

Population Pharmacokinetic Analysis of Efavirenz in African Children Using Mixture Modelling to Describe Clearance Multimodality.

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Background and Objectives

- Efavirenz is a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) and, due to its potent activity and long half life allowing once daily dosing, it is a widely used component of combined antiretroviral therapy. [1]
- The drug is mainly metabolised by CYP2B6 and previous publications report multimodality in clearance distribution due to a number of mutations in the gene coding this enzyme. [2] This effect is especially prominent in the African population where prevalence of slow metabolisers caused by G516T mutation is particularly high. [3]
- Our objective was to characterise efavirenz PK at steady state in African children and to evaluate the use of mixture modelling to account for multimodal clearance, as an alternative, in the absence of individual CYP2B6 genotype data.

Methods

- Subjects** - combined intensive data from following studies in African children:

Table 1 Patient demographics:

	ARROW	CHAPAS3	Combined
No of patients	41	51	91*
No of samples	612	402	995**
Age (years)	7.65 (4 - 12)*	5.65 (2 - 13)*	6.12 (2 - 13)*
BW (kg)	20.25 (12.5 - 32)*	15.4 (10.7 - 27.9)*	18.5 (10.7 - 32)*
Duration of treatment	1st OCC: week 36 2nd OCC: week 40	week 6	
Sampling scheme	0hr, 1hr, 2hr, 4hr, 6hr, 8hr, 12hr, (24h -2nd OCC)	0hr, 1hr, 2hr, 4hr, 6hr, 8hr, 12hr, 24h	
Dosage	WHO 2006**	WHO 2010**	

*WHO 2006: <http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf?ua=1>

WHO 2010: http://whqlibdoc.who.int/publications/2010/9789241599801_eng.pdf?ua=1

- Model building** - conducted using NONMEM 7.2 (FOCE-I); guided by differences in OFV, VPCs (generated in PSN) and other diagnostic plots (created in R). Stability of final model was validated by bootstrapping.

Results

Model structure is in Fig 1 and final parameters with results from bootstrap in Tab 2.

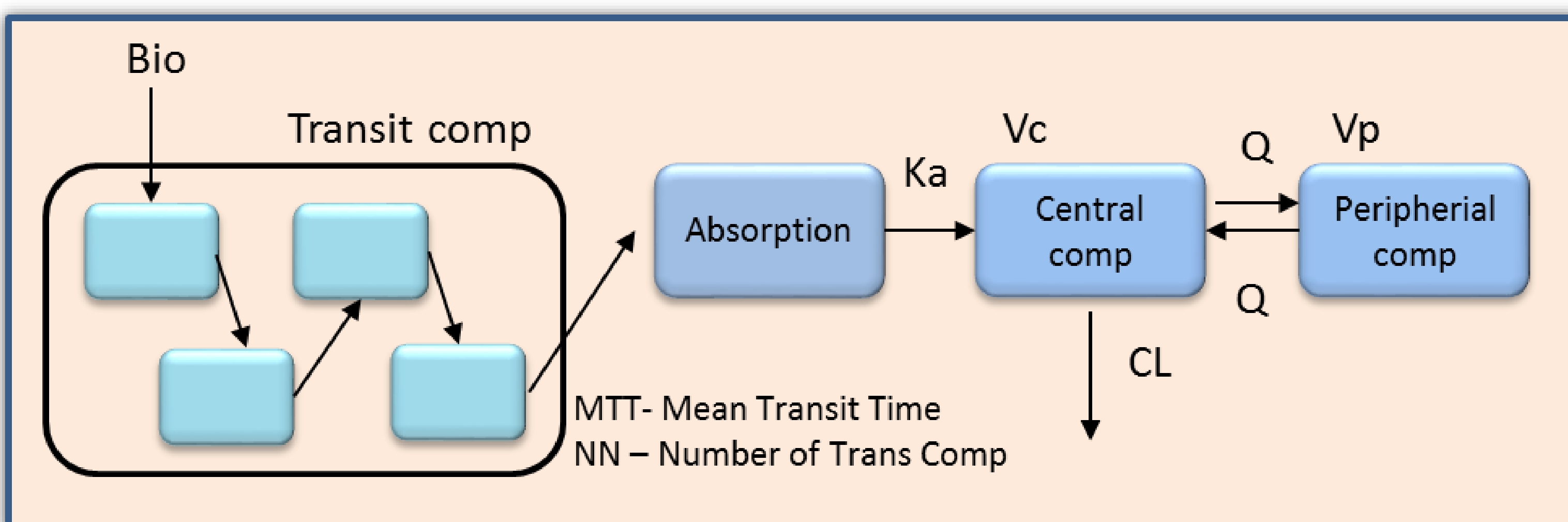


Figure 1 Structure of the final model.

