51 Therapy of Human Immunodeficiency Virus

Knox Van Dyke and Karen Woodfork

DRUG LIST

HUMAN IMMUNODEFICIENCY VIRUS

Human immunodeficiency virus (HIV) is a single-stranded RNA retrovirus that causes acquired immunodeficiency syndrome (AIDS), a condition in which individuals are at increased risk for developing certain infections and malignancies. The virus is found in two major forms: HIV-1, the most prevalent worldwide, and HIV-2, the most common in western Africa. More than 22 million people have died of HIV infection, and 40 million are believed to be infected worldwide. AIDS epidemics threaten populations in sub-Saharan Africa, Southeast Asia, Central and South America, and Russia. In the United States about 450,000 deaths have occurred and another 900,000 people are estimated to carry the virus. Although the development of new drugs, complex multidrug regimens, and behavioral modification have done much to combat the spread of HIV infection, AIDS remains a serious threat because of the expense and inaccessibility of antiretroviral agents in the developing countries in which the disease is most prevalent. In addition, the effectiveness of antiretroviral drugs has been diminished by the emergence of multidrug-resistant virus.

Production of Immunodeficiency by HIV

HIV infects CD4+ T lymphocytes, macrophages, and dendritic cells. Viral entry is initiated when *gp120* (SU), a glycoprotein on the surface of the viral envelope, attaches itself to the *CD4* surface glycoprotein of the target cell (Fig. 51.1). This interaction produces a conformational change in gp120 that allows it to bind to a chemokine coreceptor: *CXCR4* for CD-4 T (helper) cells or *CCR5* for macrophages. Chemokine coreceptor

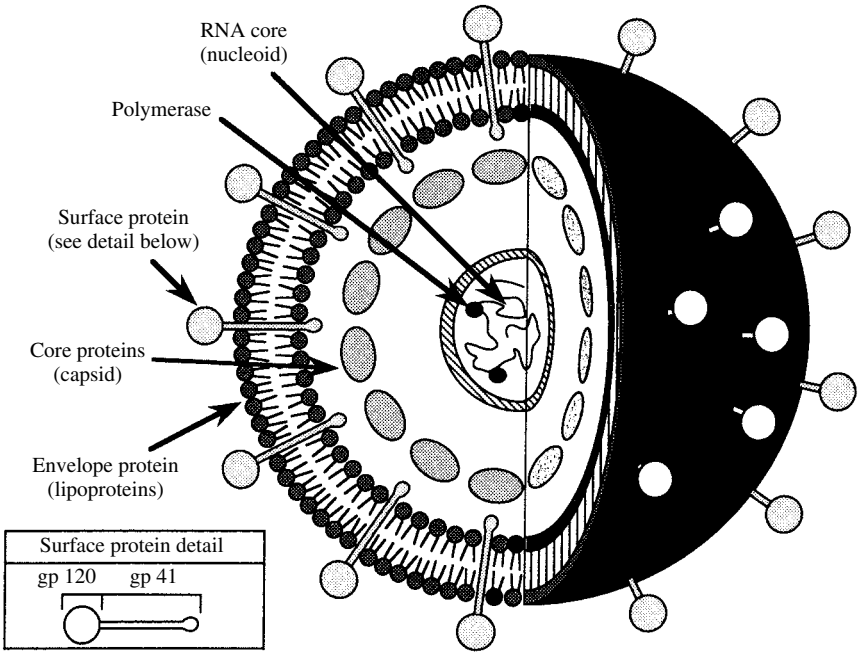

FIGURE 51.1
Exploded view of the human immunodeficiency virus. It is an RNA (retrovirus) virus that contains surface proteins composed of a knoblike glycoprotein (gp120) linked to a transmembrane stalk (gp41). These surface proteins are the infective mechanisms that allow the virus to bind to CD4 proteins of cells, such as T4 lymphocytes and monocytes.

binding is required for viral entry; individuals with genetic defects in these proteins are resistant to HIV infection. The binding of gp120 to CXCR4 or CCR5 causes a rearrangement in the envelope glycoproteins that allows the fusion of a viral transmembrane glycoprotein (*gp41*) with the target cell membrane. Fusion of the viral and cellular membranes follows as the virus enters the target cell.

After entering the host cell and uncoating, viral *reverse transcriptase* synthesizes DNA using viral RNA as a template. This DNA circularizes, enters the nucleus, and is integrated into the host genome by another viral enzyme, *integrase*. The host cell then transcribes the viral genes and produces viral proteins and progeny viral RNA. New virions assemble, bud from the cell membrane, and undergo a maturation process in which the gag-pol polyprotein is cleaved by the viral enzyme *protease*. The resultant mature virus particles spread to infect other susceptible cells.

The majority of viral replication occurs in recently infected CD4+ lymphocytes and depletes them during the first several years of infection. Macrophage populations are depleted or cease to function properly in 3 to 10 years or more. It is during this time that an HIV-infected person becomes immunodeficient and can die of infections that under normal conditions are not life threatening. Eventually the macrophages of the brain (microglia) may become infected and an inflammation-based dementia may occur.

Several pools of nonreplicating virus serve as reservoirs of infection and limit the effectiveness of antiretroviral therapy. HIV can live and multiply in monocytes and macrophages; these cells are present in all tissues and can live for many months. Infective virus can also reside in long-lived resting CD4+ lymphocytes.

DRUG THERAPY OF HIV INFECTION

The replicative cycle of HIV presents many opportunities for the targeting of antiviral agents. The drugs in clinical use are classified as nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), nucleotide reverse transcriptase inhibitors (NTRTIs), and protease inhibitors (PI).

