance genes and obtaining quantitative peripheral blood CMV viral loads may help, but the high cost of this technology limits its wide application.[90]

The patient's overall systemic health status can also contribute to refractory or recurrent CMVR. The presence of malignancy, such as lymphoma or leukemia, can directly suppress the patient's immunity. Advanced age, malnutrition and other comorbidities may prevent the patient's immune system to intervene with CMV infection.

For patients with delayed immune reconstitution, prolonging the duration of anti-CMV therapy is the preferred strategy rather than switching drugs, and subsequent prescription of higher dose of maintenance therapy. HARRT is effective in treating or preventing the relapse of CMVR in patients with HIV infection. For resistance cases to first-line therapy, consider change to a different antiviral drug. Combination therapy, such as ganciclovir with foscarnet may be more effective but also more toxic.

The introduction of HARRT has reduced the incidence of CMVR by 75–90 %.[28] There are fewer ocular complications such as secondary retinal detachment that cause vision loss due to CMVR patients with HARRT. Nonetheless, immune recovery uveitis (IRU) is one of the major principal ocular complications associated with CMVR. IRU results from a rapid and dysregulated immune system response to a pre-existing CMV infection as the immune system reconstitutes. The risk of IRU is higher among patients with inadequate treatment of CMVR.[6] The primary reason is the immune system's ability to "reconstitute", but in doing so, it overreacts to opportunistic pathogens that were previously suppressed by the immune deficiency.

It is often clinically challenging to differentiate active CMVR from IRU. In CMVR, the retinitis is due to CMV replication in the retina and the attendant retinal destruction, whereas any anterior chamber inflammation, vitritis, papillitis and/or vasculitis (Fig. 6) is due to the immunologic response to CMV. The increase in vitritis with IRU is consistent with the inflammation being largely part of the immunologic response. [91] While IRU is often associated with CMVR, it is crucial to differentiate between them. IRU typically occurs after HAART initiation, while CMVR may be present before or after. CMVR is associated with low CD4 + T-cell counts, while IRU occurs during or after HAART induced CD4 + T-cell recovery. CMVR requires antiviral therapy, while IRU responds to anti-inflammatory medications. IRU may respond to topical steroids for mild anterior chamber inflammation. Periocular, sub-Tenon's, intravitreal or oral corticosteroids are indicated for more severe cases.[92,93] Triamcinolone acetonide (40 mg) can be used via periocular or sub-Tenon's injection, while dexamethasone intravitreal implant (Ozurdex) can be used via intravitreal injection.[94,95] However, this treatment method has the risks of increased intraocular pressure, secondary cataract, and recurrence of CMVR and must be used with caution with regular follow-up visits (every 2 weeks). Cystoid macular edema and epiretinal membrane may occur in patients with IRU (Table 1).

