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Markov Model for Characterizing Neuropsychologic Impairment and Monte Carlo Simulation for Optimizing Efavirenz Therapy

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Abstract

The study was undertaken to develop a pharmacokinetic-pharmacodynamic model to characterize efavirenz-induced neuropsychologic impairment, given preexistent impairment, which can be used for the optimization of efavirenz therapy via Monte Carlo simulations. The modeling was performed with NONMEM 7.2. A 1-compartment pharmacokinetic model was fitted to efavirenz concentration data from 196 Ugandan patients treated with a 600-mg daily efavirenz dose. Pharmacokinetic parameters and area under the curve (AUC) were derived. Neuropsychologic evaluation of the patients was done at baseline and in week 2 of antiretroviral therapy. A discrete-time 2-state first-order Markov model was developed to describe neuropsychologic impairment. Efavirenz AUC, day 3 efavirenz trough concentration, and female sex increased the probability (P01) of neuropsychologic impairment. Efavirenz oral clearance (CL/F) increased the probability (P10) of resolution of preexistent neuropsychologic impairment. The predictive performance of the reduced (final) model, given the data, incorporating AUC on P01and CL /F on P10, showed that the model adequately characterized the neuropsychologic impairment observed with efavirenz therapy. Simulations with the developed model predicted a 7% overall reduction in neuropsychologic impairment probability at 450 mg of efavirenz. We recommend a reduction in efavirenz dose from 600 to 450 mg, because the 450-mg dose has been shown to produce sustained antiretroviral efficacy.

Keywords

Markov model, efavirenz, neuropsychologic impairment, NONMEM, Monte Carlo simulation

HIV infection is often associated with other comorbidities. HIV-associated CD4 cell count reduction results in opportunistic infections, and both viral and immunological factors have been associated with neurological damage.[1] The neuropsychologic impairment (NPI) observed in HIV-infected individuals is mostly but not entirely attributed to HIV-associated neurocognitive disorders, with varying severity.[2] Treatment with central nervous system penetrating antiretroviral therapy (ART) might improve neuropsychologic function; however, some ART regimens are also associated with central nervous system toxicity.[3,4]

Efavirenz, the most widely used nonnucleoside reverse transcriptase inhibitor, especially during cotreatment with rifampicin, has a prolonged half-life that allows once-daily dosing. However, central nervous system (CNS) adverse effects are frequently reported during efavirenz use. Although the CNS toxicity may be acute and transient, resolving within 2 to 4 weeks following initiation of efavirenz, persistence of neuropsychiatric disorders in more than half of patients receiving efavirenz-based ART has been reported.[5–8] Neuropsychological impairment often leads to poor adherence[9] and treatment discontinuation[5,10] occurring early in the use of the highly active antiretroviral therapy (HAART).[11] Discontinuation or interruption of efavirenz treatment occurring before attainment of steady state is especially risky because at this time viral suppression is not yet achieved. Also, the low genetic resistance barrier and long half-life of efavirenz result in persistently detectable drug levels sufficient to favor resistance development.[12–14]

Efavirenz exhibits significant genetic-based interindividual pharmacokinetic variability, especially in the African population.[15,16] This variability and the narrow efavirenz therapeutic window (plasma concentration between 1 and 4 μg/mL) result in wide heterogeneity in the response to antiretroviral therapy. Previous clinical and pharmacokinetic-pharmacodynamic simulation-based studies have demonstrated similar exposure to product label, sustained viral suppression, and reduced incidence of efavirenz-associated CNS toxicity in adults

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following efavirenz dose reduction from 600 to 450 mg, 400 and 300 mg in African populations.[17,18]

However, the CNS side effects of efavirenz may overlap significantly with the neuropsychiatric complications of HIV infection, preexisting mental illness, or substance abuse. Therefore, establishing the etiology of neuropsychologic complications observed in HIV patients on efavirenz-based HAART presents a significant challenge. There have also been reports of a higher incidence of efavirenz CNS side effects among patients with preexisting psychiatric diagnoses than in those without prior psychiatric history.[19]

