Antiviral Drugs 2

V. OVERVIEW OF THE TREATMENT FOR HIV INFECTION

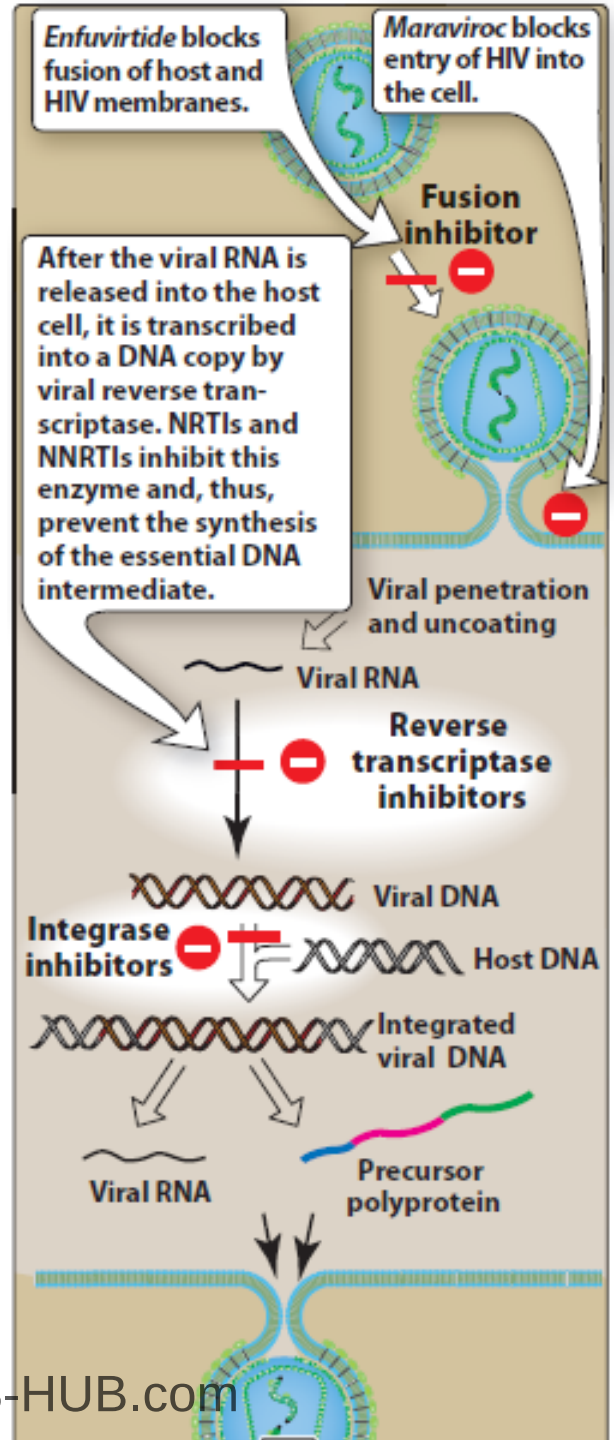
- Prior to approval of *zidovudine* in 1987, treatment of HIV infections focused on decreasing the occurrence of opportunistic infections that caused a high degree of morbidity and mortality in AIDS patients.

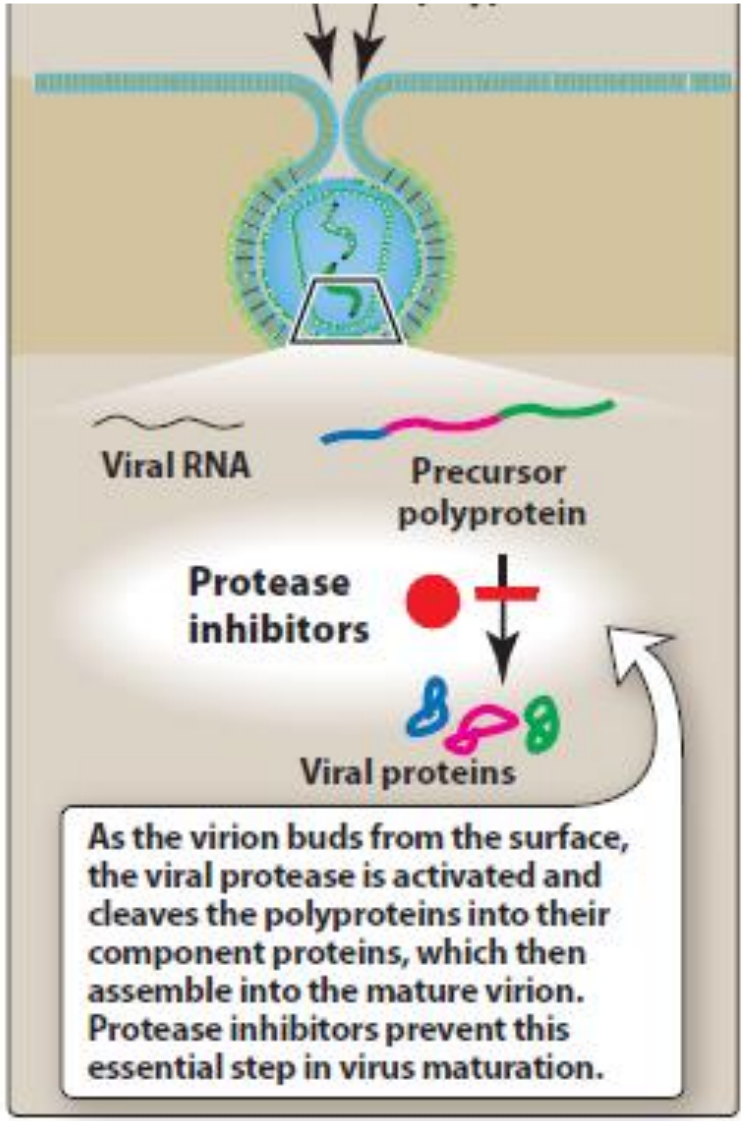
- Today, the viral life cycle is understood, and a combination of drugs is used to suppress replication of HIV and restore the number of CD4 cells and immunocompetence to the host.