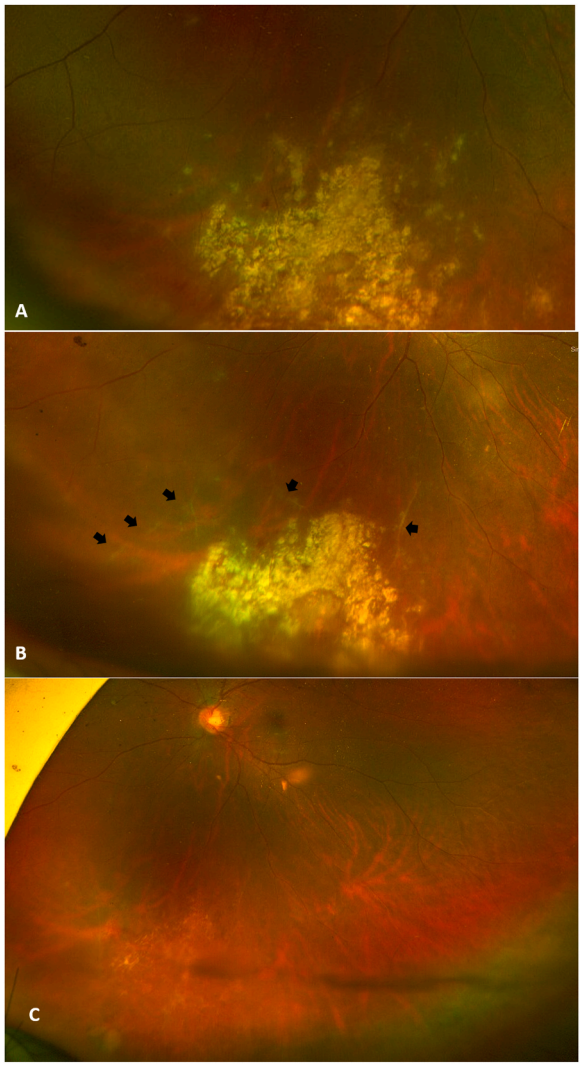

Fig. 6. A, Cytomegalovirus retinitis (CMVR) in a 30-year old human immunodeficiency virus (HIV)-positive male that had started on retroviral therapy prior to referral to ophthalmologist for screening. He was found to have granular CMVR in the inferior nasal quadrant of the left eye.
B, After two weeks of systemic ganciclovir treatment, and one month of anti-retrovirus therapy, immune recovery uveitis (IRU) presented as increased in vasculitis (black arrows) around the CMVR was seen despite a slow reduction in the central part of the CMVR. The patient was started on anti-inflammatory dose of oral prednisolone for early IRU and intravitreal foscarnet started due to the slow recovery.
C, Complete resolution of CMVR and vasculitis after 1 month of intravitreal foscarnet and therapy. This case highlights the importance of early recognition of IRU in patients who have been started on anti-retrovirus therapy prior to CMVR detection. More aggressive therapy is indicated when CMVR is slow to respond to first-line therapy. (Fig. 6 is contributed by AC, original author)

Retinal detachment is a critical cause of vision loss in CMVR, predominantly arising from retinal holes in necrotic areas. Risk factors include extensive retinal necrosis, bilateral disease onset, and active retinitis near the vitreous base.[96] The likelihood of secondary retinal detachment correlates with the extent of retinitis involvement, with peripheral retinal involvement posing a higher risk compared to isolated posterior pole involvement.[96,97] Preventive measures for high-risk patients, such as frequent monitoring and retinal photocoagulation, may reduce the risk of retinal detachment.[98] For patients who have already developed retinal detachment, vitrectomy with silicone oil tamponade should be performed. study found that for HIV patients with CMVR who had retinal detachment and underwent vitrectomy, the rate of retinal attachment decreased with the extension of follow-up time (87.2 % in the first month, 82.1 % in the third month, and 71.8 % in the sixth month), and the failure of surgery was significantly associated with the patient's CD4 + T-cell count being lower than 50/μL.[99] After vitrectomy, oral antiviral therapy should be continued until the total disappearance of lesions in cases with active retinal lesions, while withholding intravitreal injection of ganciclovir or foscarnet should be considered due to the silicone oil tamponade and the disruption of the blood-retinal barrier.

Consensus Statement 3.1: *The preferred first-line treatment for CMVR is oral valganciclovir. Adjuvant treatment with intravitreal ganciclovir injection is indicated when CMVR involves the posterior pole or when there is progression that threatens to compromise vision. (Consensus score: 83.33 % [strongly agree: 50 %; agree: 33.33 %; neutral: 8.33 %; disagree: 8.33 %; strongly disagree: 0 %])*

Consensus Statement 3.2: *Following the induction phase of antiviral therapy, maintenance treatment is necessary to prevent CMVR relapse. Cessation of treatment can be considered after 6 months when the disease remains inactive, CD4 + T-cell count is consistently above 100 cells/mm3 and HAART has been initiated (in AIDS patients). However, decision to stop treatment should be individualized, taking into account factors like the primary causes of immunosuppression, location of the lesions, vision in the other eye and the compliance to regular clinical monitoring after stopping treatment. Vigilance for CMV resistance is necessary due to its increased risk in prolonged therapy. (Consensus score: 100 % [strongly agree: 83.33 %; agree: 16.67 %; neutral: 0 %; disagree: 0 %; strongly disagree: 0 %])*

Consensus Statement 3.3: *Causes of CMVR suboptimal response or relapse include poor compliance to therapy, poor intraocular drug availability and presence of antiviral resistance. Switching to second-line antiviral agents or combination use with first-line drugs are current treatment options. The choice of therapy should be balanced between efficacy and risk of systemic side effects. (Consensus score: 100 % [strongly agree: 50 %; agree: 50 %; neutral: 0 %; disagree: 0 %; strongly disagree: 0 %])*

Consensus Statement 3.4: *Immune reconstitution is associated with IRU which indicates corticosteroid treatment. IRU may cause increase vitritis and/or anterior chamber inflammation and its clinical manifestation should be distinguished from CMVR relapse which requires antiviral treatment. (Consensus score: 91.67 % [strongly agree: 75 %; agree: 16.67 %; neutral: 8.33 %; disagree: 0 %; strongly disagree: 0 %])*

Consensus Statement 3.5: *For patients who developed retinal detachment secondary to CMVR, vitrectomy should be performed. Endotamponade with silicone oil is often indicated. Systemic antiviral therapy should be continued after vitrectomy until active retinal lesions subside. (Consensus score: 100 % [strongly agree: 75 %; agree: 25 %; neutral: 0 %; disagree: 0 %; strongly disagree: 0 %])*