- The data was described best using a 2-compartment model with absorption through a number of transit compartments. [4]
- Allometric scaling was used to account for effect of size and was applied on all CL and V parameters [5]; typical values were estimated for an 18.5 kg child
- Effect of maturation expressed by a power function of age or maturation function with Hill coefficient did not improve model fit significantly. [5]
- Inclusion of transit model to account for delay in absorption proved superior to LAG time.

Table 2 Final parameter estimates (5th and 95th percentile)*:

Fixed Effects (THETA)		Random Effects (ETA)**	
CL POP1 [L/h]	8.37 (7.59 - 9.07)	BSVCL	11.7% (0.5% - 24.5%)
CL POP2 [L/h]	3.51 (2.43 - 4.27)		
CL POP3 [L/h]	1.49 (0.89 - 1.84)		
Vc [L]	90.3 (76.6 - 103)	BSVVc	50.0% (28.0% - 61.2%)
Q [L/h]	18.7 (14.8 - 24.2)	BSVQ	70.6% (49.9% - 111.4%)
Vp [L]	113 (99.3 - 138)		
KA [1/h]	1.26 (1.03 - 1.51)	BOVKA	59.7% (49.2% - 73.7%)
MTT [h]	1.02 (0.90 - 1.14)	BOVMTT	60.7% (52.3% - 67.4%)
NN []	23.4 (16.7 - 30.0)		
BIO	1 (FIX)	BOVBIO	56.4% (45.7% - 65.5%)
Error Model			
Prop (POP1)*	58% (49% - 68%)	ADD [µg/mL]	0.0913 (0.0674 - 0.124)
Prop (POP2)*	25% (17% - 35%)	PROP [%]	5.7% (4.0% - 7.2%)
Prop (POP3)*	17% (7% - 26%)		

* Estimated from nonparametric bootstrap (n=150) of the final model, **Expressed in SD scale

* The proportions of patients in each subpopulation calculated from equation $P(POP1) = 1/(1+THETA(1)+THETA(2))$

- Inclusion of liver first pass model as per Gordi et al did not provide significant drop in OFV. [6]
- Inclusion of mixture model with 3 subpopulations in the model building process caused drop in OFV of 22.067 and drop in BSVCL from 69.6% to 18.9%.
- The model shows significant differences in clearance between the subpopulations.
- According to the model the clearance in children is higher than reported values in adults, which is in line with previous publications. [8, 9]

