Efavirenz and CYP2B6 Polymorphism: Implications for Drug Toxicity and Resistance

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(See the article by Ribaudo et al. on pages 401–7)

The brief history of pharmacogenetics has been marked by a high level of public as well as professional interest, reflecting in many respects the great promise offered by genomic approaches to biology, clinical medicine, and pharmacology over the past ~15 years. This early interest in personalized medicine was fueled by reviews [1, 2] in which it was predicted that drug prescribing could be undertaken with greater certainty and objectivity after elucidation of genetic traits determining variable drug disposition between individuals. The noted geneticist Allen Roses raised the ghost of Sir William Osler in his contemplation of the quote "If it were not for the great variability among individuals, medicine might as well be a science and not an art" (p.857) [2]. Roses’ response, made just over one hundred years later (in 2000), hinted that the end was in sight for the art of medicine, offering that “…we are on the verge of being able to identify inherited differences between individuals which can predict each patient’s response to a medicine. This ability will have far-reaching benefits in the discovery, development and delivery of medicines” (p.857) [2].

Now, more than 5 years after these observations, it is clear that much has been learned about the genetics of drug metabolism and drug disposition, and it is true that pharmacogenetic approaches to drug prescribing have proven to be selectively useful in improving drug safety and efficacy. One widely cited example, genetic testing for loss-of-function variants of thiopurine S-methyltransferase to prevent severe dose-dependent azathioprine drug toxicities (e.g., pancytopenia), has proven to be widely utilized in a recent survey of pharmacogenetic testing [3, 4]. However, when measured collectively in terms of their clinical application, these successes have remained relatively few in number. To some extent, this reflects an increased appreciation of the inherent complexity in predicting drug metabolism on the basis of single genetic traits [5], given that (1) drugs often employ multiple mechanisms of activation and catabolism, (2) genetic variation is often determined at multiple sites and/or haplotypic combinations of alleles within a gene of interest and can also be influenced by complex transcriptional signaling pathways, and (3) drug metabolism is often strongly influenced by the coadministration of prescribed, recreational, or herbal drugs. These issues are particularly relevant in the field of HIV medicine [6], in which antiretroviral regimens include combinations of drugs from multiple drug classes and there is frequent coprescription of anti-infective drugs, as well as frequent use of nonprescribed medications by patients.

It is with this history in mind that we turn our attention to the implications of a recent study investigating associations between a cytochrome P450 2B6 gene (CYP2B6) polymorphism and efavirenz metabolism, presented by Ribaudo et al. [7] as part of an analysis of the AIDS Clinical Trials Group studies A5095 and A5097s in this issue of Clinical Infectious Diseases. This study is important and timely in that it not only encompasses many of the practical issues raised by pharmacogenetic research but also identifies issues particularly pertinent and unique to the use of anti-infectives, as well as highlighting issues relevant to the clinical applicability of genetic testing. CYP2B6 is genetically polymorphic and is implicated in the metabolism of a growing number of clinically important drugs (~8% of drugs on the market are metabolized by CYP2B6). This cytochrome P isozyme is the main catalyst of efavirenz metabolism (to its inactive 8-OH metabolite), suggesting that polymorphisms in CYP2B6 may have major implications for the efficacy and toxicity of this
nonnucleoside reverse-transcriptase inhibitor (NNRTI) drug [8], which is currently recommended as an option for first-line combination therapy for HIV infection [9].

These authors have previously identified a *CYP2B6* genotype (G516T) associated with slow clearance and high plasma levels of efavirenz [8]. This association is not trivial, and, although it is clear that there is a degree of overlap between individuals who are homozygous for the variant allele (G516T) and the remainder of the population in terms of efavirenz levels, it is also apparent that the most important clinical toxicities associated with efavirenz use are dose dependent (at least in part) and are therefore influenced by the pharmacogenetics of *CYP2B6* polymorphism. This appears to be true for the CNS-related side effects of this drug (typically involving sleep disturbance, difficulties with concentration, and increased anxiety and/or depression in a subset of individuals), as demonstrated in an AIDS Clinical Trials Group–sponsored clinical trial [8] and in a Swiss HIV cohort [10]. Therefore, carriage of the deleterious *CYP2B6* 516 TT genotype by ~3% of whites and ~20% of blacks appears to predict a more complicated course of treatment and a higher risk of toxicity-driven drug discontinuation.

*CYP2B6* polymorphisms have also been reported (e.g., K262R) that may also contribute to variable enzyme function and further delineate high-risk genotypes [11], suggesting that *CYP2B6* variation may reflect a more complex set of genetic traits.

