Cytomegalovirus

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Panel's Recommendations
I. Is there an indication for cytomegalovirus (CMV) antibody testing in children with asymptomatic HIV (versus not testing) to guide clinical management? • CMV antibody testing is recommended at age 1 year (or at baseline evaluation if age >1 year at initial visit) and then annually for CMV-seronegative infants and children with HIV who are immunosuppressed (i.e., CD4 T lymphocyte [CD4] cell count <100 cells/mm^3 or CD4 percentage <10%) (strong, low). II. Should infants born to mothers with HIV undergo screening for congenital CMV infection (versus not screening)? • Testing for congenital CMV infection in the first 21 days of life is recommended for infants with vertically transmitted HIV (strong, low). CMV testing is also suggested for all infants exposed to HIV since their HIV status will be indeterminate during the first 21 days of life when congenital CMV infection can be diagnosed (weak, low). Infants with confirmed congenital CMV infection should be evaluated regularly for early detection of hearing loss and appropriate intervention. III. Is primary prophylaxis against CMV recommended for children with HIV who are CMV-seropositive (versus not providing prophylaxis)? • Primary prophylaxis against CMV disease is not recommended for children with HIV who are not severely immunocompromised (strong, moderate). CMV end-organ disease is best prevented by antiretroviral therapy (ART) to maintain the CD4 count >100 cells/mm^3 in children aged ≥6 years, or CD4 percentage >10% in children aged <6 years (strong, moderate). • Prophylaxis with valganciclovir may be appropriate for CMV-seropositive children with HIV who are severely immunosuppressed (i.e., CD4 count <50 cells/mm^3 in children aged ≥6 years, or CD4 percentage <5% in children aged <6 years) (weak, low). • Cessation of primary prophylaxis can be considered when the CD4 count is sustained at >100 cells/mm^3 for children ≥6 years of age, or CD4 percentage >10% in children <6 years (weak, low). IV. In CMV-seropositive children with HIV age <5 years, is routine ophthalmologic examination recommended to screen for CMV retinitis (versus not providing routine ophthalmologic examination)? • Children with HIV aged <5 years who are CMV infected and severely immunosuppressed (i.e., CD4 count <50 cells/mm^3 or CD4 percentage <5%) should have a dilated retinal examination performed by an ophthalmologist every 6 months (strong, low). As CMV retinitis can occur in patients with higher CD4 counts, ophthalmologic screening can be considered for young children with lesser degrees of immunosuppression who are unable to report visual symptoms. V. Among children with HIV and CMV disease, is treatment with anti-CMV antiviral agents in addition to ART (versus ART alone) associated with higher rates of remission, decreased mortality, or both? • Treatment with antiviral therapy against CMV in addition to ART is recommended for CMV disease in children with HIV (strong, moderate). Intravenous (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, and CNS disease). Transition from IV ganciclovir to oral valganciclovir can be considered for patients who improve on IV therapy (strong, moderate). • Foscarnet is an alternative drug for treating CMV disease or for use in ganciclovir-resistant CMV infections in children with HIV (strong, moderate). • Combination therapy with ganciclovir and foscarnet may delay progression of retinitis in certain patients in whom monotherapy fails and can be used as initial therapy in children with sight-threatening disease (weak, very low).

Panel's Recommendations
Combination treatment with IV ganciclovir and foscarnet may also be preferable as initial therapy to stabilize CMV neurologic disease and maximize response (weak, very low). • In children with HIV and symptomatic congenital CMV infection, treatment with valganciclovir (or IV ganciclovir) for 6 months is recommended provided it can be started during the first month of life (strong, moderate). This recommendation is based on studies among children with symptomatic congenital CMV infection but without HIV. VI. Is secondary prophylaxis after treatment of CMV disease (versus no secondary prophylaxis) recommended in severely immunocompromised children with HIV? • After induction therapy, secondary prophylaxis (chronic maintenance therapy) is recommended for most forms of CMV disease until immune reconstitution or, in the absence of immune reconstitution, for the remainder of a patient's life. Regimens for chronic suppression include IV ganciclovir, oral valganciclovir, IV foscarnet, combined IV ganciclovir and foscarnet, and IV cidofovir (strong, moderate). • Secondary prophylaxis (chronic maintenance therapy) is not routinely recommended for CMV gastrointestinal disease but should be considered if relapses occur (expert opinion). A role for secondary prophylaxis (maintenance therapy) for CMV pneumonitis also has not been established. VII. Is discontinuation of secondary prophylaxis for CMV disease recommended in children with HIV who have well-controlled HIV (versus continuation of secondary prophylaxis)? • Discontinuation of secondary prophylaxis may be considered for children who are receiving ART and have a sustained (e.g., >6 months) increase in CD4 count, defined as an increase in CD4 percentage to >15% for children aged <6 years, or an increase in CD4 count to >100 cells/mm^3 for children aged ≥6 years (weak, low). • All patients with CMV ophthalmic disease in whom anti-CMV maintenance therapy (secondary prophylaxis) has been discontinued should continue to undergo regular ophthalmologic monitoring for early detection of CMV relapse and for immune reconstitution uveitis (strong, low). • Secondary prophylaxis discontinued in children with HIV because of immune reconstitution should be resumed when the CD4 percentage decreases to <15% in those aged <6 years and when the CD4 count decreases to <100 cells/mm^3 in those aged ≥6 years (strong, moderate).
Rating System *Strength of Recommendation: Strong or Weak* *Quality of Evidence: High, Moderate, Low, or Very Low*

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.[1] Transmission can occur vertically from a pregnant person with CMV to their offspring; horizontally by contact with virus-containing breast milk, saliva, urine, or genital fluids; through transfusion of infected blood; or through transplantation of infected organs. During infancy and early childhood, infection usually occurs during breastfeeding by mothers with CMV infection or from exposure to household members with CMV, particularly siblings, who are shedding virus asymptomatically from saliva or urine. CMV infection is more apt to occur at younger ages when sanitary conditions are suboptimal. Among adolescents, sexual transmission is the major mode of CMV acquisition.

