HIV has become a chronic disease that almost always will require antiretroviral medications. Given our current knowledge and limited alternative interventions, antiretroviral therapy is likely to be lifelong and once started should not be stopped.

The management of HIV-infected patients has become increasingly complex not only because of expanding choices for therapy but also because of the emergence of resistance and the longer-term toxicity of antiretroviral agents.

The unprecedented benefits resulting from highly active antiretroviral therapy (HAART) have been well described. (1) Therapeutic options continue to expand with the development of new drugs and new strategies for using them. The benefit of HAART extends beyond the patients and to issues around public health. The correlation between HIV-1 RNA and HIV transmission has been well established, and it is assumed that by suppressing HIV replication, antiretroviral therapy (ART) also decreases the risk of transmission. (2) However, this benefit must be weighed against the potential risk for transmission of drug-resistant virus by patients failing therapy. In an adherent patient population, the benefits of therapy would likely outweigh this risk.

A broad array of antiretroviral combinations is likely to be needed to address obstacles to achieving sustained virologic suppression for decades. Some of these obstacles include adherence, tolerability, drug resistance, cost, and issues related to particular subgroups of patients such as women who desire pregnancy and those co-infected with tuberculosis, hepatitis B, or hepatitis C. New agents and combinations of new and recently approved agents are likely to play an important role in addressing many of these issues, providing potential alternatives for HIV-infected patients.

The decision to initiate antiretroviral therapy should be based on the degree of immunosuppression, as indicated primarily by the CD4+ cell count and the risk of disease progression, and to a lesser degree by the plasma HIV-1 RNA and rate of CD4+ cell count decline. (3) Patients should not begin therapy until they understand the reason for treatment, appreciate the importance of adherence, and are motivated to begin. There is growing rationale for considering earlier therapy in motivated patients who are likely to be adherent.

Studies continue to demonstrate a higher mortality rate in HIV-infected patients, even when the CD4+ cell counts are between 200 – 350. The guidelines from USA-DHHS (4) ISA – USA (5) and UK were recently revised following evidence from these studies showing the benefit of early treatment. These benefits include decreased mortality and morbidity from both opportunistic and non-opportunistic conditions such as cardiovascular, renal, (6) hepatic diseases, and malignancies (7). (SMART study, (8) STACCATO trial, PISCIS Spanish cohort (9)) Earlier initiation of therapy is also associated with a better response to therapy, including a greater likelihood of CD4+ cell count normalization.

There is widespread agreement that symptomatic patients, patients with AIDS, and asymptomatic patients with CD4+ cell count below 200 require antiretroviral therapy. The timing of antiretroviral therapy in chronically infected asymptomatic patients remains unclear, but the latest guidelines move aggressively towards earlier initiation of antiretroviral therapy, prior to a decline in CD4 cell count to less than 350/μL (10). Initiation of therapy in asymptomatic patients with CD4 cell count above 350/μL should be strongly considered where there are correlates of faster HIV disease progression such as high viral loads >100,000 copies/mL or rapid CD4 decline, over 100 per year. Patients with high risk for cardiovascular disease, co-infected with hepatitis B or C, HIV-associated nephropathy and pregnant women should be treated irrespective of CD4 cell

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count. Treatment of acute HIV infection is only considered for special circumstances. (11)

Current options for initial therapy are highly effective, durable, convenient, and well tolerated and show minimal evidence of long-term toxicity. The simplicity of the regimen further enhances adherence and therefore diminishes resistance. The 3 drugs approved since 2006, maraviroc, the first drug to target the CCR5 co-receptor, raltegravir, the first drug in the integrase inhibitor class and (12, 13) etravirine, (14, 15) a second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) with clear activity against some NNRTI-resistant viruses has presented us with more treatment options, for the second, third, and fourth lines of treatment.

There is little change in the recommendations for an initial regimen in patients who are not infected with resistant virus. The first-line choice is a backbone of either an NNRTI (efavirenz) (16) or a ritonavir-boosted protease inhibitor (PI), (17) combined with a dual nucleoside reverse transcriptase inhibitor (NRTI) (tenofovir/emtricitabine or abacavir/lamivudine). Prescribing complex regimens dosed more frequently than twice daily is no longer necessary and once-daily regimens are now standard. The choice of regimen should be based on consideration of potency, tolerability, convenience, long-term toxicity, baseline drug resistance and co-morbid conditions. The goal of therapy in both treatment-naive and experienced patients is to maintain an undetectable HIV-1 RNA with an ultrasensitive assay (less than 50 copies/ml) because anything less is associated with decreased durability and the development of drug resistance. Treatment failure should be promptly identified and managed to reduce building up of mutations, which will further compromise options for management.

First-line failure of a NNRTI-based regimen should be treated with two active NRTIs plus a ritonavir-boosted protease inhibitor (PI). Depending on the NNRTI mutations present, one might want to consider use of etravirine. Failure of a PI-based regimen can be more complicated, depending upon the genetic barriers. If caught early, changing the NRTI component to two active drugs might be sufficient to save the regimen. However, as resistance points accumulate, one should consider use of darunavir or tipranavir. The new class of drugs such as Maraviroc and raltegravir add to the choice of drugs in PI failures or in multiclass failures. One change in the recommendations is a greater emphasis on virologic suppression below 50 copies/ml in treatment experienced patients. This is only achievable due to the availability of new classes of ARV and drugs with higher genetic barrier and different mutation patterns in existing classes.

Broader application of these guidelines in resource-limited countries is hampered by the availability of drugs, monitoring of HIV makers, lack of infrastructure and the cost of follow-up regimens. Ability to sequence therapy is dependent on the availability of entire regimens. Unless these issues are addressed it will not be possible to implement the current guidelines and the gap between the developed countries and resource-limited countries will continue widen.

References


