

# Antiviral Drugs in the Immunocompetent Host: Part I. Treatment of Hepatitis, Cytomegalovirus, and Herpes Infections

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Since the release of amantadine in 1966, other agents designed to fight a diverse range of viral infections have been released. Part I of this two-part article focuses on agents used to manage hepatitis, cytomegalovirus, and herpes infections. In patients with chronic hepatitis B, interferon alfa-2b or lamivudine is the treatment of choice. Pegylated interferon alfa-2a or -2b, along with ribavirin, is standard treatment for patients with chronic hepatitis C. Although treatment of cytomegalovirus infections generally is supportive, there have been reports of severely ill patients who improved after receiving ganciclovir or foscarnet. Oral antiviral agents for initial and recurrent herpes simplex virus infections have been shown to shorten the duration of lesions. Treatment of herpes zoster infections with antiviral drugs shortens the course of infection and decreases symptoms. Studies have shown that antiviral treatment can prevent prolonged post-herpetic neuralgia, although this use remains controversial. (*Am Fam Physician* 2003;67:757-62. Copyright© 2003 American Academy of Family Physicians.)

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See page 675 for definitions of strength-of-evidence levels.

This is part I of a two-part article on antiviral drugs. Part II, "Treatment of Influenza and Respiratory Syncytial Virus Infections," appears in this issue on page 763.

Viral infections are among the most formidable conditions in the primary care setting, causing a wide range of illnesses that are difficult to treat. Developing antiviral medicines has been difficult because most drugs that kill viruses also damage the host's cells. However, since the first antiviral drug, amantadine (Symmetrel), was released in 1966, encouraging progress has been made in this area. Part I of this two-part article focuses on antiviral agents used to treat hepatitis, cytomegalovirus (CMV), and herpes infections in nonimmunosuppressed patients. Important issues in the management of viral infections in patients with human immunodeficiency virus (HIV) infection and in solid-organ or bone-marrow transplant patients are not reviewed.

## Hepatitis Viruses

### HEPATITIS B

Chronic hepatitis B virus (HBV) infection affects 5 percent of the worldwide population and may lead to cirrhosis and hepatocellular carcinoma. HBV infection is considered chronic when surface antigen persists for more

than six months. Three criteria for treating chronic HBV include alanine aminotransferase (ALT) level greater than two times normal and positive tests for HBV DNA and hepatitis B e antigen (HBeAg) (Table 1). All three criteria should be present before patients are considered for anti-HBV therapy. The treatment of choice in these patients is interferon alfa-2b (Intron A)<sup>1</sup> [Evidence level B, cohort study] or lamivudine (Epivir-HBV).<sup>2</sup> More recently, adefovir dipivoxil (Hepsera) was approved for use in chronic HBV infection.<sup>3</sup>

**Interferon Alfa-2b.** Response to interferon alfa-2b (defined as loss of HBeAg and HBV DNA) occurs in 30 to 40 percent of patients. Unfortunately, interferon is associated with significant side effects, including flu-like symptoms (e.g., headaches, fevers, myalgias, fatigue), thrombocytopenia, leukopenia, depression, weight loss, rash, cough, hypo- or hyperthyroidism, tinnitus, auto-antibody formation, and retinopathy.

**Lamivudine.** Lamivudine is a nucleoside reverse transcriptase inhibitor that is used to treat HIV and HBV infections. Response rates to lamivudine are similar to those obtained with interferon alfa-2b, and lamivudine is typi-

**TABLE 1**  
**Hepatitis B and C: Indications and Treatment**

| <i>Agent</i>             | <i>Indications</i>   | <i>Recommended treatment regimen*</i>   |
|--------------------------|--|---|
| Hepatitis B virus (HBV)  | ALT level >two times normal<br>Positive for HBV DNA<br>Positive for HBe antigen                              | Interferon alfa-2b (Intron A)†: 5 million IU SQ or IM daily or 10 million IU SQ or IM three times per week for 16 weeks<br>or<br>Lamivudine (Epivir-HBV): 100 mg daily for up to one year<br>or<br>Adefovir dipivoxil (Hepsera): 10 mg daily for up to 48 weeks   |
| Hepatitis C virus (HCV)‡ | ALT level >two times normal<br>Positive for HCV RNA<br>Cirrhosis, fibrosis, or inflammation on liver biopsy§ | Pegylated interferon alfa-2b (PEG-Intron): 1.5 mcg per kg SQ weekly with ribavirin (Rebetol), 600 mg twice daily, for up to 48 weeks  <br>or<br>Pegylated interferon alfa-2a (Pegasys): 180 mcg SQ weekly with ribavirin, 600 mg twice daily, for up to 48 weeks<br>Pegylated interferon alfa-2b: 1.5 mcg per kg SQ weekly for up to 48 weeks   (if ribavirin is contraindicated)<br>or<br>Pegylated interferon alfa-2a: 180 mcg SQ weekly for up to 48 weeks (if ribavirin is contraindicated) |

ALT = alanine aminotransferase; SQ = subcutaneously; IM = intramuscularly.