Single agents are seldom used to treat HIV infection. Instead, *multidrug therapy is used to counteract the rapid mutation rate of HIV and to minimize drug toxicity.* Highly active antiretroviral therapy (HAART) uses combinations of reverse transcriptase inhibitors and protease inhibitors (Table 51.1). In this system, drugs working by different mechanisms produce a sequential blockade of steps required for viral reproduction. It is

TABLE 51.1 Antiretroviral Drug Combinations Used in HAART

Combinations of Choice
2 NRTIs and 1 PI
2 NRTIs and 1NNRTI
2 NRTIs and 1 PI with ritonavir
2 NRTIs and abacavir
Secondary Alternatives
1 PI, 1 NRTI, and 1NNRTI
2 PIs, 1 NRTI, and 1 NNRTI

difficult for the HIV to simultaneously develop mutants that provide it with resistance to the multiple drugs that act via different mechanisms. However, even with multidrug regimens, it has been estimated that viruses in 85% of infected people develop resistance to one or more of the antiretroviral agents. Therefore, it is necessary to produce drugs that either inhibit this resistance or find compounds that produce no resistance.

New drugs are being targeted against drug-resistant HIV strains. In addition, a variety of drugs under development act as inhibitors of viral fusion or viral entry into the host cell. New agents designed to inhibit viral integrase have shown promise in early clinical trials. Current therapies do not enhance the host defense system; this may account for their incomplete effectiveness. Protection of the host immune mechanism might increase the efficacy of other drugs that inhibit viral replication.

Nucleoside Reverse Transcriptase Inhibitors

The NRTIs are nucleoside analogues that act as competitive inhibitors of reverse transcriptase. *After conversion to the triphosphate form by host cell kinases, these drugs compete with nucleoside triphosphates for access to reverse transcriptase.* All NRTIs lack a 3′-hydroxyl group; thus, their incorporation into a growing DNA chain results in its termination. These drugs block HIV replication and therefore the infection of new cells, but they have little effect on cells already infected with virus. Combination therapies often include two NRTIs that are analogues of different bases plus a protease inhibitor. The pharmacokinetic properties of the NRTIs are listed in Table 51.2.

The NRTIs inhibit cellular and mitochondrial DNA polymerases and various cellular kinases, resulting in toxicity. Toxicity varies with the state of the immune system; early in the infection there is less toxicity, while late in the infection there is substantially more. *All NRTIs can produce a potentially fatal syndrome of lactic acidosis and severe hepatomegaly with hepatic steatosis;* this results from the toxic effects of these drugs on mitochondria. Those at highest risk include women, obese individuals, alcoholics, and patients with prolonged exposure to NRTIs. All patients should be monitored for the development of hepatotoxicity; the drug should be discontinued if this occurs.

Resistance to these agents limits their usefulness, particularly as monotherapy. Resistance generally results from the appearance of mutations in reverse transcriptase; cross-resistance to multiple NRTIs also occurs.

Zidouvidine

Zidovudine (AZT, ZDV) was the first antiviral drug used against HIV. It is a thymidine analogue that is effective against HIV-1, HIV-2, and human T-cell lymphotrophic virus (HTLV) I and II. It is available as a single agent (*Retrovir*) or in fixed combinations with lamivudine (*Combivir*) or lamivudine and abacavir (*Trizivir*). Zidovudine, in combination with one or more other antiretroviral agents, is approved for the treatment of HIV infection in adults and children and for postexposure prophylaxis. It is used alone or in combination for the prevention of prenatal and perinatal transmission to the baby by HIV-infected pregnant women.

The most common adverse reactions to zidovudine are headache, nausea, vomiting, and anorexia. Fatigue, confusion, insomnia, malaise, hepatitis, myopathy, and myositis may also occur. Bone marrow toxicity occurs in up to 30% of patients taking zidovudine; anemia, neutropenia, and other hematological abnormalities can necessitate a dosage reduction, drug discontinuation, or therapy with erythropoietin or colony-stimulating factors. Cross-resistance to multiple nucleoside analogues has been documented.

Caution should be exercised when zidovudine is administered to patients with preexisting anemia or neutropenia and to those with advanced cases of AIDS. Dosage adjustment is required for patients with significant renal impairment and may also be necessary in those with hepatic impairment.

Zidovudine should be used cautiously with any other agent that causes bone marrow suppression, such as interferon-α, trimethoprim–sulfamethoxazole, dapsone, foscarnet, flucytosine, ganciclovir, and valganciclovir. Probenecid and interferon-β inhibit the elimination of zidovudine; therefore, a dosage reduction of zidovudine is necessary when the drugs are administered concurrently. Ribavirin inhibits the phosphorylation reactions that activate zidovudine, and zidovudine similarly inhibits the activation of stavudine; thus, the coadministration of zidovudine with ribavirin or stavudine is contraindicated.

TABLE 51.2 Pharmacokinetic Properties of the NRTIs and an NtRTI[a]

Drug	Oral Bioavailability (%)	Plasma Elimination Half-Life (hr)	Protein Binding (%)	Metabolism	Urinary Excretion[b] (%)	Notes
Abacavir	83	1.5	50	ADH, GT	1	H?
Didanosine[c]	42	1.5	<5	Purine elimination pathways	18	F−; H?; R
Lamivudine	86	5–7	<36	Minor	71	H?; R
Stavudine	86	1.4	Negligible	ND	40	R
Tenofovir	25	ND; accumulates in fat	<1	Minor	70–80 32[d]	F+; H?; R
Zalcitabine	>80	2	<4	Minor	60	F−; R
Zidovudine	64	0.5–3	<38	Hepatic non-P450	14	F−; FPM; H?; R

[a]Average values for fasting adult patients following a single oral dose.
[b]Unchanged drug.
[c]Data are given for non–delayed release formulations only.
[d]After multiple dosing.
ADH, alcohol dehydrogenase; F+, food (high-fat meal) increases absorption; F−, food interferes with absorption; FPM, extensive first pass metabolism; GT, glucuronyl transferase; H?, dosage adjustment in patients with hepatic impairment has not been studied; ND, not determined; R, dosage adjustment is necessary in patients with renal impairment.

