abacavir only be used as a last resort and with close monitoring in patients who are HLA-B5701-positive. Abacavir-resistant strains of HIV are typically also resistant to lamivudine, emtricitabine, didanosine, and zalcitabine. In randomized trials abacavir was found to be inferior to tenofovir in patients with baseline HIV RNA levels >100,000 copies/mL. Abacavir is formulated alone as well as in combination with lamivudine, with zidovudine and lamivudine or with lamivudine and dolutegravir.

Tenofovir disoproxil fumarate (9-[(*R*)-2-[[bis[[(isopropoxycarbonyl)oxy]methoxy]phosphinyl]methoxy]propyl]adenine fumarate [1:1]) is an acyclic nucleoside phosphonate diester analogue of adenosine monophosphate. It undergoes diester hydrolysis to form the nucleoside monophosphate (nucleotide) tenofovir and is the first nucleotide analogue to be licensed for treatment of HIV infection. It is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection and in combination with emtricitabine for pre-exposure prophylaxis for HIV-1 prevention in populations at high risk of HIV infection. HIV isolates with increased resistance typically express a K65R mutation in reverse transcriptase and a three- to fourfold reduction in sensitivity to tenofovir. Tenofovir is primarily eliminated by the kidneys, and renal impairment including a Fanconi-like syndrome with hypophosphatemia may occur. Tenofovir is contraindicated in patients with renal impairment. An investigational prodrug analogue with less renal toxicity, tenofovir alafenamide fumarate is currently in clinical trials. Small but statistically significant decreases in bone mineral density have been noted in patients receiving tenofovir. Coadministration of tenofovir with didanosine leads to a 60% increase in didanosine levels, and thus doses of didanosine need to be adjusted and patients monitored carefully if these two drugs are used in combination. In addition, CD4+ T cell increases may be blunted in patients on this combination. Coadministration of tenofovir with atazanavir leads to a decrease in atazanavir levels, and thus low-dose ritonavir (see below) needs to be added when these drugs are used in combination. Tenofovir is available alone and coformulated with emtricitabine, emtricitabine and efavirenz, emtricitabine and rilpivirine, or emtricitabine, elvitegravir and cobicistat.

Nevirapine, delavirdine, efavirenz, *etravirine*, and *rilpivirine* are nonnucleoside inhibitors of the HIV-1 reverse transcriptase and are licensed for use in combination with nucleoside analogues for the treatment of HIV-infected adults. Coformulations that include efavirenz or nevirapine are available (Table 226-22). These agents inhibit reverse transcriptase by binding to regions of the enzyme outside the active site and causing conformational changes in the enzyme that render it inactive. Although these agents are active in the nanomolar range, they are also very selective for the reverse transcriptase of HIV-1, have no activity against HIV-2, and, when used as monotherapy, are associated with the rapid emergence of drug-resistant mutants (Table 226-21; **Fig. 226-46**). Efavirenz and rilpivirine are administered once a day, nevirapine and etravirine twice a day, and delavirdine three times a day. All are associated with the development of a maculopapular rash, generally seen within the first few weeks of therapy. While it is possible to treat through this rash, it is important to be sure that one is not dealing with a more severe eruption such as Stevens-Johnson syndrome by looking carefully for signs of mucosal involvement, significant fever, or painful lesions with desquamation. Severe, life-threatening, and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure, have been reported in patients treated with nevirapine. There is a suggestion that this is more common in women with higher CD4+ T cell counts. Many patients treated with efavirenz note a feeling of light-headedness, dizziness, or out of sorts following the initiation of therapy. Some complain of vivid dreams. These symptoms tend to disappear after several weeks of therapy. Aside from difficulties with dreams, taking efavirenz at bedtime may minimize the side effects. Efavirenz may cause fetal harm when administered during the first trimester to a pregnant woman. Women of childbearing potential should undergo pregnancy testing prior to initiation of efavirenz. Efavirenz is commonly used in combination with two nucleoside analogues as part of initial treatment regimens. Etravirine is a diarylpyrimidine derivative currently licensed for treatment of HIV infection in combination with other agents. In contrast to the other nonnucleoside reverse transcriptase inhibitors, which all exhibit cross-resistance, etravirine may be active against strains of HIV that are resistant to other nonnucleoside reverse transcriptase inhibitors. Among its side effects are rash, headache, nausea, and diarrhea. Rilpivirine is effective across a broad range of NNRTI-resistant viruses and shares cross-resistance with etravirine. It is better tolerated and a has higher rate of virologic failure than efavirenz, particularly in those with HIV RNA >100,000. It is only available as part of a combination regimen with tenofovir and emtricitabine.

