A Review of Commonly Prescribed Antiviral and Antiretroviral Agents

HANINE MANSOUR, LISA DE VITO INGE, JASON FERREIRA, AND NATHAN R UNGER

Objective: To review the pharmacologic properties of and uses for the most commonly prescribed antiviral agents.

Data Sources: A MEDLINE/PubMed search (1966-September 2010) was conducted for English-language articles using the terms HIV, hepatitis, cytomegalovirus (CMV), herpes simplex virus (HSV), antiviral agents, antiretroviral agent, acyclovir, valganciclovir, valacyclovir, interferon, ribavirin, ritonavir, efavirenz, zidovudine, darunavir, lopinavir, tenofovir, raltegravir, lamivudine, atazanavir, and emtricitabine. Book chapters and recent guidelines pertaining to the pathophysiology or pharmacologic properties of antiviral agents were also reviewed.

Study Selection and Data Extraction: Articles, chapters, and guidelines pertaining to the relevant pharmacologic agents were collected for review.

Data Synthesis: Viral pathogens affect multiple organs, causing direct and indirect damage by activating an immune response. Unlike bacterial infections, which can be eradicated from the host system, viral infections are not curable. Antiviral treatments are prescribed to reduce morbidity and mortality. There are many antiviral and more than 20 antiretroviral agents currently approved by the FDA. These include acyclovir, valacyclovir, and famciclovir for HSV; ganciclovir, valganciclovir, foscarnet, and cidofovir for CMV; interferon and ribavirin for hepatitis; and efavirenz, tenofovir, emtricitabine, atazanavir, darunavir, lopinavir, ritonavir, raltegravir, zidovudine, and lamivudine as first-line agents for HIV.

Conclusions: Viral illnesses affect a large portion of the population. Given the multitude of drugs available, pharmacists and pharmacy technicians should be educated about common treatment options. Having a strong knowledge of commonly prescribed antiviral drugs allows these frontline professionals to make a significant impact on the quality of care that they provide to their patients and community.


Many common viruses (eg, influenza, rhinoviruses) are controlled or cleared by an individual’s immune system with few long-term sequelae. However, certain viral or host factors—viral type (and subtype), duration of infection, age at time of acquisition, immunosuppressive conditions or medications, and duration of the infection—increase the pathogenicity of viruses.¹ In these situations, antiviral or antiretroviral agents may be prescribed for treatment of active disease, prevention, or preemptive therapy.

Because viral replication relies on a host cell for its life cycle, most antiviral and antiretroviral agents interrupt the viral replication within the host cell.² However, interferon augments the host’s immune response and assists with viral clearing.³ Both mechanisms decrease the clinical manifestations of a virus.

Herpes Simplex Virus

Herpes simplex virus (HSV), a double-stranded DNA virus, exists as 2 subtypes, HSV-1 and HSV-2. Infection occurs by mucous membrane contact with HSV. Viral particles are secreted from active lesions and genital secretions of infected individuals. HSV-1 is primarily associated with infections of the mouth (cold sores), whereas genital herpes is predominately HSV-2. HSV acquisition results in lifelong infection that presents as alternating episodes of painful lesions and asymptomatic periods. Symptomatic reactivation may occur as a result of local tissue injury, acute illness, immunosuppression, or fever.⁴ Acyclovir, valacyclovir, and famciclovir are used in the management of HSV-1 and HSV-2.⁵
Acyclovir, an acyclic guanine nucleoside analogue, requires tri-phosphorylation by the thymidine kinase in HSV, Epstein-Barr virus (EBV), and varicella-zoster virus (VZV) for activation. Once activated, acyclovir serves as a competitive irreversible chain terminator of viral DNA replication. Although most effective for treatment of HSV-1 and HSV-2, it offers some benefit in VZV and limited benefit in cytomegalovirus (CMV) suppression.

Acyclovir’s poor oral bioavailability (10-30%) requires that large doses be administered. Valacyclovir, a prodrug L-valyl ester, was developed to overcome this limitation. Valacyclovir is converted to acyclovir by first-pass and hepatic metabolism, reaching an oral bioavailability of about 55%. Nonmetabolized acyclovir and any metabolites are eliminated through the renal system; therefore, dosing adjustments are necessary for patients with renal dysfunction. Treatment formulations, doses, and administration frequencies for FDA-approved indications in viral conditions are listed in Table 1.6,7

Adverse effects of both acyclovir and valacyclovir include headaches, nausea, and diarrhea. Central nervous system (CNS) adverse effects, including lethargy, confusion, delirium, and hallucinations, are occasionally seen in patients with renal dysfunction and those receiving the intravenous formulation.8 Severe or fatal thrombocytopenic syndromes have been reported in immunocompromised patients.9 Reversible neurotoxicity has also been reported with high serum acyclovir levels and is likely associated with a particular acyclovir metabolite.9 Renal dysfunction, obstruction, and renal tubular damage as a result of acyclovir crystallization have also been reported.

The intravenous formulation should be administered over 1 hour and accompanied by adequate hydration pre- and postinfusion as a precaution.10 Both oral formulations should be taken with plenty of water. Other adverse effects include local irritation with topical formulations and rare phlebitis with intravenous extravasation.10,11 Nephrotoxicity may be increased when acyclovir is administered with other nephrotoxic drugs or when it is administered with zidovudine or probenecid, which increase acyclovir concentrations.