- This multidrug regimen is commonly referred to as “highly active antiretroviral therapy,” or HAART

- There are five classes of antiretroviral drugs, each of which targets one of the four viral processes.
  - nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs),
  - nonnucleoside reverse transcriptase inhibitors (NNRTIs),
  - protease inhibitors (PIs),
  - entry inhibitors,
  - integrase inhibitors.

- The preferred initial therapy is a combination of two NRTIs with a PI, an NNRTI, or an integrase inhibitor.





FOR HIV: FIXED DOSE COMBINATIONS

Lamivudine + abacavir EPZICOM
Emtricitabine + tenofovir TRUVADA
Zidovudine + lamivudine COMBIVIR
Efavirenz + emtricitabine + tenofovir ATRIPLA
Rilpivirine + tenofovir + emtricitabine COMPLERA
Zidovudine + lamivudine + abacavir TRIZIVIR
Elvitegravir + cobicistat + tenofovir + emtricitabine STRIBILD

- Selection of the appropriate combination is based on
  - 1) avoiding the use of two agents of the same nucleoside analog;
  - 2) avoiding overlapping toxicities
  - 3) patient factors, such as disease symptoms and concurrent illnesses;
  - 4) impact of drug interactions; and
  - 5) ease of adherence to the regimen.

- The goals of therapy are to
  - maximally and durably suppress HIV RNA replication,
  - restore and preserve immunologic function, to
  - reduce HIV-related morbidity and mortality, and to
  - improve quality of life.

VI. NRTIS USED TO TREAT HIV INFECTION

- **1. Mechanism of action:**
- NRTIs are analogs of native ribosides (nucleosides or nucleotides containing ribose), which all lack a 3’-hydroxyl group.

- Once they enter cells, they are phosphorylated by cellular enzymes to the corresponding triphosphate analog, which is preferentially incorporated into the viral DNA by RT.

- Because the 3′-hydroxyl group is not present, a 3′,5′-phosphodiester bond between an incoming nucleoside triphosphate and the growing DNA chain cannot be formed, and DNA chain elongation is terminated.

- Affinities of the drugs for many host cell DNA polymerases are lower than they are for HIV RT, although mitochondrial DNA polymerase γ appears to be susceptible at therapeutic concentrations.

- **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.

Adverse effects:

- Many of the toxicities of the NRTIs are believed to be due to inhibition of the mitochondrial DNA polymerase in certain tissues.

- As a general rule, the dideoxynucleosides, such as *didanosine* and *stavudine*, have a greater affinity for the mitochondrial DNA polymerase, leading to toxicities such as peripheral neuropathy, pancreatitis, and lipoatrophy.

- All of the NRTIs have been associated with a potentially fatal liver toxicity

Resistance:

- NRTI resistance is well characterized, and the most common resistance pattern is a mutation at viral RT codon 184.

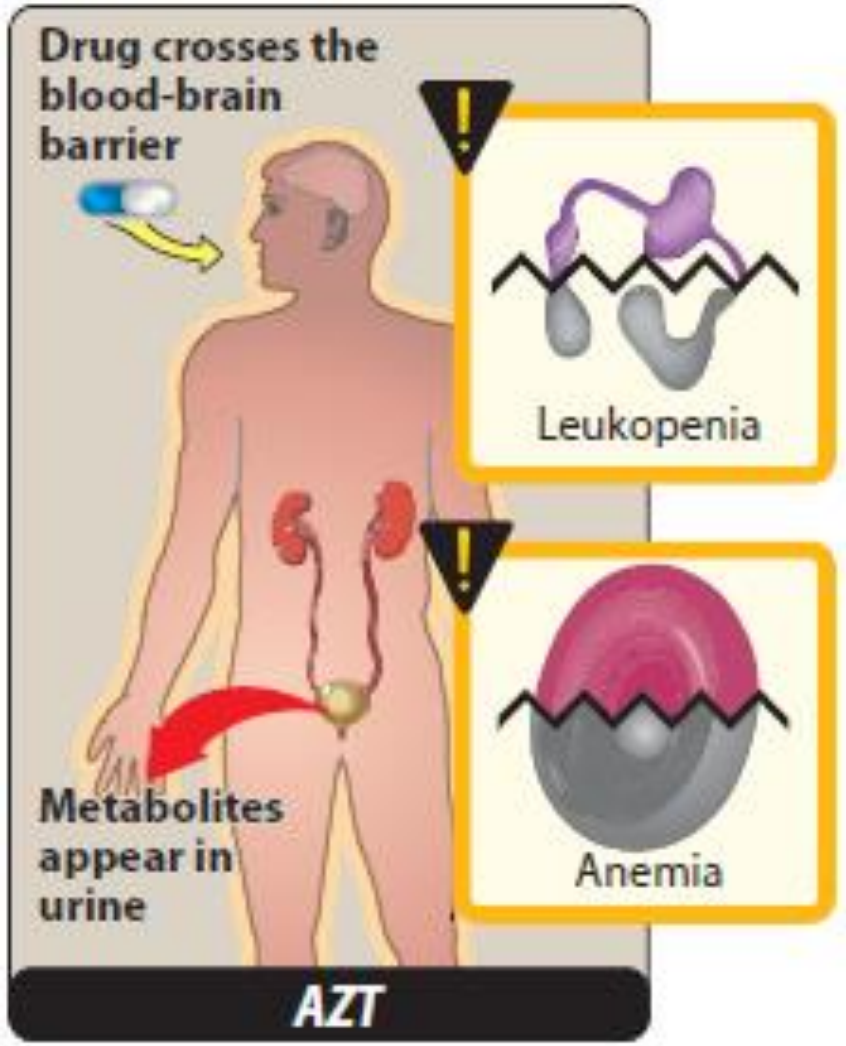
- Because cross-resistance and antagonism occur between agents of the same analog class (thymidine, cytosine, guanosine, and adenosine), concomitant use of agents with the same analog target is contraindicated

- (for example, *zidovudine* and *stavudine* are both analogs of thymidine and should not be used together).

B. Zidovudine (AZT)

- *Zidovudine*, a pyrimidine analog, was the first agent available for the treatment of HIV infection.
- *AZT* is approved for the treatment of HIV in children and adults and to prevent perinatal transmission of HIV.
- It is also used for prophylaxis in individuals exposed to HIV infection.
- *AZT* is well absorbed after oral administration.