Age-related prevalence of CMV 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.[2-4] Group care of children facilitates spread of CMV, especially in toddlers, and leads to higher prevalence of infection in children who attend childcare centers and in their caregivers.[5-8] Toddlers with CMV infection may shed CMV for many months after primary infection, which also poses a transmission risk for CMV-susceptible daycare workers.[6,9-11] 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 adults with low income is ≥80%.[12,13] Overall, among U.S. women of childbearing age, the prevalence of CMV infection is 30% to 70%, with the highest prevalence in women in lower socioeconomic strata.[14] The prevalence of CMV infection among pregnant women with HIV is higher than in the general population, with approximately 90% of pregnant women with HIV coinfected with CMV.[15,16]

CMV is the most common congenitally acquired infection, with prevalence estimates in live-born infants ranging from 0.3% to 1.3%.[17] Congenital (*in utero*) CMV infection may occur in infants born to women who have primary or non-primary CMV infection during pregnancy.[18-20] Following primary infection during pregnancy, the rate of transmission to the fetus is approximately 30% to 40%.[21,22] According to currently available diagnostic methodologies, the exact rate of transmission in non-primary maternal infections remains largely unknown and difficult to determine. Data from published cohorts and meta-analyses indicate that rates of non-primary congenital CMV (cCMV) transmission are substantially lower than for primary infection.[23-26]

Non-primary maternal infection can result in congenital infection because of reactivation of latent infection or reinfection with a different CMV strain in CMV-seropositive women during pregnancy.[18,27-30]

CMV also can be transmitted from mother to infant during the intrapartum or postpartum periods via infected maternal secretions or breast milk. Symptomatic CMV disease due to postnatal acquisition can occur in premature neonates. Long-term sequelae are rare in premature or term infants who acquire CMV perinatally or postnatally.[31-35]

Among CMV-seropositive women, the rate of CMV shedding from the cervix is higher in women with HIV coinfection than in women without HIV (52% and 6% to 21% respectively, by polymerase chain reaction [PCR]).[36] In the era before antiretroviral therapy (ART), the overall rate of cCMV infection among infants born to mothers with HIV was 4.45% and was similar for infants with HIV and those without HIV (4.3% among infants with perinatal HIV and 4.5% among those without HIV).[37] However, more recent studies from South Africa of pregnant women with HIV who are not on ART have reported prevalence rates ranging from 3.8% to 6.5% among infants exposed to HIV, with a sixfold higher cCMV rate in infants with *in utero* HIV transmission.[38,39] In the ART era, prevalence of cCMV infection in infants born to mothers with HIV has ranged from 2.2% to 5.2%.[15,40-44] From 1988 to 2004 (years encompassing both the pre-ART and ART eras), the rates of cCMV infection in infants born to mothers with HIV were 10.3% to 21% for the infants with HIV and 2.2% to 3.8% for those without HIV.[40,45] In two studies, rates of *in utero* HIV transmission to neonates born to women with HIV were higher among infants with cCMV infection (67% to 70%) than among those without cCMV infection (36% to 42%), suggesting that the rate of intrauterine viral co-transmission of HIV and CMV is high.[40,46] More recent published data from a high–HIV prevalence area in the ART era confirmed that *in utero* HIV transmission is significantly higher in neonates who are HIV exposed with cCMV compared to those without cCMV infection (odds ratio 20.1, 95% CI, 6.09–66.46).[44] In neonates with cCMV infection, the percentage of infants with

symptomatic cCMV infections was 23.1% among those coinfected with HIV-1, compared with 6.7% among those without HIV-1.[40] These data indicate that the prevalence of cCMV may be higher among infants exposed to HIV compared with those unexposed to HIV, and that rates of cCMV and HIV co-transmission as well as symptomatic cCMV infection are high among infants exposed to HIV.

The risk of acquiring CMV infection during early childhood appears to be greater for children with HIV than for children without HIV (39.9% vs. 15.3%).[37] The rate of CMV acquisition in children with HIV appears to be particularly high during the first 12 months of life (35% to 42%) and, through age 4 years, remains higher for those with HIV than for those without HIV.[4,37,46-49] In the pre-ART era, children with HIV/CMV coinfection were more likely to have HIV disease progression than children with HIV mono-infection, but in the ART era, HIV/CMV coinfection has not been associated with excess mortality.[37,48]

CMV disease occurs less frequently among children with HIV than among adults with HIV, but still contributed substantially to morbidity and mortality among children with HIV in the era before ART. In the pre-ART era, CMV caused 8% to 10% of pediatric AIDS-defining illnesses.[50] Data in adults with HIV have shown a 75% to 80% decrease in the incidence of new cases of CMV end-organ disease with the advent of ART, with an incidence estimated to be <6 cases per 100 person-years.[51] In a study of opportunistic infections in approximately 3,000 children followed in Pediatric AIDS Clinical Trials Group studies during the pre-ART 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.[52] 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% and 0.1 case per 100 child-years in children with CD4 percentage >25%. In the same cohort during the ART era, the overall rate of CMV retinitis was <0.5 per 100 child-years.[53] In the Perinatal AIDS Collaborative Transmission Study, the incidence of non-ocular CMV disease before and after January 1997 (during pre-ART and ART eras) was 1.4 per 100 child-years and 0.1 per 100 child-years, respectively, and CMV retinitis declined from 0.7 to 0.0 per 100 child-years.[54]

