Appendix

The nevirapine model presented in Figure 1 is explained in detail below.

The delay between oral administration and absorption is modelled through 2 transit compartments. After entering the absorption compartment, nevirapine is transferred to the liver, where it undergoes 1st-pass hepatic extraction (E_H). The fraction of the drug not eliminated by 1st-pass ($1-E_H$) is then transported via hepatic plasma flow (Q_H) to the central compartment and the systemic circulation. It then recirculates back to the liver, which is the site of drug clearance. In this well-stirred model, hepatic clearance (CL_H) is determined by Q_H and E_H as follows:

(1) $$CL_H = Q_H \cdot E_H$$

E_H depends on the unbound fraction of the drug (f_u), liver activity (CL_{int}), and Q_H and is defined as:

(2) $$E_H = \frac{CL_{int} \cdot f_u}{CL_{int} \cdot f_u + Q_H}$$

E_H also determines the hepatic bioavailability F_H

(3) $$F_H = 1 - E_H$$

The total oral bioavailability (F) is determined by both the pre-hepatic (F_{preH}) and hepatic (F_H) components, as follows:

(4) $$F = F_{preH} \cdot F_H$$

After a number of transformations, oral clearance can be simplified as follows:

(5) $$CL_{oral} = \frac{CL}{F} = \frac{CL_{int} \cdot f_u}{F_{preH}}$$

Due to circadian rhythm variations, CL_{int} changes with time, thus affecting both CL_H and F_H, and its value at time (t) is defined as follows:

$$CL_{int}(t) = CL_{int} \cdot e^{AMP \cdot cos\left(\frac{2\pi}{24} \cdot (t - SHIFT)\right)} \quad (6)$$

where AMP is the amplitude of the cosine oscillation and SHIFT is the phase shift of the cosine function relative to 00:00. In order to prevent negative values of CL_{int} the effect of the circadian rhythm was modelled as exponential and can be interpreted approximately as a relative change.

Furthermore, F_{preH} changes with age, as expressed by following equation:

$$F_{preH} = 1 - \left(1 - F_{preH\_BIRTH}\right) \cdot e^{-K_{FpreH} \cdot AGE} \quad (7)$$

where F_{preH_BIRTH} is the F_{preH} at birth, K_{FpreH} is the rate constant for age-driven change in F_{preH} and AGE refers to age.

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Table S1. Observed Frequencies of Tested Single Nucleotide Polymorphisms with Corresponding Hardy-Weinberg P-values						
Gene	**SNP**	**Hom-Ref†**	**Het-LOF†**	**Hom-LOF†**	**MAF**	**HWE P-value**
CYP2B6	**rs3745274 (516G>T)**	GG	GT	TT	0.36	0.18
		136 (0.43)	136 (0.43)	47 (0.15)		
	rs28399499 (983T>C)	TT	TC	CC	0.09	1
		226 (0.83)	51 (0.16)	2 (0.01)		
	rs4803419 (15582C>T)	CC	TC	TT	0.07	0.19
		227 (0.87)	39 (0.12)	3 (0.01)		
CYP3A4	**rs35599367 (CYP3A4*22)**	GG	GA	AA	0.003	1
		317 (0.99)	2 (0.01)	0		
CYP3A5	**rs776746 (6986G>A)**	GG	GA	AA	0.82	0.44
		12 (0.04)	88 (0.28)	219 (0.69)		
NR1I3 (CAR)	**rs3003596**	AA	AG	GG	0.49	1
		78 (0.24)	159 (0.50)	82 (0.26)		
	rs2307424 (540C>T)	CC	CT	TT	0.08	0.42
		272 (0.85)	44 (0.14)	3 (0.01)		
NR1I2 (PXR)	**rs2472677 (63396C>T)**	CC	CT	TT	0.36	0.14
		124 (0.39)	160 (0.50)	35 (0.11)		
ABCC10	**rs2125739**	TT	CT	CC	0.23	0.27
		185 (0.58)	120 (0.38)	13 (0.04)		

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32 †number (proportion). Hom-Ref - homozygous for the functional allele; Het-LOF - heterozygous for
33 the loss-of-function (LOF) allele; Hom-LOF - homozygous for the LOF allele; MAF – minor allele
34 frequency; HWE - Hardy-Weinberg equilibrium.

