



Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV.

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Cytomegalovirus Disease (Last updated November 4, 2015; last reviewed June 26, 2019)

NOTE: Update in Progress

Epidemiology

Cytomegalovirus (CMV) is a double-stranded DNA virus in the herpes virus family that can cause disseminated or localized end-organ disease in HIV-infected patients with advanced immunosuppression. Most clinical disease occurs in individuals previously infected with CMV (seropositive) and therefore represents either re-activation of latent infection or re-infection with a novel strain.

End-organ disease caused by CMV occurs in patients with advanced immunosuppression, typically those with CD4 T lymphocyte cell (CD4) counts <50 cells/mm³, who are either not receiving or have failed to respond to antiretroviral therapy (ART).¹⁻³ Other risk factors include previous opportunistic infections (OIs), a high level of CMV viremia (most often measured by polymerase chain reaction [PCR]), and high plasma HIV RNA levels ($>100,000$ copies/mL).

Before potent ART, an estimated 30% of patients with AIDS experienced CMV retinitis sometime between the diagnosis of AIDS and death.¹⁻³ The incidence of new cases of CMV end-organ disease has declined by $\geq 95\%$ with the advent of ART.^{4,5} For those with established CMV retinitis, recurrence of active lesions occurs at a rate substantially lower than that seen in the pre-ART era. However, even for those with immune recovery sufficient to discontinue anti-CMV therapy, that is, CD4+ counts >100 cells/mm³, relapse of the retinitis occurs at a rate of 0.03/person-year and occasionally can occur at CD4 counts as high as 1,250 cells/mm³.⁶ Therefore, whether anti-CMV therapy is continued or not, regular ophthalmologic follow-up is needed.

Clinical Manifestations

Retinitis is the most common clinical manifestation of CMV end-organ disease in HIV-infected patients. It occurs as unilateral disease in two-thirds of patients at presentation, but disease ultimately is bilateral in most patients in the absence of therapy or immune recovery.⁶ In patients with unilateral CMV retinitis and CD4 count <50 cells/mm³, rates of contralateral disease approach those of the pre-ART era.⁶

Peripheral retinitis may be asymptomatic or present with floaters, scotomata, or peripheral visual field defects. Central retinal lesions or lesions impinging on the macula or optic nerve are associated with decreased visual acuity or central field defects. CMV retinitis is a full-thickness necrotizing retinitis, and the characteristic ophthalmologic appearance is that of fluffy, yellow-white retinal lesions, with or without intraretinal hemorrhage, with little inflammation of the vitreous unless immune recovery with ART intervenes.¹ Blood vessels near the lesions may appear to be sheathed. Occasionally, CMV retinitis lesions, particularly peripheral lesions, may have a more granular appearance.

In the absence of ART or specific anti-CMV therapy, retinitis invariably progresses, usually within 10 to 21 days after presentation. Progression of retinitis occurs in fits and starts and causes a characteristic brushfire pattern, with a granular, white leading edge advancing before an atrophic gliotic scar.⁷

Colitis occurs in 5% to 10% of patients with AIDS and CMV end-organ disease.² The most frequent clinical manifestations are weight loss, anorexia, abdominal pain, debilitating diarrhea, and malaise. In the colon, and especially in the cecum, CMV can produce perforation and present as an acute abdomen. If CMV colitis is present, computed tomography may show colonic thickening. 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. Colitis and esophagitis may cause fever.

CMV pneumonitis is extremely uncommon. CMV is detected frequently in the bronchoalveolar lavage but is a bystander most of the time and should trigger a search for a more likely causative agent.

CMV neurologic disease includes dementia, ventriculoencephalitis, and polyradiculomyelopathies.⁸ Patients with dementia caused by CMV encephalitis typically have lethargy, confusion, and fever. Cerebrospinal fluid (CSF) typically demonstrates lymphocytic pleocytosis (although a mixture of neutrophils and lymphocytes might be evident), low-to-normal glucose levels, and normal-to-elevated protein levels. 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-related neurologic disease. CMV polyradiculomyelopathy causes a Guillian-Barre–like syndrome characterized by 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 100–200 neutrophils/ μ L and some erythrocytes) accompanied by hypoglycorrhachia and elevated protein levels.