In principle, HIV patients may develop neuropsychological impairment secondary to HIV infection or efavirenz CNS toxicity, and those with neuropsychological impairment may experience overlap in CNS toxicity, or improvement in neuropsychologic symptoms as a result of HAART.[19] The neuropsychological impairment consequent on efavirenz administration occurs within the first 2 weeks of therapy, and this is the period when treatment interruption or discontinuation is likely to occur as a result of neuropsychologic impairment or CNS toxicity leading to possible emergency of resistance.[9–11] Like many chronic diseases, neuropsychological impairment progression stages observed in a real-world clinical setting can be categorized into discrete states with transitions between states possible in either direction. Thus, a Markov process[20] can be used to model and predict the probability of patients experiencing efavirenz-induced CNS toxicity.

This analysis was performed to develop a novel pharmacokinetic-pharmacodynamic model for the characterization and prediction of pre-steady-state neuropsychiatric impairment following efavirenz-based ART initiation and to apply the model in simulating neuropsychologic impairment rates following dose reduction to 450 and 400 mg.

Methods

Study Setting, Design, and Participants

Newly diagnosed antiretroviral therapy (ART)–naive HIV patients with (n = 138) and without (n = 58) tuberculosis (TB) coinfection attending the HIV/TB or HIV clinic at Mulago and Butabika National Referral Hospitals in Kampala, Uganda, were recruited and enrolled into the study during the years 2008 and 2009. The participants were initiated on efavirenz-based ART according to the World Health Organization CD4 count criteria. HIV and TB coinfected patients received rifampicin-based anti-TB regimen, initiated 2–8 weeks before ART. The ART regimen comprised efavirenz 600 mg daily in combination with zidovudine and lamivudine. Blood samples for genotyping were collected at enrollment, whereas additional samples were collected between 11 and 18 hours post–efavirenz dosing on the day of initiation, during and between follow-up visits for at least 6 months. The patients were evaluated for neuropsychiatric disorders at baseline and during follow-up visits at weeks 2 and 12.

The study was approved by the institutional review boards of Mulago and Butabika hospitals and the Uganda National Council for Science and Technology. Written informed consent was obtained from each study participant. Details of the sample collection, efavirenz plasma concentration analysis, clinical chemistry, genotyping, and neuropsychological evaluation have been reported elsewhere.[8]

Pharmacokinetic Model Development

A population pharmacokinetic (PK) model of efavirenz was built using NONMEM version 7.2.0 software[21,22] with the aid of Perl speaks NONMEM (PsN 3.4.2).[23] R software (version 3.0.1)[24] and Xpose4[25] were used for data set construction, graphical, and statistical analysis. The first-order conditional estimation method with interaction was used. A 1-compartment PK model with first-order absorption incorporating lag time (specified in NONMEM with the ADVAN2 and TRANS2 routines) was assumed. Absorption rate constant (KA), apparent clearance (CL/F), relative bioavailability (F1), apparent distribution volume (V/F), and absorption lag time were estimated. The individual apparent clearance and volume of distribution were assumed to be log-normally distributed. Therefore, between-subject variability in these parameters was modeled as exponential random effects. Residual error was described with the combined error model (additive plus proportional error model). Model discrimination was based on relative objective function values computed in NONMEM as -2× log likelihood, precision of parameter estimates, and goodness-of-fit plots.

Covariate analysis was performed on CL/F, V/F, and KA in a stepwise manner using the likelihood ratio test at a 5% significance threshold for forward stepping, followed by backward elimination at a 1% significance threshold. Plasma albumin concentration, sex, age, TB disease status, and pharmacogenetic covariates including *CYP2B6* (**6* and **11*) and *ABCB1 c.4046A>G* were tested in the model. Goodness-of-fit plots were also inspected. The most conservative model was selected for linking PK with pharmacodynamics (PD).

Pharmacodynamics

Neuropsychological evaluation for sleep disorders (insomnia, vivid dreams, and sleep walking), hallucinations (visual, auditory, and tactile) and cognitive effects were performed at baseline and 2 weeks following ART initiation. Data for the analysis were from pre-steady-state (efavirenz steady state was assumed to occur after

2 weeks) neuropsychologic evaluations; therefore, only baseline and week 2 data were used.

