**Chapter 38 part 2**

**H. Trifluridine**

Trifluridine [trye-FLURE-i-deen] is a fluorinated pyrimidine nucleoside analog. It is structurally very similar to thymidine, the only difference

Page 470 missing

polymerases are lower than they are for HIV reverse transcriptase, although mitochondrial DNA polymerase γ appears to be susceptible at therapeutic concentrations.

**2. Pharmacokinetics**: The NRTIs are primarily renally excreted, and all require dosage adjustment in renal insufficiency except abacavir, which is metabolized by alcohol dehydrogenase and glucuronyl transferase. Dosage adjustment is required when the creatinine clearance drops below 50 mL/min.

**3. Adverse effects**: Many of the toxicities of the NRTIs are believed to be due to inhibition of the mitochondrial DNA polymerase in cer- tain tissues. As a general rule, the dideoxynucleosides, such as zalcitabine, didanosine, and stavudine, have a greater affinity for the mitochondrial DNA polymerase, leading to such toxicities as peripheral neuropathy, pancreatitis, and lipoatrophy. When more than one NRTI is given, care is taken not to have overlapping toxicities. All of the NRTIs have been associated with a potentially fatal liver toxicity characterized by lactic acidosis and hepatomegaly with steatosis.

**4. Drug interactions**: Due to the renal excretion of the NRTIs, there are not many drug interactions encountered with these agents except for zidovudine and tenofovir (see below). **5. Resistance**: NRTI resistance is well characterized, and the most common mutation is the mutation at viral codon 184, which confers a high degree of resistance to lamivudine and emtricitabine but, more importantly, restores sensitivity to zidovudine and tenofovir. Because cross-resistance and antagonism occur between agents of the same analog class (thymidine, cytosine, guanosine, and adenosine), concomitant use of agents in the same class is contraindicated (for example, zidovudine plus stavudine).

**B. Zidovudine** (AZT, ZDV)

Approved in 1987, the first agent available for treatment of HIV infection is the pyrimidine analog, 3’-azido-3’-deoxythymidine (AZT). AZT has the generic name of zidovudine [zye-DOE-vyoo-deen]. AZT is approved for use in children and adults and to prevent prenatal infection in pregnancy. It is also used for prophylaxis in individuals exposed to HIV infection. The drug is well absorbed after oral administration. If taken with food, peak levels may be lower, but the total amount of drug absorbed is not affected. Penetration across the blood-brain barrier is excellent, and the drug has a half-life of 1 hour. The intracellular half-life, however, is approximately 3 hours. Most of the AZT is glucuronidated by the liver and then excreted in the urine (see Figure 38.18). In spite of its seem- ing specifi city, AZT is toxic to bone marrow. Headaches are also com- mon. The toxicity of AZT is potentiated if glucuronidation is decreased by co-administration of drugs like probenecid, acetaminophen, loraze- pam, indomethacin, and cimetidine. They should be avoided or used with caution in patients receiving AZT. Both stavudine and ribavirin are activated by the same intracellular pathways and should not be given with AZT.

**C.Stavudine** (d4T)

Stavudine [STAV-yoo-deen] is an analog of thymidine, in which a double bond joins the 2’ and 3’ carbons of the sugar. Stavudine is a strong inhibitor of cellular enzymes such as the β and γ DNA polymerases, thus reducing mitochondrial DNA synthesis and resulting in toxicity. The drug is almost completely absorbed on oral ingestion and is not affected by food. Stavudine penetrates the blood-brain barrier. About half of the parent drug can be accounted for in the urine. Renal impairment interferes with clearance. The major and most common clinical toxicity is peripheral neuropathy along with lipoatrophy and hyperlipidemia.