Stavudine

Stavudine (d4T, *Zerit*) is a thymidine nucleoside analogue that is active against HIV-1 and HIV-2. It is approved for the therapy of HIV infection as part of a multidrug regimen and is also used for postexposure prophylaxis.

The adverse effects with which stavudine is most frequently associated are headache, diarrhea, skin rash, nausea, vomiting, insomnia, anorexia, myalgia, and weakness. Peripheral neuropathy consisting of numbness, tingling, or pain in the hands or feet is also common with higher doses of the drug. Significant elevation of hepatic enzymes may be seen in approximately 10 to 15% of patients. Lactic acidosis occurs more frequently with stavudine than with other NRTIs. Viral resistance to stavudine may develop, and cross-resistance to zidovudine and didanosine may occur.

Stavudine should be used with caution in patients at risk for hepatic disease and those who have had pancreatitis. Persons with peripheral neuropathy, the elderly, and those with advanced HIV disease are at increased risk for neurotoxicity. Dosage adjustment is required for patients with renal insufficiency.

Stavudine possesses several clinically significant interactions with other drugs. Although hydroxyurea enhances the antiviral activity of stavudine and didanosine, combination therapy that includes stavudine and didanosine, with or without hydroxyurea, increases the risk of pancreatitis. Combinations of stavudine and didanosine should not be given to pregnant women because of the increased risk of metabolic acidosis. Zidovudine inhibits the phosphorylation of stavudine; thus, this combination should be avoided.

Didanosine

Didanosine (ddI, *Videx*) is an adenosine analogue with activity against HIV-1, HIV-2, and HTLV-I. It is approved as part of a multidrug regimen for the therapy of HIV infection and is also used as postexposure HIV prophylaxis.

The most common adverse effect produced by didanosine is diarrhea. Abdominal pain, nausea, vomiting, anorexia, and dose-related peripheral neuropathy may occur. Pancreatitis occurs rarely, as do hyperuricemia, bone marrow suppression, retinal depigmentation, and optical neuritis. Resistance to didanosine appears to result from mutations different from those responsible for zidovudine resistance.

Didanosine should be used with great caution in individuals who have a history of pancreatitis. Didanosine tablets contain phenylalanine and should not be taken by phenylketonurics. Didanosine should be used cautiously in patients with gout, peripheral neuropathy, and advanced AIDS.

Buffering agents that are compounded with didanosine to counteract its degradation by gastric acid may interfere with the absorption of other drugs that require acidity (e.g., indinavir, delavirdine, ketoconazole, fluoroquinolones, tetracyclines, dapsone). An enteric-coated formulation (*Videx EC*) that dissolves in the basic pH of the small intestine is not susceptible to these interactions. Ganciclovir and valganciclovir can increase blood levels of didanosine. The use of zalcitabine with didanosine is not recommended because that combination carries an additive risk of peripheral neuropathy. The combination of didanosine with stavudine increases the risk of pancreatitis, hepatotoxicity, and peripheral neuropa-

thy. Stavudine should not be given with didanosine to pregnant women because of the increased risk of metabolic acidosis.

Lamivudine

Lamivudine (3TC, *Epivir*) is a cytosine nucleoside analogue with activity against HIV-1, HIV-2, and hepatitis B virus. It is approved as part of a multidrug regimen for the therapy of HIV infection in adults and children and has been used for HIV postexposure prophylaxis. Combination products contain lamivudine with either zidovudine (*Combivir*) or zidovudine and abacavir (*Trizivir*). The use of low-dose lamivudine in the treatment of chronic hepatitis B is described in Chapter 50.

Lamivudine is the best-tolerated NRTI. Its most common adverse effects include headache, malaise, fatigue, and insomnia. Pancreatitis is rare. Gastrointestinal complaints are common with lamivudine–zidovudine therapy but are probably mainly due to the zidovudine component. Lamivudine resistance sometimes occurs early in treatment. Cross-resistance to zalcitabine, didanosine, and abacavir can occur simultaneously. Withdrawal of lamivudine in patients infected with both hepatitis B virus and HIV can cause a flare-up of hepatitis symptoms.

Lamivudine is associated with an increased risk of pancreatitis in children and should be used with great caution in children who have had pancreatitis or are at high risk for it. Dosage adjustment is necessary in patients with renal impairment. Lamivudine should not be used in combination with zalcitabine, because they inhibit each other's activation by phosphorylation. Trimethoprim inhibits the renal elimination of lamivudine.

Abacavir

Abacavir (*Ziagen*) is a guanosine nucleoside analogue indicated for the therapy of HIV-1 infection in adults and children. It is used as part of a multidrug regimen and is available in a fixed-dose combination with zidovudine and lamivudine (*Trizivir*). It is also used for postexposure HIV infection prophylaxis.

Abacavir is associated with side effects such as anorexia, nausea, vomiting, malaise, headache, and insomnia. *A potentially fatal hypersensitivity reaction develops in approximately 5% of patients, usually early in the course of treatment.* Fever and rash are the most common symptoms of this reaction; malaise, respiratory symptoms, and gastrointestinal complaints may also occur. Resistance to abacavir may be associated with resistance to zidovudine, didanosine, and lamivudine.