Famciclovir, a prodrug of penciclovir, requires metabolism in the gastrointestinal tract, blood, and liver for conversion to its active form. It is a competitive inhibitor of viral DNA polymerase and is as effective as acyclovir against herpes.8 Dosage adjustments are necessary in severe renal dysfunction. Like acyclovir and valacyclovir, rare adverse effects include headache, nausea, and diarrhea. Data on use of famciclovir in pregnancy are limited but animal studies with very high doses found that the drug may have mutagenic potential. To date, no drug interactions have been identified.12

Cytomegalovirus

CMV, a DNA virus in the herpes family, is also transmitted by bodily fluids. Acute infection is a result of mouth-to-mouth transmission (ie, kissing), intimate sexual contact, perinatal transmission, and blood transfusion.12 Although 50-80% of chronic adult CMV infections are asymptomatic, acute exposure often begins as a mild illness with symptoms of fever, sore throat, swollen glands, and fatigue.13 Occasionally, CMV complications occur during the chronic viral carrier state, particularly in patients with immunosuppressive conditions (eg, HIV, malignancy, transplant recipients, neonates) or those receiving immunosuppressive medications. Manifestations of active viral replication can involve a variety of organs, including the eyes, lungs, CNS, and digestive tract. The corresponding symptoms include blindness or visual impairment, pneumonia, digestive tract ulceration, polyradiculopathies, and coma or seizures in the brain.13 Antiviral agents active against CMV are often prescribed for immunocompromised persons to prevent or treat these complications. Ganciclovir, foscarnet, and cidofovir are all approved for CMV treatment.13

Ganciclovir, a deoxyguanosine analogue, is an irreversible DNA-chain terminator. It is extremely active against CMV because the CMV phosphotransferase has a greater affinity for ganciclovir than for acyclovir. This affinity, in addition to its longer intracellular half-life, makes ganciclovir the treatment of choice for CMV, as opposed to acyclovir. It is prescribed for CMV retinitis, as well as treatment and prevention of other CMV organ-specific diseases in immunosuppressed or transplant patients.14-16

As a result of ganciclovir’s poor bioavailability (8-9%), valganciclovir, another L-valyl ester prodrug, was developed.17 Valganciclovir is converted to ganciclovir in the intestine and the liver, offering great bioavailability (60%).8 It also possesses good penetration into the cerebrospinal fluid and brain tissue. Elimination of this unmetabolized drug occurs by renal excretion, making renal dosing necessary.

Adverse effects of ganciclovir include reversible myelosuppression, specifically neutropenia (15-40%) and thrombocytopenia (5-20%).18 This risk increases 2 weeks into therapy, but is reversible upon drug discontinuation or with cell line stimulation administration (ie, granulocyte stimulating factor). Five percent to 15% of patients also experience CNS adverse effects ranging from headaches to behavior changes or coma as a result of CNS penetration.

▲

Most antiviral and antiretroviral agents interrupt the viral replication within the host cell.

▼
### Table 1. Antiviral Agents

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSAGE/FORM</th>
<th>STANDARD ADULT DOSE</th>
<th>COMMON ADVERSE EFFECTS/COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valganciclovir*</td>
<td>450-mg tablet, 50-mg/mL powder for solution</td>
<td>CMV retinitis: 900 mg twice daily for 14-21 days followed by 900 mg once daily for small peripheral lesions; in combination with intraocular ganciclovir implant for sight-threatening lesions Prevention of CMV infection in solid organ transplant: 900 mg once daily started within 10 days of transplantation and continued for 100 days after transplantation</td>
<td>Diarrhea, nausea, GI disturbances, fever, graft rejection, bone marrow suppression, birth defects</td>
</tr>
<tr>
<td>Acyclovir*</td>
<td>200-mg capsule, 400- and 800-mg tablets, 200-mg/5-mL oral suspension, 50-mg/mL injection, 100- and 500-mg/vial as powder for injection, 5% (15-g tube) topical ointment, 5% (2- and 5-g tubes) topical cream</td>
<td>Immunocompetent pts.: Initial genital herpes episode: 400 mg 3 times daily or 200 mg 5 times daily for 7-10 days Recurrent genital herpes episode: 400 mg by mouth 3 times daily for 5 days, 800 mg by mouth for 5 days or 800 mg by mouth 3 times daily for 2 days Herpes zoster: 800 mg by mouth 5 times daily for 7-10 days HSV encephalitis: 20 mg/kg iv every 8 h Immunocompromised pts.: Herpes or varicella zoster: 10 mg/kg/dose iv or 500 mg/m²/dose by mouth every 8 h for 7 days Mucocutaneous HSV: 5 mg/kg/dose iv every 8 h for 7 days or 400 mg 5 times daily for 7-14 days</td>
<td>Nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td>Valacyclovir*</td>
<td>500-mg and 1-g caplets</td>
<td>Initial genital herpes episode: 1 g by mouth twice daily for 7-10 days Recurrent genital herpes episode: 500 mg by mouth twice daily for 3 days or 1 g by mouth daily Herpes zoster: 1 g by mouth 3 times daily for 7 days</td>
<td>Headache, nausea, abdominal pain</td>
</tr>
<tr>
<td>Famciclovir*</td>
<td>125-, 250-, and 500-mg tablets</td>
<td>Herpes labialis (cold sores): 1500 mg as a single dose Immunocompetent pts.: Initial genital herpes episode: 250 mg by mouth 3 times daily for 7-10 days Recurrent genital herpes episode: 125 mg by mouth twice daily for 5 days or 1 g by mouth twice daily for 1 day Chronic suppressive therapy: 250 mg by mouth twice daily Immunocompromised pts.: Recurrent genital herpes episode: 500 mg by mouth twice daily for 5-10 days Chronic suppressive therapy: 500 mg by mouth twice daily</td>
<td>Headache, nausea, diarrhea</td>
</tr>
<tr>
<td>Peginterferon alfa-2a*</td>
<td>180-mg/0.5- mL prefilled syringes, 180-µg/mL solution for injection</td>
<td>Chronic hepatitis C: 180 µg injected subcutaneously once weekly in combination with ribavirin for 24-48 h Chronic hepatitis B: 180 µg injected subcutaneously for 48 wk</td>
<td>Flu-like syndrome, nausea, vomiting, diarrhea, worsening of psychosis, psychiatric effects, insomnia, irritability, cardiovascular effects, increased risk of stroke or myocardial infarction, bone marrow suppression; contraindicated in pts. with estimated creatinine clearance &lt;50 mL/min; not for use in pts. with severe hepatic impairment</td>
</tr>
<tr>
<td>Ribavirin*</td>
<td>200-mg tablets</td>
<td>Genotypes 1 and 4: In combination with peginterferon alfa-2a for 48 wk: weight &lt;75 kg, 1000 mg; weight ≥75 kg, 1200 mg Genotypes 2 and 3: In combination with peginterferon alfa-2a for 24 wk: 800 mg</td>
<td>Hemolytic anemia, hypersensitivity reactions, headache Pregnancy category X Contraindicated in hepatic impairment: Child-Pugh classes B and C</td>
</tr>
</tbody>
</table>