**D. Didanosine** (ddI)

The second drug approved to treat HIV-1 infection was didanosine [dye-DAN-oh-seen] (dideoxyinosine, ddI), which is missing both the 2’- and 3’-hydroxyl groups. Upon entry into the host cell, ddI is biotrans- formed into dideoxyadenosine triphosphate (ddATP) through a series of reactions that involve phosphorylation of the ddI, amination to dide- oxyadenosine monophosphate, and further phosphorylation. Like AZT, the resulting ddATP is incorporated into the DNA chain, causing termination of chain elongation. Due to its acid lability, absorption is best if ddI is taken in the fasting state. The drug penetrates into the CSF but to a lesser extent than does AZT. About 55 percent of the parent drug appears in the urine (Figure 38.19). Pancreatitis, which may be fatal, is a major tox icity of ddI treatment and requires monitoring of serum amy- lase. The dose-limiting toxicity of ddI is peripheral neuropathy. Because of its similar adverse eff ect profi le, concurrent use of stavudine is not recommended.

**E.Tenofovir** (TDF)

Tenofovir [te-NOE-fo-veer] is the first approved drug that is a nucleotide analog, namely, an acyclic nucleoside phosphonate analog of adenosine 5’-monophosphate. It is converted by cellular enzymes to the diphosphate, which is the inhibitor of HIV reverse transcriptase. Cross-resistance with other NRTIs may occur, but some AZT-resistant strains retain susceptibility to tenofovir. Tenofovir has a long half-life, allowing once-daily dosing. Most of the drug is recovered unchanged in the urine, and elimination is by filtration and active secretion. Serum creatinine must be monitored and doses adjusted in renal insufficiency. GI complaints are frequent and include nausea, diarrhea, and bloating (Figure 38.20). Tenofovir is the only NRTI with significant antiretrovi- ral drug interactions. Tenofovir increases the concentrations of ddI to the point that ddI dosage reductions are required if the two are given together. However, these two agents are no longer recommended for combined use. Tenofovir decreases the concentrations of atazanavir such that atazanavir must be boosted with ritonavir (see p. 476) if given with tenofovir to maintain eff ective atazanavir concentrations.

1. **Lamivudine** (3TC)

Lamivudine [la-MI-vyoo-deen] (2’-deoxy-3’-thiacytidine, 3TC) is approved for treatment of HIV in combination with AZT, but it should not be used with other cytosine analogs due to antagonism. Lamivudine terminates the synthesis of the proviral DNA chain, and it inhibits the reverse tran- scriptase of both HIV and HBV. However, it does not aff ect mitochondrial DNA synthesis or bone marrow precursor cells. It has good bioavailabil- ity on oral administration, depends on the kidney for excretion, and is well tolerated.

1. **Emtricitabine (FTC)**

Emtricitabine [em-tri-SIGH-ta-been], a fluoro-derivative of lamivu dine, inhibits both HIV and HBV reverse transcriptase. In a small clinical trial, it was shown to be at least as effective as lamivudine in the treatment of HIV-infected individuals. Emtricitabine is orally active, with a mean bioavailability of 93 percent. Plasma half-life is about 10 hours, whereas it has a long intracellular half-life of 39 hours. Emtricitabine is eliminated essentially unchanged in urine. It does not affect cytochrome P450 (CYP450) isozymes and has no significant interactions with other drugs. Headache, diarrhea, nausea, and rash are its most common adverse eff ects. Emtricitabine causes hyperpigmentation of the soles and palms, and it has been associated with lactic acidosis, fatty liver, and hepatomegaly. Withdrawal of emtricitabine in HBV-infected patients may result in worsening of the hepatitis.

1. **Zalcitabine** (ddC)

Zacitabine [zal-SIGH-ta-been] was the first cytosine analog developed. However, due to severe toxicity, it was removed from the market.

1. **Abacavir** (ABC)

Abacavir [a-BA-ka-veer] is a guanosine analog. There may be some cross-resistance with strains resistant to AZT and lamivudine. Abacavir is well absorbed orally, and metabolites appear in the urine (Figure 38.21). Most of the drug is metabolized by non-CYP450–dependent reactions. A carboxylic acid derivative and a glucuronidated form have been identified. Common side effects include GI disturbances, headache, and dizziness. Approximately 5 percent of patients exhibit the “hypersensitivity reaction,” which is usually characterized by drug fever, plus one or more of the following symptoms of rash, GI symptoms, malaise, and respiratory distress (Figure. 38.22). Sensitized individuals should never be re-challenged because of rapidly appearing, severe reactions that lead to death. There is a newly approved HLA genetic test available to screen patients for the potential of this reaction. Figure 38.23 shows some adverse reactions commonly seen with nucleoside analogs.