Diagnosis

CMV viremia can be detected by PCR, antigen assays, or culture and is usually, but not invariably, present in end-organ disease. Viremia as detected by one of these assays can be present in disease-free patients with low CD4 cell counts—that is, in the absence of end-organ disease.^{8–13} 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. A negative serum or plasma PCR assay also does not rule out CMV end-organ disease.

Of note, patients with CMV retinitis have CMV DNA detected in the vitreous in around 80% of cases, but in only 70% in the blood, with the remaining cases diagnosed by clinical criteria plus response to therapy.^{14,15} CMV PCR can be particularly useful in assessing CSF or vitreous or aqueous humor specimens; a positive result is highly suggestive that CMV is the cause of end-organ disease. However, PCR assays are not standardized; therefore, sensitivity, specificity, and interassay comparability are not clearly delineated.

Presence of serum antibodies to CMV is not diagnostically useful, although a negative immunoglobulin G antibody level indicates that CMV is unlikely to be the cause of the disease process.

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, diagnosis may be difficult and PCR of aqueous or vitreous specimens for CMV and other pathogens—especially herpes simplex virus, varicella zoster virus, and toxoplasmosis—can be useful for establishing the diagnosis.

CMV colitis is usually diagnosed based on demonstration of mucosal ulcerations on endoscopic examination, combined with with histopathologic demonstration of characteristic intranuclear and intracytoplasmic inclusions.^{2,16} CMV esophagitis is diagnosed by presence of ulcers of the distal esophagus and biopsy evidence of intranuclear inclusion bodies in the endothelial cells with an inflammatory reaction at the edge of the ulcer.² Specimens may contain many inclusion bodies or rare, isolated inclusion bodies. The significance of such inclusion bodies is determined by clinical judgment plus the presence or absence of other plausible etiologies.

Culturing CMV 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 have positive cultures in the absence of clinical disease.¹³

The diagnosis of CMV pneumonitis is difficult and 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.¹¹

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.^{3,9,12}

Preventing Exposure

HIV-infected patients who belong to groups with relatively low seroprevalence rates for CMV and, therefore, cannot be presumed to be seropositive may be tested for antibody to CMV (**BIII**). That includes individuals who have not had contact with men who have sex with men or used injection drugs, and patients without extensive exposure to children in day care centers. HIV-infected adolescents and adults should be advised that CMV is shed in semen, cervical secretions, and saliva and that latex condoms must always be used during sexual contact to reduce the risk of exposure to CMV as well as other sexually transmitted pathogens (**AII**).

HIV-infected adults and adolescents who are CMV-seronegative and provide child care (or are parents of children in day care facilities) should be informed that they are at increased risk of acquiring CMV infection (**BI**). Risk of acquiring CMV infection can be diminished with optimal hygienic practices, such as handwashing and use of latex gloves (**AIII**). HIV-infected adolescents, and adults who are seronegative for CMV and who require blood transfusion should be given only CMV antibody-negative or leukocyte-reduced cellular blood products in nonemergency situations (**BIII**).

Preventing Disease

CMV end-organ disease is best prevented using ART to maintain the CD4 count >100 cells/mm³. Before ART was widely available, daily use of oral ganciclovir (no longer marketed in the United States) for primary prophylaxis significantly reduced incidence of CMV disease in a randomized, placebo-controlled trial.¹⁷ However, such prophylactic therapy never became standard of care because of the cost, toxicity, and number-needed-to-treat to reduce disease. More recently, another randomized, placebo-controlled trial addressed whether valganciclovir (the current standard oral agent for treatment of CMV disease) might reduce CMV end-organ disease in AIDS patients at high risk (CD4 count <100 cells/mm³ and CMV viremia detected by plasma CMV DNA PCR assay) in the era of modern ART.¹⁸ This study failed to show a benefit for such preventive therapy; therefore, valganciclovir primary prophylaxis **is not recommended** either in patients who will be receiving ART, or in patients who will not be receiving ART (**AI**).

The primary method for preventing severe CMV disease is recognizing the early manifestations of the disease and instituting proper therapy. Patients should be made aware of the implications of increased floaters in the eye and should be advised to assess their visual acuity regularly using simple techniques, such as reading newsprint (**BIII**). In the pre-modern ART era, some specialists recommended ophthalmologic examinations every 3 to 4 months for patients with CD4 cells <50 cells/mm³, as 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.