- Penetration across the blood–brain barrier is excellent, and the drug has a half-life of 1 hour with an intracellular half-life of approximately 3 hours.
- Most of the drug is glucuronidated by the liver and then excreted in the urine
- *AZT* is toxic to bone marrow and can cause anemia and neutropenia.
- Both *stavudine* and *ribavirin* are activated by the same intracellular pathways and should not be given with *AZT*.



C. Stavudine (d4T)

- *Stavudine* is an analog of thymidine approved for the treatment of HIV.
- The drug is well absorbed after oral administration, and it penetrates the blood–brain barrier.
- The majority of the drug is excreted unchanged in the urine. Renal impairment interferes with clearance.

- *Stavudine* is a strong inhibitor of cellular enzymes such as the DNA polymerases, thus reducing mitochondrial DNA synthesis and resulting in toxicity.

- The major and most common clinical toxicity is peripheral neuropathy, along with headache, rash, diarrhea, and lipoatrophy.

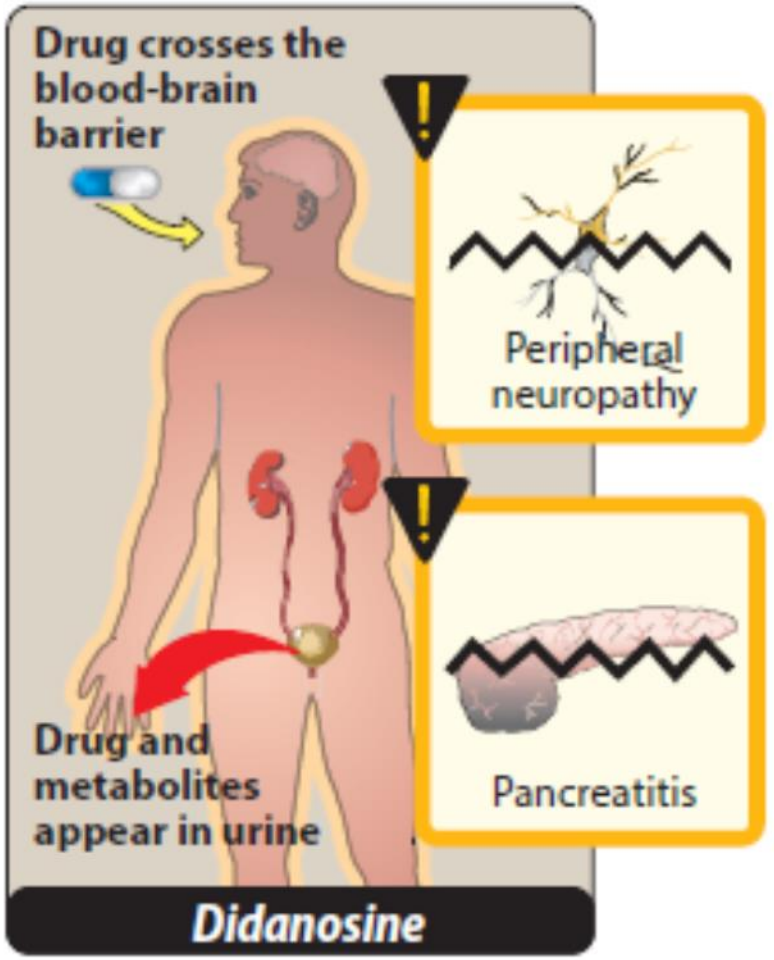
D. Didanosine (ddI)

- Upon entry of *didanosine* (*dideoxyinosine*, *ddI*) into the host cell, *ddI* is biotransformed into dideoxyadenosine triphosphate (ddATP)

- 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*.

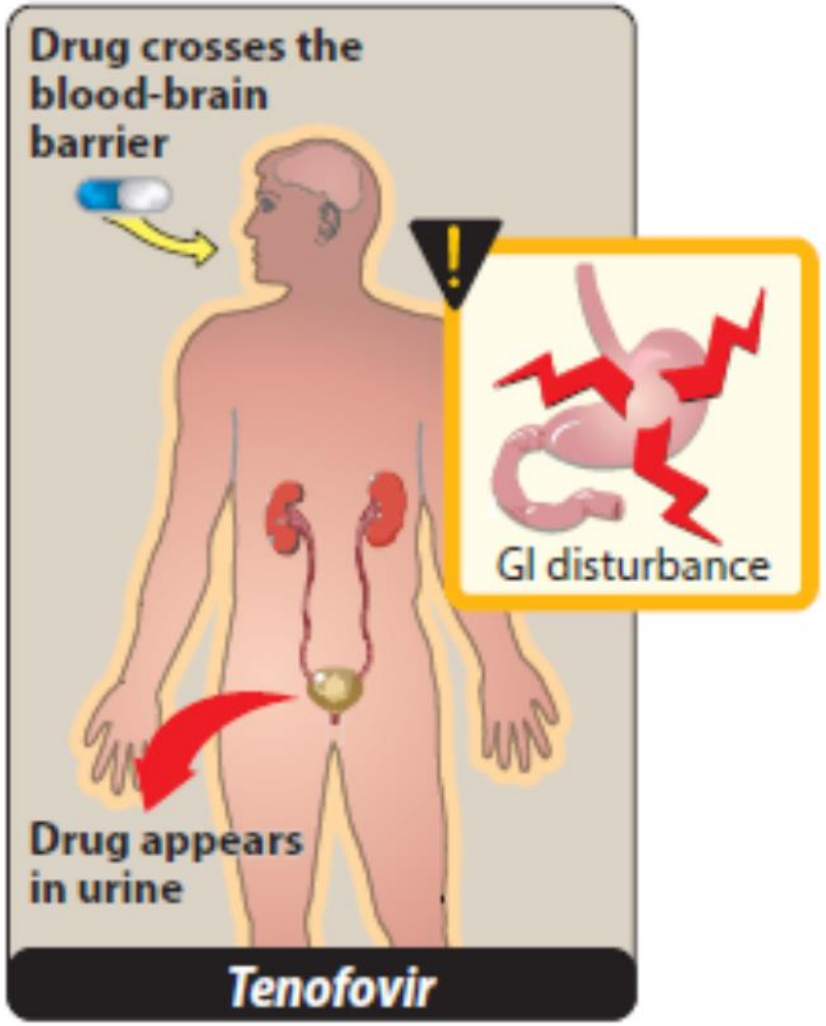
- Most of the parent drug appears in the urine.
- Pancreatitis, which may be fatal, is a major toxicity with *ddI* and requires monitoring of serum amylase.
- The dose-limiting toxicity of *ddI* is peripheral neuropathy.
- Because of its similar adverse effect profile, concurrent use of *stavudine* is not recommended.



