Pharmacogenetics of Plasma Efavirenz Exposure after Treatment Discontinuation: An Adult AIDS Clinical Trials Group Study

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Background. Efavirenz has a long plasma half-life and a low genetic barrier to resistance. Simultaneously stopping treatment with all agents in efavirenz-containing regimens may result in functional efavirenz monotherapy that selects for drug-resistant human immunodeficiency virus type 1. Lower plasma efavirenz clearance is associated with a cytochrome P450 2B6 gene (CYP2B6) polymorphism (516G→T) that is more frequent among African American individuals than among European American individuals.

Methods. We characterized relationships between this polymorphism and predicted plasma efavirenz concentration-time profiles after discontinuation of therapy with use of data obtained from subjects receiving therapy. Pharmacokinetic parameters were estimated using population-based methods. Concentrations after discontinuation of therapy were predicted from subject-specific estimates.

Results. Median estimated efavirenz half-lives were 23, 27, and 48 h for patients with CYP2B6 position 516 GG (78 patients), GT (60), and TT (14) genotypes, respectively (P<.001). After therapy was stopped, plasma efavirenz concentrations in patients with GG, GT, and TT genotypes were predicted to exceed 46.7 ng/mL (the estimated protein-adjusted 95% inhibitory concentration for wild-type virus) for a median of 5.8 days (interquartile range [IQR], 4.4–8.3 days), 7.0 days (IQR, 5.0–8.0 days), and 14 days (IQR, 11.1–21.2 days), respectively (P<.001). Plasma efavirenz levels were predicted to exceed 46.7 ng/mL for >21 days in 5% of subjects with GG genotype, 5% of subjects with GT genotype, and 29% of subjects with TT genotype.

Conclusions. The CYP2B6 position 516 TT genotype or a prolonged measured elimination half-life may predict increased risk of developing drug resistance among patients who discontinue efavirenz-containing regimens. This has implications for strategies to safely discontinue antiretroviral regimens while avoiding the emergence of drug resistance.

Antiretroviral regimens that include the nonnucleoside reverse-transcriptase inhibitor efavirenz plus 2 nucleoside reverse-transcriptase inhibitors are recommended among preferred initial therapies for HIV-1 infection [1–4]. Efavirenz has a long plasma half-life but a relatively low genetic barrier to HIV-1 resistance. In phase I clinical trials, a single-nucleotide change in the HIV-1 reverse-transcriptase gene emerged within 2 weeks after initiation of efavirenz monotherapy [5]. The associated K103N amino acid substitution confers resistance to efavirenz and other approved nonnucleoside reverse-transcriptase inhibitors [5]. Simultaneously stopping treatment with all drugs in a multidrug regimen that includes antiretrovirals with half-lives that are shorter than that of efavirenz could, therefore, result in functional efavirenz monotherapy, which might select for drug-resistant virus.

Efavirenz pharmacokinetic profiles vary between in-
diagonals and populations [6–8]. Efavirenz is metabolized primarily by cytochrome P450 (CYP) 2B6, with some involvement of CYP3A [9]. A G-to-T polymorphism at position 516 of CYP2B6 is associated with higher plasma efavirenz concentrations and slower plasma efavirenz clearance, as well as increased CNS-related side effects [10]. Increased frequency of this polymorphism in African American individuals, compared with European American individuals, may explain reported population differences in efavirenz pharmacokinetics [6–8]. The present study explored relationships between CYP2B6 516G→T and the predicted duration of plasma efavirenz exposure following treatment discontinuation, which is an index of selective pressure for drug resistance.

MATERIALS AND METHODS

Study design and patients. This analysis included subjects who received efavirenz while enrolled in both Adult AIDS Clinical Trials Group (ACTG) study A5095 and ACTG study A5097s, for whom both pharmacokinetic and host genetic data were available. Associations between CYP2B6 516G→T, steady-state plasma efavirenz pharmacokinetics, and CNS-related side effects in these subjects have been reported [10]. Study A5095 randomized 1147 antiretroviral-naïve subjects in the United States and Puerto Rico to receive efavirenz (600 mg once daily), abacavir (300 mg twice daily), or both, together with zidovudine and lamivudine [11]. Study A5097s, a substudy of A5095, characterized efavirenz pharmacokinetics and neurologic side effects during the first 24 weeks of treatment [12]. Of 303 subjects in A5097s, 202 were randomized to receive efavirenz. Human DNA was obtained under ACTG protocol A5128 [13]. Extended serial determinations of efavirenz levels in plasma from individuals who discontinue therapy are rarely available.