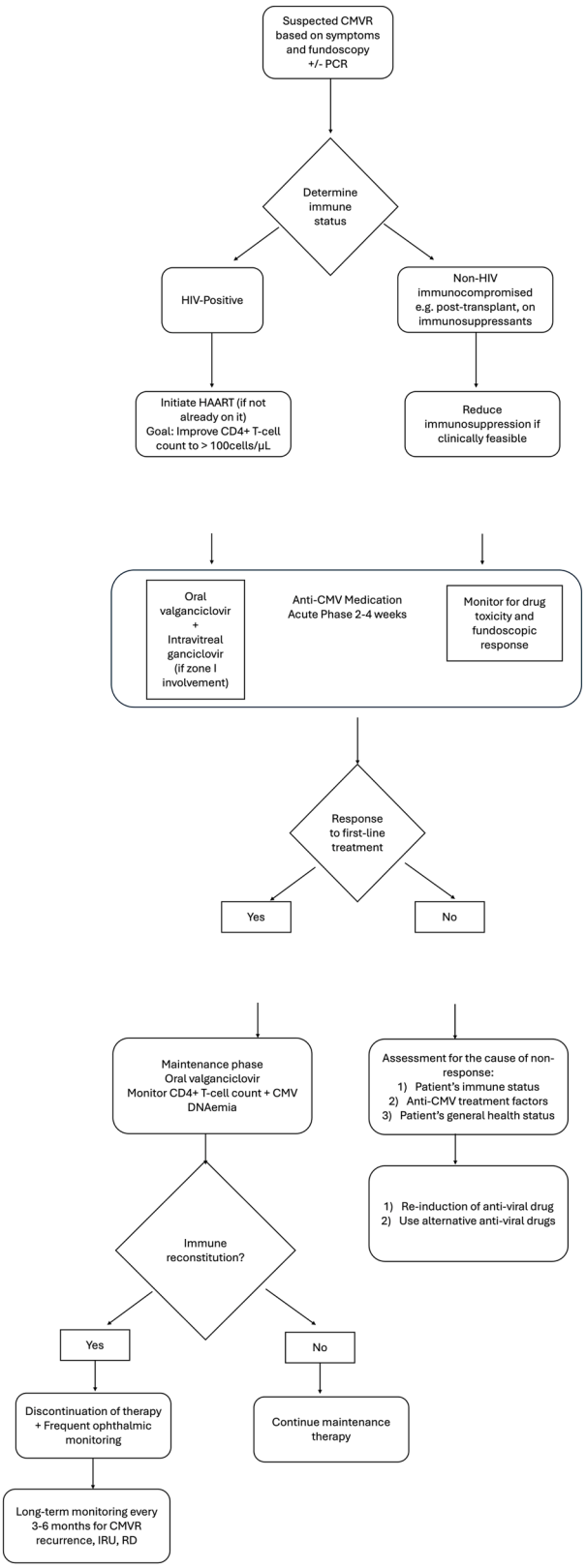

Fig. 7. Suggested management algorithm of cytomegalovirus retinitis.
CMVR, cytomegalovirus retinitis; PCR, polymerase chain reaction; HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy; IRU, immune recovery uveitis; RD, retinal detachment. Zone 1 disease is defined as a circle with a radius of 1500 microns (or 1.5 mm) from the edge of the optic disc or 3000 microns (3 mm) from the fovea.

3.4. Special population controversies

Pregnancy

CMV can be transmitted to the fetus during pregnancy, especially if the mother experiences a primary infection or reactivation of a previous infection during pregnancy. Primary CMV infection during pregnancy carries a higher risk of transmission (around 40 %) and more severe complications for the fetus compared to recurrent infections.[100] Maternal CMV serology should be performed in the first trimester of pregnancy, as adverse sequelae of congenital CMV are limited to maternal infection acquired in the first trimester of pregnancy.[101] Oral valganciclovir at a dose of 8 g/day is used to treat CMVR in pregnant women, potentially reducing the risk of transmission and severity of the disease.

Congenital CMVR

CMVR is a rare but serious manifestation of CMV infection acquired in utero. It is the most common congenital viral infection and many infants are asymptomatic at birth, while a small number develop severe sequalae including CMVR. The global prevalence of congenital CMV infection is 0.64 %1 and there is a 17–20 % risk of deafness, mental retardation, and vision loss in infected children.[102] There is no consensus on universal screening for congenital CMV, even though early detection could help prevent complications like retinitis. Some argue for targeted screening in symptomatic infants or those who fail newborn hearing tests, while others advocate for broader screening.[103] CMVR in newborns can be missed because fundoscopic examination is not routinely performed unless there are overt signs of systemic CMV disease.