E. Tenofovir (TDF)

- *Tenofovir* is a nucleotide analog, namely, an analog of adenosine 5’-monophosphate.
- It is converted by cellular enzymes to the diphosphate, which is the inhibitor of HIV RT.
- *Tenofovir* has a long half-life, allowing once-daily dosing.
- Most of the drug is recovered unchanged in the urine. Serum creatinine must be monitored and doses adjusted in renal insufficiency.

- GI complaints are frequent and include nausea and bloating.
- The drug should not be used with *ddI* due to drug interactions.
- *Tenofovir* decreases the concentrations of the PI *atazanavir* such that *atazanavir* must be boosted with *ritonavir* if these agents are given concurrently.



F. Lamivudine (3TC)

- *Lamivudine* [la-MI-vyoo-deen] (*2′-deoxy-3′-thiacytidine, 3TC*) inhibits the RT of both HIV and HBV.

- However, it does not affect mitochondrial DNA synthesis or bone marrow precursor cells, resulting in less toxicity.

- It has good bioavailability on oral administration, depends on the kidney for excretion, and is well tolerated.

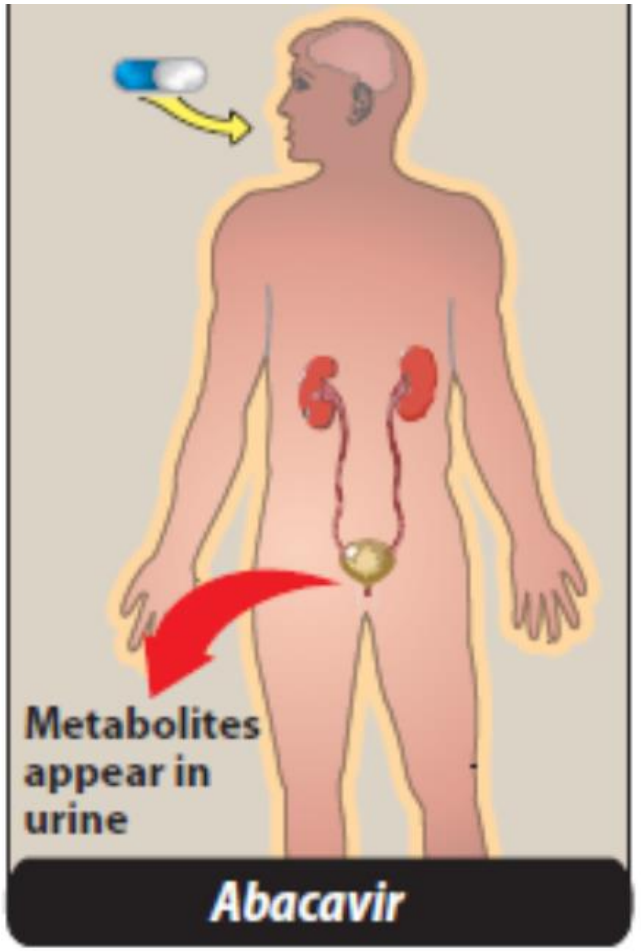
G. Emtricitabine (FTC)

- a fluoro derivative of *lamivudine,*
- inhibits both HIV and HBV RT.
- *Emtricitabine* is well absorbed after oral administration.
- 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 has no significant interactions with other drugs.
- Headache, diarrhea, nausea, and rash are the most common adverse effects.
- *Emtricitabine* may also cause hyperpigmentation of the soles and palms.
- Withdrawal of *emtricitabine* in HBVinfected patients may result in worsening hepatitis.

H. Abacavir (ABC)

- is a guanosine analog.
- *Abacavir* is well absorbed orally.
- It is metabolized to inactive metabolites via alcohol dehydrogenase and glucuronyl transferase, and metabolites appear in the urine .



- Common adverse effects include GI disturbances, headache, and dizziness.

- Approximately 5% of patients exhibit the "hypersensitivity reaction," which is usually characterized by drug fever, plus a rash, GI symptoms, malaise, or respiratory distress.

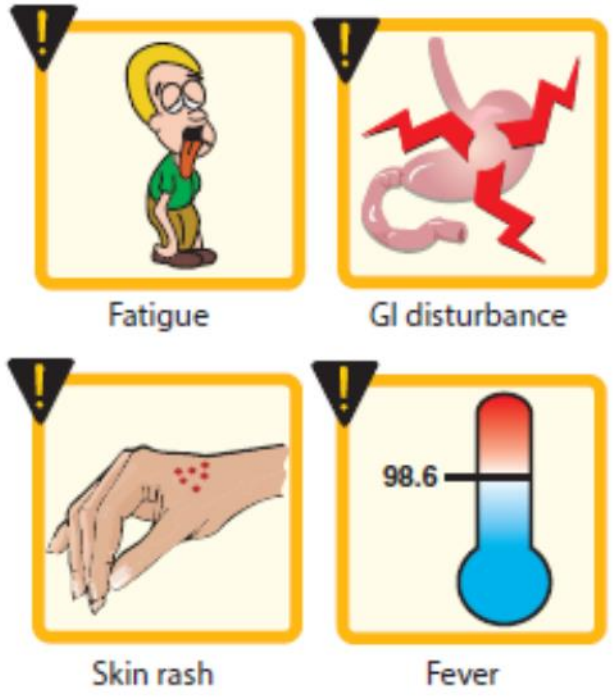


Figure 45.21
Hypersensitivity reactions to *abacavir*.

