Antiviral Drugs for Viruses Other Than Human Immunodeficiency Virus

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On completion of this article, you should be able to (1) discuss the different regimens for the prevention and treatment of human herpesviruses; (2) discuss options for the prevention and treatment of influenza virus, including infections with resistant strains; and (3) discuss antiviral drugs for the treatment of chronic hepatitis B and C infections, including novel nucleos(t)ide analogues and serine protease inhibitors, respectively.

Most viral diseases, with the exception of those caused by human immunodeficiency virus, are self-limited illnesses that do not require specific antiviral therapy. The currently available antiviral drugs target 3 main groups of viruses: herpes, hepatitis, and influenza viruses. With the exception of the antisense molecule fomivirsen, all antiherpes drugs inhibit viral replication by serving as competitive substrates for viral DNA polymerase. Drugs for the treatment of influenza inhibit the ion channel M_2 protein or the enzyme neuraminidase. Combination therapy with Interferon-α and ribavirin remains the backbone treatment for chronic hepatitis C; the addition of serine protease inhibitors improves the treatment outcome of patients infected with hepatitis C virus genotype 1. Chronic hepatitis B can be treated with interferon or a combination of nucleos(t)ide analogues. Notably, almost all the nucleos(t)ide analogues for the treatment of chronic hepatitis B possess anti–human immunodeficiency virus properties, and they inhibit replication of hepatitis B virus by serving as competitive substrates for its DNA polymerase. Some antiviral drugs possess multiple potential clinical applications, such as ribavirin for the treatment of chronic hepatitis C and respiratory syncytial virus and cidofovir for the treatment of cytomegalovirus and other DNA viruses. Drug resistance is an emerging threat to the clinical utility of antiviral drugs. The major mechanisms for drug resistance are mutations in the viral DNA polymerase gene or in genes that encode for the viral kinases required for the activation of certain drugs such as acyclovir and ganciclovir. Widespread antiviral resistance has limited the clinical utility of M_2 inhibitors for the prevention and treatment of influenza infections. This article provides an overview of clinically available antiviral drugs for the primary care physician, with a special focus on pharmacology, clinical uses, and adverse effects.

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ALT = alanine aminotransferase; CHB = chronic hepatitis B; CHC = chronic hepatitis C; CMV = cytomegalovirus; CSF = cerebrospinal fluid; EBV = Epstein-Barr virus; FDA = US Food and Drug Administration; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HHV = human herpesvirus; HIV = human immunodeficiency virus; HSV = herpes simplex virus; HSV-1 = HSV type 1; HSV-2 = HSV type 2; IFN = interferon; IV = intravenous; mRNA= messenger RNA; RSV = respiratory syncytial virus; SC = subcutaneous; SVR = sustained virologic response; TK = thymidine kinase; VZV = varicella zoster virus

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Most diseases caused by viral pathogens are self-limited and do not require specific antiviral therapy. Other than therapies targeting the human immunodeficiency virus (HIV), currently available antiviral drugs in the clinical setting target 3 principal groups of viruses—the herpes, hepatitis, and influenza viruses. This review article is structured to discuss antiviral therapeutics on the basis of these 3 major antiviral categories, with the caveat that some drugs discussed in these sections possess other potential applications, such as ribavirin for the treatment of respiratory syncytial virus (RSV) and cidofovir for the treatment of cytomegalovirus (CMV) and other DNA viral infections. Nucleos(t)ide analogues for the treatment of chronic hepatitis B (CHB) may also possess anti-HIV properties, but their clinical utility for the treatment of HIV will be discussed in a separate article in this symposium. Experimental and novel therapies that have not reached clinical application will not be reviewed.

ANTIHERPES DRUGS

Acyclovir

Acyclovir is a synthetic guanosine analogue used for treating herpes simplex virus (HSV) and varicella zoster virus (VZV) infections.[1-3] Intravenous (IV) acyclovir provides excellent tissue and fluid penetration, including the cerebrospinal fluid (CSF), whereas oral acyclovir provides modest bioavailability of 15% to 30%. Bioavailability is improved with the use of valacyclovir, the valyl ester formulation of acyclovir. Acyclovir is excreted by glomerular filtration and tubular secretion.

Herpesviruses have varying degrees of susceptibility to acyclovir, with HSV type 1 (HSV-1) being most susceptible, followed by HSV type 2 (HSV-2) and VZV, and to a lesser extent Epstein-Barr virus (EBV).[1-3] High acyclovir concentrations may also inhibit CMV in vitro, but acyclovir is not recommended clinically for CMV treatment. Acyclovir is not active against human herpesvirus (HHV) 6, 7, and 8.

To exert antiviral activity, acyclovir *must* be converted to acyclovir-triphosphate; this process is initially catalyzed by

viral thymidine kinase (TK) and subsequently by human enzymes. Acyclovir-triphosphate serves as a competitive substrate for viral DNA polymerase, and its incorporation into the DNA chain results in termination of viral replication.

Acyclovir is approved for the treatment of primary and recurrent genital HSV infection (Table 1).[2,4,5] Topical acyclovir may be used to treat genital herpes, but the oral formulation is generally recommended[6]; IV acyclovir is used for severe cases.[1,4] Suppressive therapy with oral acyclovir is also indicated to reduce the incidence of recurrent genital herpes.[4,7]

Oral acyclovir is modestly efficacious against orolabial herpes. In immunocompetent individuals, orolabial herpes is often self-limited, and antiviral treatment is generally not recommended.[7] However, oral acyclovir may be indicated for severe cases, for those with recurrent orolabial herpes, and in those who are immunocompromised.[7,8]

Intravenous acyclovir is the first-line treatment for HSV encephalitis[9] and should be started as soon as the disease is suspected clinically. Magnetic resonance imaging of the brain typically demonstrates temporal lobe involvement, and diagnosis is confirmed by detection of HSV DNA in the CSF. Major studies have evaluated the efficacy of 10 days of acyclovir treatment for HSV encephalitis; however, the recommended duration of treatment in the clinical setting is 2 to 3 weeks because shorter durations have been associated with relapse.[10] The treatment duration may be further prolonged in immunocompromised patients.[8]

Acyclovir is also approved by the US Food and Drug Administration (FDA) for the treatment of VZV[11,12]; however, young immunocompetent patients with zoster may not require treatment if the lesions are localized and have been present for more than 72 hours. Intravenous acyclovir is recommended for patients with disseminated zoster disease or visceral involvement. Acyclovir treatment of zoster reduces duration of viral shedding, formation of new lesions, and short- and long-term neuralgia.[13] Therapy should be started early, but even delayed initiation of acyclovir may still be beneficial in immunocompromised patients. Short-course prednisone may be added as an adjunct to acyclovir treatment of zoster to improve quality of life, especially in elderly patients.

Acyclovir has been used in the treatment of acute retinal necrosis (which is associated with HSV or VZV), eczema herpeticum, and oral hairy leukoplakia due to EBV. Oral acyclovir is used to prevent HSV during the early period after transplant in patients not receiving ganciclovir or valganciclovir prophylaxis.[14]

Acyclovir is generally well tolerated. However, IV acyclovir may cause reversible nephrotoxicity in 5% to 10% of patients because of intratubular precipitation of acyclovir crystals. Acyclovir crystalline nephropathy is more common when acyclovir is given as a rapid infusion (reaching serum concentrations >25 μg/mL)[15] and in patients with dehydration and preexisting renal impairment.[16] Adequate hydration, a slower rate of infusion, and dosing based on renal function may reduce this risk. Reversible neurologic symptoms such as delirium and seizures may occur rarely in elderly people and those with renal impairment; this toxicity has been associated with high serum acyclovir concentrations[15] and high CSF levels of its metabolite 9-carboxymethoxymethylguanine.[17-19] Other adverse effects are gastrointestinal symptoms, myelosuppression, and rash.[3,20,21]

Acyclovir-resistant HSV has been reported, especially in immunocompromised patients.[22-24] Resistance occurs by selection of viral mutants that are deficient in TK (which results in an inability to activate acyclovir) or that have altered DNA polymerase with reduced affinity to acyclovir-triphosphate.[23]