In this study [7], the authors hypothesized that a slow decay of efavirenz levels after combination antiretroviral therapy is discontinued can lead to the emergence of drug resistance to the entire class of NNRTI drugs. This clearly has important and widespread implications for antiretroviral treatment in resource-poor settings, where the prevalence of the *CYP2B6* 516 TT genotype is high, treatment options are limited, and treatment has relied heavily on nevirapine in single-dose perinatal prophylaxis and, more recently, on nevirapine as part of fixed-dose combinations with nucleoside analogues. This argument has a sound theoretical basis, because (1) the NNRTI drugs efavirenz and nevirapine, both of which are metabolized by *CYP2B6*, are characterized by a low genetic barrier to resistance, so that a single mutation within the reverse-transcriptase sequence (e.g., K103N) can confer high-level drug resistance and preclude any further use of currently licensed members of this drug class, and (2) efavirenz has a very long terminal half-life, and previous studies have suggested that it may present as monotherapy 2–3 weeks or longer after drug discontinuation [12, 13]. A recent case report highlights the potential for acquired drug resistance in a woman who stopped taking efavirenz without guidance and had detectable drug levels 8 weeks after discontinuation of therapy. Of interest, she was heterozygous for the G516T polymorphism and was wild type for other *CYP2B6* polymorphisms [13].

In this study [7], the induction and steady-state levels of efavirenz in study A5097s were assessed (with the exception of 1 case patient from the aborted A5131 study, for whom data from treatment discontinuation could be assessed directly), and rates of efavirenz clearance were subsequently estimated on the basis of these results. It is therefore important to acknowledge that the data relating to efavirenz clearance after discontinuation of therapy are derived (rather than observed) values. The points that are made are still important and valid, although the assumptions made in the pharmacokinetic analyses (i.e., a 1-compartment model with first-order absorption) may differ significantly from observed data (i.e., the 2-compartment model described for the one A5131 study participant). The main reported result was that >50% of individuals with the *CYP2B6* 516 TT genotype had persistently detectable drug levels (sufficient to favor the development of drug resistance) for >21 days. However, perusal of the data also points to the fact that there was a wide distribution of drug levels in each *CYP2B6* genotype group, so that there is no clear delineation of a patient group in which efavirenz can be safely discontinued without risk of inducing resistance.

Are there any clinical practice points that may be derived from these data? To some extent, the findings from this study reinforce a view of drug prescribing that is closer to Dr. Osler’s reckoning than to Dr. Rose’s, although the “art” of managing efavirenz treatment can certainly be informed by the observations that drug disposition is inherently variable between individuals (due to genetic variation) and that this variation may have significant impact on drug toxicity and on the development of drug resistance when treatment withdrawal is unplanned. In terms of current practice, we can imagine 3 proactive scenarios that could be considered further to minimize both drug toxicity and the potential for drug resistance:

1. The current standard of care, in which all patients receive a 600-mg dose of efavirenz once per day, with clinical monitoring and careful counseling regarding unplanned interruption. This approach would also plan for coverage with alternative antiretroviral therapy (e.g., nucleoside reverse-transcriptase inhibitor and protease inhibitor regimens) for planned drug interruptions.

2. Use of therapeutic drug monitoring in defining the “slow metabolizer” phenotype so that dose reduction may be considered. This approach may also alleviate drug toxicity and improve adherence to therapy. In this scenario, dose adjustment should make the issue of prolonged NNRTI decay less significant, and therapeutic drug monitoring would still be a useful tool for monitoring the need for alternative HIV drug coverage following discontinuation of therapy with NNRTIs.

3. Use of a combination of *CYP2B6* genotyping and therapeutic drug monitoring to direct therapy. With this approach, “high risk” *CYP2B6* genotypes could be identified, thereby identifying...
those individuals who might benefit most from therapeutic drug monitoring early, with a view to dose adjustment.

At present and in the absence of further evidence, it would seem to be prudent to take a broad approach to the issue, as outlined in the first scenario described above. It remains to be determined whether a pharmacogenetic approach could (or should) be used to identify patients who are likely to benefit more from appropriate protease inhibitor–based therapy as a primary treatment option (avoiding efavirenz because of the high risk of treatment toxicity), particularly within populations with a higher frequency of deleterious genotypes. However, it is these same populations at risk that are currently overrepresented in resource-poor settings, where NNRTI-based treatment may be the only option. Therefore, this again highlights the need for more research to define both feasible and optimal treatment and discontinuation strategies. At this stage, such studies—like much of pharmacogenetics research and clinical application—remain resolutely in the future.

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