

Cytomegalovirus (Last updated November 6, 2013; last reviewed November 6, 2013)

Panel's Recommendations

- 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/mm³ 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/mm³ or CD4 percentage $<5\%$) should have a dilated retinal examination performed by an ophthalmologist every 6 months (**AIII**).
- CMV end-organ disease is best prevented by antiretroviral therapy (ART) to maintain the CD4 cell count >100 cells/mm³ 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/mm³ 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/mm³ 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) (**BI**).
- 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 reinstatement of maintenance therapy (**AI***). If drug resistance is suspected, change to an alternative drug is reasonable (**AIII**). 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/mm³ 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 (**AI***).
- Secondary prophylaxis should be reinstated 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/mm³ in those aged ≥ 6 years (**BIII**).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials *in children*[†] with clinical outcomes and/or validated endpoints; I* = One or more randomized trials *in adults* with clinical outcomes and/or validated laboratory endpoints with accompanying data *in children*[†] from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies *in children*[†] with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies *in adults* with long-term clinical outcomes with accompanying data *in children*[†] from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

[†] Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

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.¹ 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.^{2,3} 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 $\geq 80\%$.⁴ 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.^{5,6} 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 coinfecting with CMV.^{7,8}

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%.⁹ 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%.^{5,10} In comparison, the rate of congenital infection after non-primary maternal CMV infection is believed to be significantly lower (range: 0.15%–1.0%).^{11–13} 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.^{14,15}

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.^{16–20}

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).²¹ 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%,²² 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.²³ 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.²⁴

HIV-infected children appear to be at higher risk of CMV infection during early childhood than are HIV-

uninfected children.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.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.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.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.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.²⁹ Similarly, CMV retinitis declined from 0.7 to 0.0 per 100 child-years.

Symptomatic HIV-infected children coinfecting with CMV have a higher rate of CMV viremia 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.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.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.^{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.^{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 coinfecting with CMV than in those without CMV infection.^{22,25,33} In one study from the pre-cART era, 53% of infants coinfecting 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 coinfecting with CMV compared with children without CMV was 2.6 (95% CI: 1.1–6.0).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.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.^{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.^{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/mm³ 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/mm³ 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/mm³ (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/mm³, 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.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.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 coinfecting 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 foscarnet, 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 foscarnet (**AI***). Foscarnet 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 foscarnet delays progression of retinitis in certain patients in whom monotherapy fails^{34,53,56,57} 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.

Intravitreal injections of ganciclovir, foscarnet, 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 intravitreal 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 Foscarnet concentrations in the CSF are about two-thirds of those in serum.⁵⁹ Hence, combination treatment with ganciclovir and

foscarnet may be preferable as initial therapy to stabilize disease and maximize response (**BII***).⁶⁰ 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***).^{61,62} Limited and uncontrolled data suggest that ganciclovir therapy is useful in patients with AIDS and CMV pneumonia (**BII***).⁶³ 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 foscarnet are decreased renal function and metabolic derangements. Renal toxicity and foscarnet 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 foscarnet 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 foscarnet therapy. For patients receiving ganciclovir, valganciclovir, or foscarnet, 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).⁶⁴ 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 intravitreal injections of ganciclovir, foscarnet, and cidofovir reportedly are effective for secondary prophylaxis of CMV retinitis,^{74,75} although intraocular therapy alone does not protect the contralateral eye or other organ systems and therefore typically is combined with systemic treatment.⁶⁶ Frequent intravitreal 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 adults^{83,84} 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.⁸⁶ 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 *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/mm³ (**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**).^{87,88}

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/mm³.⁷⁴ Reinstitution of secondary prophylaxis is recommended for HIV-infected adults when their CD4 cell counts fall to <100 cells/mm³. For HIV-infected children in whom secondary prophylaxis has been discontinued because of immune reconstitution, secondary prophylaxis should be reinstated 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/mm³ (**BIII**).