Children with symptomatic HIV who are coinfected with CMV have a higher rate of CMV viruria than do children who have asymptomatic HIV or are HIV exposed.[55] Overall, up to 60% of children with AIDS shed CMV. This compares with one-third of all children with HIV; 15% to 20% of children with CMV infection who are HIV exposed but uninfected; and <15% of infants with CMV infection who are not exposed to HIV.[56] Similarly, in older children and adolescents with perinatally acquired HIV who are on ART or ART-naive, the frequency of CMV DNAemia was higher compared to HIV-uninfected controls and was associated with impaired growth and poor lung function.[57]

Clinical Manifestations

In the general population, approximately 10% of infants with cCMV infection are symptomatic at birth. The rate of symptomatic infection among infants with congenitally acquired CMV is higher in infants with HIV (23.1%) than in children who are HIV exposed but uninfected (6.7%), even in the ART era.[40] In studies of cohorts of neonates without HIV with symptomatic cCMV disease, clinical presentations commonly observed included size that was small for gestational age, petechiae, jaundice, hepatosplenomegaly, chorioretinitis, microcephaly, intracranial calcifications, and sensorineural hearing loss (SNHL).[58,59] Mortality of children with symptomatic cCMV disease is as high as 30%. Approximately 40% to 58% (and in specific cohorts, as many as 90%) of infants with

symptomatic CMV disease at birth who survive have late complications, including substantial hearing loss, intellectual and developmental disabilities, chorioretinitis, optic atrophy, seizures, or learning disabilities.[17,60] Although most children with cCMV infection do not have symptoms at birth, 10% to 15% of children with asymptomatic cCMV infection are at risk of later developmental abnormalities, SNHL, chorioretinitis, or neurologic deficits. Infants with asymptomatic cCMV infection may have early or late-onset SNHL as the only manifestation of congenital infection. Rates of hearing loss and other late complications of cCMV infection among infants with vertically transmitted, asymptomatic, HIV/CMV coinfection are unknown. Premature neonates who acquire CMV postnatally can be asymptomatic or can have evidence of disease, such as hepatitis, thrombocytopenia, or pneumonitis.

Among children with HIV, HIV disease seems to progress more quickly in those coinfected with CMV than in those without CMV infection.[37,45,50,55] In one study from the pre-ART era, 53% of infants coinfected with HIV and CMV had progression to AIDS or had died by age 18 months, compared with 22% of children with HIV 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).[37] Limited data indicate that infants with HIV/CMV coinfection treated with ART do not experience accelerated HIV disease progression.[61,62]

CMV retinitis is the most frequent severe manifestation of CMV disease among children with HIV, accounting for approximately 25% of CMV AIDS-defining illnesses in the pre-ART era. CMV retinitis among young children with HIV is frequently asymptomatic and discovered on routine eye examination.[63] 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. Children with HIV with CD4 counts <100 cells/mm^3 are more likely than those with higher CD4 counts to develop CMV retinitis; however, CD4 count is less predictive of risk of CMV disease in young infants, and systemic and localized CMV disease can occur in infants with HIV with higher, age-adjusted CD4 counts.[56,64] The rate of CMV retinitis in children with HIV has decreased in the ART era, with reported rates of 0.0% to 0.4%. [53,65,66]

End-organ CMV disease has been reported in the lung, liver, gastrointestinal (GI) tract, pancreas, kidney, sinuses, and CNS of children with HIV, but is rare in the era of ART.[64,67-69] In children with HIV who have extraocular CMV disease, predominantly nonspecific symptoms (e.g., fever, poor weight gain, and 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 themselves contribute to these findings is unclear.[56] Gastrointestinal (GI) manifestations among children with HIV 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 children with HIV is difficult to assess because CMV 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% of patients), and low glucose (30% of patients). 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.[70]

Diagnosis

Because CMV is a persistent infection and may reactivate asymptomatically during inflammatory states, CMV disease is diagnosed by a combination of consistent clinical manifestations with supportive virologic testing indicative of CMV infection. A positive CMV immunoglobulin G (IgG) antibody assay in an infant aged <12 months can reflect transplacental maternal antibody transfer and may not indicate infection of the infant. In older children, a positive CMV IgG antibody assay indicates CMV infection. In children of any age, a positive CMV culture or PCR assay confirms CMV infection.

CMV can be isolated in cell culture from peripheral blood leukocytes, body fluids (e.g., urine, saliva), or tissues. A positive blood buffy-coat culture establishes CMV infection and increases the likelihood that disease or symptoms are caused by CMV because children with CMV-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) with supportive histopathology provides evidence of disease causation in symptomatic patients. The limitation of cell culture 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.[71,72] Using centrifugation-assisted shell vial culture amplification techniques, CMV can be detected within 16 to 40 hours of culture inoculation. 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.

Several methods have been used to detect CMV antigen or DNA directly and identify patients at risk of CMV disease; these methods 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.[73] The National Institute of Standards and Technology and the World Health Organization Expert Committee on Biological Standardization have developed reference standards for nucleic acid–based assays for CMV DNA, permitting comparison of quantitative DNA PCR test results among clinical laboratories.[74,75]

To diagnose cCMV infection, the traditional gold standard is a positive viral culture from saliva or urine collected within the first 21 days of life. More recently, saliva and urine PCR (but not blood PCR) also have been validated to diagnose cCMV infection.[76,77] Beyond 21 days of age, positive cultures and PCR tests can be due to postnatally acquired CMV infection.

