Treatment Guidelines
from The Medical Letter®

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IN THIS ISSUE (starts on next page)

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Tables

Antiviral Drugs

The drugs of choice for treatment of viral infections (other than HIV) and their dosages are listed in Tables 1-6 on the pages that follow. Some of the indications and dosages recommended here have not been approved by the FDA. Vaccines used for the prevention of viral infections are discussed elsewhere.[1]

VARICELLA-ZOSTER AND HERPES SIMPLEX VIRUS

ACYCLOVIR — Available in topical, oral and IV formulations, acyclovir (*Zovirax*, and generics) is used to treat and suppress varicella-zoster virus (VZV) and herpes simplex virus (HSV) infections.

Oral acyclovir begun within 24 hours of rash onset decreases the severity of primary **VZV** infection (chicken pox). It can also reduce pain and the risk of post-herpetic neuralgia in patients with localized zoster if taken within 48-72 hours after the onset of rash. Suppression with oral acyclovir is often used to prevent VZV and HSV reactivation in immunocompromised patients, including those undergoing bone marrow transplantation.

Topical acyclovir cream reduces the duration of recurrent orolabial **HSV** by about 0.5 days. Taken early (generally within 24 hours of symptom onset), oral acyclovir can shorten the duration of pain, healing time, new lesion formation and viral shedding by 1-2 days in orolabial, genital and anorectal HSV infections. Long-term oral suppression with acyclovir reduces the frequency and/or severity of symptomatic genital HSV recurrences and asymptomatic viral shedding.

IV acyclovir is the drug of choice for serious or disseminated VZV infections and for HSV infections that are visceral, disseminated or involve the central nervous system (CNS). In neonates with HSV infection, treatment of acute CNS disease or disseminated disease with CNS involvement with IV acyclovir for 3 weeks (2 weeks for skin, eye and mouth disease) decreases morbidity and mortality; 6 months of oral acyclovir suppression following acute treatment improves neurodevelopmental outcomes.[2]

Table 1. Drugs for Varicella-Zoster Virus Infections[1]

	Drug	Usual Adult Dosage[2]	Cost[3]
Varicella[4]			
	Acyclovir – generic	800 mg PO qid x 5d	$8.10
	Zovirax		239.00
or	Valacyclovir[5] – generic	1 g PO tid x 5d	109.95
	Valtrex		175.65
Herpes Zoster			
	Valacyclovir – generic	1 g PO tid x 7d	153.93
	Valtrex		245.91
or	Famciclovir – generic	500 mg PO tid x 7d	103.99
	Famvir		272.92
or	Acyclovir – generic	800 mg PO 5x/d x 7d	14.18
	Zovirax		418.25
Varicella or Zoster in Immunocompromised Patients[6]			
	Acyclovir – generic	10 mg/kg IV q8h x7d[7]	137.25[8]
Acyclovir-resistant Zoster			
	Foscarnet.– generic	40-60 mg/kg IV q8h	1520.80[8]
	Foscavir	x 14-21d	4368.60[8]

1. Some of the drugs and/or doses listed here have not been approved for such use by the FDA.
2. Dosage adjustment may be required for renal insufficiency.
3. Wholesale acquisition cost (WAC) for the shortest treatment duration with the lowest recommended maintenance dose. $ource® Monthly (Selected from FDB MedKnowledge™) February 6, 2013. Reprinted with permission by FDB, Inc. All rights reserved. ©2013. www.fdbhealth.com/policies/drug-pricing-policy/. Actual retail prices may be higher.
4. Treatment is effective if started within 24 hours of onset of rash. Antiviral treatment is not recommended for healthy children with uncomplicated varicella. Treatment can be considered in adults and children >12 years old, in those with chronic skin or respiratory disorders, in those taking a corticosteroid or a long-term salicylate, or in secondary cases within a household.
5. Clinical trial data are lacking.
6. Or other serious or disseminated VZV infections.
7. There is currently a shortage of IV acyclovir in the US. If IV acyclovir is unavailable, possible alternatives include ganciclovir (5 mg/kg IV q12h) or foscarnet (90 mg/kg IV q12h or 60 mg/kg IV q8h). Data on their efficacy for this indication are lacking and both are more toxic than IV acyclovir.
8. Cost of treatment for a 70-kg patient.

Adverse Effects – Acyclovir is generally well tolerated. GI disturbances, headache and malaise can occur with oral or IV acyclovir. IV acyclovir can also cause

phlebitis and inflammation at the site of infusion and reversible renal dysfunction due to crystalline nephropathy; high dosage, rapid infusion, dehydration and pre-existing renal impairment increase the risk of nephrotoxicity. IV and, rarely, oral acyclovir have been associated with myalgia, rash, Stevens-Johnson syndrome, tremors, lethargy, confusion, hallucinations, seizures, encephalopathy and coma. CNS effects are more likely to occur in older patients and in those with renal impairment. Neutropenia and other signs of bone marrow toxicity have been reported rarely. Topical acyclovir can cause skin reactions at the site of application.

Pregnancy – Acyclovir is classified as category B (no evidence of risk in humans) for use during pregnancy. Use of the drug during pregnancy, even during the first trimester, has not been associated with an increased risk of congenital abnormalities.[3] The American College of Obstetricians and Gynecologists recommends offering suppressive acyclovir therapy (400 mg three times daily) beginning at week 36 to pregnant women with active recurrent genital herpes to reduce the risk of recurrence at delivery and possibly the need for cesarean section.[4] Whether such use reduces neonatal infection has not been established.

Resistance – Despite widespread use of acyclovir, the development of HSV resistance is uncommon in immunocompetent patients (prevalence <1%). Almost all acyclovir-resistant HSV infections have occured in immunocompromised patients treated with the drug; isolates are usually cross-resistant to famciclovir. Valacyclovir is a prodrug of acyclovir; isolates resistant to acyclovir are also resistant to valacyclovir. Acyclovir-resistant VZV or HSV infections may respond to foscarnet or cidofovir.

VALACYCLOVIR — Valacyclovir (*Valtrex*, and generics), the L-valyl ester of acyclovir, is metabolized to acyclovir after oral administration, resulting in a 3- to 5-fold increase in bioavailability compared to oral acyclovir. The area under the plasma concentration-time curve (AUC) following 1 gram 3 times daily of oral valacyclovir resembles that following IV administration of acyclovir 5 mg/kg every 8 hours.