**VII. NNRTIs USED TO TREAT HIV INFECTION**

NNRTIs are highly selective, non-competitive inhibitors of HIV-1 reverse transcriptase. They bind to HIV reverse transcriptase at a site adjacent to the active site, inducing a conformational change that results in enzyme inhibition. They do not require activation by cellular enzymes. Their major advantage is their lack of effect on the host blood-forming elements and their lack of cross-resistance with NRTIs. These drugs, however, do have common characteristics that include cross-resistance within the NNRTI class, drug interactions, and a high incidence of hypersensitivity reactions, including rash.

**A. First-generation NNRTI's**

**1. Nevirapine (NVP**): Nevirapine [ne-VYE-ra-peen] is used in combina- tion with other antiretroviral drugs for the treatment of HIV-1 infections in adults and children. Due to potential severe hepatotoxicity, nevirapine should not be initiated in women with CD4+ T-cell counts greater than 250 cells/mm3 or in men with CD4+ T cell counts greater than 400 cells/mm3. Nevirapine is well absorbed orally, and its absorption is not affected by food and antacids. The lipophilic nature of nevirapine accounts for its entrance into the fetus and mother’s milk and for its wide tissue distribution, including the CNS. Nevirapine is dependent upon metabolism for elimination, and most of the drug is excreted in urine as the glucuronide of hydroxylated metabolites (Figure 38.24). Nevirapine is an inducer of the CYP3A4 family of CYP450 drug-metabolizing enzymes. Nevirapine increases the metabolism of protease inhibitors, but most combinations do not require dosage adjustment. Nevirapine increases the metabolism of a number of drugs, such as oral contraceptives, ketoconazole, methadone, metronidazole, quinidine, theophylline, and warfarin. The most frequently observed side effects are rash, fever, headache, and elevated serum transaminases and fatal hepatotoxicity. Severe dermatologic effects have been encountered, including Stevens- Johnson syndrome and toxic epidermal necrolysis. A 14-day titration period at half the dose is mandatory to reduce the risk of seri- ous epidermal reactions and hepatotoxicity.

**2. Delavirdine** (DLV): Delavirdine [de-LA-vir-deen] has not undergone clinical trials as extensive as those of nevirapine and is not recommended as a preferred or alternate agent in the U.S. Department of Health and Human Services (DHHS) guidelines for initial therapy. Delavirdine is rapidly absorbed after oral administration and is unaffected by the presence of food. Delavirdine is extensively metabolized, and very little is excreted as the parent compound. Fecal and urinary excretion each account for approximately half the elimination. Delavirdine is an inhibitor of CYP450–mediated drug metabolism, including that of protease inhibitors. Fluoxetine and ketoconazole increase plasma levels of delavirdine, whereas phenytoin, phenobarbital, and carbamazepine result in substantial decreases in plasma levels of delavirdine. Rash is the most common side eff ect of delavirdine.

**3. Efavirenz** (EFV): Efavirenz [e-FA-veer-enz] treatment results in increases in CD4+ cell counts and a decrease in viral load comparable to that achieved by protease inhibitors when used in combination with NRTIs. Therefore, it is the preferred NNRTI on the DHHS guide- lines. Following oral administration, efavirenz is well distributed, including to the CNS (Figure 38.25). It should be administered on an empty stomach to reduce adverse CNS eff ects. Most of the drug is bound to plasma albumin (99 percent) at therapeutic doses. A half- life of more than 40 hours accounts for its recommended once-a- day dosing. Efavirenz is extensively metabolized to inactive prod- ucts. Efavirenz is a potent inducer of CYP450 enzymes and, there- fore, may reduce the concentrations of drugs that are substrates of the CYP450. Most adverse effects are tolerable and are associated with the CNS, including dizziness, headache, vivid dreams, and loss of concentration (Figure 38.26). Nearly half of the patients experience these complaints, which usually resolve within a few weeks. Rash is the other most common side eff ect, with an incidence of approximately 25 percent. Severe, life-threatening reactions are rare. Efavirenz should be avoided in pregnant women.