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 and therefore do not diagnose CMV disease in the absence of clinical findings. Alternatively, localized CMV disease (e.g., GI disease) may not be accompanied by positive culture or PCR of blood, and diagnosis may require direct sampling of the involved organ for CMV testing.

Prevention Recommendations

Preventing Exposure

Although breastfeeding can result in breastmilk-associated CMV transmission to infants, maternal CMV infection is not a contraindication to breastfeeding.[3,78,79]

Infants who were exposed to HIV but are uninfected and children, adolescents, and adults with HIV 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.

Adults and adolescents with HIV who are childcare providers or parents of children in childcare facilities should be informed that they are at increased risk of CMV infection. Risk of CMV infection can be diminished by optimal hygienic practices (e.g., handwashing). 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 in children with HIV are prevention of severe immunosuppression by treating with ART and recognition of the early manifestations of disease. CMV antibody testing is recommended at age 1 year (or at baseline evaluation for children >1 year of age) and then annually for CMV-seronegative infants and children with HIV who are immunosuppressed (i.e., CD4 count <100 cells/mm^3 or CD4 percentage <10%). Children with HIV aged <5 years who have CMV and are severely immunosuppressed (i.e., CD4 count <50 cells/mm^3 or CD4 percentage <5%) should have a dilated retinal examination performed by an ophthalmologist every 6 months. Older children should be counseled to report floaters in the eye and visual changes immediately, as recommended for adults with HIV.[80]

Since the advent of ART, CMV end-organ disease has diminished to such an extent that primary prophylaxis with antiviral agents in people coinfected with CMV and HIV is not recommended.[54] CMV end-organ disease is best prevented by ART to maintain a CD4 count >100 cells/mm^3 (CD4 percentage >10% in children <6 years). If this is not possible, prophylaxis with valganciclovir can be considered for children and adolescents with HIV who are CMV-seropositive and who have severe immunosuppression, defined as CD4 counts of <50 cells/mm^3 for children age ≥6 years or as a CD4 percentage <5% for children age <6 years. However, data supporting the efficacy of antiviral prophylaxis against CMV in pediatric patients with HIV are lacking, and CMV disease has been

observed in children with higher CD4 counts than the thresholds suggested for primary prophylaxis.[52,81] Randomized clinical trials of ganciclovir prophylaxis in adult patients with AIDS and low CD4 counts produced conflicting results, with one trial showing a 49% reduced risk of CMV disease and the other trial showing no benefit.[82-84] Ganciclovir is associated with hematologic toxicity, and animal studies indicate teratogenicity and carcinogenicity. Therefore, ART remains the preferred approach to prevent CMV disease in children with HIV.

In a retrospective cohort study in adults with HIV with CD4 counts <100 cells/mm^3 and CMV viremia who did and did not receive preemptive treatment with antiviral therapy (ganciclovir, valganciclovir, or foscarnet), preemptive CMV therapy resulted in a 25% decreased incidence of CMV end-organ disease.[85] The use of CMV preemptive therapy has not been studied in pediatric patients with HIV.

The rate of CMV and HIV co-transmission *in utero* is higher than the rate of cCMV infection in newborns who do not have HIV.[40,44,45,48] Therefore, testing for cCMV infection in infants known to have vertically transmitted HIV is recommended in the first 21 days of life. Some experts also recommend testing all infants born to mothers with HIV for cCMV, because of the increased risk of HIV/CMV co-transmission and the narrow postnatal window (21 days) during which the diagnosis of cCMV infection can be made. Asymptomatic cCMV infection is associated with late-onset hearing loss in children without HIV.[59] Based on experience in infants without HIV, serial evaluation for hearing loss (e.g., at 3 to 6 month intervals for the first year, then every 6 to 9 months until 3 years of age, then annually at least until 6 years of age) should be considered for infants with cCMV infection (symptomatic and asymptomatic).[86]

Discontinuing Primary Prophylaxis

Because primary prophylaxis with antiviral agents in individuals coinfected with CMV and HIV usually is not recommended (as discussed above), consideration for discontinuing primary prophylaxis usually is unnecessary. When valganciclovir primary prophylaxis is provided, cessation of prophylactic treatment can be considered when the CD4 count is sustained at >100 cells/mm^3 in children aged ≥6 years, or CD4 percentage >10% in children aged <6 years.

Treatment Recommendations

Treating Disease

Congenital CMV Infection

Treatment of newborns who have symptomatic cCMV disease involving the CNS with intravenous (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.[87,88] All infants in these studies did not have HIV. In a Phase 3 randomized controlled trial, infants with CNS disease due to cCMV infection who received IV ganciclovir for 6 weeks were less likely to have hearing deterioration over the first 2 years of life and had fewer neurodevelopmental delays at 1 year of life than infants receiving no antiviral therapy.[88,89] However, approximately two-thirds of the infants developed substantial neutropenia during therapy.[88] A subsequent trial comparing 6 weeks to 6 months of oral valganciclovir treatment in infants with symptomatic cCMV infection showed no difference in the primary endpoint of best-ear hearing at 6 months, but showed modest benefit of 6-month valganciclovir therapy for hearing and developmental secondary endpoints at 12 and 24

months in adjusted analysis. The rate of neutropenia observed in valganciclovir-treated infants was lower than previously observed in ganciclovir-treated infants.[90] Consensus recommendations have been published for prevention, diagnosis, and treatment of cCMV infection in pregnant people and neonates.[91]

Based on these results in infants without HIV, oral valganciclovir therapy for 6 months is recommended for infants who are exposed to or have HIV and who have symptomatic cCMV disease, if valganciclovir can be initiated within the first month of life. Neonates with symptomatic cCMV disease can be referred to a pediatric infectious diseases specialist for consideration of valganciclovir therapy and long-term monitoring for sequelae.[88,91,92]

CMV retinitis should be managed in collaboration with an experienced ophthalmologist, and CMV treatment should be instituted in addition to ART. IV ganciclovir, oral valganciclovir, IV foscarnet, and IV cidofovir are all effective treatments for CMV retinitis in adults with HIV.[93-100] For infants and children with HIV, 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). Oral valganciclovir, a prodrug of ganciclovir, is one of the first-line treatments for adults with HIV who have CMV retinitis[95] and is an option in both older children and patients with HIV who have mild CMV disease. 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 can be considered for transitioning from IV ganciclovir to oral valganciclovir to complete treatment and/or for secondary prophylaxis once improvement in retinitis is noted.