Valacyclovir 1 gram three times daily is at least as effective as acyclovir 800 mg taken 5 times a day in shortening the duration of pain and postherpetic neuralgia in patients with localized **zoster**. Suppression with valacyclovir for up to 2 years reduced VZV reactivation in hematopoietic stem cell transplant recipients.[5]

For episodic treatment of orolabial **herpes**, one day of treatment with oral valacyclovir (2 gm twice daily) improved time to healing by about 1 day compared to placebo.[6] In first-episode or recurrent genital herpes, valacyclovir twice daily is as effective as acyclovir given 5 times a day. Once-daily valacyclovir (500 mg) is effective for chronic suppression of genital HSV; a higher dose may be needed for patients with frequent (≥10 per year) recurrences. In one study, valacyclovir was superior to famciclovir for virologic suppression of recurrent genital herpes.[7] In HSV-discordant heterosexual couples, valacyclovir suppressive therapy taken by the infected partner can reduce the risk of HSV transmission to the susceptible partner by about 50%.[8]

Adverse Effects – Valacyclovir is generally well tolerated; adverse effects are similar to those with acyclovir. GI disturbances, headache and CNS effects, such as agitation, confusion, delerium, hallucinations and seizures, can occur. Acute renal impairment has been reported; older age, dehydration and concomitant use of nephrotoxic drugs may increase this risk. Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome has been reported in some severely immunocompromised patients taking high doses of valacyclovir (8 g/day).

Pregnancy – Like acyclovir, use of valacyclovir has not been associated with an increased risk of major birth defects, even when taken during the first trimester of pregnancy.[3] It is classified as category B (no evidence of risk in humans) for use during pregnancy.

Resistance – Valacyclovir is a prodrug of acyclovir; isolates resistant to acyclovir are also resistant to valacyclovir.

FAMCICLOVIR — Famciclovir (*Famvir*, and generics) is rapidly converted to penciclovir after oral administration. In patients with **zoster**, famciclovir begun within 48 hours after the onset of rash is effective in speeding the resolution of pain and shortening the duration of postherpetic neuralgia. It is also effective in treating first episodes and recurrences of genital **HSV** and for chronic suppression. Single-day, patient-initiated famciclovir reduces time to healing of orolabial herpes and genital herpes lesions by 1-2 days compared to placebo.[9,10] It is similar in efficacy and safety to a 3-day course of valacyclovir for recurrent genital herpes.[11] In one study, valacyclovir was superior to famciclovir in suppressing recurrences of genital herpes and in reducing viral shedding.[7]

Adverse Effects – Famciclovir is generally well tolerated. Headache, nausea and diarrhea can occur. Thrombocytopenia, confusion, hallucinations and nephrotoxicity have been reported.

Table 2. Drugs for Herpes Simplex Virus Infections[1]

		Drug	Usual Adult Dosage[2]	Cost[3] (Generic/Brand)
Orolabial				
First episode[4]		Acyclovir – *Zovirax*	400 mg PO tid x 7-10d	$5.44/129.11
	or	Famciclovir – *Famvir*	500 mg PO bid-tid x 7-10d	69.33/181.94
	or	Valacyclovir – *Valtrex*	1 g PO bid x 7-10d	93.94/164.08
Recurrences[5] – Topical[6]		Acyclovir – *Zovirax*	5% cream 5x/d x 4d	124.48[7]
	or	Penciclovir – *Denavir*	1% cream q2h while awake x 4d	96.10[7]
	or	Docosanol – *Abreva*[8]	10% cream 5x/d until healed (max 10 days)	13.70[7]
Oral		Famciclovir – *Famvir*	1500 mg PO single dose	14.86/38.99
	or	Valacyclovir – *Valtrex*	2 g PO bid x 1d	26.84/46.88
	or	Acyclovir – *Zovirax*	400 mg PO 5x/d x 5d	6.47/153.70
Suppression[9]		Acyclovir – *Zovirax*	400 mg PO bid[10]	15.60/368.88
	or	Valacyclovir – *Valtrex*	500 mg-1 g PO once/d[11]	120.00/205.35
	or	Famciclovir – *Famvir*	500 mg PO bid	297.12/779.76
Genital				
First episode		Acyclovir – *Zovirax*	400 mg PO tid x 7-10d	5.46/129.11
	or	Famciclovir – *Famvir*	250 mg PO tid x 7-10d	50.80/163.17
	or	Valacyclovir – *Valtrex*	1 g PO bid x 7-10d	93.94/164.08
Recurrences[5]		Acyclovir – *Zovirax*	800 mg PO tid x 2d or bid x 5d	3.90/92.22
	or	Famciclovir – *Famvir*	1 g PO bid x 1d	19.81/51.98
	or	Valacyclovir – *Valtrex*	500 mg PO bid x 3d or 1 g once/d x 5d	13.42/23.44
Suppression[9]		Acyclovir – *Zovirax*	400 mg PO bid[10]	15.60/368.88
	or	Valacyclovir – *Valtrex*	500 mg-1 g PO once/d[11,12]	120.40/205.35
	or	Famciclovir – *Famvir*	250 mg PO bid[11]	145.14/466.20
Mucocutaneous in Immunocompromised Patients				
		Acyclovir – generic	5 mg/kg IV q8h x 7-14d or 400 mg PO 5x/d x 7-10d	5.80[13]
	or	Famciclovir – *Famvir*	500 mg PO bid x 7-10d	69.33/181.94
	or	Valacyclovir – *Valtrex*	500 mg-1 g PO bid x 7-10d	56.00/95.83
Acyclovir-resistant Mucocutaneous				
Severe infection, immunocompromised		Foscarnet – *Foscavir*	40 mg/kg IV q8h x 14-21d or until healed	1520.80/4368.60[14]
Encephalitis				
		Acyclovir[15] – generic	10-15 mg/kg IV q8h x 14-21d	5.80[13]
Other Severe or Disseminated				
		Acyclovir[15] – generic	5-10 mg/kg IV q8h x 14-21d	5.80[13]
Keratitis[16]				
		Trifluridine – *Viroptic*	1% ophth solution 1 drop q2h while awake (max 9 drops/d)[17]	129.24/169.39[7]
	or	Ganciclovir – *Zirgan*	0.15% ophth gel 1 drop q3h while awake[17]	201.29[7]

1. Some of the drugs and/or doses listed here have not been approved for such use by the FDA.
2. Dosage adjustment may be required for renal insufficiency.
3. Wholesale acquisition cost (WAC) of the lowest recommended adult dosage for the shortest frequency of administration and duration of treatment; for suppression, cost of 30 days' treatment is provided. $ource® Monthly (Selected from FDB MedKnowledge™) February 6, 2013. Reprinted with permission by FDB, Inc. All rights reserved. ©2013. www.fdbhealth.com/policies/ drug-pricing-policy/. Actual retail prices may be higher.
4. For moderate or severe primary infection. Clinical trial data establishing the efficacy of recommended drugs and doses are lacking. Some expert clinicians would treat a first episode of orolabial herpes with the same doses as a first episode of genital herpes.
5. Antiviral therapy is variably effective and only if started early.
6. Immunocompromised patients or those with mucosal or disseminated disease should not be treated with topical antivirals.
7. Cost of the smallest size available.
8. Available without a prescription.
9. Some expert clinicians discontinue suppressive treatment for 1-2 months once a year to assess the frequency of recurrences.
10. 400-800 mg bid for patients with HIV.
11. 500 mg bid for patients with HIV.
12. 500 mg once/d in immunocompetent patients with <10 recurrences per year and 500 mg bid or 1 g/d in patients with ≥10 recurrences per year.
13. Cost of one 1-g vial.
14. Cost of treatment for a 70-kg patient
15. There is currently a shortage of IV acyclovir in the US. If IV acyclovir is unavailable, possible alternatives include ganciclovir (5 mg/kg IV q12h) or foscarnet (90 mg/kg IV q12h or 60 mg/kg IV q8h). Data on their efficacy in treating herpes encephalitis are lacking and both are more toxic than IV acyclovir. Oral valacyclovir may achieve therapeutic levels in the CSF (T Pouplin et al. Antimicrob Agent Chemother 2011; 55:3624), but its use is not generally recommended because of the severity of the disease and the uncertainty of adequate GI absorption.
16. An ophthalmic preparation of acyclovir is available in some countries. Treatment of HSV ocular infection should be supervised by an ophthalmologist; duration of therapy and dosage depend on response. Oral antivirals (acyclovir, valacyclovir, famciclovir) are probably as effective as ophthalmic preparations without adverse ocular effects.
17. Once the cornea has re-epithelialized, the dose can be decreased to 1 drop q4h while awake x 7d for trifluridine and 1 drop tid x7d for ganciclovir.