CMV = cytomegalovirus; GI = gastrointestinal; HSV = herpes simplex virus.

*Dose adjustment needed in renal insufficiency.
When ganciclovir and zidovudine are combined, the effectiveness of both agents decreases. If used with didanosine, the risk of didanosine toxicity is increased. Valganciclovir also has major interactions with probenecid, mycophenolate mofetil, phenytoin, entecavir, or tenofovir. Concomitant use of ganciclovir with these agents may enhance the adverse effects of thymine analogues or may potentiate renal problems.

Foscarnet and cidofovir are also effective against CMV infections, but are administered by intravenous route only. Their dose-limiting adverse effects include leukopenia and neutropenia with cidofovir and renal impairment with foscarnet.

Hepatitis

Hepatitis may be caused by hepatitis A, B, C, D, and E viruses. Hepatitis A and E viruses are transmitted by oral and fecal routes, while hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis D virus are transmitted by blood and bodily fluids. Perinatal transmission of HBV and HCV are also possible.

Viral hepatitis exhibits both an acute and chronic disease course. After acute infection, some patients enter into a noninfectious phase, referred to as remission. Alternatively, others enter into a chronic phase with long-term inflammation that results in extensive liver damage. Viral hepatitis is a common cause of liver failure and the most common cause of hepatocellular carcinoma and liver failure requiring transplantation. The goal of treatment is to prevent chronic sequelae.

Therapeutic choices vary depending on the hepatitis subtype, tolerability of indicated drugs, and treatment response. Interferon products, with and without the addition of ribavirin, are prescribed for use in treatment of HCV and HBV, respectively. HBV can also be treated with oral tenofovir, emtricitabine, or lamivudine. Patients coinfected with HIV and HBV are often prescribed a combination of tenofovir and emtricitabine as part of antiretroviral regimens. These nucleoside analogues are reviewed under antiretroviral agents.

RIBAVIRIN

Ribavirin, a nucleoside analogue, is used in the treatment of HCV and in an aerosolized form to treat respiratory syncytial virus in infants. Ribavirin, in combination with PIA2A, is also indicated for the treatment of chronic HCV. Although its mechanism of action has not been determined, ribavirin should not be used alone.

Ribavirin dosing for the treatment of HCV depends on the patient’s weight and the viral genotype. It has not been studied in patients with creatinine clearance less than 50 mL/min; thus, it is not recommended in this population or in patients with decompensated liver disease.

Because ribavirin has only been studied in combination with PIA2A for safety and efficacy, reported adverse effects are the result of both agents. Ribavirin’s primary toxicity is hemolytic anemia (hemoglobin <10 g/dL). This anemia has been linked with risks of cardiac events such as heart attacks. Patients should be assessed for cardiac risk factors prior to and after initiation of ribavirin.
Hypersensitivity reactions manifesting as urticaria, bronchoconstriction, and angioedema are rare (<1%) with the combination therapy of ribavirin and PIA2A. If such a reaction is observed, treatment should be stopped immediately. Ribavirin is also associated with teratogenic and embryogenic effects. A negative pregnancy test should be obtained before initiating treatment with ribavirin. Pregnancy should be avoided for at least 6 months after stopping ribavirin therapy in both the male and female partner.

The use of both ribavirin and didanosine increases the risk of hepatic failure, peripheral neuropathy, pancreatitis, and lactic acidosis. Ribavirin also exacerbates anemia and neutropenia when coadministered with zidovudine and pancytopenia when used with azathioprine.

Human Immunodeficiency Virus

The manifestations of HIV, an RNA virus, are associated with the destruction of the body’s immune response, particularly CD4+ cells. As a patient’s cell count declines (indicating immune system damage), he or she is at increased risk for opportunistic infections, a frequent cause of death in patients not receiving antiretroviral therapy (ART). ART may prevent additional damage to vital organs as a result of the inflammatory response to HIV itself.

HIV treatment utilizes ART combinations to prevent the development of viral resistance. Infected individuals should be initiated on ART when their CD4 cell count is between 350 and 500 cells/mm³. Other factors for which treatment should be initiated can be found in Table 2.

ART’s effectiveness is assessed by viral load. An effective treatment regimen will result in an undetectable viral load (<20 copies/mL), indicating reduced viral replication. When viral replication is controlled, immune system recovery should occur. Immune recovery is assessed by measuring the CD4+ cell count every 3-6 months.