An alternative drug for treating CMV disease or for use in ganciclovir-resistant CMV infections in children with HIV is foscarnet. Foscarnet used as CMV-suppressive therapy has been associated with increased length of survival relative to ganciclovir in adults with HIV. 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.

Combination therapy with ganciclovir and foscarnet may delay progression of retinitis in certain patients in whom monotherapy fails[101,102] and can be used as initial therapy in children with sight-threatening disease. Combination therapy also has been used for adults with retinitis that has relapsed on single-agent therapy. However, adverse effects, such as hematologic and renal toxicity, can be associated with combination therapy.

Intravitreous injections of ganciclovir, foscarnet, or cidofovir have been used to control retinitis, but biweekly intraocular injections are required. Data in children are limited, and biweekly injections are impractical in most children. Implantation of an intravitreous ganciclovir medication-release device in the posterior chamber of the eye also has been used in adults and adolescents with HIV; however, this device is no longer commercially available. In adults, the combination of oral ganciclovir with a ganciclovir sustained-release intraocular implant, replaced every 6 to 9 months, was superior to daily IV ganciclovir in preventing relapse of retinitis.[103] Among adults with HIV who have sight-threatening CMV lesions adjacent to the optic nerve or fovea, initial treatment with intraocular ganciclovir implant (no longer manufactured) plus IV ganciclovir or oral valganciclovir was preferred by some adult HIV specialists.[93-97] Use of systemic therapy in addition to intraocular ganciclovir has the additional benefit of reducing development of retinitis in the contralateral eye. In adults, small peripheral lesions can be treated with systemic therapy without local treatment. Use of

intraocular cidofovir in children is not recommended because of lack of pediatric use data and the risk of ocular hypotony in adults.[104]

Other CMV Disease Entities

For acquired CMV neurologic disease, prompt initiation of CMV 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.[105] Foscarnet concentrations in the CSF are about two-thirds of those in serum.[106] Combination treatment with ganciclovir and foscarnet may be preferable as initial therapy to stabilize disease and maximize response.[64,107] However, this approach may be associated with adverse effects (renal, gastrointestinal, or hematopoietic systems), and the optimal treatment for neurologic disease in children receiving optimized ART is unknown.

Patients with AIDS and recipients of solid organ transplants who have GI disease attributed to CMV appear to benefit from ganciclovir therapy.[108,109] Limited data and data from uncontrolled studies suggest that ganciclovir therapy is useful in patients with AIDS and CMV pneumonia.[110] As with other CMV disease, antiviral management for CMV disease of the GI tract or lungs should also include ART.

Monitoring Response to Therapy and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome

CMV retinitis should be managed in concert with an experienced ophthalmologist. Recommendations for adults with HIV include indirect ophthalmoscopy of both eyes through a dilated examination of the retina performed at the time of diagnosis of CMV retinitis, 2 weeks after initiating therapy, and monthly thereafter while the patient is on anti-CMV treatment.[80] By extrapolation, similar recommendations are made for children with HIV who have CMV retinitis. 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. 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. Dosing in patients with renal dysfunction should be adjusted according to the measured or estimated creatinine clearance. 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, led 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. Nephrotoxicity can be reduced with pre-hydration, and metabolic disturbances can be minimized if foscarnet is administered by slow rates of infusion not exceeding 1 mg/kg/minute and by monitoring serum electrolytes to guide electrolyte replacement.[111-113] 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, serum electrolytes, and renal function should be monitored twice weekly during induction therapy and once weekly thereafter.

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.[114] 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 the drug is administered 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 ART is an immunologic reaction to CMV that is associated with inflammation in the anterior chamber and/or the vitreous and, therefore, is a form of immune reconstitution inflammatory syndrome (IRIS).[115] Ocular complications of uveitis include macular edema and development of epiretinal membranes, which can cause loss of vision. Patients with low CD4 counts who are starting ART are at risk of IRIS. Frequent ophthalmologic examinations are warranted during the period of immune reconstitution in children who are unable to report symptoms, and ophthalmologic examination is indicated for children of any age who develop visual 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.[116]

Managing Treatment Failure

CMV resistance to ganciclovir and valganciclovir can be conferred by mutations in the viral phosphotransferase gene, UL97, or the viral DNA polymerase gene, UL54.[117,118] Resistance to foscarnet or cidofovir occurs because of mutations in the UL54 DNA polymerase gene.[119,120] Resistant strains of CMV should be suspected when progressive disease and continued recovery of virus occurs despite ganciclovir therapy. Viral culture and phenotypic antiviral drug susceptibility testing are not generally available in clinical laboratories, but sequencing of the CMV UL97 and UL54 genes from PCR-amplified specimens may be performed in commercial laboratories. Results of genotypic resistance testing have been shown to correlate with clinical outcome of ganciclovir treatment in patients with HIV who have CMV retinitis.[121] Foscarnet is the empiric drug of choice when ganciclovir resistance is suspected.

