

# Cytomegalovirus Disease (Last updated July 1, 2021; last reviewed October 13, 2021)

## Epidemiology

Cytomegalovirus (CMV) is a double-stranded DNA virus in the herpesvirus family that can cause disseminated or localized end-organ disease in people with HIV with advanced immunosuppression. Most clinical disease occurs in individuals previously infected with CMV experiencing reactivation of latent infection. Infection with a novel strain also may occur.

End-organ disease caused by CMV occurs in patients with HIV and advanced immunosuppression, typically those with CD4+ T lymphocyte cell (CD4) counts  $<50$  cells/mm<sup>3</sup> who are not receiving, adherent to, or responding to antiretroviral therapy (ART).<sup>1-3</sup> Among those treated with ART who have achieved virologic control, a new diagnosis of CMV end-organ disease is exceedingly rare.

Before potent ART, an estimated 30% of patients with AIDS experienced CMV retinitis, the most common CMV end-organ disease in such patients.<sup>1-3</sup> The incidence of new cases of CMV end-organ disease has declined by  $\geq 95\%$  with the advent of potent ART.<sup>4,5</sup> For those with established CMV retinitis, recurrence of active lesions occurs at a rate substantially lower than that seen in the era before potent ART. Nevertheless, even for those with immune recovery sufficient to warrant discontinuation of anti-CMV therapy (i.e., CD4+ counts  $>100$  cells/mm<sup>3</sup>) relapse of the retinitis occurs at a rate of 0.03/ person-year and has been documented<sup>6</sup> at CD4 counts as high as 1,250 cells/mm<sup>3</sup>. Therefore, regardless of whether or not anti-CMV therapy is continued, regular ophthalmologic follow-up is needed.

## Clinical Manifestations

Retinitis is the most common clinical manifestation of CMV end-organ disease in people with HIV. It occurs as unilateral disease in two-thirds of patients at presentation, but disease ultimately progresses to bilateral in most patients in the absence of therapy or immune recovery.<sup>6</sup> In patients with unilateral CMV retinitis and CD4 count  $<50$  cells/mm<sup>3</sup>, rates of contralateral disease approach those of the prepotent ART era.<sup>6</sup>

Peripheral retinitis (i.e., outside the major vascular arcades, not involving the macula or optic disc) may be asymptomatic or present with floaters, scotomata, or peripheral visual field defects. Posterior retinal lesions, especially those impinging on the macula or optic disc, are associated with decreased visual acuity or central visual field defects. CMV retinitis is a full-thickness necrotizing retinal infection. The characteristic ophthalmologic appearance is that of fluffy, yellow-white retinal lesions, with or without intraretinal hemorrhage. The most typical feature is the lesion border, which has tiny dry-appearing, granular, dot-like “satellites” at the interface between infected and normal retina. There will be little inflammation of the vitreous humor unless immune recovery with ART occurs.<sup>1</sup> Blood vessels near the lesions may appear to be sheathed. Occasionally, CMV retinitis lesions, particularly peripheral lesions, may have only a granular appearance throughout the lesion.

In the absence of effective ART or specific anti-CMV therapy, retinitis lesions invariably enlarge. Untreated lesions in severely immunodeficient individuals will involve the entire retina over a period of no longer than 6 months. Movement of lesion borders occurs at variable rates in different directions,<sup>7</sup> causing a characteristic “brushfire” pattern, with their granular, leading edges advancing before an atrophic gliotic scar.<sup>8</sup>

Colitis occurs in 5% to 10% of patients with AIDS and CMV end-organ disease.<sup>2</sup> The most frequent clinical manifestations are weight loss, fever, anorexia, abdominal pain, diarrhea, and malaise. In the colon, and especially in the cecum, CMV can cause perforation and present as an acute abdomen. Computed tomography may show colonic thickening or a colonic mass that may be mistaken for malignancy or other opportunistic infections (OI). Hemorrhage and perforation can be life-threatening complications.

Esophagitis occurs in a small percentage of patients with AIDS who experience CMV end-organ disease and causes odynophagia, nausea, and occasionally midepigastic or retrosternal discomfort as well as fever.

CMV pneumonitis is uncommon in people with HIV, which is in contrast to other conditions with severe immunosuppression, such as solid organ and stem-cell transplant patients. CMV is detected frequently in the bronchoalveolar lavage (BAL) using DNA-specific polymerase chain reaction (PCR), but is a bystander most of the time and should trigger a search for a more likely causative pathogen. CMV PCR from the BAL has not been shown to have diagnostic value in people with HIV.