To emphasize the relevance of efavirenz clearance after discontinuation of therapy, we present such data from the 1 subject who participated in ACTG study A5131. Study A5131 was designed to characterize relationships between plasma efavirenz decay kinetics after discontinuation of therapy, viral rebound, and drug resistance in patients with plasma HIV-1 RNA levels of <50 copies/mL who stopped treatment with all drugs in efavirenz-containing regimens. The study involved weekly determinations of efavirenz levels in plasma >28 days after stopping treatment with efavirenz and determinations of plasma viral loads until HIV-1 RNA levels were >1000 copies/mL. A5131 was designed to enroll 36 subjects, but the study closed early, after 1 subject enrolled. Population-based viral genotypic susceptibility testing for this subject was performed by the Trugene HIV-1 genotyping test (Visible Genetics). All clinical studies complied with the Helsinki Declaration and were approved by institutional review boards for each site, and subjects gave written informed consent. Guidelines for human experimention of the US Department of Health and Human Services were followed in the conduct of this clinical research.

Subjects self-identified as black not Hispanic or white not Hispanic, in accordance with National Institutes of Health standards [14], are hereafter referred to as “African American” and “European American,” respectively.

Identification of genetic variants. The CYP2B6 516G→T genetic polymorphism was identified by real-time PCR, as described elsewhere [10]. In our previous analyses, CYP2B6 516G→T showed the strongest association with efavirenz plasma half-life among polymorphisms examined in multiple genes, including CYP2B6 (1459C→T), CYP3A4 (−392A→G), CYP3A5 (6986A→G), and MDR1 (2677G→T/A and 3435C→T). We therefore limited the present study to CYP2B6 516G→T.

Pharmacokinetic analyses. Pharmacokinetic parameters were estimated with use of data from all A5097s subjects with evaluable efavirenz pharmacokinetic data (190 of 202 subjects). Plasma for efavirenz assay by high-performance liquid chromatography [15] was collected at weeks 1, 4, 12, and 24. The lower limit of quantification for the assay was 50 ng/mL. Data from specimens obtained >96 h after administration of the dose (16 observations) or without detectable efavirenz levels (9 observations) were excluded from analysis because of concern regarding adherence to therapy. Population pharmacokinetic modeling assumed a 1-compartment, open, mixed-effect model with first-order absorption. Estimation used NLME, version 3.2, library in S-PLUS 6.0 (MathSoft). This functional form has been frequently used to characterize efavirenz pharmacokinetics and is parameterized in terms of drug clearance, volume of distribution, and absorption rate [16]. Complete absorption of the administered dose was assumed. To minimize spurious associations due to confounding with modeled covariates, derived parameters for each subject were obtained using empirical Bayes estimates of clearance and volume from a model without covariates. Because the distribution of sample collection over the dosing interval was insufficient for concurrent estimation of an absorption rate parameter, the model was fit over a range of fixed values for the absorption rate from 0.6 to 1.8 with increments of 0.1, based on reported efavirenz pharmacokinetic data [7]. By sensitivity analyses, the Spearman rank correlation of subject estimates of parameters of interest for all pairs of models exceeded 0.99. Also, the distributions of subject (empirical Bayes) estimates of parameters of interest were invariant to the choice of absorption rate. Final model selection was based on examination of residual distributions. The subject-specific estimates on which the following analyses were based were derived from a model with a multiplicative error structure and a fixed absorption rate parameter of 1.4 h, equivalent to an absorption half-life of 0.5 h. The population estimates for volume of distribution and drug clearance were 421 L (coefficient of variation, 99%) and 10.7 L/h (co-
efficient of variation, 49%), respectively, and were consistent with reported efavirenz pharmacokinetic data [7, 17]. Efavirenz half-life for the study subject from A5131 was estimated by fitting a series of compartmental models, starting with a 1-compartment first-order elimination model and progressing to a 2-compartment model, to the concentration-time data by use of maximum likelihood regression [18]. A proportional variance model was used to describe the error associated with the concentration-time data. The best fit model was selected by Akaike information criteria [19].

