Correspondence

Switching from Efavirenz to Nevirapine

To the Editor—In their substudy of the AIDS Clinical Trials Group A5095, Schouten et al [1] address the relevant question of the safety of switching from one non-nucleoside reverse-transcriptase inhibitor (NNRTI) to another in the context of toxicity. The majority (71%) of patients discontinued efavirenz therapy <2 weeks before switching to nevirapine (51% <1 week). Efavirenz, like nevirapine a substrate of CYP3A4, will induce the metabolism of both drugs [2]. In this context, it seems to be counterintuitive to initiate nevirapine with the standard introduction dosage escalation scheme (2 weeks of once-daily 200-mg doses and then the standard maintenance strategy of twice-daily 200-mg doses), as done in this study. This practice might even be associated with a higher chance of virologic failure, because of suboptimal drug levels during the introduction phase [3]. Schouten et al [1] do not mention whether the relatively high failure rate (24%) at 24 weeks after switching was correlated with the interval after discontinuation of the NNRTI. More clinical data are needed to determine the optimal switching scheme.

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References


Reply to Gelinck and Burger

To the Editor—Gelinck and Burger [1] note that nevirapine (NVP) and efavirenz (EFV) are both substrates and inducers of the CYP3A4 enzyme system and question the need for a 2-week lead-in with NVP when switching from EFV. At the time that the AIDS Clinical Trials Group A5095 study performed enrollment (March 2001–November 2002), there were few data on the proper dosing strategy to use when substituting NVP for EFV. We took a conservative approach in dosing NVP at the once-daily 200-mg dose for 14 days, as recommended by the NVP package insert, when switching patients from EFV to NVP [2]. However, it may be possible to begin with the twice-daily dose of NVP when switching patients from EFV to NVP. A subsequent comparison of immediate twice-daily NVP dosing versus a 2-week period of once-daily dosing in 12 patients supported twice-daily dosing of NVP after EFV exposure [3]. It was initially observed in 2001 [4] and was confirmed in 2005 [5] that NVP, if dosed together with EFV, increases EFV clearance. However, plasma EFV clearance in subjects is variable and prolonged. Subjects with CYP2B6 GG genotype at position 516 were predicted to yield EFV protein-adjusted IC₅₀ at a concentration higher than 46.7 ng/mL for a median of 5.8 days; subjects with CYP2B6 GT genotype at position 516 were predicted to yield EFV protein-adjusted IC₅₀ at a concentration higher than 46.7 ng/mL for a median of 14 days [6]. In a cohort of 394 patients who switched from EFV to twice-daily NVP because of a change in the drug formulary, adverse event rates were similar to those in patients who initiated NVP at 200 mg once daily for the first 2 weeks [7].

This clinical decision is further complicated in that not all patients switch immediately when experiencing adverse effects from EFV. Our report was a post hoc analysis of prospective data, and the small number of subjects with virologic failure after a switch to NVP prevented us from analyzing the risk of failure as a function of time from discontinuation of EFV to the start of NVP. The long half-life of EFV probably allows for some margin of flexibility in making the clinical decision about whether should patients switch immediately or within 7–14 days, as the majority of our patients did in the A5095 study. In light of the data that have become available since our study enrolled its participants, it is reasonable to dose NVP 200 mg twice daily, with close monitoring of hepatic enzymes, when NVP is started immediately after discontinuing EFV. How-