Brivudin

Brivudin is a 5′-halogenated thymidine nucleoside analogue that is highly active against HSV-1 and VZV.[25,26] Brivudin is phosphorylated by viral TK and cellular kinases to brivudin-triphosphate, which serves as a competitive inhibitor of viral DNA polymerase, thereby terminating viral DNA synthesis. It is available in some countries for the treatment of herpes zoster and herpes simplex. However, concerns about its toxicity halted its clinical development in the United States. Its metabolite, bromovinyluracil, irreversibly inhibits dihydropyridine dehydrogenase, which regulates nucleoside metabolism. Coadministration with 5-fluorouracil has resulted in lethal bone marrow toxicity and severe gastrointestinal toxicity.[25,26]

Cidofovir

Cidofovir is a nucleoside analogue used for the treatment of CMV, other herpesviruses, and other DNA viral infections.[27] It is available as an IV formulation, and an oral prodrug of cidofovir (known as *CMX-001*) is under clinical development.[28] This investigational lipid ester formulation of cidofovir has enhanced bioavailability, resulting in improved 50% inhibitory concentrations.[28] Direct intraocular injection of cidofovir is contraindicated due to ocular hypotony.[27] Serum cidofovir concentrations decline rapidly after IV infusion, with a half-life of 2 hours; however, the intracellular half-life of active cidofovir-diphosphate is as long as 65 hours. Cidofovir is eliminated by glomerular filtration and tubular secretion; probenecid reduces its excretion by blocking tubular secretion.[29,30]

Cidofovir is phosphorylated by cellular kinases into cidofovir-diphosphate, a competitive substrate for viral

TABLE 1. **Suggested Antiviral Drugs for the Treatment of Herpesvirus infections**[a,b,c]

Virus	Clinical disease	Drug name (route)	Recommended dosage	Comments
Herpes simplex viruses 1 and 2	Mucocutaneous disease	Acyclovir (IV)	5 mg/kg IV every 8 h	IV therapy is preferred for severe and disseminated disease Risk of crystalline nephropathy
		Acyclovir (oral)	400 mg orally 3 times daily 800 mg orally twice daily 200 mg orally 5 times daily	Localized disease and genital herpes
		Valacyclovir (oral)	1 g orally twice daily 500 mg orally twice daily	First episode of genital herpes Recurrent episodes of genital herpes
	HSV encephalitis	Acyclovir (IV)	10 mg/kg IV every 8 h	Risk of crystalline nephropathy
	Long-term suppression	Acyclovir (oral)	400 mg orally twice daily (400-800 mg 2 to 3 times daily for HIV-infected patients)	
		Valacyclovir (oral)	500 mg orally once daily 1 g orally once daily	Recurrence of <9 episodes per year Recurrence of >9 episodes per year
Varicella zoster virus	Varicella zoster	Acyclovir (IV)	10-12 mg/kg IV every 12 h	Recommended for immunocompromised hosts
		Acyclovir (oral)	600-800 mg orally 5 times daily 1 g orally every 6 h	Less preferred than valacyclovir because of poor bioavailability
		Valacyclovir (oral)	1 g orally 3 times daily	Preferred oral therapy for mild or localized disease
CMV	CMV disease in transplant recipients	Ganciclovir (IV)	5 mg/kg IV every 12 h	IV therapy is preferred for severe CMV disease, gastrointestinal disease, pneumonia, and encephalitis Transition to oral valganciclovir on clinical and virologic improvement Duration of therapy is guided by CMV surveillance using PCR or pp65 antigenemia Risk of myelosuppression
		Valganciclovir (oral)	900 mg orally twice daily	Indicated for CMV syndrome and mild to moderate CMV disease Duration of therapy is guided by CMV surveillance using PCR or pp65 antigenemia Risk of myelosuppression
		Foscarnet (IV)	Induction: 90 mg/kg every 12 h OR 60 mg/kg every 8 h Maintenance: 90-120 mg/kg every 24 h	Second-line therapy Indicated for ganciclovir-resistant CMV disease High risk of nephrotoxicity and electrolyte abnormalities Duration of therapy is guided by CMV surveillance using PCR or pp65 antigenemia
		Cidofovir (IV)	Induction: 5 mg/kg per dose once weekly for 2 doses Maintenance: 5 mg/kg every 2 wk	Alternative treatment of CMV disease; second-line agent Indicated for ganciclovir-resistant CMV disease High risk of nephrotoxicity; requires concomitant hydration and probenecid use Duration of therapy is guided by CMV surveillance using PCR or pp65 antigenemia
	Antiviral prophylaxis for CMV prevention in transplant recipients	Valganciclovir (oral)	900 mg orally once daily	Preferred drug for CMV prophylaxis Duration is generally for 3-6 mo; may be longer for lung transplant recipients Myelosuppression is major adverse effect
		Ganciclovir (IV)	5 mg/kg IV once daily	Preferred for intestinal transplant recipients or in clinical situations in which absorption is a concern
		Ganciclovir (oral)	1 g orally 3 times daily	Effective for CMV prevention but no longer a preferred drug because of its poor bioavailability; valganciclovir is preferred
		Valacyclovir (oral)	2 g orally 4 times daily	Shown to be effective mainly in kidney transplant recipients; not effective for other organ transplant recipients High doses increase risk of hallucinations and neurologic toxicities

(continued on next page)

TABLE 1. **Continued**[a,b,c]

Virus	Clinical disease	Drug name (route)	Recommended dosage	Comments
CMV (continued)	Preemptive therapy for asymptomatic CMV infection in transplant recipients	Valganciclovir (oral)	900 mg orally twice daily	CMV replication is detected by weekly CMV surveillance using PCR or pp65 antigenemia Preferred drug for the treatment of asymptomatic CMV infection in solid organ and hematopoietic stem cell transplant recipients
		Ganciclovir (IV)	5 mg/kg IV every 12 h	Less preferred than valganciclovir because of the logistics of IV administration Oral ganciclovir should not be used for treating active CMV infection
	CMV retinitis in HIV-infected patients	Valganciclovir (oral)	Induction: 900 mg orally twice daily for 14-21 d Maintenance: 900 mg orally once daily until immune reconstitution	For sight-threatening retinitis, use in combination with ganciclovir intraocular implant (see below)
		Ganciclovir (IV)	Induction: 5 mg/kg IV every 12 h for 14-21 d Maintenance: 5 mg/kg IV every 24 h until immune reconstitution	For sight-threatening retinitis, use in combination with ganciclovir intraocular implant (see below)
		Ganciclovir (intraocular implant)	One sustained-release intravitreal implant (4.5 mg/implant) every 6-8 mo	Replace every 6-8 mo until immune reconstitution Use in combination with systemic ganciclovir (or valganciclovir) because of the systemic nature of CMV disease
		Foscarnet (IV)	Induction: 90 mg/kg every 12 h OR 60 mg/kg every 8 h Maintenance: 90-120 mg/kg every 24 h	Second-line therapy Indicated for ganciclovir-resistant CMV disease High risk of nephrotoxicity and electrolyte abnormalities
		Cidofovir (IV)	Induction: 5 mg/kg per dose once weekly for 2 doses Maintenance: 5 mg/kg every 2 wk	Alternative treatment of CMV disease Indicated for ganciclovir-resistant CMV disease High risk of nephrotoxicity; requires concomitant hydration and probenecid use
	CMV disease other than retinitis in HIV-infected patients	Valganciclovir (oral)	Induction: 900 mg orally twice daily for 14-21 d Maintenance: 900 mg orally once daily until immune reconstitution	
		Ganciclovir (IV)	Induction: 5 mg/kg IV every 12 h for 14-21 d Maintenance: 5 mg/kg IV every 24 h until immune reconstitution	Preferred for severe disease (eg, pneumonitis, encephalitis) and for those with poor intestinal absorption
		Foscarnet (IV)	Induction: 90 mg/kg every 12 h OR 60 mg/kg every 8 h Maintenance: 90-120 mg/kg every 24 h	Second-line therapy Indicated for ganciclovir-resistant CMV disease High risk of nephrotoxicity and electrolyte abnormalities
		Cidofovir (IV)	Induction: 5 mg/kg per dose once weekly for 2 doses Maintenance: 5 mg/kg every 2 wk	Alternative treatment for CMV disease Indicated for ganciclovir-resistant CMV disease High risk of nephrotoxicity; requires concomitant hydration and probenecid use

[a] CMV = cytomegalovirus; HIV = human immunodeficiency virus; IV = intravenous; PCR = polymerase chain reaction.
[b] Doses are given for persons with normal renal function. Please consult individual drug's package insert for dose adjustments in persons with impaired renal function.
[c] No antiviral drugs have been approved for the treatment of Epstein-Barr virus or human herpesviruses 6, 7, and 8.