Pregnancy – Like acyclovir, famciclovir is classified as category B (no evidence of risk in humans) for use during pregnancy.

Resistance – HSV and VZV strains resistant to acyclovir are generally also resistant to famciclovir.

OTHER DRUGS FOR HSV — Topical - Immunocompromised patients or those with mucosal or disseminated disease should not be treated with topical medications. **Penciclovir** *(Denavir)* cream applied every 2 hours for 4 days while awake shortens the healing time of recurrent orolabial herpes by <1 day in immunocompetent adults. Erythema at the application site and headache are common. **Docosanol** *(Abreva)* cream started within 12 hours of prodromal symptoms, decreases healing time by about 0.5-0.75 days in recurrent orolabial herpes.[12] Application site reactions, rash and pruritus can occur.

Ophthalmic – Trifluridine (*Viroptic*, and generics), a nucleoside analog active against HSV, including some acyclovir-resistant strains, is FDA-approved for treatment of primary HSV keratoconjunctivitis and recurrent epithelial keratitis. It is also active against vaccinia virus and has been used to treat accidental ocular infection following smallpox vaccination.[13] **Ganciclovir** *(Zirgan)* gel is approved by the FDA for treatment of acute herpetic keratitis (dendritic ulcers). Blurred vision and eye irritation can occur.

INFLUENZA

Antiviral drugs can be used as an adjunct to vaccination for prophylaxis and treatment of influenza. In recent years, the susceptibility of circulating influenza virus strains has evolved rapidly and treatment recommendations have changed during the influenza season. Frequently updated information on antiviral resistance is available at www.cdc.gov/flu/professionals/antivirals.

OSELTAMIVIR AND ZANAMIVIR — The neuraminidase inhibitors oseltamivir *(Tamiflu)*, which is taken orally, and zanamivir *(Relenza)*, which is inhaled, have generally been about 70-90% effective for chemoprophylaxis after exposure to susceptible strains of seasonal influenza A or B.[14]

Treatment with a neuraminidase inhibitor started within 48 hours after the onset of illness in patients infected with a susceptible strain of influenza virus can decrease the duration of symptoms. It can also decrease viral shedding and transmission and reduce the risk of complications such as pneumonia. In hospitalized and critically ill patients, these drugs can decrease the risk of death and shorten the duration of hospitalization, even when they are started as late as 5 days after the onset of symptoms.[15-17] The typical duration of treatment is 5 days, but a prolonged treatment course (e.g., 10 days) may be beneficial for critically ill or immunocompromised patients, in whom viral replication may be protracted.

Adverse Effects – Nausea, vomiting and headache are the most common adverse effects of **oseltamivir**; taking the drug with food may reduce the incidence of nausea and vomiting. Neuropsychiatric events including self-injury and delirium have occurred in some patients, particularly children treated with oseltamivir, but it is not clear that the drug was the cause of these events.[18] Bronchospasm can occur with inhaled **zanamivir**. Neuraminidase inhibitors administered within 48 hours before or <2 weeks after administration of the live-attenuated intranasal influenza vaccine *(FluMist)* may interfere with the vaccine's efficacy.

Table 3. Drugs for Influenza[1]

	Adult Dosage		Pediatric Dosage		
Drug[2]	Prophylaxis[3]	Treatment[4]	Prophylaxis[3]	Treatment[4]	Cost[5]
Oseltamivir – *Tamiflu*	75 mg PO once/d[6]	75 mg PO bid x 5d[6,7]	See footnote 8	See footnote 8	$101.50
Zanamivir – *Relenza*[9]	2 inhalations (10 mg) once/d	2 inhalations (10 mg) bid x 5d	≥5 yrs: 2 inhalations (10 mg) once/d	≥7 yrs: 2 inhalations (10 mg) bid x 5d	59.00

1. Otherwise healthy persons who are not considered at high-risk (Med Lett Drugs Ther 2012; 54:97) generally do not require antiviral prophylaxis or treatment for influenza.
2. Antiviral drugs may interfere with the efficacy of *FluMist*, the live-attenuated intranasal vaccine; they should be stopped at least 48 hours before and should not be started until ≥2 weeks after *FluMist* administration. Inactivated vaccines are not affected by antiviral drug therapy.
3. For post-exposure prophylaxis in households, a 10-day course is recommended. For prophylaxis of exposures in institutions, the drug should be taken for at least 2 weeks and continued for 1 week after the end of the outbreak. For prophylaxis during community outbreaks, oseltamivir has been shown to be effective and safe when taken for up to 42 days, and zanamivir for up to 28 days. Some experts would use twice-daily therapeutic doses for post-exposure prophylaxis in highly immunocompromised persons.
4. Hospitalized, critically ill or immunocompromised patients may require longer treatment.
5. Wholesale acquisition cost (WAC) for 5 days' treatment at adult dosages. $ource® Monthly (Selected from FDB MedKnowledge™) February 6, 2013. Reprinted with permission by FDB, Inc. All rights reserved. ©2013. www.fdbhealth.com/policies/drug-pricing-policy/. Actual retail prices may be higher.
6. In patients with CrCl 10-30 mL/min, the dose should be 75 mg every other day or 30 mg once/d for prophylaxis and 75 mg once/d for treatment.
7. In adults with pneumonia or severe lower respiratory tract disease, some experts recommend 150 mg bid x 10 days for treatment.
8. Dose for children ≥1 yr old: ≤15 kg: 30 mg; 15.1-23 kg: 45 mg; 23.1-40 kg: 60 mg; ≥40.1 kg: 75 mg (once daily for prophylaxis and twice daily for 5 days treatment). The treatment dose for children 2 weeks to <1 year old is 3 mg/kg bid. Although not FDA-approved for prophylaxis in children <1 year old, the ACIP and CDC recommend that children ≥3 months and <1 year old receive 3 mg/kg once/day. The dose for children ≥13 years old is 75 mg.
9. Not recommended for use in patients with underlying respiratory disease such as asthma or COPD.

