Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children

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Cytomegalovirus (CMV) antibody testing is recommended at age 1 year and then annually for CMV-seronegative, HIV-infected infants and children who are immunosuppressed (i.e., CD4 T-lymphocyte (CD4) cell count <100 cells/mm$^3$ or CD4 percentage <10%) (BII).

HIV-infected children aged <5 years who are CMV-infected and severely immunosuppressed (i.e., CD4 cell count <50 cells/mm$^3$ or CD4 percentage <5%) should have a dilated retinal examination performed by an ophthalmologist every 6 months (AII).

CMV end-organ disease is best prevented by antiretroviral therapy (ART) to maintain the CD4 cell count >100 cells/mm$^3$ in children aged ≥6 years, or CD4 percentage >10% in children <6 years (BIII). Prophylaxis with valganciclovir can be considered for HIV-infected children aged ≥6 years who are CMV-seropositive and have CD4 cell counts <50 cells/mm$^3$ and for HIV-infected children aged <6 years who are CMV-seropositive and have a CD4 percentage <5% (CIII). Cessation of primary prophylaxis can be considered when the CD4 cell count is >100 cells/mm$^3$ for children ≥6 years of age, or >10% in children <6 years (CIII).

Intravenous (IV) ganciclovir therapy (6 mg/kg/dose administered every 12 hours) for 6 weeks can be considered for HIV-exposed or HIV-infected infants who have symptomatic congenital CMV disease involving the central nervous system (CNS) (BII).

For HIV-infected infants and children, IV ganciclovir is the drug of choice for initial treatment for acquired CMV disease, including retinitis and other end-organ disseminated CMV disease (e.g., colitis, esophagitis, CNS disease) (AI*). Oral valganciclovir has not been evaluated in HIV-infected children with CMV retinitis, but is an option primarily for older children who weigh enough to receive the adult dose and formulation of valganciclovir (CIII). Transition from IV ganciclovir to valganciclovir oral solution can be considered for younger patients who improve on IV therapy (CIII).

Foscarnet is an alternative drug for treating CMV disease or for use in ganciclovir-resistant CMV infections in HIV-infected children (AI*).

Combination therapy with ganciclovir and foscarnet delays progression of retinitis in certain patients in whom monotherapy fails and can be used as initial therapy in children with sight-threatening disease (BIII).

Combination treatment with IV ganciclovir and foscarnet may be preferable as initial therapy to stabilize CMV neurologic disease and maximize response (BII*).

Many experts would initially treat early first relapse of retinitis with reinduction using the same drug, followed by reinstitution of maintenance therapy (AII*). If drug resistance is suspected, change to an alternative drug is reasonable (AIIII). Combination IV ganciclovir and foscarnet can be considered.

After induction therapy, secondary prophylaxis (chronic maintenance therapy) is given for most forms of CMV disease until immune reconstitution or, in absence of immune reconstitution, for the remainder of a patient’s life (AI*). Regimens recommended for chronic suppression include IV ganciclovir, oral valganciclovir, IV foscarnet, combined IV ganciclovir and foscarnet, and parenteral cidofovir (AI*).

Chronic maintenance therapy is not routinely recommended for gastrointestinal disease but should be considered if relapses occur (BII*). A role for maintenance therapy for CMV pneumonitis has not been established (CIII).

Discontinuing secondary prophylaxis may be considered for children who are receiving ART and have a sustained (such as >6 months) increase in CD4 cell count, defined as an increase in CD4 percentage to >15% for children aged <6 years, or an increase in CD4 cell count to >100 cells/mm$^3$ for children aged ≥6 years (CIII).

All patients with CMV ophthalmic disease in whom anti-CMV maintenance therapy has been discontinued should continue to undergo regular ophthalmologic monitoring at 3- to 6-month intervals for early detection of CMV relapse and for immune reconstitution uveitis (AII*).

Secondary prophylaxis should be re instituted in HIV-infected children in whom it was discontinued because of immune reconstitution when the CD4 percentage decreases to <15% in those aged <6 years and when the CD4 cell count decreases to <100 cells/mm$^3$ in those aged ≥6 years (BIII).
Epidemiology

Infection with human cytomegalovirus (CMV) is common and usually not apparent; CMV can be acquired in utero, or during infancy, early childhood, or adolescence. Transmission can occur vertically from an infected woman to her offspring; horizontally by contact with virus-containing breast milk, saliva, urine, or sexual fluid; through transfusion of infected blood; or transplantation of infected organs. During infancy and early childhood, infection usually occurs secondary to ingestion of virions in breast milk of CMV-infected mothers or from exposure to virus shed in saliva or urine. Infection occurs at younger ages in locations where sanitation is less than optimal. Among adolescents, sexual transmission is the major mode of CMV acquisition.

Age-related prevalence of infection varies widely depending on living circumstances and social customs. Breastfeeding, child-rearing practices, crowding, sanitation, and sexual behavior most likely influence age-related variations in CMV prevalence. Where rates of maternal seropositivity are high and breastfeeding is common, more than half of infants acquire CMV during the first year of life. Group care of children facilitates spread of CMV, especially in toddlers, and leads to higher prevalence of infection in children who attend child care centers and in their caregivers. In Africa, Asia, and Latin America, most children are infected with CMV before adolescence. In the United States and western Europe, the prevalence of antibody to CMV in adults from middle and upper socioeconomic strata is 40% to 60%, whereas the prevalence in low-income adults is ≥80%. Overall, among U.S. women of childbearing age, the prevalence of CMV infection is 50% to 80%, with the highest prevalence in women in lower socioeconomic strata. The prevalence of CMV infection among HIV-infected pregnant women is higher than in the general population, with approximately 90% of HIV-infected pregnant women coinfected with CMV.