In patients with CMV retinitis, although drug resistance can occur in patients receiving long-term CMV therapy, early relapse may be caused by the limited intraocular penetration of systemically administered drugs. In adults with HIV 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.[122,123] Early first relapse of retinitis should generally be treated with reinduction with the same drug used for initial treatment, followed by reinstitution of maintenance therapy. However, if drug resistance is suspected or if side effects or toxicities interfere with optimal courses of the initial agent, changing to an alternative drug is reasonable. Combination ganciclovir and foscarnet can be considered, but the combination is associated with greater toxicity.

Preventing Recurrence

Courses of antiviral agents (e.g., ganciclovir, valganciclovir, foscarnet, cidofovir) do not cure CMV infection in any host. For most forms of CMV disease in the context of HIV, after induction therapy, patients are given secondary prophylaxis (chronic maintenance therapy) until reconstitution of the immune system or for the remainder of their lives in the absence of immune reconstitution. Regimens that can be considered for chronic maintenance therapy in adults and adolescents include IV ganciclovir, oral valganciclovir, IV foscarnet, combined IV ganciclovir and foscarnet, and IV cidofovir; these regimens also are recommended for children.[103,124-130] Repetitive intravitreous injections of ganciclovir, foscarnet, and cidofovir reportedly are effective for secondary prophylaxis of CMV retinitis,[131,132] although intraocular therapy alone does not protect the contralateral eye or other organ systems and therefore typically is combined with systemic treatment.[103] Frequent intravitreous injections also are impractical in most children.

Chronic maintenance regimens for patients treated for CMV disease should be chosen in consultation with relevant specialists. Chronic maintenance therapy is not routinely recommended for GI disease but should be considered if relapses occur. A role for maintenance therapy for CMV pneumonitis has not been established. For patients with retinitis, decisions should be made in consultation with an ophthalmologist, considering the anatomic location of the retinal lesion, vision in the contralateral eye, and patients' immunologic and virologic status.

Discontinuing Secondary Prophylaxis

Multiple case series have reported that maintenance therapy can be discontinued safely in adults and adolescents with CMV retinitis whose CD4 counts have increased substantially in response to ART.[133-139] These patients have remained disease free for >30 and up to 95 weeks of follow-up. Plasma HIV RNA levels varied among the patients in these studies, supporting the hypothesis that the CD4 count is the primary determinant of recovery of the immune response. However, CMV retinitis can occur in ART-treated adults with high CD4 counts,[140] suggesting that CMV-specific cellular immunity may be important in controlling CMV in adults with HIV with immune reconstitution[141,142] and reinforcing the importance of ongoing monitoring. In adults with HIV with CMV retinitis, discontinuation of secondary prophylaxis can be considered for patients whose lesions have been treated for at least 3 to 6 months and are inactive and who have sustained (i.e., 3–6 months) increases in CD4 cell counts to >100 cells/mm^3 in response to ART.[80]

The safety of discontinuing secondary prophylaxis after immune reconstitution with ART in children with HIV 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.[143] Early institution of ART may help control CMV infection in children with HIV by maintaining or restoring normal CD4 count and cytotoxic T-lymphocyte responses.[144] Significant toxicities associated with antiviral drugs, including those identified in *in vitro* and animal models, must be considered when deciding whether to discontinue secondary prophylaxis.

Recognizing the limitations of the data in children but drawing on the 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 an increase in CD4 count to >100 cells/mm^3 for children aged ≥6 years (as for adults). When the manifestation of CMV disease is ocular, such decisions should be made in close consultation with an ophthalmologist and consider factors such as magnitude and duration of CD4 count increase,

anatomic location of the retinal lesion, vision in the contralateral eye, and the feasibility of regular ophthalmologic monitoring.

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. CMV viral load or other markers of CMV infection (such as antigenemia or viral DNA tests) are not well standardized, and given that their role in predicting relapse remains to be defined, they are not recommended for routine monitoring of patients with any manifestation of CMV disease.[145,146]

Reinitiating Secondary Prophylaxis

Relapse of CMV retinitis occurs in adults whose CD4 counts have decreased to <50 cells/mm^3 and whose anti-CMV maintenance therapies have been discontinued.[138,140] Reinstitution of secondary prophylaxis is recommended for adults with HIV when their CD4 counts fall to <100 cells/mm^3. For children with HIV in whom secondary prophylaxis has been discontinued because of immune reconstitution, secondary prophylaxis should be reinstituted in those aged <6 years when their CD4 percentages decrease to <15%, and in those aged ≥6 years when their CD4 cell counts decrease to <100 cells/mm^3.

Recommendations

Primary Prevention

I. Is there an indication for CMV antibody testing in children with HIV who are asymptomatic (versus not testing) to guide clinical management?

- CMV antibody testing is recommended at age 1 year (or at baseline evaluation if age >1 year at initial visit) and then annually for CMV-seronegative infants and children with HIV who are immunosuppressed (i.e., CD4 count <100 cells/mm^3 or CD4 percentage <10%) **(strong, low).**
- Children with perinatal HIV have a higher rate of CMV coinfection than children who are HIV exposed but uninfected. In children with HIV, CMV coinfection is associated with morbidity and mortality and, in the pre-ART era, HIV disease in children seemed to progress more quickly in those with CMV coinfection than in those without CMV infection. Although CD4 count is less predictive of risk of CMV disease in young children than in adults, children with HIV who have low CD4 counts are at increased risk of developing CMV disease.

II. Should infants born to mothers with HIV undergo screening for congenital CMV infection (versus not undergoing screening)?

