Impact of Concomitant Antiretrovirals, and CYP2C9 and CYP2C19 Polymorphisms on the Pharmacokinetics of Etravirine

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INTRODUCTION

HIV type-1 (HIV-1) infected patients are routinely treated with combinations of three or four drugs (highly active antiretroviral therapy, HAART). Etravirine (ETR, TMC125) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) indicated in combination with other antiretrovirals (ARV) for treatment-experienced patients of at least 6 years of age. A population PK model was previously developed using data from two phase III trials and pediatric trials. Despite the large variability in the ETR PK, only limited covariates could be identified to explain this variability. More recent data for ETR have become available, looking at specific concomitant ARV and polymorphisms of CYP2C9 and CYP2C19.

OBJECTIVES

The objectives of this analysis were:

- To develop a population PK model for ETR using data from studies TMC125-C206, TMC125-C216, TMC125-C238 and TMC125IFD3002 in adult treatment-experienced HIV-infected patients;
- To determine the influence of subject characteristics on the PK parameters of ETR, and possible drug drug interactions with other ARVs;
- To evaluate the final population PK model using simulation techniques.

METHODS

Data

A summary of the data used in the analysis is shown in **Table 1**. In study TMC125-C238, all subjects underwent rich PK sampling after 2 weeks of treatment, with sparse PK samples being taken at later visits. In studies TMC125-C206, -C216 and IFD3002, sparse PK samples were available for all subjects, and a richly sampled PK substudy was performed in a small subset of the enrolled subjects.

Table 1. Summary of the available data

Study	TMC125-C206	TMC125-C216	TMC125-C238	TMC125IFD3002
No. of subjects with available ETR concentrations	294	281	42	200
ETR dose	200 mg BID	200 mg BID	200 mg BID	200 mg BID
Sampling occasions	At least 6 per subject	At least 6 per subjects	9 per subject	4 per subject
Nominal sparse sampling time	Week 4: pre-dose & ≥1 hr; anytime for other occasions	Week 4: pre-dose & ≥1 hr; anytime for other occasions	Anytime	Week 4 & 24: pre-dose & ≥1 hr; anytime for other occasions
Rich sampling time range	0-12 hr	0-12 hr	0-24 hr*	0-24 hr*
No. of PK observations	≥6 samples/ subject	≥6 samples/ subject	~25 samples/ subject	≥6 samples/ subject

*: 0-12 hr for ETR and BID ARVs; 0-24 hr for QD ARV

The final dataset consisted of 4728 ETR plasma concentrations from 817 subjects. Covariates included in the analysis were age, total body weight (WT), creatinine clearance (CRCL), sex, race, co-administered ARV and CYP2C9 & CYP2C19 metaboliser status. The algorithm used for mapping CYP2C9 and CYP2C19 genotype to phenotype is shown in **Table 2**. The summaries of subjects demographics used in the analysis are shown in **Table 3** for continuous variables and in **Table 4** for categorical variables.

Table 2. CYP2C9 & 2C19 Phenotype Classification Based on Genotype

Phenotype	CYP2C9 Genotype	CYP2C19 Genotype
Extensive (EM, e.g. Wild type)	*1/*1	*1/*1
Intermediate (IM)	*1/allele other than *1	*1/allele other than *1 or *17
Poor (PM)	allele other than *1/allele other than *1	allele other than *1 or *17/ allele other than *1 or *17
Rapid (RM)	NA	*1/*17
Ultra-rapid (URM)	NA	*17/*17
Unknown (UM)	NA	*17/allele other than *1 or *17

NA: Not applicable

Table 3. Summary of Continuous Demographic Variables for all Studies (pooled)

	N	Mean (%CV)	Range
Age (yrs)	817	44.6 (19.4)	18-77
WT (kg)	817	71.7 (21.4)	34.5-160
CRCL (mL/min)	817	104 (29.2)	22.2-310

Analysis

A base model was developed, which considered a previously developed model for ETR. Covariates were then evaluated to determine if they could explain some of the variability in the PK of ETR. A mixture model was used to assign CYP2C9 and CYP2C19 phenotype for subjects where this information was not available. The analysis was performed using NONMEM (version 7.2 or higher) using the Intel Fortran Compiler. Models were fit to untransformed data using the FOCE method with the Interaction option.

