

Background and Objectives

- Nevirapine is a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) widely used for treatment of HIV-infected adults and children [1], including new born [2].
- It is metabolised mainly by *CYP3A4* and *CYP2B6* [3]. *CYP2B6* polymorphisms significantly influence the disposition of the drug and their prevalence is significantly higher in African population [4].
- The aim was to characterise the pharmacokinetics (PK) of nevirapine in African children and to identify patient characteristics influencing its disposition.

Methods

- Subjects** - Combined data from following studies in African children:

Tab 1 Patient demographics:

	CHAPAS-1	CHAPAS-3	Combined
No of patients	84	334	418
No of samples	547 (8)*	3004 (238)*	3501 (246)*
Age (years)	6.16 (0.4 - 15)*	3.73 (0.44 - 12.3)*	4.22 (0.4 - 15)*
Body Weigh (kg)	15.11 (3.5 - 29)*	13.45 (5.5 - 30.0)*	14.5 (3.5 - 30)*
Duration of treatment	iPK at week 6	sPK at week 6, 36, 60, 84, 108, 136**	
Sampling scheme	0h, 1h, 2h, 4h, 6h, 8h, 12h	1-2 samples, 2-3h apart	*Samples excluded **Median (range)
Dosage	WHO 2006**	WHO 2010**	**Not equal number per patient

**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

- Samples excluded** from analysis: unclear dosage history – 111, implausible (visual check confirmed by CWRES) – 87, BLQ confirmed by absence of the other drugs – 48.
- Model building** - conducted using NONMEM 7.3 (FOCE-I) following an approach previously suggested to combine intensive and sparse data [5]; 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 3.

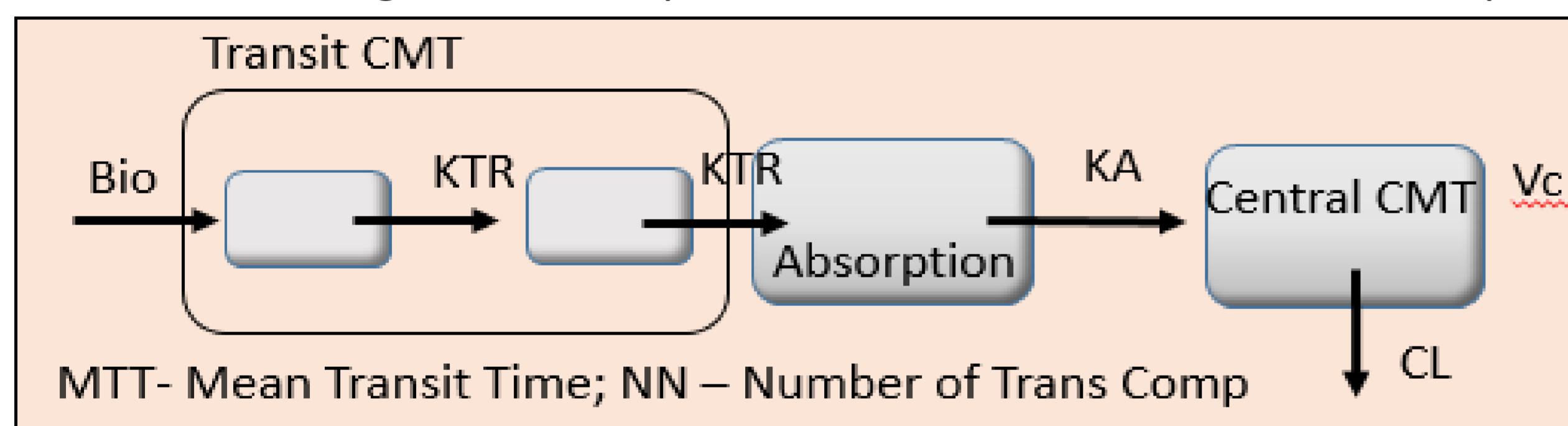


Figure 1 Structure of the final model.

- The data was best described using a 1-compartment model with absorption through 2 transit compartments [6] and first-order elimination.

- Allometric scaling was used to account for effect of size and was applied to CL and V [7]; typical values were estimated for a 14.5 kg child.

- The most significant determinant of nevirapine PK was a composite PGx SNP vector *CYP2B6* 516/983 on CL [2]. Patients were allocated to 4 metaboliser groups based on their genotype (Table 2).

