TABLE 226-23 PRINCIPLES OF THERAPY OF HIV INFECTION

1. Ongoing HIV replication leads to immune system damage, progression to AIDS, and systemic immune activation.
2. Plasma HIV RNA levels indicate the magnitude of HIV replication and the rate of CD4+ T cell destruction. CD4+ T cell counts indicate the current level of competence of the immune system.
3. Maximal suppression of viral replication is a goal of therapy; the greater the suppression the less likely the appearance of drug-resistant quasispecies.
4. The most effective therapeutic strategies involve the simultaneous initiation of combinations of effective anti-HIV drugs with which the patient has not been previously treated and that are not cross-resistant with antiretroviral agents that the patient has already received.
5. The antiretroviral drugs used in combination regimens should be used according to optimum schedules and dosages.
6. The number of available drugs is limited. Any decisions on antiretroviral therapy have a long-term impact on future options for the patient.
7. Women should receive optimal antiretroviral therapy regardless of pregnancy status.
8. The same principles apply to children and adults. The treatment of HIV-infected children involves unique pharmacologic, virologic, and immunologic considerations.
9. Compliance is an important part of ensuring maximal effect from a given regimen. The simpler the regimen, the easier it is for the patient to be compliant.

Source: Modified from *Principles of Therapy of HIV Infection*, USPHS, and the Henry J. Kaiser Family Foundation.

intermittent treatment regimens designed to minimize exposure to the drugs in question, all efforts to do so have paradoxically been associated with an increase in serious adverse events in the patients randomized to intermittent therapy, suggesting that some "non-AIDS-associated" serious adverse events such as heart attack and stroke may be linked to HIV replication. Thus, unless contraindicated for reasons of toxicity, patients started on cART should remain on cART.

At present, the U.S. Department of Health and Human Services Guidelines panel recommends that everyone with HIV infection be treated with cART. The evidence for this is strongest for patients with CD4+ T cell counts <350/μL. Clinical trials are underway to more carefully determine the benefit of initiating therapy in patients with CD4+ T cell counts ≥350/μL. In addition, one may wish to administer a 6-week course of therapy to uninfected individuals immediately following a high-risk exposure to HIV. The combination of tenofovir and emtricitabine is also indicated for pre-exposure prophylaxis in individuals at high risk of HIV infection. For patients diagnosed with an opportunistic infection and HIV infection at the same time, one may consider a 2- to 4-week delay in the initiation of antiretroviral therapy during which time treatment is focused on the opportunistic infection. This delay may decrease the severity of any subsequent immune reconstitution inflammatory syndrome by lowering the antigenic burden of the opportunistic infection. For patients with advanced HIV infection (CD4+ <50 cells/μL), however, cART should be initiated as soon as possible.

Once the decision has been made to initiate therapy, the health care provider must decide which drugs to use as the first regimen. The decision regarding choice of drugs not only will affect the immediate response to therapy but also will have implications regarding options for future therapeutic regimens. The initial regimen is usually the most effective insofar as the virus has yet to develop significant resistance. HIV is capable of rapidly developing resistance to any single agent, and therapy must be given as a multidrug combination. Given that patients can be infected with viruses that harbor drug resistance mutations, it is recommended that a viral genotype be done prior to the initiation of therapy to optimize the selection of antiretroviral agents. The combination regimens currently recommended for initial therapy in any treatment-naïve patient are listed in **Table 226-24**. Other regimens containing abacavir and rilpivirine may be appropriate for patients with HIV RNA levels <100,000 copies/mL. It is currently unclear whether treatment-naïve individuals with

TABLE 226-24 INITIAL COMBINATION REGIMENS FOR ANY TREATMENT-NAÏVE PATIENT REGARDLESS OF HIV RNA LEVEL OR CD4 COUNT

I. Non-Nucleoside Reverse Transcriptase Inhibitor Based:
Efavirenz + tenofovir + emtricitabine
II. Protease Inhibitor Based:
Atazanavir/ritonavir + tenofovir + emtricitabine
Darunavir/ritonavir + tenofovir + emtricitabine
III. Integrase Inhibitor Based:
Dolutegravir + tenofovir + emtricitabine
Raltegravir + tenofovir + emtricitabine

Source: *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents*, USPHS.

<50 copies/mL of HIV RNA benefit from cART. Following the initiation of therapy one should expect a rapid, at least 1-log (tenfold) reduction in plasma HIV RNA levels within 1–2 months and then a slower decline in plasma HIV RNA levels to <50 copies/mL within 6 months. During this same time there should be a rise in the CD4+ T cell count of 100–150/μL that is also particularly brisk during the first month of therapy. Subsequently, one should anticipate a CD4+ T cell count increase of 50–100 cells/year until numbers approach normal. Many clinicians feel that failure to achieve these endpoints is an indication for a change in therapy. Other reasons for a change in therapy include a persistently declining CD4+ T cell count, a consistent increase in HIV RNA levels to >200 copies/mL, clinical deterioration, or drug toxicity **(Table 226-25)**. As in the case of initiating therapy, changing therapy may have a lasting impact on future therapeutic options. When changing therapy because of treatment failure (clinical progression or worsening laboratory parameters), it is important to attempt to provide a regimen with at least two new active drugs. This decision can be guided by resistance testing (see below). In the patient in whom a change is made for reasons of drug toxicity, a simple replacement of one drug is reasonable. It should be stressed that in attempting to sort out a drug toxicity it may be advisable to hold all therapy for a period of time to distinguish between drug toxicity and disease progression. Drug toxicity will usually begin to show signs of reversal within 1–2 weeks. Prior to changing a treatment regimen because of drug failure, it is important to ensure that the patient has been adherent to the prescribed regimen. As in the case of initial therapy, the simpler the new therapeutic regimen, the easier it is for the patient to be compliant. Plasma HIV RNA levels should be monitored every 3–6 months during therapy and more frequently if one is contemplating a change in regimen due to an increase in viral load or immediately following a change in regimen.

In order to determine an optimal therapeutic regimen for initial therapy or for a patient on a failing regimen, one may attempt to measure antiretroviral drug susceptibility through genotyping or phenotyping of HIV quasispecies and to determine adequacy of dosing through measurement of drug levels. Genotyping may be done through cDNA sequencing. Phenotypic assays typically measure the

TABLE 226-25 INDICATIONS FOR CHANGING ANTIRETROVIRAL THERAPY IN PATIENTS WITH HIV INFECTION[a]

Less than a 1-log drop in plasma HIV RNA by 4 weeks following the initiation of therapy
A reproducible significant increase (defined as threefold or greater) from the nadir of plasma HIV RNA level not attributable to intercurrent infection, vaccination, or test methodology
Persistently declining CD4+ T cell numbers
Clinical deterioration
Side effects

[a]Generally speaking, a change should involve the initiation of at least two drugs felt to be effective in the given patient. The exception to this is when change is being made to manage toxicity, in which case a single substitution is reasonable.

Source: *Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents*, USPHS.