CMV is the most common congenitally transmitted infection, with incidence estimates in live-born infants in the United States ranging from 0.5% to 1.2%. Congenital (in utero) CMV infection occurs most commonly among infants born to women who have primary CMV infection during pregnancy. Following primary infection during pregnancy, the rate of transmission to the fetus is approximately 30% to 40%. In comparison, the rate of congenital infection after non-primary maternal CMV infection is believed to be significantly lower (range: 0.15%–1.0%). More recent studies demonstrate that in utero transmission of non-primary maternal infection can occur because of reactivation of infection in women infected before pregnancy or reinfection with a different CMV strain in CMV-seropositive women.

CMV also can be transmitted from mother to infant during the intrapartum or postpartum periods. Up to 57% of infants whose mothers shed CMV at or around delivery become infected with CMV, and up to 53% of children who are breastfed milk containing infectious virus can become CMV-infected. Symptomatic CMV disease in the infant is much less common when CMV is acquired intrapartum or through breastfeeding than when acquired antenatally and occurs primarily in premature neonates. Long-term sequelae are rare in premature infants who acquire CMV perinatally or postnatally.

HIV-infected women with CMV infection have a higher rate of CMV shedding from the cervix than do women who are HIV-uninfected (52%–59% and 14%–35%, respectively). The risk for mother-to-infant transmission of CMV may be higher among infants born to women dually infected with CMV and HIV. In one study of 440 infants born to HIV-infected U.S. women, the overall rate of in utero infection was 4.5%, higher than the <2% rate of in utero infection in the general U.S. population. In a more recent study of 367 U.S. infants born to HIV-infected mothers, a 3% prevalence of congenital CMV infection was reported among HIV-uninfected infants born to HIV-infected mothers, suggesting that the rate of congenital CMV infection is similar to or slightly higher than the prevalence of congenital CMV infection among HIV-uninfected mothers. In a study in France, the prevalence of congenital CMV infection among HIV-infected infants was 10.3%, compared with 2.2% in HIV-uninfected infants born to HIV-positive mothers, and the rate of in utero HIV transmission was higher among infants with congenital CMV infection compared with infants without congenital CMV infection.

HIV-infected children appear to be at higher risk of CMV infection during early childhood than are HIV-
uninfected children.\textsuperscript{22} The rate of CMV acquisition in HIV-infected children appears to be particularly high during the first 12 months of life but remains higher among HIV-infected than HIV-uninfected children through age 4 years.

CMV disease occurs less frequently among HIV-infected children than HIV-infected adults, but still contributed substantially to morbidity and mortality in the era before combination antiretroviral therapy (cART). In the pre-antiretroviral era, CMV caused 8\% to 10\% of pediatric AIDS-defining illnesses.\textsuperscript{25} Data in HIV-infected adults have shown a 75\% to 80\% decrease in the incidence of new cases of CMV end-organ disease with the advent of cART, with an incidence now estimated to be <6 cases per 100 person-years.\textsuperscript{26} In a study of opportunistic infections in approximately 3,000 children followed in Pediatric AIDS Clinical Trials Group studies during the pre-cART era, the frequency of CMV retinitis was 0.5 cases per 100 child-years and, of other CMV disease, 0.2 cases per 100 child-years.\textsuperscript{27} The rate varied significantly by CD4 T-lymphocyte (CD4) cell percentage; the incidence of CMV retinitis was 1.1 cases per 100 child-years in children with CD4 percentage <15\%, compared with 0.1 case per 100 child-years in children with CD4 percentage >25\%. In the same cohort during the cART era, the overall rate of CMV retinitis was <0.5 per 100 child-years.\textsuperscript{28} In the Perinatal AIDS Collaborative Transmission Study, the incidence of nonocular CMV before and after January 1997 (pre- and post-cART eras) was 1.4 per 100 child-years and 0.1 per 100 child-years, respectively.\textsuperscript{29} Similarly, CMV retinitis declined from 0.7 to 0.0 per 100 child-years.

Symptomatic HIV-infected children coinfected with CMV have a higher rate of CMV viruria than do asymptomatic HIV-infected or HIV-exposed children. Overall, up to 60\% of children with AIDS shed CMV. This compares with one third of all HIV-infected children; 15\% to 20\% of CMV-infected, HIV-exposed but uninfected children; and <15\% of CMV-infected infants not exposed to HIV.\textsuperscript{30}

**Clinical Manifestations**

Approximately 10\% of infants with in utero CMV infection are symptomatic at birth with congenital CMV syndrome (i.e., CMV inclusion disease). The rate of symptomatic CMV infection among infants infected with CMV in utero is higher in HIV-infected infants (23.1\%) than in HIV-uninfected children (6.7\%) even in the cART era.\textsuperscript{24} In studies of cohorts of neonates with symptomatic congenital CMV disease, conditions commonly observed included size that was small for gestational age, petechiae, jaundice, hepatosplenomegaly, chorioretinitis, microcephaly, intracranial calcifications, and hearing impairment.\textsuperscript{31,32} Mortality of children with symptomatic disease is as high as 30\%. Approximately 40\% to 58\% (and in specific cohorts, as many as 90\%) of infants with symptomatic disease at birth who survive have late complications, including substantial hearing loss, mental retardation, chorioretinitis, optic atrophy, seizures, or learning disabilities.\textsuperscript{5,9} Although most children with in utero CMV infection do not have symptoms at birth, 10\% to 15\% are at risk of later developmental abnormalities, sensorineural hearing loss, chorioretinitis, or neurologic defects. Premature neonates who acquire CMV postnatally can be asymptomatic or can have evidence of disease such as hepatitis, thrombocytopenia, or pneumonitis.