Due to the paucity of data, the optimal management for congenital CMVR remains unknown. In a 10-year prospective study that screened for congenital infections, only 1 immunocompetent newborn had active retinitis.[104] Because the disease is considered to be self-limiting and systemic treatment can be harmful, treatment remains controversial. In 2003, the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group conducted a pharmacokinetic-pharmacodynamic study establishing a safe dose of intravenous ganciclovir in infants with CMV. [105] A subsequent phase 3 randomized controlled study demonstrated the benefit of systemic ganciclovir therapy in reduction of hearing loss in congenital CMV infection with central nervous system involvement.[105] While two-thirds of infants receiving treatment developed neutropenia, no deaths were related to the use of intravenous ganciclovir. [106] Rapid resolution of CMVR in immunocompetent infants has been reported with systemic ganciclovir treatment in 2 isolated cases.[104,107] A case report of a newborn with active CMVR and optic neuritis had systemic treatment withheld owing to risk of neutropenia. Intravitreal ganciclovir was administered at a dose of 600 μg in 0.03mnL derived from the standard adult dose (2 mg/0.1 mL) by adjusting for the smaller eye volume in the infant. Rapid response was reported without ocular complications (such as cataract, retinal toxicity or intraocular inflammation) or systemic complications such as neutropenia. There was no sign of active disease in the eye after 12 injections. [105]

Consensus Statement 4.1: *Prompt serological diagnosis of CMV and treatment with oral valganciclovir during the first trimester of pregnancy are crucial in reducing the risk of congenital CMVR. (Consensus score: 80 % [strongly agree: 30 %; agree: 50 %; neutral: 20 %; disagree: 0 %; strongly disagree: 0 %])*

Consensus Statement 4.2: *The treatment for vision threatening congenital CMVR involves systemic and intravitreal antiviral therapies. The dosage for antiviral therapies must be titrated against the risk of side effects. More data and collaboration are necessary for determining the optimal treatment strategy for active congenital CMVR in future. (Consensus score: 75 % [strongly agree: 50 %; agree: 25 %; neutral: 25 %; disagree: 0 %; strongly disagree: 0 %])*

Table 1
Cytomegalovirus Retinitis (CMVR) Reactivation versus Immune Recovery Uveitis (IRU).

Features	CMVR Reactivation	IRU
Basic Definition	Active viral infection and necrosis of the retina caused by the CMV.	Inflammatory condition occurring in eyes with a history of inactive CMV retinitis, triggered by immune reconstitution.
Underlying Cause	Insufficient anti-CMV immunity, allowing the latent virus to replicate and destroy retinal tissue.	A restored, overly robust immune system (specifically CD4 + T-cells) mounting an inflammatory response against residual CMV antigens in the eye.
Patient Immune Status	Low CD4 + T-cell count (typically < 50 cells/μL). Often occurs when HAART is failing, not yet started, or during immunosuppressive therapy.	Rising or restored CD4 + T-cell count (typically > 100 cells/μL). Undetectable or low Human immunodeficiency virus (HIV) viral load.
Onset	Can occur at any time when the patient is immunocompromised.	Typically occurs 1–12 weeks after starting highly active antiretroviral therapy (HAART), but can be delayed by several months. [6]
Symptoms	Photopsia, blurred vision, or visual field loss. Maybe asymptomatic if in peripheral retina.	Floaters and blurred vision. Pain and redness are uncommon.
Key Clinical Signs	Active, Necrotic Lesions: • Cottage cheese & ketchup" appearance (yellow-white granular areas with hemorrhage). • Progressive border with satellite lesions. • Vitreous haze is usually mild or absent.	Inflammation in a Healed Scar: • Vitritis (vitreous haze/flare). [91] • Papillitis (optic nerve head swelling) and/or vasculitis. • Cystoid macular edema (CME). • Epiretinal membrane formation. • No active retinal necrosis or progression of the old CMV scar.
Diagnostic Tests	• Clinical appearance is paramount. • PCR of aqueous or vitreous humor for CMV DNA	• Clinical appearance is key (inflammation in a stable scar). • PCR for CMV DNA is typically negative or very low. • Optical Coherence Tomography (OCT) to detect CME or epiretinal membrane.
Primary Treatment Goal	Halt viral replication to stop retinal destruction and prevent blindness.	Control intraocular inflammation to prevent vision loss from complications like CME.
Treatment	Re-initiate or intensify systemic and/or intravitreal anti-CMV therapy.	Topical, periocular, or systemic corticosteroids + /- Steroid-sparing anti-inflammatory medications. [92,93] DO NOT stop HAART. Anti-CMV therapy is not indicated unless there is co-existing active retinitis.
Prognosis	Poor if untreated; leads to retinal detachment and blindness. Good if treated promptly, but vision loss from scar tissue is permanent.	Variable.

3.5. Future directions and emerging controversies

Several new anti-CMV agents and treatment strategies are developed, including letermovir (LET), maribavir (MBV) and immunotherapies. LET and MBV target CMV terminase and CMV DNA kinase UL97 respectively,[108,109] while immunotherapies enhance the patient's immune ability against CMV. Both CMV anti-viral therapy and a host immune response are needed to control CMV infection. But there is no uniform consensus regarding the optimal timing and indications for these treatments. LET targets the CMV terminase complex, offering a novel therapeutic approach. Compared to traditional antivirals, oral or intravenous LET is generally well tolerated, making it a suitable choice for preventing CMV infections and diseases in transplant recipients.[110] MBV is an oral drug primarily used for CMV in hematopoietic stem cell transplantation and solid organ transplantation recipients.[111] Its unique mechanism of action renders it effective against traditional antiviral-resistant CMV strains. While generally well tolerated orally, MBV exhibits poor retinal penetration.[112] Despite this limitation, MBV's resistance profile and oral administration make it a valuable option for treating refractory or drug-resistant CMV infections in transplant recipients. The clinical use of LET and MBV mitigates the systemic toxicity and resistance associated with traditional antivirals, offering new possibilities for combination therapy.

