

# Maternal zidovudine infusions in HIV-1 infected women:

## Impact on fetal concentrations and exposures

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### INTRODUCTION

Administration of zidovudine (ZDV) to pregnant women has significantly decreased the mother to child HIV transmission. The dosing regimen recommended during pregnancy is an oral administration, continuous intravenous infusion during labor with a rate of 2 mg/kg the first hour followed by a rate of 1mg/kg/h up to the end of delivery and an oral administration to the neonate in his first 12 hours of life.

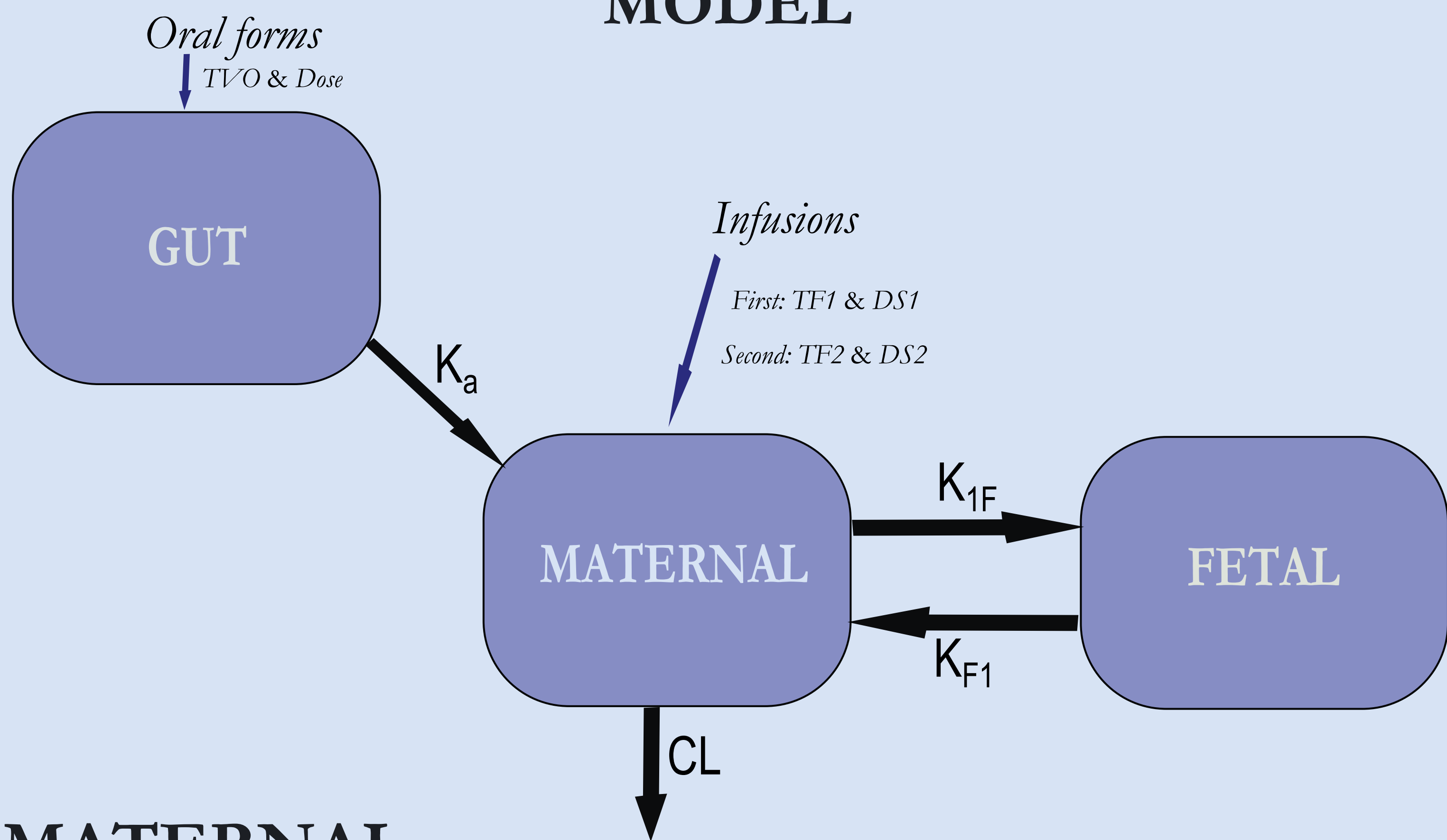
Although ZDV toxicity has been established in neonates, the consequences of maternal dosing regimen during pregnancy (oral) and/or labor (intravenous) have never been described on fetal concentrations and exposures.