CMV neurologic disease includes dementia, ventriculoencephalitis, and polyradiculomyelopathies.<sup>9</sup> Patients with dementia caused by CMV encephalitis typically have lethargy or confusion in the presence or absence of fever. Cerebrospinal fluid (CSF) typically demonstrates lymphocytic pleocytosis, low-to-normal glucose levels, and normal-to-elevated protein levels, although normal CSF findings do not rule out the diagnosis of CMV encephalitis. Patients with ventriculoencephalitis have a more acute course, with focal neurologic signs, often including cranial nerve palsies or nystagmus, and rapid progression to death. Periventricular enhancement of computed tomography or magnetic resonance images is highly suggestive of CMV ventriculoencephalitis, rather than HIV-associated neurocognitive disorder. CMV polyradiculomyelopathy or transverse myelitis causes a Guillain-Barre-like syndrome characterized by radicular back pain, urinary retention, and progressive bilateral leg weakness. Clinical symptoms usually progress over several weeks to include loss of bowel and bladder control and flaccid paraplegia. A spastic myelopathy has been reported, and sacral paresthesia can occur. The CSF in CMV polyradiculopathy usually demonstrates neutrophilic pleocytosis (usually 100 to 200 neutrophils/ $\mu$ L and some erythrocytes) accompanied by hypoglycorrhachia and elevated protein levels.

## Diagnosis

The diagnosis of CMV end-organ disease is typically made on the basis of the clinical presentation and, when possible, evidence of the virus in tissue. CMV retinitis usually is diagnosed based on recognition of characteristic retinal changes observed through a dilated pupil during an ophthalmoscopic examination performed by an experienced ophthalmologist. Diagnosis in that setting has a 95% positive predictive value. In rare cases, the diagnosis may be unclear, and PCR of aqueous or vitreous humor specimens for CMV and other pathogens—especially herpes simplex virus, varicella zoster virus, and *Toxoplasma gondii*—can be useful for establishing the diagnosis. Detection of CMV DNA in CSF or vitreous or aqueous humor specimens is highly suggestive that CMV is the cause of ocular disease. In one study, CMV DNA was detected in 82% of vitreous specimens collected at diagnosis of CMV retinitis, in 77% of relapsed retinitis, and in 23% of quiescent retinitis.<sup>10</sup> Therefore, failure to detect CMV DNA in vitreous specimens does not rule out the presence of CMV retinitis. A response to empiric anti-CMV therapy also can be an important diagnostic indicator.

CMV colitis usually is diagnosed based on demonstration of mucosal ulcerations on endoscopic examination, combined with histopathologic demonstration of characteristic intranuclear and intracytoplasmic inclusions on hematoxylin and eosin stains.<sup>2,11</sup> Similarly, CMV esophagitis is diagnosed by presence of ulcers of the distal esophagus together with biopsy evidence of intranuclear inclusion bodies in the endothelial cells with an inflammatory reaction at the edge of the ulcer.<sup>2</sup> The number of inclusion bodies in specimens varies from many inclusion bodies to rare or isolated inclusion bodies. Immunohistochemistry also may be used to detect CMV in tissue. Culturing CMV, or detection of CMV DNA by PCR, from a biopsy or cells brushed from the colon or the esophagus is insufficient to establish the diagnosis of CMV colitis or esophagitis in the absence of histopathologic changes, because a substantial number of patients with low CD4 cell counts may shed CMV and have positive cultures in the absence of clinical disease.<sup>12</sup>

The diagnosis of CMV pneumonitis requires consistent clinical and radiological findings (i.e.,

diffuse pulmonary interstitial infiltrates, fever, and cough or dyspnea), identification of multiple CMV inclusion bodies in lung tissue or cytology, and the absence of any other pathogens that are more commonly associated with pneumonitis.<sup>13</sup> Detection of CMV in the lungs in the absence of these criteria typically represents shedding, rather than clinical disease.

CMV neurologic disease is diagnosed on the basis of a compatible clinical syndrome and the presence of CMV in CSF or brain tissue, most often evaluated with PCR.<sup>3,14,15</sup> Blood tests to detect CMV by antigen detection, culture, or PCR are not recommended for diagnosis of CMV end-organ disease because of their poor positive predictive value in people with advanced AIDS.<sup>16</sup> CMV viremia can be detected by PCR, antigen assays, or culture and is often present in endorgan disease. A negative serum or plasma PCR assay does not rule out CMV end-organ disease. CMV viremia may be present in the absence of end-organ disease in people with HIV with low CD4 cell counts.<sup>9,12–15,17</sup> Monitoring for CMV viremia is not recommended.

The presence of serum antibodies to CMV, in and of itself, does not establish the presence of CMV disease, because a large proportion of the general population has been exposed to CMV and is seropositive. However, a negative immunoglobulin G (IgG) antibody level indicates that CMV is unlikely to be the cause of the disease process.

## Preventing Exposure

Although CMV infection is common in the general population, geographic, socioeconomic, and racial and ethnic differences exist in CMV prevalence.<sup>10</sup> In the National Health and Nutrition Examination Survey (NHANES) 1999–2004, CMV seropositivity was associated with older age, female sex, foreign birthplace, and markers of socioeconomic status, such as low household income and education and high household crowding. Some people with HIV may belong to groups with relatively low seroprevalence rates for CMV and, therefore, cannot be presumed to be seropositive. Adolescents and adults with HIV should be advised that CMV is shed in semen, cervical secretions, and saliva and that latex condoms used during sexual contact reduce the risk of exposure to CMV, as well as other sexually transmitted pathogens (**AII**).