Parenteral Formulations – Oral oseltamivir can be administered safely and effectively by nasogastric tube in critically ill patients.[19] Both oseltamivir and zanamivir are available in IV formulations on a compassionate use basis from the manufacturer (Genentech: 1-800-821-8590; GSK: 1-877-626-8019). IV zanamivir has been used successfully to treat severely ill patients with proven or suspected oseltamivir resistance.[20-22]

Pregnancy – Pregnant women with influenza are at high risk for complications, including death. Even though oseltamivir and zanamivir are classified as category C (risk cannot be ruled out) for use during pregnancy, prompt treatment with one of these antiviral medications is recommended for this high-risk population. Chemoprophylaxis can be considered for pregnant (or ≤2 weeks postpartum) women who have had close contact with someone suspected of being infected with influenza. Clinical experience with use in pregnancy has been most extensive with oseltamivir.

Resistance – During treatment with oseltamivir, resistant variants emerge in about 2% of patients; they occur more frequently in children ≤5 years old.[23] Higher levels of resistance have been described when oseltamivir was used to treat H5N1 (avian influenza) infection. Zanamivir is active against most oseltamivir-resistant strains. Emergence of zanamivir resistance during therapy has been reported in immunocompromised patients.

ADAMANTANES — In recent years there has been a high rate of resistance of influenza A virus isolates to amantadine and rimantadine (*Flumadine*, and generics). These drugs are not effective for prevention or treatment of influenza B. They are not currently recommended for prevention or treatment of influenza.[24]

CHRONIC HEPATITIS B

In recent years, hepatitis B has become a treatable disease. There are currently 5 oral nucleoside/tide analogs (tenofovir, entecavir, telbivudine, adefovir and lamivudine) and two interferons approved for treatment of chronic hepatitis B virus (HBV) infection. The oral antivirals are better tolerated, and most have better rates of virological suppression than the interferons, and are now considered the first line of therapy. In treatment-naïve patients, tenofovir or entecavir is preferred. Alternative regimens may be needed in the presence of coinfection, comorbid disease and/or viral resistance. Combination therapies may reduce the development of resistance, but they may not improve efficacy. The optimal duration of treatment is not known; many patients are treated for up to 5 years and some are treated indefinitely. Discontinuation or sudden withdrawal of antiviral drugs can cause a rapid increase in HBV DNA levels and a flare of disease that can be severe, and sometimes fatal.

TENOFOVIR — Tenofovir disoproxil fumarate *(Viread)* is a prodrug that requires diester hydrolysis for conversion to tenofovir, a nucleotide analog of adenosine 5-monophosphate. Tenofovir has potent activity against HBV and is often a first choice in patients with chronic HBV infection. In two double-blind controlled trials, after 48 weeks more patients treated with tenofovir had undetectable HBV DNA levels (<400 copies per mL) and histologic improvement than those treated with adefovir (71% vs. 49% among HBeAg-negative patients; 67% vs. 12% among HBeAg-positive patients).[25] Tenofovir is also active against HIV and is often used as part of a first-line regimen for patients with HBV/HIV coinfection.

Adverse Effects – Nausea, abdominal pain, diarrhea, dizziness, fatigue and rash have been the most common adverse effects of tenofovir in patients with hepatitis B. Renal toxicity, including a Fanconi-like syn-

Table 4. Drugs for Chronic Hepatitis B

Drug	Usual Adult Dosage[1]	Cost[2]
Oral Nucleoside/Nucleotide Analogs[3]		
Tenofovir disoproxil – *Viread*	300 mg once/d	$832.20
Entecavir – *Baraclude*	0.5 mg once/d[4]	999.60
Telbivudine – *Tyzeka*	600 mg once/d	886.80
Adefovir dipivoxil – *Hepsera*	10 mg once/d	1052.70
Lamivudine – *Epivir HBV*[5]	100 mg once/d	406.80
Emtricitabine – *Emtriva*	200 mg once/d[6]	478.50
Interferons		
Interferon alfa-2b[7] – *Intron A*	5 million units once/d or 10 million units 3x/wk SC or IM x 16 wks[8]	2234.16
Peginterferon alfa-2a[7] – *Pegasys*	180 mcg once/wk SC x 48 wks[9]	5389.16[10]

1. Dosage adjustment may be required for renal insufficiency.
2. Wholesale acquisition cost (WAC) for 30 days' treatment with the shortest frequency of administration $ource® Monthly (Selected from FDB MedKnowledge™) February 6, 2013. Reprinted with permission by FDB, Inc. All rights reserved. ©2013. www.fdbhealth.com/policies/drug-pricing-policy/. Actual retail prices may vary.
3. Optimal duration of therapy with oral antivirals is uncertain. Many patients are treated for up to 5 years and some are treated indefinitely.
4. Dose for nucleoside-naïve patients. The drug is no longer recommended for use in patients with lamivudine-resistant HBV; if used in such patients, the dose should be increased to 1 mg/d.
5. *Epivir HBV* cannot be substituted for lamivudine *(Epivir)* in HIV treatment regimens. *Epivir* 150 mg bid or 300 mg once/d should be used in patients with HPV/HIV coinfection.
6. Dosage of oral solution is 240 mg (24 mL) once/d.
7. Should not be used in patients with decompensated cirrhosis.
8. For patients with HBeAg-postive chronic hepatitis B; continuing treatment for a total of 32 weeks may improve HBeAg seroconversion rates. HBeAg-negative hepatitis B should be treated for at least 12 months.
9. FDA-approved dosage and duration for HBeAg-positive and HBeAg-negative patients.
10. Cost of 30 days' treatment using a pen injector.

drome and progression to renal failure, has been reported; patients with pre-existing renal impairment are at increased risk. Tenofovir can also decrease bone density and cause osteomalacia. Lactic acidosis with severe hepatomegaly and steatosis occurs with several nucleoside analogs used to treat HIV infection, and the addition of tenofovir appears to increase the risk of this complication.

Pregnancy – Tenofovir is classified as category B (no evidence of risk in humans) for use during pregnancy. It is a drug of choice for treatment of chronic HBV in pregnant women and for prevention of perinatal transmission.

Resistance – Tenofovir has remained active in patients with lamivudine, telbivudine or entecavir resistance; it has some activity against adefovir-resistant HBV, but cross-resistance can occur.

ENTECAVIR — Entecavir *(Baraclude)*, a guanosine nucleoside analog, is well absorbed after oral administration; its prolonged plasma half-life (128-149 hours) allows once-daily dosing. Entecavir appears to be more effective than lamivudine or adefovir in suppressing HBV DNA levels.[26,27] It is no longer recommended in patients with lamivudine-resistant HBV.

Adverse Effects – Entecavir is generally well tolerated. Adverse effects reported during therapy include headache, fatigue, dizziness, nausea, rash and fever.

Pregnancy – Entecavir is classified as category C (risk cannot be ruled out) for use during pregnancy.