\*—Adult dosages.

†—All three indications must be fulfilled before initiating treatment with interferon alfa-2b.

‡—Treatment recommendations based on HCV genotypes 1a/1b or 4.

§—Positive ALT and positive HCV RNA are required to initiate treatment; liver biopsy is recommended but not required.

||—HCV RNA should be assessed at week 24 and, if positive, treatment should be discontinued, unless treatment goal is to slow fibrosis progression (this use is controversial).

cally much better tolerated.<sup>2</sup> [Evidence level A, randomized controlled trial (RCT)] However, drug resistance is a major difficulty associated with lamivudine. Resistance develops after one year of treatment in 15 to 30 percent of patients. Unlike interferon alfa-2b, lamivudine is approved for use in patients with decompensated cirrhosis resulting from HBV infection.

**Adefovir Dipivoxil.** Adefovir dipivoxil is a nucleotide reverse transcriptase inhibitor with a mechanism of action similar to that of lamivudine. In early studies, resistance to adefovir dipivoxil appears to be uncommon. Adefovir dipivoxil also can be used effectively in patients who are resistant to lamivudine.<sup>3,4</sup> It is likely that future treatment protocols for HBV infection will use multiple combination regimens, although such regimens are currently experimental.

#### HEPATITIS C

Hepatitis C virus (HCV) is the most frequent cause of end-stage liver disease in the United States and the leading indication for liver transplant.<sup>5</sup> Therefore, as with chronic HBV, it is

important that physicians consider treatment options in any HCV-infected patient.

Therapy for chronic HCV infection is indicated in patients with a detectable HCV RNA viral load and a persistently elevated ALT level. Findings of cirrhosis, fibrosis, or even moderate inflammation on liver biopsy support the choice of therapeutic intervention, but biopsy is not mandatory before initiating therapy.<sup>5</sup>

**Pegylated Interferon Alfa and Ribavirin.** The standard treatment regimen for chronic HCV infection is outlined in *Table 1*. Pegylated interferon alfa-2a (Pegasys) and pegylated interferon alfa-2b (PEG-Intron) are modified forms of interferon alfa with much longer half-lives, which allow these drugs to be taken once a week. In addition, they are significantly more effective against HCV, either alone or in combination with ribavirin (Rebetol), compared with unmodified interferon alfa, and they have side effect profiles similar to that of unmodified interferon alfa.<sup>6,7</sup> [References 6 and 7—Evidence level A, RCT]

The HCV viral load should be assessed after 24 weeks of therapy. Recent studies suggest

that patients infected with HCV genotype 2 or 3 should receive a total course of 24 weeks of therapy, while patients with genotypes 1 or 4 have higher sustained virologic response rates if they are treated for 48 weeks. In patients with genotype 1a or 1b infection, the detection of viremia at 24 weeks predicts viral persistence despite therapy. Thus, it is recommended that patients with viremia at 24 weeks discontinue therapy. Because viremia at 12 weeks now appears to predict persistent HCV infection, some experts recommend discontinuing therapy at 12 weeks if HCV viremia is detected. In patients with genotype 1a or 1b (and probably genotype 4, as well) and an undetectable HCV viral load at 24 weeks, continuation of therapy for the full 48-week course is indicated.

Treatment of newly established HCV infection with unmodified interferon alfa-2b for 24 weeks was recently found to eliminate the virus in the vast majority of patients studied.<sup>8</sup> [Evidence level B, nonrandomized clinical trial] Unfortunately, few patients present to their physicians with acute HCV infection, although it is sometimes found during screening (after a needlestick exposure, for example). Comparable data have not been collected for the response of acute HCV infection to pegylated interferons, but it is reasonable to anticipate a similar benefit.