DNA polymerase, thereby halting viral DNA synthesis.[27] The major clinical indication for cidofovir is the treatment of CMV retinitis in HIV-infected patients (Table 1).[31] Cidofovir is also used as rescue therapy for immunocompromised patients with CMV disease resistant or unresponsive to ganciclovir.[32] Because activation of cidofovir does not rely on viral kinases, it retains activity against CMV with the UL97 mutation and HSV with the TK mutation.[33] Resistance to cidofovir occurs when the virus develops mutations in the DNA polymerase gene (ie, *CMV-UL54* gene

mutations).[33] Cidofovir has also been used off-label for various illnesses, such as acyclovir-resistant HSV disease, condyloma acuminatum, BK virus–associated hemorrhagic cystitis, JC virus–associated progressive multifocal leukoencephalopathy, and other infections due to double-stranded DNA viruses.[34-47]

Nephrotoxicity is the most common serious adverse effect of cidofovir.[27] The incidence and severity of nephrotoxicity may be reduced by hydration and probenecid.[48] Blood cell counts should be monitored to assess myelosuppression, and ophthalmological surveillance is recommended because of the risk of ocular hypotony, uveitis, and iritis.[49,50]

Famciclovir

Famciclovir is a diacetyl 6-deoxy analogue of penciclovir. Oral famciclovir is rapidly absorbed and achieves a bioavailability of 77%.[51] Famciclovir is metabolized into penciclovir, reaching peak plasma penciclovir concentrations within 1 hour. Because of extensive hepatic metabolism, virtually no famciclovir is detectable in plasma.[51] Famciclovir is excreted renally as penciclovir and its 6-deoxy precursor.[9]

Famciclovir is active against HSV-1, HSV-2, and VZV, and, to a lesser extent, against EBV. Its mechanism of action is through penciclovir; penciclovir triphosphate inhibits herpes DNA synthesis by acting as a substrate for viral DNA polymerase. The major clinical indications for famciclovir use are treatment of herpes zoster, recurrent genital herpes,[52] and recurrent herpes labialis.[53] Famciclovir can also be used as suppression therapy to reduce the risk of recurrent genital herpes as well as oral treatment of uncomplicated varicella in HIV-infected patients.

The most common adverse effects of famciclovir are headache and nausea.[54] Rare adverse events include jaundice, rash, pruritus, somnolence, and confusion.[54] Acute renal failure has occurred in patients taking inappropriately high doses of famciclovir.

Fomivirsen

Fomivirsen is a 21-nucleotide phosphorothionate oligonucleotide complementary to messenger RNA (mRNA) of the immediate-early region of CMV.[55-57] Its antiviral property is exerted by antisense inhibition of target gene expression. Other potential mechanisms of antiviral activity include its nonspecific interactions with viral particles that may prevent adsorption or lead to inhibition of enzymes required for viral DNA synthesis.

Fomivirsen is given intravitreally. Its main indication is the treatment of CMV retinitis in patients with AIDS who have not benefited from or are intolerant of standard CMV therapies, or whose virus is resistant to ganciclovir and foscarnet.[55-57] The main adverse effect of fomivirsen is increased intraocular pressure and inflammation. Blurred vision, conjunctival hemorrhage, retinal detachment, and retinal edema are other adverse effects.[55-57]

Foscarnet

Foscarnet is a nonnucleoside pyrophosphate analogue that is given intravenously for the treatment of herpesviruses.[58] Its pharmacokinetic profile is complicated by a high incidence of nephrotoxicity and by its deposition and subsequent gradual release from bone.[58] Its half-life depends on the duration of therapy; in patients with normal renal function, the plasma half-life is about 2 to 4 hours, but terminal half-lives up to about 8 days may occur when it has accumulated in bones. Foscarnet is excreted through glomerular filtration.

Foscarnet selectively inhibits pyrophosphate binding on viral DNA polymerases, thus suppressing HSV-1, HSV-2, and CMV replication. It is also active against VZV, HHV-6, and EBV.[59] Unlike ganciclovir, foscarnet does not require intracellular conversion to active triphosphate, thus maintaining activity against herpesviruses with TK or UL97 kinase mutations.[33]

Foscarnet is approved for the treatment of CMV retinitis in patients with AIDS.[58] It has been used to treat other CMV diseases in immunocompromised patients, especially those unable to tolerate ganciclovir and those infected with ganciclovir-resistant virus.[60,61] Foscarnet is also used for treating acyclovir-resistant mucocutaneous HSV and VZV in immunocompromised patients.[58] On rare occasion, it has been used for prevention of CMV in transplant recipients; however, its toxicity limits this clinical indication.[60,61]

Nephrotoxicity is the most common serious adverse effect of foscarnet, affecting 30% of patients. It is caused by deposition of foscarnet crystals in the glomerular capillary lumen.[62,63] Foscarnet may cause myelosuppression, with anemia as the most common effect. It can chelate bivalent metal ions and may lead to reductions in ionized calcium. Other electrolyte disturbances are hypokalemia, hypomagnesemia, and hypophosphatasemia, which could manifest as paresthesias, cardiac dysrhythmias, and neurologic symptoms, including seizures.[64] Patients should be hydrated to prevent nephrotoxicity, and electrolyte abnormalities should be corrected to avoid cardiac and neurologic complications.

Ganciclovir

Ganciclovir is an acyclic 2′-deoxyguanosine analogue for the management of CMV.[65] It is available in oral and parenteral formulations. Oral ganciclovir is poorly absorbed, with a bioavailability of only 5%.[65] Management of active CMV disease is therefore with IV ganciclovir or its oral valyl prodrug valganciclovir. Intravitreal ganciclovir im-

plants are also available, with minimal systemic absorption. Ganciclovir is excreted renally.

Ganciclovir undergoes triphosphorylation to become active, with the initial monophosphorylation catalyzed by UL97-encoded kinase and subsequently by cellular kinases. Ganciclovir triphosphate inhibits viral DNA synthesis through competitive incorporation during viral DNA synthesis, thereby leading to DNA chain termination. In vitro, it is 10 times more potent than acyclovir against CMV and EBV and is just as effective as acyclovir against HSV-1, HSV-2, and VZV.[66] Ganciclovir is active against HHV-6 and HHV-8 but not against HHV-7.[67]

Ganciclovir is approved for the treatment of CMV retinitis in patients with AIDS, the treatment of herpes simplex keratitis, and CMV prophylaxis in transplant recipients. Intravenous ganciclovir may also be used to treat other forms of CMV disease, such as colitis or esophagitis. Induction therapy with IV ganciclovir for CMV retinitis in patients with AIDS has an efficacy of 85% to 95% in stabilizing disease.[68] Because it is poorly absorbed, oral ganciclovir should not be used for induction treatment of CMV disease.[69] Because CMV disease often recurs or progresses in patients with advanced AIDS, oral or IV ganciclovir (or valganciclovir) is given as maintenance therapy until immune reconstitution is achieved.[69] Intravitreal ganciclovir may also be surgically implanted for the treatment of CMV retinitis, although this treatment should be used together with systemic therapy with IV ganciclovir or oral valganciclovir therapy.

Oral ganciclovir may be used to prevent CMV in patients with AIDS; however, the benefit of this strategy is not as pronounced in the era of highly active antiretroviral therapy. Although IV and oral ganciclovir have also been used to prevent CMV disease in transplant recipients, valganciclovir is currently the preferred drug for this indication.[60,61,70] Intravenous ganciclovir is also used as a first-line treatment of CMV disease in bone marrow and solid organ transplant recipients.[61]

Reversible bone marrow suppression is the most common adverse effect of ganciclovir. Other adverse effects of the drug are rash, pruritus, diarrhea, nausea, vomiting, and increased levels of serum creatinine and liver enzymes. Neurotoxicity may occur occasionally.