Abacavir undergoes extensive hepatic metabolism; therefore, patients with liver disease should be monitored closely if this drug is given. Ethanol inhibits the metabolism of abacavir because it competes for metabolism by alcohol dehydrogenase. Abacavir is not known to inhibit or induce cytochrome P450 isozymes.

Zalcitabine

Zalcitabine (ddC, *Hivid*) is a cytidine analogue active against HIV-1, HIV-2, and hepatitis B virus. It is used for the treatment of HIV infection in adults and asymptomatic children as part of a multidrug regimen. It may be less effective than the other nucleoside inhibitors and is used less frequently.

Peripheral neuropathy occurs in up to 50% of patients taking zalcitabine. Stomatitis, esophageal ulceration, hepatotoxicity, rash, and pancreatitis may occur. Zalcitabine should be used with caution in individuals with a history of pancreatitis, liver disease, or alcohol abuse. Dosage adjustment is necessary for individuals with renal impairment. Zalcitabine should not be used in combination with didanosine, lamivudine, or stavudine.

Nucleotide Reverse Transcriptase Inhibitors

Tenofovir

Tenofovir disoproxil fumarate (*Viread*) is a prodrug of tenofovir, a phosphorylated adenosine nucleoside analogue, and is the only available agent of its class . It is converted by cellular enzymes to tenofovir diphosphate, which competes with deoxyadenosine triphosphate (dATP) for access to reverse transcriptase and causes chain termination following its incorporation. Tenofovir was approved as part of a combination therapy for HIV in adults who failed treatment with other regimens; it appears to be effective against HIV strains that are resistant to NRTIs. The pharmacokinetic properties of tenofovir are provided in Table 51.2.

Tenofovir is taken once daily and is generally well tolerated, perhaps because it produces less mitochondrial toxicity than the NRTIs. Nausea, vomiting, flatulence, and diarrhea occur in 10% or fewer patients. Resistance to tenofovir has been documented, and cross-resistance to NRTIs may occur.

Tenofovir should not be given to patients with renal insufficiency. Its coadministration with didanosine results in increased plasma levels of didanosine that can produce toxicity. Because lactic acidosis and severe hepatomegaly with steatosis have been reported with NRTIs, it is important to monitor patients with known risk factors during treatment with tenofovir.

Nonnucleoside Reverse Transcriptase Inhibitors

The NNRTIs inhibit viral reverse transcriptase by binding adjacent to its active site and inducing a conformational change that causes the enzyme's inactivation. When combined with NRTIs or protease inhibitors,

NNRTIs produce additive and possibly synergistic effects against HIV. The pharmacokinetic parameters of these agents are listed in Table 51.3.

All NNRTIs are active against HIV-1 reverse transcriptase only and do not require phosphorylation for activation. These agents share certain adverse effects (e.g., rash) and are subject to numerous drug interactions due to their metabolism by and induction of hepatic cytochrome P450 enzymes. NNRTIs may modify plasma levels of protease inhibitors, which are also metabolized by cytochrome P450 enzymes (Table 51.4). *The list of drug interactions provided in this text is not all-inclusive; it is necessary to check for all drug interactions when prescribing NNRTIs.* These agents should be used with caution in patients with hepatic disease.

When NNRTIs are used alone, resistance develops rapidly as a result of the development of mutations in reverse transcriptase; therefore, monotherapy with these agents is not recommended. Cross-resistance between NNRTIs occurs frequently but is not seen between NNRTIs and NRTIs or the protease inhibitors.

Efavirenz

Efavirenz (*Sustiva*) is approved for the therapy of HIV infection of adults and children and is also used for postexposure prophylaxis. It is the only NNRTI approved for once-daily dosing. Rash, although rarely severe, is a common adverse effect of efavirenz. Elevated liver enzymes and serum cholesterol also may occur. Central nervous system (CNS) effects in approximately half of patients may include dizziness, headache, insomnia, drowsiness, euphoria, agitation, impaired cognition, nightmares, vivid dreams, and hallucinations. These effects often subside after several weeks to months of therapy.

Efavirenz should be avoided during pregnancy because primate studies have shown it to be teratogenic at doses near therapeutic levels. Women of childbearing

TABLE 51.3 Pharmacokinetic Properties of Selected NNRTIs[a]

Drug	Oral Bioavailability (%)	Plasma Elimination Half-Life (hr)	Protein Binding (%)	Metabolism	Urinary Excretion[b] (%)	Notes
Delavirdine	85	5.8[c]	98	CYP3A4, CYP2D6	<5	H?; R?
Efavirenz	50	40-55	>99	CYP3A4, CYP2B6	<5	F+ (avoid); H?
Nevirapine	>90	25-30	60	CYP3A4	<3	H?; R?

[a]Average values for fed adult patients, following a multiple oral dosing
[b]Unchanged drug
[c]Elimination half-life increases with dose; this value is for dose of 400 mg tid.
F+, food (high-fat meal) increases absorption; H?, dosage adjustment in patients with hepatic impairment has not been studied; R?, dosage adjustment in patients with renal impairment has not been studied.

TABLE 51.4 Interactions Between NNRTIs and Protease Inhibitors

Drug	Increases Plasma AUC of	Decreases Plasma AUC of	Plasma AUC Increased by	Plasma AUC Decreased by
Delavirdine	Amprenavir Indinavir Lopinavir Nelfinavir Ritonavir Saquinavir			Nelfinavir
Efavirenz	Nelfinavir Ritonavir	Amprenavir Indinavir Lopinavir Saquinavir	Ritonavir	Saquinavir
Nevirapine		Amprenavir Indinavir Lopinavir Saquinavir		

potential should use two methods of birth control to avoid becoming pregnant when taking this drug.