Immunotherapy using CMV-specific adoptive T-cell avoids the potential side effects of traditional antiviral therapies. Studies indicate that infusing CMV-specific T cells can restore protective immunity.[113] For hematopoietic stem cell transplant recipients, immune reconstitution using these T cells effectively reduces viral reactivation-related morbidity and mortality.[114] Clinical trials have demonstrated the therapeutic potential of autologous T cells for treating recurrent or antiretroviral-resistant CMV infection in solid organ transplant recipients.[115] Compared to antiviral therapies requiring laboratory monitoring for adverse effects and drug resistance, this approach rebuilds immunity with fewer side effects.

CMVR prophylaxis involves giving antiviral drugs to all at-risk patients to prevent initial CMV infection, while preemptive therapy treats only patients with detected asymptomatic CMV replication (using PCR or antigenemia assays) to prevent progression to active disease. CMV prophylaxis protocols for solid organ transplant and hematopoietic stem cell transplant recipients aim to prevent CMVR as well as other systemic infection, which can cause serious complications. The principles of prophylaxis are based on a risk stratification approach, depending on donor/recipient serostatus and type of transplant. For solid organ transplant recipients, high risk patients (Donor+/Recipient-) receive oral valganciclovir prophylaxis for 3–6 months, potentially up to 12 months for lung transplants.[116] Intermediate-risk (Recipient+) recipients may receive preemptive therapy with CMV DNA monitoring and initiation of antiviral treatment upon viremia. Low-risk (Donor-/-Recipient-) recipients generally do not require prophylaxis or monitoring. LET is an alternative for Donor+ /Recipient- kidney transplant recipients, especially those intolerant to valganciclovir.[116]

Hematopoietic stem cell transplant recipients have been managed with preemptive therapy, monitoring for CMV replication and treating upon viremia detection.[117] When antiviral treatment is indicated, LET is preferred due to better safety with less myelosuppression. A hybrid approach combining prophylaxis and preemptive therapy is increasingly used to balance early prevention with reduced antiviral exposure.[118] A "hybrid therapy" for CMVR is a combination of prophylaxis (preventing CMV from ever starting) and preemptive therapy (monitoring for early signs of CMV replication to start treatment before it causes retinitis). This strategy aims to balance the benefits of both approaches, for example, a period of universal prophylaxis followed by preemptive therapy with weekly monitoring to prevent late-onset invasive disease.[117] Tailoring CMV prophylaxis and treatment to individual patient risk factors, including organ type, immunosuppression, and serostatus, is crucial. Late onset CMV disease after discontinuation of prophylaxis remains a challenge, necessitating ongoing monitoring and research into new strategies. CMV-specific immune monitoring and genetic polymorphisms are being investigated to further individualize CMV management.[119]

It was reported that the level of IL-8 instead of IL-1b, IL-12p70 and TNF-a in the aqueous humor was significantly associated with the aqueous level of CMV copies and continuously declined during a course of effective treatment that involved multiple intravitreal injections of antiviral drugs, which suggested that intraocular IL-8 be a good quantitative laboratory indicator of the recovery of CMVR.[120] The levels of

CMV DNA and interleukin-8 in the aqueous can help the clinician to decide the timing of withdrawal of intravitreal injections of anti-virus drugs or change of anti-virus drugs due to drug resistance.[121]

Artificial intelligence (AI) has showed its capability in image-processing tasks and has deeply incorporated into several clinical practice.[122] Combination of AI, wide-field image capturing system and telemedicine shows potential application in automated detection of CMVR. The applicable populations, ethical regulations, and usage protocols for AI remain to be standardized.

Consensus Statement 5.1: *Novel antiviral medications, including letermovir (LET) and maribavir (MBV), may be used in resistant cases, with their efficacy due to alternative mechanisms. (Consensus score: 58.33 % [strongly agree: 33.33 %; agree: 25 %; neutral: 41.67 %; disagree: 0 %; strongly disagree: 0 %])*

Consensus Statement 5.2: *Immunotherapies, including CMV-specific adoptive T-cell therapy and CMV immunoglobulin, are proposed to be applied in cases of poor tolerance with traditional antiviral therapy. But the complex procedures, difficult donor selection, and high cost limit the large-scale application. (Consensus score: 83.33 % [strongly agree: 50 %; agree: 33.33 %; neutral: 16.67 %; disagree: 0 %; strongly disagree: 0 %])*