## Preventing Disease

CMV end-organ disease is best prevented using ART to maintain the CD4 count  $>100$  cells/mm<sup>3</sup> (**BI**). A randomized, placebo-controlled trial addressed whether valganciclovir (the current standard oral agent for treatment of CMV disease) in addition to ART might reduce CMV end-organ disease in AIDS patients at high risk (CD4 count  $<100$  cells/mm<sup>3</sup> and CMV viremia detected by plasma CMV DNA PCR assay).<sup>18</sup> This study failed to show a benefit for such preventive therapy; therefore, valganciclovir primary prophylaxis **is not recommended** to prevent CMV end-organ disease in people with HIV, even among patients who have CMV viremia (**AI**).

The primary method for preventing severe CMV disease is recognizing the early manifestations of the disease and instituting proper therapy. Patients who have a low CD4 cell count ( $<100$  cells/mm<sup>3</sup>) and are not on ART should be made aware of the implications of increased floaters in the eye and be advised to assess their visual acuity regularly using simple techniques, such as reading newsprint. Development of floaters or changes in visual acuity should prompt an urgent referral to ophthalmology (**AIII**). In the premodern ART era, some specialists recommended ophthalmologic examinations every 3 to 4 months for patients with CD4+ cells  $<50$  cells/mm<sup>3</sup>, because up to one-half of early CMV retinitis was asymptomatic (**CIII**). However, with the decline in CMV incidence in the modern ART era, the value of this recommendation is unknown. Some clinicians do recommend a baseline ophthalmologic exam for people with HIV with CD4  $<100$  cells/mm<sup>3</sup> (**CIII**).

## Treating Disease

The therapeutic approach to CMV retinitis should be individualized based on tolerance of systemic medications, prior exposure to anti-CMV drugs, and possibly the location of lesions (**AIII**). CMV retinitis should ideally be treated with the active participation of an ophthalmologist who is familiar with the diagnosis and management of this retinal disease (**AIII**).

Oral valganciclovir (**AI**), intravenous (IV) ganciclovir (**AI**), or IV ganciclovir induction followed by oral valganciclovir maintenance (**AI**) are first-line therapies for treating CMV retinitis. Although IV foscarnet (**BI**), and IV cidofovir (**CI**) are also effective treatments for CMV retinitis, substantial toxicities, including nephrotoxicity, make these less-preferred options.<sup>8,19–26</sup> Systemic therapy has been documented to reduce CMV involvement of the contralateral eye,<sup>19</sup> to reduce CMV visceral disease, and to improve survival.<sup>20,27</sup> Given the evident benefits of systemic anti-CMV therapy, treatment regimens for CMV retinitis should include a systemic component. Few trials have compared regimen efficacy during the past 15 years. None of the listed regimens has been proven in a clinical trial to have superior efficacy related to protecting vision. Therefore, clinical judgment must be used when choosing a regimen.<sup>21–25</sup>

When systemic therapy is indicated, most clinicians will prescribe IV ganciclovir (**AI**) or oral valganciclovir (**AI**) for an induction period lasting a minimum of 14 to 21 days, with the duration determined by clinical response based on retinal examination. Many prefer the IV formulation when retinitis is more central and sight-threatening or when adequate gastrointestinal (GI) absorption is a concern. In such cases, the patient's transition to oral valganciclovir can be considered when there is evidence of clinical response. In cases where toxicity of ganciclovir and valganciclovir (i.e., severe cytopenias) is a concern and there is not renal insufficiency, or when ganciclovir-resistant CMV is a concern, IV foscarnet may be used (**BI**). IV cidofovir is rarely used, unless there is the need to avoid both ganciclovir and foscarnet (**CI**). Cidofovir administration is complicated by the need to co-administer IV fluid hydration and probenecid to counter the nephrotoxicity of the drug. In addition, IV cidofovir is associated with increased risk of immune recovery uveitis, hypotony, and neutropenia.<sup>28</sup>

In the presence of immediately sight-threatening lesions (those within 1,500 microns of the fovea or optic disc) at presentation (**AIII**), some clinicians will supplement systemic therapy with intravitreal injections of ganciclovir or foscarnet, at least initially, to provide immediate, high intraocular levels of the drug and presumably faster control of the retinitis (**AIII**). Injections are continued on a weekly basis until lesion inactivity is achieved, at which time systemic treatment alone is considered to be adequate for maintenance therapy. The recommendation to supplement systemic therapy with intravitreal injections is based on pharmacokinetic considerations, but the clinical benefit of such supplementation has not been confirmed in clinical trials. Although intravitreal injections deliver high concentrations of the drug to the target organ immediately while steady-state concentrations in the eye are being achieved over time with systemically delivered medications,<sup>19</sup> such injections can be complicated by bacterial or fungal infections, hemorrhage, or retinal detachment. Repeated intravitreal injections of ganciclovir or of foscarnet alone have appeared to be effective for maintenance therapy of CMV retinitis in uncontrolled case series,<sup>29</sup> but this strategy should be reserved for those individuals who cannot be treated systemically. Intravitreal cidofovir is associated with hypotony and uveitis—and a substantially increased risk of immune recovery uveitis—and should be avoided (**AIII**).<sup>30</sup>

For patients without sight-threatening lesions, oral valganciclovir alone often is adequate (**AI**). The ganciclovir implant, a surgically implanted reservoir of ganciclovir that lasts for approximately 6 months, is no longer manufactured.