- Testing for congenital CMV infection in the first 21 days of life is recommended for infants with vertically transmitted HIV **(strong, low).** CMV testing also is suggested for all HIV-exposed infants because their HIV status will be indeterminate during the 21-day period in which congenital CMV infection can be diagnosed **(weak, low).** Infants with confirmed congenital CMV infection should be evaluated regularly for early detection of hearing loss and appropriate intervention.
- The rate of congenital CMV infection among neonates born to mothers with HIV (2.2% to 6.5%) is higher than the prevalence of congenital CMV infection in the general population

(0.3% to 1.3%).[15,17,37,39-43] Co-transmission of congenital CMV may be higher among infants with HIV, with higher rates of congenital CMV infection reported among infants infected with HIV (4.3% to 21%) compared to HIV-exposed but uninfected infants (2.2% to 4.9%).[37,39,40,45-47] The rate of symptomatic congenital CMV infection also may be increased with HIV coinfection (23.1%) compared with those with CMV mono-infection (6.7%).[40] The rate of HIV progression in infants with congenital CMV/HIV dual infection is not well documented but may be faster than in infants with HIV mono-infection.[37,48] As the time of diagnosis for congenital CMV infection is limited to the first 21 days of life, a recommendation for CMV testing of HIV-exposed infants is influenced by the difficulty of diagnosing congenital CMV in infants beyond the first 21 days of age.

III. Is primary prophylaxis against CMV recommended for children with HIV who are CMV seropositive (versus not providing prophylaxis)?

- Primary prophylaxis against CMV disease is not recommended for children with HIV who are not severely immunocompromised **(strong, moderate).** CMV end-organ disease is best prevented by antiretroviral therapy (ART) to maintain the CD4 count >100 cells/mm^3 in children aged ≥6 years or CD4 percentage >10% in children aged <6 years **(strong, moderate).**
- Prophylaxis with valganciclovir may be appropriate for CMV-seropositive children with HIV who are severely immunosuppressed (i.e., CD4 count <50 cells/mm^3 in children aged ≥6 years, or a CD4 percentage <5% in children aged <6 years) **(weak, low).**
- Cessation of primary prophylaxis can be considered when the CD4 count is sustained at >100 cells/mm^3 for children ≥6 years of age, or >10% in children <6 years of age **(weak, low).**
- The rate of CMV end-organ disease in children with HIV remains low since the advent of ART.[54,81] Primary prophylaxis in adults with HIV is not recommended.[80] Data supporting the efficacy of antiviral prophylaxis against CMV in pediatric patients with HIV are lacking, but some experts would suggest using valganciclovir primary prophylaxis for children with severe immunosuppression to reduce the risk of CMV disease.

IV. In CMV-seropositive children with HIV aged <5 years, is routine ophthalmologic examination recommended to screen for CMV retinitis (versus not performing routine ophthalmologic examination)?

- Children with HIV aged <5 years who acquired CMV and are severely immunosuppressed (i.e., CD4 count <50 cells/mm^3 or CD4 percentage <5%) should have a dilated retinal examination performed by an ophthalmologist every 6 months **(strong, low).** As CMV retinitis can occur in patients with higher CD4 counts, ophthalmologic screening can be considered for young children with lesser degrees of immunosuppression who are unable to report visual symptoms.
- The rate of CMV retinitis in children with HIV who are CMV seropositive has diminished substantially in the ART era. However, severe immunosuppression increases the risk of CMV retinitis. Therefore, children with HIV who are CMV seropositive and severely immunosuppressed should undergo routine ophthalmologic screening for CMV retinitis. CMV retinitis can also occur in patients without severe immunosuppression, so some experts recommend that young children with lesser degrees of immunosuppression undergo routine ophthalmologic screening until they are old enough to report visual symptoms reliably.

Treatment

V. Among children with HIV and CMV disease, is treatment with anti-CMV antiviral agents in addition to ART (versus ART alone) associated with higher rates of remission and/or decreased mortality?

- Treatment with antiviral therapy against CMV in addition to ART is recommended for CMV disease in children with HIV **(strong, moderate)**. 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, and CNS disease). Transition from IV ganciclovir to oral valganciclovir can be considered for patients who improve on IV therapy **(strong, moderate).**
- Foscarnet is an alternative drug for treating CMV disease or for use in ganciclovir-resistant CMV infections in children with HIV **(strong, moderate).**
- Combination therapy with ganciclovir and foscarnet may delay progression of retinitis in certain patients in whom monotherapy fails and can be used as initial therapy in children with sight-threatening disease **(weak, very low)**. Combination treatment with IV ganciclovir and foscarnet may also be preferable as initial therapy to stabilize CMV neurologic disease and maximize response **(weak, very low).**
- In children with HIV and symptomatic congenital CMV infection, treatment with valganciclovir (or IV ganciclovir) for 6 months is recommended provided it can be started during the first month of life **(strong, moderate).** This is based on studies among children with symptomatic congenital CMV infection but without HIV.
- Treatment of CMV disease in children with HIV has not been studied rigorously, and recommendations are extrapolated from published results of studies in adults with HIV or in pediatric populations with non-HIV related immunosuppression (e.g., organ transplant recipients). Immune reconstitution via ART is necessary for long-term control of CMV disease. Most experts recommend CMV antiviral therapy to treat CMV disease until end-organ disease is controlled, and immune reconstitution is achieved. However, no pediatric studies have compared the rates of disease remission and mortality with anti-CMV therapy plus ART versus those with ART alone.
- A study of infants with symptomatic congenital CMV infection but without HIV who were treated with 6 months of oral valganciclovir demonstrated modest benefit in neurodevelopmental and hearing outcomes.[90] Similar studies have not been conducted in children with HIV.

