

# ALTERNATIVE VIEWPOINTS

## Efavirenz Dose Adjustment in HIV Patients with Impaired CYP2B6 Function

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Efavirenz dosage adjustment in several patients with high EFV levels and presenting CNS toxicity have been successfully achieved in Switzerland over the past seven years but many others have not benefited from dosage reduction owing to the lack of prospective studies evaluating the safety and clinical benefit of reduced dosage regimens.

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The recent Case Report by Torno et al<sup>1</sup> comes at the right time to stimulate debate on dosage individualization in ART treatment, based on genotypic and phenotypic considerations. Efavirenz, a non-nucleoside reverse transcriptase inhibitor, is commonly used at fixed dosage regimen of 600 mg daily despite its very large interindividual variability<sup>2, 3</sup> and although dose ranging phase II studies have shown good virological efficacy at 400 mg or 200 mg daily.<sup>4</sup> Among various factors, recent evidence shows that polymorphisms of *CYP2B6*, but also of *CYP2A6* and *3A4/A5*, account for more than half of this pharmacokinetic variability, thus suggesting that unusual efavirenz concentrations

profile are strongly related to patients' genetic constitution.<sup>5, 6</sup>

As part of the Swiss HIV Cohort Study, we are prospectively following patients under ART, a number of whom are offered concentration levels determinations. In the past 16 months, 85 patients under efavirenz benefited from efavirenz blood measurements. A dosage reduction from 600 mg to 400 mg (n = 6, 7.0 %) or to 200 mg (n=3, 3.5 %) daily had been applied to those patients to either reverse SNC toxicity (n = 8) or as a preventive measure (n = 1) in presence of multiple co-morbidities. No virological breakthrough was observed for up to 7 years of follow up. Dosage adjustment based on therapeutic drug monitoring (TDM) is slowly becoming standard of care for efavirenz-containing regimens as for other antiretroviral agents in Switzerland. However, no dose reduction was made for another 21 individuals (25% of patients) with efavirenz plasma concentrations at the higher tail of the therapeutic target. This evidence points out that dosage individualization in ART treatment, based on genotypic and/or phenotypic considerations is still not widely performed; this might probably be due to a lack of prospective controlled trials evaluating the safety and clinical benefit of reduced dosage regimens. Whether the

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systematic genetic testing of *CYP2B6* might either replace or complement TDM to guide efavirenz-based therapy should also be prospected,<sup>1, 7</sup> considering the contribution of accessory pathways on efavirenz elimination and the modulation of cytochrome activity by induction or inhibition.

## References

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## Authors' Reply

We appreciate and concur with the excellent points made by Dr. Csajka and his colleagues. Prospective, controlled trials are needed to evaluate the value of genetic testing in conjunction with therapeutic drug monitoring to guide individualized dosing of efavirenz-based therapy. We applaud the efforts of Dr. Csajka and his colleagues and the Swiss HIV Cohort study in addressing this need. We eagerly await the final results of their study.

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