Resistance to ganciclovir occurs most commonly in severely immunocompromised patients with prolonged exposure to the drug. The most common mechanism for ganciclovir resistance is *UL97* gene mutation[71]; this mutation leads to deficiency in the viral kinase that is necessary for the initial phosphorylation of ganciclovir into its active form. A less common mechanism is a mutation in the *UL54* gene, which encodes for the CMV DNA polymerase.[71]

Penciclovir

Penciclovir is an acyclic guanine analogue that is chemically similar to acyclovir. Because it is poorly absorbed from the gastrointestinal tract, it is only available as topical therapy for mucocutaneous herpes. For systemic use, penciclovir has been reformulated into the oral prodrug famciclovir.

The antiviral activity of penciclovir is similar to that of acyclovir, with efficacy against HSV-1, HSV-2, and VZV, and, to a lesser extent, against EBV.[72] Penciclovir is monophosphorylated by TK and subsequently by cellular kinases into active penciclovir-triphosphate, which inhibits herpes DNA polymerase activity by serving as a competitive inhibitor of deoxyguanosine triphosphate.[73] Penciclovir is approved as topical therapy for recurrent herpes labialis, resulting in a faster healing rate and reduction in pain and viral shedding.[74]

Valacyclovir

Valacyclovir, an L-valyl ester prodrug of acyclovir,[75] provides a higher bioavailability (55%) than oral acyclovir. After absorption, valacyclovir is hydrolyzed almost completely to acyclovir by first-pass intestinal and hepatic metabolism. It achieves peak serum concentration in 1 to 3 hours. Serum acyclovir levels are much higher with valacyclovir than with oral acyclovir.[75]

The mechanism of action and spectrum of activity of valacyclovir is identical to those of acyclovir. It is approved for the treatment of initial or recurrent episodes of genital herpes[76] and for the treatment of recurrent herpes labialis.[4] Treatment is most efficacious when initiated at the earliest onset of symptoms.[4] Suppressive therapy with valacyclovir is recommended to prevent recurrent genital herpes[76] and has the potential to reduce transmission to sexual partners.[4]

Valacyclovir is approved for treatment of VZV. Varicella often resolves without antiviral therapy in those who are immunocompetent. However, in immunocompromised patients, such as HIV-infected patients and transplant recipients, valacyclovir may be used to treat varicella, even if it is uncomplicated.[77] Valacyclovir is the most commonly used drug for the treatment of zoster.[75,77] In a randomized double-blind trial of older immunocompetent patients, valacyclovir was as effective as acyclovir, with similar resolution rates of cutaneous zoster but accelerated resolution of herpetic pain and a lower risk of postherpetic neuralgia.[75] The typical course of zoster treatment is 7 days, and the first dose should be started within 48 hours of rash onset. Treatment can be prolonged, continuing until all lesions have crusted, in immunocompromised patients.[77]

Valacyclovir has also been used to treat acute retinal necrosis and for prevention of CMV disease in kidney

transplant recipients.[78] Although ganciclovir is the backbone for CMV prevention in transplant recipients, the efficacy of valacyclovir prophylaxis for CMV prevention was demonstrated in kidney transplant recipients.[78] However, valacyclovir has not been proven effective for preventing CMV in heart, liver, lung, pancreas, and small bowel transplant recipients.

The adverse effects of valacyclovir are similar to those of acyclovir. At very high doses, neurotoxicity characterized by confusion, hallucinations, and seizures may occur,[78] especially in elderly patients and in those with dehydration and renal disease. The mechanism of resistance for valacyclovir is identical to that of acyclovir (TK mutation); however, achieving higher serum acyclovir levels with valacyclovir could reduce the risk of resistance compared with oral acyclovir.

Valganciclovir

Valganciclovir is the L-valyl ester prodrug of ganciclovir. Oral valganciclovir is well absorbed and converted to ganciclovir by first-pass intestinal or hepatic metabolism.[79] The bioavailability of ganciclovir after valganciclovir administration is about 60%, and peak plasma concentrations are achieved in 1 to 3 hours.[80,81] Valganciclovir is eliminated renally as ganciclovir.[80,82]

Valganciclovir exerts its antiviral activity in the form of ganciclovir-triphosphate, which inhibits viral replication by serving as a competitive substrate for CMV DNA polymerase. Valganciclovir was first approved by the FDA for treatment of CMV retinitis in patients with AIDS.[83] For immediate sight-threatening lesions, valganciclovir is used in combination with an intravitreal ganciclovir implant. Valganciclovir is also used for preventing CMV disease in high-risk CMV donor-positive/recipient-negative recipients of kidney, heart, or kidney-pancreas transplants.[61,84] In the United States, valganciclovir is not approved for preventing CMV disease in liver recipients because of a higher incidence of tissue-invasive CMV disease in patients who received valganciclovir vs oral ganciclovir prophylaxis. In other countries, valganciclovir is used for preventing CMV disease in all solid organ transplant recipients. It has recently gained approval for the prevention of CMV disease in pediatric heart and kidney transplant recipients. It can also be used to preemptively treat asymptomatic CMV infection in transplant recipients.[85-88] Valganciclovir was recently demonstrated to be as effective as IV ganciclovir for treating mild to moderate CMV disease in transplant recipients.[86,87,89]

Bone marrow suppression is the most common adverse effect of valganciclovir. Gastrointestinal manifestations, such as diarrhea, nausea, and vomiting, may be observed. Resistance to valganciclovir occurs through mechanisms identical to those underlying ganciclovir resistance, ie, through mutations in the *UL97* gene, which encodes for CMV kinase, and the *UL54* gene, which encodes for CMV DNA polymerase.[71]

Vidarabine

Vidarabine, a purine nucleoside obtained from *Streptomyces antibioticus,* was historically used for treating HSV and VZV. Acyclovir has since become the preferred drug for these conditions.[90] Vidarabine is currently available only as an ophthalmic solution for treating recurrent epithelial keratitis and acute keratoconjunctivitis.[90] Once phosphorylated into its active form, vidarabine inhibits viral DNA polymerase. Adverse effects of ophthalmic vidarabine include irritation, pain, photophobia, lacrimation, and occlusion of the lacrimal duct.[90]

ANTIVIRAL DRUGS FOR INFLUENZA

M_2 Inhibitors

Amantadine. Amantadine is a symmetric tricyclic amine that inhibits replication of influenza A virus by impairing the function of the membrane protein M_2.[91] Present only in influenza A virus, M_2 is an acid-activated ion channel required for nucleocapsid release.[91] Amantadine is well absorbed after oral administration. It has an elimination half-life of 11 to 15 hours and is excreted by glomerular filtration and tubular secretion.

Amantadine is effective for treating susceptible influenza A virus infection.[91] It results in a more rapid functional recovery and reduces the duration of fever and other symptoms by about 1 day, if given within 48 hours of disease onset.[91] Amantadine is effective as prophylaxis for preventing symptomatic influenza A infection in exposed persons.[92,93] It is usually given for 14 days or for at least 7 days after the last confirmed illness. Seasonal influenza vaccination, however, remains the preferred method for prevention.

Amantadine is generally well tolerated. Among its adverse effects are mild neurologic symptoms such as anxiety, disorientation, and headache, especially in elderly patients and those taking neuroaffective drugs. Emergence of amantadine resistance has limited its use in the clinical setting.[94,95] Amantadine resistance, characterized by amino acid substitutions in the M_2 protein, emerges within 2 to 4 days of treatment. Because of widespread resistance, amantadine is no longer recommended for empiric treatment of influenza.[94,95] M_2 mutation confers cross-resistance with rimantadine.

Rimantadine. Rimantadine is a symmetric tricyclic amine that inhibits influenza virus.[93] It is well absorbed after oral administration, reaching peak plasma concentration

in 3 to 5 hours. Rimantadine undergoes extensive hepatic metabolism before it is excreted in the urine.