HIV disease seems to progress more quickly in HIV-infected children coinfected with CMV than in those without CMV infection.\textsuperscript{22,25,33} In one study from the pre-cART era, 53\% of infants coinfected with HIV and CMV had progression to AIDS or had died by age 18 months, compared with 22\% of HIV-infected children without CMV infection; those with HIV/CMV coinfection also were more likely to have central nervous system (CNS) manifestations (36\% versus 9\%). The relative risk of HIV disease progression in children coinfected with CMV compared with children without CMV was 2.6 (95\% CI: 1.1–6.0).\textsuperscript{22} CMV retinitis is the most frequent severe manifestation of CMV disease among HIV-infected children, accounting for approximately 25\% of CMV AIDS-defining illnesses. CMV retinitis among young HIV-infected children is frequently asymptomatic and discovered on routine examination. Older children with CMV retinitis present similarly to adults, with floaters, loss of peripheral vision, or reduction in central vision. Diagnosis of CMV retinitis is based on clinical appearance with white and yellow retinal infiltrates and associated retinal hemorrhages. A more indolent, granular retinitis also can occur. HIV-infected children with CD4 cell counts
<100 cells/mm³ are more likely than those with higher CD4 cell counts to develop CMV retinitis; however, CD4 cell count is less predictive of risk of CMV disease in young infants, and systemic and localized CMV disease can occur in HIV-infected infants with higher, age-adjusted CD4 cell counts.30,34

End-organ CMV disease has been reported in the lung, liver, gastrointestinal (GI) tract, pancreas, kidney, sinuses, and CNS of HIV-infected children but is rare in the era of cART.34-37 In children with extraocular CMV disease, predominantly nonspecific symptoms (e.g., fever, poor weight gain, loss of developmental milestones with laboratory abnormalities of anemia, thrombocytopenia, and elevated lactic dehydrogenase) are initially observed, although the extent to which CMV or HIV infection themselves contribute to these findings is unclear.30 GI manifestations among HIV-infected children include CMV colitis (the most common GI manifestation), oral and esophageal ulcers, hepatitis, ascending cholangiopathy, or gastritis. Odynophagia is a common presentation of CMV esophagitis, whereas abdominal pain and hematochezia frequently occur with CMV colitis. Sigmoidoscopy in CMV colitis is nonspecific, demonstrating diffuse erythema, submucosal hemorrhage, and diffuse mucosal ulcerations. Esophageal or colonic ulcerations may cause perforation or hemorrhage.

The role of CMV in pulmonary disease among HIV-infected children is difficult to assess because it often is isolated with other organisms (e.g., Pneumocystis jirovecii). Histologic evidence of CMV disease is needed to determine whether active disease is present. CMV pneumonia is an interstitial process with gradual onset of shortness of breath and dry, nonproductive cough; auscultatory findings may be minimal.

CNS manifestations of CMV include subacute encephalopathy, myelitis, and polyradiculopathy (primarily observed in adults but rarely reported in children). The subacute or chronic encephalopathy of CMV can be difficult to differentiate clinically from HIV dementia, with symptoms of confusion and disorientation attributable to cortical involvement. Focal signs can be attributed to lesions in the brainstem. Cerebrospinal fluid (CSF) findings are nonspecific and may include leukocytosis with polymorphonuclear predominance (>50% of patients), elevated protein (75%), and low glucose (30%). However, up to 20% of children with CMV CNS involvement have completely normal CSF indices. CMV also can cause a rapidly progressive, often fatal, CNS disease with cranial nerve deficits, nystagmus, and increasing ventricular size.38

**Diagnosis**

It can be difficult to distinguish CMV infection from CMV disease in HIV-infected children. Because of transplacental transfer of antibody, a positive CMV immunoglobulin G (IgG) antibody assay in an infant aged <12 months can indicate infection in the mother but not necessarily in the infant. In an infant aged >12 months, a positive CMV IgG antibody assay indicates CMV infection of the child but not necessarily active disease. In children of any age, a positive CMV culture or polymerase chain reaction (PCR) assay indicates infection but not necessarily disease.

CMV can be isolated in cell culture from peripheral blood leukocytes, body fluids (e.g., urine, saliva), or tissues. Using centrifugation-assisted shell vial culture amplification techniques, CMV can be detected within 16 to 40 hours of culture inoculation. A positive blood buffy-coat culture establishes CMV infection and increases the likelihood that disease or symptoms were caused by CMV because children with positive blood cultures are at higher risk of end-organ disease. Recovery of virus from tissues (e.g., with endoscopically guided biopsies of GI or pulmonary tissue) provides evidence of disease causation in symptomatic patients. The limitation of this method is that detection of visible cytopathic effects in cell culture takes 1 to 6 weeks. Staining of shell vial culture with CMV monoclonal antibodies or tissue immunostaining for CMV antigens can allow earlier diagnosis of infection. Histopathology demonstrates characteristic “owl’s eye” intranuclear and smaller intracytoplasmic inclusion bodies in biopsy specimens. Staining with monoclonal antibodies for CMV antigens also can be done on cells obtained from bronchoalveolar lavage.