Treatment with systemic anti-CMV therapy, such as oral valganciclovir for the first 3 to 6 months until ART has induced immune recovery, is beneficial (**AII**). Ocular complications, such as immune recovery uveitis (IRU) and retinal detachment, are related to lesion size, so minimizing lesion size with anti-CMV therapy until immune recovery is sufficient to control the retinitis is logical. Furthermore, evidence from both the pre-ART and ART eras demonstrate that specific anti-CMV therapy decreases mortality among immune-compromised patients with CMV retinitis.<sup>12,20,26,31</sup>

For patients who have colitis or esophagitis, many HIV specialists recommend anti-CMV therapy for 21 to 42 days (**CII**) or until signs and symptoms have resolved. IV ganciclovir generally is the therapy of choice and can be switched to oral valganciclovir once the patient can tolerate and absorb oral medications (**BI**). Foscarnet can be used as an alternative if ganciclovir-related toxicity is treatment-limiting or in cases of ganciclovir-resistant virus (**BIII**). Oral valganciclovir can be used in patients with mild disease (**BIII**).

Experience treating well-documented CMV pneumonia in patients with HIV infection is limited and anecdotal. Treatment with IV ganciclovir or, alternatively, with foscarnet, is logical (**CIII**). The optimal duration of therapy and the role of oral valganciclovir have not been established.

Therapy for well-documented neurologic disease also has not been extensively studied. Given the poor outcomes in many patients with CMV-related neurologic disease, some experts would initiate therapy with both IV ganciclovir and IV foscarnet, despite the substantial toxicities associated with such an approach (**CIII**). The optimal duration of therapy and the role of oral valganciclovir have not been established.

### ***Special Considerations with Regard to Starting Antiretroviral Therapy***

Immune reconstitution inflammatory syndrome (IRIS) from CMV may occur in patients who have active retinitis and those who have had CMV retinitis in the recent or distant past. One study demonstrated a substantial increase in immune reconstitution uveitis (IRU) in association with immediate, as opposed to deferred initiation of ART (71% vs. 31%).<sup>32</sup> However, in the current era, the rate of clinically significant IRU following initiation of ART appears to be low (approximately 0.02 per person-year). Delaying ART until retinitis is controlled may reduce the likelihood or severity of IRU; however, this strategy must be weighed against the potential for a worsened immunocompromised state and the occurrence of other OIs. Several trials have demonstrated benefits of early versus delayed ART, including reduced risk of mortality, reduced AIDS progression, and shorter time to viral suppression.<sup>33–36</sup> Only one study has evaluated the benefits of early ART during treatment of an active OI, and it included few participants with CMV disease.<sup>34</sup>

As CMV replication usually declines within 1 to 2 weeks after anti-CMV therapy is initiated, most experts would initiate ART no later than 1 to 2 weeks after starting anti-CMV therapy for retinitis, esophagitis, colitis, or other end-organ diseases caused by CMV (**CIII**). IRIS is a particular concern with any neurologic disease, including CMV encephalitis, ventriculitis, and radiculitis. In these cases, however, most experts would not defer initiation of ART for more than 2 weeks, although clinical judgment based on individual cases is needed (**CIII**).

### ***Monitoring of Response to Therapy and Adverse Events (Including IRIS)***

Indirect ophthalmoscopy of both eyes through dilated pupils should be performed at the time of diagnosis of CMV retinitis, 2 weeks after initiating therapy, and monthly thereafter while the patient is on anti-CMV treatment (**CIII**). The purpose of such examinations is to evaluate efficacy of treatment, identify second eye involvement in cases of unilateral disease, and detect IRU or such complications as retinal detachment. Monthly fundus photographs, using a standardized technique that documents the appearance of the retina, provide the optimum method for following patients and detecting early lesion reactivation. For patients who have experienced immune recovery (CD4+ count >100 cells/mm<sup>3</sup> for ≥3 months), the frequency of ophthalmologic follow-up can be decreased to every 3 months, but clinicians should be aware that lesion reactivation and retinal complications still occasionally occur in patients with immune reconstitution.