Consensus Statement 5.3: *In solid organ transplant recipients, the indication of prophylactic regimen is based on a risk stratified approach, according to the recipient and donor CMV serostatus, type of organ transplant, tolerance to antiviral medication and immunosuppression regimen. (Consensus score: 81.82 % [strongly agree: 27.27 %; agree: 54.55 %; neutral: 9.09 %; disagree: 9.09 %; strongly disagree: 0 %])*

Consensus Statement 5.4: *In hematopoietic stem cell transplant recipients, antiviral prophylaxis is generally avoided due to concerns regarding drug-induced toxicity, particularly the risk of bone marrow suppression. It is recommended to closely monitor CMV viral replication and initiate preemptive therapy when replication reaches a predefined threshold. (Consensus score: 91.67 % [strongly agree: 41.67 %; agree: 50 %; neutral: 0 %; disagree: 0 %; strongly disagree: 0 %])*

Consensus Statement 5.5: *Deep learning-based diagnostic systems show promising accuracy in identifying vision-threatening CMVR cases, representing a cost-effective triage tool for healthcare systems in developing regions. (Consensus score: 83.34 % [strongly agree: 41.67 %; agree: 41.67 %; neutral: 8.33 %; disagree: 8.33 %; strongly disagree: 0 %])*

4. Results of voting and discussion

Table 2 provides a summary of the key consensus statements along with the corresponding voting results.

Consensus-based guideline is crucial for managing CMVR in order to ensure consistent and efficacious treatment, enhanced patient outcomes and to facilitate research and clinical trials. Regardless of the global differences in clinical circumstances and accessibility to healthcare resources, our consensus provides a sturdy scaffold for the management principles of CMVR based on the comprehensive appraisal of available clinical evidence and corroborative insight from all members of the IPE. The IPE has reached a consensus that CMVR is mainly diagnosed by fundus examination in the context of patient's susceptibility due to immunocompromised status. PCR for CMV DNA is indicated for confirmation of its diagnosis when it is necessary to distinguish the clinical feature from other infectious retinitis. Slightly less than two-thirds of the IPE members agreed that FA, OCT and OCTA do not substantiate additional diagnostic and monitoring value for CMVR. This highlights the emerging roles of these ancillary investigations for CMVR. When retinal microhemorrhages are persistent with treatment, FA can be useful for differentiating HIV-related angiopathy changes as well as to reveal the degree of ischemia which may necessitate laser therapy. Oral valganciclovir is the preferred first-line treatment, and intravitreal injection of ganciclovir during the induction phase when necessary for rapid control of retinitis that has already involved or threatens to involve the posterior pole. When CMVR is clinically highly suspected, particularly those with zone 1 involvement, systemic anti-CMV therapy with adjunct intravitreal injection should be considered. Maintenance treatment can be stopped after 6 months of inactive disease and restoration of immunity (CD4 + T-cell counts and initiation of HAART in HIV patients).

There remains a number of unresolved controversial issues for the management of CMVR, due to the trade-offs between ocular and systemic outcomes, as well as the limited data from controlled clinical trials and the conundrum of managing patients with serious comorbidities that are highly vulnerable to the side effects of antiviral treatment. While HAART has substantially reduced the incidence of CMVR among AIDS patients, some patients suffer from paradoxical worsening of retinitis. The timing of HAART initiation is still under debate, whether it should be postponed in patients with active CMVR to prevent IRU. However, such postponement may deprive HIV patients from receiving prompt antiretroviral treatment and increases the risk of mortality from other opportunistic infections such as pneumocystis and tuberculosis. While CD4 + counts is a well-established biomarker for immune reconstitution in HIV/AIDS patients, the threshold criteria to indicate the cessation of maintenance therapy for non-HIV patients is not yet standardized. Similarly, there is consensus for the indication of routine CMVR screening in low CD4 + count HIV patients, but risk stratified guidelines for CMVR screening needs to be established for non-HIV patients using other clinical criteria. The future integration of artificial intelligence is promising to enhance the coverage of CMVR screening in affordable ways.

Over 21 % of IPE members voted neutral about the use of novel antiviral medications, such as LET and MBV, because of the paucity of large-scale clinical trial and long-term data. Although there are alternative drugs for CMVR patients that are resistant to first-line antiviral therapy, these patients must be carefully monitored for side effects such as nephrotoxicity. The role of resistance testing via PCR and/or genotyping is not yet standardized and more clinical data is necessary to determine the optimal therapy for safety and long-term efficacy to control CMVR in resistant cases.

Management of CMVR during pregnancy is challenging due to the potential teratogenicity of anti-CMV drugs and risk of maternal blindness and congenital CMV transmission without treatment. Over 20 % of IPE members voted neutral about the use of oral valganciclovir during the first trimester. Embryotoxicity of ganciclovir/valganciclovir has been demonstrated in animal studies. [123] Deferring treatment until the third trimester reduces the risk of teratogenicity but irreversible damage to the mother's retina may occur. Intravitreal ganciclovir may be considered during early pregnancy for sight-threatening retinitis but the long-term side effects to the embryo is not yet known. Ultrasound imaging and amniocentesis PCR for CMV are indicated for fetal monitoring. Congenital CMVR is rare and the data on optimal dosing, drug safety and long-term outcomes in infant and young children is scarce. Therefore, collaboration in clinical data and interpretation will be necessary for future consensus on the management of CMVR in these difficult but rare case scenarios.

