Pharmacogenetic-Based Pharmacokinetic Modeling of Plasma and Intracellular Concentrations of Efavirenz on Adult Ethiopian HIV and TB/HIV Patients

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Objectives: As HIV replicates within immune cells, it is important to delineate the intracellular (IC) pharmacokinetic (PK) behavior of antiretroviral drugs like efavirenz (EFV). No previous study modeled PK of EFV in IC observations. Objective: To describe the population PK of plasma and IC EFV concentrations and explore covariates of PK.

Methods: From 313 patients, 1811 steady state plasma (n=1132) and corresponding IC (n=679) EFV concentrations were analyzed using LC/MS/MS after 600mg per day. Baseline body weight and organ function values; age, sex, type of combination antiretroviral therapy and pharmacogenetic markers were explored as covariates. CYP2B6*6 alleles were included in the base model. PK parameters and random inter-individual variability (IIV) were estimated using NONMEM 7.1.

Results: One-, two- and three-compartment models with first-order absorption; lag-time or transit compartments were explored. A two-compartment model, plasma as central compartment (Vc/F=93L; CV=36%) with first-order absorption and Alag and IC as peripheral compartment (Vp/F=130L; CV=65%), described the data well (Figure 1). IC clearance followed a nonlinear transfer rate (CLp/F=32L/h; Vmax=25µg/mL/h; Km=4.1µg/mL). The estimated CL/F for CYP2B6*1/*1, CYP2B6*1/*6 and CYP2B6*6/*6 were 18, 14 and 8.7 L/h, respectively. Covariate relationships on CL/F, Vc/F and Vmax were also explored using delta plots and added to the base model, when identified. Among the covariates identified, only CYP3A5*1 showed significant effect on CL/F (ΔOFV = 8.259, df =1, α = 0.01), contributing for 1% CL/F IIV.

Conclusions: The present study revealed that EFV IC accumulated to higher concentrations than in plasma and was well described by zero-order transfer rate from peripheral cells to the plasma. Besides CYP2B6*6, CYP3A5*1 alleles minimally contribute for IIV of CL/F.