and hypo- or hyperphosphatemia can develop. Saline hydration and slow infusion appear to protect the patient against nephrotoxicity and electrolyte disturbances. Although hematologic abnormalities have been documented (most commonly anemia), foscarnet is not generally myelosuppressive and can be administered concomitantly with myelosuppressive medications.

TRIFLURIDINE

Trifluridine is a pyrimidine nucleoside active against HSV-1, HSV-2, and CMV. Trifluridine monophosphate irreversibly inhibits thymidylate synthetase, and trifluridine triphosphate inhibits viral and, to a lesser extent, cellular DNA polymerases. Because of systemic toxicity, trifluridine's use is limited to topical therapy. Trifluridine is approved for treatment of HSV keratitis, against which trials have shown that it is more effective than topical idoxuridine but similar in efficacy to topical vidarabine. The drug has benefited some patients with HSV keratitis who have failed to respond to idoxuridine or vidarabine. Topical application of trifluridine to sites of acyclovir-resistant HSV mucocutaneous infection has also been beneficial in some cases.

VIDARABINE

Vidarabine is a purine nucleoside analogue with activity against HSV-1, HSV-2, VZV, and EBV. Vidarabine inhibits viral DNA synthesis through its 5′-triphosphorylated metabolite, although its precise molecular mechanisms of action are not completely understood. IV-administered vidarabine has been shown to be effective in the treatment of herpes simplex encephalitis, mucocutaneous HSV infections, herpes zoster in immunocompromised patients, and neonatal HSV infections. Its use has been supplanted by that of IV acyclovir, which is more effective and easier to administer. Production of the IV preparation has been discontinued by the manufacturer, but vidarabine is available as an ophthalmic ointment, which is effective in the treatment of HSV keratitis.

AGENTS OF INVESTIGATIVE INTEREST

Maribavir is a benzimidazole that inhibits CMV and EBV. This drug inhibits the CMV UL97 kinase and does not require intracellular phosphorylation for its antiviral activity. Its mechanism of action involves blocking viral DNA synthesis and virion egress. Maribavir is orally administered and has been associated with taste disturbance and diarrhea. In phase 3 studies, it was not efficacious in the prevention of CMV infection in recipients of hematopoietic stem cell and adult liver transplants. However, when used at somewhat higher doses, it may be efficacious for the treatment of refractory or resistant CMV infections in transplant recipients.

Letermovir is an investigational drug with activity against CMV. It is a dihydroquinozoline that acts through inhibition of the viral terminase enzyme complex. This mechanism of action differs from that of ganciclovir, foscarnet, and cidofovir, which inhibit viral DNA polymerase; therefore, letermovir is active against CMV isolates that are resistant to those drugs. It is orally administered and is reportedly well tolerated. Letermovir is being evaluated as prophylaxis against CMV in hematopoietic stem cell recipients.

Inhibition of the helicase-primase heterotrimeric complex of HSV-1 and HSV-2 represents a novel mechanism of action of amenamevir and pritelivir. These drugs are being assessed for prevention and treatment of HSV genital infection. The efficacy of amenamevir, administered as a single oral dose of 1200 mg for recurrent genital herpes, was comparable to that of valacyclovir given for 3 days. Pritelivir has a long half-life (up to 80 h) and was studied in a placebo-controlled trial of suppression of genital HSV infections. Compared with placebo, pritelivir—a loading dose followed by either a daily oral dose of 75 mg for 4 weeks or a weekly dose of 400 mg for 4 weeks—reduced HSV shedding and days of genital lesions. Additional clinical studies of the helicase-primase inhibitors of HSV are planned.