**Efavirenz inhibitory concentrations.** Susceptibility of viral isolates can be quantified by determining the drug concentration required to produce a 50% (IC₅₀) or 95% (IC₉₅) reduction in viral replication in vitro. Although selection of a particular threshold concentration for the present analyses was somewhat arbitrary, we used IC₅₀ because this is closer to the maximum drug effect. Based on analyses of ∼1000 viral isolates, the median IC₅₀ of efavirenz for wild-type HIV-1 was 0.0058 μM (N. Parkin, personal communication), which is equivalent to 1.83 ng/mL. Because the IC₅₀ does not consider the effects of plasma protein binding, it was multiplied by a correction factor of 25.5 [20] to yield a protein-adjusted IC₅₀ of 46.7 ng/mL. Similarly, the median IC₅₀ among ∼800 HIV-1 isolates with only the K103N mutation (which is most frequently selected by efavirenz) was 0.309 μM, equivalent to a protein-adjusted IC₅₀ of 2486 ng/mL.

**Statistical analyses.** The empirical Bayes estimated pharmacokinetic parameters for each subject were used to predict at what time after the last efavirenz dose the efavirenz concentration would reach median protein-adjusted IC₅₀ values for wild-type and resistant viruses. Although the main focus of the analysis was on estimating the distribution of these predicted times to reach the respective concentrations, they were also compared across groups by use of a Kruskall-Wallis test for k sample comparisons. There was no adjustment for multiple comparisons.

**RESULTS**

**Baseline demographics and genetic variants.** Among 152 evaluable subjects included in the present analysis, the median age was 37.5 years, 82% were male, and the median weight was 75.8 kg. Of these 152 subjects, 32% were African American, 57% were European American, and 10% were Hispanic; the remaining subjects were Asian or Pacific Islanders. Genotype at position 516 of CYP2B6 was GG for 78 (51%) of the subjects, GT for 60 (39%), and TT for 14 (9%). Among these study subjects, CYP2B6 position 516 genotype was TT in 10 (21%) of the African American subjects, 3 (3%) of the European American subjects, and 1 (7%) of the Hispanic subjects.

**Efavirenz elimination and CYP2B6 genotype.** The median estimated efavirenz plasma half-life among all evaluable subjects was 26 h (interquartile range [IQR], 19–39 h). Among African American subjects, European American subjects, and Hispanic subjects, the median estimated plasma half-lives were 31 h (IQR, 23–51 h), 22 h (IQR, 18–29 h), and 38 h (IQR, 24–45 h), respectively (P < .001). As expected from previous analyses of these data, efavirenz half-lives varied according to CYP2B6 genotype. The median estimated plasma half-lives associated with GG, GT, or TT genotypes at CYP2B6 position 516 were 23 h (IQR, 18–35 h), 27 h (IQR, 19–31 h), and 48 h (IQR, 39–77 h), respectively (P < .001).

Among all study subjects, plasma efavirenz levels were predicted to exceed the protein-adjusted IC₅₀ (46.7 ng/mL) for a median of 6.7 days (IQR, 4.7–9.2 days) after the last dose of efavirenz, with the assumption that treatment had been stopped. Among African American subjects, European American subjects, and Hispanic subjects, these intervals were predicted to be 8.1 days (IQR, 6.0–13.7 days), 5.5 days (IQR, 4.4–7.5 days), and 8.7 days (IQR, 6.0–12.5 days), respectively (P < .001). In addition, plasma efavirenz concentrations after discontinuation of therapy were predicted to exceed 46.7 ng/mL for >21 days in 14.5%, 3.5%, and 6.7% of African American subjects, European American subjects, and Hispanic subjects, respectively.