The presence of a neuropsychological impairment was defined and limited to reporting at least 1 sleep disorders or hallucination. Insomnia was categorized as mild (failure to sleep within 15 minutes), moderate (failure to sleep in 1 hour), and severe (failure to sleep for more than 1 hour). Other sleep disorders and hallucinations were assessed as "yes" or "no" as declared by the participants. A participant could experience 1 or more of these symptoms, and the number of symptoms experienced does not necessarily translate to the level of severity of neuropsychologic impairment. Rather, different symptoms are associated with different levels of severity as categorized by Gutierrez et al.[5] Therefore, the data were binarized as neuropsychologically impaired (coded as 1) if a participant reported at least 1 of the symptoms or as unimpaired (coded as 0) if the participant did not report any symptom. The neuropsychiatric assessment was administered by a trained psychiatric nurse under the supervision of a physician.

Markov Model. A Markov process (chain) is a memoryless series of probable transitions between states whereby a future state is only dependent on the current state and not on previous states. This is strictly referred to as first order. Transition between states is a random process whose probability of occurrence can be modeled. This probability is referred to as the transition probability. The covariate effect on the probability of transition between states is analyzed using logistic functions.[26] For most Markov processes, a finite number of states is defined, and discrete time intervals characterize the Markov chain. Markov processes have been used to describe acute and chronic diseases in humans.[20]

Pharmacokinetic-Transition Pharmacodynamic Model Development. A discrete-time 2-state first-order Markov model was developed to characterize the transition between the 2 defined neuropsychological states on initiation of efavirenz-based ART. The transition probabilities between the 2 states in the first 2 weeks of ART were modeled as binary logistic functions. The likelihood ratio test was used to select covariate predictors of transition probabilities at a 5% significance threshold. Age, baseline body weight, CD4 count, viral load, and TB disease status and individual PK parameters were tested as potential covariates, one at a time.

The sequential PK-PD modeling approach was used whereby individual PK parameters were estimated first, assuming no errors, and then linked to the PD data. The PK parameters were used to derive the single-dose area under the concentration–time curve (AUC)

$$AUC = \frac{F1^{*}DOSE}{CL} \quad (1)$$

The relationship between AUC and the transition probabilities was modeled using the alternative parameterization Emax model suggested by Schoemaker et al,[27]

$$P = \frac{e\left[E_0 + \left(\frac{S_0 * E_{max} * AUC}{E_{max} + S_0 * AUC}\right) + \boldsymbol{\beta Z} + \eta\right]}{1 + e\left[E_0 + \left(\frac{S_0 * E_{max} * AUC}{E_{max} + S_0 * AUC}\right) + \boldsymbol{\beta Z} + \eta\right]},$$

$$\textbf{where } S_0 = \frac{E_{max}}{AUC_{50}} \quad (2)$$

where E_0 is the baseline log odds of transitioning between neuropsychological state, AUC_{50} is the single-dose AUC required to cause half the maximal log odds of transition, E_{max} is the maximal log odds of transitioning between states, S_0 is the slope of the tangent of the exposure–response curve at zero exposure (baseline), β is the vector of proportional log odd changes for each covariate increase, Z is the matrix of individual covariates, and $\acute{\eta}$ is the random-effect parameter assumed to be symmetrically distributed with zero mean and variance ω^2, the probability (P) of transitioning from one neuropsychological state to another in the 2 weeks is given by equation 2 above.

Parameter estimation was done using the Laplacian algorithm in NONMEM 7.2. The reliability and predictive performance of the model were assessed using nonparametric bootstrap and categorical predictive check plots.