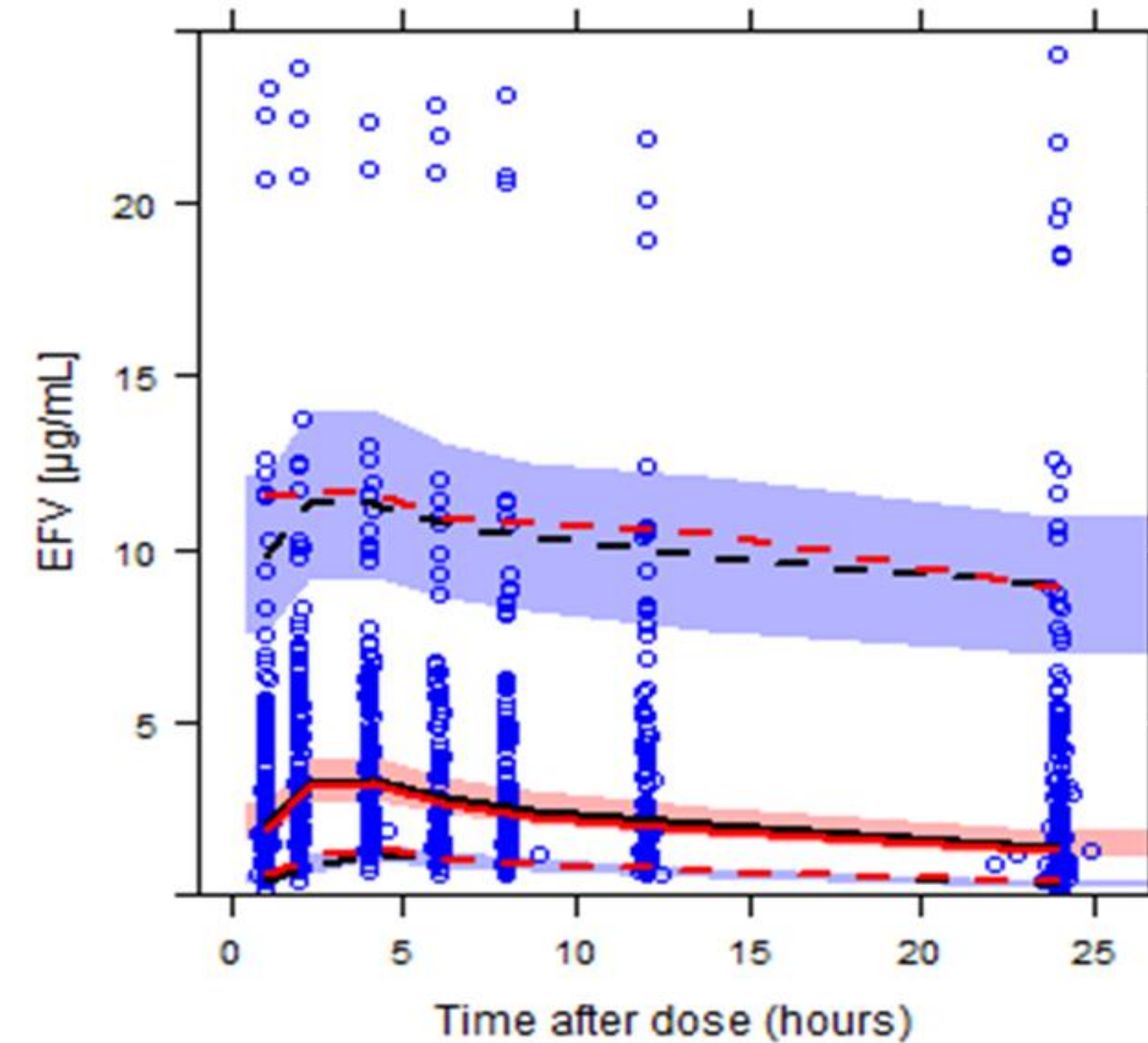


Figure 2 Visual predictive check of the final model (log scale)

Table 2 Comparison of clearance estimates with previous publications:

	Nyakutria et al [7]			Viljoen et al [8]			Our model	
	74 African adults, age* - 39 years			60 African children, age* - 6.8 years (3.2 - 14.8)			92 African children, age* - 6.8 years (2.12-13.9)	
	CL[L/h]		Prop*	CL [L/h]		Prop*	CL[L/h]	Prop*
Weight**	60kg	18.5kg		20kg	18.5kg		18.5kg	
Extensive	9.4	3.89	30%	7.3	6.89	35%	8.37	58%
Intermediate	7.2	2.98	44%	4.6	4.34	42%	3.51	25%
Slow	4	1.66	27%	2.46	2.32	23%	1.49	17%

*mean, (range), ** study/ scaled = $CL*(18.5/study)^{0.75}$, * The proportions of patients in each subpopulation

- Simulated trough concentrations (median, IQR) in slow, intermediate and extensive metabolisers are respectively: 8.11 µg/mL (6.17 – 10.34), 2.84 µg/mL (2.1 – 3.79), 1.05 µg/mL (0.63 – 1.34).