Secondary Prevention

VI. Is secondary prophylaxis after treatment of CMV disease (versus no secondary prophylaxis) recommended in severely immunocompromised children with HIV?

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

- Secondary prophylaxis (chronic maintenance therapy) is not routinely recommended for CMV gastrointestinal disease but should be considered if relapses occur **(expert opinion).** A role for secondary prophylaxis (maintenance therapy) for CMV pneumonitis has also not been established.
- Courses of antiviral agents (e.g., ganciclovir, valganciclovir, foscarnet, cidofovir) do not cure CMV infection in any host. After induction therapy, secondary prophylaxis (chronic maintenance therapy) is given for most forms of CMV disease in the context of HIV until immune reconstitution is achieved, or in the absence of immune reconstitution, for the remainder of patients' lives. Recommendations for secondary prophylaxis in pediatric patients derive from adult studies given the lack of pediatric trials investigating secondary prophylaxis after CMV disease.

VII. Is discontinuation of secondary prophylaxis for CMV disease recommended in children who have well-controlled HIV (versus continuation of secondary prophylaxis)?

- Discontinuation of secondary prophylaxis may be considered for children who are receiving ART and have a sustained (such as >6 months) increase in CD4 count, defined as an increase in CD4 percentage to >15% for children aged <6 years, or an increase in CD4 count to >100 cells/mm^3 for children aged ≥6 years **(weak, low).**
- All patients with CMV ophthalmic disease in whom anti-CMV maintenance therapy (secondary prophylaxis) has been discontinued should continue to undergo regular ophthalmologic monitoring for early detection of CMV relapse and for immune reconstitution uveitis **(strong, low).**
- Secondary prophylaxis—discontinued in children with HIV because of immune reconstitution—should be resumed when the CD4 percentage decreases to <15% in those aged <6 years and when the CD4 count decreases to <100 cells/mm^3 in those aged ≥6 years **(strong, moderate).**
- Studies regarding the safety and efficacy of discontinuing secondary prophylaxis for CMV disease in children with HIV have not been conducted. Studies in adults support the safety of discontinuing secondary prophylaxis for CMV retinitis in patients manifesting immune reconstitution with ART. Studies have not been performed in the setting of non-ocular CMV disease.

Dosing Recommendations for Preventing and Treating Cytomegalovirus

Indication	First Choice	Alternative	Comments/Special Issues
Primary Prophylaxis	• 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 to 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 m^2) orally once daily with food (maximum dose 900 mg/day)	N/A	Primary Prophylaxis Can Be Considered for— • CMV antibody positivity and severe immunosuppression (i.e., CD4 count <50 cells/mm^3 in children age ≥6 years; CD4 percentage <5% in children age <6 years). Criteria for Discontinuing Primary Prophylaxis • Age ≥6 years with CD4 count >100 cells/mm^3 • Age <6 years with CD4 percentage >10% Criteria for Considering Restarting Primary Prophylaxis • Age ≥6 years with CD4 count <50 cells/mm^3 • Age <6 years with CD4 percentage <5%
Secondary Prophylaxis	• 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 aged 4 months to 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 m^2) orally once daily with food, or • Foscarnet 90–120 mg/kg body weight IV once daily	• Cidofovir 5 mg/kg body weight per dose IV every other week. Must be given with probenecid and IV hydration.	Secondary Prophylaxis Indicated for— • Prior disseminated disease, retinitis, neurologic disease, or GI disease with relapse. Criteria for Discontinuing Secondary Prophylaxis (All of the Following Criteria Must Be Fulfilled) • Completed ≥6 months of ART • Age <6 years with CD4 percentage ≥15% for >6 consecutive months • Age ≥6 years with CD4 count >100 cells/mm^3 for >6 consecutive months • Consultation with ophthalmologist (if retinitis) o Routine (i.e., every 3–6 months) ophthalmological follow-up is recommended for early detection of relapse or immune restoration uveitis.

Dosing Recommendations for Preventing and Treating Cytomegalovirus

Indication	First Choice	Alternative	Comments/Special Issues
			Criteria for Restarting Secondary Prophylaxis • Age <6 years with CD4 percentage <15% • Age ≥6 years with CD4 count <100 cells/mm^3
Treatment	Symptomatic Congenital Infection • Ganciclovir 6 mg/kg body weight per dose IV every 12 hours for 6 weeks or valganciclovir 16 mg/kg body weight per dose orally twice daily for 6 months Disseminated Disease and Retinitis *Induction Therapy* • 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) *Chronic Maintenance Therapy* • Ganciclovir 5 mg/kg body weight once daily for 5–7 days Central Nervous System Disease *Induction Therapy* • 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	Disseminated Disease and Retinitis *Induction Therapy* • Foscarnet, 60 mg/kg body weight per dose IV every 8 hours or 90 mg/kg body weight per dose IV every 12 hours for 14–21 days *Chronic Maintenance Therapy* • Foscarnet 90–120 mg/kg body weight IV once daily *Alternative Therapy for Retinitis (Followed by Chronic Maintenance Therapy; See Secondary Prophylaxis)* • Valganciclovir tablets 900 mg per dose orally twice daily for 14–21 days, followed by chronic suppressive therapy (see above). o Note: This is an option in older children who can receive the adult dose (based on their BSA) and in patients with mild disease. • 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 who are 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	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 ART. 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.

Dosing Recommendations for Preventing and Treating Cytomegalovirus

Indication	First Choice	Alternative	Comments/Special Issues
	Chronic Maintenance Therapy • See Secondary Prophylaxis above.	(see above); however, data on dosing in children are unavailable. Must be given with probenecid and IV hydration.	

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

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