Tab 2 Patient metabolic status

Status	516GT	983TC	Preval.
Fast	GG	TT	33.1%
Inter	GG	TC	44.6%
Slow	GT	TT	21.7%
U-slow	GG	CC	0.6%

Tab 3 Final parameter estimates (5th and 95th percentile)*:

Fixed Effects (THETA)		Random Effects (ETA)**	
Fast CL [L/h]	1.83 (1.75-1.90)	BSV CL	37.8% (29.15%-37.78%)
Inter CL [L/h]	1.31 (1.29-1.47)	BOV BIO for observed Intake	6.3% (6.19%-7.22%)
Slow CL [L/h]	0.843 (0.82-0.94)	BOV BIO increase for self-reported intake	5.72x (5.36-5.79)
U-slow CL [L/h]	0.383 (0.38-0.50)	BOV KA	52.6% (35.12%-53.01%)
Vc [L]	32.4 (29.75-32.99)	BOV MTT	180% (174.2%-228.8%)
KA [1/h]	1.15 (1.03-1.18)	Error Model	
MTT [h]	0.204 (0.20-0.34)	Additive [mg/L]	0.455 (0.42-0.53)
NN []	2 (FIXED)	Proportional [%]	4.27% (4.22%-6.18%)
BIO []	1 (FIXED)	Increase for sparse data	1.67x (1.25-1.67)

* Estimated from nonparametric bootstrap (n=50) of the final model, **Expressed as approximate %CV

- The model shows significant differences in clearance between the genotype sub-populations.
- Children with no available genotype information (n=79) were assigned to a group using a mixture model reflecting the prevalence in the rest of the cohort [8].
- Effect of age on CL (i.e. maturation) either expressed as a power function or sigmoidal function with Hill coefficient did not significantly improve model fit [7].
- Accounting for the effect of poor adherence and increased uncertainty about the time of unobserved doses preceding the sparse sampling by introducing a correction terms on RUV and BOV BIO improved fit.

