patients achieved a reduction in HIV RNA viral loads to <50 copies/mL. Studies in treatment-naïve patients demonstrated efficacy superior to lopinavir/ritonavir-containing regimens but inferior to dolutegravir. Skin rash, which may be severe, is seen in 7% of patients and may be related to the sulfonamide moiety contained in the molecule. GI intolerance and headache are the other most frequent side effects.

Entry inhibitors act by interfering with the binding of HIV to its receptor or co-receptor or by interfering with the process of fusion (see above). The first drug in this class to be licensed was the fusion inhibitor *enfuvirtide*, or T-20, followed by the CCR5 antagonist *maraviroc*. A variety of additional small molecules that bind to HIV-1 co-receptors are currently in clinical trials.

Enfuvirtide is a linear 36-amino-acid synthetic peptide with the *N* terminus acetylated and the *C* terminus a carboxamide. It is composed of naturally occurring L-amino acid residues and interferes with the fusion of the viral and cellular membranes by binding to the HR1 region in the gp41 subunit of the HIV-1 envelope. This binding interferes with the coil-coil interaction required to approximate the viral envelope and the host cell membrane during the process of viral fusion. Enfuvirtide was licensed in 2003 for treatment of HIV-1 infection in combination with other antiretroviral agents in treatment-experienced patients with ongoing viral replication despite antiretroviral therapy. Enfuvirtide is not active against HIV-2. Enfuvirtide-resistant isolates of HIV exhibit amino acid changes in positions 36–45 of gp41. In two independent studies, patients who had persistent viremia despite prior treatment with agents from all three available classes of drugs were randomized to receive an individualized regimen (based on prior treatment history and resistance profile) with or without enfuvirtide. The change in plasma HIV-1 RNA from baseline was ~1 log greater (–1.53 vs –0.68) in patients randomized to receive enfuvirtide. Among the drawbacks of this agent are the requirement for twice-a-day injection, the occurrence of injection-site reactions in close to 100% of patients, and an increase in bacterial pneumonia in the enfuvirtide-treated patients compared with the control patients (4.68 vs 0.61 events per 100 patient-years) in the phase III studies.

Maraviroc is a CCR5 antagonist that interferes with HIV binding at the stage of co-receptor engagement. It was licensed in 2007 for treatment of HIV infection in combination with other agents in treatment-experienced patients infected with only CCR5-tropic (R5) virus resistant to multiple agents. The license was extended in 2009 to include treatment-naïve patients with R5 virus. A co-receptor tropism assay should be performed if one is considering the use of maraviroc to ensure that the potential patient is only harboring R5 viruses. In phase III trials of treatment-experienced patients randomized to receive optimal therapy plus maraviroc or placebo, 61% of patients randomized to maraviroc achieved HIV RNA levels <400 copies/mL compared with 28% of patients randomized to placebo. An allergic reaction–associated hepatotoxicity has been reported with maraviroc. Among the most common side effects of maraviroc are dizziness due to postural hypotension, cough, fever, colds, rash, muscle and joint pain, and stomach pain. Maraviroc is a substrate of CYP3A and Pgp, and the recommend dose varies depending on concomitant medications. In combination with nucleoside analogues, tipranavir/ritonavir, enfuvirtide, and/or nevirapine, the dose is 300 mg twice daily. In the presence of CYP3A inhibitors, such as most protease inhibitors, the dose is 150 mg twice daily. In the presence of CYP3A inducers such as efavirenz, the dose is 600 mg twice daily.

Integrase inhibitors act by blocking the action of the HIV integrase enzyme and thus preventing integration of the HIV provirus into the host cell genome. They are among the most potent and safest of the antiretroviral drugs and frequently part of initial combination regimens. The three licensed integrase inhibitors are raltegravir, elvitegravir and dolutegravir.

Raltegravir is an inhibitor of the viral enzyme integrase and the first of this class to be approved. It acts by interfering with the binding of the preintegration complex to host DNA and as such is referred to as an integrase strand transfer inhibitor (INSTI). Raltegravir was approved in 2007 for treatment of HIV infection in combination with other agents in treatment-experienced patients, and the approval was extended in 2009 to include treatment-naïve patients. Raltegravir exhibits a wide range of activity against HIV-1 and HIV-2, including viruses with multiple resistance mutations to other classes of drugs. As with several other compounds, resistance to raltegravir comes at the expense of replicative fitness. In two phase III studies in which 436 patients with 3-class antiretroviral drug resistance were randomized to an optimized background regimen with raltegravir or placebo, 76% of patients receiving raltegravir achieved HIV RNA levels <400 copies/mL compared with 41% of patients randomized to the placebo arm. In contrast to many other antiretroviral drugs the side-effect profile of raltegravir is minimal, with similar side-effect profiles noted for the raltegravir and placebo groups.

Elvitegravir is an integrase inhibitor that was approved in 2012 as part of a fixed-dose combination tablet also containing tenofovir, emtricitabine, and cobicistat (Stribild). The cobicistat acts much in the same way as low-dose ritonavir to boost the concentrations of elvitegravir by inhibiting CYP3A such that once-a-day dosing of Stribild is sufficient. Elvitegravir demonstrates cross-resistance with raltegravir. In two randomized, controlled trials, elvitegravir was found to be noninferior to efavirenz in one study and noninferior to atazanavir/ritonavir in the other. The most common side effects experienced with elvitegravir are diarrhea, nausea, upper respiratory infection, and headache. The cobicistat component of the fixed-dose tablet inhibits tubular secretion of creatinine, resulting in increases in serum creatinine, and is not recommended for patients with estimated creatinine clearances <70 mL/min.

Dolutegravir was approved in 2013 for use as part of a combination regimen in either treatment-naïve or -experienced patients. It comes as a 50-mg tablet and is given once daily in treatment-naïve patients and twice daily in treatment-experienced patients. Isolates of HIV that have developed resistance to raltegravir or elvitegravir may still be sensitive to dolutegravir. Its main side effects are insomnia and headache. In two randomized, controlled trials it has been shown to be superior to either efavirenz (n = 833) or darunavir/ritonavir (n = 484) in combination with nucleos(t)ide analogues due to lower rates of discontinuation. In a third trial of 822 patients it was shown to be noninferior to raltegravir.

PRINCIPLES OF THERAPY

The principles of therapy for HIV infection have been articulated by a panel sponsored by the U.S. Department of Health and Human Services as a working group of the NIH Office of AIDS Research Advisory Council. These principles are summarized in **Table 226-23**. As noted in these guidelines, cART of HIV infection does not lead to eradication or cure of HIV. The single possible exception to this is an individual with HIV infection who received an allogeneic stem cell transplant for treatment of acute myelogenous leukemia. His conditioning regimen included cytotoxic chemotherapy, total-body irradiation, and antithymocyte immunoglobulin. The donor cells were homozygous for the CCR5Δ32 mutation (see above) and thus resistant to HIV infection. Despite cART being stopped the day of the transplant, the patient has exhibited no signs of active HIV infection for more than 8 years.

Treatment decisions must take into account the fact that one is dealing with a chronic infection that requires daily therapy. While early therapy is generally the rule in infectious diseases, immediate treatment of every HIV-infected individual upon diagnosis may not be prudent, and therapeutic decisions must take into account the balance between risks and benefits. Patients initiating antiretroviral therapy must be willing to commit to life-long treatment and understand the importance of adherence to their prescribed regimen. The importance of adherence is illustrated by the observation that treatment interruption is associated with rapid increases in HIV RNA levels, rapid declines in CD4+ T cell counts, and an increased risk of clinical progression. While it seems reasonable to assume that the complications associated with cART could be minimized by