References

1. Stagno S, Reynolds DW, Pass RF, Alford CA. Breast milk and the risk of cytomegalovirus infection. *N Engl J Med*. May 8 1980;302(19):1073-1076. Available at <http://www.ncbi.nlm.nih.gov/pubmed/6245360>.
2. Pass RF, Hutto SC, Reynolds DW, Polhill RB. Increased frequency of cytomegalovirus infection in children in group day care. *Pediatrics*. Jul 1984;74(1):121-126. Available at <http://www.ncbi.nlm.nih.gov/pubmed/6330661>.
3. Adler SP. Cytomegalovirus and child day care. Evidence for an increased infection rate among day-care workers. *N Engl J Med*. Nov 9 1989;321(19):1290-1296. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2552316>.
4. Pass RF. Epidemiology and transmission of cytomegalovirus. *J Infect Dis*. Aug 1985;152(2):243-248. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2993429>.
5. Stagno S, Pass RF, Cloud G, et al. Primary cytomegalovirus infection in pregnancy. Incidence, transmission to fetus, and clinical outcome. *JAMA*. Oct 10 1986;256(14):1904-1908. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3020264>.
6. Yow MD, Williamson DW, Leeds LJ, et al. Epidemiologic characteristics of cytomegalovirus infection in mothers and their infants. *Am J Obstet Gynecol*. 1998; 158(5):1189-1195. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=2835906.
7. Mussi-Pinhata MM, Yamamoto AY, Figueiredo LT, Cervi MC, Duarte G. Congenital and perinatal cytomegalovirus infection in infants born to mothers infected with human immunodeficiency virus. *J Pediatr*. Feb 1998;132(2):285-290. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9506642>.
8. Quinn TC, Piot P, McCormick JB, et al. Serologic and immunologic studies in patients with AIDS in North America and Africa. The potential role of infectious agents as cofactors in human immunodeficiency virus infection. *JAMA*. May 15 1987;257(19):2617-2621. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3494857>.
9. Dollard SC, Grosse SD, Ross DS. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. *Rev Med Virol*. Sep-Oct 2007;17(5):355-363. Available at

<http://www.ncbi.nlm.nih.gov/pubmed/17542052>.