Resistance – Development of resistance to entecavir is uncommon, but it is more likely to occur in patients with lamivudine-resistant HBV. Entecavir-resistant HBV remains susceptible to adefovir and tenofovir, but data on the efficacy of these drugs in treating entecavir-resistant strains are limited.

Entecavir has weak anti-HIV activity and can induce the development of the M184V variant (HIV resistance to lamivudine and emtricitabine) in patients coinfected with HIV and HBV. Entecavir should not be used as monotherapy for HBV in HIV/HBV coinfected patients.

TELBIVUDINE — Telbivudine *(Tyzeka)*, the L-isomer of thymidine, is FDA-approved for the treatment of chronic HBV infection.[28] In the second year of a randomized trial, telbivudine-treated patients had a superior rate of virologic response compared to those treated with lamivudine (63% vs 48% in HBeAg-positive patients; 78% vs 66% in HBeAg-negative patients).[29] In an open-label trial, telbivudine was also more effective than adefovir in suppressing HBV DNA in patients with HBeAg-positive chronic hepatitis.[30] It is not effective in patients with lamivudine-resistant HBV.

Adverse Effects – Headache, cough, myalgia, nausea, diarrhea, rash, fever and fatigue are common. Peripheral neuropathy and myopathy, manifested by muscle aches and/or weakness with increased CPK, can occur; the risk may be increased when telbivudine is taken with peginterferon alfa.

Pregnancy – Telbivudine is classified as category B (no evidence of risk in humans) for use during pregnancy. When taken by highly viremic pregnant women, the drug can reduce maternal-fetal transmission of HBV.[31]

Resistance – The rate of resistance to telbivudine increases substantially after 1 year of treatment. After 2 years of treatment, 25.1% of HBeAg-positive and 10.8% of HBeAg-negative patients who responded to the drug had a rebound of HBV DNA levels that was associated with resistance mutations.[29] Lamivudine-resistant HBV strains have a high level of cross-resistance to telbivudine. Some adefovir-resistant strains remain susceptible to telbivudine.

ADEFOVIR DIPIVOXIL — Adefovir *(Hepsera)*, an adenosine 5-monophosphate nucleotide analog, can reduce HBV DNA and normalize aminotransferase levels in patients with HBeAg-negative and HBeAg-positive chronic hepatitis B,[32,33] but appears to be less effective than other nucleoside/tide analogs.[25,30] In patients with lamivudine-resistant chronic hepatitis B with a significant viral load, the use of adefovir with lamivudine is superior to adefovir alone and can decrease the development of adefovir resistance.[34] Adefovir has some activity against HIV, but in treatment of HIV/HBV coinfection, antiretroviral therapy that included adefovir led to less reduction in HBV DNA levels than antiretroviral therapy that included tenofovir.[35]

Adverse Effects – Adefovir is generally well tolerated, but asthenia, headache, diarrhea and abdominal pain can occur. Higher-than-recommended doses (30-60 mg/d) and pre-existing renal impairment are risk factors for azotemia and renal tubular dysfunction. In clinical trials, severe acute exacerbations of hepatitis have been reported in up to 25% of patients who discontinued adefovir.

Pregnancy – Adefovir is classified as category C (risk cannot be ruled out) for use in pregnancy.

Resistance – Adefovir-resistant variants emerge at a low frequency (8% of patients after 3 years of use and

20% after almost 5 years in HbeAg-negative patients)[36] and have been associated with a rebound in HBV DNA levels; these variants may remain susceptible to lamivudine and entecavir. Primary resistance to adefovir has been reported.[37]

LAMIVUDINE — In patients with chronic HBV and cirrhosis or advanced fibrosis, treatment with lamivudine *(Epivir-HPV)* for a median of 32 months reduced the risk of clinical progression of disease and development of hepatocellular cancer by about 50%.[38] However, use of the drug to treat HBV has been limited by high rates of resistance, and it is no longer recommended for first-line treatment. Lamivudine is also FDA-approved in a higher-dose formulation for treatment of HIV infection that can be used as part of a multidrug treatment regimen in patients with HBV/HIV coinfection.[39]

Adverse Effects – Lamivudine is generally well tolerated. Nausea, vomiting, diarrhea, headache, dizziness, myalgia and malaise can occur. Pancreatitis has been reported in adults and children coinfected with HBV and HIV.

Pregnancy – Lamivudine is classified as category C (risk cannot be ruled out) for use during pregnancy. Lamivudine has been effective in preventing vertical transmission of HBV from mother to newborn when given in the last 4 weeks of gestation.

Resistance – Resistance emerges in 14-32% of HBV-infected patients receiving lamivudine for one year and increases up to 69% at 5 years.[40] Resistant variants have been associated with hepatitis flares, rebound viremia and progressive liver disease. Resistant variants may respond to adefovir or tenofovir.

EMTRICITABINE — Although FDA-approved only for treatment of HIV infection, emtricitabine *(Emtriva)* has produced histologic, virologic and biochemical improvement in patients with chronic HBV infection in placebo-controlled trials, particularly in patients coinfected with HIV.[41,42] While current data are inadequate to support using it to treat HBV, emtricitabine may be considered as part of an effective antiretroviral regimen in HIV/HBV coinfected patients. Emtricitabine (5-fluorothiocytidine), like lamivudine (3-thiocytidine), is an L-enantiomer and substituted analog of cytosine; these two agents are similar in spectrum of activity, potency, side effects and patterns of resistance.

INTERFERON — Interferon alfa-2b *(Intron A)* and pegylated interferon alfa-2a *(Pegasys)* are FDA-approved for treatment of hepatitis B. The pegylated formulation has largely replaced standard interferon.[43] Despite the fixed duration of therapy and the lack of drug resistance compared with oral drugs, interferons are generally not the preferred therapy for hepatitis B due to a high incidence of side effects and the need for administration by injection.

In about one-third of patients with chronic HBV, treatment with interferon alfa-2b leads to loss of HBeAg, return to normal aminotransferase activity, sustained histological improvement and, in adults, a lower risk of progressive liver disease. The efficacy of peginterferon alfa-2a is similar to or slightly better than that of conventional interferon.[44] Compared to lamivudine, it has been associated with higher rates of sustained HBV DNA suppression in HBeAg-negative and HBeAg-positive chronic hepatitis B patients.[45,46] Peginterferon alfa-2b *(PegIntron)* may also be effective in treating chronic hepatitis B[47]; it is not FDA-approved for such use.

Patients with genotype A or B infection may respond better to interferon than those with other genotypes. Patients coinfected with HBV and HIV generally respond poorly to interferon. Interferons are contraindicated in patients with decompensated cirrhosis.

Adverse Effects – Injection of interferon is commonly associated with an influenza-like syndrome, especially during the first weeks of therapy. Other adverse effects include bone marrow suppression, fatigue, myalgia, weight loss, rash, cough, increased susceptibility to bacterial infections, psychiatric disorders including depression, anxiety, psychosis, mania, agitation and neurocognitive impairment, increased aminotransferase activity, alopecia, hypo- or hyperthyroidism, tinnitus, visual and hearing loss, auto-antibody formation, retinopathy, pneumonitis and possibly cardiotoxicity. Injection-site reactions and dose-related neutropenia and thrombocytopenia can also occur and are more common with pegylated interferons than with standard interferons. Autoimmune chronic hepatitis and other autoimmune diseases like thyroiditis may be induced or exacerbated by treatment with peginterferon.