**B. Second-generation NNRTIs**

**1. Etravirine** (ETR): Etravirine [et-ra-VYE-rine] is the first second-generation NNRTI. It is active against many of the strains of HIV that are resistant to the first-generation NNRTIs. HIV strains with the common K103N resistance mutation to the first generation of NNRTIs are fully susceptible to etravirine. Following oral administration, etravirine is well distributed, and bioavailability is enhanced when taken with a high-fat meal. Although it has a half-life of approximately 40 hours, it is indicated for twice-daily dosing. Etravirine is extensively metabolized to inactive products. Because etravirine is a potent inducer of CYP450, the doses of CYP450 substrates may need to be increased when given with etravirine. Rash is the most common side eff ect. Etravirine is otherwise well tolerated, does not have the CNS side eff ects that are seen with efavirenz, and is pregnancy category B. Etravirine is indicated for HIV treatment–experienced, multidrug-resistant adult patients who have evidence of ongoing viral replication.

**VIII. HIV PROTEASE INHIBITORS USED TO TREAT HIV INFECTION**

Inhibitors of HIV protease have significantly altered the course of this devastating viral disease. Within a year of their introduction in 1995, the number of deaths in the United States due to AIDS declined, although the trend appears to be levelling off (Figure 38.27). **A. Overview**

These potent agents have several common features that characterize their pharmacology.

**1. Mechanism of action**: All of the drugs in this group are reversible inhibitors of the HIV aspartyl protease, which is the viral enzyme responsible for cleavage of the viral polyprotein into a number of essential enzymes (reverse transcriptase, protease, and integrase) and several structural proteins. The protease inhibitors exhibit at least a thousand fold greater affinity for HIV-1 and HIV-2 enzymes than they have for comparable human proteases, such as renin and cathepsin D/E. This accounts for their selective toxicity. The inhibition prevents maturation of the viral particles and results in the production of noninfectiousvirions. Treatment of antiretroviral naïve patients (those who have never had HIV therapy) with a pro- tease inhibitor and two NRTIs results in a decrease in the plasma viral load to undetectable levels in 60 to 95 percent of patients. Treatment failures under these conditions are most likely due to a lack of patient adherence.

**2. Pharmacokinetics**: Most protease inhibitors have poor oral bioavailability. High-fat meals substantially increase the bioavailability of some, such as nelfi navir and saquinavir, whereas the bioavailability of indinavir is decreased, and others are essentially unaff ected. All are substrates for the CYP3A4 isozyme of CYP450, and individual protease inhibitors are also metabolized by other P450 isozymes. Metabolism is extensive, and very little of the protease inhibitors are excreted unchanged in urine. Dosage adjustments are unnecessary in renal impairment. Distribution into some tissues may be affected because protease inhibitors are substrates for the P-glycoprotein multidrug efflux pump. The presence of this pump in endothelial cells of capillaries in the brain may limit protease inhibitor access to the CNS. The HIV protease inhibitors are all substantially bound to plasma proteins, specifi cally α1-acid glycoprotein. This may be clinically important, because the concentration of α1-acid glycoprotein increases in response to trauma and surgery.

**3. Adverse eff ects:** Protease inhibitors commonly cause paresthesias, nausea, vomiting, and diarrhea (Figure 38.28). Disturbances in glucose and lipid metabolism also occur, including diabetes, hypertriglyceridemia, and hypercholesterolemia. Chronic administration results in fat redistribution, including loss of fat from the extremities, fat accumulation in the abdomen and the base of the neck (“buff alo hump”; Figure 38.29), and breast enlargement. These physical changes may indicate to others that an individual is HIV infected.