The mechanism of action of rimantadine is similar to that of amantadine; it inhibits the ion channel function of M_2, thereby inhibiting viral uncoating. Rimantadine is indicated for prevention and treatment of influenza A virus[93]; however, its clinical utility is currently limited by drug resistance.[96,97] A few trials that compared amantadine and rimantadine suggested similar efficacy; however, neurologic adverse events are less severe and frequent with rimantadine.

Neuraminidase Inhibitors

Oseltamivir. Oseltamivir phosphate is a prodrug of oseltamivir carboxylate, which is an inhibitor of neuraminidase that is essential in the replication of influenza A and B viruses.[98] Oral oseltamivir is well absorbed and reaches peak serum concentrations in 1 hour. Bioavailability of oseltamivir phosphate is at least 75%. The prodrug oseltamivir phosphate undergoes extensive hepatic metabolism via ester hydrolysis. More than 99% of active oseltamivir carboxylate is excreted renally.

Oseltamivir carboxylate, the active drug metabolite, selectively blocks viral neuraminidase, thereby preventing the release of virus from infected cells.[98] Oseltamivir is approved for the treatment of children (≥1 year) and adults with influenza A or B viral infections.[98] Treatment should start within 48 hours of disease onset and continue for 5 days. Oseltamivir is as effective as the other neuraminidase inhibitor, zanamivir, in reducing the febrile period during infection with influenza A (H1N1), influenza A (H3N2), and influenza B virus.[99]

Oseltamivir is also used for postexposure prophylaxis against influenza A and B, including pandemic strains. For this indication, oseltamivir should be started within 48 hours of exposure and continued daily for at least 10 days or for up to 6 weeks during an outbreak. A systematic review reported no statistically significant difference between oseltamivir and zanamivir prophylaxis for preventing symptomatic influenza among immunocompetent adults.[100]

The most common adverse effects of oseltamivir are nausea, vomiting, diarrhea, abdominal pain, insomnia, and vertigo. Neuropsychiatric adverse effects, including delirium, abnormal behavior, and hallucinations, have been reported. Oseltamivir-resistant influenza A virus has been reported.[101-103] Mutations in the neuraminidase gene, such as R292K[101] and H274Y,[98] account for oseltamivir resistance. Surveillance conducted during the 2009 H1N1 influenza pandemic detected sporadic and infrequent incidence of oseltamivir-resistant pandemic (H1N1) 2009 influenza virus. All resistant viruses had neuraminidase mutations (most commonly H275Y mutation) that conferred resistance to oseltamivir, but not to zanamivir.[104] Oseltamivir resistance among influenza B viruses occurs less frequently.[105]

Zanamivir. Zanamivir is an inhaled neuraminidase inhibitor that is used for the treatment and prophylaxis of influenza A and B viruses.[106] Zanamivir is not available orally since it is poorly absorbed.[106] Inhaled zanamivir produces high concentrations in the respiratory tract where influenza virus infection occurs. About 4% to 20% of inhaled zanamivir is absorbed systemically, producing peak serum concentrations at 1 to 2 hours. The absorbed drug is not metabolized and is excreted unchanged in the urine, while the unabsorbed drug is excreted in the feces.[106]

The mechanism of action of zanamivir is similar to oseltamivir, by inhibiting neuraminidase, which is essential for release of newly formed viral particles from infected cells.[106] For treatment, zanamivir is given by inhalation twice daily for 5 days, with the therapy begun within 48 hours after symptom onset. Zanamivir can be given once daily for 10 days as postexposure prophylaxis of influenza A and B in household or close contacts. Zanamivir prophylaxis during community outbreaks may be given for 28 days. Zanamivir has occasionally been given IV to treat critically ill patients with influenza.[107,108]

Inhaled zanamivir is well tolerated.[106] Acute bronchospasm with decline in respiratory function has been reported; a bronchodilator should be available if given as treatment for patients with underlying pulmonary disease. Other adverse effects include headache and gastrointestinal symptoms. Hypersensitivity reactions and neuropsychiatric adverse effects occur rarely.[109]

ANTIVIRAL DRUGS FOR HEPATITIS AND OTHER VIRUSES

Interferons

Interferons (IFNs) are naturally occurring proteins produced in response to viral infection.[110] The 3 major classes of IFNs are α, β, and γ; IFN-α and IFN-β are further classified as type I, whereas IFN-γ is type II.[110] Available only in parenteral formulation, more than 80% of a subcutaneous (SC) or intramuscular dose of IFN-α is absorbed.[110] After an intramuscular injection, peak IFN concentrations occur within 4 to 8 hours and return to baseline levels in 16 to 24 hours.[110] Pegylation, which is the process of attachment of IFN to a large inert polyethylene glycol, markedly reduces the rate of absorption and excretion of IFN and therefore increases its plasma concentration.[111] For example, after an SC dose of peginterferon α-2b, the peak serum concentration occurs in 15 to 44 hours, high concentrations are maintained for 48 to 72 hours, and the mean terminal half-life is about 40 hours.[110] In contrast, the peak serum concentration of peginterferon α-2a is reached in 72 to 96 hours after

an SC dose, and the mean terminal half-life is 160 hours.[110] Interferon-α undergoes extensive renal catabolism, and negligible amounts of IFN are excreted in the urine.

Interferons have multiple overlapping biological activities, including antiviral, antiproliferative, and immunoregulatory functions. After binding to receptors, IFNs initiate a cascade of events that lead to various cellular responses, such as inhibition of virus replication, suppression of cell proliferation, enhancement of the phagocytic activity of macrophages, and augmentation of the specific cytotoxicity of lymphocytes for target cells.

Interferons have been used in treating multiple viral infections and are most commonly used for treating chronic viral hepatitis.[112] Interferon-α was the first drug approved for treatment of compensated liver disease due to CHB; it is not approved for treating acute hepatitis B. For CHB, IFN α-2a or α-2b is given parenterally, depending on dosing schedule, for 4 to 6 months or up to 48 weeks.[112,113] Interferon was most effective in patients with recently acquired hepatitis B virus (HBV), high pretreatment levels of alanine aminotransferase (ALT), and low levels of HBV DNA. Subcutaneous peginterferon-α is as effective or slightly more effective than SC IFN-α.[114] Likewise, SC peginterferon-α may be more effective than lamivudine in hepatitis B e antigen (HBeAg)–positive and HBeAg-negative patients with CHB,[115-117] and the addition of lamivudine to peginterferon-α did not significantly enhance efficacy.[118] Interferon-α is effective in patients with HBV and hepatitis D virus coinfection,[119] although they are less responsive than patients infected with HBV alone.[120] Guidelines for the management of CHB in HIV-infected patients were recently published[121,122]; for patients not requiring anti-HIV therapy, peginterferon-α for 12 months is considered a therapeutic option. Lamivudine and the other antiviral nucleos(t)ides for the treatment of HBV often have anti-HIV properties and may result in the development of HIV resistance if given as monotherapy in HBV-HIV coinfected patients.

Interferon-α-2a and -2b are approved for the treatment of chronic hepatitis C (CHC); however, they are not approved for acute hepatitis C. A meta-analysis found that IFN-α for at least 12 months had the best risk-benefit ratio for patients with CHC.[123] Once-weekly peginterferon-α was more effective than IFN-α given 3 times weekly in patients with CHC.[124-126] However, combination therapy with IFN-α and oral ribavirin is more effective than either drug used alone.[127] Combining oral ribavirin with peginterferon-α may be more effective than combining it with IFN-α.[128,129] Therefore, the British Society for Gastroenterology and the American Association for the Study of Liver Diseases[130] recommends once-weekly SC peginterferon-α combined with oral ribavirin as the first line of treatment of CHC. The recommended duration of treatment of CHC in patients not infected with HIV is 24 weeks (for hepatitis C virus [HCV] genotype 2 or 3) or 48 weeks (for HCV genotype 1).