Bootstrap Reliability Testing

The reduced model was fitted to 1000 bootstrap data sets, created by resampling with replacement from the original data set and the parameters estimated. The summary statistics (mean, median, 2.5th percentile, 97.5th percentile, minimum, and maximum) for the distribution of each model parameter were obtained. The reduced model parameter estimates were compared with the mean and percentile 95% confidence intervals (CIs) of the nonparametric bootstrap replicates as described by Ette et al.[28]

Predictive Check

The reduced model, given the data, was used to simulate 1000 new data sets of 196 individuals each. For each simulated data set, the proportion of neuropsychological impairment outcomes at baseline and week 2 was computed. Histograms of the neuropsychologic impairment proportions at baseline and week 2 were constructed for the 1000 data sets. The mean simulated neuropsychologic impairment proportions and the observed proportions at both times were superimposed into the histograms as vertical blue and red lines, respectively. Best fit was achieved if the red line lay close to the mean (blue line) in the histogram.

Model Application

The PK-PD model was used to simulate 1000 data sets of 196 patients each, with the same CYP2B6 and *ABCB1 c.4046A>G* genotype frequency as the original data set. Fixed and random model effects were set equal to the reduced (final) PK-PD model, given the data. The probability of the development of neuropsychiatric impairment at 2 weeks, given efavirenz doses of 400, 450, and 600 mg, was simulated for each of the 5 *CYP2B6*6* and *CYP2B6*11* genotypes in the study population. The 450- and 400-mg doses were chosen because of previous dose reduction recommendations by Mukonzo et al[18] and the ENCORE trial,[17] respectively. The Student *t* test was used to determine whether there is a significant difference between the mean simulated NPI proportions of the 450- and 600-mg doses in the population.

Results

Baseline characteristics and dose-relevant genotype information on study subjects are presented in Table 1. Details of these characteristics were reported by Mukonzo et al.[8]

Pharmacokinetics

The pharmacokinetic data set contained 1850 efavirenz concentration values collected from 196 HIV/AIDS patients (n = 138 with TB coinfections) over 252 days of daily treatment with efavirenz-based HAART. A 1-compartment model with first-order absorption described our data well, as observed in Figure 1. Significant covariate relationships were identified for KA, CL/F, and F1. Thus, TB disease status was a significant predictor of KA, *CYP2B6*6*, and *CYP2B6*11* genotypes had significant effects on CL/F and *ABCB1 c.4046A>G* on F1.The reduced (final) model population pharmacokinetic parameters, given the data, are reported in Table 2.

Table 1. Baseline Demographic Characteristics of the Study Participants

Baseline Demographics	All Participants (n = 196)
Women (n)	109
Body weight (kg) ± SD	53.6 ± 10.1
Age (years) ± SD	33.8 ± 7.2
Mean CD4 count ± SD	97.4 ± 77.1
Mean $\log_{10}$ viral load ± SD	4.9 ± 0.7
Day 3 efavirenz concentration (mg/L), median (IQR)	2.1 (1.4–2.9)
*CYP2B6*6* (**1/*1*), n	86
*CYP2B6*6* (**1/*6*), n	93
*CYP2B6*6* (**6/*6*), n	17

IQR, interquartile range.

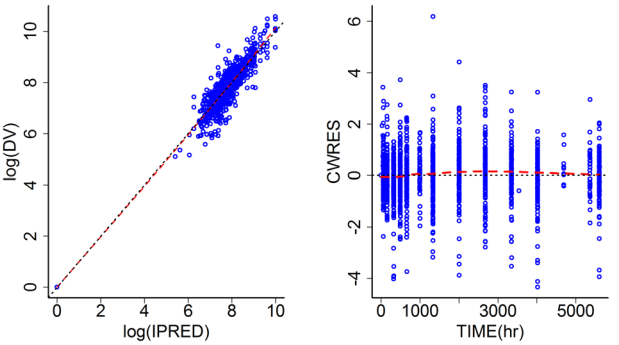

Figure 1. Goodness-of-fit plot for the pharmacokinetic model.