Efavirenz interacts with many drugs via the cytochrome P450 pathways. It induces and is metabolized by CYP3A4 and inhibits CYP2C9 and CYP2C19. It should not be given with cisapride, ergot alkaloids, midazolam, or triazolam because of the potential for life-threatening reactions. Efavirenz has the potential to decrease blood levels of methadone, rifabutin, ketoconazole, and itraconazole. It may inhibit the metabolism of drugs such as alosetron, diazepam, ethinyl estradiol, imipramine, losartan, omeprazole, warfarin, tolbutamide, and topiramate. Efavirenz interacts with cytochrome P450 inducers and substrates (e.g., phenytoin, phenobarbital) in a complex manner; blood levels and side effects should be closely monitored. Patients taking efavirenz should avoid herbal preparations containing St. John's wort because the herb induces CYP3A4 and may cause drug failure or viral resistance. Saquinavir should not be used as the sole protease inhibitor in a regimen containing efavirenz.

Nevirapine

Nevirapine (*Viramune*) is approved for the treatment of HIV infection in adults and children as part of a combination therapy. *During the first 12 weeks of treatment, patients must be closely monitored for the development of potentially fatal hepatic toxicity (i.e., hepatitis, hepatic necrosis, and hepatic failure) and skin reactions (i.e., Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions).* Although these toxicities are rare, common side effects include mild to moderate rash, fever, nausea, fatigue, headache, and elevated liver enzymes.

Nevirapine induces and is metabolized by CYP3A4; therefore, coadministration of drugs that induce or are metabolized by this isoenzyme may result in interactions. Nevirapine may decrease the effectiveness of ethinyl estradiol–based contraceptives and can lower plasma concentrations of methadone. Nevirapine should not be administered with ketoconazole, rifampin, or rifabutin.

Delavirdine

Delavirdine (*Rescriptor*) is approved for the treatment of HIV-1 infection in adults and adolescents over age 16 as part of a combination therapy. Rash accompanied by pruritus is the most frequent adverse effect of this agent; however, it usually resolves within several weeks of treatment. Severe skin reactions are rare. Headache, nausea, vomiting, diarrhea, fatigue, and elevated hepatic enzymes also may be associated with delavirdine administration.

Drugs that decrease stomach acidity (e.g., antacids, H_2 receptor blockers, and proton pump inhibitors) decrease the absorption of delavirdine. In vivo and in vitro studies have shown that delavirdine is metabolized by and inhibits CYP3A4. In vitro studies have shown that it also is metabolized by CYP2D6 and inhibits CYP2C9, CYP2D6, and CYP2C19. Delavirdine should not be used in combination with alprazolam, cisapride, ergot alkaloids, midazolam, or triazolam because of the potential for serious adverse reactions. Delavirdine increases serum concentrations of certain protease inhibitors and may reverse the resistance of zidovudine-resistant HIV.

Protease Inhibitors

These drugs inhibit the activity of HIV protease. This enzyme, which is required for the production of a mature infectious virus, cleaves the gag-pol polyprotein into structural proteins and active enzymes. The pharmacokinetic parameters of the protease inhibitors are listed in Table 51.5.

The protease inhibitors are used in the multidrug therapy of HIV infection. Resistance to the HIV protease inhibitors results from mutations in the protease gene and perhaps the cleavage sites of gag-pol. Although different protease mutations tend to be associated with resistance to individual drugs, resistance to one protease inhibitor is often associated with a less than optimal response to other agents of this class. Indinavir, ritonavir, and lopinavir require more mutations to lose their effectiveness than do the other protease inhibitors.

All protease inhibitors can produce nausea, vomiting, diarrhea, and paresthesia. Drug-induced hyperglycemia and insulin resistance may precipitate the onset of diabetes mellitus or worsen existing cases. Protease inhibitors may also cause hypercholesterolemia and hypertriglyceridemia. Liver enzymes may be increased, and hepatic toxicity may occur at high doses. Fat redistribution is common and can manifest as central fat accumulation, peripheral wasting, buffalo hump at the base of the neck, breast enlargement, and/or lipomas.

Protease inhibitors may increase the risk of bleeding in hemophiliacs. These drugs should be used with caution in patients with diabetes, lipid disorders, and hepatic disease. Dosage adjustment may be necessary.

Protease inhibitors interact with a large number of drugs because they are metabolized by and inhibit CYP3A4. Ritonavir is the most potent inhibitor of CYP3A4, with indinavir, amprenavir, and nelfinavir being much less potent and saquinavir the least potent. When given as part of a combination therapy, the protease inhibitors affect plasma levels of NNRTIs as well as each other (Tables 51.4 and 51.6). Many drugs interact with protease inhibitors by inhibiting or inducing their metabolism; similarly, protease inhibitors inhibit or induce the metabolism of numerous drugs (Table 51.7).

TABLE 51.5 Pharmacokinetic Properties of Selected Protease Inhibitors[a]

Drug	Oral Bioavailability (%)	Plasma Elimination Half-Life (hr)	Protein Binding (%)	Metabolism	Urinary Excretion[b] (%)	Notes
Amprenavir	ND	7 –11	90	CYP3A4	<2	F−; H; R?
Indinavir	60–65	1.8	60	CYP3A4	10 –12	F−; H; R?
Lopinavir, ritonavir	ND	5–6	98 –99	CYP3A4	<3	F+; (h); R?
Nelfinavir	ND	3.5–5	>98	CYP3A4[c] CYP2C19	<2	F+; H?; R?
Ritonavir[d]	ND	3–5	>98	CYP3A4[c] CYP2D6	3.5	F+; (h); R?
Saquinavir	13	7–12	97	CYP3A4	<3	F+; FPM; H?; R?
Saquinavir mesylate	4	7–12	97	CYP3A4	<3	F+; FPM; H?; R?