10. Revello MG, Zavattoni M, Furione M, Lilleri D, Gorini G, Gerna G. Diagnosis and outcome of preconceptional and periconceptional primary human cytomegalovirus infections. *J Infect Dis*. Aug 15 2002;186(4):553-557. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12195384>.
11. Prober CG, Enright AM. Congenital cytomegalovirus (CMV) infections: hats off to Alabama. *J Pediatr*. Jul 2003;143(1):4-6. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12915814>.
12. Fowler KB, Stagno S, Pass RF. Maternal immunity and prevention of congenital cytomegalovirus infection. *JAMA*. Feb 26 2003;289(8):1008-1011. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12597753>.
13. Azam AZ, Vial Y, Fawer CL, Zufferey J, Hohlfield P. Prenatal diagnosis of congenital cytomegalovirus infection. *Obstet Gynecol*. Mar 2001;97(3):443-448. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11239654>.
14. Boppana SB, Fowler KB, Britt WJ, Stagno S, Pass RF. Symptomatic congenital cytomegalovirus infection in infants born to mothers with preexisting immunity to cytomegalovirus. *Pediatrics*. Jul 1999;104(1 Pt 1):55-60. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10390260>.
15. Boppana SB, Rivera LB, Fowler KB, Mach M, Britt WJ. Intrauterine transmission of cytomegalovirus to infants of women with preconceptional immunity. *N Engl J Med*. May 3 2001;344(18):1366-1371. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11333993>.
16. Neuberger P, Hamprecht K, Vochem M, et al. Case-control study of symptoms and neonatal outcome of human milk-transmitted cytomegalovirus infection in premature infants. *J Pediatr*. Mar 2006;148(3):326-331. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16615961>.
17. Kothari A, Ramachandran VG, Gupta P. Cytomegalovirus infection in neonates following exchange transfusion. *Indian J Pediatr*. Jun 2006;73(6):519-521. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16816515>.
18. Mussi-Pinhata MM, Yamamoto AY, do Carmo Rego MA, Pinto PC, da Motta MS, Calixto C. Perinatal or early-postnatal cytomegalovirus infection in preterm infants under 34 weeks gestation born to CMV-seropositive mothers within a high-seroprevalence population. *J Pediatr*. Nov 2004;145(5):685-688. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15520780>.
19. Yasuda A, Kimura H, Hayakawa M, et al. Evaluation of cytomegalovirus infections transmitted via breast milk in preterm infants with a real-time polymerase chain reaction assay. *Pediatrics*. Jun 2003;111(6 Pt 1):1333-1336. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12777549>.
20. Vollmer B, Seibold-Weiger K, Schmitz-Salue C, et al. Postnatally acquired cytomegalovirus infection via breast milk: effects on hearing and development in preterm infants. *Pediatr Infect Dis J*. Apr 2004;23(4):322-327. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15071286>.
21. Mostad SB, Kreiss JK, Ryncarz A, et al. Cervical shedding of herpes simplex virus and cytomegalovirus throughout the menstrual cycle in women infected with human immunodeficiency virus type 1. *Am J Obstet Gynecol*. Oct 2000;183(4):948-955. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11035345>.
22. Kovacs A, Schluchter M, Easley K, et al. Cytomegalovirus infection and HIV-1 disease progression in infants born to HIV-1-infected women. Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection Study Group. *N Engl J Med*. Jul 8 1999;341(2):77-84. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10395631>.
23. Duryea EL, Sanchez PJ, Sheffield JS, et al. Maternal human immunodeficiency virus infection and congenital transmission of cytomegalovirus. *Pediatr Infect Dis J*. Oct 2010;29(10):915-918. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20431424>.
24. Guibert G, Warszawski J, Le Chenadec J, et al. Decreased risk of congenital cytomegalovirus infection in children born to HIV-1-infected mothers in the era of highly active antiretroviral therapy. *Clin Infect Dis*. Jun 1 2009;48(11):1516-1525. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19388872>.
25. Kitchen BJ, Engler HD, Gill VJ, et al. Cytomegalovirus infection in children with human immunodeficiency virus infection. *Pediatr Infect Dis J*. Apr 1997;16(4):358-363. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9109136>.
26. Jabs DA, Van Natta ML, Holbrook JT KJ, Meinert CL, Davis MD. Longitudinal Study of the Ocular Complications of AIDS I. Ocular Diagnoses at Enrollment. *Ophthalmology* 2007 January 24. 2007.
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