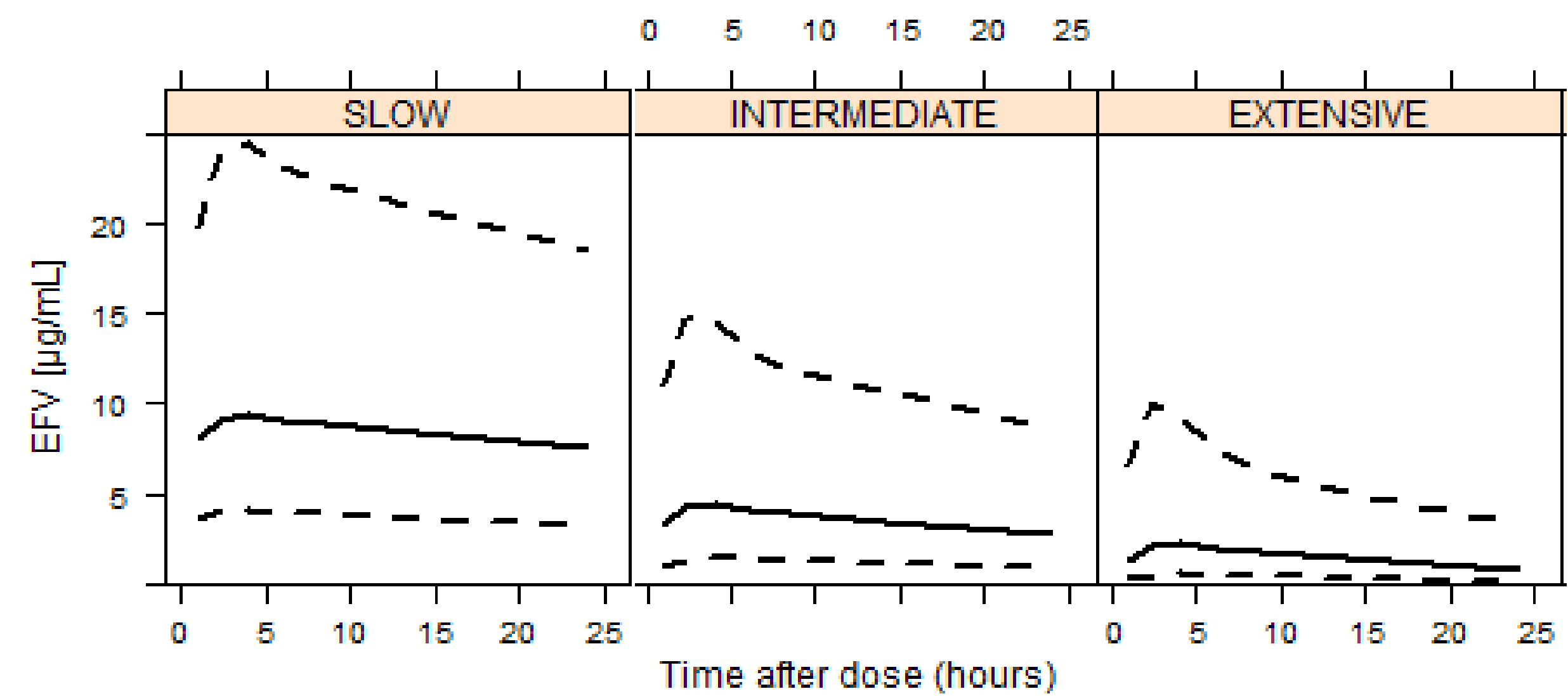


Figure 3 Concentration vs time profiles in subpopulations (solid lines are median values obtained through 1000 simulations of final model, dashed lines are the 5th and 95th percentiles)

Conclusions

- The model adequately describes the data and the mixture model significantly improved the fit.
- This multimodality for efavirenz clearance is consistent with previous reports, although the typical values and frequency of each subgroup found in this analysis differ from previous publications.
- This may be due to the fact that in mixture modelling approach those values are estimated empirically based on the data and not on the robust information about genotype, and may be affected by other confounders.
- Issues related to dosing in children (e.g. splitting tablets) and poor adherence can be expected to be contributory factors to high BOV in BIO seen in the model.
- The lack of a maturation effect could be due to the fact that most children in the study were older than 3 years.
- In order to improve stability of the model and characterise other sources of variability incorporation of information on patients' genotype is needed.

References

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*ARROW, *CHAPAS-3