An adherence rate of at least 95% to all antiretroviral agents is the key to treatment success. This can be a challenging goal with a large number of pills, an increased dosing frequency, or intolerable adverse effects. To increase adherence, many manufacturers have developed combination pills that incorporate at least 2 or 3 medications or have investigated dosing regimens of reduced frequency. There are 6 antiretroviral drug classes.

### Table 2. Criteria for Starting Antiretroviral Therapy

<table>
<thead>
<tr>
<th>DEPARTMENT OF HEALTH AND HUMAN SERVICES GUIDELINES</th>
<th>INTERNATIONAL AIDS SOCIETY GUIDELINES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Should be initiated:</td>
<td>Should be initiated:</td>
</tr>
<tr>
<td>AIDS-defining illness or opportunistic infections</td>
<td>AIDS-defining illness or opportunistic infections</td>
</tr>
<tr>
<td>CD4 cell count &lt;350 cells/mm³</td>
<td>CD4 cell count &lt;350-500 cells/mm³</td>
</tr>
<tr>
<td>pregnancy</td>
<td>pregnancy</td>
</tr>
<tr>
<td>HIV-associated nephropathy</td>
<td>CD4 cell count decline &gt;100 per year</td>
</tr>
<tr>
<td>treatment for hepatitis B is warranted</td>
<td>HIV-1 RNA &gt;100,000 copies/mL</td>
</tr>
<tr>
<td>Recommend initiation:</td>
<td>Recommend initiation:</td>
</tr>
<tr>
<td>CD4 cell count &gt;350-500 cells/mm³ and</td>
<td>active HBV or HCV</td>
</tr>
<tr>
<td>possibly &gt;500 cells/mm³</td>
<td>active or high risk for cardiovascular disease</td>
</tr>
<tr>
<td>Factors to consider:</td>
<td>&gt;60 years of age</td>
</tr>
<tr>
<td>CD4 cell count decline &gt;100 cells/mm³ per year</td>
<td>HIV-associated nephropathy</td>
</tr>
<tr>
<td>high viral load &gt;100,000 copies/mL</td>
<td>symptomatic primary HIV infection</td>
</tr>
<tr>
<td></td>
<td>HIV-serodiscordant couples</td>
</tr>
<tr>
<td></td>
<td>Consider initiation:</td>
</tr>
<tr>
<td></td>
<td>CD4 count &gt;500 cells/mm³</td>
</tr>
</tbody>
</table>

HBV = hepatitis B virus; HCV = hepatitis C virus.

### Table 3. First-Line Antiretroviral Treatment

<table>
<thead>
<tr>
<th>DRUG CLASS</th>
<th>DRUG/DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside/nucleotide reverse transcriptase inhibitors</td>
<td>Tenofovir 300 mg and emtricitabine 200 mg by mouth daily</td>
</tr>
<tr>
<td>Nonnucleoside reverse transcriptase inhibitors</td>
<td>Efavirenz 600 mg by mouth daily on empty stomach</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td>Atazanavir 300 mg/ritonavir 100 mg by mouth daily with food</td>
</tr>
<tr>
<td>Integrase strain transfer inhibitors</td>
<td>Darunavir 800 mg/ritonavir 100 mg by mouth daily with food</td>
</tr>
<tr>
<td></td>
<td>Raltegravir 400 mg by mouth twice daily</td>
</tr>
</tbody>
</table>


*bIn combination with other first-line drugs from any of the above drug classes.
First-line treatment agents are shown in Table 3. Also, a full list of antiretroviral agents, with doses and adverse effects, can be found in Table 4.

The manifestations of HIV, an RNA virus, are associated with the destruction of the body’s immune response, particularly CD4+ cells.

NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), the backbone of current antiretroviral regimens, inhibit the production of HIV DNA from RNA. They compete for the use of the reverse transcriptase enzyme that prevents chain elongation and terminates viral replication. All NRTIs may be administered without regard to meals except didanosine, which must be taken on an empty stomach. All except stavudine and zidovudine can be administered once daily. Lastly, all NRTIs, with the exception of abacavir, should be renally adjusted. Abacavir has recommendations for dosing in hepatic impairment.

This class carries a black-box warning for lactic acidosis, with risk of hepatic impairment, severe liver enlargement, and death. Female sex, obesity, and pregnancy increase this risk. Other adverse effects include fat redistribution and lipodystrophy, which are primarily associated with stavudine, didanosine, and zidovudine as a result of their affinity for mitochondrial DNA polymerase. Although the onset of these physical changes is gradual, patients eventually exhibit central obesity, limb atrophy, and, potentially, dorsocervical fat enlargement.

Most antiretroviral regimens incorporate either lamivudine or emtricitabine in combination with tenofovir or abacavir. Patients coinfected with HBV and HIV require treatment for both infections. Tenofovir with either lamivudine or emtricitabine can be used, as they are active against HBV and HIV. However, it is important to note that patients coinfected with HIV/HBV are at risk of hepatitis B exacerbation at medication initiation or upon withdrawal. Monitoring for such manifestations is warranted.

Although lamivudine is indicated for treatment of both HIV and HBV, dosing is different for each disease state. HIV dosing is higher, making Epivir-HBV an inappropriate choice for coinfected patients. All doses of lamivudine are generally well tolerated.