Adverse effects of ganciclovir/valganciclovir include anemia, neutropenia, thrombocytopenia, nausea, diarrhea, and renal dysfunction. Ganciclovir-related neutropenia often can be reversed with granulocyte colony stimulating factor (G-CSF).<sup>33,34</sup> In patients receiving ganciclovir or valganciclovir,

complete blood counts and renal function should be monitored twice weekly during induction and at least once weekly during maintenance therapy (**AIII**). Adverse effects of foscarnet include nephrotoxicity and electrolyte abnormalities; seizures that occur characteristically in the context of renal insufficiency; and anemia. Genital ulcers also can occur during foscarnet administration in those who are incontinent to urine due to the toxic effects of excreted drug on exposed skin. Foscarnet often is given in the inpatient setting because of the intensity of monitoring and need for hydration. For patients receiving foscarnet in the outpatient setting, serum electrolytes (including potassium, magnesium, calcium, and phosphorus) and renal function should be measured at least twice weekly during induction and at least weekly during maintenance therapy. Complete blood counts should be monitored weekly (**AIII**).

Adverse effects of cidofovir include dose-related nephrotoxicity, neutropenia, uveitis, and hypotony (low intraocular pressure). The risk of severe renal injury from IV cidofovir can be reduced by prehydration and oral probenecid before cidofovir administration. In patients receiving IV cidofovir, analysis of blood urea nitrogen and creatinine levels and urinalysis should be performed before each infusion. Drug administration is contraindicated if renal dysfunction or substantial proteinuria is detected. Particular attention is needed for patients receiving other potentially nephrotoxic medications, including tenofovir disoproxil fumarate. Periodic ophthalmologic examinations are needed to monitor for cidofovir-associated uveitis or hypotony, even when CMV disease does not include retinitis.

As noted previously, patients with CMV retinitis must have careful ophthalmologic monitoring to detect and manage the wide range of complications related to CMV, the drugs used to treat CMV, and IRIS. IRU, an ocular form of IRIS presumed to be an adverse immunologic reaction to CMV, is characterized by inflammation in the anterior chamber or vitreous body in the setting of immune recovery after initiation of ART. IRU usually is observed in patients with a substantial rise in CD4 cell count in the first 4 to 12 weeks after initiation of ART.<sup>28,35–38</sup> The estimated incidence of IRU is 0.02/person-year after immune recovery.<sup>39</sup> Ocular complications of IRU include macular edema and development of epiretinal membranes, which can cause loss of vision. Although the inflammatory reactions seen at the onset of IRU can be transient as immune reconstitution occurs, the complications may persist, permanently compromising vision.

Treatment of IRU usually consists of some type of corticosteroid therapy. The benefit of anti-CMV therapy is unclear.<sup>35,40</sup> Many experts would use both corticosteroids and anti-CMV therapy (**CIII**). Data are insufficient on which to base a recommendation regarding the preferred route of corticosteroid administration; periocular, intravitreal, and oral administration all have been reported to be potentially successful. When oral corticosteroids are used, a short course rather than chronic therapy usually is recommended (**BIII**).<sup>41</sup> IRU can occur months or years after successful treatment of CMV retinitis in patients with a history of CMV retinitis who subsequently start taking ART or have such therapy optimized.

People with advanced HIV remain at risk for development of CMV retinitis prior to immune reconstitution, even after initiation of ART.<sup>42,43</sup> Development of CMV retinitis in the setting of recent ART initiation should be treated with systemic anti-CMV therapy, similar to any patient with CMV retinitis, and the same ART regimen should be continued (**AI**). Corticosteroids are not recommended (**AIII**). In addition, in the absence of uveitis, corticosteroids should not be used in patients undergoing treatment for CMV retinitis who have worsening of retinitis upon ART initiation. In this situation, anti-CMV therapy and ART regimens should be continued (**AIII**).

### ***Managing Treatment Failure***

Failure of therapy for CMV retinitis or reactivation of lesions is most likely in patients who do not have substantial immune reconstitution after initiation or optimization of ART.<sup>44</sup> Treatment failure

also may be a result of inadequate anti-CMV drug levels in the eye, CMV drug resistance, or nonadherence. Many experts believe that early progression of disease (enlargement of lesions or new lesions) is most often caused by the limited intraocular penetration of systemically administered drugs.<sup>40,45,46</sup>

When reactivation of lesions occurs in patients receiving maintenance therapy, retinitis usually can be controlled with re-induction of the same drug used for maintenance followed by re-institution of maintenance therapy (**BIII**).<sup>47</sup> Ganciclovir and foscarnet in combination appear to be superior in efficacy to either agent alone and should be considered for patients whose disease does not respond to single-drug therapy and for patients with continued progression or multiple reactivations of retinitis (**CIII**).<sup>47</sup> This drug combination, however, is associated with substantial toxicity.