### AIMS

The main goal of the study was to develop a model, linking the fetal concentrations to the maternal concentrations, in order to evaluate the impact of ZDV maternal administrations on fetus.

Then, fetal exposures due to maternal administration during pregnancy and labor were derived from the model and compared to (i) effective and non-toxic exposures, (ii) postpartum neonate exposures.

### MODEL



### MODELING

The data were analyzed using NONMEM and the first order conditional estimation with interaction (FOCEI) method was applied. One and two compartment models were tested to describe plasma ZDV concentrations in mother.

The fetal compartment was modeled as virtual compartment with a negligible volume and was connected to the maternal compartment by one or two constants which do not modify the compartmental model in mother. After delivery, the fetal compartment was disconnected, the time was reset to zero and newborn had his own rate of absorption and elimination.

### PARAMETERS

TAD was the time elapsed between the last maternal administration (oral or infusion) and the sampling time. TVO was the time elapsed between the last maternal oral administration and the start of the first infusion. TF1 and TF2 were the times of the first and the second infusions. DS1 and DS2 were the total doses received during the infusion; DOSE was the maternal oral dose.

The parameters estimated were maternal bioavailability (F), absorption rate constant (Ka), volume of distribution (V), elimination clearance (CL), maternal to fetal rate (K1F) and fetal to maternal rate (KF1).

### PATIENTS

Item	Number of Patients (Number of samples)	Median Age (years)(range)	Median Bodyweight (kg)(range)	Median gestational age (week)(range)
Whole Population	195 (263)	33 (16-59)	72 (41-110)	35 (0-42)
Women in active labor	74 (79)	33 (21-44)	73 (50-104)	38 (28-42)
Pregnant Women	56 (72)	33 (21-44)	73 (53-110)	27 (8-39)
Non Pregnant Women	89 (122)	31 (16-59)	64 (41-100)	-

### MATERNAL

$$Cp = \frac{F * Dose * Ka}{V * (Ka - Ke)} \left( \frac{e^{-Ke(TAD)}}{(1 - e^{-Ke\tau})} - \frac{e^{-Ka(TAD)}}{(1 - e^{-Ka\tau})} \right) + \frac{DS1}{TF1 * Ke * V} \left( (1 - e^{-Ke*TF1}) * e^{-Ke*(TAD-TV0-TF1)} \right) + \frac{DS2}{TF2 * Ke * V} \left( (1 - e^{-Ke*TF2}) * e^{-Ke*(TAD-TV0-TF1-TF2)} \right)$$