Note: information for 319 children from CHAPAS-3 study (aside from rs2125739 – data on 318 children).

Table S2. Model estimated clearance intrinsic and corresponding hepatic clearance, hepatic extraction, hepatic bioavailability and oral clearance by metaboliser status.

Metabolizer Status	CL_{int} [L/h]	CL_H [L/h]	E_H	F_H	CL_{oral} [L/h]
Fast	3.27	1.20	7.9%	91.1%	1.29
Intermediate	2.72	1.01	6.6%	93.4%	1.09
Slow	1.65	0.63	4.1%	95.9%	0.68
Very slow	1.04	0.40	2.6%	96.4%	0.43

CL_{int} – clearance intrinsic; CL_H – clearance hepatic; E_H – hepatic extraction; F_H – hepatic component of bioavailability; CL_{oral} – oral clearance

Note: The relationship between parameters and how they can be derived explained in the Appendix. Presented values relate to an average child of 14.5 kg, 4.1 years of age and corresponding pre-hepatic bioavailability of 93% and hepatic plasma flow of 15.35 (L/h).

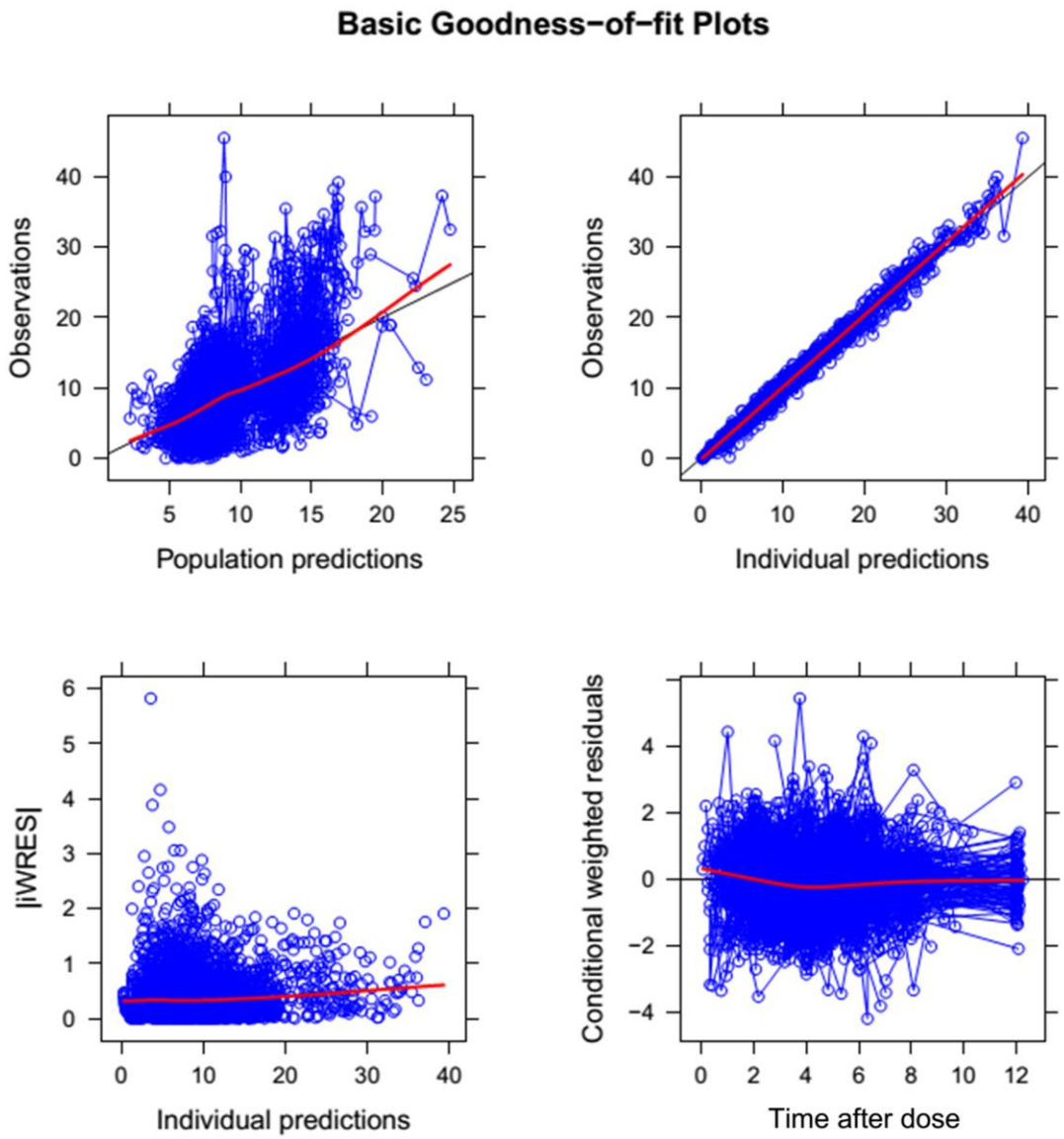
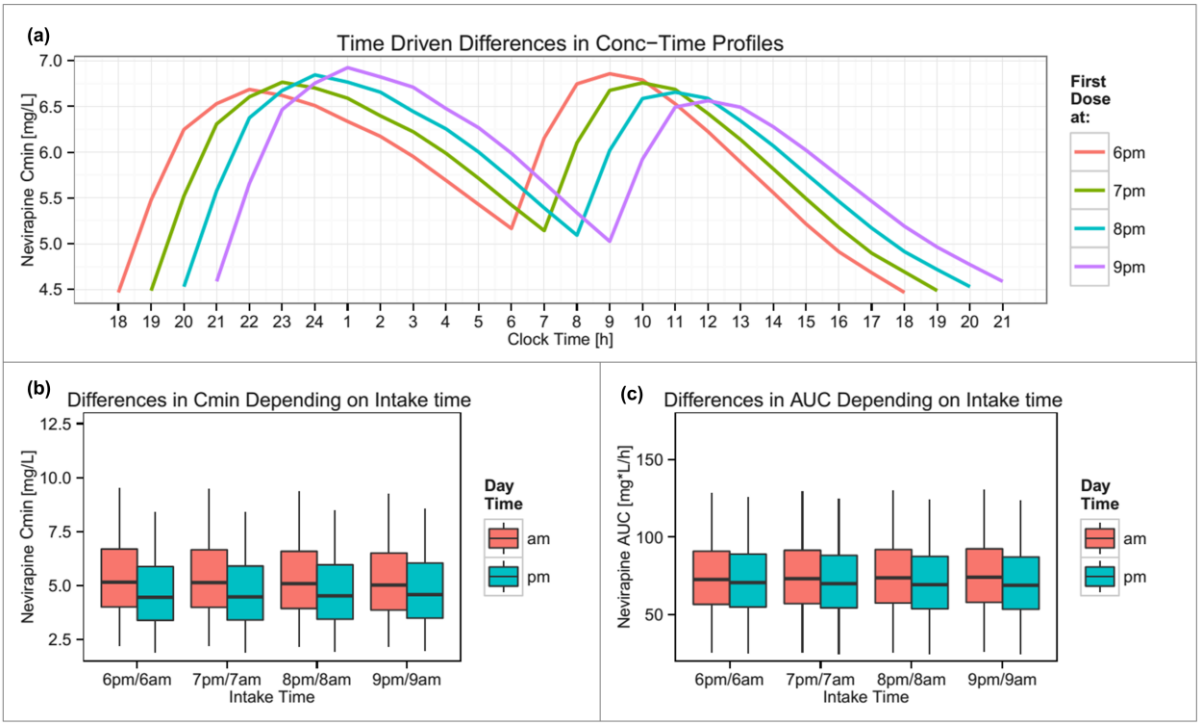


