Optimizing efavirenz treatment: *CYP2B6* genotyping or therapeutic drug monitoring?

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Received: 27 November 2007 / Accepted: 30 November 2007 / Published online: 11 January 2008
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Cytochrome P450 2B6 (*CYP2B6*) participates in the metabolism of important therapeutic drugs such as the nonnucleoside reverse transcriptase inhibitors efavirenz and nevirapine, used in the treatment of HIV infection [1, 2]. There is significant interindividual variability in hepatic expression and catalytic activity of *CYP2B6* [3, 4]. Accordingly, the pharmacokinetics of efavirenz is characterized by high interindividual variability in plasma levels [5].

Generally, therapeutic drug monitoring is recommended for drugs with a narrow therapeutic range, whereas pharmacogenetics is aimed at personalizing prescription, which in a perfect world would render therapeutic drug monitoring unnecessary. Both approaches would possibly lead to dose reduction (and drug saving) if many individuals are exposed to supratherapeutic dosing in a given population. These conditions are partially fulfilled for efavirenz. There is a certain ground for dose adjustment by using drug levels, although there is no consensus on the association of pharmacokinetics and efavirenz neuropsychological toxicity [6–8]. However, some individuals that present significant neuropsychological toxicity may benefit from dose reduction [9, 10]. In contrast, there is a good understanding of genetic variation of *CYP2B6* that allows prediction of the pharmacokinetics of efavirenz [11–14]. Thus arises the question as to whether therapeutic drug monitoring or pharmacogenetic prediction should be used to optimize efavirenz therapy. Finally, there would be an interest to use less drug in areas such as Africa, with the goal being less expenditure and the possibility of treating more individuals; however, it would be

very difficult to implement therapeutic drug monitoring or pharmacogenetic testing in this continent.

Despite these considerations, it is in the African population that Nyakutira et al. (in this issue) investigate the usefulness of *CYP2B6* genotyping in a population pharmacokinetic model that considers gender and the presence of *CYP2B6**6 as covariates. *CYP2B6**6 is the most common diminished-function allele across human populations. The high allele frequency in blacks (49% in this study), and the fact that 50% of the participants were found to have efavirenz plasma levels above the generally recommended threshold of 4 mg/l, led the authors to propose a priori dose reduction for genetically defined poor metabolizer individuals. Nyakutira et al. propose that poor metabolizer individuals could start efavirenz treatment with a reduced daily dose of 400 mg with the goal of reducing drug use and minimizing toxicity [15].

At population level, prediction could be improved if studies included multiple additional *CYP2B6* alleles associated with diminished metabolic function (<http://www.cypalleles.ki.se>). We have previously shown that variability in efavirenz plasma levels were better explained by including in the analysis other loss-of-function alleles in addition to *CYP2B6**6 [13]. Considering variants such as the *CYP2B6**16, *18, *19, *20, *21, *27, and *28, which are relevant in the African population, would help reduce the 76% unexplained interindividual variability in efavirenz drug levels described by Nyakutira et al [15].

Would genotyping dictate how much drug reduction to effect? Recently, Gatanaga et al. performed a priori dose reduction to 400 mg in four efavirenz-naïve individuals homozygous for the *CYP2B6* *6/*6 and one individual with *6/*26. Despite the preemptive dose reduction, only one individual remained with the 400 mg dose, two individuals required a further decrease to 200 mg/day, and efavirenz

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was discontinued in two patients (in one because of intolerance) [9]. These results emphasize that despite the prediction afforded by *CYP2B6* genotyping, drug monitoring may be needed to assess the outcome of such pharmacogenetic intervention.

Should these proof-of-concept studies prompt a pharmacogenetic-guided trial for efavirenz? The usefulness of a pharmacogenetic-guided treatment strategy has been recently proved by the PREDICT-1 study, where prospective screening for *HLA-B*5701* prior to treatment with abacavir resulted in a significantly lower incidence of hypersensitivity reactions (Mallal et al., *In 4th International AIDS Conference on HIV Pathogenesis, Treatment and Prevention; Sydney 2007*). Conducting such trial may be of limited relevance in the case of efavirenz given the unclear association between drug levels and neuropsychological toxicity, the frequently time-limited nature of efavirenz adverse events, and the rarity of severe toxicity. In addition, if one is to hope for maximal predictability, the study would need to consider multiple *CYP2B6* alleles and possibly genotyping of the accessory metabolic pathways of efavirenz (di Iulio et al., *In 15th Conference on Retroviruses and Opportunistic Infections; Boston 2008*).

A formal prospective controlled clinical trial would be, however, an important step in reconciling pharmacogenetics and therapeutic drug monitoring, a way to understanding the determinants of efavirenz toxicity, and a step toward evaluating the economic value of dose reduction of antiretroviral agents.

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