**4 Drug interactions**: Drug interactions are a common problem for all protease inhibitors, because they are not only substrates but also potent inhibitors of CYP isozymes. The inhibitory potency of the compounds lies between that of ritonavir, the most potent, and that of saquinavir, the least potent inhibitor of CYP isoenzymes. Drug interactions are, therefore, quite common. Drugs that rely on metabolism for their termination of action may accumulate to toxic levels. Examples of potentially dangerous interactions from drugs that are contraindicated with protease inhibitors include rhab- domyolysis from simvastatin or lovastatin, excessive sedation from midazolam or triazolam, and respiratory depression from fentanyl (Figure 38.30). Other drug interactions that require dosage modifi - cation and cautious use include warfarin, sildenafi l, and phenytoin (Figure 38.31). In addition, inducers of CYP isozymes may result in the lowering of protease inhibitor plasma concentrations to sub- optimal levels, contributing to treatment failures. Thus, drugs such as rifampin and St. John’s wort are also contraindicated with pro- tease inhibitors. Meticulous attention must be paid to all of these detrimental interactions.

**5. Resistance**: Resistance occurs as an accumulation of stepwise muta- tions of the protease gene. Initial mutations result in decreased ability of the virus to replicate, but as the mutations accumulate, virions with high levels of resistance to the protease emerges. Suboptimal concentrations result in the more rapid appearance of resistant strains.

**B. Ritonavir (RTV)**

Ritonavir [ri-TOE-na-veer] is no longer used as a single protease inhibitor but, instead, is used as a pharmacokinetic enhancer or "booster” of other protease inhibitors. Ritonavir is a potent inhibitor of CYP3A, and concomitant ritonavir administration (at low doses) increases the bioavailability of the second protease inhibitor, often allowing for lon- ger dosing intervals. The resulting higher Cmin levels of the “boosted" protease inhibitors also help to prevent the development of resis- tance. Therefore, “boosted" protease inhibitors are preferred agents in the DHHS treatment guidelines. Metabolism and biliary excretion are the primary methods of elimination. Ritonavir has a half-life of 3 to 5 hours. Because it is primarily an inhibitor of CYP450 isozymes, numerous drug interactions have been identified. Nausea, vomiting, diarrhea, headache, and circumoral paresthesias are among the more common adverse effects.

**C.Saquinavir (SQV**

To maximize bioavailability, saquinavir [sa-KWIH-na-veer] is always given along with a low dose of ritonavir. High-fat meals also enhance absorption. Elimination of saquinavir is primarily by metabolism, fol- lowed by biliary excretion. Its half-life is 7 to 12 hours, requiring twice daily doses. Drugs that enhance the metabolism of saquinavir, such as rifampin, rifabutin, nevirapine, efavirenz, and other enzyme inducers, should be avoided if possible. The most common adverse effects of saquinavir treatment include headache, fatigue, diarrhea, nausea, and other GI disturbances. Increased levels of hepatic aminotransferases have been noted, particularly in patients with concurrent viral hepatitis B or C infections.

**D.Indinavir (IDV)**

Indinavir [in-DIH-na-veer] is well absorbed orally and, of all the protease inhibitors, is the least protein bound, at 60 percent. Acidic gastric conditions are necessary for absorption. Absorption is decreased when administered with meals, although a light, low-fat snack is permissible. Ritonavir overcomes this problem and also permits twice-a-day dosing. Metabolism and hepatic clearance account for elimination of indinavir. The dosage should, therefore, be reduced in the presence of hepatic insuffi ciency. Indinavir has the shortest half-life of the protease inhibitors, at 1.8 hours. It is well tolerated, with the usual GI symptoms and headache predominating. Indinavir characteristically causes nephrolithiasis and hyperbilirubinemia. Adequate hydration is important to reduce the incidence of kidney stone formation, and patients should drink at least 1.5 L of water per day. Fat redistribution is particularly troublesome with this drug.