For patients coinfected with HIV and HCV, the rate of intolerance to a combination regimen of IFN-α and ribavirin is higher and the rate of sustained virologic response (SVR) lower than in patients infected with HCV alone.[131-133] Use of peginterferon-α resulted in a higher SVR rate than use of IFN-α.[131,133] The APRICOT study reported an SVR rate of 40% for patients treated with peginterferon-α plus ribavirin, compared with 20% for those treated with peginterferon-α monotherapy, and 12% for those treated with IFN-α plus ribavirin.[132] A lower SVR rate to combination peginterferon-α plus ribavirin therapy was observed in patients coinfected with HCV genotype 1 (29%) than with HCV genotypes 2 and 3 (62%).[132,133] Guidelines for the management of HIV and HCV coinfection have been published recently.[130] In general, the guidelines recommend combination therapy with peginterferon-α and ribavirin for 48 weeks.

Interferons are generally not recommended in acute viral hepatitis, but treatment of acute HCV with IFN-α has resulted in a more rapid resolution of viremia and reduced progression to chronic hepatitis.[134,135] The American Association for the Study of Liver Diseases recommends either IFN-α or peginterferon-α for at least 6 months for acute HCV if infection persists for 2 to 4 months after diagnosis.

Interferons are also approved as intralesional therapy for condyloma acuminatum of genital and perianal areas.[136] Intralesional injection ensures relatively high concentrations of IFN at the local site of infection, but occurrence of systemic adverse effects suggests its absorption from this site. Currently, HSV is generally treated with acyclovir, but beneficial responses to topical IFN-α have been reported for genital herpes[137] and HSV keratitis.[90] Beneficial responses to IFN-α have been reported for HIV-associated progressive multifocal leukoencephalopathy[138]; however, these findings are debatable because IFN-α may not provide added benefits when used with highly active antiretroviral therapy.[139]

Most patients receiving IFN may develop flulike symptoms, which appear to be dose-related, are more likely to occur at the start of treatment, and typically respond to acetaminophen. Among the more serious adverse effects are neuropsychiatric disorders (eg, depression and homicidal and suicidal ideation), neurologic disturbances (eg, confusion and seizures), myelosuppression (neutropenia [most commonly] and aplastic anemia [rarely]), cardiovascular disorders (eg, arrhythmias), endocrine disorders (eg, thyroid disorders), and pulmonary disorders (eg, dyspnea and pneumonitis).[140-142] Patients at risk for developing depression are those with preexisting mood and anxiety dis-

orders, those with a history of major depression, and those receiving higher doses of IFN-α or undergoing long-term treatment regimens. Selective serotonin reuptake inhibitors have been used successfully to treat patients with IFN-associated depression, allowing therapy to be continued,[143] and as a pretreatment to prevent its occurrence in high-risk patients.[144] Other adverse effects are altered liver function,[145] renal insufficiency,[146] and gastrointestinal manifestations.[147]

Ribavirin

Ribavirin, a synthetic nucleoside analogue of guanine, is available in oral, aerosolized, and IV formulations. Oral ribavirin is absorbed extensively, but its bioavailability is only 65% because of first-pass metabolism. Peak plasma ribavirin concentrations occur within 1 to 2 hours after oral dose.[148] Peak plasma concentrations increase over time and are 6 times higher after 4 weeks of treatment. Administration of aerosolized ribavirin leads to high concentrations in the respiratory tract, with some ribavirin absorbed systemically. Ribavirin is mainly excreted in the urine.[149]

The mechanism of action of ribavirin is known to be diverse but is not completely understood. It may be a competitive inhibitor of cellular enzymes because its antiviral activity is reversed by guanosine. Its triphosphorylated form, ribavirin triphosphate, is a potent competitive inhibitor of inosine monophosphate dehydrogenase, influenza virus RNA polymerase, and mRNA guanylyltransferase. As a result of this competitive inhibition, intracellular guanosine triphosphate pools are markedly reduced and viral nucleic acid and protein synthesis are inhibited. Ribavirin does not alter viral attachment, penetration, or uncoating, nor does it induce IFN production.

Ribavirin inhibits multiple viruses in vitro. Among the susceptible DNA viruses are herpesviruses, adenoviruses, and poxviruses. Susceptible RNA viruses include HCV, Lassa virus, influenza, parainfluenza, measles, mumps, RSV, and HIV. However, no correlation has been found between ribavirin's in vitro activity and its activity against human infections.

Oral ribavirin is approved for use, in combination with IFN-α or peginterferon-α, for the treatment of CHC. However, it is not effective when given as monotherapy.[150,151] The duration of treatment, and sometimes its dose, may be dictated by HCV genotype. Treatment for infections with HCV genotype 1, and probably with genotype 4, should generally continue for 48 weeks, whereas those with genotype 2 or 3 may be treated for 24 weeks. Treatment of HCV in patients coinfected with HIV should be for 48 weeks.[150,151]

Ribavirin is approved for the treatment of RSV in children, including hematopoietic stem cell transplant recipients. When used for the treatment of RSV pneumonia, ribavirin is usually given by the aerosol route, which delivers high concentrations at the site of infection.[152] Oral ribavirin has also been used with good outcomes.[153] Ribavirin has been used, off-label, for the treatment of HSV, influenza, severe acute respiratory syndrome coronavirus,[154,155] La Crosse encephalitis,[156] Nipah encephalitis,[157] Lassa fever,[158] hemorrhagic fever with renal syndrome,[159] Crimean-Congo hemorrhagic fever,[160,161] Bolivian hemorrhagic fever,[162] and hantavirus pulmonary syndrome.[163]

Aerosolized ribavirin can cause sudden deterioration of respiratory function and cardiovascular effects. Precipitation of inhaled ribavirin may occur in ventilatory tubings. Hemolytic anemia occurs commonly,[154] and ribavirin should not be given to patients with preexisting medical conditions exacerbated by ribavirin-induced hemolysis, including significant cardiac disease or hemoglobinopathies. Severe depression, suicidal ideation, and relapse of drug abuse may occur, and ribavirin is contraindicated in patients with a history of, or existing, psychiatric disorders. Significant teratogenic and/or embryocidal effects have been observed in animals exposed to ribavirin. Ribavirin is therefore contraindicated in pregnant women and their male partners, and it is recommended that patients use 2 forms of contraception and avoid pregnancy during therapy and for 6 months thereafter.

Nucleos(t)ide Analogues for CHB

In addition to IFN, several nucleos(t)ide analogues are available for the treatment of CHB (Table 2). With the exception of telbivudine, these drugs possess anti-HIV properties, serving as inhibitors of the HIV reverse transcriptase inhibitors. The specific mechanism of their anti-HBV property is through competitive inhibition of HBV DNA polymerase. Because of their anti-HIV properties, it is highly recommended that CHB patients considered for treatment with these drugs be tested for HIV infection, and monotherapy with these drugs should be avoided for HIV-infected patients to reduce the risk of HIV resistance. Hepatitis B virus may also develop resistance to these drugs, usually after prolonged exposure, and this risk may be reduced by a strategy of combination antiviral therapies. The exact duration of anti-HBV treatment is not defined, and HBV relapse often occurs after discontinuation of treatment. Severe exacerbation of hepatitis may also occur on discontinuation of these drugs; hence, monitoring for hepatotoxicity should be performed after stopping treatment. Lactic acidosis may occur with nucleos(t)ide analogues, and the drugs should be withdrawn if there is a rapid increase in ALT levels, progressive hepatomegaly or steatosis, or acidosis.