Associations between CYP2B6 genotype and predicted plasma efavirenz exposure after discontinuation of therapy are presented in figure 1. Plasma efavirenz concentrations in subjects with CYP2B6 GG, GT, and TT genotypes at position 516 were predicted to exceed 46.7 ng/mL for a median of 5.8 days (IQR, 4.4–8.3 days), 7.0 days (IQR, 5.0–8.0 days), and 14 days (IQR, 11.1–21.2 days), respectively (P < .001). Furthermore, plasma efavirenz levels were predicted to exceed 46.7 ng/mL for >21 days in 29% of TT homozygotes, compared with 5% of GT heterozygotes and 5% of GG homozygotes.

Plasma efavirenz concentrations that exceed 2486 ng/mL may suppress replication of many HIV-1 isolates with the K103N efavirenz-associated resistance mutation, as discussed in Materials and Methods. We therefore assessed the interval after discontinuation of therapy during which plasma efavirenz concentrations would be <2486 ng/mL but >46.7 ng/mL. This may better reflect the window of maximal selective drug pressure. Plasma efavirenz concentrations in subjects with CYP2B6 GG, GT, and TT genotypes at position 516 were predicted to be within this concentration range for 5.6 days (IQR, 4.3–7.4 days), 6.4 days (IQR, 4.5–7.3 days), and 11.4 days (IQR, 8.7–17.1 days), respectively (P < .001).

**Viral rebound after stopping treatment with efavirenz.** Serial drug assay and plasma HIV-1 RNA determinations are generally not available from individuals who discontinue treatment with efavirenz. Figure 2 shows data from an HIV-infected participant from ACTG protocol A5131 who was homozygous for G at CYP2B6 position 516; simultaneously stopped treat-
Figure 1. Modeled associations between CYP2B6 516G>T genotype and predicted plasma efavirenz concentrations after discontinuation of therapy. Panels show predicted efavirenz concentrations after discontinuation of therapy for subjects with genotype GG at CYP2B6 position 516 (A), subjects with GT at CYP2B6 position 516 (B), and subjects with TT at CYP2B6 position 516 (C). Dashed horizontal lines, the efavirenz protein-adjusted 95% inhibitory concentration values for wild-type HIV-1 (46.7 ng/mL) and for efavirenz-resistant HIV-1 with the K103N mutation (2486 ng/mL); solid lines, modeled plasma efavirenz decay curves for individual study subjects.

Figure 2. Plasma efavirenz concentrations and viral rebound in a patient who discontinued treatment with efavirenz. Data are from a subject who participated in Adult AIDS Clinical Trials Group study A5131. Closed circles, plasma efavirenz concentrations; dashed horizontal line, the efavirenz protein-adjusted 95% inhibitory concentration values for wild-type HIV-1 (46.7 ng/mL); open boxes, plasma HIV-1 RNA concentrations.
Because a single base change in reverse-transcriptase confers high-level efavirenz resistance, all HIV-infected individuals almost certainly harbor efavirenz-resistant virus in lymphoid tissues, regardless of prior receipt of antiretroviral therapy. The present findings are therefore relevant to all individuals who completely discontinue otherwise-effective antiretroviral therapy that includes efavirenz. The relatively long half-life of efavirenz, even among CYP2B6 position 516 GG homozygotes, suggests that, among subjects with therapeutic control of HIV-1 replication (i.e., those with a plasma HIV-1 RNA level <500 copies/mL) who then interrupt efavirenz-containing antiretroviral regimens for <1 week, there will be little difference between CYP2B6 genotype groups with regard to risk of developing drug resistance. This is consistent with a previous report that, among subjects who underwent repeated cycles of 1 week of therapy followed by 1 week of no therapy, there was minimal risk of selecting for efavirenz resistance during the initial treatment-interruption cycles [26]. The present study is not directly relevant to individuals who stop treatment with efavirenz and promptly switch to another effective multidrug regimen, in which case functional efavirenz monotherapy does not occur.

Many patients discontinue otherwise-effective antiretroviral therapy, despite current treatment guidelines that suggest initiating antiretroviral therapy for individuals with CD4+ T cell counts of <350 cells/mm³ and continuing such therapy indefinitely and without interruption [1]. Reasons for treatment interruption include the side effects of medication, intercurrent clinical events (e.g., major abdominal surgery), travel, loss of insurance, and various other factors [27]. As recommendations for when to start antiretroviral therapy have evolved, many individuals who initiated therapy on the basis of earlier, more aggressive guidelines have chosen to stop therapy to minimize exposure to potentially toxic drugs [28]. In addition, some prospective clinical trials involve treatment discontinuation to test the effectiveness of novel treatment strategies or immunologic interventions [26].