#### HEPATITIS D

Hepatitis D virus affects only patients who are already infected with HBV. Co-infected patients are more likely to develop cirrhosis and hepatocellular carcinoma. Treatment for hepatitis B and D co-infection is similar to treatment for chronic HBV infection, although some protocols use higher interferon dosages.<sup>9</sup>

#### Cytomegalovirus

CMV infection generally causes an asymptomatic or mildly symptomatic acute illness in immunocompetent adults. Approximately 10 percent of patients develop a self-limited, mononucleosis-like syndrome.<sup>10</sup> Treatment of CMV mononucleosis is generally supportive.

*Interferon alfa-2b or lamivudine is the preferred therapy for hepatitis B when the patient's alanine aminotransferase level is more than two times the normal level and the patient is positive for HBV DNA and HBeAg.*

Severe CMV disease in immunocompetent patients is rare and has been associated with a nearly 50 percent mortality rate.<sup>10</sup>

*Ganciclovir and Foscarnet.* There are no established recommendations for treating severe CMV infection in immunocompetent patients. However, case reports of severely ill patients who received either intravenous ganciclovir (Cytovene) or foscarnet (Foscavir) describe an improved outcome compared with untreated patients.<sup>10</sup> Patients were treated with various dosages for various durations.

The major toxic effect of ganciclovir is myelosuppression. Ganciclovir also can cause fever, rash, and abnormal liver function. Foscarnet is associated with nausea, vomiting, anemia, electrolyte abnormalities, central nervous system disturbances, and renal impairment. Both ganciclovir and foscarnet should be used with caution in patients with concomitant renal impairment.

#### Herpes Viruses

Herpes viruses are DNA viruses that can lie dormant in sensory neurons after initial infection, then later reactivate and cause disease. Viruses in this family include herpes simplex virus (HSV) and varicella zoster virus (VZV). The dominant manifestations of these viruses are dermatologic and sensory. Antiviral agents used in the treatment of herpes viruses are listed in *Table 2*.<sup>11</sup>

#### GENITAL HERPES

Initial and recurrent episodes of genital HSV can be treated, and recurrent episodes (more than six per year) can be suppressed with antiviral medications. Suppressive treatment is much more effective than episodic treatment.

After one year of treatment with valacyclovir, 40 to 50 percent of patients with recurrent genital herpes are episode free.

**Acyclovir.** Acyclovir (Zovirax) is a guanosine analog that inhibits DNA polymerase. It has poor bioavailability and a short half-life. Treatment with daily oral acyclovir decreases episodes from 11.4 to 1.8 per year.<sup>12,13</sup> [Reference 13—Evidence level A, RCT] Topical acyclovir is not an effective treatment for episodic genital HSV.

**Valacyclovir.** Valacyclovir (Valtrex) is a prodrug that metabolizes to acyclovir. It has better bioavailability and less frequent dosing than acyclovir. After one year of daily treatment with valacyclovir, 40 to 50 percent of patients are episode free, and the mean rate of occurrence is 0.8 episodes per year.<sup>14,15</sup> Compared with placebo, valacyclovir decreases the length of episodes and mean healing time by two days.<sup>16</sup> It is as effective as acyclovir for initial and episodic treatment and for suppression of genital HSV.

**Famciclovir and Penciclovir.** Famciclovir (Famvir) is a prodrug of penciclovir (Denavir), a purine analog. It has high bioavailability and quickly metabolizes to penciclovir. In episodic

treatment of genital HSV, famciclovir decreases time to healing.<sup>17</sup> A study of its use in the suppression of recurrent genital HSV infection showed an average of 1 to 1.8 episodes per year in treated patients versus 5.1 episodes per year in patients who received placebo.<sup>18</sup> Topical penciclovir decreases time to crusting by one day.<sup>19</sup>

Acyclovir, valacyclovir, and famciclovir have similar side effects, which include nausea, vomiting, headache, and diarrhea. When used in high dosages as an intravenous medication, acyclovir can crystallize the renal tubules, causing acute renal failure.

#### OROLABIAL HERPES

Initial orolabial HSV infection (gingivostomatitis) often affects young children, and treatment with oral antiviral medications may be helpful in certain populations (i.e., skiers with a sunlight trigger). Few studies have investigated the use of oral antiviral drugs for episodic or recurrent orolabial HSV infection.

**Acyclovir.** Treatment with oral acyclovir significantly shortens the course of initial orolabial HSV infection in children (by approximately six days) and decreases symptoms and duration of viral shedding.<sup>20</sup>

**Famciclovir.** When taken within 48 hours of exposure to the precipitating stimulus, oral famciclovir decreases time to healing by two days in ultraviolet radiation-induced orolabial herpes.<sup>21</sup>

**Valacyclovir.** Valacyclovir was recently approved by the U.S. Food and Drug Administration for the treatment of orolabial HSV infections in adults and children 12 years of age and older.