Emtricitabine, in combination with tenofovir, is recommended as the preferred backbone for HIV-treatment-naïve patients. Since emtricitabine and lamivudine are structurally related, patients who develop resistance to lamivudine also have resistance to emtricitabine. For this reason, this combination of NRTIs is not recommended. Although emtricitabine is active in vivo and in vitro against HBV, it does not carry FDA approval. Instead, it is a therapeutic option, in combination with tenofovir, for the treatment of HBV in HIV patients.

Abacavir is available as a coformulation with lamivudine (Epzicom) or with zidovudine and lamivudine (Trizivir). It possesses a black-box warning for a potentially deadly hypersensitivity reaction. This hypersensitivity reaction manifests as a diffuse skin rash, fever, chills, malaise, nausea, muscle pain, and shortness of breath. All patients should be screened for the HLA-B*5701 allele before an abacavir-containing regimen is initiated. If a hypersensitivity reaction is suspected, the patient should never be rechallenged, as death may occur. Use of abacavir has also been controversially linked to the development of myocardial infarctions. Thus clinicians should weigh the risk versus benefit of use of abacavir in patients who are already at high risk or who have had a cardiovascular event or those with a viral load >100,000 copies/mL.

Zidovudine, in combination with lamivudine and lopinavir/ritonavir twice daily, is indicated for pregnant patients, as there is significant data on prevention of maternal to fetal HIV-1 transmission. Common adverse effects include bone marrow suppression, anemia, and less often, neutropenia. A complete blood cell count should be monitored 2-8 weeks postinitiation of zidovudine, then every 3-6 months. Myopathy, lactic acidosis, and hepatotoxicity have also been reported. In such cases, treatment should be discontinued under medical supervision. Patients should contact their provider to report any seizure, weight loss, loss of appetite, or weight gain.

Didanosine in combination with efavirenz and emtricitabine or lamivudine is considered an acceptable regimen in treatment-naïve patients only. Didanosine and emtricitabine should not be used with atazanavir due to inferior response. Didanosine carries a black-box warning for pancreatitis, which occurs more frequently at higher doses. Other adverse effects include optic neuritis and retinal changes; a routine eye exam while on didanosine therapy is recommended. Peripheral neuropathy that manifests as numbness, leg pains or tingling, and portal hypertension has also been reported. This may warrant the discontinuation of didanosine.

Adverse effects associated with stavudine are extensive and include pancreatitis and peripheral neuropathy. Fatal and nonfatal pancreatitis has been reported when
stavudine is used with didanosine, resulting in a black-box warning against the use of this combination. Zidovudine inhibits stavudine metabolism, leading to drug accumulation and increasing toxicity; this combination is contraindicated. The use of stavudine in any first-line combination is not encouraged.

Efavirenz is a preferred treatment for HIV and HBV coinfection. Tenofvir in combination with emtricitabine is the preferred NRTI for treatment-naïve patients. This combination is also coformulated with efavirenz, providing potent virologic suppression.

Although generally well tolerated, tenofovir possesses a black-box warning for HBV exacerbation with treatment discontinuation. Another adverse event is bone loss; however, the long-term effect of tenofovir use on bone health and the risk of fractures is unknown. Fanconi syndrome—acute renal failure and kidney injury, with reduction in phosphate level—has also been associated with tenofovir use. Its use with other nephrotoxic agents or in patients with preexisting renal disease should be avoided, if possible.

Tenofovir use with other antiretroviral agents should be assessed. When used in combination with didanosine, tenofovir increases didanosine toxicity. Didanosine dose reduction or discontinuation is recommended to reduce the incidence of pancreatitis and neuropathy. Atazanavir increases tenofovir concentrations, while tenofovir reduces atazanavir concentrations. Patients on tenofovir should be monitored for nephrotoxicity, and ritonavir should be added to enhance the effect of atazanavir. Lopinavir/ritonavir also increases tenofovir concentration. Monitoring of renal function is always recommended.

**NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS**

Nonnucleoside reverse transcriptase inhibitors (NNRTIs) bind to the nonactive site of the reverse transcriptase enzyme, interrupting viral protein synthesis at the HIV binding site. All NNRTIs are metabolized by the liver and inhibit or induce cytochrome P450 system enzymes. Their long half-lives allow once- or twice-daily dosing. Potential adverse effects of this class of drugs are hepatotoxicity and rash. Unfortunately, poor adherence to these agents can result in cross-resistance between efavirenz and nevirapine. Etravirine may still have some activity in such cases and is therefore recommended as a second-line agent, in combination with a protease inhibitor (PI)–containing regimen.

Efavirenz, a preferred agent, is recommended for use in conjunction with 2 NRTIs, preferably tenofovir and emtricitabine. This triple-drug combination pill (Atripla) can be taken once daily, improving patient adherence. CNS effects include vivid dreams, confusion, dizziness, and sedation. These effects are worse in the first 2-4 weeks of therapy. To reduce these effects, efavirenz-containing regimens should be taken on an empty stomach, just prior to bedtime. Moreover, in a clinical trial, 26% of patients developed a rash compared with 17% in the placebo arm. Most rashes resolved within the first 2 weeks of use. Less than 0.1% of rashes progressed to a severe form, Stevens-Johnson syndrome, in which blistering and shedding of the outer layers of skin occur. Efavirenz is contraindicated in women of childbearing age who are not using 2 forms of birth control or those considering pregnancy within 12 weeks. Case reports on efavirenz exposure during the first trimester of pregnancy have described neural tube defects; however, a meta-analysis and a systematic review of outcomes of an observational cohort concluded that a larger sample size is needed to prove the relationship between neural tube defects in the first trimester of pregnancy and efavirenz exposure. Meanwhile, efavirenz remains classified as pregnancy category D. Lastly, multiple interactions with this drug class should prompt a review for potential interactions between any NNRTI and other heptatically metabolized medications.