The HIV-1 protease inhibitors (saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, fosamprenavir, lopinavir/ritonavir, atazanavir, tipranavir, and darunavir) are a major part of the therapeutic armamentarium of antiretrovirals. When used as part of initial regimens in combination with reverse transcriptase inhibitors, these agents have been shown to be capable of suppressing levels of HIV replication to under 50 copies/mL in the majority of patients for a minimum of 5 years. As in the case of reverse transcriptase inhibitors, resistance to protease inhibitors can develop rapidly in the setting of monotherapy, and thus these agents should be used only as part of combination therapeutic regimens. A summary of known resistance mutations for protease inhibitors is shown in Fig. 226-46. The protease inhibitors preferred for use according to the DHHS Panel on the use of antiretroviral drugs are ritonavir (only as a pharmacokinetic enhancer), atazanavir, and darunavir.

Ritonavir was the first protease inhibitor for which clinical efficacy was demonstrated. In a study of 1090 patients with CD4+ T cell counts <100/μL who were randomized to receive either placebo or ritonavir in addition to any other licensed medications, patients receiving ritonavir had a reduction in the cumulative incidence of clinical progression or death from 34% to 17%. Mortality decreased from 10.1% to 5.8%. At full doses, ritonavir is poorly tolerated. Among the main side effects are nausea, diarrhea, abdominal pain, hyperlipidemia, and circumoral paresthesia. Ritonavir has a high affinity for several isoforms of cytochrome P450 (3A4, 2D6), and its use can result in large increases in the plasma concentrations of drugs metabolized by these pathways. Among the agents affected in this manner are most other protease inhibitors, macrolide antibiotics, *R*-warfarin, ondansetron, rifabutin, most calcium channel blockers, glucocorticoids, and some of the chemotherapeutic agents used to treat KS and/or lymphomas. In addition, ritonavir may increase the activity of glucuronyltransferases, thus decreasing the levels of drugs metabolized by this pathway. Overall, great care must be taken when prescribing additional drugs to patients taking protease inhibitors in general and ritonavir in particular. As mentioned above, the pharmacodynamic boosting property of ritonavir, seen with doses as low as 100–200 mg once or twice a day, is often used in the setting of cART for HIV infection to derive more convenient regimens. For example, when given with low-dose ritonavir, saquinavir and indinavir can be given on twice-a-day schedules and taken with food.

Atazanavir is an azapeptide inhibitor of the HIV-1 protease that was licensed in 2003. An advantage of atazanavir is that total cholesterol and triglyceride levels do not increase as much with atazanavir as with other protease inhibitors. This coupled with the fact that it can be given on a once-daily schedule made atazanavir a popular component of initial treatment regimens following its licensure. Atazanavir is associated with increases in serum bilirubin, renal stones, and prolongations of the ECG PR interval. Atazanavir-resistant isolates emerging in previously treatment-naïve individuals frequently harbor an I50L substitution. This mutation in some instances is associated with increased sensitivity to other protease inhibitors. Atazanavir requires an acidic gastric pH for absorption, and its use in combination with a proton pump inhibitor is contraindicated due to concerns about absorption. Atazanavir is an inhibitor of cytochrome P3A, and its use may be associated with