ANTIVIRAL DRUGS ACTIVE AGAINST HEPATITIS VIRUSES

LAMIVUDINE

Lamivudine is a pyrimidine nucleoside analogue that is used primarily in combination therapy against HIV infection (Chap. 226). Its activity against HBV is attributable to inhibition of the viral DNA polymerase. This drug has also been approved for the treatment of chronic HBV infection. At doses of 100 mg/d given for 1 year to patients positive for hepatitis B e antigen (HBeAg), lamivudine is well tolerated and results in suppression of HBV DNA levels, normalization of serum aminotransferase levels in 40–75% of patients, and reduction of hepatic inflammation and fibrosis in 50–60% of patients. Loss of HBeAg occurs in 30% of patients. Lamivudine also appears to be useful in the prevention or suppression of HBV infection associated with liver transplantation. Resistance to lamivudine develops in 24% of patients treated for 1 year and is associated with changes in the YMDD motif of HBV DNA polymerase. Because of the frequency of development of resistance, lamivudine has been largely supplanted by less-resistance-prone drugs for the treatment of HBV infection.

ADEFOVIR DIPIVOXIL

Adefovir dipivoxil is the oral prodrug of adefovir, an acyclic nucleotide analogue of adenosine monophosphate that is active against HBV, HIV, HSV, CMV, and poxviruses. It is phosphorylated by cellular kinases to the active triphosphate moiety, which is a competitive inhibitor of HBV DNA polymerase and results in chain termination after incorporation into nascent viral DNA. Adefovir is administered orally and is eliminated primarily by the kidneys, with a plasma half-life of 5–7.5 h. In clinical studies, therapy with adefovir at a dose of 10 mg/d for 48 weeks resulted in normalization of serum alanine aminotransferase (ALT) levels in 48–72% of patients and improved liver histology in 53–64%; it also resulted in a 3.5- to 3.9-$\log_{10}$ reduction in the number of HBV DNA copies per milliliter of plasma. Adefovir was effective in treatment-naïve patients as well as in those infected with lamivudine-resistant HBV. Resistance to adefovir appears to develop less readily than that to lamivudine, but adefovir resistance rates of 15–18% have been reported after 192 weeks of treatment and may reach 30% after 5 years. This agent is generally well tolerated. Significant nephrotoxicity attributable to adefovir is uncommon at the dose used in the treatment of HBV infections (10 mg/d) but is a treatment-limiting adverse effect at the higher doses used in therapy for HIV infections (30–120 mg/d). In any case, renal function should be monitored in patients taking adefovir, even at the lower dose. Adefovir is approved only for treatment of chronic HBV infection.

TENOFOVIR DISOPROXIL FUMARATE

Tenofovir disoproxil fumarate is a prodrug of tenofovir, a nucleotide analogue of adenosine monophosphate with activity against both retroviruses and hepadnaviruses. In both immunocompetent and immunocompromised patients (including those co-infected with HIV and HBV), tenofovir given at a dose of 300 mg/d for 48 weeks reduced HBV replication by 4.6–6 $\log_{10}$, normalized ALT levels in 68–76% of patients, and improved liver histopathology in 72–74% of patients. Resistance develops uncommonly during ≥2 years of therapy, and tenofovir is active against lamivudine-resistant HBV. The safety profile of tenofovir is similar to that of adefovir, but nephrotoxicity has not been encountered at the dose used for HBV therapy. Tenofovir is approved for the treatment of HIV and chronic HBV infections. **For a more detailed discussion of tenofovir, see Chap. 226.**

ENTECAVIR

Entecavir is a cyclopentyl 2′-deoxyguanosine analogue that inhibits HBV through interaction of entecavir triphosphate with several HBV DNA polymerase functions. At a dose of 0.5 mg/d given for 48 weeks, entecavir reduced HBV DNA copies by 5.0–6.9 $\log_{10}$, normalized serum aminotransferase levels in 68–78% of patients, and improved histopathology in 70–72% of patients. Entecavir inhibits lamivudine-resistant viruses that have M550I or M550V/L526M mutations but only at serum concentrations 20- or 30-fold higher than those obtained with the 0.5-mg/d dose. Thus, higher doses of entecavir (1 mg/d) are recommended for the treatment of patients infected with lamivudine-resistant HBV. Development of resistance to entecavir is uncommon in treatment-naïve patients but does occur at unacceptably high rates