Selective pressure for drug-resistant HIV-1 in vivo is dynamic and relates, in part, to the duration that plasma drug concentrations are sufficiently high to inhibit replication of wild-type (but not mutant) viruses. In some individuals who stop therapy, plasma efavirenz concentrations may briefly exceed the IC₉₀ for both wild-type virus and variants that contain K103N. Selective pressure favoring drug-resistant variants will increase as plasma efavirenz concentrations decrease to below the IC₉₀ for drug-resistant variants while still exceeding the IC₉₀ for drug-susceptible virus, and selective pressure will then abate as plasma efavirenz concentrations approach the IC₉₀ for drug-susceptible virus. Factors other than drug concentration are also likely to influence the probability that drug-resistant virus will emerge, such as the total body pool of HIV-1, the proportion of proviral DNA that is already drug resistant, and the relative replication capacities of wild-type and mutant viruses. Although some studies recommend stopping efavirenz therapy at some interval before stopping treatment with nucleoside reverse-transcriptase inhibitors or protease inhibitors, in the absence of data there is no widely accepted approach to safely discontinuing efavirenz-containing regimens [1]. The relative half-life of each concomitant antiretroviral drug is also an important consideration. Nucleosides or nucleotides whose analogies have longer intracellular half-lives may decrease the window of functional efavirenz monotherapy [29, 30].

The present study suggests that it will not be feasible to develop a standard staggered treatment interruption strategy that is ideal for all individuals. Although our findings suggest that nucleoside reverse-transcriptase inhibitors or protease inhibitors with shorter half-lives than efavirenz should, in general, be continued longer for individuals with the CYP2B6 position 516 TT genotype than for individuals with GG or GT genotypes, this approach is not optimal for the substantial proportion of individuals who are TT homozygotes and have shorter elimination half-lives. An alternative approach (if feasible) is to obtain at least 2 determinations of efavirenz plasma level in real-time several days apart after therapy is stopped; these determinations can be used to inform the decision of when to stop treatment with other agents in the regimen. Another option is to replace efavirenz with an HIV protease inhibitor for a duration that is sufficient to assure efavirenz clearance and then to stop treatment with all antiretroviral drugs simultaneously [1]. Importantly, given the considerable overlap between efavirenz pharmacokinetic profiles among different racial and ethnic groups, strategies to safely discontinue efavirenz-containing regimens should not differ on the basis of race or ethnicity.

A limitation of the present study is that the population pharmacokinetic modeling of plasma efavirenz concentrations determined while therapy was being received was extrapolated to predict efavirenz levels at later time points. This assumes a constant rate of plasma efavirenz clearance and a 1-compartment model, which may not be correct. In fact, data from the sole A5131 participant were best fit by a 2-compartment model. To confirm our predictions would require serial drug assays after efavirenz-containing regimens were discontinued in many individuals of known genotype, as was done for the A5131 participant. In addition, although CYP2B6 G516T is associated with efavirenz pharmacokinetics, many additional CYP2B6 single-nucleotide polymorphisms and haplotypes have been identified [31, 32]. Other CYP2B6 polymorphisms in linkage disequilibrium with G516T or CYP2B6 haplotypes may better predict efavirenz concentration-time profiles after discontinuation of therapy.

More than 90% of HIV-infected people worldwide live in resource-limited countries, and nonnucleoside reverse-tran-
scriptase inhibitor–based antiretroviral regimens are recommended as first-line treatment [33]. As major initiatives provide antiretroviral drugs to such individuals, it will become increasingly important to understand the influence of human genetics on antiretroviral treatment outcomes. Future studies should more fully characterize the influence of host genetic variants on plasma clearance of nonnucleoside reverse-transcriptase inhibitors in diverse populations and the likelihood of selecting for drug-resistant virus following treatment discontinuation.

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