Different methods have been used to detect viral antigen or DNA directly and to identify patients at risk of CMV disease; these include detection of pp65 antigenemia, qualitative and quantitative PCR, and DNA
hybridization. The DNA assays are more sensitive than buffy coat or urine cultures for detecting CMV and can be used to identify patients at higher risk of clinically recognizable disease. CMV DNA detection in CSF by DNA PCR is highly sensitive for CMV CNS disease. Quantitative DNA PCR can be used as a marker for risk of disease and to monitor response to therapy.\textsuperscript{39} Anticipated international standardization of PCR assays for CMV DNA may allow for the establishment of quantitative PCR breakpoints that correlate with CMV disease and facilitate monitoring response to therapy. The National Institute of Standards and Technology and the World Health Organization Expert Committee on Biological Standardization recently developed reference standards for assays for CMV DNA.\textsuperscript{40,41}

To diagnose congenital CMV infection, the gold standard remains a positive viral culture from saliva or urine within the first 21 days of life. Beyond this age, positive cultures can be due to postnatally acquired CMV infection. Other methodologies to diagnose congenital CMV infection (blood or saliva PCR) have been investigated but do not yet replace culture as a recommended diagnostic standard.\textsuperscript{42,43} To diagnose acquired CMV disease, culture, antigenemia, and PCR can be used to provide supportive laboratory evidence for clinically suspected CMV disease. However, these tests may be positive in the absence of clinical disease, due to asymptomatic reactivations, and therefore do not themselves constitute a diagnosis of CMV disease in the absence of clinical findings. Alternatively, localized CMV disease (e.g., GI disease) may not manifest with positive blood tests and laboratory diagnosis may require direct sampling of the involved organ for CMV testing.

**Prevention Recommendations**

**Preventing Exposure**

HIV-exposed infants and HIV-infected children, adolescents, and adults who are seronegative for CMV and require blood transfusion should be administered only CMV antibody-negative or leukocyte-reduced cellular blood products in nonemergency situations (BIII).

HIV-infected adults and adolescents who are child care providers or parents of children in child care facilities should be informed that they are at increased risk of CMV infection (BII*). Risk of CMV infection can be diminished by optimal hygienic practices (e.g., hand-washing) (AIII). Sexually active adolescents are at risk of CMV acquisition through oral-oral contact (kissing) and genital-genital contact; the latter risk may be decreased with condom use.

**Preventing First Episode of Disease**

The primary methods of preventing severe CMV disease are prevention of severe immunosuppression by treating with cART and recognition of the early manifestations of disease. CMV antibody testing is recommended at age 1 year and then annually thereafter for CMV-seronegative HIV-infected infants and children who are immunosuppressed (e.g., CD4 cell count <100 cells/mm\textsuperscript{3} or CD4 percentage <10%) (BII). HIV-infected children aged <5 years who are CMV-infected and severely immunosuppressed (e.g., CD4 cell count <50 cells/mm\textsuperscript{3} or CD4 percentage <5%) should have a dilated retinal examination performed by an ophthalmologist every 6 months (AIII). Older children should be counseled to report floaters in the eye and visual changes, similar to the recommendation for adults (BIII). Since the advent of cART, CMV end-organ disease has diminished to such an extent that primary prophylaxis with antiviral agents in CMV- and HIV-coinfected people usually is not recommended (BIII). CMV end-organ disease is best prevented by ART to maintain the CD4 cell count >100 cells/mm\textsuperscript{3} (CD4 percentage >10% in children <6 years). If this is not possible, prophylaxis with valganciclovir can be considered for HIV-infected children aged ≥6 years and adolescents who are CMV-seropositive and have CD4 cell counts of <50 cells/mm\textsuperscript{3}, and for young HIV-infected children aged <6 years who are CMV-seropositive and have a CD4 percentage <5% (CIII). Data supporting the efficacy of antiviral prophylaxis against CMV in pediatric HIV-infected patients are lacking, however, and CMV disease has been observed in children with higher CD4 cell counts than those suggested for primary prophylaxis.\textsuperscript{27} A randomized study of ganciclovir prophylaxis in adult patients with AIDS and low CD4 counts did not show efficacy, and ganciclovir is associated with hematologic toxicity.\textsuperscript{44} Therefore,
ART remains the preferred approach to prevent CMV disease in HIV-infected children.

Valganciclovir dosing in neonates and young infants has been defined in non-HIV-infected patients with symptomatic congenital CMV disease, with a 16 mg/kg body weight dose of oral valganciclovir producing similar systemic exposure to a 6 mg/kg body weight dose of intravenous (IV) ganciclovir.45 In children aged 4 months to 16 years, the dose should be based upon body surface area (BSA) and creatinine clearance (CrCl), with the dose in milligrams = 7 x BSA x CrCl (calculated using a modified Schwartz formula); if the calculated Schwartz CrCl exceeds 150 mL/min/1.73m², then a maximum value of 150 mL/min/1.73m² should be used in the equation.46 All calculated doses should be rounded to the nearest 25-mg increment for the actual deliverable dose. If the calculated dose exceeds 900 mg, a maximum dose of 900 mg should be administered.

Valganciclovir oral solution is the preferred formulation for children aged 4 months to 16 years because it provides the ability to administer a dose calculated according to the formula above; however, valganciclovir tablets can be used if the calculated doses are within 10% of available tablet strength (450 mg).

