Treatment of advanced HIV infection

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Keywords: efavirenz, protease inhibitors, advanced HIV infection

One of the few aspects of HIV infection for which there is universal agreement is that patients with advanced HIV disease, such as those with a history of opportunistic diseases or severe immunological impairment (<100 CD4 lymphocytes/mm3), should receive antiretroviral treatment.1 It is ironic, however, that for this group of patients, who undoubtedly need treatment, there are virtually no controlled data to help clinicians choose the optimal combination of antiretroviral drugs.

Expert recommendations on initial therapy favour the use of regimens that include a single (or boosted) protease inhibitor, or a non-nucleoside reverse transcriptase inhibitor,1,2 without any specific preference based on the immunological status of the patient. Nevertheless, there is widespread belief among clinicians treating HIV infection in the higher efficacy of regimens containing protease inhibitors for patients with very low CD4 lymphocyte counts. Surprisingly, the notion that protease inhibitors are the drugs of choice for very immuno-suppressed patients is not supported by the available evidence. During the highly active antiretroviral therapy (HAART) era, clinical trials evaluating antiretroviral regimens have systematically excluded patients with recent opportunistic diseases and/or a very low CD4 cell count. In an overview of 23 trials involving triple therapy in antiretroviral-naive adults, the mean baseline CD4 cell count was 375 cells/mm3 (ranging from 185 to 473 cells/mm3), and very few patients had <100 CD4 cells/mm3.3 The lack of studies comparing the efficacy of different antiretroviral regimens in the treatment of advanced HIV infection has favoured treatment based more on opinion than on accurate evidence.

The ‘belief’ in the higher efficacy of protease inhibitors in the treatment of patients with advanced HIV infection is based on the personal experiences acquired by many clinicians during the initial years of the ‘HAART era’, when a dramatic decline in clinical progression and HIV-related deaths followed the utilization of protease inhibitor-based regimens.4 However, it should be recognized that the clinical benefits seen at that time were due not only to the introduction of protease inhibitors but also to the emergent strategy of using triple antiretroviral combinations.

A few years after the advent of protease inhibitors, a large clinical trial (DMP-226 006 study)5 showed that a regimen sparing of protease inhibitors, but which included efavirenz, had superior antiviral efficacy in naive patients than the at that time, ‘standard’ regimen that included indinavir (64% versus 43% patients with a viral load <50 copies/mL at week 48, intention-to-treat, missing = failure). The superior antiviral activity of efavirenz over another protease inhibitor (nelfinavir) was also demonstrated in nucleoside-experienced patients.6 In addition to clinical trials, a number of cohort studies, in real-life conditions, have repeatedly confirmed the superior effectiveness of efavirenz over protease inhibitor-based regimens in antiretroviral-naive patients.7-9 It is important to note that all the aforementioned clinical trials and cohort studies were performed mostly in patients with moderately advanced HIV infection, with mean CD4 cell counts ranging from 172 to 350 cells/mm3.5,7-9

Several studies have shown that when antiretroviral drugs are compared in the setting of advanced HIV infection, differences in antiviral activity increase. For example, a recent trial comparing nelfinavir with lopinavir/ritonavir showed greater differences favouring lopinavir, in patients with a CD4 cell count <50 cells/mm3.10 Another clinical trial, comparing abacavir- and indinavir-based therapy, showed overall equivalence, but differences became apparent when both drugs were compared in the high baseline HIV RNA stratum (31% versus 45%, reaching <50 copies/mL on an intention-to-treat analysis).11 These two studies clearly show that antiretroviral drugs need to be tested in a wide range of CD4 cell and HIV viral loads. Importantly, the 006 trial showed that efavirenz was superior to indinavir in the subgroup of patients with baseline viral loads >100,000 copies/mL (66% versus 34%, with viral loads <50 copies/mL at week 48, intention-to-treat, missing = failure).5

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Until recently, there were very limited data regarding the efficacy of efavirenz in patients with low CD4 cell counts. The 006 study excluded patients with a baseline CD4 cell count <50 cells/mm³. In a substudy analysing those patients with baseline CD4 counts between 50 and 100 cells/mm³, there was a trend favouring efavirenz. Given the lack of data from controlled trials, it is very important to accumulate evidence from cohort studies that include patients with advanced HIV infection.

In a recent retrospective study, we have analysed, for the first time, therapeutic outcomes of efavirenz-based versus protease inhibitor-based HAART, in a cohort of 310 HIV-infected adults naive to antiretrovirals and profoundly immunosuppressed. All of them had <100 CD4 lymphocytes/mm³. In an intention-to-treat analysis, 69% of 92 patients treated with efavirenz–HAART had reached viral load <50 copies/mL at 48 weeks. This result is not worse than the result expected in naive patients receiving efavirenz-based treatment. It is remarkable that quantitative increases in CD4 cell counts were comparable to the CD4 cell count increases reported in clinical trials and cohort studies of patients treated with efavirenz-based HAART. The clinical effectiveness of efavirenz-based HAART was also corroborated: only one patient died during the first year of follow-up, there were very few opportunistic diseases (new or relapses) and 11 patients with either Kaposi sarcoma, progressive multifocal leucoencephalopathy or intestinal cryptosporidiasis experienced complete resolution or clinical improvement. Overall results of our retrospective cohort showed that virological outcomes were better with efavirenz than with protease inhibitors. Time to treatment failure and time to virological failure were significantly longer for efavirenz-treated patients. In addition, there were no statistically significant differences in CD4 cell count recovery after 1 year of treatment. This cohort study clearly supports the use of efavirenz for the treatment of advanced HIV-infected patients.

There are very few available comparisons among efavirenz and boosted protease inhibitors in non-advanced HIV-infected patients, and no data at all in the setting of advanced immunosuppression. Efavirenz has been compared with saquinavir/ritonavir in a once-daily regimen, and to amprenavir/ritonavir. In both studies, efavirenz-based therapy showed superior antiviral activity and was better tolerated than the boosted protease inhibitor. However, there are no data comparing efavirenz with lopinavir/ritonavir. Lopinavir/ritonavir has convincingly demonstrated its efficacy, even in patients with HIV RNA levels >100,000 copies/mL, or CD4 counts <50 cells/mm³. Therefore, further studies should compare the two most potent drugs available: lopinavir/ritonavir and efavirenz, both in advanced and non-advanced HIV infection.

In summary, although limited, current evidence does not support the use of non-boosted protease inhibitors for the treatment of advanced HIV infection. In this hard-to-treat population, clinicians should favour using drugs that have proven efficacy in the setting of low CD4 cell counts and/or high viral loads. The old controversy, about the comparative merits of protease inhibitors versus non-nucleosides, should no longer be discussed as if all the drugs within each family were identical. We are now in the seventh year of the HAART era. Enough clinical trials and cohort studies have shown that there are important differences among specific antiretroviral drugs. Expert guidelines should incorporate available data to individualize more precisely the level of recommendation for each drug in the same group. For patients with advanced HIV infection, evidence is starting to show that highly potent drugs, such as efavirenz or lopinavir/ritonavir, might be more appropriate than non-boosted protease inhibitors.

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