[a]Average values for fed adult patients following multiple oral doses.
[b]Unchanged drug.
[c]Major isoform responsible for drug metabolism.
[d]Capsule formulation.
F+, food (high fat meal) increases absorption; F−, food decreases absorption; FPM, extensive first-pass metabolism; H, dosage adjustment is necessary in patients with hepatic impairment; (h), dosage adjustment may be required in patients with hepatic impairment; H?, dosage adjustment in patients with hepatic impairment has not been studied; R, dosage adjustment is necessary in patients with renal impairment; R?, dosage adjustment in patients with renal impairment has not been studied.

TABLE 51.6 Interactions Among Protease Inhibitors

Drug	Increases Plasma AUC of	Decreases Plasma AUC of	Plasma AUC Increased by	Plasma AUC Decreased by
Amprenavir	Nelfinavir	Indinavir	Indinavir Nelfinavir Ritonavir	
Indinavir	Amprenavir Nelfinavir Saquinavir		Nelfinavir Ritonavir	Amprenavir
Lopinavir[a]			Ritonavir	Amprenavir
Nelfinavir	Amprenavir Indinavir Saquinavir		Amprenavir Indinavir Ritonavir Saquinavir	
Ritonavir	Amprenavir Indinavir Lopinavir Nelfinavir Saquinavir			
Saquinavir	Nelfinavir		Indinavir Nelfinavir Ritonavir	

[a]Coformulation of lopinavir and ritonavir.

Saquinavir

Saquinavir is a potent inhibitor of HIV-1 and HIV-2 protease. *Fortovase,* a soft gel preparation of saquinavir, has largely replaced saquinavir mesylate capsules (*Invirase*) because it has improved bioavailability. Saquinavir is usually well tolerated and most frequently produces mild gastrointestinal side effects.

Ritonavir

Although ritonavir (*Norvir*) is a potent inhibitor of HIV-1 and HIV-2 protease, it is not well tolerated in higher doses. It is mainly used in low doses to increase blood levels of other protease inhibitors and to extend their dosing interval. Ritonavir is more commonly associated with gastrointestinal side effects, altered taste

TABLE 51.7 Drug Interactions Commonly Seen with Protease Inhibitors[a]

Drugs Contraindicated for Use with Protease Inhibitors Because of Risk of Life-Threatening Toxicity

Cisapride (arrhythmias)[b]	Lovastatin (rhabdomyolysis)	Simvastatin (rhabdomyolysis)
Ergot alkaloids (vasospasm)	Midazolam (resp. depression)	Triazolam (resp. depression)

Drugs That May Decrease Plasma Levels of Protease Inhibitors

Dexamethasone
Phenytoin
Rifampin
Phenobarbital
Rifabutin
St. John's wort[c]

Drugs That May Increase Plasma Levels of Protease Inhibitors

Clarithromycin
Itraconazole
Ketoconazole

Drugs Whose Plasma Levels May Be Decreased by Protease Inhibitors

Ethinyl estradiol
Phenytoin

Drugs Whose Plasma Levels May Be Increased by Protease Inhibitors

Antiarrhythmic agents (some)
Benzodiazepines (some)[d]
Ketoconazole
Antidepressants (some)
Ca^{++} channel blockers (some)
Rifabutin
β-Blockers (some)
HMG-CoA reductase inhibitors (some)[c]
Sildenafil

[a]Interactions may be seen to varying degrees with different protease inhibitors. This list is not all-inclusive; it is important to check individual drug interactions when prescribing protease inhibitors.
[b]Pharmacy sales of this drug have been discontinued in the United States. It is available only via registered prescribers to patients who meet specific eligibility conditions.
[c]The use of St. John's wort is contraindicated in patients taking protease inhibitors because their antiviral activity may be lost and/or drug resistance may result.
[d]Some are absolutely contraindicated for use with protease inhibitors.

sensation, paresthesias, and hypertriglyceridemia than are other protease inhibitors. Pancreatitis may occur in the presence or absence of hypertriglyceridemia.

Of all the protease inhibitors, ritonavir is the most potent inhibitor of CYP3A4; therefore, it tends to produce more frequent and severe interactions with other drugs. It inhibits an additional cytochrome P450 isozyme, CYP2D6, and can increase plasma concentrations of drugs that are metabolized by it (e.g., most antidepressants, some antiarrhythmics, some opioid analgesics, some neuroleptics). For example, ritonavir should not be used in conjunction with amiodarone, bepridil, flecainide, propafenone, quinidine, or pimozide. In addition to CYP3A4, ritonavir induces CYP1A2 and possibly CYP2C9 and may inhibit the breakdown of drugs metabolized by these enzymes.

Indinavir

Indinavir (*Crixivan*) is a potent inhibitor of HIV reverse transcriptase. It produces the side effects common to all protease inhibitors and also may produce nephrolithiasis, urolithiasis, and possibly renal insufficiency or renal failure. *This problem occurs more frequently in children (approximately 30%) than adults (approximately 10%) and can be minimized by drinking at least 1.5 L of water daily.* Additional side effects include asymptomatic hyperbilirubinemia, alopecia, ingrown toenails, and paronychia. Hemolytic anemia rarely occurs. Rifampin should not be given with indinavir.