**Topical Medications.** Topical penciclovir and docosanol (Abreva) decrease time to healing by 0.7 days.<sup>22,23</sup>

#### VARICELLA ZOSTER VIRUS

Studies have linked treatment with antiviral agents to a decrease in the duration of post-herpetic neuralgia, although the use of drugs for this purpose is controversial.

**Acyclovir.** In a randomized, double-blind

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TABLE 2

**Antiviral Medicines for Herpes Infections**

| <i>Drug</i>            | <i>Indication</i>                | <i>Dosage</i>                                   | <i>Side effects</i>  | <i>Cost (generic)*</i>                        |
|------------------------|----------------------------------|---|--|---|
| <b>Oral agents</b>     |                                  |   |  |   |
| Acyclovir (Zovirax)    | Initial genital herpes infection | 200 mg five times daily for 10 days             | Nausea, vomiting, headache, diarrhea, vertigo, myalgia, rash, renal failure, CNS changes | 100 capsules at 200 mg: \$140 (\$98 to \$112) |
|                        | Episodic genital herpes          | 200 mg five times daily for five days           |  |   |
|                        | Genital herpes suppression       | 400 mg twice daily for up to 12 months          |  |   |
|                        | Episodic orolabial herpes        | 15 mg per kg five times daily for seven days†   |  |   |
|                        | Herpes zoster                    | 800 mg five times daily for seven to 10 days    |  |   |
| Famciclovir (Famvir)   | Initial genital herpes infection | 250 mg twice daily for seven to 10 days‡        | Headache, nausea, vomiting, fatigue, paresthesias, pruritus                              | 30 tablets at 250 mg: \$110                   |
|                        | Episodic genital herpes          | 125 mg twice daily for five days                |  |   |
|                        | Genital herpes suppression       | 250 mg twice daily for up to 12 months          |  |   |
|                        | Herpes zoster                    | 500 mg every eight hours for seven days         |  |   |
| Valacyclovir (Valtrex) | Initial genital herpes infection | 1 g twice daily for 10 days                     | Nausea, vomiting, headache, dizziness  | 21 tablets at 1 g: \$130                      |
|                        | Episodic genital herpes          | 500 mg twice daily for three days               |  |   |
|                        | Genital herpes suppression       | 500 mg or 1 g daily for up to one year§         |  |   |
|                        | Episodic orolabial herpes        | 2 g twice daily for one day                     |  |   |
|                        | Herpes zoster                    | 1 g three times daily for seven days            |  | 42 tablets at 500 mg: \$162                   |
| <b>Topical agents</b>  |                                  |   |  |   |
| Acyclovir (Zovirax)    | Initial genital herpes infection | Apply six times daily for seven days            | Pain, pruritus   | 15-g tube: \$75<br>3-g tube: \$20             |
| Penciclovir (Denavir)  | Episodic orolabial herpes        | Apply every two hours while awake for four days | Headache, skin irritation  | 1.5-g tube: \$24                              |
| Docosanol (Abreva)     | Episodic orolabial herpes        | Apply five times daily until healed             | Headache, reaction at site   | 2-g tube: \$14                                |

CNS = central nervous system.

\*—Estimated cost to the pharmacist based on average wholesale prices for listed quantity in Red book. Montvale, N.J.: Medical Economics Data, 2002. Cost to the patient will be higher, depending on prescription filling fee.

†—Not approved by the U.S. Food and Drug Administration (FDA) for treatment of orolabial herpes.

‡—Not FDA-approved for treatment of initial genital herpes infection. Supplemental new drug application pending.

§—Patients with a history of nine or fewer recurrences per year can receive the 500-mg dosage.

Information from Physicians' Desk Reference. Accessed November 2002 at [www.pdr.net](http://www.pdr.net) (with password).

study, acyclovir accelerated healing, decreased frequency of rash dissemination, and reduced acute pain.<sup>24</sup>

**Valacyclovir.** In patients older than 50 years, valacyclovir decreases the duration of acute pain and post-herpetic neuralgia compared with acyclovir.<sup>25</sup>

**Famciclovir.** Famciclovir is effective in decreasing time to resolution of VZV lesions

and decreasing duration of post-herpetic neuralgia.<sup>26</sup> There is no difference in effectiveness between famciclovir and valacyclovir in the treatment of VZV.<sup>27</sup>

The authors thank David Oldach, M.D., for review of the manuscript.

The authors indicate that they do not have any conflicts of interest. Sources of funding: none reported.

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