### FETAL

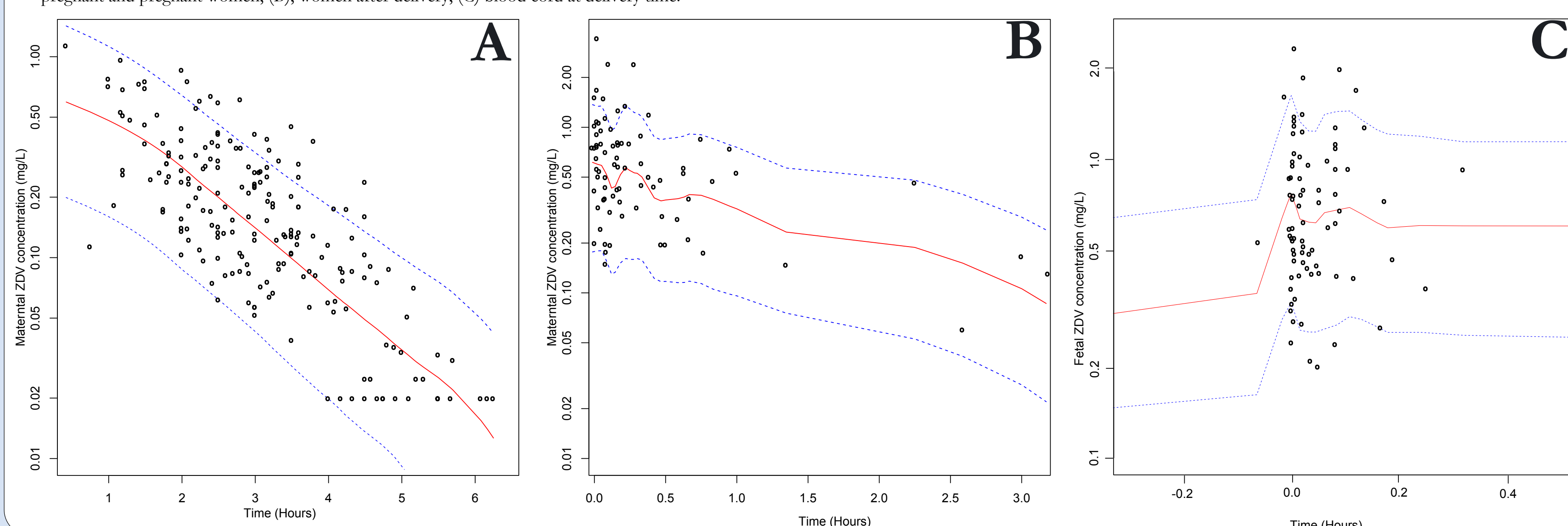
$$Cp = \frac{F * Dose * Ka * K1F}{V} \left( \frac{e^{-Ka(TAD)}}{(Ke - Ka) * (KF1 - Ka) * (1 - e^{-Ka\tau})} + \frac{e^{-Ke(TAD)}}{(Ka - Ke) * (KF1 - Ke) * (1 - e^{-Ke\tau})} + \frac{e^{-KF1(TAD)}}{(Ka - KF1) * (Ke - KF1) * (1 - e^{-KF1\tau})} \right) + \frac{DS1 * K1F}{(TF1 * KF1 * Ke * V * (KF1 - Ke))} \left( -Ke * (1 - e^{-KF1*TF1}) * e^{-KF1*(TAD-TV0-TF1)} + KF1 * (1 - e^{-Ke*TF1}) * e^{-Ke*(TAD-TV0-TF1)} \right) + \frac{DS2 * K1F}{(TF2 * KF1 * Ke * V * (KF1 - Ke))} \left( -Ke * (1 - e^{-KF1*TF2}) * e^{-KF1*(TAD-TV0-TF1-TF2)} + KF1 * (1 - e^{-Ke*TF2}) * e^{-Ke*(TAD-TV0-TF1-TF2)} \right)$$