Asymptomatic congenital CMV infection is associated with late-onset hearing loss in HIV-uninfected children.32 Therefore, infants of mothers who were infected with CMV during pregnancy or those in whom in utero HIV transmission has been documented should be evaluated for the presence of congenital, asymptomatic CMV infection by urine shell vial testing (CIII). Some experts recommend testing all infants born to HIV-infected mothers for congenital CMV infection, because HIV transmission to infants may not be clearly defined within the 21-day window for congenital CMV testing. Infants with congenital CMV infection (symptomatic and asymptomatic) should be evaluated for hearing loss at 6-month intervals for at least the first 3 years of life (AII).47

Discontinuing Primary Prophylaxis

Because primary prophylaxis with antiviral agents in individuals coinfected with CMV and HIV usually is not recommended (as discussed above), consideration of discontinuing primary prophylaxis usually is unnecessary. When valganciclovir primary prophylaxis is provided, cessation of prophylactic treatment can be considered when the CD4 cell count is >100 cells/mm³ for children aged ≥6 years, or CD4 percentage >10% in children aged <6 years (CIII).

Treatment Recommendations

Treating Disease

Treatment of newborns who have symptomatic congenital CMV disease involving the CNS with IV ganciclovir for 6 weeks has been evaluated in a series of clinical trials conducted by the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group;48,49 all infants in these studies were HIV-uninfected. Infants receiving therapy cleared their urine of CMV by culture by the end of the 6-week treatment period, but they all experienced a rebound in their viruria after the drug was discontinued.48 In a Phase III, randomized, controlled trial, infants with CNS disease who received IV ganciclovir for 6 weeks were less likely to have hearing deterioration over the first 2 years of life than were infants receiving no antiviral therapy.49 Treated infants also had more rapid resolution of liver enzyme abnormalities and a greater degree of growth during the course of therapy. They also experienced fewer neurodevelopmental delays at 1 year of life than did untreated infants.50 However, approximately two-thirds of the infants developed substantial neutropenia during therapy.49 Among patients developing neutropenia, 48% required dose modification, but most were able to complete the 6 weeks of therapy.

On the basis of these results, IV ganciclovir therapy (6 mg/kg body weight/dose administered every 12 hours) for 6 weeks can be considered for HIV-exposed or HIV-infected infants who have symptomatic congenital CMV disease involving the CNS (BI). If during the 6 weeks of therapy an infant is confirmed as HIV infected, some experts might recommend treatment for a longer period (>6 weeks), but the benefit of extended therapy is unproven (CIII). A controlled trial conducted by the Collaborative Antiviral Study Group of 6 weeks versus 6 months of oral valganciclovir in HIV-uninfected infants with symptomatic
congenital CMV disease is nearing completion. Neonates with symptomatic congenital CMV disease can be referred to a pediatric infectious diseases specialist for consideration of ganciclovir or valganciclovir therapy and long-term monitoring for sequelae (AI).45,49

CMV retinitis should be managed in collaboration with an experienced ophthalmologist and CMV treatment should be instituted in addition to cART. IV ganciclovir, oral valganciclovir, IV fosarnet, and IV cidofovir, and the ganciclovir intraocular implant coupled with valganciclovir are all effective treatments for CMV retinitis in HIV-infected adults (AI*).51-55 Ganciclovir intraocular implant, however, is no longer available from the manufacturer for treatment with CMV retinitis. For HIV-infected infants and children, IV ganciclovir is the drug of choice for initial treatment (induction therapy) for acquired CMV disease, including CMV retinitis and other end-organ disseminated CMV disease (e.g., colitis, esophagitis, CNS disease) (AI*). Oral valganciclovir, a prodrug of ganciclovir, is one of the first-line treatments for HIV-infected adults with CMV retinitis (AI*)53 and is an option in older children who weigh enough to receive the adult dose and tablet formulation of valganciclovir (CIII). The drug is well absorbed from the GI tract and rapidly metabolized to ganciclovir in the intestine and liver. Valganciclovir oral solution has not been studied in pediatric patients for treatment of CMV retinitis, but consideration can be given to its use for transitioning from IV ganciclovir to oral valganciclovir to complete treatment and/or for secondary prophylaxis once improvement in retinitis is noted (CIII).

An alternative drug for treating CMV disease or for use in ganciclovir-resistant CMV infections in HIV-infected children is fosarnet (AI*). Fosarnet used as suppressive therapy has been associated with increased length of survival relative to ganciclovir in HIV-infected adults. Doses should be modified in patients with renal insufficiency. Cidofovir is effective in treating CMV retinitis in adults who are intolerant of other therapies. Cidofovir has not been studied in children with CMV disease, but can be considered when other options cannot be used (CIII).

Combination therapy with ganciclovir and fosarnet delays progression of retinitis in certain patients in whom monotherapy fails34,53,56,57 and can be used as initial therapy in children with sight-threatening disease (BIII). Combination therapy also has been used for adults with retinitis that has relapsed on single-agent therapy. However, substantial rates of adverse effects are associated with combination therapy.

Intravitreous injections of ganciclovir, fosarnet, or cidofovir have been used to control retinitis, but biweekly intraocular injections are required. Data are limited in children, and biweekly injection is impractical for use in most children (BIII). Implantation of an intravitreous ganciclovir medication-release device in the posterior chamber of the eye also has been used in HIV-infected adults and adolescents. In adults, the combination of oral valganciclovir with a ganciclovir sustained-release intraocular implant, replaced every 6 to 9 months, was superior to daily IV ganciclovir in preventing relapse of retinitis, and intraocular ganciclovir implant plus IV ganciclovir or oral valganciclovir was preferred by some adult HIV specialists for initial treatment of patients who have sight-threatening CMV lesions adjacent to the optic nerve or fovea (AI).51-55 Use of systemic therapy in addition to the ocular implant may reduce development of retinitis in the contralateral eye. Because the ganciclovir implant is no longer available from the manufacturer, this route of administration is currently not available for treatment and chronic suppression of CMV retinitis in older children large enough to receive the intraocular implant and oral valganciclovir.