For recipients of solid organ transplant or hematopoietic stem cell transplant, further establishment for the risk stratified approach is necessary to determine the indication of prophylactic treatment vs. preemptive therapy, which requires regular ophthalmic screening and CMV viremia tests but sparing from unnecessary side effects of prophylactic antiviral drugs.

This consensus article has several limitations. Recommendations in several areas including the optimal screening intervals for non-HIV immunocompromised populations are based on expert opinion rather than high quality randomized controlled trials because of the scarcity of clinical data. More recent medications for CMVR treatment, including LET, MBV, and CMV-specific immunotherapy, lack long-term safety and efficacy data, limiting their immediate clinical adoption. CMVR treatment during pregnancy and pediatric dosing are limited by very small sample sizes or case reports, reducing the generalizability of these guidelines. Most of the data and experiences for CMVR management

Table 2
Results of the voting on the consensus statements of CMV Retinitis.

Section	Consensus Statement	C Score	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
1. Diagnostic controversies							
1.1	The clinical diagnosis of CMVR relies on patient's susceptibility due to compromised immune function and characteristic fundus manifestations of granula, wedge-shaped or hemorrhagic retinitis.	**100 %**	83.33 %	16.67 %	0 %	0 %	0 %
1.2	The differential diagnosis of CMVR include other infectious retinitis, such as acute retinal necrosis (ARN), active ocular toxoplasmosis in immunocompromised patients, syphilis and tuberculosis may sometimes be difficult to distinguish from CMVR.	**91.66 %**	58.33 %	33.33 %	0 %	8.33 %	0 %
1.3	PCR for detection of CMV in intraocular fluid is preferred to confirm the diagnosis of CMVR. It requires an invasive procedure, and the high cost of laboratory setup precludes its routine indication in low resource environments. Furthermore, a positive PCR result cannot distinguish between active or old infection. Clinical correlation with investigation findings is always necessary.	**91.66 %**	58.33 %	33.33 %	0 %	8.33 %	0 %
1.4	For immunosuppressed patients highly suspected of having CMVR, particularly those with macular involvement, more aggressive intervention should be considered, including potentially initiating empiric anti-CMV treatment.	**100 %**	91.67 %	8.33 %	0 %	0 %	0 %
1.5	Imaging modalities (fluorescein angiography (FA), optical coherence tomography (OCT), and optical coherence tomography angiography (OCTA)) do not substantiate additional diagnostic or monitoring value.	66.67 %	25 %	41.67 %	16.67 %	8.33 %	8.33 %
2. Screening controversies							
2.1	HIV patients with CD4 + T-cell counts below 50 cells/μL should undergo monthly fundoscopic screening, while those with counts below 100 cells/μL require quarterly screening.	**75 %**	41.67 %	33.33 %	16.67 %	8.33 %	0 %
2.2	The indication for CMVR screening is risk stratified for non-HIV immunocompromised patients. Patients with known CMV viremia and those who are on high-dose immunosuppression therapy are indicated for screening.	**100 %**	50 %	50 %	0 %	0 %	0 %
2.3	Increase uptake of CMVR screening is recommended in low-income countries due to higher frequency of visual comorbidities. The use of telemedicine and artificial intelligence for interpretation of fundal images potentially reduces the demand for manpower and resources for CMVR screening.	**91.66 %**	58.33 %	33.33 %	0 %	8.33 %	0 %
3. Treatment controversies							
3.1	The preferred first-line treatment for CMVR is oral valganciclovir. Adjuvant treatment with intravitreal ganciclovir injection is indicated when CMVR involves the posterior pole or when there is rapid progression that threatens to compromise vision.	**83.33 %**	50 %	33.33 %	8.33 %	8.33 %	0 %
3.2	Following the induction phase of antiviral therapy, maintenance treatment is necessary to prevent CMVR relapse. Cessation of treatment can be considered after 6 months when the disease remains inactive, CD4 + T-cell count is consistently above 100 cells/mm3 and HAART has been initiated (in AIDS patients). However, decision to stop treatment should be individualized, taking into account factors like the primary causes of immunosuppression, location of the lesions, vision in the other eye and the compliance to regular clinical monitoring after stopping treatment. Vigilance for CMV resistance is necessary due to its increased risk in prolongedin prolonged therapy.	**100 %**	66.67 %	33.33 %	0 %	0 %	0 %
3.3	Causes of CMVR suboptimal response or relapse include poor compliance to therapy, poor intraocular drug availability and presence of antiviral resistance. Switching to second-line antiviral agents or combination use with first-line drugs are current treatment options. The choice of therapy should be balanced between efficacy and risk of systemic side effects.	**100 %**	50 %	50 %	0 %	0 %	0 %
2.4	Immune reconstitution is associated with immune recovery uveitis (IRU) which indicates corticosteroid treatment. IRU may cause increase vitritis and/or anterior chamber inflammation and its clinical manifestation should be distinguished from CMVR relapse which requires antiviral treatment.	**91.67 %**	75 %	16.67 %	8.33 %	0 %	0 %
3.5	For patients who developed retinal detachment secondary to CMVR, vitrectomy should be performed. Endotamponade with silicone oil is often indicated. Systemic antiviral therapy should be continued after vitrectomy until active retinal lesions subside.	**100 %**	75 %	25 %	0 %	0 %	0 %
4. Special population considerations							
4.1	Prompt serological diagnosis of CMV and treatment with oral valganciclovir during the first trimester of pregnancy are crucial in reducing the risk of congenital CMVR.	**80 %**	30 %	50 %	20 %	0 %	0 %
4.2	The treatment for vision threatening congenital CMVR involves systemic and intravitreal antiviral therapies. The dosage for antiviral therapies must be titrated against the risk of side effects. More data and collaboration are necessary for determining the optimal treatment strategy for active congenital CMVR in future.	**75 %**	50 %	25 %	25 %	0 %	0 %