HIV/HBV COINFECTION — Resistance to antivirals is more common in HBV patients coinfected with HIV. Coinfected patients should take antiretrovirals that are active against both HBV and HIV, such as tenofovir, emtricitabine or lamivudine, as part of a regimen for adequate suppression of HIV. Tenofovir and emtricitabine together appear to be more effective than other regimens for long-term suppression of HBV in coinfected patients.[48] Tenofovir and emtricitabine are available in a fixed-dose combination *(Truvada)*. Lamivudine and emtricitabine are structurally similar and should not be used together. Use of entecavir is discouraged in patients who are coinfected with HBV

and HIV because it has weak anti-HIV activity and rapidly leads to resistance.

HBV/HCV COINFECTION – HBV and hepatitis C virus (HCV) coinfection should initially be treated with a pegylated interferon and ribavirin-based regimen to target HCV.

CHRONIC HEPATITIS C

PEGINTERFERON PLUS RIBAVIRIN — For many years, the standard treatment for chronic, genotype 1 hepatitis C was subcutaneously injected pegylated interferon alfa combined with oral ribavirin for 48 weeks. This regimen usually achieved a sustained virologic response (SVR; undetectable HCV RNA 24 weeks after stopping treatment) in 40%-50% of patients with hepatitis C genotype 1 infection (the most common genotype in the US and Europe). Genotype 1 infection requires 48 weeks of peginterferon/ribavirin therapy; genotypes 2 and 3 have much higher response rates and only require 24 weeks' treatment.[49] Interferon is contraindicated in patients with decompensated cirrhosis.

Adverse Effects – The adverse effects of **interferon** were discussed under Hepatitis B on page 25.

Systemic **ribavirin** often causes red cell hemolysis and anemia. Oral ribavirin plus peginterferon appears to cause a higher incidence of anemia, cough, pruritus and rash than peginterferon alone. Because of the risk of severe anemia, the drug should not be used in patients with a history of significant or unstable cardiac disease and should be used with caution in those coinfected with HIV who are taking zidovudine.

Pregnancy – Interferons are classified as category C (risk cannot be ruled out) for use during pregnancy.

Ribavirin is teratogenic and embryotoxic; it is contraindicated for use in pregnant women (category X). Both male and female patients exposed to the drug should not conceive children during treatment or for 6 months after stopping the drug.

BOCEPREVIR AND TELAPREVIR — In 2011, two oral protease inhibitors, telaprevir *(Incivek)* and boceprevir *(Victrelis)*, were approved by the FDA for use in combination with peginterferon and ribavirin for treatment of HCV genotype 1 infection.[50] Addition of either one of these drugs to peginterferon and ribavirin increases SVR rates and is now the standard of care for this indication. No controlled trials are available comparing telaprevir with boceprevir, but they appear to be similarly effective for HCV genotype 1 infection.[51] They are not recommended for treatment of patients infected with other genotypes. Both drugs must be taken every 8 hours to minimize the risk of developing resistance.

Boceprevir – Boceprevir inhibits HCV replication by binding to the NS3/4A protease that cleaves HCV-encoded polyproteins. The addition of boceprevir to peginterferon and ribavirin for 24 or 44 weeks in treatment-naïve patients produced SVRs in 67% and 68% of non-black patients, respectively. SVRs were lower in black patients (42% and 53% at 24 and 44 weeks, respectively).[52] In patients with HCV genotype 1 infection previously treated with interferon-based therapy, the addition of boceprevir for 32 or 44 weeks to standard peginterferon-ribavirin therapy produced SVRs in 58% and 68% of non-black patients, respectively.[53]

Patients should receive 4 weeks of peginterferon and ribavirin therapy before starting boceprevir. Treatment naïve patients with undetectable virus at weeks 8 and 24 of triple therapy can stop the 3 drug regimen at week 28. Those previously treated for hepatitis C with undetectable virus at weeks 8 and 24 can stop the 3-drug regimen at week 36. All patients with detectable virus at week 8, but undetectable virus at week 24, should receive 32 weeks of boceprevir and 48 weeks of peginterferon and ribavirin.

Table 5. Drugs for Chronic Hepatitis C

	Drug	Usual Adult Dosage[1]	Cost[2]
	Peginterferon alfa-2b – *PegIntron*	1.5 mcg/kg once/wk SC[3]	$2534.72[4]
	plus ribavirin –	800-1400 mg/d PO[3,5]	
	generic		211.20
	Rebetol		1059.60
or	Peginterferon alfa-2a – *Pegasys*	180 mcg once/wk SC[3]	5389.16[6]
	plus ribavirin –	800-1200 mg/d PO[3,5]	
	generic		211.20
	Copegus		1968.00
plus	Telaprevir – *Incivek*[7]	750 mg tid PO x 12 wks[8]	19740.60
or	Boceprevir – *Victrelis*[7]	800 mg tid PO x 24-44 wks[9]	5396.40

1. Dosage adjustment may be required for renal insufficiency.
2. Wholesale acquisition cost (WAC) for 30 days' treatment at the lowest recommended maintenance dose. $ource® Monthly (Selected from FDB MedKnowledge™) February 6, 2013. Reprinted with permission by FDB, Inc. All rights reserved. ©2013. www.fdbhealth.com/policies/drug-pricing-policy/. Actual retail prices may be higher.
3. Therapy with peginterferon and ribavirin (PR) is usually given for 48 weeks in patients with HCV genotype 1 infection (24 weeks for genotype 2 or 3); when a protease inhibitor is added, PR treatment duration should be based on patient response: with boceprevir it can be 28, 36 or 48 weeks (includes 4 weeks of peginterferon and ribavirin before starting boceprevir) and with telaprevir, 24 or 48 weeks.
4. Cost of treating a 70-kg patient.
5. Should be taken with food. Dosage is based on patient body weight. The dose of *Copegus* for all patients with genotype 2 or 3 infection is 800 mg/d.
6. Cost of treatment using a pen injector.
7. Only approved for treatment of patients with HCV genotype 1 infection. Must be taken with peginterferon and ribavirin.
8. Must be taken with food (not low fat).
9. Must be taken with a light meal or snack.

Adverse Effects – The most commonly reported adverse effects of boceprevir in clinical trials were fatigue, anemia, nausea, headache and dysgeusia. About 50% of patients taking boceprevir in addition to ribavirin and peginterferon developed anemia, compared to about 25% with ribavirin and peginterferon alone. Neutropenia also occurred more often in patients treated with boceprevir.