- 2001;20(1):40-48. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11176565>.
28. Gona P, Van Dyke RB, Williams PL, et al. Incidence of opportunistic and other infections in HIV-infected children in the HAART era. *JAMA*. Jul 19 2006;296(3):292-300. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16849662>.
 29. Nesheim SR, Kapogiannis BG, Soe MM, et al. Trends in opportunistic infections in the pre- and post-highly active antiretroviral therapy eras among HIV-infected children in the Perinatal AIDS Collaborative Transmission Study, 1986-2004. *Pediatrics*. Jul 2007;120(1):100-109. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17606567>.
 30. Chandwani S, Kaul A, Bebenroth D, et al. Cytomegalovirus infection in human immunodeficiency virus type 1-infected children. *Pediatr Infect Dis J*. Apr 1996;15(4):310-314. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8866799>.
 31. Boppana SB, Pass RF, Britt WJ, Stagno S, Alford CA. Symptomatic congenital cytomegalovirus infection: neonatal morbidity and mortality. *Pediatr Infect Dis J*. Feb 1992;11(2):93-99. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1311066>.
 32. Fowler KB, Boppana SB. Congenital cytomegalovirus (CMV) infection and hearing deficit. *J Clin Virol*. Feb 2006;35(2):226-231. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16386462>.
 33. Doyle M, Atkins JT, Rivera-Matos IR. Congenital cytomegalovirus infection in infants infected with human immunodeficiency virus type 1. *Pediatr Infect Dis J*. Dec 1996;15(12):1102-1106. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8970220>.
 34. Zaknun D, Zangerle R, Kapelari K, Fischer H, Sailer M, McIntosh K. Concurrent ganciclovir and foscarnet treatment for cytomegalovirus encephalitis and retinitis in an infant with acquired immunodeficiency syndrome: case report and review. *Pediatr Infect Dis J*. Aug 1997;16(8):807-811. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9271045>.
 35. Mueller BU, MacKay K, Cheshire LB, et al. Cytomegalovirus ureteritis as a cause of renal failure in a child infected with the human immunodeficiency virus. *Clin Infect Dis*. Apr 1995;20(4):1040-1043. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7795047>.
 36. Olivero MT, Nelson RP, Jr., Andrews T, Washington K, Good RA. Cytomegalovirus sinus disease in a human immunodeficiency virus-infected child. *Pediatr Infect Dis J*. Jul 1995;14(7):629-631. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7567298>.
 37. Marriage SC, Booy R, Hermione Lyall EG, et al. Cytomegalovirus myelitis in a child infected with human immunodeficiency virus type 1. *Pediatr Infect Dis J*. Jun 1996;15(6):549-551. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8783359>.
 38. Kalayjian RC, Cohen ML, Bonomo RA, Flanigan TP. Cytomegalovirus ventriculoencephalitis in AIDS. A syndrome with distinct clinical and pathologic features. *Medicine (Baltimore)*. Mar 1993;72(2):67-77. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8386795>.
 39. Nigro G, Krzysztofiak A, Gattinara GC, et al. Rapid progression of HIV disease in children with cytomegalovirus DNAemia. *AIDS*. Sep 1996;10(10):1127-1133. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8874630>.
 40. Haynes RJ, Kline MC, Toman B, et al. Standard reference material 2366 for measurement of human cytomegalovirus DNA. *The Journal of molecular diagnostics: JMD*. Mar 2013;15(2):177-185. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23321018>.
 41. Fryer JF, Heath AB, Anderson R, Minor PD. Collaborative Study to Evaluate the Proposed 1st WHO International Standard for Human Cytomegalovirus (HCMV) for Nucleic Acid Amplification (NAT)-Based Assays. 2010. Available at http://www.nibsc.ac.uk/PDF/HCMV_IS.pdf.
 42. Boppana SB, Ross SA, Novak Z, et al. Dried blood spot real-time polymerase chain reaction assays to screen newborns for congenital cytomegalovirus infection. *JAMA*. Apr 14 2010;303(14):1375-1382. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20388893>.
 43. Boppana SB, Ross SA, Shimamura M, et al. Saliva polymerase-chain-reaction assay for cytomegalovirus screening in newborns. *N Engl J Med*. Jun 2 2011;364(22):2111-2118. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21631323>.
 44. Brosgart CL, Louis TA, Hillman DW, et al. A randomized, placebo-controlled trial of the safety and efficacy of oral ganciclovir for prophylaxis of cytomegalovirus disease in HIV-infected individuals. Terry Bein Community Programs for Clinical Research on AIDS. *AIDS*. Feb 12 1998;12(3):269-277. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9517989>.
 45. Kimberlin DW, Acosta EP, Sanchez PJ, et al. Pharmacokinetic and pharmacodynamic assessment of oral valganciclovir in the treatment of symptomatic congenital cytomegalovirus disease. *J Infect Dis*. Mar 15 2008;197(6):836-845.

Available at <http://www.ncbi.nlm.nih.gov/pubmed/18279073>.