**E.Nelfi navir (NFV)**

Nelfi navir [nel-FIN-a-veer] is a nonpeptide protease inhibitor. It is well absorbed and does not require strict food or fluid conditions, although it is usually given with food. Nelfi navir undergoes metabolism by sev- eral CYP isozymes. The major metabolite of nelfi navir produced by isoenzyme CYP2C19 has an antiviral activity equal to that of the parent compound, but it achieves plasma concentrations of only 40 percent of those of the parent compound. Nelfi navir is the only protease inhibitor that cannot be boosted by ritonavir, because it is not extensively metabolized by CYP3A. The half-life of nelfi navir is 5 hours. Diarrhea is the most common side eff ect and can be controlled by loperamide. Like other members of the class, nelfi navir can inhibit the metabolism of other drugs, resulting in required alterations of drug dosage or the prohibition of combined use.

**F.Fosamprenavir** (fAPV)

Fosamprenavir [fos-am-PREN-a-veer] is a prodrug that is metabolized to amprenavir following oral absorption. Its long plasma half-life permits twice-a-day dosing. Co-administration of ritonavir increases the plas- ma levels of amprenavir and lowers the total daily dose. Fosamprenavir boosted with ritonavir is one of the alternative protease inhibitors according to the 2011 DHHS treatment guidelines. Nausea, vomiting, diarrhea, fatigue, paresthesias, and headache are common adverse eff ects. Like other members of the class, fosamprenavir can inhibit the metabolism of other drugs, resulting in required alterations of drug dosage or the prohibition of combined use.

**G.Lopinavir (LPV/r)**

Lopinavir [loe-PIN-a-veer] is a peptidomimetic alternative protease inhibitor, according to the 2011 DHHS treatment guidelines. Lopinavir has very poor intrinsic bioavailability, which is substantially enhanced by including a low dose of ritonavir in the formulation. GI adverse eff ects and hypertriglyceridemia are the most common side effects for lopinavir, in addition to the other protease inhibitor class side effects.

Like other members of the class, lopinavir can inhibit the metabolism of other drugs, resulting in required alterations of drug dosage or the prohibition of combined use. Enzyme inducers as well as St. John’s wort should be avoided, because they lower the plasma concentrations of lopinavir. Because the oral solution contains alcohol, disulfiram or met- ronidazole administration can cause unpleasant reactions.

**H.Atazanavir (ATV)**

Atazanavir [ah-ta-ZA-na-veer] is a preferred protease inhibitor. It inhibits HIV protease and is structurally unrelated to other HIV pro- tease inhibitors. Atazanavir is well absorbed orally. It must be taken with food, because food increases absorption and bioavailability. The drug is highly protein bound (86 percent) and undergoes extensive CYP3A4-catalyzed biotransformation. It is excreted primarily in bile. Its half-life is about 7 hours, but it only needs to be administered once a day. Atazanavir is a competitive inhibitor of glucuronyl transferase, and benign hyper bilirubinemia and jaundice are known side effects. In the heart, atazanavir prolongs the PR interval and slows the heart rate. Atazanavir exhibits a decreased risk of hyperlipidemia, but it is not known if atazanavir is less likely to cause insulin resistance and lipodystrophy, as seen with other protease inhibitors. Like the other protease inhibitors, atazanavir is a potent inhibitor of CYP3A4 and has the potential for many drug interactions. Unboosted atazanavir is con- traindicated with the use of proton-pump inhibitors, and administra- tion must be spaced 10 hours apart from H2-blockers and 1 hour after taking antacids.

**I.Tipranavir (TPV)**

Tipranavir [ti-PRA-na-veer] inhibits HIV protease in viruses that are resistant to the other protease inhibitors. Tipranavir is well absorbed when taken with food. The half-life is 6 hours, and it must be administered twice daily in combination with ritonavir. Tipranavir has unique actions both as a CYP450 inducer and a substrate that is different from the other protease inhibitors. Side effects are similar to those of the other protease inhibitors with the exception of two U.S. Food and Drug Administration black box warnings for severe and fatal hepatitis and rare cases of fatal and nonfatal intracranial hemorrhages. Most patients experiencing these severe side effects had underlying comorbidities. Tipranavir is useful in “salvage” regimens in patients with multidrug resistance.