Nelfinavir

Nelfinavir (*Viracept*) is probably the most commonly used protease inhibitor because of its low incidence of serious adverse effects. Its most common side effects are diarrhea and flatulence; these may resolve with continued use. In addition to the drugs contraindicated for use with all protease inhibitors, amiodarone, rifampin, and quinidine are contraindicated in patients taking nelfinavir.

Amprenavir

Amprenavir (*Agenerase*) is administered twice daily, providing the patient with an advantage over other protease inhibitors that must be taken more frequently (e.g., indinavir, saquinavir). Common side effects of am-

prenavir include nausea, vomiting, diarrhea, and perioral paraesthesias. Rash occurs in approximately 20 to 30% of patients and can be mild or severe (Stevens-Johnson syndrome).

Amprenavir oral solution contains large amounts of the excipient propylene glycol and should not be given to children under age 4 because it can produce hyperosmolality, lactic acidosis, seizures, and/or respiratory depression. Pregnant women should not take amprenavir oral solution, as fetal toxicity may result. Amprenavir is a sulfonamide and should be used with caution in patients with sulfonamide allergy. Amprenavir oral solution and capsules contain high levels of vitamin E; therefore, patients are advised not to take supplemental vitamin E. In addition to the drugs contraindicated for use with all protease inhibitors, amprenavir should not be given with pimozide or rifampin.

Lopinavir–Ritonavir

Lopinavir is available in the United States only as a fixed-dose combination with ritonavir (*Kaletra*). *In this regimen, a low dose of ritonavir is used to inhibit the rapid inactivation of lopinavir by CYP3A4.* Side effects, which are generally mild, include diarrhea, nausea, asthenia, and headache. Pancreatitis occurs rarely. Ritonavir is a potent inhibitor of CYP3A4 and also inhibits CYP2D6. In addition to the drugs contraindicated for all protease inhibitors, flecainide, propafenone, pimozide, and rifampin should not be given with lopinavir–ritonavir combination therapy.

THE USE OF ANTIRETROVIRAL DRUGS IN PREGNANCY

Zidovudine was the first agent to be used to prevent the transmission of HIV from a pregnant woman to her child. It was given to the mother at 14 to 34 weeks' gestation and to the child for the first 6 weeks of life. Current combination therapies employ zidovudine with another NRTI and a protease inhibitor.

The teratogenic risk associated with administration of antiretroviral drugs during the first trimester of pregnancy is not clear. Women who have not begun therapy prior to becoming pregnant may consider waiting until after 10 to 12 weeks' gestation to begin antiviral treatment. If a woman decides to discontinue antiretroviral therapy during pregnancy, all drugs should be stopped and reintroduced simultaneously to avoid the development of resistance. Pregnant women may be particularly susceptible to hyperglycemia caused by protease inhibitors.

In the United States, the Centers for Disease Control recommend that HIV-infected mothers avoid breast-feeding to prevent the transmission of the virus to their infants. The risk of this type of vertical transmission ranges from 5 to 20%; longer durations of breast-feeding, mastitis, and abscesses are associated with increased risk. In developing countries in which safe infant formula is not readily available, the avoidance of breast-feeding can increase the infant's risk of death from malnutrition and food-borne infection. The World Health Organization recommends that under these circumstances exclusive breast-feeding should be maintained for the first months of life and discontinued when replacement feeding is acceptable, feasible, affordable, sustainable, and safe.

Study Questions

1. The mechanism of action of lamivudine differs from that of efavirenz in that
(A) Lamivudine inhibits HIV protease; efavirenz inhibits reverse transcriptase.
(B) Lamivudine inhibits reverse transcriptase; efavirenz inhibits HIV protease.
(C) Lamivudine is a cytosine nucleoside analogue; efavirenz is an adenosine nucleotide analogue.
(D) Lamivudine binds to the active site of reverse transcriptase; efavirenz binds adjacent to it.
(E) Lamivudine and efavirenz exhibit the same mechanism of action; there is no difference.

2. Sharon M. is a 35-year-old woman who is approximately 60% above the normal body weight for her height. She has a history of alcohol abuse and has been taking zidovudine and abacavir for the past 3 years to treat HIV infection. These factors put her at high risk for drug-induced
(A) Lactic acidosis, hepatomegaly, and hepatic steatosis
(B) Peripheral neuropathy
(C) Stevens-Johnson syndrome
(D) Hyperuricemia
(E) Hypersensitivity reaction

3. Mark C. is taking a regimen consisting of zidovudine, lamivudine, and efavirenz for the treatment of HIV infection. To help him fall asleep at night, he took a normal dose of diazepam (10 mg before bed), which he got from a friend. He then had symptoms of diazepam overdose, including grogginess and

difficulty waking and maintaining consciousness. The most likely reason for this is that
(A) Efavirenz inhibits the hepatic metabolism of diazepam
(B) Efavirenz competes with diazepam for renal elimination
(C) Lamivudine potentiates the depressant activity of diazepam
(D) Zidovudine induces the metabolism of diazepam
(E) Lamivudine stimulates conversion of diazepam to its active form

4. Adverse effects commonly associated with NRTIs include
(A) Central fat accumulation and peripheral fat wasting
(B) Drug interactions involving cytochrome P450 enzymes
(C) Myelotoxicity and hemolytic anemia
(D) Hypercholesterolemia and hypertriglyceridemia
(E) Hyperglycemia and insulin resistance

5. A fixed-dose combination of lopinavir and ritonavir is used to treat HIV infection in the United States. This combination is particularly effective because
(A) Ritonavir and lopinavir inhibit HIV reverse transcriptase in different ways
(B) Ritonavir decreases the hepatic metabolism of lopinavir
(C) Ritonavir decreases the renal elimination of lopinavir
(D) Lopinavir inhibits the ability of HIV to mutate in response to ritonavir
(E) Lopinavir inhibits the mutant HIV structural protein that confers viral resistance on ritonavir