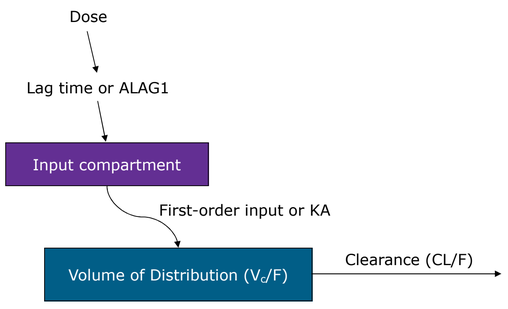
Table 4. Summary of Categorical Demographic Variables and Concomitant ARV for all Studies (pooled)

	N (%)
RACE	
Caucasian	396 (48.5)
Black/African American	215 (26.3)
Hispanic	103 (12.6)
Asian	15 (1.8)
Not allowed to ask	67 (8.2)
Other	21 (2.6)
SEX	
Male	633 (77.5)
Female	184 (22.5)
CYP2C9 Phenotype	
Poor Metaboliser	2 (0.2)
Intermediate Metaboliser	26 (3.2)
Extensive Metaboliser	88 (10.8)
Not Available	701 (85.8)
CYP2C19 Phenotype	
Poor Metaboliser	3 (0.4)
Intermediate Metaboliser	21 (2.6)
Extensive Metaboliser	55 (6.7)
Rapid Metaboliser	26 (3.2)
Ultra-rapid Metaboliser	5 (0.6)
Unknown	6 (0.7)
Not Available	701 (85.8)
Tenofovir	423 (30.8)
Enfuvirtide	252 (30.8)
Atazanavir	66 (8.1)
Darunavir	575 (70.4)
Lopinavir	124 (15.2)
Ritonavir	775 (94.9)

RESULTS

A schematic overview of the model is shown in **Figure 1**. The model included between-subject variability (BSV) on CL/F, V_c/F and F, with between-occasion variability (BOV) on F. Residual unknown variability (RUV) was included in the model as a single proportional term, with 2 separate additive terms based upon study.

Figure 1. Model Schematic



To evaluate if any covariates should be included in the model, 24 separate models were run in a univariate analysis.
The first covariate model evaluated CYP2C9 on CL/F. Subjects with known phenotype were included in the model with CL/F individually estimated for PM, IM and EM. Subjects with unavailable phenotype were estimated to be one of these 3 categories by use of a mixture model. Although the model minimised successfully with a significant drop of objective function (OBJ), one of the mixture parameters had a SE of 924% suggesting model over-parameterisation. The mixture model was then modified with only 2 parts on CL/F with subjects assigned to a PM group or combined IM/EM group and resulted in a significant drop of OBJ with all parameters estimated with good precision. The same approach was undertaken for evaluating CYP2C9 phenotype on F but did not lead to significant drop of OBJ.
CYP2C19 was also evaluated as a covariate on CL/F and F in the same way as CYP2C9, the mixture model consisting of 5 parts. Reduction of the mixture model was also necessary to avoid over-parameterisation. A final reduced 2-part mixture model with subjects assigned to either PM or an "other" could describe the influence of CYP2C19 on CL/F. This approach was also applied to F and had a significant drop in OBJ compared to the base model.

There was no effect of age or sex as a covariate, while weight was found to be a significant covariate on CL/F. CRCL was also found to be a significant covariate on CL/F. There were no other covariates identified during the univariate analysis, with none of the concomitant ARVs found to describe any of the variability in CL/F of ETR.

The full model included all the covariates identified in the univariate analysis and minimised successfully. Backward deletion and bootstrap analysis were performed. CYP2C19 influence on F was removed as its presence on both CL/F and F was not identifiable, leading to an unphysiological value of F. The shift in CL/F for subjects that were not in the poor metaboliser group was also removed.

Equation 1 shows the parameterisation of CL/F in the final model. Parameter estimates for the covariate model are presented in **Table 5**.

$$\mathrm{CL/F}=\left(\theta_2 \cdot CLPM^{\theta_1} \cdot CLUKPM^{\theta_3} \cdot \left(\frac{WT}{71}\right)^{\theta_9} \cdot \left(\frac{CRCL}{6}\right)^{\theta_{10}}\right) \cdot e^{\eta_1} \qquad \textbf{Equation 1.}$$

All structural parameters were estimated with good precision, with a minor exception for the mixture model parameters due to the small number of subjects in the known PM group. The goodness-of-fit plots (**Figure 2** & **Figure 3**) show minimal bias, although it can be seen that some individual observations were much lower than expected. This could have been due to a lack of compliance with medication intake on a few occasions.