Treating Disease

CMV retinitis should ideally be treated with the active participation of an ophthalmologist who is familiar with the diagnosis and management of retinal disease.

Oral valganciclovir (**AI**), intravenous (IV) ganciclovir (**AI**), IV ganciclovir followed by oral valganciclovir (**AI**), IV foscarnet (**AI**), and IV cidofovir (**BI**) are all effective treatments for CMV retinitis.^{7,19-26} The ganciclovir implant, a surgically-implanted reservoir of ganciclovir, which lasts approximately 6 months, also is very effective but it no longer is being manufactured. In its absence, some clinicians will use intravitreal injections of ganciclovir or foscarnet in conjunction with oral valganciclovir, at least initially, to provide immediate high intraocular levels of drug and presumably faster control of the retinitis (**AIII**). The choice of initial therapy for CMV retinitis should be individualized based on the location and severity of the lesion(s), the level of underlying immune suppression, and other factors such as concomitant

medications and ability to adhere to treatment (**AIII**). Systemic therapy has been documented to reduce CMV involvement of the contralateral eye,¹⁹ to reduce CMV visceral disease, and to improve survival.^{20,27} Prevention of contralateral eye involvement, visceral disease, and the benefits on survival should be considered when choosing among oral, IV, and local options. Given the evident benefits of systemic treatment, when medically and logistically feasible, treatment regimens for CMV retinitis should include a systemic component. There have been few comparative trials comparing 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. Thus, clinical judgment must be used when choosing a regimen.²¹⁻²⁵ Early clinical trials were conducted with oral ganciclovir, a preparation with poor bioavailability that is no longer marketed in the United States. In these guidelines, valganciclovir has replaced oral ganciclovir in recommendations even though the best data in some situations come from early trials with oral ganciclovir.

In studies conducted in the pre-ART era,²³ ganciclovir intraocular implant (no longer available) plus oral ganciclovir was superior to once-daily IV ganciclovir for treatment of CMV retinitis. Assuming that this observation can be extended to other combinations of systemically and locally administered drugs, HIV specialists often recommend intravitreal ganciclovir or foscarnet injections plus oral valganciclovir as the preferred initial therapy for patients with immediate sight-threatening lesions (within 1500 microns of the fovea) (**AIII**). Intravitreal injections deliver high concentrations of the drug to the target organ immediately while steady-state concentrations in the eye are achieved with systemically delivered medications.¹⁹ For patients with small peripheral lesions, oral valganciclovir alone often is adequate (**AI**).

Because ART can control CMV retinitis without anti-CMV therapy in patients who develop substantial immune recovery, some clinicians may consider not treating small peripheral CMV lesions with anti-CMV therapy in ART-naïve patients who are initiating ART. However, this strategy has multiple potential drawbacks: ART can take 3 to 6 months to fully control HIV replication and stimulate sufficient immune recovery to control the retinitis. 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 there is sufficient immune recovery 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 patients with CMV retinitis and immune compromise.^{13,20,26,28} In addition data from the ART era demonstrate that the use of systemic therapy for patients with CMV retinitis is associated with decreased retinitis progression, contralateral eye involvement, and visceral disease, as well as a reduction in mortality.²⁷ Moreover, some reports in the current era indicate that only 50% of some patient populations with CMV retinitis will experience immune recovery sufficient to meet criteria for discontinuation of anti-CMV therapy.²⁹ Therefore, even in ART-naïve patients with small peripheral lesions, treatment with systemic anti-CMV therapy, such as oral valganciclovir for the first 3 to 6 months until ART has induced immune recovery will be beneficial (**AII**). Systemic therapy is given twice daily for the first 14 to 21 days (induction) followed by once daily dosing (maintenance) until immune reconstitution occurs (see When to Stop Maintenance Therapy below).

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. Some HIV specialists would withhold therapy for mild disease if ART is to be initiated soon or can be optimized (**CIII**). IV ganciclovir generally is the therapy of choice, therapy can be switched to oral valganciclovir once the patient can tolerate oral medications (**BI**); foscarnet can be used as an alternative if ganciclovir-related toxicity is treatment limiting or in unusual 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). Optimizing ART is important, as in all types of CMV disease (BIII). The optimal duration of therapy and the role of oral valganciclovir have not been established.