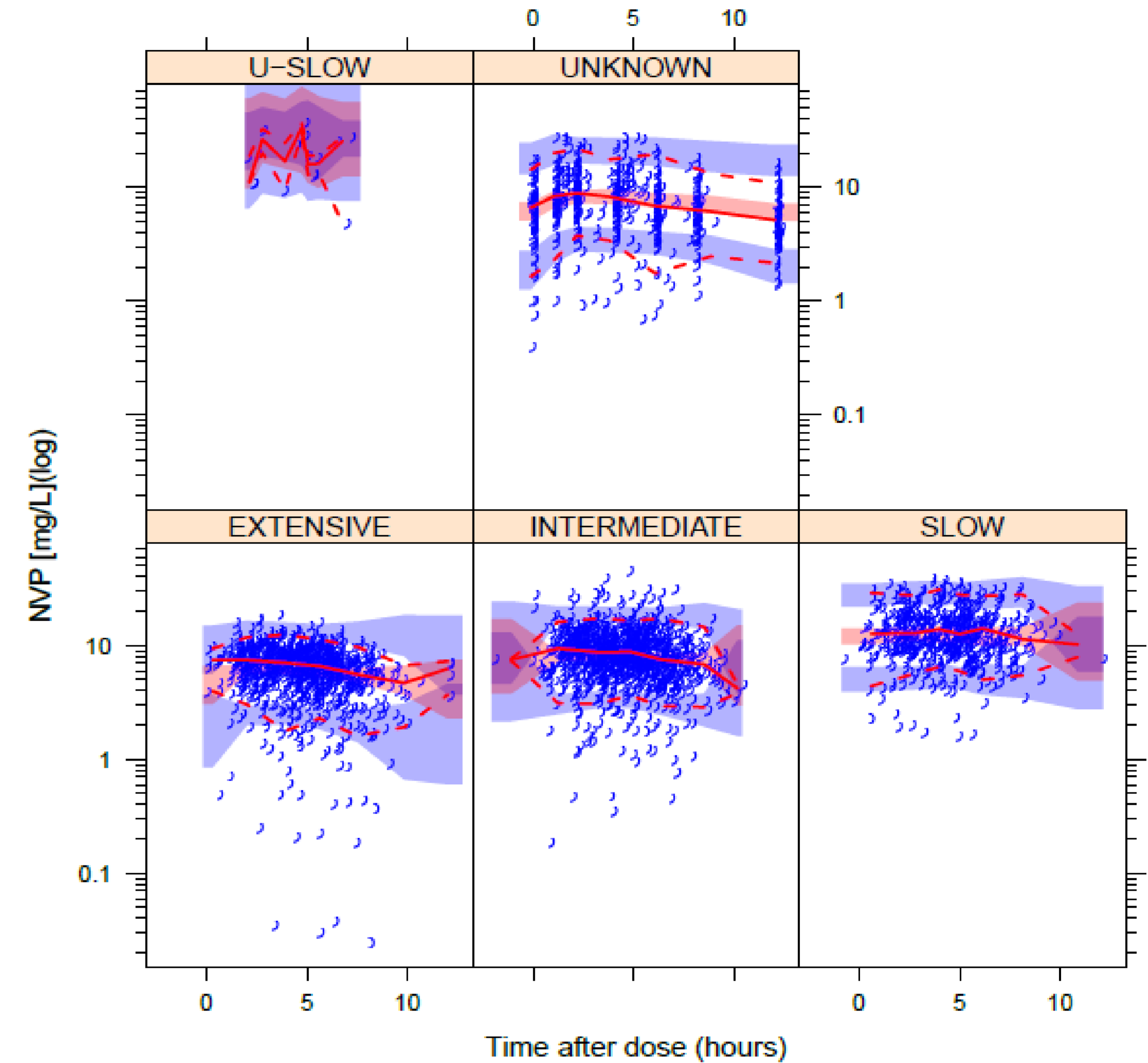


Figure 2 Visual predictive check of the final model by metabolic group

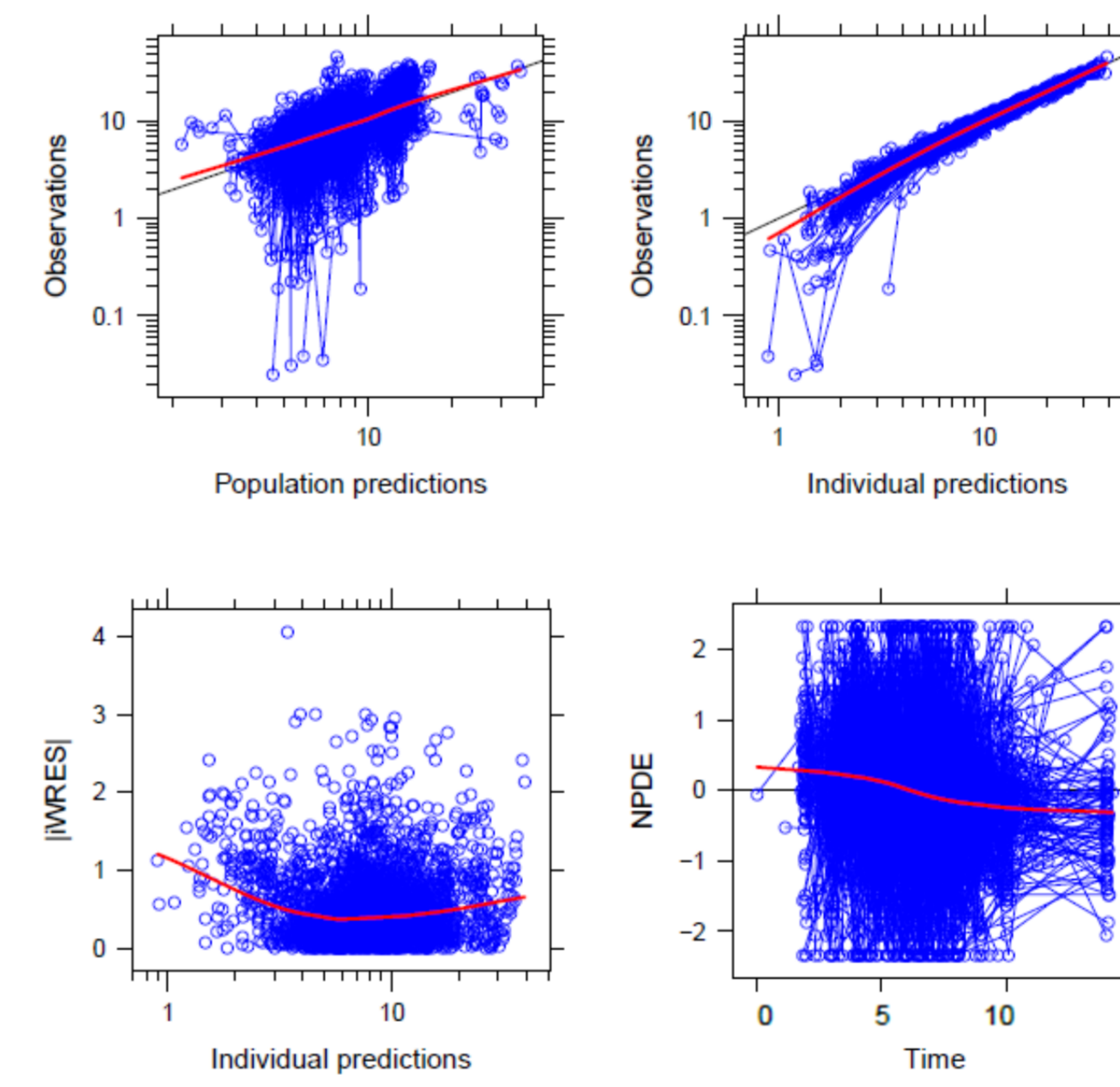


Figure 3 GOF plots

The VPC and GOF plots indicate good fit, although the model is slightly under-predicting morning concentrations. This could be due to circadian rhythm in hepatic CYP 3A4 activity, as previously reported [9].

Conclusions

- The model adequately describes the data. Uncertainty about the intake of the evening dose complicates the investigation of the observed lower trough concentrations in the evening than in the morning.
- Nevirapine metabolism in children is affected by a composite effect of 2 SNPs in *CYP2B6*: 516GT (*rs3745274*) and 983TC (*rs28399499*).
- Based on differences in clearance, slow metabolisers should receive about 50% and ultra-slow (more rare) only 20% of the standard dose to maintain exposures comparable to the rest of the subjects.
- The lack of significance of a maturation effect could be due to small proportion of observations under 2 years of age.

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