Table 5. Parameter Estimates for the Covariate Model

Parameter		Estimate (SE %)	BSV (CV%) (SE %)	BOV (CV%) (SE %)
CL/F (L/h)	θ_2	41.7 (2.9)	39.4 (29.5)	
Shift for known CYP2C9 or CYP2C19 PM	θ_1	0.364 (17.6)		
Shift for unknown PM in mixture model	θ_3	0.226 (48.2)		
Proportion of subjects in PM mixture model (%)	θ_8*	1.57 (24.4)		
Exponent for WT	θ_9	0.291 (40.9)		
Exponent for CRCL	θ_{10}	0.246 (36.7)		
V_c/F (L)	θ_4	972 (9.4)	35.9 (48.0)	
KA (/hr)	θ_5	1.16 (10.4)		
ALAG1 (hr)	θ_6	1.32 (0.3)		
F	θ_7	1 FIX	35.5 (51.2)	30.0 (21.7)
Proportional Error (CV%)		31.0 (7.2)		
Additive Error for study TMC125-C206 & -C216 (ng/mL)		26.5 (39.7)		
Additive Error for study TMC125-C238 & IFD3002 (ng/mL)		56.7 (36.6)		

*: parameter transformed out of logit transformation.

Figure 2. Goodness of Fit Plots of the Covariate Model

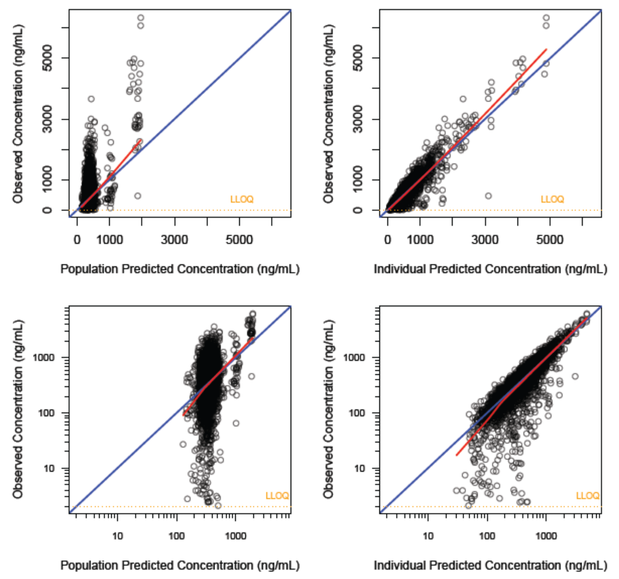
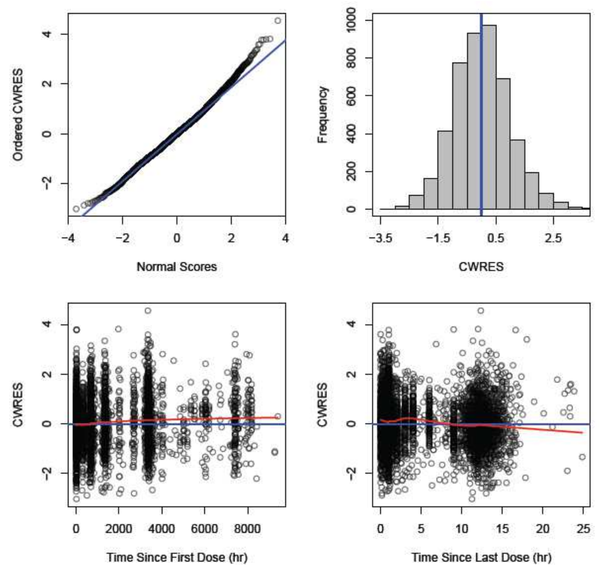


Figure 3. Conditional Weighted Residuals of the Covariate Model



A numerical predictive check was performed and indicated that approximately 5% of the observations were above and below the 5th and 95th percentiles of the prediction intervals, respectively.

DISCUSSION & CONCLUSION

The model was able to describe the PK of ETR following oral administration of ETR at a dose of 200 mg BID with good precision and no bias.

WT and CRCL were included as covariates on CL/F, together with CYP2C9 and CYP2C19 phenotype. The exponent of 0.291 on WT aligns with the allometric theory by approximating a value of 0.75 on lean body weight[1,2]. A mixture model was used to partition subjects of unavailable CYP2C9 and CYP2C19 phenotype into one of two groups: an "unknown" PM group, or the population estimate of CL/F. Known CYP2C9 or CYP2C19 PM were assigned a parameter describing a shift in their CL/F. The model predicted that 1.57% of subjects of unavailable phenotype were in the PM group, which is in alignment with the proportion found in the trials population (**Table 4**). The covariates on CL/F were found to be responsible for 5.1% of the overall variability estimated in the base model.

In conclusion, WT, CRCL, and CYP2C9 or CYP2C19 phenotype were found to describe some of the variability in ETR CL/F, although the effects were not considered clinically relevant. Also, there were no apparent clinically relevant differences in the effect of concomitant ARVs on the PK of ETR for adult subjects predominantly taking co-administered boosted protease inhibitors (PIs) as a background ARV regimen.

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MODEL ANSWERS

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