- Sensitized individuals should *never* be rechallenged because of rapidly appearing, severe reactions that may lead to death.

- A genetic test (HLA-B*5701) is available to screen patients for the potential of this reaction.

VII. NNRTIS USED TO TREAT HIV INFECTION

- NNRTIs are highly selective, noncompetitive inhibitors of HIV-1 RT.
- They bind to HIV RT at an allosteric hydrophobic site adjacent to the active site, inducing a conformational change that results in enzyme inhibition.
- They do not require activation by cellular enzymes.
- These drugs have common characteristics that include
  - cross-resistance with other NNRTIs,
  - drug interactions,
  - high incidence of hypersensitivity reactions, including rash.

A. Nevirapine (NVP)

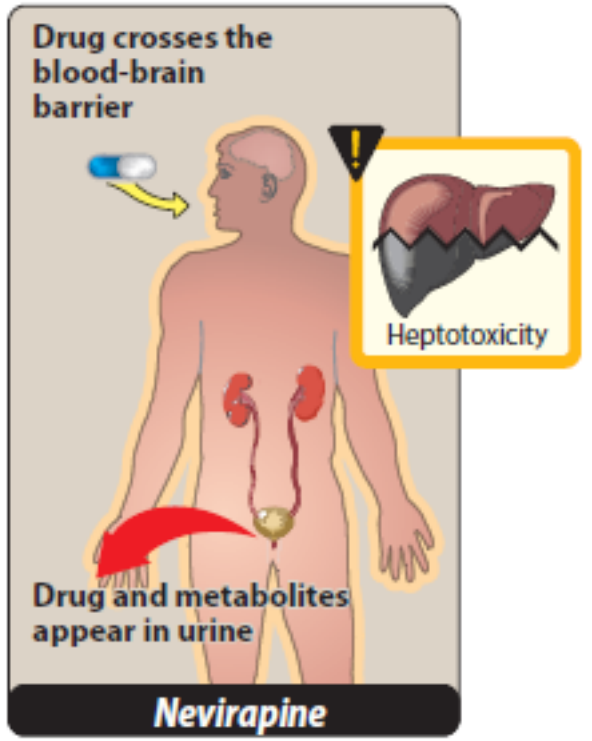
- *Nevirapine* is used in combination with other antiretroviral drugs for the treatment of HIV infections in adults and children.

- Due to the potential for severe hepatotoxicity, *nevirapine* should not be initiated in women with CD4 cell counts greater than 250 cells/mm3 or in men with CD4 cell counts greater than 400 cells/mm3.

- *Nevirapine* is well absorbed orally.

- The lipophilic nature of *nevirapine* accounts
- for its wide tissue distribution, including the CNS, placenta (transfers to the fetus), and breast milk.

- *Nevirapine* is metabolized via hydroxylation and subsequent glucuronide conjugation. The metabolites are excreted in urine



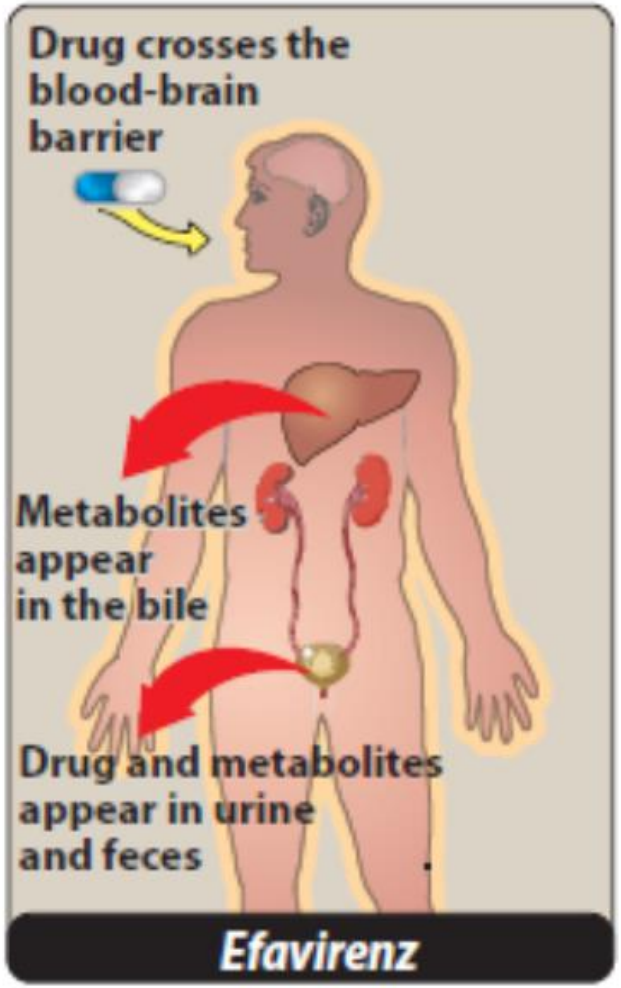
- *Nevirapine* is an inducer of the CYP3A4 isoenzymes, and it increases the metabolism of a number of drugs, such as oral contraceptives, *ketoconazole, methadone, quinidine,* and *warfarin*.

- The most frequently observed adverse 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.

C. Efavirenz (EFV)

- *Efavirenz* is the preferred NNRTI.
- Following oral administration, *efavirenz* is well distributed, including to the CNS.
- Most of the drug is bound to plasma albumin at therapeutic doses.
- A half-life of more than 40 hours accounts for its recommended once-a-day dosing.



- The drug is a potent inducer of CYP450 enzymes.
- Most adverse effects are tolerable and are associated with the CNS,
  - including dizziness,
  - headache,
  - vivid dreams, and
  - loss of concentration.
- Nearly half of patients experience these complaints, which usually resolve within a few weeks. Rash is another common adverse effect.
- *Efavirenz* should be avoided in pregnant women.