Table 2. Pharmacokinetic Model Parameters

Description	Estimate	RSE
$KA_{no\ TB}$ (/h)	0.053	13.9%
KA_{TB} (/h)	0.250	11.4%
V (L)	102	14%
CL (homozygous), L/h	5.84	5.8%
CL (*CYP2B6*11* [**1/*6*], *CYP2B6*11* (**6/*6*])	−0.393[a]	15.6%
CL (*CYP2B6*6* [**1/*6*])	0.39[a]	25.4%
CL (*CYP2B6*6* [**6/*6*])	−0.495[a]	17.1%
F1 (ABRS homozygous)	0.467 FIX	–
F1 (ABRS [1,2])	0.0926[a]	48.4%
IIV_KA	–	–
IIV_V (%CV)	62.66	23.2%
IIV_CL (%CV)	46.75	6.9%
Residual	0.113	9%

[a]Proportional addition to the homozygous parameter value. FIX parameters were fixed to a prior estimated value. Concentrations were measured in mg/L. IIV, interindividual variability in the population parameter; CV, coefficient of variation.

Pharmacodynamics

Neuropsychological impairment was reported in 38 patients (19.4%) at baseline and in 118 (60.2%) at 2 weeks. The estimated probability of transition from normal state to neuropsychologic impairment state was 0.578 (%RSE = 6.8%). On the other hand, the probability of transition from neuropsychologic impairment state to normal state was 0.289 (%RSE = 25.5%) in the first 2 weeks of ART. Day 3 mid-dose efavirenz concentrations (odds ratio [OR], 1.19; 95%CI, 1.08–1.30), being female (OR, 2.07; 95%CI, 1.09–3.93), and single-dose AUC, independently increased the chance of developing neuropsychologic impairment (P01). An increase in CL/F increased probability (OR, 1.36; 95%CI, 1.01–1.84) of transition from neuropsychologic impairment to normal state (P10). Unlike CL/F, AUC did not significantly affect the transition from neuropsychologic impairment to normal state. Because either CL/F or AUC was tested in the model on a single transition probability at a given time, the one that led to significant improvement in

Table 3. Full Pharmacokinetic-Pharmacodynamic Markov Model Parameters

Parameter	Description	Value	RSE(%)	Bootstrap 95%CI
E_{01}	Baseline log odds of transition from normal to neuropsychologic impairment	−4.52 FIX	—	—
E_{max}	Maximum attainable log odds of transition from normal to neuropsychologic impairment	6.67	11.2	5.57–9.11
S_0	Slope of the tangent of the exposure–response curve at baseline	0.37	30.2	0.22–0.77
E_{10}	Baseline log odds of transition from neuropsychologic impairment to normal	−2.83 FIX	—	—
β_{10}	Increase in log odds of transition from neuropsychologic impairment to normal per unit increase in efavirenz clearance.	0.31	17.5	0.19–0.43

FIX-parameters were fixed to a prior estimated value.

goodness-of–fit criteria was preferred and retained in the model on a given parameter. This was done to avoid the problem of colinearity. Therefore, AUC on P01 and CL/F on P10 were the only covariates left in the final parsimonious model (Table 3), which best described the data as shown in the simulation-based predictive check plots in Figure 2. The confidence intervals of the estimated parameters did not include zeros. In addition, mean bootstrap parameter estimates lay within ± 15% of the reduced model parameter estimates.

Model Application

Overall, there was a 7% reduction in simulated probability of having neuropsychologic impairment at week 2 following a dose reduction from 600 to 450 mg. The reduction was statistically significant ($P < .001$). The reduction was greatest (8%) in the *CYP2B6*6* wild-type variants and least (4%) in the *CYP2B6*6* homozygous variants who even at a dose of 400 mg had a simulated week 2 neuropsychologic impairment probability of 0.72, higher than that of the general population at normal dose. The simulation results together with the observed neuropsychologic impairment proportions, for comparison, are reported in Table 4.

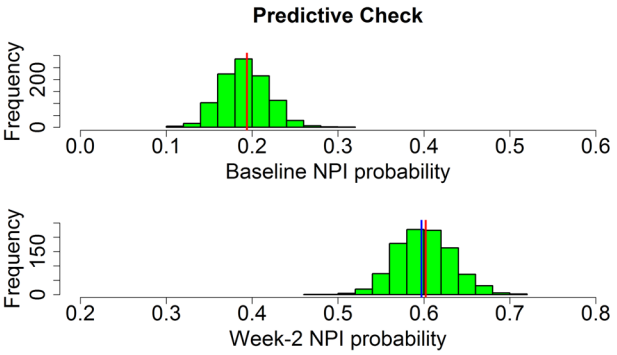

Figure 2. Predictive check for the reduced PK-transitional PD model. The vertical red lines show the proportion of observed neuropsychologic impairment. The vertical blue line shows the mean predicted NPI. The histograms show distribution of neuropsychologic impairment prediction for 1000 simulations at each time.