Nevirapine is contraindicated for use in men whose CD4 count is more than 400 cells/mm³ and in women with a CD4 cell count more than 250 cells/mm³. Use in individuals with CD4 cell counts above these cut offs or in persons with underlying hepatic disease (ie, hepatitis) increases the risk of rash, hepatotoxicity, and death. Etravirine has a greater barrier to resistance. It too possesses the risk for erythema multiforme (Stevens-Johnson syndrome). Twice-daily administration with food is recommended to achieve appropriate concentrations.

**PROTEASE INHIBITORS**

PIs prevent the protease enzyme cleavage of provirus particles into active viral components. Although this class is extremely potent, tolerability, adverse effects, pill burden, and drug interactions remain a challenge. Administration requirements vary; but most should be taken with food to improve tolerability. All PIs are heptatically metabolized by and inhibit or induce the cytochrome P450 enzymes, making drug interactions a common concern. Interactions may decrease ART effectiveness or increase potential toxicities of other medications. Class adverse effects include gastrointestinal upset, hyperglycemia, hyperlipidemia, hepatotoxicity, cardiovascular events, and increased bleeding in hemophiliacs. The extent of these effects varies among agents.

Ritonavir was one of the first PIs introduced. However, due to poor tolerability (ie, diarrhea and vomiting) and an extensive adverse effect profile, this drug is no longer a primary treatment agent. Instead, ritonavir 100 mg or 200 mg is currently recommended for use in combination with most PIs and fewer other antiretroviral agents to boost concentrations. Ritonavir inhibits drug metabolism, reducing dosing frequency and pill burden of other agents.

In 2010, a new tablet formulation was FDA approved. This formulation does not require refrigeration, which is a requirement of the capsule formulation. The newer...
### TABLE 4. HIV Medications