Small peripheral lesions can be treated with systemic therapy without local treatment (BII*). Intraocular implants have not been studied in patients younger than age 9 years and were not recommended in children aged <3 years because of the small size of their eyes (AIII). Intraocular cidofovir is not recommended in children because of lack of data and the risk of hypotony in adults (AIII).

For acquired CMV neurologic disease, prompt initiation of therapy is critical for an optimal clinical response, as well as ART to enable immune reconstitution. Levels of ganciclovir in the CSF are 24% to 70% of plasma levels, and levels in the brain are approximately 38% of plasma levels.58 Fosarnet concentrations in the CSF are about two-thirds of those in serum.59 Hence, combination treatment with ganciclovir and
foscartern may be preferable as initial therapy to stabilize disease and maximize response (BII*). However, this approach is associated with substantial rates of adverse effects, and optimal treatment for neurologic disease in children receiving optimized cART is unknown.

Patients with AIDS and recipients of solid organ transplants who have GI disease attributed to CMV appear to benefit from ganciclovir therapy (AI*). Limited and uncontrolled data suggest that ganciclovir therapy is useful in patients with AIDS and CMV pneumonia (BII*). As with other CMV disease, antiviral management for CMV disease should also include cART.

Monitoring Response to Therapy and Adverse Events (Including IRIS)

CMV retinitis should be managed in concert with an experienced ophthalmologist. Recommendations for HIV-infected adults include indirect ophthalmoscopy through a dilated pupil performed at diagnosis of CMV retinitis, after completion of induction therapy, 1 month after initiation of therapy, and monthly thereafter while patients are on anti-CMV treatment; recommendations should be similar for HIV-infected children with CMV retinitis (AIII). Monthly fundus photographs using a standardized photographic technique that documents the appearance of the retina provide the optimum method for following patients and detecting early relapse (AIII). For patients who have experienced immune recovery, the frequency of ophthalmologic follow-up can be decreased to every 3 months. However, because relapse of retinitis can occur in patients with immune recovery, regular ophthalmologic follow-up still is needed.

The major side effects of ganciclovir and valganciclovir are myelosuppression (i.e., anemia, neutropenia, and thrombocytopenia) and renal toxicity. Dose reduction or interruption because of hematologic toxicity may be necessary in up to 40% of patients receiving IV ganciclovir; granulocyte colony-stimulating factor can be used to ameliorate neutropenia. The main toxicities of foscartern are decreased renal function and metabolic derangements. Renal toxicity and foscartern binding to divalent metal ions, such as calcium, lead to metabolic abnormalities in approximately one-third of patients, and serious electrolyte imbalances (including abnormalities in calcium, phosphorus, magnesium, and potassium levels) and secondary seizures, cardiac dysrhythmias, abnormal liver transaminases, and CNS symptoms can occur. Metabolic disturbances can be minimized if foscartern is administered by slow infusion, with rates not exceeding 1 mg/kg/minute. Concomitant use of other nephrotoxic drugs increases the likelihood of renal dysfunction associated with foscartern therapy. For patients receiving ganciclovir, valganciclovir, or foscartern, complete blood counts and serum electrolytes and renal function should be monitored twice weekly during induction therapy and once weekly thereafter (AIII).

The major side effect of cidofovir is potentially irreversible nephrotoxicity; the drug produces proximal tubular dysfunction including proteinuria, glycosuria, Fanconi syndrome, and acute renal failure. To minimize nephrotoxicity, probenecid should be administered before each infusion, and IV hydration with normal saline should be administered before and after each cidofovir infusion. For patients receiving IV cidofovir, blood urea nitrogen, creatinine, and urinalysis should be performed before each infusion; administration of the drug is contraindicated if renal dysfunction or proteinuria is detected. Other reported adverse events include anterior uveitis and ocular hypotony; serial ophthalmologic monitoring for anterior segment inflammation and intraocular pressure is needed while receiving the drug systemically. Cidofovir should not be administered concomitantly with other nephrotoxic agents. Cidofovir therapy must be discontinued if serum creatinine increases ≥0.5 mg/dL above baseline.

Immune recovery uveitis after initiation of effective cART is an immunologic reaction to CMV associated with inflammation in the anterior chamber and/or the vitreous and therefore is a form of immune reconstitution inflammatory syndrome (IRIS). Ocular complications of uveitis include macular edema and development of epiretinal membranes, which can cause loss of vision. Patients with low CD4 cell counts who are starting cART are at risk of IRIS. Frequent surveillance ophthalmologic examination is warranted during the period of immune reconstitution in children who are unable to report symptoms, and ophthalmologic examination is indicated for children able to report vision changes who develop symptoms. Immune recovery uveitis may respond to periocular corticosteroids or a short course of systemic steroids.
Oral valganciclovir was beneficial in one small uncontrolled study.65

Managing Treatment Failure

Resistant strains of CMV should be suspected when progressive disease and continued recovery of virus occurs despite ganciclovir therapy. Foscarnet is the drug of choice when ganciclovir resistance is suspected (AI*).

In patients with CMV retinitis, although drug resistance occurs in patients receiving long-term therapy, early relapse may be caused by the limited intraocular penetration of systemically administered drugs. In HIV-infected adults whose retinitis has relapsed during systemic treatment, placement of a ganciclovir implant was recommended because it achieved higher drug levels in the eye and often would control the retinitis for 6 to 8 months until the implant required replacement; however, the ganciclovir implant is no longer available from the manufacturer. Early first relapse of retinitis should be treated with reinduction with the same drug, followed by reinstatement of maintenance therapy (AII*). However, if drug resistance is suspected or if side effects or toxicities interfere with optimal courses of the initial agent, change to an alternative drug is reasonable (AIII). Combination ganciclovir and foscarnet can be considered but is accompanied by greater toxicity.