Discussion

The *CYP2B6*6* and *CYP2B6*11* mutations had a significant effect on efavirenz PK as previously reported.[16] This resulted in high variability in efavirenz exposure, especially during the start of ART. An association between the *CYP2B6*6* genotype and neuropsychologic impairment observed at week 2 of ART treatment has been reported.[8]

Previous reports of analyses of efavirenz CNS toxicity data did not take into account preexisting neuropsychologic impairment, and the authors attributed all observed symptoms to efavirenz toxicity.[5,7,8] Therefore, the analyses did not reflect real-world clinical settings and might overestimate the efavirenz CNS toxicity rates. One study has attempted to model efavirenz CNS toxicity and simulate its proportions following dose reduction.[29] However, this study used logistic regression to link CNS toxicity outcomes to the pharmacokinetics and did not take into account the possibility of those outcomes being independent of treatment. By making use of neuropsychological impairment data at baseline, our analysis is able to more accurately quantify efavirenz CNS toxicity versus neuropsychological impairment from other causes and the possible impact of HAART on improvement of neuropsychological symptoms. A Markov model is more capable of achieving this because the propensity of developing efavirenz-induced CNS toxicity is influenced by background neuropsychologic impairment, making it a Markov process. Markov models have been used before to model sleep patterns, gastrointestinal movements, seizures, and study dropout rates. A review of the methods employed was presented by Ette.[20] A discrete-time first-order 2-state Markov model was therefore employed to more realistically model and predict efavirenz-induced CNS toxicity and neuropsychologic impairment following ART initiation.

The Shoemaker modification of the E_{max} model is the recommended choice for in vivo experiments, especially ones in which the concentration required to cause maximal effect may not be clearly known or is practically unattainable. A good example is the type we investigated

Table 4. Observed Proportion With Neuropsychologic Impairment and Simulated Probability of Developing Neuropsychologic Impairment Following Efavirenz Dose Reduction

	Observed Neuropsychologic Impairment Proportion			Probability of Developing Neuropsychologic Impairment (95%PI)		
Genotype	Number	Baseline (%)	Week 2 (%)	600 mg	450 mg	400 mg
All	196	19.4	60.2	0.60 (0.53–0.66)[a]	0.53 (0.46–0.60)[a]	0.50 (0.43–0.57)
*CYP2B6*6 (*1/*1)*	86	11.6	58.1	0.53 (0.43–0.64)	0.45 (0.35–0.56)	0.42 (0.32–0.53)
*CYP2B6*6 (*1/*6)*	93	27.9	58.1	0.63 (0.52–0.72)	0.56 (0.46–0.66)	0.53 (0.44–0.63)
*CYP2B6*6 (*6/*6)*	17	11.7	82.4	0.78 (0.56–0.95)	0.74 (0.47–0.93)	0.72 (0.46–0.93)

PI, prediction interval.
[a]Significant difference between the 2 group means ($P < .001$).

in this study, where the effect is a toxic outcome. Instead of AUC_{50}, a parameter, S_0, for the initial sensitivity to efavirenz toxicity at low concentrations was estimated.[27] The parameters for the baseline log odds of transition were fixed to prior estimated values, to reduce the number of estimable parameters. This enabled precise estimation of the treatment-related parameters S_0, E_{max}, and β_{10}.

As observed from the predictive check (Figure 2), the simulated outcomes from the model are in agreement with the observed outcomes at baseline and at week 2, indicating good predictive performance and generalizability. Also, the bootstrap 95% confidence intervals showed that the parameter estimates were precise.