ANSWERS

1. **D.** Lamivudine, a cytosine analogue, is a nucleoside reverse transcriptase inhibitor that acts as a competitive inhibitor of reverse transcriptase. Efavirenz is a nonnucleoside reverse transcriptase inhibitor; it acts by binding to a site adjacent to the enzyme's active site. Neither drug exhibits significant activity against HIV protease.
2. **A.** The NRTIs can produce a potentially fatal syndrome of lactic acidosis and severe hepatomegaly with hepatic steatosis. Risk factors associated with the development of this syndrome include female sex, obesity, alcoholism, and prolonged exposure to NRTIs. Peripheral neuropathy is a common side effect of some NRTIs (e.g., stavudine., didanosine, and zalcitabine) but not associated with these risk factors. Stevens-Johnson syndrome is rarely associated with NNRTIs, such as nevirapine, and not with these risk factors. Hyperuricemia is not associated with these risk factors. Hypersensitivity reaction may occur in the early months of treatment with abacavir but is not associated with this subject's risk factors.
3. **A.** Diazepam is metabolized in the liver by CYP3A4 and CYP2C19; efavirenz inhibits both of these isozymes and is likely to increase plasma levels of diazepam. Diazepam is almost completely converted to inactive metabolites; therefore, renal elimination is not much of a concern. Lamivudine may produce fatigue as a side effect but does not potentiate the depressant activity of diazepam. Zidovudine does not induce cytochrome P450 activity, and diazepam does not have to be converted to an active form for sedative activity.
4. **C.** Myelotoxicity is associated with certain NRTIs such as zidovudine. Fat redistribution, drug interactions involving CYP3A4, dyslipidemia, and diabetic symptoms are all side effects common to the protease inhibitors.
5. **B.** Ritonavir is a potent inhibitor of CYP3A4, the enzyme that rapidly inactivates lopinavir. This combination includes a low dose of ritonavir that is not likely to cause serious side effects but instead inhibits lopinavir metabolism. Ritonavir and lopinavir are HIV protease inhibitors and do not affect reverse transcriptase. Lopinavir is almost completely eliminated by metabolism to inactive metabolites; little is eliminated unchanged by the kidney. Lopinavir is not known to inhibit the ability of HIV to mutate. Lopinavir inhibits the enzyme HIV protease, not a structural protein.

SUPPLEMENTAL READING

Bartlett JA. Addressing the challenges of adherence. J Acquir Immune Defic Syndr 2002;29 Suppl 1:S2–S10.
Campiani G et al. Non-nucleoside HIV-1 reverse transcriptase (RT) inhibitors: Past, present, and future perspectives. Curr Pharm Des 2002;8:615–657.
Greene WC and Peterlin BM. Charting HIV's remarkable voyage through the cell: Basic science as a passport to future therapy. Nat Med 2002;8:673–680.
Jiang S, Zhao Q, and Debnath AK. Peptide and nonpeptide HIV fusion inhibitors. Curr Pharm Des 2002;8:563–580.
Moyle G. Use of HIV protease inhibitors as pharmacoenhancers. AIDS Read 2001;11:87–98.
Pierson T et al. Characterization of chemokine receptor utilization of viruses in the latent reservoir for human immunodeficiency virus type 1. J Virol 2000;74:7824–7833.
Piot P et al. The global impact of HIV/AIDS. Nature 2001;410:968–973.
Sepkowitz KA. AIDS: the first 20 years. N Engl J Med 2001;344:1764–1772.
Setti M et al. Identification of key mutations in HIV reverse transcriptase gene can influence the clinical outcome of HAART. J Med Virol 2001;64:199–206.

Sonza S and Crowe SM. Reservoirs for HIV infection and their persistence in the face of undetectable viral load. AIDS Patient Care STDS. 2001;15:511–518.
Tarrago-Litvak L et al. Inhibitors of HIV-1 reverse transcriptase and integrase: Classical and emerging therapeutical approaches. Curr Pharm Des 2002; 8:595–614.
Tozser J. HIV inhibitors: Problems and reality. Ann N Y Acad Sci 2001;946:145–159.

CASE Study HIV and Nutriceuticals

Jerome R. is HIV positive and has been taking saquinavir 1200 mg tid and zidovudine 200 mg tid for the past 8 months. During this time, his CD4 count raised from 200 cells/mm^3 to 725 cells/mm^3. Two months later, Mr. R returned to his physician with a severe herpes outbreak on one side of his face. His CD4 count had fallen to 280 cells/mm^3. What happened?

ANSWER: Two months ago, Mr. R. began taking St. John's wort to counteract depression. St. John's wort is a potent inducer of intestinal and hepatic CYP3A4. Saquinavir undergoes extensive first-pass metabolism by intestinal CYP3A4 and is metabolized in the liver by CYP3A4. The use of St. John's wort is contraindicated for individuals taking protease inhibitors because it may decrease protease inhibitor concentrations to subtherapeutic levels, resulting in the loss of virological response and possible resistance to the protease inhibitor. In this case, it appears that saquinavir was no longer present at an effective concentration and the HIV virus became resistant to zidovudine. Discontinuation of St. John's wort and a change in treatment regimen, perhaps to two different NRTIs and an NNRTI, are in order. Mr. R's depression should be treated with a different agent. Many antidepressants are metabolized by cytochrome P450 systems; thus, a reduction in antidepressant dosage may be necessary because NNRTIs and protease inhibitors inhibit cytochrome P450 isoenzymes.