J**.Darunavir (DRV)**

Darunavir [da-RU-na-veer] is the most recently approved protease inhibitor and is preferred by DHHS guidelines. Darunavir is approved for both initial therapy in naïve HIV-infected patients as well as the treatment of experienced patients with HIV that is resistant to other pro- tease inhibitors. Darunavir must be taken with food to increase absorption. Its terminal elimination half-life is 15 hours when combined with ritonavir. Darunavir is extensively metabolized by the CYP3A enzymes and is also an inhibitor. The side effects are similar to those of the other protease inhibitors with the addition of possible rash. Early reports demonstrate a decreased risk of hyperlipidemia, but it is not known if darunavir is less likely to cause insulin resistance and lipodystrophy, as seen with other protease inhibitors. A summary of protease inhibitors is presented in Figure 38.32.

**IX. ENTRY INHIBITORS USED TO TREAT HIV INFECTION**

1. **Enfuvirtide**

Enfuvirtide [en-FU-veer-tide] was the first of a new class of antiretroviral drugs known as entry inhibitors. Enfuvirtide is a fusion inhibitor. For HIV to gain entry into the host cell, it must fuse its membrane with that of the host cell. This is accomplished by changes in the conformation of the viral transmembrane glycoprotein gp41, which occurs when HIV binds to the host cell surface. Enfuvirtide is a 36-amino-acid peptide that binds to gp41, preventing the conformational change. Enfuvirtide, in combination with other antiretroviral agents, is approved for therapy of treatment-experienced patients with evidence of viral replication despite ongoing antiretroviral drug therapy. As a peptide, it must be given subcutaneously. Most of the adverse effects are related to the injection, including pain, erythema, induration, and nodules, which occur in almost all patients. However, only 3 percent discontinue treatment because of them. Enfuvirtide must be reconstituted prior to administration. It is an expensive medication.

1. **Maraviroc**

Maraviroc [ma-RA-vi-roc] is the second entry inhibitor. Because it is well absorbed orally, it is formulated as an oral tablet. Maraviroc blocks the CCR5 co-receptor that works together with gp41 to facilitate HIV entry through the membrane into the cell. HIV may express preference for either the CCR5 co-receptor or the CXCR4 co-receptor or both. A test to determine viral tropism is required to distinguish the virus's use of the CCR5 from the CXCR4 co-receptor as well as mixed and dual tropic virus. Only the R5 virus that uses CCR5 to gain access to the cell can be treated with maraviroc. Maraviroc is metabolized by CYP450 liver enzymes, and the dose must be reduced when given with most protease inhibitors and increased in patients receiving the NNRTIs efavirenz, and etravirine. Maraviroc is generally well tolerated.

**X. INTEGRASE INHIBITOR USED TO TREAT HIV INFECTION: RALTEGRAVIR**

Raltegravir [ral-TEG-ra-veer] is the first of a new class of antiretroviral drugs known as integrase inhibitors. Raltegravir specifically inhibits the final step in integration of strand transfer of the viral DNA into our own host cell DNA. Raltegravir has a half-life of approximately 9 hours and is, therefore, dosed twice daily. The route of metabolism is UGT1A1-mediated glucuronidation and, therefore, drug interactions with CYP450 inducers, inhibitors, or substrates do not occur. Raltegravir is well tolerated, with nausea, headache, and diarrhea as the most com- mon side effects. More serious side effects reported include elevated CK (creatine kinase) with muscle pain and rhabdomyolysis and possible depression with suicidal ideation. In combination with other antiret- roviral agents, raltegravir is approved for both initial therapy of both treatment-naïve patients as well as treatment-experienced patients with evidence of viral replication despite ongoing antiretroviral drug therapy.