Efavirenz exposure was a significant predictor of transitioning from normal state to neuropsychologic impairment. Because exposure depends on clearance, it follows that the probability of developing neuropsychologic impairment at week 2 is associated with the *CYP2B6* genotype. Also, the probability of transitioning from neuropsychologic impairment to normal state increased with increase in clearance. This could mean that high efavirenz exposure also worsens or leads to the persistence of preexistent neuropsychologic impairment. Because the transition from normal state to neuropsychologic impairment at week 2 was positively associated with efavirenz exposure, it can be concluded that the neuropsychologic impairment observed in week 2 is predominantly due to efavirenz therapy. Whereas efavirenz-induced CNS toxicity may be transient, subsiding within 30 days, some patients may not tolerate this toxicity, leading to withdrawal from treatment.[30] This interruption of therapy may have both direct and hidden costs associated with switching treatment and treatment failure.

Simulation with the model demonstrated overall reduction in reported CNS toxicities, with dose reduction from 600 to 450 and 400 mg similar to what is reported in other studies.[17] The reduction was least in the *CYP2B6*6* homozygous variant (4%) and greatest in the *CYP2B6*6* wild-type variants (8%), which could correspond to the respective reduction in efavirenz exposure as reported previously.[18]

In summary, a discrete-time Markov model was used to describe neuropsychologic impairment following exposure to efavirenz. Simulations using the model revealed a reduction in efavirenz-induced events of CNS toxicity following dose reduction from 600 to 450 and 400 mg. The magnitude of reduction in CNS toxicity varies with the *CYP2B6*6* genotype. Because of this reduction in incidence of central nervous system toxicity and the previously reported retention of viral suppression efficacy at 450 mg, we recommend dose reduction in the Ugandan population from 600 to 450 mg, taking precaution where drug interactions are suspected.

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References

1. Rao VR, Ruiz AP, Prasad VR. Viral and cellular factors underlying neuropathogenesis in HIV associated neurocognitive disorders (HAND). *AIDS Res Ther.* 2014;11:13.
2. Woods SP, Moore DJ, Weber E, Grant I. Cognitive neuropsychology of HIV-associated neurocognitive disorders. *Neuropsychol Rev.* 2009;19(2):152–168.
3. Cysique LA, Vaida F, Letendre S, et al. Dynamics of cognitive change in impaired HIV-positive patients initiating antiretroviral therapy. *Neurology.* 2009;73(5):342–348.
4. Cysique LA, Waters EK, Brew BJ. Central nervous system antiretroviral efficacy in HIV infection: a qualitative and quantitative review and implications for future research. *BMC Neurol.* 2011;11:148.
5. Gutierrez F, Navarro A, Padilla S, et al. Prediction of neuropsychiatric adverse events associated with long-term efavirenz therapy, using plasma drug level monitoring. *Clin Infect Dis.* 2005;41(11):1648–1653.
6. Fumaz CR, Munoz-Moreno JA, Molto J, et al. Long-term neuropsychiatric disorders on efavirenz-based approaches: quality of life, psychologic issues, and adherence. *J Acquir Immune Defic Syndr.* 2005;38(5):560–565.
7. Blanch J, Martinez E, Rousaud A, et al. Preliminary data of a prospective study on neuropsychiatric side effects after initiation of efavirenz. *J Acquir Immune Defic Syndr.* 2001;27(4):336–343.
8. Mukonzo JK, Okwera A, Nakasujja N, et al. Influence of efavirenz pharmacokinetics and pharmacogenetics on neuropsychological disorders in Ugandan HIV-positive patients with or without