Telaprevir – Like boceprevir, telaprevir is an inhibitor of HCV NS3/4A protease. In treatment-naïve patients, addition of telaprevir to peginterferon and ribavirin for the first 12 weeks of treatment produced SVRs in 75% of patients, compared to 44% of those receiving only peginterferon and ribavirin.[54] In previously-treated patients, treatment with telaprevir for 12 weeks plus peginterferon and ribavirin for 48 weeks achieved SVRs in 29% of patients who previously had no response to peginterferon/ribavirin and in 83% of those who responded previously but relapsed.[55]

Treatment-naïve patients should be treated with telaprevir plus peginterferon and ribavirin for 12 weeks. Those with undetectable virus at weeks 4 and 12 should receive peginterferon and ribavirin for an additional 12 weeks. Those with detectable virus at weeks 4 and/or 12 and those who were previously treated for hepatitis C should receive peginterferon and ribavirin for a total of 48 weeks.

Adverse Effects – Rash, anemia, fatigue, pruritus, nausea and vomiting were the most frequent adverse effects leading to discontinuation of telaprevir in clinical trials. Rash was reported in 56% of patients taking telaprevir combination therapy and in 34% of those taking only peginterferon and ribavirin; serious skin reactions including Stevens-Johnson syndrome were reported in <1% of patients taking teleprevir. A boxed warning about serious, sometime fatal, skin reactions occurring during treatment with telaprevir is now included in the labeling; telaprevir, peginterferon and ribavirin should be stopped and not restarted in patients with a severe rash.

The addition of telaprevir to peginterferon and ribavirin increases the risk of anemia; hemoglobin ≤10 g/dL occurred in 36% of patients taking telaprevir compared to 17% of those taking only ribavirin and peginterferon. Telaprevir may reduce white blood cell and platelet counts and increase bilirubin and uric acid levels. Anorectal adverse effects including hemorrhoids, pruritus and burning are also common.

Drug Interactions – Coadministration of **boceprevir** or **telaprevir** with strong inducers of CYP3A4 such as rifampin is contraindicated; concurrent use may reduce their serum concentrations, possibly leading to a loss of antiviral activity. Boceprevir and telaprevir are both strong inhibitors of CYP3A4 and P-gp *in vitro*. Drugs that inhibit or induce these pathways may increase or decrease serum concentrations of either drug. Both drugs are contraindicated for use with drugs highly dependent on CYP3A4 for clearance that may have significant toxicity at elevated serum concentrations, such as simvastatin. Both drugs may reduce the effectiveness of systemic hormonal contraceptives.

Pregnancy – Because **boceprevir** and **telaprevir** are always given in combination with ribavirin, which is embryotoxic and teratogenic, they are contraindicated for use in pregnant women (category X) and in men whose female partners are pregnant.

CYTOMEGALOVIRUS

GANCICLOVIR — IV ganciclovir (*Cytovene*, and others) is FDA-approved for both induction and maintenance treatment of cytomegalovirus (CMV) retinitis in immunocompromised patients and for prevention of CMV infection in transplant recipients. It is also used to treat CMV infections at other sites (colon, esophagus, lungs, etc.) and for preemptive treatment of immunosuppressed patients with CMV antigenemia or viremia. Ganciclovir also has activity against HSV and VZV. Oral ganciclovir is no longer available in the US.

Limited data in infants with symptomatic congenital CMV disease involving the CNS suggest that treatment with IV ganciclovir may decrease hearing loss.[56]

Intravitreal injections of ganciclovir, in combination with systemic ganciclovir or valganciclovir, have been

Table 6. Drugs for Cytomegalovirus

Drug	Usual Adult Dosage[1]	Cost[2]
Ganciclovir – generic *Cytovene*	5 mg/kg IV q12h x 14-21d, then 5 mg/kg IV once/d or 6 mg/kg IV 5x/wk	$1378.02 1487.16
Valganciclovir – *Valcyte*	900 mg PO bid x 21d, then 900 mg once daily	3408.60
Foscarnet – generic *Foscavir*	60 mg/kg IV q8h or 90 mg/kg IV q12h x 14-21d, then 90-120 mg/kg IV once/d[3]	2412.00 6989.96
Cidofovir – generic *Vistide*	5 mg/kg IV once/wk x 2 wks, then 5 mg/kg IV q2wks	1332.00 1480.00

1. Induction and maintenance dosage for treatment of CMV retinitis. Dosage adjustment may be required for renal insufficiency.
2. Wholesale acquisition cost (WAC) for 30 days' treatment for a 70-kg patient with the lowest recommended maintenance dose and the shortest frequency of administration. $ource® Monthly (Selected from FDB MedKnowledge™) February 6, 2013. Reprinted with permission by FDB, Inc. All rights reserved. ©2013. www.fdbhealth.com/policies/drug-pricing-policy/. Actual retail prices may be higher.
3. Higher doses (120 mg/kg/d) may be more effective, but less well tolerated.

used to treat CMV retinitis. An intraocular ganciclovir implant (*Vitrasert*) used to treat CMV retinitis is no longer available in the US.

Adverse Effects – Granulocytopenia, anemia and thrombocytopenia, which are usually reversible, are common and often dose-limiting. Severe myelosuppression may occur more frequently when the drug is given with zidovudine, probenecid, azathioprine or mycophenolate mofetil. Other adverse effects of systemic ganciclovir include fever, rash, phlebitis, confusion, abnormal liver function, renal dysfunction, headache, GI toxicity and, rarely, psychiatric disturbances and seizures. Intravitreal ganciclovir has been associated with loss of visual acuity, vitreous hemorrhage and acute retinal detachment.

Pregnancy – Ganciclovir is classified as category C (risk cannot be ruled out) for use during pregnancy. In animals, the drug is teratogenic, carcinogenic and mutagenic, and causes aspermatogenesis. Women of child-bearing age should use effective contraception during treatment, and men treated with the drug should use barrier contraception during treatment and for at least 90 days afterward.

Resistance – Ganciclovir resistance may be associated with persistent viremia and progressive disease in immunocompromised patients. Ganciclovir-resistant CMV can emerge and cause morbidity when the drug is used for prophylaxis in solid-organ transplant recipients taking highly potent immunosuppressive drugs. CMV strains resistant to ganciclovir *in vitro* may be susceptible to foscarnet or cidofovir.

VALGANCICLOVIR — Valganciclovir *(Valcyte)*, an oral prodrug of ganciclovir, achieves plasma concentrations similar to those with IV administration of ganciclovir. It is as effective as IV ganciclovir for CMV retinitis. Valganciclovir is FDA-approved for prevention of CMV disease in high-risk solid organ (kidney, heart, kidney-pancreas) transplant patients. The drug is also used in bone marrow transplant recipients for preemptive treatment of CMV disease (treating after detection of viremia or antigenemia). Both prophylactic and preemptive therapy are beneficial in those at risk of CMV disease; prophylactic therapy may be superior to preemptive therapy in high-risk patients.

Adverse Effects – Adverse effects are similar to those of IV ganciclovir.

Pregnancy – Like ganciclovir, valganciclovir is classified as category C (risk cannot be ruled out) for use during pregnancy. Women of child-bearing age should use effective contraception during and for at least 30 days after treatment, and men treated with the drug should use barrier contraception during treatment and for at least 90 days afterward.