46. Genetech. Valganciclovir Package Insert, <http://www.gene.com/gene/products/information/valcyte/pdf/pi.pdf>. 2010. Available at <http://www.gene.com/gene/products/information/valcyte/pdf/pi.pdf>.
47. Kadambari S, Williams EJ, Luck S, Griffiths PD, Sharland M. Evidence based management guidelines for the detection and treatment of congenital CMV. *Early human development*. Nov 2011;87(11):723-728. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21962770>.
48. Whitley RJ, Cloud G, Gruber W, et al. Ganciclovir treatment of symptomatic congenital cytomegalovirus infection: results of a phase II study. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. *J Infect Dis*. May 1997;175(5):1080-1086. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9129069>.
49. Kimberlin DW, Lin CY, Sanchez PJ, et al. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. *J Pediatr*. Jul 2003;143(1):16-25. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12915819>.
50. Oliver SE, Cloud GA, Sanchez PJ, et al. Neurodevelopmental outcomes following ganciclovir therapy in symptomatic congenital cytomegalovirus infections involving the central nervous system. *J Clin Virol*. Dec 2009;46 Suppl 4:S22-26. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19766534>.
51. Studies of Ocular Complications of AIDS Research, Group in collaboration with the AIDS Clinical Trials Group. Foscarnet-Ganciclovir Cytomegalovirus Retinitis Trial. 4. Visual outcomes. *Ophthalmology*. 1994;101(7):1250-1261. Available at http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=8035989&ordinalpos=9&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum.
52. Musch DC, Martin DF, Gordon JF, Davis MD, Kuppermann BD. Treatment of cytomegalovirus retinitis with a sustained-release ganciclovir implant. The Ganciclovir Implant Study Group. *N Engl J Med*. Jul 10 1997;337(2):83-90. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9211677>.
53. Martin DF, Sierra-Madero J, Walmsley S, et al. A controlled trial of valganciclovir as induction therapy for cytomegalovirus retinitis. *N Engl J Med*. Apr 11 2002;346(15):1119-1126. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11948271>.
54. Kempen JH, Jabs DA, Wilson LA, Dunn JP, West SK, Tonascia JA. Risk of vision loss in patients with cytomegalovirus retinitis and the acquired immunodeficiency syndrome. *Arch Ophthalmol*. Apr 2003;121(4):466-476. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12695243>.
55. Studies of Ocular Complications of AIDS Research Group. The AIDS Clinical Trials Group. The ganciclovir implant plus oral ganciclovir versus parenteral cidofovir for the treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome. *Am J Ophthalmol*. 2001;131:475-67.
56. Walton RC, Whitcup SM, Mueller BU, Lewis LL, Pizzo PA, Nussenblatt RB. Combined intravenous ganciclovir and foscarnet for children with recurrent cytomegalovirus retinitis. *Ophthalmology*. Dec 1995;102(12):1865-1870. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9098289>.
57. Butler KM, De Smet MD, Husson RN, et al. Treatment of aggressive cytomegalovirus retinitis with ganciclovir in combination with foscarnet in a child infected with human immunodeficiency virus. *J Pediatr*. Mar 1992;120(3):483-486. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1311378>.
58. Fletcher C, Sawchuk R, Chinnock B, de Miranda P, Balfour HH, Jr. Human pharmacokinetics of the antiviral drug DHPG. *Clin Pharmacol Ther*. Sep 1986;40(3):281-286. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3017630>.
59. Hengge UR, Brockmeyer NH, Malessa R, Ravens U, Goos M. Foscarnet penetrates the blood-brain barrier: rationale for therapy of cytomegalovirus encephalitis. *Antimicrob Agents Chemother*. May 1993;37(5):1010-1014. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8390807>.
60. Anduze-Faris BM, Fillet AM, Gozlan J, et al. Induction and maintenance therapy of cytomegalovirus central nervous system infection in HIV-infected patients. *AIDS*. Mar 31 2000;14(5):517-524. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10780714>.
61. Dieterich DT, Kotler DP, Busch DF, et al. Ganciclovir treatment of cytomegalovirus colitis in AIDS: a randomized, double-blind, placebo-controlled multicenter study. *J Infect Dis*. Feb 1993;167(2):278-282. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8380610>.
62. Gerna G, Sarasini 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