tuberculosis: a prospective cohort study. *BMC Infect Dis.* 2013; 13:261.
9. Hinkin CH, Castellon SA, Durvasula RS, et al. Medication adherence among HIV+ adults: effects of cognitive dysfunction and regimen complexity. *Neurology.* 2002;59(12):1944–1950.
10. Marzolini C, Telenti A, Decosterd LA, Greub G, Biollaz J, Buclin T. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. *AIDS. J* 2001;15(1):71–75.
11. Shafran S, Lefebvre E, Baril J, Cornelson B, Walmsley S, Fong I. Retrospective analysis of factors associated with discontinuation of EFV due to adverse effects. Paper presented at: 1st International AIDS Society Conference on HIV Pathogenesis and Treatment; July 8–11, 2001; Buenos Aires, Argentina.
12. Zaccarelli M SF, Liuzzi G, et al. CNS side effects as main risk factor for EFV failure and transient HIV-RNA elevation. Paper presented at: 9th Conference of Retroviruses and Opportunistic Infections; February 24–28, 2002; Seattle, Washington.
13. Sadiq ST, Fredericks S, Khoo SH, Rice P, Holt DW. Efavirenz detectable in plasma 8 weeks after stopping therapy and subsequent development of non-nucleoside reverse transcriptase inhibitor-associated resistance. *AIDS*. 2005;19(15):1716–1717.
14. Ribaudo HJ, Haas DW, Tierney C, et al. Pharmacogenetics of plasma efavirenz exposure after treatment discontinuation: an Adult AIDS Clinical Trials Group Study. *Clin Infect Dis.* 2006;42(3):401–407.
15. Nyakutira C, Roshammar D, Chigutsa E, et al. High prevalence of the CYP2B6 516G->T(*6) variant and effect on the population pharmacokinetics of efavirenz in HIV/AIDS outpatients in Zimbabwe. *Eur J Clin Pharmacol.* 2008;64(4):357–365.
16. Mukonzo JK, Roshammar D, Waako P, et al. A novel polymorphism in ABCB1 gene, CYP2B6*6 and sex predict single-dose efavirenz population pharmacokinetics in Ugandans. *Br J Clin Pharmacol.* 2009;68(5):690–699.
17. ENCORE1 Study Group, Puls R, Amin J, Losso M, et al. Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial. *Lancet.* 2014; 383(9927):1474–1482.
18. Mukonzo JK, Owen JS, Ogwal-Okeng J, et al. Pharmacogenetic-based efavirenz dose modification: suggestions for an African population and the different CYP2B6 genotypes. *PLoS One.* 2014; 9(1):e86919.
19. Goldenberg D, Boyle B. Psychiatric safety of efavirenz. Paper presented at 13th International AIDS Conference; July 9–14, 2000; Durban, South Africa.
20. Ette IE. Transition models in pharmacodynamics. In: Ette IE, Williams JP, eds. *Pharmacometrics: The Science of Quantitative Pharmacology*. Hoboken, NJ: John Wiley & Sons, Inc.; 2007.
21. Beal SL, Sheiner LB. The nonmem system. *Amer Statist.* 1980;34: 118–119.
22. Boeckmann AJ, Sheiner LB, Beal SL. NONMEM Users Guides, NONMEM Project Group. San Francisco: University of California; 1994.
23. Lindbom L, Ribbing J, Jonsson EN. Perl-speaks-NONMEM (PsN) —a Perl module for NONMEM related programming. *Comput Methods Programs Biomed.* 2004;75(2):85–94.
24. *R: A Language and Environment for Statistical Computing* [computer program]. Version 3.0.1. Vienna, Austria: R Foundation for Statistical Computing; 2013.
25. Jonsson EN, Karlson MO. Xpose-an S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. *Comput Methods Programs Biomed.* 1999;58:51–64.
26. Muenz LR, Rubinstein LV. Markov models for covariate dependence of binary sequences. *Biometrics.* 1985;41(1):91–101.
27. Schoemaker RC, van Gerven JM, Cohen AF. Estimating potency for the Emax-model without attaining maximal effects. *J Pharmacokinet Biopharm.* 1998;26(5):581–593.
28. Ette EI, Williams PJ, Kim YH, Lane JR, Liu MJ, Capparelli EV. Model appropriateness and population pharmacokinetic modeling. *J Clin Pharmacol.* 2003;43(6):610–623.
29. Siccardi M, Almond L, Schipani A, et al. Pharmacokinetic and pharmacodynamic analysis of efavirenz dose reduction using an in vitro-in vivo extrapolation model. *Clin Pharmacol Ther.* 2012; 92(4):494–502.
30. Clifford DB, Evans S, Yang Y, et al. Impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals. *Ann Intern Med.* 2005;143(10):714–721.