general, foscarnet is also the first choice for infections with ganciclovir-resistant CMV.

Cidofovir is a nucleotide analogue with a long intracellular half-life that allows intermittent IV administration. Induction regimens of 5 mg/kg weekly for 2 weeks are followed by maintenance regimens of 3–5 mg/kg every 2 weeks. Cidofovir can cause severe nephrotoxicity through dose-dependent proximal tubular cell injury; however, this adverse effect can be tempered somewhat by saline hydration and probenecid. Cidofovir is used primarily for ganciclovir-resistant virus.

HUMAN HERPESVIRUS (HHV) TYPES 6, 7, AND 8

HHV-6 AND HHV-7

HHV-6 and -7 seropositivity rates are generally high throughout the world. HHV-6 was first isolated in 1986 from peripheral-blood leukocytes of six persons with various lymphoproliferative disorders. Two genetically distinct variants (HHV-6A and HHV-6B) are now recognized. HHV-6 appears to be transmitted by saliva and possibly by genital secretions.

Infection with HHV-6 frequently occurs during infancy as maternal antibody wanes. The peak age of acquisition is 9–21 months; by 24 months, seropositivity rates approach 80%. Older siblings appear to serve as a source of transmission. Congenital infection also may occur, and 1% of newborns are infected with HHV-6; placental infection with HHV-6 has been described. Most postnatally infected children develop symptoms (fever, fussiness, and diarrhea). A minority develop exanthem subitum (roseola infantum; see Fig. 25e-5), a common illness characterized by fever with subsequent rash. In addition, ~10–20% of febrile seizures without rash during infancy are caused by HHV-6. After initial infection, HHV-6 persists in peripheral-blood mononuclear cells as well as in the central nervous system, salivary glands, and female genital tract.

In older age groups, HHV-6 has been associated with mononucleosis syndromes; in immunocompromised hosts, encephalitis, pneumonitis, syncytial giant-cell hepatitis, and disseminated disease are seen. In transplant recipients, HHV-6 infection may also be associated with graft dysfunction. Acute HHV-6-associated limbic encephalitis has been reported in hematopoietic stem cell transplant recipients and is characterized by memory loss, confusion, seizures, hyponatremia, and abnormal electroencephalographic and MRI results. High plasma loads of HHV-6 DNA in hematopoietic stem cell transplant recipients are associated with allelic-mismatched donors, use of glucocorticoids, delayed monocyte and platelet engraftment, development of limbic encephalitis, and increased all-cause mortality rates. Like many other viruses, HHV-6 has been implicated in the pathogenesis of multiple sclerosis, although further study is needed to distinguish between association and etiology.

HHV-7 was isolated in 1990 from T lymphocytes from the peripheral blood of a healthy 26-year-old man. The virus is frequently acquired during childhood, albeit at a later age than HHV-6. HHV-7 is commonly present in saliva, which is presumed to be the principal source of infection; breast milk also can carry the virus. Viremia can be associated with either primary or reactivation infection. The most common clinical manifestations of childhood HHV-7 infections are fever and seizures. Some children present with respiratory or gastrointestinal signs and symptoms. An association has been made between HHV-7 and pityriasis rosea, but evidence is insufficient to indicate a causal relationship.

Clustering of HHV-6, HHV-7, and CMV infections in transplant recipients can make it difficult to sort out the roles of the various agents in individual clinical syndromes. HHV-6 and HHV-7 appear to be susceptible to ganciclovir and foscarnet, although definitive evidence of clinical response is lacking.

HHV-8

Unique herpesvirus-like DNA sequences were reported during 1994 and 1995 in tissues derived from Kaposi's sarcoma (KS) and body cavity–based lymphoma occurring in patients with AIDS. The virus from which these sequences were derived is designated HHV-8 or Kaposi's sarcoma–associated herpesvirus (KSHV). HHV-8, which infects B lymphocytes, macrophages, and both endothelial and epithelial cells, appears to be causally related not only to KS and a subgroup of AIDS-related B cell body cavity–based lymphomas (primary effusion lymphomas) but also to multicentric Castleman's disease, a lymphoproliferative disorder of B cells. The association of HHV-8 with several other diseases has been reported but not confirmed.

HHV-8 seropositivity occurs worldwide, with areas of high endemicity influencing rates of disease. Unlike other herpesvirus infections, HHV-8 infection is much more common in some geographic areas (e.g., central and southern Africa) than in others (North America, Asia, northern Europe). In high-prevalence areas, infection occurs in childhood, seropositivity is associated with having a seropositive mother or (to a lesser extent) older sibling, and HHV-8 may be transmitted in saliva. In low-prevalence areas, infections typically occur in adults, probably with sexual transmission. Concurrent epidemics of HIV-1 and HHV-8 infections among certain populations (e.g., men who have sex with men) in the late 1970s and early 1980s appear to have resulted in the frequent association of AIDS and KS. Transmission of HHV-8 may also be associated with organ transplantation, injection drug use, and blood transfusion; however, transmission via blood transfusion in the United States appears to be quite rare.

Primary HHV-8 infection in immunocompetent children may manifest as fever and maculopapular rash. Among individuals with intact immunity, chronic asymptomatic infection is the rule, and neoplastic disorders generally develop only after subsequent immunocompromise. Immunocompromised persons with primary infection may present with fever, splenomegaly, lymphoid hyperplasia, pancytopenia, or rapid-onset KS. Quantitative analysis of HHV-8 DNA suggests a predominance of latently infected cells in KS lesions and frequent lytic replication in multicentric Castleman's disease.

Effective antiretroviral therapy for HIV-infected individuals has led to a marked reduction in rates of KS among persons dually infected with HHV-8 and HIV in resource-rich areas. HHV-8 itself is susceptible in vitro to ganciclovir, foscarnet, and cidofovir. A small, randomized, double-blind, placebo-controlled, crossover trial suggested that oral valganciclovir administered once daily reduced HHV-8 replication. However, clinical benefits of valganciclovir or other drugs in HHV-8 infection have not yet been demonstrated. Sirolimus has been shown to inhibit the progression of dermal KS in kidney transplant recipients while providing effective immunosuppression.