Adefovir. Adefovir dipivoxil is an acyclic nucleotide analogue of adenosine monophosphate.[164] Oral adefovir

TABLE 2. **Antiviral Nucleos(t)ides for the Treatment of Chronic Hepatitis B**[a]

Drug name	Suggested dosage	Drug characteristics[b]	Toxicity[c]	Resistance
Adefovir	10 mg orally once daily	Acyclic nucleotide analogue of adenosine monophosphate	Nephrotoxicity Lactic acidosis Rebound hepatitis	rtN236T is most common
Emtricitabine	200 mg orally once daily	Nucleoside analogue of cytidine Very similar to lamivudine Used often in combination with tenofovir	Lactic acidosis Rebound hepatitis	rtM204V/I provides cross-resistance with lamivudine
Entecavir	0.5 mg orally once daily for treatment-naive patients 1 mg orally once daily for treatment-experienced patients and patients with decompensated liver disease	Nucleoside analogue of guanosine One of the most potent anti-HBV drugs	Well tolerated Lactic acidosis Rebound hepatitis	High barrier to resistance; requires 3 mutations for phenotype: rtM204V/I plus rtL180M plus rtT184S/A/I/L or rtS202G/C or rtM250L
Lamivudine	100 mg orally once daily	Nucleoside analogue of cytosine	Lactic acidosis Myopathy Rebound hepatitis	rtM204V/I is most frequent
Telbivudine	600 mg orally once daily	Synthetic thymidine nucleoside analogue No activity against HIV	Myopathy Peripheral neuropathy Lactic acidosis Rebound hepatitis	rtM204I is most frequent mutation; others include rtL80I/V, rtA181T, rtL180M, and rtL229W/V
Tenofovir	300 mg orally once daily	Acyclic nucleoside phosphonate diester analogue of adenosine monophosphate One of the most potent anti-HBV drugs	Nephrotoxicity Lactic acidosis Rebound hepatitis	Not well-defined; rtN236T is suggested but not yet confirmed

[a] HBV = hepatitis B virus; HIV = human immunodeficiency virus.
[b] All drugs inhibit hepatitis B replication by acting as a competitive substrate for the HBV DNA polymerase. All drugs except telbivudine have anti-HBV properties, and all patients with chronic hepatitis B who are considered for treatment should be screened for HIV.
[c] A common toxicity of the nucleos(t)ide analogues is lactic acidosis, with the potential to cause increases in serum alanine aminotransferase levels and hepatomegaly.

dipivoxil is rapidly absorbed and converted to adefovir. Its oral bioavailability is about 59%. Excretion of the drug is by glomerular filtration and active tubular secretion.

Adefovir is converted intracellularly by cellular kinases to its active metabolite, adefovir diphosphate, which competitively inhibits HBV DNA polymerase.[165] Although adefovir has the distinction of being the least potent among currently available anti-HBV drugs, it has been used in adults with decompensated liver disease, or with compensated liver disease with evidence of active viral replication, persistently elevated ALT levels, and histologic evidence of active inflammation and fibrosis.[164]

The major adverse effect of adefovir is nephrotoxicity, including proximal renal tubular dysfunction and Fanconi syndrome. Gastrointestinal symptoms, such as nausea, diarrhea, and abdominal pain, may be observed. Adefovir resistance, characterized by the rtN236T mutation, gradually increases over time to 11%, 18%, and 29% at year 3, 4, and 5, respectively.[166-169] To minimize the risk of resistance, adefovir is used in combination with other drugs such as lamivudine.[165] However, concomitant use with the related drug tenofovir disoproxil fumarate is not recommended because of the augmented risk of nephrotoxicity.

Emtricitabine. Emtricitabine is an analogue of cytidine. Although not currently approved for the treatment of CHB, emtricitabine has been used clinically in combination with tenofovir in HIV/HBV–coinfected patients. Emtricitabine is very similar to lamivudine, and cross-resistance between these drugs is common. Emtricitabine may be more potent than lamivudine; however, it should not be used as monotherapy because of high rates of resistance development.[170] The rate of emtricitabine resistance among patients with HBV monoinfection is 18% at 96 weeks.[170] Adverse effects are reportedly uncommon and include mild to moderate headache, nausea, diarrhea, and rash.[170]

Entecavir. Entecavir, a nucleoside guanosine analogue,[171] is considered one of the most potent agents for the treatment of patients with CHB, including those resistant to lamivudine.[172] Oral entecavir is extensively absorbed: peak plasma concentrations occur in 30 to 90 minutes, and oral bioavailability is almost 100%. Despite low plasma concentrations, entecavir maintains its potency by the long intracellular half-life of its active metabolite entecavir triphosphate. Entecavir is mainly excreted by glomerular filtration and active tubular secretion.

The mechanism of action of entecavir is somewhat unique because it inhibits 3 specific functions of the HBV DNA polymerase: priming of the HBV DNA polymerase, reverse transcription of the negative strand from the pregenomic mRNA, and synthesis of positive-strand HBV DNA.[172] Entecavir is approved for the treatment of CHB, at a dose of 0.5 mg orally once daily for nucleoside

treatment–naive patients, and a dose of 1 mg orally once daily for patients with a history of HBV viremia while receiving lamivudine, those with lamivudine- or telbivudine-resistant mutations, and those with decompensated liver disease.[173] In randomized trials of HBeAg-positive and HBeAg-negative patients, entecavir demonstrated better outcomes than lamivudine, with improvement in histologic responses, higher percentages of HBV DNA suppression, and normalization or improvement of ALT levels.

Adverse effects of entecavir are generally mild and include headache, fatigue, nausea, diarrhea, and insomnia. Entecavir has a high barrier to resistance and requires at least 3 mutations for phenotypic resistance. Entecavir resistance requires a baseline rtM204V/I and rtL180M mutation plus either rtT184S/A/I/L, rtS202G/C, or rtM250L. Among nucleoside-naive patients, the rate of entecavir resistance is less than 1% after 5 years, but patients with preexisting rtM204V/I have a higher rate of entecavir resistance (51%) after 5 years.[173]

Lamivudine. Lamivudine is a nucleoside analogue of cytosine. Oral lamivudine provides bioavailability of about 85%, and peak serum concentrations occur in 1.0 to 1.5 hours. Hepatic metabolism is low, and up to 70% is excreted unchanged by the kidneys.[174]

Lamivudine is phosphorylated intracellularly into its active 5′-triphosphate metabolite, lamivudine triphosphate. When the active metabolite is incorporated into viral DNA by HBV polymerase, it results in DNA chain termination.

Lamivudine was the first drug to be used as an alternative to IFN-α for the treatment of CHB.[175,176] In a double-blind study involving about 350 patients with CHB, lamivudine was associated with substantial histologic improvement, HBeAg antibody seroconversion, and ALT normalization.[177] However, relapses are common once treatment is discontinued.[178]

The adverse effects of lamivudine are mild and include abdominal pain, nausea, and headache. The clinical utility of lamivudine is limited by the rapid development of antiviral resistance. Lamivudine shares with the L-nucleosides the primary resistance mutation, rtM204V/I, which occurs easily and confers cross-resistance. After 4 years of lamivudine monotherapy, rtM204V/I resistance develops in up to 70% and 90% of patients with HBV monoinfection and HIV/HBV coinfection, respectively.

Telbivudine. Telbivudine is a synthetic thymidine nucleoside analogue. Unlike other anti-HBV drugs, telbivudine has no activity against HIV. Oral telbivudine is well absorbed and achieves peak plasma concentrations after about 3 hours. It is mainly excreted by glomerular filtration, with a terminal elimination half-life of 30 to 50 hours.[179]

Telbivudine-triphosphate inhibits HBV by competitive inhibition of viral DNA polymerase. Oral telbivudine is approved for the treatment of CHB in patients with compensated liver disease and evidence of active viral replication, persistently increased serum ALT concentrations, and histologic evidence of active liver inflammation and fibrosis.[180,181] It is considered more effective than lamivudine and adefovir.[182,183] Compared with lamivudine, telbivudine was associated with a higher degree of reduction in HBV DNA levels; however, no significant differences were found in ALT level normalization, loss of HBeAg, or anti-HBe seroconversion.

The most common adverse effects reported for telbivudine are dizziness, fatigue, gastrointestinal symptoms, and rash. Unique adverse effects are peripheral neuropathy and myopathy with elevation in creatine kinase levels. Telbivudine treatment should be discontinued if either peripheral neuropathy or myopathy is diagnosed. The rate of resistance to telbivudine is 25% after 96 weeks of treatment.