Figure S1. Goodness of fit plots. Top left – observations vs population predictions (log scale); top right – observations vs individual predictions (log scale); bottom left – absolute values of individual weighted residuals vs individual predictions bottom right – conditional weighted residuals (CWRESI) vs time after dose;



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55 **Figure S2.** Results of simulations evaluating the effect of intake time on nevirapine exposures (see

56 Methods): (a) concentration-time curves for evaluated intake time scenarios; (b) differences

57 between morning and evening C_{min} depending on intake time; (c) differences between morning and

58 evening AUC depending on intake time.

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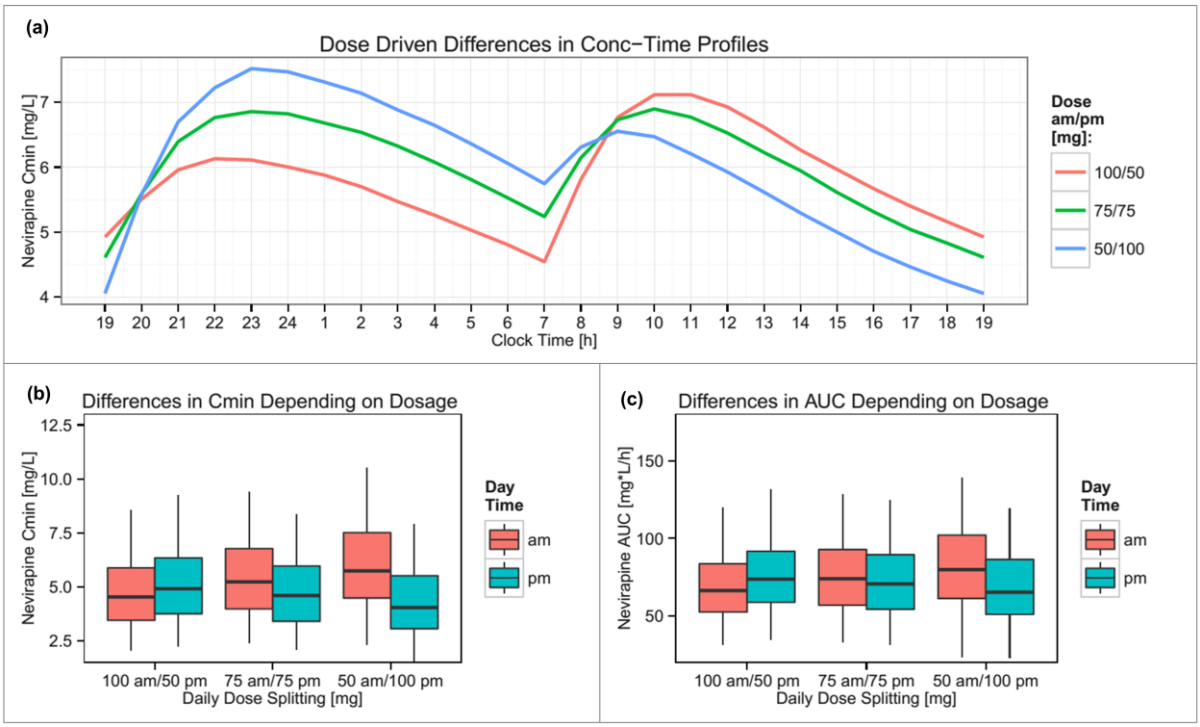

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61 **Figure S3.** Nevirapine exposures obtained using different dose-splitting strategies (see Methods): (a)
62 concentration-time curves for the evaluated dosing scenarios; (b) differences between morning and
63 evening C_{min} depending on dose-splitting strategy; (c) differences between morning and evening AUC
64 depending on dose-splitting strategy.

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