- patients with AIDS. Italian Foscarnet GID Study Group. *Antiviral Res.* Mar 1997;34(1):39-50. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9107384>.
63. Markham A, Faulds D. Ganciclovir. An update of its therapeutic use in cytomegalovirus infection. *Drugs.* Sep 1994;48(3):455-484. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7527763>.
 64. Nguyen QD, Kempen JH, Bolton SG, Dunn JP, Jabs DA. Immune recovery uveitis in patients with AIDS and cytomegalovirus retinitis after highly active antiretroviral therapy. *Am J Ophthalmol.* May 2000;129(5):634-639. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10844056>.
 65. Kosobucki BR, Goldberg DE, Bessho K KH, Rodanant N, Labree L et al. Valganciclovir therapy for immune recovery uveitis complicated by macular edema. *Am J Ophthalmol* 2004 April;137(4):636-8. 2004. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15059701>.
 66. Martin DF, Kuppermann BD, Wolitz RA, Palestine AG, Li H, Robinson CA. Oral ganciclovir for patients with cytomegalovirus retinitis treated with a ganciclovir implant. Roche Ganciclovir Study Group. *N Engl J Med.* Apr 8 1999;340(14):1063-1070. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10194235>.
 67. Drew WL, Ives D, Lalezari JP, et al. Oral ganciclovir as maintenance treatment for cytomegalovirus retinitis in patients with AIDS. Syntex Cooperative Oral Ganciclovir Study Group. *N Engl J Med.* Sep 7 1995;333(10):615-620. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7637721>.
 68. Studies of Ocular complications of AIDS Research Group in Collaboration with the AIDS Clinical Trials Group. Parenteral cidofovir for cytomegalovirus retinitis in patients with AIDS: the HPMPC peripheral cytomegalovirus retinitis trial. A randomized, controlled trial. Studies of Ocular complications of AIDS Research Group in Collaboration with the AIDS Clinical Trials Group. *Ann Intern Med.* Feb 15 1997;126(4):264-274. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9036798>.
 69. Palestine AG, Polis MA, De Smet MD, et al. A randomized, controlled trial of foscarnet in the treatment of cytomegalovirus retinitis in patients with AIDS. *Ann Intern Med.* Nov 1 1991;115(9):665-673. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1656826>.
 70. Spector SA, Weingeist T, Pollard RB, et al. A randomized, controlled study of intravenous ganciclovir therapy for cytomegalovirus peripheral retinitis in patients with AIDS. AIDS Clinical Trials Group and Cytomegalovirus Cooperative Study Group. *J Infect Dis.* Sep 1993;168(3):557-563. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8394858>.
 71. The Studies of the Ocular Complications of AIDS Research Group icwtACTG. Combination foscarnet and ganciclovir therapy vs monotherapy for the treatment of relapsed cytomegalovirus retinitis in patients with AIDS. The cytomegalovirus retreatment trial. *Arch Ophthalmol.* 1996;114(1):23-33. Available at http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=8540847&ordinalpos=6&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum.
 72. Diaz-Llopis M, Espana E, Munoz G, et al. High dose intravitreal foscarnet in the treatment of cytomegalovirus retinitis in AIDS. *The British journal of ophthalmology.* Feb 1994;78(2):120-124. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8123619>.
 73. de Smet MD, Meenken CJ, van den Horn GJ. Fomivirsen - a phosphorothioate oligonucleotide for the treatment of CMV retinitis. *Ocular immunology and inflammation.* Dec 1999;7(3-4):189-198. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10611727>.
 74. Kirsch LS, Arevalo JF, Chavez de la Paz E, Munguia D, de Clercq E, Freeman WR. Intravitreal cidofovir (HPMPC) treatment of cytomegalovirus retinitis in patients with acquired immune deficiency syndrome. *Ophthalmology.* Apr 1995;102(4):533-542; discussion 542-533. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7724170>.
 75. Young S, Morlet N, Besen G, et al. High-dose (2000-microgram) intravitreal ganciclovir in the treatment of cytomegalovirus retinitis. *Ophthalmology.* Aug 1998;105(8):1404-1410. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9709750>.
 76. Tural C, Romeu J, Sirera G, et al. Long-lasting remission of cytomegalovirus retinitis without maintenance therapy in human immunodeficiency virus-infected patients. *J Infect Dis.* Apr 1998;177(4):1080-1083. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9534987>.
 77. Vrabcic TR, Baldassano VF, Whitcup SM. Discontinuation of maintenance therapy in patients with quiescent cytomegalovirus retinitis and elevated CD4+ counts. *Ophthalmology.* Jul 1998;105(7):1259-1264. Available at

<http://www.ncbi.nlm.nih.gov/pubmed/9663231>.