Drug resistance can occur in patients receiving long-term anti-CMV therapy.<sup>48–51</sup> Drug resistance rates of approximately 25% per person-year were reported in the pre-ART era<sup>48,52,53</sup> for ganciclovir, foscarnet, and cidofovir.<sup>48,49</sup> In the ART era, the rate of resistance appears to be lower (approximately 5% per person-year).<sup>54</sup> Low-level resistance to ganciclovir occurs through mutations in the CMV UL97 (phosphotransferase) gene, and high-level resistance to ganciclovir typically occurs because of mutations in both the CMV UL97 and UL54 (DNA polymerase) genes.<sup>50,55–59</sup> Resistance to foscarnet or cidofovir occurs because of mutations in the CMV UL54 gene. High-level resistance to ganciclovir often is associated with cross-resistance to cidofovir<sup>57</sup> and occasionally to foscarnet.<sup>58</sup> Although early CMV disease progression typically is not a result of drug resistance, late CMV reactivation may be. By themselves, peripheral blood CMV viral load measurements have poor positive predictive value for treatment failure.

Ganciclovir resistance in patients who fail therapy can be detected by CMV DNA PCR of blood specimens followed by detection of UL97 mutations by DNA sequencing or by a point mutation assay<sup>60–62</sup> Sequencing the UL97 gene from PCR-amplified specimens from blood can be accomplished in less than 48 hours and correlates well with conventional drug susceptibility testing and clinical outcomes.<sup>62</sup> Circulating CMV in blood and vitreous fluid have identical UL97 sequences in more than 90% of cases;<sup>63</sup> therefore, evaluating the blood for resistance is reasonable, and detection of resistance in the blood or urine correlates with clinical behavior of the retinitis in most cases.<sup>64</sup> Viral culture and susceptibility testing and viral DNA sequencing often are not available in clinical laboratories because they are too time consuming or costly. UL97 mutants usually respond to foscarnet, as do some UL54 mutants.<sup>65</sup> Many clinicians will treat ganciclovir-resistant CMV with a series of intravitreal injections of foscarnet and/or IV foscarnet or cidofovir (**CIII**).

## Preventing Recurrence

### *When to Start Maintenance Therapy*

After induction therapy for CMV retinitis, chronic maintenance therapy should be continued,<sup>9,14,19,22,66</sup> until immune reconstitution occurs as a result of ART (**AI**). Maintenance therapy is started after induction has achieved control of retinitis, as evidenced by resolved or markedly reduced retinal lesion opacity, indicating virus inactivity. Although several regimens are effective for chronic suppression—including parenteral ganciclovir, parenteral foscarnet, and parenteral cidofovir—oral valganciclovir may be the easiest and least toxic to administer to an outpatient population, provided that GI absorption is adequate. Systemic therapy must be administered to prevent disease in the contralateral eye until immune reconstitution has occurred.

The choice of regimen (i.e., which drug[s] and whether given intravitreally, orally, or intravenously) should be made in consultation with an ophthalmologist. Considerations should include the anatomic location of the retinal lesion; vision in the contralateral eye; and a patient's immunologic and virologic status, comorbidities, concomitant medications, and response to ART.

After resolution of the acute CMV syndrome and initiation of effective ART, chronic mainte-

nance therapy is not routinely recommended for CMV GI disease, pneumonitis, and central nervous system disease unless there is concurrent retinitis, there have already been recurrent infections, or severe disease was present initially (**BII**).

### ***When to Stop Maintenance Therapy***

Maintenance therapy can be discontinued safely in adults and adolescents with CMV retinitis whose lesions have been treated for at least 3 to 6 months and are inactive and who have had sustained (i.e., 3–6 months) increases in CD4 cell counts to  $>100$  cells/mm<sup>3</sup> in response to ART (**AII**).<sup>4,67–73</sup> Such decisions should be made in consultation with an ophthalmologist. A 3% reactivation rate is reported in patients whose anti-CMV therapy has been discontinued for immune recovery, and no level of CD4 cell count is absolutely safe (reactivations have been reported at CD4 cell counts of 1,250 cells/mm<sup>3</sup>). Therefore, in all patients for whom anti-CMV maintenance therapy has been discontinued, ophthalmologic monitoring for early detection of CMV relapse and for IRU should be performed at least every 3 months and periodically after immune reconstitution (**AIII**). Monitoring CMV viral load in blood has poor positive predictive value for relapse of retinitis and, therefore, is not recommended (**AII**).<sup>16</sup>

Reactivation of CMV retinitis occurs frequently in patients whose CD4 cell counts have decreased to  $<50$  cells/mm<sup>3</sup> and whose anti-CMV maintenance therapies have been discontinued.<sup>74</sup> Therefore, reinstatement of maintenance therapy should occur when the CD4 cell count has decreased to  $<100$  cells/mm<sup>3</sup> (**AIII**).

### **Special Considerations During Pregnancy**

The diagnostic considerations among pregnant women are the same as for nonpregnant women. Indications for treatment of CMV infection during pregnancy are the same as for nonpregnant people with HIV (**AIII**). For retinal disease, use of intravitreal injections for local therapy should be considered in the first trimester, if possible, to limit fetal exposure to systemically administered antiviral drugs (**BIII**). Systemic antiviral therapy should then be started after the first trimester. For life-threatening indications, treatment with systemic antiviral therapy during the first trimester may be necessary.