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSAGE FORM</th>
<th>STANDARD ADULT DOsing</th>
<th>ADVERSE EFFECTS/COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudinea</td>
<td>Epivir 10 mg/mL (240 mL) strawberry-banana flavor for treatment of HIV</td>
<td>HIV: 150 mg by mouth twice daily or 300 mg by mouth daily in combination with 2 other antiretroviral agents</td>
<td>Hepatitis treatment agent, lactic acidosis, Pregnancy category C</td>
</tr>
<tr>
<td></td>
<td>Epivir-HBV 5 mg/mL (240 mL) strawberry-banana flavor</td>
<td>HIV: 150 mg by mouth twice daily or 300 mg by mouth daily in combination with 2 other antiretroviral agents</td>
<td>Peel or other skin reactions, mild to moderate rash, nausea, vomiting, flatulence</td>
</tr>
<tr>
<td></td>
<td>Epivir 150 mg, 300-mg tablets</td>
<td>HIV: 150 mg by mouth twice daily or 300 mg by mouth daily in combination with 2 other antiretroviral agents</td>
<td>Peel or other skin reactions, mild to moderate rash, nausea, vomiting, flatulence</td>
</tr>
<tr>
<td></td>
<td>Epivir-HBV 100-mg tablets</td>
<td>HIV: 150 mg by mouth twice daily or 300 mg by mouth daily in combination with 2 other antiretroviral agents</td>
<td>Peel or other skin reactions, mild to moderate rash, nausea, vomiting, flatulence</td>
</tr>
<tr>
<td>Emtricitabinea</td>
<td>200-mg capsule and 10-mg/mL solution in cotton candy flavor</td>
<td>200 mg by mouth (capsule) once daily or 240 mg by mouth (solution) daily; capsule and oral solution not interchangeable on mg-to-mg basis</td>
<td>Skin hypopigmentation (more frequent among non-white pts.), Pregnancy category B</td>
</tr>
<tr>
<td>Abacavirb</td>
<td>300-mg tablet, Ziagen 20 mg/mL (240 mL) in a strawberry-banana flavor</td>
<td>300 mg by mouth twice daily or 600 mg by mouth daily in combination with other ART</td>
<td>Severe hypersensitivity reaction (most common within first 4-6 wk of therapy and linked to presence of the HLA-B*5701 allele); pts. should not be rechallenged due to increased risk of anaphylaxis, hypotension, and death; myocardial infarction when used with didanosine in observational cohort studies</td>
</tr>
<tr>
<td>Zidovudinea</td>
<td>300-mg tablet, 100-mg capsule, 50-mg/5-mL strawberry flavor syrup</td>
<td>600 mg/day in 2 divided doses with other ART Labor and delivery: 2 mg/kg loading dose followed by a 1-mg/kg/h continuous infusion until umbilical cord is clamped</td>
<td>Bone marrow suppression, anemia, neutropenia, GI intolerance, myopathy, hepatotoxicity, nail pigmentation, headache, lactic acidosis</td>
</tr>
<tr>
<td>Didanosinea</td>
<td>Videx EC 125-, 200-, 250-, 400-mg capsules; buffered tablets (non-EC) no longer available Oral solution Videx 10 mg/mL</td>
<td>Dose based on body weight: ≥60 kg, 400 mg once daily, with tenofovir, 250 mg once daily; &lt;60 kg, 250 mg once daily, with tenofovir, 200 mg once daily (without tenofovir, taken on empty stomach)</td>
<td>GI intolerance, pancreatitis, peripheral neuropathy, lactic acidosis with hepatic steatosis, non-cirrhotic portal hypertension</td>
</tr>
<tr>
<td>stavudina</td>
<td>15-, 20-, 30-, and 40-mg capsules or 1-mg/mL oral solution</td>
<td>Body weight ≥60 kg, 40 mg twice daily; &lt;60 kg, 30 mg twice daily</td>
<td>Peripheral neuropathy, lipoatrophy, pancreatitis, lactic acidosis with hepatic steatosis, hyperlipidemia, rapidly progressive ascending neuromuscular weakness</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>300-mg tablet</td>
<td>HIV and hepatitis B infection: 300 mg by mouth daily</td>
<td>Renal insufficiency, Fanconi’s syndrome, osteomalacia; decrease in bone mineral density, asthenia, headache, diarrhea, nausea, vomiting, flatulence</td>
</tr>
<tr>
<td>Efavirenza</td>
<td>50- and 200-mg capsules, 600-mg tablet</td>
<td>600 mg once daily on an empty stomach</td>
<td>Rash, Stevens-Johnson syndrome, dizziness, nausea, headache, vivid dreams, hallucinations, suicidal ideation and depression, hepatotoxicity risk</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>200-mg tablets, 50-mg/5-mL suspension</td>
<td>200 mg once daily for 14 days (lead-in period); then 200 mg twice daily Repeat lead-in period if off medication &gt;7 days Mild-to-moderate rash without constitutional symptoms, continue lead-in period until rash resolves &lt;28 days</td>
<td>Rash, including Stevens-Johnson syndrome; hepatitis, including fatal hepatic necrosis</td>
</tr>
<tr>
<td>Antiviral Agent</td>
<td>Dosage Form</td>
<td>Dosage</td>
<td>Side Effects</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------</td>
<td>--------</td>
<td>-------------</td>
</tr>
<tr>
<td>Etravirine (Intelicence)</td>
<td>100-mg tablet</td>
<td>200 mg bid with food</td>
<td>Rash, hypersensitivity reactions with possible organ dysfunction, including hepatic failure</td>
</tr>
<tr>
<td>Atazanavir b (Reyataz)</td>
<td>100-, 150-, 300-, and 400-mg capsules</td>
<td>300 mg with ritonavir, 100 mg, or 400 mg with food</td>
<td>Indirect hyperbilirubinemia, neutral lipid profile, nephrolithiasis (flank pain, abdominal pain, dysuria, increase in urinary frequency), possible PR prolongation, hyperglycemia, skin rash, Stevens-Johnson syndrome, GI intolerance</td>
</tr>
<tr>
<td>Darunavir (Prezista)</td>
<td>75-, 150-, 400-, 600-, and 800-mg tablets</td>
<td>800 mg with ritonavir, 100 mg (treatment-naïve pts.) or 600 mg with ritonavir 100 mg (treatment-experienced pts.) twice daily with food</td>
<td>Skin rash (10%), hyperlipidemia, hyperglycemia, fat maldistribution, diarrhea and nausea, vomiting</td>
</tr>
<tr>
<td>Fosamprenavir b (Lexiva)</td>
<td>700-mg tablet, 50-mg/mL oral suspension</td>
<td>1400 mg twice daily without ritonavir, 1400 mg once daily with ritonavir 100 or 200 mg, or 700 mg with ritonavir 100 mg twice daily</td>
<td>Skin rash (19%) (use caution in pts. with known sulfa allergy), diarrhea, rash, headache, hyperlipidemia, transaminase elevations, rare nephrolithiasis, vomiting</td>
</tr>
<tr>
<td>Indinavir b (Crixivan)</td>
<td>100-, 200-, and 400-mg capsules</td>
<td>800 mg every 8 h on an empty stomach, or 800 mg with ritonavir 100-200 mg twice daily without regard to meals</td>
<td>Pregnancy category C</td>
</tr>
<tr>
<td>Nelfinavir (Viracept)</td>
<td>625- and 250-mg tablets; 50 mg/g powder for reconstitution</td>
<td>1250 mg twice daily or 750 mg 3 times daily with food</td>
<td>Diarrhea, nausea, increased liver enzymes, increased triglycerides and cholesterol, hyperglycemia</td>
</tr>
<tr>
<td>Tipranavir (Aptivus)</td>
<td>250-mg capsule, 100-mg/mL oral solution</td>
<td>500 mg with ritonavir, 200 mg twice daily</td>
<td>Rash, hypertriglyceridemia, hypercholesterolemia, hepatotoxicity; intracranial hemorhage when used in combination with ritonavir</td>
</tr>
<tr>
<td>Saquinavir (Invirase)</td>
<td>200-mg capsule-tablets; 500-mg tablet</td>
<td>1000 mg coadministered with ritonavir 100 mg twice daily</td>
<td>Nausea, vomiting, hyperlipidemia, hepatotoxicity</td>
</tr>
<tr>
<td>Lopinavir/ritonavir (Kaletra)</td>
<td>200-mg/50-mg tablets; 100 mg/25 mg oral solution</td>
<td>400 mg/100 mg twice daily (treatment-experienced or pregnant) or 800 mg/200 mg daily (treatment-naïve)</td>
<td>Gl intolerance, hyperlipidemia, increased LFT results, including transaminites; hyperglycemia, cardiovascular PR and QT interval prolongation (rare)</td>
</tr>
<tr>
<td>Ritonavir (Norvir)</td>
<td>100-mg capsule; 100-mg tablet</td>
<td>only for boosting</td>
<td>GI intolerance, increases in triglycerides and lipids</td>
</tr>
<tr>
<td>Raltegravir (Sentress)</td>
<td>400-mg tablet</td>
<td>400 mg twice daily</td>
<td>Few drug interactions, rare creatinine kinase elevations</td>
</tr>
<tr>
<td>Enfuvirtide (Fuzeon)</td>
<td>108-mg lyophilized powder</td>
<td>90 mg subcutaneously twice daily</td>
<td>Local injection site reactions, rare (&lt;1%) hypersensitivity reaction</td>
</tr>
<tr>
<td>Maraviroc (Selzentry)</td>
<td>150- and 300-mg tablets</td>
<td>150 mg twice daily with strong inhibitors (all protease inhibitors except tipranavir); 300 mg twice daily with enfuvirtide, nevirapine, NRTIs, and tipranavir/ritonavir; 600 mg twice daily with efavirenz, etravirine</td>
<td>Abdominal pain, musculoskeletal symptoms, pyrexia, rash, orthostatic hypotension</td>
</tr>
</tbody>
</table>