Tenofovir. Tenofovir disoproxil fumarate, an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate, is considered one of the most potent anti-HBV drugs. In oral form, it is rapidly absorbed and converted to tenofovir, reaching peak plasma concentrations in 1 to 2 hours.[184] Oral bioavailability, which is only 25% in the fasting state, can be enhanced when taken with a high-fat meal. The terminal elimination half-life of tenofovir is 12 to 18 hours, and it is excreted mainly by active tubular secretion and glomerular filtration.[184]

Tenofovir disoproxil fumarate is a prodrug that requires diester hydrolysis for conversion to tenofovir. Subsequent phosphorylation by cellular enzymes forms tenofovir diphosphate, which competes with the natural substrate deoxyadenosine 5′-triphosphate for incorporation into the viral DNA strand.

Tenofovir is used for the treatment of CHB. In a randomized trial comparing tenofovir and adefovir, a higher percentage of patients receiving tenofovir achieved HBV DNA level suppression. In HBeAg-positive patients, the biochemical response was higher with tenofovir; however, the anti-HBe seroconversion rates and histologic responses were similar for adefovir and tenofovir.[185-188]

The adverse effects of tenofovir include gastrointestinal symptoms, dizziness, fatigue, and headache. Renal toxicities, including nephritis, proximal renal tubulopathy (including Fanconi syndrome), and renal failure, have been associated with tenofovir.[189-193]

Primary tenofovir resistance mutations have not been well defined. Although viruses with rtN236T are not resistant to tenofovir, they have a slower response than do wild-type viruses. One study reported rtA194T as a tenofovir re-

sistance mutation; however, this pattern was not confirmed in other studies.

Protease Inhibitors for the Treatment of CHC

The current standard treatment of CHC is peginterferon-α in combination with ribavirin for 24 weeks (for HCV genotype 2 or 3) or 48 weeks (for HCV genotype 1). The major aim of treatment is to achieve SVR, which is defined as undetectable HCV RNA at 24 weeks after completion of treatment. A combination regimen of peginterferon-α and ribavirin results in SVR rates between 38% and 46%, and the rate is even lower among black patients. Hence, major efforts have been made to develop novel therapies for CHC. Recently, 2 serine protease inhibitors were approved as novel therapies for CHC due to genotype 1 infection. The addition of serine protease inhibitors to the backbone therapies of peginterferon-α and ribavirin will emerge as the standard of care for the HCV genotype 1 infection, both in treatment-naive and treatment-experienced patients.

Boceprevir. Boceprevir is a linear peptidomimetic ketoamide serine protease inhibitor that was recently approved for the treatment of CHC, particularly for genotype 1.[194] It is available in oral formulation, and the time to peak concentration after oral administration is 2 hours. Food enhances its absorption. Boceprevir is metabolized primarily in the liver. It has an elimination half-life of 3 hours and is excreted mostly in the feces.[194]

Boceprevir exerts anti-HCV properties by binding reversibly to the HCV nonstructural 3 protein, ultimately inhibiting viral replication. In a recently conducted phase 3 international randomized placebo-controlled trial that enrolled previously untreated black and nonblack adults with HCV genotype 1 infection (SPRINT-2 [serine protease inhibitor therapy 2] trial), the addition of boceprevir for 22 weeks or 44 weeks to standard therapy (peginterferon-α-2b and ribavirin) resulted in significantly higher SVR rates compared with standard therapy alone for the nonblack cohort (67% and 68% vs 40%, respectively) and the black cohort (42% and 53% vs 23%, respectively).[195] The relative increases in SVR rates for the nonblack cohort were 68% and 70%, respectively, compared with the standard therapy.[195]

The HCV RESPOND-2 (Retreatment with HCV Serine Protease Inhibitor Boceprevir and PegIntron/Rebetol 2) trial evaluated boceprevir for the treatment of patients who had experienced a relapse or who had not achieved SVR to peginterferon-ribavirin treatment.[196] In this randomized open-label trial that enrolled 403 patients, the SVR rates were significantly higher for patients who received peginterferon-ribavirin plus boceprevir treatment for 32 weeks (59%) or 44 weeks (66%) compared with standard peginterferon-ribavirin treatment alone (21%).[196] In a multivariable stepwise logistic regression analysis, the baseline factors associated with SVR were boceprevir use, previous relapse (compared with previous nonresponder), low viral load at baseline, and absence of cirrhosis.[196]

Boceprevir (800 mg 3 times daily) was approved by the FDA as the first HCV protease inhibitor for the treatment of CHC, specifically for genotype 1; it should be combined with peginterferon and ribavirin. The most common adverse effects of boceprevir are flulike illness, fatigue, nausea, dysgeusia, and anemia.[194] The addition of boceprevir nearly doubled the rate of anemia compared with the use of standard peginterferon and ribavirin therapy, with many patients requiring the use of erythropoietin.[195]

Telaprevir. Telaprevir is an orally available inhibitor specific to the HCV nonstructural 3/4A serine protease.[197] It inhibits HCV replication by binding reversibly to nonstructural 3 serine protease. After oral administration, telaprevir achieves peak plasma concentrations in 4 to 5 hours. It is metabolized primarily in the liver and it has an elimination half-life of 4 to 5 hours. Most of the drug is excreted in the feces.

Early-phase studies demonstrated the potent anti-HCV properties of telaprevir.[198-200] In a recent phase 3 international randomized double-blind placebo-controlled clinical trial, the addition of telaprevir to the standard treatment of peginterferon-ribavirin was associated with significantly higher SVR rates compared with standard peginterferon-ribavirin alone in a cohort of 1088 patients with previously untreated HCV genotype 1 infections.[201] Specifically, the group of patients who received 12 weeks of telaprevir combined with peginterferon-ribavirin, followed by peginterferon-ribavirin for 12 weeks (if HCV RNA was undetectable at weeks 4 and 12) or 36 weeks (if HCV RNA was still detectable at weeks 4 and 12), had SVR rates of 75% vs 44% with standard therapy.[201] The SVR rates were also significantly higher compared with standard therapy among patients who received only 8 weeks of telaprevir combined with peginterferon-ribavirin (69% vs 44%).[201] In the second randomized phase 3 trial that evaluated telaprevir in treatment-experienced patients with HCV genotype 1 infection, the addition of telaprevir to the standard treatment regimen of peginterferon-α and ribavirin was associated with significantly higher SVR rates compared with the standard regimen of peginterferon-ribavirin alone.[202]

Collectively, these studies indicate that the addition of telaprevir to standard peginterferon-ribavirin therapy can significantly improve SVR rates in treatment-naive patients infected with HCV genotype 1 and in those who did not benefit from initial treatment with peginterferon-α-2a and ribavirin. As a result of these findings, the FDA approved telaprevir (750 mg 3 times daily) for this treatment

indication. The most common adverse effects are anemia, neutropenia, leukopenia, and rash.[201] In one study, 41% to 60% of patients reported some kind of rash.[199] Rashes can be mild to severe, and Stevens-Johnson syndrome and drug rash with eosinophilia and systemic symptoms have been reported. Telaprevir therapy should be discontinued if these dermatologic complications occur, especially in cases of severe rash or even mild to moderate rash if accompanied by systemic symptoms. The mechanism underlying rash development is unknown.[199] Fatigue, pruritus, and gastrointestinal sympotoms (eg, nausea, diarrhea, and taste disturbance) may also be observed.[199]

CONCLUSION

This review has highlighted the pharmacokinetics, mechanisms of action, clinical indications, and adverse effects of clinically available drugs for the management of viruses other than HIV. The currently available antiviral drugs target 3 main groups of viruses: herpes, hepatitis, and influenza viruses. The antiviral therapeutic armamentarium has evolved over the years and is rapidly expanding. Some of the "old" antiviral drugs retain their clinical utility for most infections, such as acyclovir for herpes simplex virus and ganciclovir for CMV. However, other of these "old" antiviral drugs (eg, amantadine and rimantadine for influenza virus infections) have lost their clinical utility because of the rapid and widespread development of resistance. This serves as a catalyst for the development of novel therapies and, more importantly, should urge the medical community to use these drugs optimally in the clinical setting. Indeed, increased resistance has been observed to the neuraminidase inhibitors for the treatment of influenza viruses and the nucleos(t)ide analogues for the treatment of CHB. As novel therapies develop (eg, the serine protease inhibitors for the treatment of CHC), care must be taken to optimize their use so that the clinical life span of these drugs is not abbreviated by the development of resistance.

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