78. Macdonald JC, Torriani FJ, Morse LS, Karavellas MP, Reed JB, Freeman WR. Lack of reactivation of cytomegalovirus (CMV) retinitis after stopping CMV maintenance therapy in AIDS patients with sustained elevations in CD4 T cells in response to highly active antiretroviral therapy. *J Infect Dis*. May 1998;177(5):1182-1187. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9593001>.
79. Whitcup SM, Fortin E, Lindblad AS, et al. Discontinuation of anticytomegalovirus therapy in patients with HIV infection and cytomegalovirus retinitis. *JAMA*. Nov 3 1999;282(17):1633-1637. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10553789>.
80. Jabs DA, Bolton SG, Dunn JP, Palestine AG. Discontinuing anticytomegalovirus therapy in patients with immune reconstitution after combination antiretroviral therapy. *Am J Ophthalmol*. Dec 1998;126(6):817-822. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9860006>.
81. Jouan M, Saves M, Tubiana R, et al. Discontinuation of maintenance therapy for cytomegalovirus retinitis in HIV-infected patients receiving highly active antiretroviral therapy. *AIDS*. Jan 5 2001;15(1):23-31. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11192865>.
82. Torriani FJ, Freeman WR, Macdonald JC, et al. CMV retinitis recurs after stopping treatment in virological and immunological failures of potent antiretroviral therapy. *AIDS*. Jan 28 2000;14(2):173-180. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10708288>.
83. Lilleri D, Piccinini G, Genini E, et al. Monitoring of human cytomegalovirus (HCMV)-specific CD4+ T cell frequency by cytokine flow cytometry as a possible indicator for discontinuation of HCMV secondary prophylaxis in HAART-treated AIDS patients. *J Clin Virol*. Apr 2004;29(4):297-307. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15018859>.
84. Tamarit A, Alberola J, Mira JV, Tornero C, Galindo MJ, Navarro D. Assessment of human cytomegalovirus specific T cell immunity in human immunodeficiency virus infected patients in different disease stages following HAART and in long-term non-progressors. *J Med Virol*. Nov 2004;74(3):382-389. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15368523>.
85. Weinberg A, Wiznia AA, Lafleur BJ, Shah S, Levin MJ. Cytomegalovirus-specific cell-mediated immunity in HIV-infected children on HAART. *AIDS Res Hum Retroviruses*. Mar 2006;22(3):283-288. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16545015>.
86. Saitoh A, Viani RM, Schrier RD, Spector SA. Treatment of infants coinfecting with HIV-1 and cytomegalovirus with combination antiretrovirals and ganciclovir. *J Allergy Clin Immunol*. Oct 2004;114(4):983-985. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15480350>.
87. Spector SA, Wong R, Hsia K, Pilcher M, Stempien MJ. Plasma cytomegalovirus (CMV) DNA load predicts CMV disease and survival in AIDS patients. *J Clin Invest*. Jan 15 1998;101(2):497-502. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9435323>.
88. Salmon-Ceron D, Mazon MC, Chaput S, et al. Plasma cytomegalovirus DNA, pp65 antigenaemia and a low CD4 cell count remain risk factors for cytomegalovirus disease in patients receiving highly active antiretroviral therapy. *AIDS*. May 26 2000;14(8):1041-1049. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10853987>.