Special Considerations with Regard to Starting Antiretroviral Therapy

Visual impairment caused by complications of immune reconstitution inflammatory syndrome (IRIS), such as macular edema, may occur in patients who have active CMV retinitis and those who have had CMV retinitis in the recent or distant past. One historical controlled study suggested a substantial increase in immune reconstitution uveitis (IRU, described below) in association with immediate as opposed to deferred initiation of ART (71% vs. 31%),³⁰ suggesting that a delay in therapy until retinitis was controlled might be beneficial in reducing the likelihood or severity of IRU. However, this strategy must be weighed against the potential for occurrence of other OIs if ART initiation is delayed.

CMV replication usually is controlled within 1 to 2 weeks after anti-CMV therapy is initiated, and in the current era, the rate of clinically significant IRU following initiation of ART appears to be low (approximately 0.04 per person-year).²⁹ Most experts would not delay ART for more than 2 weeks after starting anti-CMV therapy for retinitis or for 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 through a dilated pupil 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. The purpose of such examinations is to evaluate efficacy of treatment and to detect complications such 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 relapse. For patients who have experienced immune recovery, the frequency of ophthalmologic follow-up can be decreased to every 3 months, but clinicians should be aware that relapses and other 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 hematopoietic growth factors.^{31,32} Adverse effects of foscarnet include nephrotoxicity, and electrolyte abnormalities; seizures occur, characteristically in the context of renal insufficiency, and anemia.

In patients receiving ganciclovir or foscarnet, complete blood counts, serum electrolytes (including potassium, magnesium, calcium, and phosphorus), and renal function should be monitored twice weekly during induction and at least once weekly during maintenance therapy (AIII). Cidofovir is associated with dose-related nephrotoxicity, neutropenia, uveitis, and hypotony. In patients receiving IV cidofovir, blood urea nitrogen and creatinine levels should be tested and urinalysis performed before each infusion; drug administration is contraindicated if renal dysfunction or significant proteinuria is detected. IV cidofovir requires prehydration and oral probenecid before administration. Periodic ophthalmologic examinations are needed to monitor for cidofovir-associated uveitis or hypotony even when organ dysfunction does not appear to include retinitis. Intraocular injections can be associated with bacterial or fungal infections, hemorrhage, or retinal detachment.

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 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.³³⁻³⁷ The estimated incidence of IRU is 0.02/person-year after immune recovery.³⁸ Ocular complications of IRU include macular edema and development of epiretinal membranes, which can cause loss of vision.

Treatment of IRU usually consists of some type of corticosteroid therapy. The benefit of anti-CMV therapy is unclear.^{33,39} 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**).⁴⁰ IRU can occur even 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.

Early after the initiation of ART, patients remain at risk for development of CMV retinitis.⁴¹ Development of CMV retinitis in the setting of recent ART initiation should be treated with systemic anti-CMV therapy, similarly to any patient with CMV retinitis, and continuing the same ART regimen (**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 relapse is most likely in patients who do not have substantial immune reconstitution after initiation or optimization of ART.⁴² Treatment failure also may be a result of inadequate anti-CMV drug levels in the eye or CMV drug resistance. Many experts believe that early relapse is most often caused by the limited intraocular penetration of systemically administered drugs.^{39,43,44}

When relapse occurs in patients receiving maintenance therapy, retinitis usually can be controlled with re-induction with the same drug as used for maintenance followed by re-institution of maintenance therapy, although results are likely to be seen for progressively shorter periods with each relapse (**BIII**).⁴⁵ 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 multiple relapses of retinitis (**CIII**).⁴⁵ That drug combination, however, is associated with substantial toxicity.

Drug resistance occurs in patients receiving long-term anti-CMV therapy.⁴⁶⁻⁴⁹ Rates of approximately 25% per person-year were reported in the pre-ART era^{46,50,51} and reported rates are similar for ganciclovir, foscarnet, and cidofovir.^{46,47} In the ART era, the rate of resistance appears to be lower (approximately 5% per person-year).⁵² 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.^{48,53-57} 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 cidofovir⁵⁵ and occasionally to foscarnet.⁵⁶ Although early relapse typically is not a result of resistance, later relapse may be. Because patients with resistant CMV are most likely to have mutations in the CMV UL97 gene, and because a limited number of mutations are responsible for most drug resistance, susceptibility testing in peripheral blood using a CMV DNA PCR assay and sequencing for CMV UL97 mutations or using a point mutation assay^{58,59} may be reasonable for patients who relapse on therapy.⁶⁰ Virus in the eye and in the blood are identical in more than 90% of cases;¹⁴ 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, but not all, cases.⁶¹