(*continued on next page*)

Table 2 (*continued*)

Section	Consensus Statement	C Score	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
5. Future directions and Emerging controversies							
5.1	Novel antiviral medications, including letermovir (LET) and maribavir (MBV), may be used in resistant cases, with their effects relying on alternative mechanisms.	58.33 %	33.33 %	25 %	41.67 %	0 %	0 %
5.2	Immunotherapies, including CMV-specific adoptive T-cell therapy and CMV immunoglobulin, are proposed to be applied in cases of poor tolerance with traditional antiviral therapy. But the complex procedures, difficult donor selection, and high cost limit the large-scale application.	**83.33 %**	50 %	33.33 %	16.67 %	0 %	0 %
5.3	In solid organ transplant (SOT) recipients, a prophylactic regimen combining intravenous ganciclovir followed by oral valganciclovir is recommended for 3–12 months.	**81.82 %**	27.27 %	54.55 %	9.09 %	9.09 %	0 %
5.4	In hematopoietic stem cell transplant recipients, antiviral prophylaxis is generally avoided due to concerns regarding drug-induced toxicity, particularly the risk of bone marrow suppression. It is recommended to closely monitor CMV viral replication and initiate preemptive therapy when replication reaches a predefined threshold.	**91.67 %**	41.67 %	50 %	8.33 %	0 %	0 %
5.5	Deep learning-based diagnostic systems show promising accuracy in identifying vision-threatening CMVR cases, representing a cost-effective triage tool for healthcare systems in developing regions.	**83.34 %**	41.67 %	41.67 %	8.33 %	8.33 %	0 %

Consensus Score (C Score) was defined as the value of the summation of the 'strongly agree', and 'agree' percentages; C Score ≥ 75 % was considered 'consensus achieved' and C Score < 75 % was 'consensus not reached'. Only two statements were 'consensus not achieved' (with the C Score underlined).

predominantly reflect tertiary-center perspectives, potentially limiting applicability in resource-limited or rural settings. The integration of emerging technologies like AI for screening remains constrained by the need for high-quality imaging, standardization, and regulatory frameworks. Nevertheless, the rapid development and validation of AI will be one of the most important implementations to enhance CMVR management for resource-limited settings. The dissemination of generic valganciclovir medications will also lower the price and improve access to CMVR treatment worldwide.

Future Directions

Current anti-CMV therapies are virostatic and have significant limitations due to toxicity, CMV genotypic resistance and need for frequent administration. Next-generation antiviral drugs in the pipeline has novel mechanism of action (e.g., targeting the viral terminase complex) that are effective against ganciclovir-resistant strains and have better safety profiles. [124] Research into oral formulations with high bioavailability could reduce the need for invasive intravitreal injections. Clinical trials for standardization of protocol for screening and prophylaxis specifically for post-transplant immunosuppressed patients are needed to determine the optimal strategy to prevent CMVR and the development of severe vision-debilitating complications. Future clinical data on the use of targeted biologic agents[125] (e.g., anti-TNF-α, anti-IL-6 drugs) will be available for managing severe, refractory IRU, moving beyond corticosteroids.

5. Conclusion

The management of CMVR continues to evolve as new diagnostic technologies, Asiaacific treatments, and preventive strategies emerge. Many controversies remain unresolved, highlighting the need for ongoing research, consensus-building among specialists, and individualized approaches to patient care. As the epidemiology of CMVR shifts with changes in the HIV/AIDS landscape and an expanding population of immunocompromised patients, addressing these controversies becomes increasingly important for optimal patient outcomes.

Consent

All authors consent to be co-authors of this manuscript.

Declaration of Competing Interest

None.

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