Preventing Recurrence

Courses of antiviral agents (e.g., ganciclovir, valganciclovir, foscarnet, cidofovir) do not cure CMV infection. After induction therapy, secondary prophylaxis (chronic maintenance therapy) is given for most forms of CMV disease until immune reconstitution, or in the absence of immune reconstitution, for the remainder of patients’ lives (AI*).

Regimens that can be considered for chronic suppression in adults and adolescents include IV ganciclovir, oral valganciclovir, IV foscarnet, combined IV ganciclovir and foscarnet, and parenteral cidofovir; these regimens also are recommended for children (AI*).66-73 Repetitive intravitreous injections of ganciclovir, foscarnet, and cidofovir reportedly are effective for secondary prophylaxis of CMV retinitis, although intravitreous therapy alone does not protect the contralateral eye or other organ systems and therefore typically is combined with systemic treatment.66 Frequent intravitreous injections also are impractical for use in most children (AIII).

A chronic maintenance regimen for patients treated for CMV disease should be chosen in consultation with a specialist. Chronic maintenance therapy is not routinely recommended for GI disease but should be considered if relapses occur (BII*). A role for maintenance therapy for CMV pneumonitis has not been established (CIII). For patients with retinitis, decisions should be made in consultation with an ophthalmologist, taking into consideration the anatomic location of the retinal lesion, vision in the contralateral eye, and patients’ immunologic and virologic status (BIII).

Discontinuing Secondary Prophylaxis

Multiple case series have reported that maintenance therapy can be discontinued safely in adults and adolescents with CMV retinitis whose CD4 cell counts have increased substantially in response to cART.76-81 These patients have remained disease free for >30 and up to 95 weeks of follow up, whereas during the pre-cART era, retinitis typically reactivated in <6 to 8 weeks after stopping CMV therapy. Plasma HIV RNA levels varied among these patients, supporting the hypothesis that the CD4 cell count is the primary determinant of immune recovery to CMV. However, CMV retinitis can occur in cART-treated adults with high CD4 cell counts,82 suggesting that CMV-specific cellular immunity may be important in controlling CMV in immune-reconstituted HIV-infected adults83,84 and reinforcing the importance of ongoing monitoring. In HIV-infected adults with CMV retinitis, discontinuation of secondary prophylaxis can be considered for patients with a sustained increase in CD4 cell count to >100 cells/mm3 in response to ART.

The safety of discontinuing secondary prophylaxis after immune reconstitution with ART in HIV-infected children has not been as well studied. Low or undetectable HIV replication in children is the strongest correlate with CMV immune reconstitution and a higher frequency of CMV-specific CD4 cells.85 Early
institution of cART may help control CMV infection by maintaining normal CD4 cell count and cytotoxic T-lymphocyte responses in HIV-infected children. In deciding whether to discontinue secondary prophylaxis, consideration must be given to the significant toxicities associated with antiviral drugs active against CMV, including those in \textit{in vitro} and animal models.

Recognizing the limitations of the data in children but drawing on the growing experience in adults, discontinuing prophylaxis can be considered in children who are receiving ART and have a sustained (i.e., >6 months) increase in CD4 percentage to >15% in children aged <6 years, or for children aged ≥6 years (as for adults), an increase in CD4 cell count to >100 cells/mm$^3$ (CIII). When the manifestation of CMV disease is ocular, such decisions should be made in close consultation with an ophthalmologist and should account for factors such as magnitude and duration of CD4 cell count increase, anatomic location of the retinal lesion, vision in the contralateral eye, and the feasibility of regular ophthalmologic monitoring (CIII).

All patients with CMV ophthalmic disease in whom anti-CMV maintenance therapy has been discontinued should continue to undergo regular ophthalmologic monitoring at 3- to 6-month intervals for early detection of CMV relapse and for immune reconstitution uveitis (AII*). For patients with any CMV disease, CMV viral load or other markers of CMV infection (such as antigenemia or viral DNA tests) are not well standardized; their role in predicting relapse remains to be defined, and they are not recommended for routine monitoring (BIII).

\textbf{Reinitiating Secondary Prophylaxis}

Relapse of CMV retinitis occurs in adults whose anti-CMV maintenance therapies have been discontinued and whose CD4 cell counts have decreased to <50 cells/mm$^3$. Reinstitution of secondary prophylaxis is recommended for HIV-infected adults when their CD4 cell counts fall to <100 cells/mm$^3$. For HIV-infected children in whom secondary prophylaxis has been discontinued because of immune reconstitution, secondary prophylaxis should be reinstituted in those aged <6 years when the CD4 percentage decreases to <15%, and in those aged ≥6 years when the CD4 cell count decreases to <100 cells/mm$^3$ (BIII).

\textbf{References}


27. Dankner WM, Lindsey JC, Levin MJ, Pediatric ACTGPT. Correlates of opportunistic infections in children infected with the human immunodeficiency virus managed before highly active antiretroviral therapy. *Pediatr Infect Dis J*. Jan


62. Germa G, Sarasin A, Baldanti F, Percivalle E, Zella D, Revello MG. Quantitative systemic and local evaluation of the antiviral effect of ganciclovir and foscarnet induction treatment on human cytomegalovirus gastrointestinal disease of...