Sequencing the UL97 gene from PCR-amplified specimens from blood can be accomplished in less than 48 hours, correlates well with conventional drug susceptibility testing and clinical outcomes,⁶⁰ and therefore has clinical utility for patients in whom therapy has failed. Conventional methods of culture and susceptibility testing and viral sequencing often are not available in clinical laboratories because they are too time-consuming or costly. By themselves, peripheral blood CMV viral load measurements have poor positive predictive value for treatment failure. UL97 mutants usually respond to foscarnet, as do some UL54 mutants. Patients with high-level ganciclovir-resistant isolates will require a switch to alternative therapy.⁶² Many clinicians will treat with a series of intravitreal injections of foscarnet and/or systemic foscarnet (**CIII**).

Preventing Recurrence

When to Start Maintenance Therapy

With regard to CMV retinitis, after induction therapy, chronic maintenance therapy should be continued,^{8,12,19,22,63} until immune reconstitution occurs as a result of ART (**AI**). Regimens demonstrated to be effective for chronic suppression in randomized, controlled clinical trials include parenteral ganciclovir, oral valganciclovir, parenteral foscarnet, combined parenteral ganciclovir and foscarnet, and parenteral cidofovir. Intravitreal therapy alone will not protect against contralateral or extraocular disease, however: oral or intravenous therapy must be administered to prevent disease in the contralateral eye until immune reconstitution has occurred. Repetitive intravitreal injections of fomivirsen also have been demonstrated to be effective in randomized clinical trials, but that drug, is no longer available in the United States.

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

Repetitive intravitreal injections of ganciclovir or of foscarnet have appeared to be effective for maintenance therapy of CMV retinitis in uncontrolled case series. Because of the risk of hypotony and uveitis, and the substantially increased risk of immune recovery uveitis with intravitreal cidofovir, intravitreal administration of cidofovir should be reserved for extraordinary cases.⁶⁴

CMV retinitis requires a chronic regimen until an increase in CD4 cell count to >100 cells/mm³ in response to ART has been sustained for 3 to 6 months (**AI**).⁶⁵

After resolution of the acute CMV syndrome, and after initiation of effective ART, chronic maintenance therapy is not routinely recommended for CMV gastrointestinal disease, pneumonitis, and central nervous system disease unless there is concurrent retinitis or relapses have occurred (**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/mm³ in response to ART (**AII**).^{4,66-72} Such decisions should be made in consultation with an ophthalmologist. A 3% relapse 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 (relapses have been reported at CD4 cell counts of 1250 cells/mm³). 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 (**BII**).

Relapse of CMV retinitis occurs frequently in patients whose anti-CMV maintenance therapies have been discontinued and whose CD4 counts have decreased to <50 cells/mm³.⁷³ Therefore, reinstatement of maintenance therapy should occur when the CD4 count has decreased to <100 cells/mm³ (**AIII**).

Special Considerations During Pregnancy

The diagnostic considerations among pregnant women are the same as for non-pregnant women. Indications for treatment of CMV infection during pregnancy are the same as for nonpregnant HIV-infected adults (**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 as discussed should then be started after the first trimester.

Ganciclovir is embryotoxic among rabbits and mice and teratogenic (i.e., cleft palate, anophthalmia, aplastic kidney and pancreas, and hydrocephalus) in rabbits.⁷⁴⁻⁷⁶ Safe use in human pregnancy after organ

transplantation has been reported,^{74,75} and use in late pregnancy to treat fetal CMV infection in non-HIV-infected women has also been reported.⁷⁷