Ganciclovir is embryotoxic among rabbits and mice and teratogenic (i.e., cleft palate, anophthalmia, aplastic kidney and pancreas, and hydrocephalus) in rabbits.<sup>75–77</sup> However, safe use in all trimesters of human pregnancy after organ transplantation and in other patient populations has been reported.<sup>75–79</sup>

Foscarnet is associated with an increase in skeletal anomalies or variants in rats and rabbits. No experience with use early in human pregnancy has been reported. A single case report of use in the third trimester described normal infant outcome.<sup>80</sup> Because toxicity of foscarnet is primarily renal, weekly monitoring of amniotic fluid volumes by ultrasound is recommended after 20 weeks of gestation to detect oligohydramnios if foscarnet is used.

Cidofovir is embryotoxic and teratogenic (i.e., meningomyelocele and skeletal abnormalities) among rats and rabbits. No experience with use of cidofovir in human pregnancy has been reported; use in pregnancy is not recommended (**AIII**).

On the basis of limited data, toxicity reports, and ease of use of the various drugs, valganciclovir is recognized as the treatment of choice during pregnancy (**BIII**). The fetus should be monitored by fetal-movement counting in the third trimester and by periodic ultrasound monitoring after 20 weeks of gestation to look for evidence of hydrops fetalis indicating substantial anemia. No data exist to support use of pooled or CMV-specific intravenous immunoglobulin in this clinical situation.

Primary infection, reactivation, and reinfection with a different strain of CMV during pregnancy (non-primary infection)<sup>81</sup> all can lead to *in utero* transmission and congenital CMV. Maternal ART in pregnancy has been associated with decreased rates of perinatal/early postnatal CMV and decreased



CMV-related clinical symptoms among infants exposed to or infected with HIV.<sup>82</sup> Recent studies indicate the prevalence of congenital CMV among infants in the United States who are exposed to HIV is 1.2% to 1.3%.<sup>83</sup> Risk factors for congenital CMV include mothers with CD4+ <200 cells/mm<sup>3</sup>, mothers with urinary CMV shedding,<sup>84</sup> and HIV transmission to infants. Maternal CMV and infant congenital CMV also have been associated with increased risk of HIV perinatal transmission in pregnant women with HIV who have not received antenatal ART.<sup>85</sup>

In women diagnosed with primary CMV infection in pregnancy, the fetus should be monitored by periodic ultrasound after 20 weeks gestation (**CIII**). In studies in HIV-uninfected populations, about 5% to 25% of newborns infected with CMV had ultrasound evidence of congenital infection (e.g., cerebral calcifications, abdominal and liver calcifications, hydrops, microcephaly, ventriculomegaly, ascites, and echogenic fetal bowel).<sup>86</sup> Any ultrasound findings suspicious for congenital CMV infection should prompt consideration of invasive testing (i.e., amniocentesis) for definitive diagnosis. Referral to a maternal–fetal medicine specialist for evaluation, counseling, and potential further testing is recommended. Potential noninvasive biomarkers for predicting congenital CMV infection are under study.<sup>87</sup>

If fetal CMV infection is confirmed, no standard therapy exists for *in utero* treatment. Available clinical studies support the possible effectiveness and safety of CMV hyperimmune globulin in pregnancy for prevention or treatment of congenital CMV.<sup>88,89</sup> A nonrandomized trial of CMV hyperimmune globulin in women not infected with HIV with primary CMV infection in pregnancy found decreased incidence of having a symptomatic newborn at birth<sup>90</sup> and regression of fetal cerebral abnormalities;<sup>91</sup> however, a well-designed, prospective, randomized, placebo-controlled study with relatively large sample size subsequently found no benefit of CMV hyperimmune globulin in pregnant women.<sup>88,92,93</sup> A second randomized clinical trial that planned to enroll 800 patients with primary CMV infection at <24 weeks gestation was stopped for futility after enrollment of 399 participants when a planned interim analysis suggested that complete enrollment would not provide a significant outcome.<sup>93</sup>

Routine screening for CMV infection in pregnancy is not recommended in the absence of effective *in utero* therapy. Treatment of asymptomatic maternal CMV infection during pregnancy solely to prevent infant infection is not indicated (**AIII**).

## Recommendations for Treating Cytomegalovirus Infections

### Preventing CMV Disease

- CMV end-organ disease is best prevented by using ART to maintain CD4+ count >100 cells/mm<sup>3</sup>.

### Managing CMV Retinitis

- The choice of therapy for CMV retinitis should be individualized, based on tolerance of systemic medications; prior exposure to anti-CMV drugs; and on the location of lesions (**AIII**).
- Given the evident benefits of systemic therapy in preventing contralateral eye involvement, reducing CMV visceral disease, and improving survival, treatment should include systemic therapy whenever feasible.