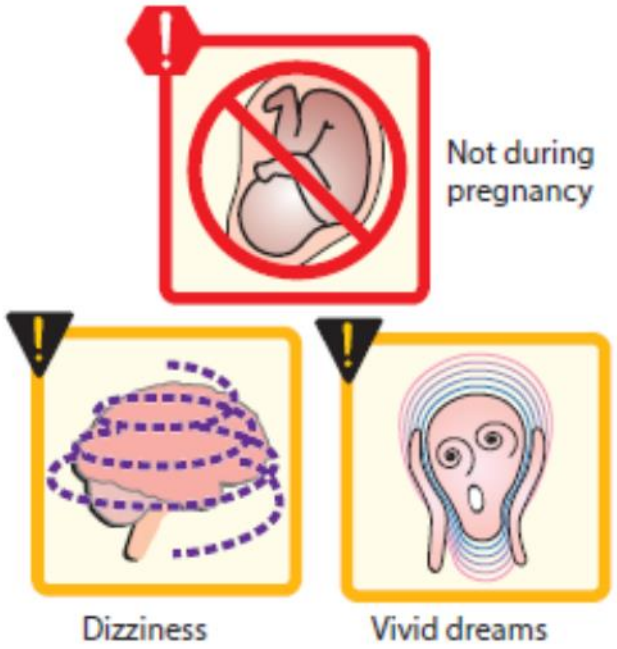


Figure 45.25
Adverse reactions of *efavirenz*.

D. Etravirine (ETR)

- *Etravirine* is a second-generation NNRTI active against many HIV strains that are resistant to the first-generation NNRTIs.
- The bioavailability of *etravirine* 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 and excreted mainly in the feces.

- 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 adverse effect.

E. Rilpivirine (RPV)

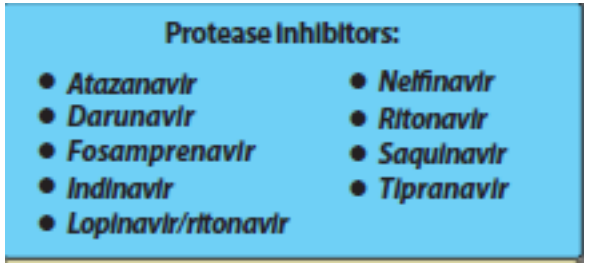
- *Rilpivirine* is approved for HIV treatment-naïve patients in combination with other antiretroviral agents.
- It is administered orally once daily with meals and has pH-dependent absorption.
- Therefore, it should not be coadministered with proton pump inhibitors and requires dose separation from H2-receptor antagonists and antacids.
- *Rilpivirine* is highly bound to plasma proteins, primarily albumin.

- *Rilpivirine* is a substrate of CYP3A4, and coadministration with other medications that are inducers or inhibitors of this isoenzyme may affect levels of the drug.

- *Rilpivirine* is mainly excreted in the feces.

- The most common adverse reactions are depressive disorders, headache, insomnia, and rash.

VIII. 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 leveling off

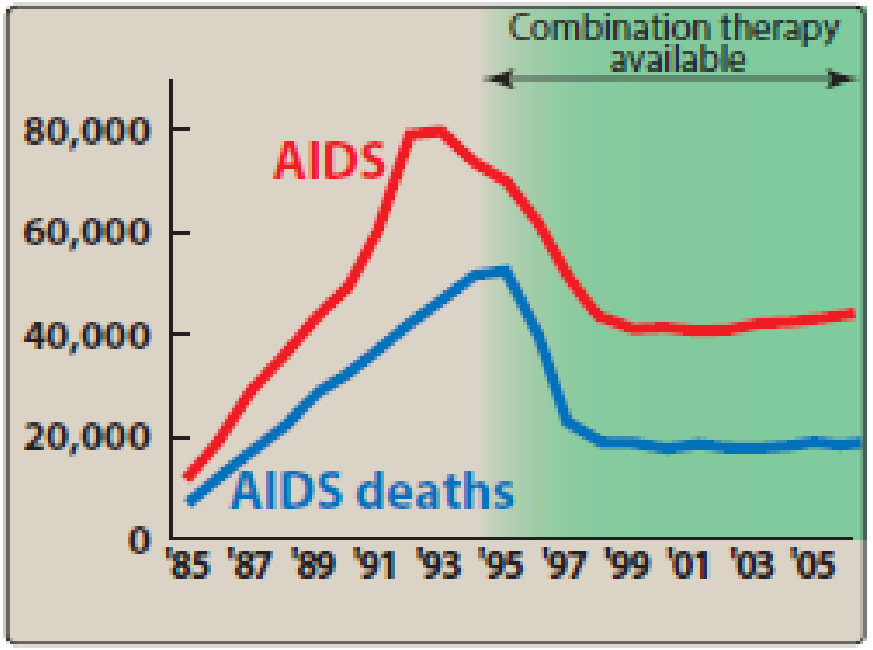


Figure 45.26

Estimated number of AIDS cases and deaths due to AIDS in the United States. *Green* background indicates years in which combination antiretroviral therapy came into common usage.

1. Mechanism of action:

- All of the drugs in this group are reversible inhibitors of the HIV aspartyl protease (retropepsin), which is the viral enzyme responsible for cleavage of the viral polyprotein into a number of essential enzymes (RT, protease, and integrase) and several structural proteins.

- The inhibition prevents maturation of the viral particles and results in the production of noninfectious virions.

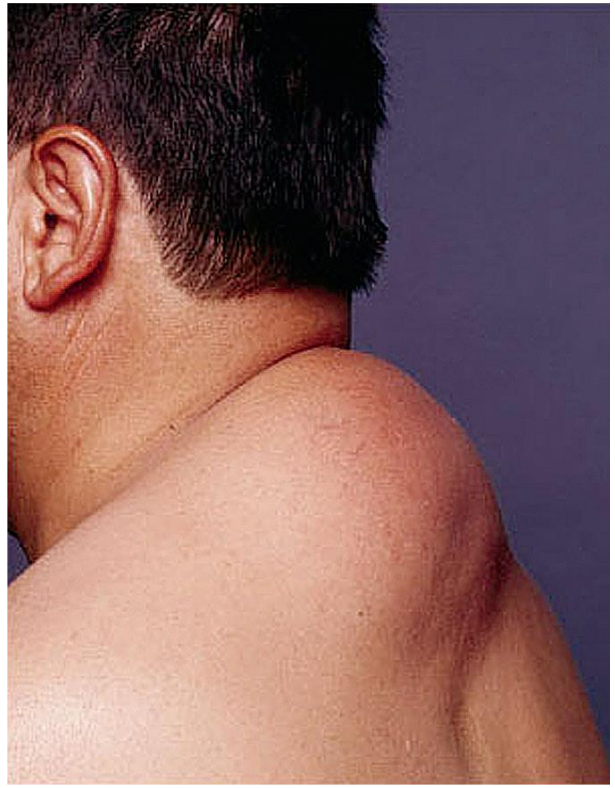
2. Pharmacokinetics:

- High-fat meals substantially increase the bioavailability of some PIs, such as *nelfinavir* and *saquinavir*, whereas the bioavailability of *indinavir* is decreased, and others are essentially unaffected.