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.⁷⁸ 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 studies, and ease of use of the various drugs, valganciclovir is recognized as the treatment of choice during pregnancy (**BIII**). No experience has been reported with the use of valganciclovir in human pregnancy, but concerns are expected to be the same as with ganciclovir. 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 different CMV strains during pregnancy⁷⁹ can all lead to in utero transmission and congenital CMV. Although about one-third of newborns acquire congenital CMV infection after primary infection, only approximately 1% to 2% of newborns acquire CMV after a recurrent infection in HIV-uninfected women. Because >90% of HIV-infected pregnant women are CMV antibody positive in the majority of studies, the risk for symptomatic infection in the fetus is expected to be low.⁸⁰⁻⁸⁴ However, recent studies of HIV-exposed infants suggest that rates of congenital CMV may be increased, ranging from 2% to 7%,^{85,86} with higher rates in babies born to mothers with CD4 <200 cells/mm³ and in HIV-infected infants. Maternal ART in pregnancy has been associated with decreased rates of perinatal/early postnatal CMV and occurrence of related clinical symptoms among HIV-infected and HIV-exposed infants.⁸⁷

Up to 90% of infants who are symptomatic at birth will have serious long-term problems, including hearing loss, visual impairment, mental retardation and/or cognitive impairment, but only 5% to 15% of asymptomatic newborns are at risk for serious long-term impairment. However, asymptomatic congenital CMV infection is associated with late-onset hearing loss in non-HIV-infected children.⁸⁸ In women with CMV disease in pregnancy, the fetus should be monitored by periodic ultrasound after 20 weeks gestation, although from studies in HIV-uninfected populations, only about 5% to 25% of infected newborns have ultrasound evidence of congenital infection (e.g., cerebral calcifications, abdominal and liver calcifications, hydrops, microcephaly, ventriculomegaly, ascites, and echogenic fetal bowel). Any ultrasound findings suspicious for congenital CMV infection should prompt consideration of invasive testing (i.e., amniocentesis) for definitive diagnosis. Although invasive fetal testing was associated with increased rates of perinatal HIV transmission in early studies,⁸⁹ more recent data suggests that risk may be minimal in women on effective ART and with undetectable HIV-RNA levels.⁸⁹⁻⁹¹ Referral to a maternal-fetal medicine specialist for evaluation, counseling, and potential further testing is recommended.

If fetal CMV infection is confirmed, there is no standard therapy for *in utero* treatment. A non-randomized trial of CMV hyperimmune globulin suggested potential benefit of passive immunotherapy for treatment of acute fetal CMV infection, with decreased incidence of having a symptomatic newborn at birth⁹² and regression of fetal cerebral abnormalities.⁹³ 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.⁹⁴ A larger placebo-controlled trial of CMV hyperimmune globulin currently is underway at NICHD Maternal Fetal Units across the United States [ClinicalTrials.gov Identifier NCT01376778].

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 (page 1 of 2)

Preventing CMV Disease

- CMV end-organ disease is best prevented by using ART to maintain CD4 count >100 cells/mm³.

Managing CMV Retinitis

- The choice of initial therapy for CMV retinitis should be individualized, based on location and severity of the lesion(s), the level of immunosuppression, and other factors (e.g., concomitant medications, ability to adhere to treatment) **(AIII)**.
- Given the evident benefits of systemic therapy in preventing contralateral eye involvement, reduce CMV visceral disease and improve survival, whenever feasible, treatment should include systemic therapy.
- The ganciclovir ocular implant, which is effective for treatment of CMV retinitis, is no longer available.

Initial Therapy Followed by Chronic Maintenance Therapy—For Immediate Sight Threatening Lesions (within 1500 microns of the fovea)

Preferred Therapy:

- Intravitreal injections of ganciclovir (2 mg/injection) or foscarnet (2.4 mg/injection) for 1–4 doses over a period of 7–10 days to provide higher intraocular levels of drug and faster control of the infection until steady state intraocular ganciclovir concentrations are achieved **(AIII)**; *plus*
- Valganciclovir 900 mg PO BID for 14–21 days, then 900 mg once daily **(AI)**

Alternative Therapy

- Intravitreal injections as listed above **(AIII)**; *plus* one of the following systemic 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*
 - Foscarnet 60 mg/kg IV q8h or 90 mg/kg IV q12h for 14–21 days, then 90–120 mg/kg IV q24h **(AI)**, *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) **(BI)**.

Note: This regimen should be avoided in patients with sulfa allergy because of cross hypersensitivity with probenecid

For Peripheral Lesions

- Administer one of the systemic antiviral therapy listed above 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 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/mm³ for 3 to 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 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/mm³ **(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*
- For mild cases: If ART can be initiated or optimized without delay, withholding CMV therapy may be considered **(CII)**.

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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