### Initial Therapy Followed by Chronic Maintenance Therapy—For Immediate Sight-Threatening Lesions (within 1,500 microns of the fovea)

#### Preferred Therapy

- Ganciclovir 5 mg/kg IV q12h for 14–21 days, then 5 mg/kg IV daily (**AI**), *or*
- Ganciclovir 5 mg/kg IV q12h for 14–21 days, then valganciclovir 900 mg PO daily (**AI**), *or*
- Valganciclovir 900 mg PO q12h for 14–21 days, then 900 mg once daily (**AI**); *or* with or without
- Intravitreal injections of ganciclovir (2 mg/injection) or foscarnet (2.4 mg/injection) repeat weekly until lesion inactivity is achieved. This is to provide higher intraocular levels of drug and faster control of the infection until steady-state intraocular ganciclovir concentrations are achieved. (**AIII**)
  - **Note:** IV ganciclovir can be switched to oral valganciclovir if the patient is clinically improving and there are no concerns about gastrointestinal absorption.

#### Alternative Therapy

- Intravitreal injections as listed above (**AIII**); plus one of the following systemic therapies:
  - Foscarnet 60 mg/kg IV q8h or 90 mg/kg IV q12h for 14–21 days, then 90–120 mg/kg IV q24h (**BI**), *or*
  - Cidofovir 5 mg/kg/week IV for 2 weeks, then 5 mg/kg every other week with saline hydration before and after therapy and probenecid 2 g PO 3 hours before the dose followed by 1 g PO 2 hours after the dose, and 1 g PO 8 hours after the dose (total of 4 g) (**CI**). Cidofovir is contraindicated in patients with a serum creatinine >1.5 mg/dL, a calculated creatinine clearance ≤5 mL/min or a urine protein ≥100 mg/dL (equivalent to ≥2+ proteinuria). Given the nephrotoxic potential of cidofovir, cautious use of cidofovir with tenofovir is advised
    - **Note:** This regimen should be avoided in patients with sulfa allergy because of cross-hypersensitivity with probenecid.

### For Peripheral Lesions

- Valganciclovir 900 mg PO q12h for 14–21 days, then 900 mg once daily (**AI**) for the first 3–6 months until ART-induced immune recovery (**AII**).

### IRU

- Minimizing lesion size by treating all CMV retinitis lesions until there is immune recovery may reduce the incidence of IRU (**BII**).
- IRU might develop in the setting of immune reconstitution.

#### Treatment of IRU

- Periocular or intravitreal corticosteroid or a short course of systemic steroid (**BIII**).

### Stopping Chronic Maintenance Therapy for CMV Retinitis

- CMV treatment for at least 3–6 months, and lesions are inactive, and with CD4+ count >100 cells/mm<sup>3</sup> for 3–6 months in response to ART (**AII**).
- Therapy should be discontinued only after consultation with an ophthalmologist, taking into account magnitude and duration of CD4 cell count increase, anatomic location of the lesions, vision in the contralateral eye, and the feasibility of regular ophthalmologic monitoring.
- Routine (i.e., every 3 months) ophthalmologic follow-up is recommended after stopping chronic maintenance therapy for early detection of relapse or IRU, and then periodically after sustained immune reconstitution (**AIII**).

### Reinstating Chronic Maintenance for CMV Retinitis

- CD4 count <100 cells/mm<sup>3</sup> (**AIII**).

### Managing CMV Esophagitis or Colitis

- Doses are the same as for CMV retinitis.

#### Preferred Therapy

- Ganciclovir 5 mg/kg IV q12h; may switch to valganciclovir 900 mg PO q12h once the patient can absorb and tolerate PO therapy (BI).

#### Alternative Therapy

- Foscarnet 60 mg/kg IV q8h or 90 mg/kg IV q12h (BIII)—for patients with treatment-limiting toxicities to ganciclovir or with ganciclovir resistance; *or*
- Oral valganciclovir may be used if symptoms are not severe enough to interfere with oral absorption (BIII); *or*

#### Duration of Anti-CMV Therapy

- 21–42 days or until signs and symptoms have resolved (CII).

**Note:** Maintenance therapy is usually not necessary, but should be considered after relapses (BII).

### Managing Well-Documented CMV Pneumonitis

- Doses are the same as for CMV retinitis.
- Treatment experience for CMV pneumonitis in HIV patients is limited. Use of IV ganciclovir or IV foscarnet is reasonable (CIII).
- The role of oral valganciclovir has not been established.
- The optimal duration of therapy has not been established.

### Managing CMV Neurological Disease

- Doses are the same as for CMV retinitis.
- **Treatment should be initiated promptly.**
- Combination of ganciclovir IV plus foscarnet IV to stabilize disease and maximize response (CIII).
- Optimal duration of therapy has not been established.
- The role of oral valganciclovir has not been established.
- Optimize ART to achieve viral suppression and immune reconstitution (BIII).

**Key to Acronyms:** ART = antiretroviral therapy; BID = twice a day; CMV = cytomegalovirus; IRU = immune recovery uveitis; PO = orally; IV = intravenously; q(n)h = every “n” hours

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