*ART = antiretroviral therapy; GI = gastrointestinal; HBV = hepatitis B virus; LFT = liver function tests; NRTIs = nucleoside reverse transcriptase inhibitors.
*aDose adjustment required in renal impairment.
*bDose adjustment required in hepatic impairment.
tablet does require administration with food to achieve appropriate concentrations.\textsuperscript{51,52}  
Kaletra, a combination PI, incorporates ritonavir with lopinavir to provide effective drug concentrations. Dosing for treatment-naïve patients is once daily, as opposed to twice daily for treatment-experienced patients with drug resistance.\textsuperscript{52} Despite gastrointestinal upset and increases in cholesterol, particularly triglycerides, it remained a preferred agent for years. In 2009, Kaletra was noted to increase the risk of PR and QT interval prolongation.\textsuperscript{89} It has been reclassified as an alternative treatment agent in treatment-naïve patients.\textsuperscript{23} It remains a preferred agent in pregnancy, in which case it is administered twice daily.\textsuperscript{52}

Atazanavir offers improved tolerability with a good lipid profile.\textsuperscript{23,54} Its once-daily dosing, with or without ritonavir, increases adherence. Boosting with ritonavir is preferred and required with tenofovir use.\textsuperscript{23} Administration with food is required to increase absorption and limit variability in drug concentrations.\textsuperscript{55} Use of antacids, H\textsubscript{2} antagonists, or proton pump inhibitors can decrease the effectiveness of atazanavir. Assessment of administration times and doses is important as they may result in treatment failure because of insufficient atazanavir levels.\textsuperscript{55}

Adverse effects of hyperbilirubinemia, occasionally resulting in mild symptoms of jaundice or scleral icterus, are possible although not pathogenic. Less common adverse events include a mild-to-moderate rash, prolongation of PR intervals, and rare cases of nephrolithiasis at increased concentrations.\textsuperscript{55}

Darunavir in combination with ritonavir offers good tolerability, once-daily dosing, and potency.\textsuperscript{56-58} Treatment-experienced patients currently receive twice-daily dosing.\textsuperscript{23} Administration with food is required.\textsuperscript{56-58} Darunavir is generally well tolerated except that a skin rash may occur in about 10\% of patients as a result of its sulfa moiety. Occasionally this rash is severe, with erythema multiforme and Stevens-Johnson syndrome occurring. Caution should be used in patients with HBV or HBC, as darunavir use can result in liver enzyme increases.\textsuperscript{56-58}

Dosing and potential adverse effects of nonpreferred PIs, fosamprenavir, indinavir, nelfinavir, tipranavir, and saquinavir may be found in Table 4.\textsuperscript{59-63}

**INTEGRASE STRAND TRANSFER INHIBITOR**

Raltegravir blocks the integrase enzyme’s ability to incorporate newly manufactured HIV DNA into the host’s cell DNA. Although a preferred treatment agent with tenofovir and emtricitabine, it can also be used in combination with other effective antiretroviral agents for treatment-experienced patients.\textsuperscript{23,24} Dosing is twice daily without food restrictions. Potential drug interactions are limited, as raltegravir is not metabolized nor is it an inducer or inhibitor of the cytochrome P450 system, but instead is metabolized by glucuronidation.\textsuperscript{64,65}

It was well tolerated in clinical trials, with limited gastrointestinal upset compared with placebo, and did not increase cholesterol levels.\textsuperscript{64,65} Rare creatinine kinase elevations associated with myopathy and rhabdomyolysis have been reported with raltegravir, particularly when used in combination with other drugs that have the same risk factors.\textsuperscript{66}

Dosing and common adverse effects of less commonly used agents, namely enfuvirtide, a fusion inhibitor, and maraviroc, a CCR5 antagonist, can be found in Table 4.\textsuperscript{67,68}

**Summary**

Viral infections (ie, HIV, HSV, HCV, and HBV) are often sexually transmitted. The Centers for Disease Control and Prevention and the Department of Health and Human Services offer easily accessible detailed guidelines that help with the management of hepatitis, sexually transmitted diseases, and HIV. Although expert clinicians are often the primary health-care professionals involved in the management of viral infections, pharmacy technicians are on the front line with pharmacists during the dispensing of these antiviral agents. Being knowledgeable about commonly prescribed antiviral medications and related diseases improves the pharmacist’s identification of drug interactions, management of adverse effects, appropriate dosing, and key counseling points. \(\approx\)

**References**


52. Croxell JD, Perry CM, Lopinarv /ritonavir: a review of its use in the management of HIV-1 infection. Drugs 2010;70:1885-915.


57. DeMeyer SM, Spinosa-Guzman S, Vangeneugden TJ, et al. Efficacy of once-daily darunavir/ritonavir 800 mg /100 mg in HIV-infected treatment experienced patients with no baseline reis-