Dosing Recommendations for Preventing and Treating CMV (page 1 of 2)

Indication	First Choice	Alternative	Comments/Special Issues
Primary Prophylaxis	<ul style="list-style-type: none"> • For older children who can receive adult dose (based on their BSA), valganciclovir tablets 900 mg orally once daily with food • 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) 	N/A	<p><u>Primary Prophylaxis Can Be Considered for:</u></p> <ul style="list-style-type: none"> • CMV antibody positivity and severe immunosuppression (i.e., CD4 cell count <50 cells/mm³ in children ≥6 years; CD4 percentage <5% in children <6 years) <p><u>Criteria for Discontinuing Primary Prophylaxis:</u></p> <ul style="list-style-type: none"> • CD4 cell count >100 cells/mm³ for children ≥6 years; CD4 percentage >10% in children <6 years <p><u>Criteria for Considering Restarting Primary Prophylaxis:</u></p> <ul style="list-style-type: none"> • CD4 cell count <50 cells/mm³ in children ≥6 years; CD4 percentage <5% in children <6 years
Secondary Prophylaxis	<ul style="list-style-type: none"> • Ganciclovir 5 mg/kg body weight IV once daily, or • For older children who can receive adult dose (based on their BSA), valganciclovir tablets 900 mg orally once daily with food, or • 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 • Foscarnet 90–120 mg/kg body weight IV once daily 	<ul style="list-style-type: none"> • Cidofovir 5 mg/kg body weight per dose IV every other week. Must be given with probenecid and IV hydration. 	<p><u>Secondary Prophylaxis Indicated For:</u></p> <ul style="list-style-type: none"> • Prior disseminated disease, retinitis, neurologic disease, or GI disease with relapse <p><u>Criteria for Discontinuing Secondary Prophylaxis</u></p> <p><i>If All of the Following Criteria Are Fulfilled:</i></p> <ul style="list-style-type: none"> • Completed ≥6 months of cART • Consultation with ophthalmologist (if retinitis) • Age <6 years with CD4 percentage ≥15% for >6 consecutive months • Age ≥6 years with CD4 cell count >100 cells/mm³ for >6 consecutive months • For retinitis, routine (i.e., every 3–6 months) ophthalmological follow-up is recommended for early detection of relapse or immune restoration uveitis. <p><u>Criteria for Restarting Secondary Prophylaxis:</u></p> <ul style="list-style-type: none"> • Age <6 years with CD4 percentage <15% • Age ≥6 years with CD4 cell count <100 cells/mm³

Dosing Recommendations for Preventing and Treating CMV (page 2 of 2)

Indication	First Choice	Alternative	Comments/Special Issues
Treatment	<p><u>Symptomatic Congenital Infection with Neurologic Involvement:</u></p> <ul style="list-style-type: none"> Ganciclovir 6 mg/kg body weight per dose IV every 12 hours for 6 weeks <p><u>Disseminated Disease and Retinitis:</u> <i>Induction Therapy (Followed by Chronic Suppressive Therapy):</i></p> <ul style="list-style-type: none"> 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 <p><u>Central Nervous System Disease (Followed by Chronic Suppressive Therapy; See Secondary Prophylaxis):</u></p> <ul style="list-style-type: none"> 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 	<p><u>Disseminated Disease and Retinitis:</u> <i>Induction Therapy (Followed by Chronic Suppressive Therapy):</i></p> <ul style="list-style-type: none"> Foscarnet, 60 mg/kg body weight per dose IV every 8 hours or 90 mg/kg body weight per dose IV every 12 hours x 14 to 21 days, then 90–120 mg/kg body weight IV once daily for chronic suppression <p><u>Alternatives for Retinitis (Followed by Chronic Suppressive Therapy; See Secondary Prophylaxis):</u></p> <ul style="list-style-type: none"> Valganciclovir tablets 900 mg per dose orally twice daily for 14–21 days, followed by chronic suppressive therapy (see above). Note: This is an option in older children who can receive the adult dose (based on their BSA). 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. 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 	<ul style="list-style-type: none"> 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. Intravitreal injections of ganciclovir, foscarnet, or cidofovir are used in adults for retinitis but are not practical for most children. 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. 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.

Key to Acronyms: BSA = body surface area; cART = combined antiretroviral therapy; CD4 = CD4 T lymphocyte; CMV = cytomegalovirus; CrCl = creatinine clearance; GI = gastrointestinal; IV = intravenous