- The HIV PIs are all substantially bound to plasma proteins.

- All are substrates for the CYP3A4 isoenzyme, and individual PIs are also metabolized by other CYP450 isoenzymes.
- Metabolism is extensive, and very little of the PIs are excreted
- unchanged in urine.

3. Adverse effects:



- PIs commonly cause nausea, vomiting, and diarrhea
- Disturbances in glucose and lipid metabolism.
- Chronic administration results in fat redistribution, including loss of fat from the extremities, fat accumulation in the abdomen and the base of the neck “buffalo hump” and breast enlargement.
- These physical changes may indicate to others that an individual is HIV infected.

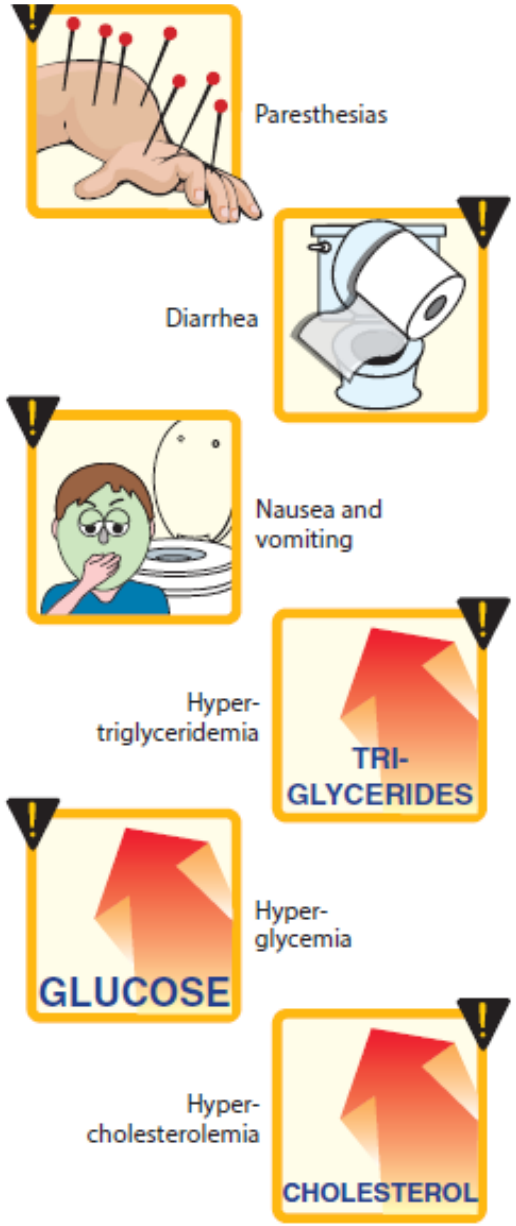
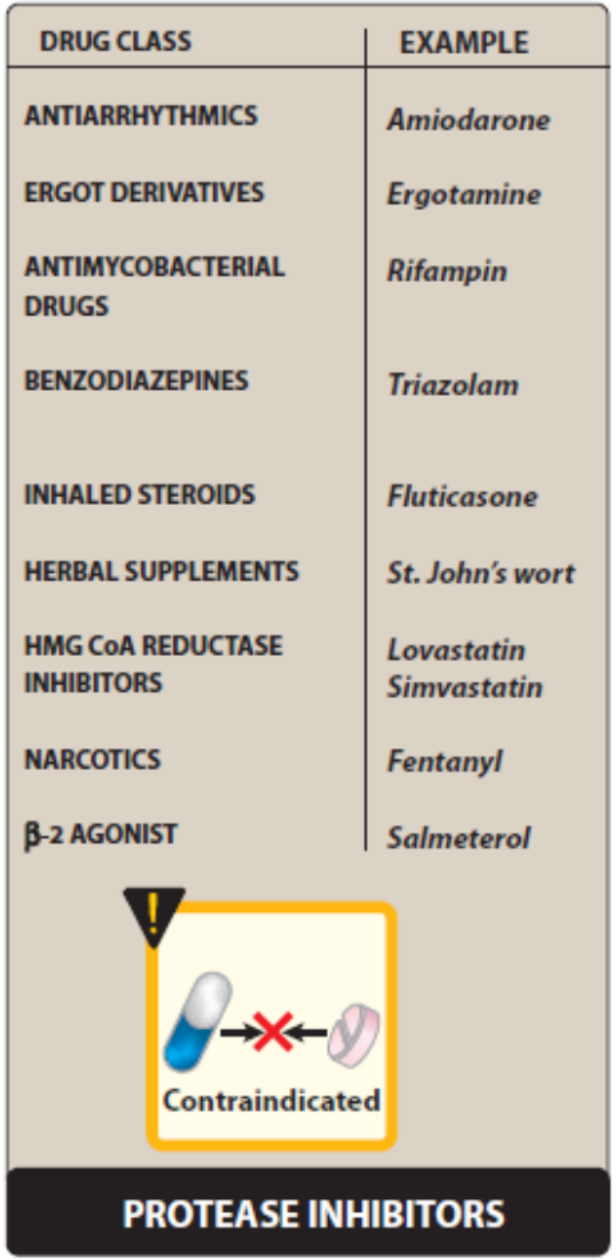


Figure 45.27
Some adverse effects of the HIV protease inhibitors.