## Dosing Recommendations for Preventing and Treating CMV

<table>
<thead>
<tr>
<th>Indication</th>
<th>First Choice</th>
<th>Alternative</th>
<th>Comments/Special Issues</th>
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<tbody>
<tr>
<td><strong>Primary Prophylaxis</strong></td>
<td>For older children who can receive adult dose (based on their BSA), valganciclovir tablets 900 mg orally once daily with food</td>
<td>N/A</td>
<td>Primary Prophylaxis Can Be Considered for:</td>
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<td>For children aged 4 months–16 years, valganciclovir oral solution 50 mg/mL at dose in milligrams = 7 x BSA x CrCl (up to maximum CrCl of 150 mL/min/1.73 m²) orally once daily with food (maximum dose 900 mg/day)</td>
<td></td>
<td>• CMV antibody positivity and severe immunosuppression (i.e., CD4 cell count &lt;50 cells/mm³ in children ≥6 years; CD4 percentage &lt;5% in children &lt;6 years)</td>
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<td><strong>Secondary Prophylaxis</strong></td>
<td>Ganciclovir 5 mg/kg body weight IV once daily, or</td>
<td>• Cidofovir 5 mg/kg body weight per dose IV every other week. Must be given with probenecid and IV hydration.</td>
<td>Secondary Prophylaxis Indicated For:</td>
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<td>For older children who can receive adult dose (based on their BSA), valganciclovir tablets 900 mg orally once daily with food, or</td>
<td></td>
<td>• Prior disseminated disease, retinitis, neurologic disease, or GI disease with relapse</td>
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<td></td>
<td>For children age 4 months–16 years, valganciclovir oral solution 50 mg/mL (at dose in milligrams = 7 x BSA x CrCl up to maximum CrCl of 150 mL/min/1.73 m²) orally once daily with food, or</td>
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<td>Criteria for Discontinuing Secondary Prophylaxis:</td>
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<td>Foscarnet 90–120 mg/kg body weight IV once daily</td>
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<td>• Completed ≥6 months of cART</td>
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<td></td>
<td>• Consultation with ophthalmologist (if retinitis)</td>
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<td></td>
<td>• Age &lt;6 years with CD4 percentage ≥15% for &gt;6 consecutive months</td>
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<td>• Age ≥6 years with CD4 cell count &gt;100 cells/mm³ for &gt;6 consecutive months</td>
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<td>• For retinitis, routine (i.e., every 3–6 months) ophthalmological follow-up is recommended for early detection of relapse or immune restoration uveitis.</td>
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<td>Criteria for Restarting Secondary Prophylaxis:</td>
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<td>• Age &lt;6 years with CD4 percentage &lt;15%</td>
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<td></td>
<td></td>
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<td>• Age ≥6 years with CD4 cell count &lt;100 cells/mm³</td>
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<tr>
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<tr>
<td>Treatment</td>
<td><strong>Symptomatic Congenital Infection with Neurologic Involvement:</strong></td>
<td><strong>Disseminated Disease and Retinitis:</strong></td>
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<tr>
<td></td>
<td>• Ganciclovir 6 mg/kg body weight per dose IV every 12 hours for 6 weeks</td>
<td><strong>Induction Therapy (Followed by Chronic Suppressive Therapy):</strong></td>
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<td>• Ganciclovir 5 mg/kg body weight per dose IV every 12 hours for 14–21 days (may be increased to 7.5 mg/kg body weight per dose IV twice daily), then 5 mg/kg body weight once daily for 5–7 days per week for chronic suppression</td>
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<td><strong>Central Nervous System Disease (Followed by Chronic Suppressive Therapy; See Secondary Prophylaxis):</strong></td>
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<td>• Ganciclovir 5 mg/kg body weight per dose IV every 12 hours PLUS foscarnet 60 mg/kg body weight per dose IV every 8 hours (or 90 mg/kg body weight per dose IV every 12 hours) continued until symptomatic improvement, followed by chronic suppression</td>
<td>• Valganciclovir tablets 900 mg per dose orally twice daily for 14–21 days, followed by chronic suppressive therapy (see above). <strong>Note:</strong> This is an option in older children who can receive the adult dose (based on their BSA).</td>
<td>• Data on valganciclovir dosing in young children for treatment of retinitis are unavailable, but consideration can be given to transitioning from IV ganciclovir to oral valganciclovir after improvement of retinitis is noted.</td>
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<td>• IV ganciclovir plus IV foscarnet (at above induction doses) may be considered as initial induction therapy in children with sight-threatening disease or for treatment following failure/relapse on monotherapy.</td>
<td>• Intravitreal injections of ganciclovir, foscarnet, or cidofovir are used in adults for retinitis but are not practical for most children.</td>
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<td>• Cidofovir is also used to treat CMV retinitis in adults intolerant to other therapies. Induction dosing in adults is 5 mg/kg body weight IV once weekly for 2 weeks, followed by chronic suppressive therapy (see secondary prophylaxis); however, data on dosing in children are unavailable. Must be given with probenecid and IV hydration.</td>
<td>• Combination ganciclovir and foscarnet is associated with substantial rates of adverse effects, and optimal treatment for neurologic disease in children is unknown, particularly if receiving optimized cART.</td>
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<td>• Chronic suppressive therapy (secondary prophylaxis) is recommended in adults and children following initial therapy of disseminated disease, retinitis, neurologic disease, or GI disease with relapse.</td>
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**Key to Acronyms:** BSA = body surface area; cART = combined antiretroviral therapy; CD4 = CD4 T lymphocyte; CMV = cytomegalovirus; CrCl = creatinine clearance; GI = gastrointestinal; IV = intravenous