Resistance – Because valganciclovir is a prodrug of ganciclovir, isolates that are resistant to ganciclovir are also resistant to valganciclovir.

FOSCARNET — IV foscarnet (*Foscavir*, and others) is FDA-approved for treatment of CMV retinitis in patients with AIDS, including progressive disease due to ganciclovir-resistant strains, and for treatment of acyclovir-resistant mucocutaneous HSV infections in immunocompromised patients. It is also used for treatment of acyclovir-resistant VZV infections. Foscarnet is more expensive and generally less well tolerated than ganciclovir, and requires controlled infusion rates and large volumes of fluid. In allogeneic stem cell transplant recipients with CMV infection, treatment with foscarnet is as effective as IV ganciclovir and causes less hematologic toxicity.[57]

Adverse Effects – Renal dysfunction often develops during treatment with foscarnet and is usually reversible, but renal failure requiring dialysis may occur. Renal toxicity is increased in patients receiving other nephrotoxic drugs; adequate hydration may decrease the risk. Nausea, vomiting, anemia, fatigue, headache, genital ulceration, CNS disturbances, hypocalcemia, hypo- and hyperphosphatemia, hypokalemia and hypomagnesemia have also occurred. Seizures and arrythmia have been reported.

Pregnancy – Foscarnet is classified as category C (risk cannot be ruled out) for use during pregnancy.

Resistance – HSV, VZV and CMV strains resistant to foscarnet can emerge during treatment. Combined use of foscarnet and ganciclovir may benefit some patients, but CMV strains resistant to both ganciclovir and foscarnet have been reported.

CIDOFOVIR — Given once weekly for 2 weeks and then once every 2 weeks for maintenance therapy, IV cidofovir (*Vistide*, and generics) can delay progression of CMV retinitis in patients with AIDS. Cidofovir has been used to treat other CMV infections (pneumonitis, gastroenteritis), acyclovir- or foscarnet-resistant HSV and VZV infections, certain forms of human papillomavirus disease, and invasive adenoviral and BK virus infections in transplant populations. It has been shown to be effective in progressive vaccinia (small pox vaccine) in mice.

IV and topical cidofovir (3% cream; not available commercially) have been reported to produce resolu-

tion of molluscum contagiosum in immunosuppressed patients.[58] Cidofovir has also been used to treat adenovirus infection in allogeneic stem cell transplant recipients. *In vitro*, cidofovir is active against vaccinia, variola and other pox viruses, and has been effective in animal models of lethal infection with these viruses.[59]

Adverse Effects – About 25% of patients discontinue cidofovir because of adverse effects including nephrotoxicity, neutropenia and metabolic acidosis. To decrease the risk of nephrotoxicity, pre-treatment with IV fluids and oral probenecid must be given with each cidofovir dose. Cidofovir is contraindicated in patients taking other nephrotoxic agents. Iritis, uveitis or ocular hypotony can also occur.

Pregnancy – Cidofovir is classified as category C (risk cannot be ruled out) for use during pregnancy. The drug is carcinogenic and teratogenic, and causes hypospermia in animals.

Resistance – Although most ganciclovir-resistant CMV isolates remain susceptible to cidofovir, cross-resistance can occur. Acyclovir-resistant HSV and VZV are often susceptible to cidofovir.

RESPIRATORY SYNCYTIAL VIRUS

RIBAVIRIN — An aerosolized formulation of ribavirin *(Virazole)*, a synthetic nucleoside, may decrease morbidity in some children hospitalized with respiratory syncytial virus (RSV) bronchiolitis and pneumonia, but because of its potential adverse effects, it is not generally recommended for such use. Ribavirin is teratogenic and embryotoxic; pregnant women should not directly care for patients receiving aerosolized ribavirin.

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Through this program, The Medical Letter expects to provide the healthcare community with unbiased, reliable and timely educational content that they will use to make independent and informed therapeutic choices in their practice.

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Upon completion of this program, the participant will be able to:

1. Explain the current approach to the management of patients with viral infections.
2. Discuss the pharmacologic agents available for treatment and/or prophylaxis of viral infections and compare them based on their efficacy, dosage and administration, potential adverse effects and drug interactions.
3. Determine the most appropriate therapy given the clinical presentation of an individual patient.

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Issue 127 Questions

1. The drug of choice for the treatment of serious or disseminated varicella-zoster virus infections is:
   a. famciclovir
   b. IV acyclovir
   c. valacyclovir
   d. tenofovir

   Issue 127

2. Herpes simplex virus and varicella-zoster virus strains resistant to acyclovir may respond to which of the following?
   a. foscarnet
   b. cidofovir
   c. both a and b
   d. neither a nor b

3. Thrombotic thrombocytopenic purpura has been reported in severely immunocompromised patients taking high doses of:
   a. valacyclovir
   b. foscarnet
   c. ganciclovir
   d. tenofovir

   Issue 127

4. Which of the following has been used to treat accidental ocular infection following smallpox vaccination?
   a. acyclovir
   b. famiciclovir
   c. penciclovir
   d. trifluridine

   Issue 127

5. Which of the following can decrease the severity and duration of symptoms caused by influenza A or B if started within 48 hours of symptom onset?
   a. ribavirin
   b. oseltamivir
   c. tenofovir
   d. cidofovir

   Issue 127

6. Which of the following is not currently recommended for treatment or prophylaxis of influenza?
   a. amantadine
   b. rimantadine
   c. both a and b
   d. neither a nor b

   Issue 127

7. Which of the following is often used first for the treatment of hepatitis B in treatment-naïve patients?
   a. tenofovir
   b. lamivudine
   c. telbivudine
   d. adefovir

   Issue 127

8. Lamivudine-resistant hepatitis B virus strains generally remain susceptible to:
   a. entecavir
   b. telaprevir
   c. telbivudine
   d. adefovir

   Issue 127

9. A 65-year-old, otherwise healthy man is diagnosed with hepatitis C virus genotype 1 infection. Which of the following would be the best choice for the management of chronic hepatitis C in this patient?
   a. interferon alfa-2b alone
   b. peginterferon and ribavirin plus boceprevir or telaprevir
   c. telbivudine
   d. telaprevir alone

   Issue 127

10. When given without telaprevir or boceprevir for treatment of genotype 1 HCV, peginterferon and ribavirin should be continued for:
    a. 24 weeks
    b. 48 weeks
    c. 52 weeks
    d. 60 weeks

    Issue 127

11. A 64-year-old woman with HIV is being evaluated for antiviral therapy for the treatment of CMV retinitis that has not responded to ganciclovir or foscarnet therapy. Which of the following would be the best choice for the management of CMV retinitis in this patient?
    a. cidofovir
    b. oseltamivir
    c. penciclovir
    d. zanamivir

    Issue 127

12. To minimize the risk of renal toxicity, patients receiving IV cidofovir should be pre-treated with:
    a. IV fluids
    b. probenecid
    c. both a and b
    d. neither a nor b

    Issue 127

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