4. Drug interactions:

- Drug interactions are a common problem for all PIs, because they are not only substrates but also potent inhibitors of CYP450 isoenzymes.

- Examples of potentially dangerous interactions from drugs that are contraindicated with PIs include
  - rhabdomyolysis from *simvastatin* or *lovastatin*,
  - excessive sedation from *midazolam* or *triazolam*, and
  - respiratory depression from *fentanyl* .



- Other drug interactions that require dosage modification and cautious use include *warfarin*, *sildenafil*, and *phenytoin*.

- In addition, inducers of CYP450 isoenzymes may decrease PI plasma concentrations to suboptimal levels, contributing to treatment failures. Thus, drugs such as *rifampin* and *St. John's wort* are also contraindicated with PIs.

DRUG CLASS	EXAMPLE
ANTICOAGULANTS	*Warfarin*
ANTICONVULSANTS	*Phenytoin*
ANTIFUNGALS	*Voriconazole*
ANTIMYCOBACTERIALS	*Rifabutin*
ERECTILE DYSFUNCTION AGENTS	*Sildenafil* *Tadalafil* *Vardenafil*
LIPID-LOWERING AGENTS	*Atorvastatin*
NARCOTICS	*Methadone*

PROTEASE INHIBITORS

Figure 45.30
Drugs that require dose modifications or cautious use with any protease inhibitor.

5. Resistance:

- Resistance occurs as an accumulation of stepwise mutations 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 inhibitors emerge.

- Suboptimal concentrations of PI result in the more rapid appearance
- of resistant strains.

B. Ritonavir (RTV)

- *Ritonavir* is no longer used as a single PI but, instead, is used as a pharmacokinetic enhancer or “booster” of other PIs.

- *Ritonavir* is a potent inhibitor of CYP3A, and concomitant *ritonavir* administration at low doses increases the bioavailability of the second PI, often allowing for longer dosing intervals.

- The resulting higher Cmin levels of the “boosted” PI also help to prevent the development of resistance. Therefore, “boosted” PIs are preferred agents in the HIV treatment guidelines.

C. Saquinavir (SQV)

- To maximize bioavailability, *saquinavir* is always given along with a low dose of *ritonavir.*
- High-fat meals also enhance absorption.
- Elimination of *saquinavir* is primarily by hepatic metabolism, followed by biliary excretion.
- Its half-life is 7 to 12 hours, requiring twice-daily dosing.
- Increased levels of hepatic aminotransferases have been.

D. Indinavir (IDV)

- *Indinavir* is well absorbed orally and, of all the PIs, is the least protein bound.
- *Indinavir* has the shortest half-life of the PIs, at 1.8 hours.
- Boosting with *ritonavir* overcomes this problem and also permits twice-daily dosing.
- *Indinavir* is extensively metabolized, and the metabolites are excreted in the feces and urine.

- The dosage should, therefore, be reduced in the presence of hepatic insufficiency.
- GI symptoms and headache are the predominant adverse effects.
- *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.

Other PIs

- **Nelfinavir** **(not extensively metabolized by CYP3A)**
- **Fosamprenavir**
- **Lopinavir**
- **Atazanavir**
- **Tipranavir** **inhibits HIV protease in viruses that are resistant to the other PIs**
- **Darunavir**

ENTRY INHIBITORS

- **A. Enfuvirtide**
- **B. Maraviroc**

A. Enfuvirtide

- *Enfuvirtide* [en-FU-veer-tide] 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 polypeptide 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.

B. Maraviroc

- *Maraviroc* [ma-RAV-i-rok] is another entry inhibitor. Because it is well absorbed orally, it is formulated as an oral tablet.

- *Maraviroc* blocks the CCR5 coreceptor that works together with gp41 to facilitate HIV entry through the membrane into the cell.

- *Maraviroc* is metabolized by CYP450 liver enzymes, and the dose
- must be reduced when given with most PIs or strong CYP450 inhibitors.

- Conversely, it should be increased in patients receiving *efavirenz*, *etravirine*, or strong CYP450 inducers. *Maraviroc* is generally well tolerated.

INTEGRASE INHIBITORS

- The integrase strand transfer inhibitors (INSTIs), often called integrase inhibitors, work by inhibiting the insertion of proviral DNA into the host cell genome.

- The active site of the integrase enzyme binds to the host cell DNA and includes two divalent metal cations that serve as chelation targets for the INSTIs.

- As a result, when an INSTI is present, the active site of the enzyme is occupied and the integration process is halted.

- The INSTIs are generally well tolerated.
- Importantly, INSTIs are subject to chelation interactions with antacids resulting in significant reductions in bioavailability.
- Resistance to INSTIs occurs with single-point mutations within the integrase gene.

A. Raltegravir

- In combination with other antiretroviral agents, *raltegravir* is approved for both initial therapy of treatment-naïve patients and treatment-experienced patients with evidence of viral replication despite ongoing antiretroviral drug therapy.

- *Raltegravir* has a half-life of approximately 9 hours and is dosed twice daily.

- *Raltegravir* is well tolerated, although serious adverse effects, such as elevated creatine kinase with muscle pain and rhabdomyolysis and possible depression with suicidal ideation, have been reported.

B. Elvitegravir

- *Elvitegravir* is currently only available in a fixeddose combination single tablet containing *tenofovir*, *emtricitabine*, *elvitegravir*, and *cobicistat*.

- [Note: *Cobicistat* is a pharmacokinetic enhancer or booster drug used in combination treatments of HIV since it inhibits CYP3A enzymes.]

- The half-life of *elvitegravir* is 3 hours when administered alone, but increases to approximately 9 hours when boosted by *cobicistat*. Pharmacokinetic boosting of *elvitegravir* allows it to be dosed orally once daily with food.

C. Dolutegravir

- *Dolutegravir* is rapidly absorbed following oral administration.
- *Dolutegravir* is highly protein bound and undergoes extensive hepatic metabolism.
- Potent inducers and/or inhibitors of UGT1A1 and CYP3A4 can significantly alter *dolutegravir* concentrations.
- *Dolutegravir* can be given once daily without the use of a pharmacokinetic booster in patients without preexisting INSTI resistance.