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Efavirenz

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Efavirenz is an orally active non-nucleoside reverse transcriptase inhibitor (NNRTI). A series of phase II and III studies have examined the use of efavirenz in combination with the protease inhibitors indinavir or nelfinavir, and with the nucleoside reverse transcriptase inhibitors (NRTIs) zidovudine, lamivudine and stavudine in antiretroviral therapy-experienced and -naive patients. Although these studies have demonstrated superior virological and immunological responses when compared with protease inhibitor monotherapy or double NRTI therapy, they have generally been of relatively short duration (typically 16 to 36 weeks). To date, longer term follow-up data (>60 weeks) are available from only 1 controlled clinical trial.

A wide range of CNS symptoms have been reported in patients receiving efavirenz, including light-headedness, abnormal dreams, insomnia, somnolence, inability to concentrate and dysphoria. These adverse events can be associated with a high discontinuation rate, although many cases resolve within a few weeks of initiating treatment or with a dose modification. Other adverse effects associated with the use of this drug in combination regimens are diarrhoea and maculopapular rash.

To date, the more widespread use of other NNRTIs has been limited by the rapid development of *in vitro* and *in vivo* viral resistance, sometimes within only a few days of initiation of monotherapy. Although the resistance profile of efavirenz partially overlaps that of other NNRTIs, probably because of their similar modes of action, the drug does appear to be active against HIV virus containing some of the mutations that are associated with high-level resistance to nevirapine and delavirdine *in vitro*. However, certain mutations such as K103N, K101E and Y188L confer moderate to high levels of resistance to all NNRTIs.

The current standard of care for maximal and sustained suppression of HIV viral load involves treatment with a protease inhibitor and usually 2 NRTIs. Efavirenz once daily in combination with 2 NRTIs such as zidovudine and lamivudine twice daily may offer a simple, alternative, protease inhibitor-sparing regimen for antiretroviral therapy-naive asymptomatic patients. This would allow protease inhibitors to be saved for second-line therapy. Alternatively, the use of a combination treatment regimen comprising efavirenz with either indinavir or nelfinavir offers an NRTI-sparing approach in both antiretroviral therapy-naive and NRTI-experienced patients.

Efavirenz pharmacokinetic data support once-daily administration and it is hoped that with this simplified schedule, both patient compliance and virological outcome will improve. The key factor that will determine the usefulness of efavirenz as part of the HIV therapeutic armamentarium is the durability of viral suppression and the long term tolerability of different combination regimens. ▲