### MODEL PARAMETERS

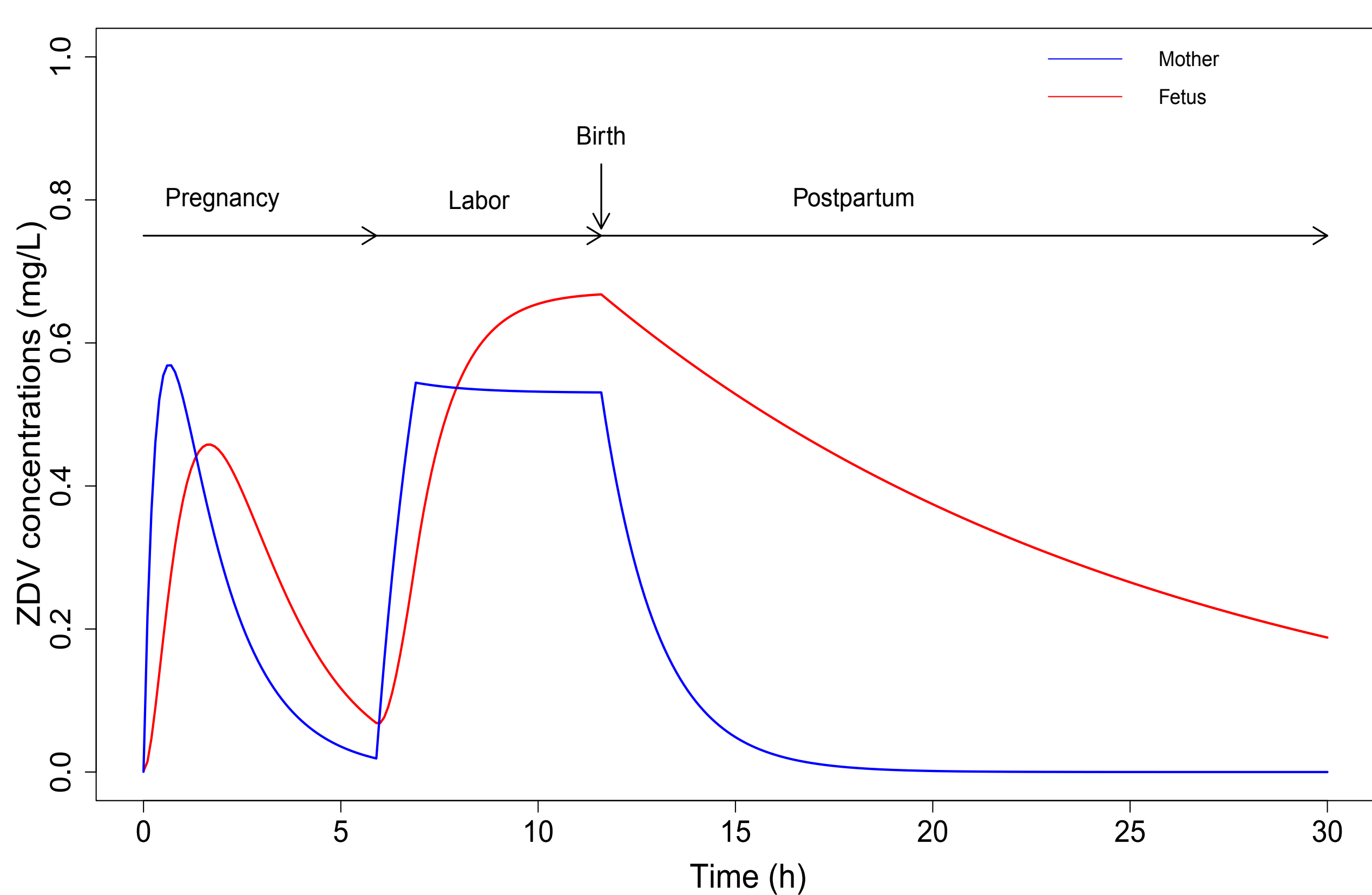
Parameters	Structural model			Statistical model			
	Estimate	RSE%	95%CI	Parameters	Estimate	RSE%	95%CI
Ka (h <sup>-1</sup> )	2.86 <sup>a</sup>	-	-				
CL (L.h <sup>-1</sup> )	131	5.8	118-147	ω <sub>CL</sub>	0.358	22.3	0.286-0.450
V (L)	188	10.1	156-227	ω <sub>V</sub>	0.363	47.5	0.216-0.554
F (%)	56	9.2	47-67	Corr <sub>(CL/V)</sub>	0.885	13.0	0.748-0.984
K <sub>1F</sub> (h <sup>-1</sup> )	1.21	38.8	0.66-13.5	σ <sub>maternal</sub>	0.390	15.4	0.335-0.451
K <sub>F1</sub> (h <sup>-1</sup> )	0.946	41.9	0.48-11.5	σ <sub>fetal</sub>	0.278	28.9	0.163-0.336

Key: RSE% relative standard error (standard error of estimate/estimate \*100); a, fixed value; ω and σ between-subject and residual variabilities; Corr, correlation between two parameters.

Visual predictive check: comparison between the 5 th (dashed line), 50 th (full line) and 95 th (dashed line) percentiles obtained from 1000 simulations and the ZDV observed plasma concentrations (o) for: (A) non pregnant and pregnant women, (B) women after delivery, (C) blood cord at delivery time.



### PHARMACOKINETIC PROFILES

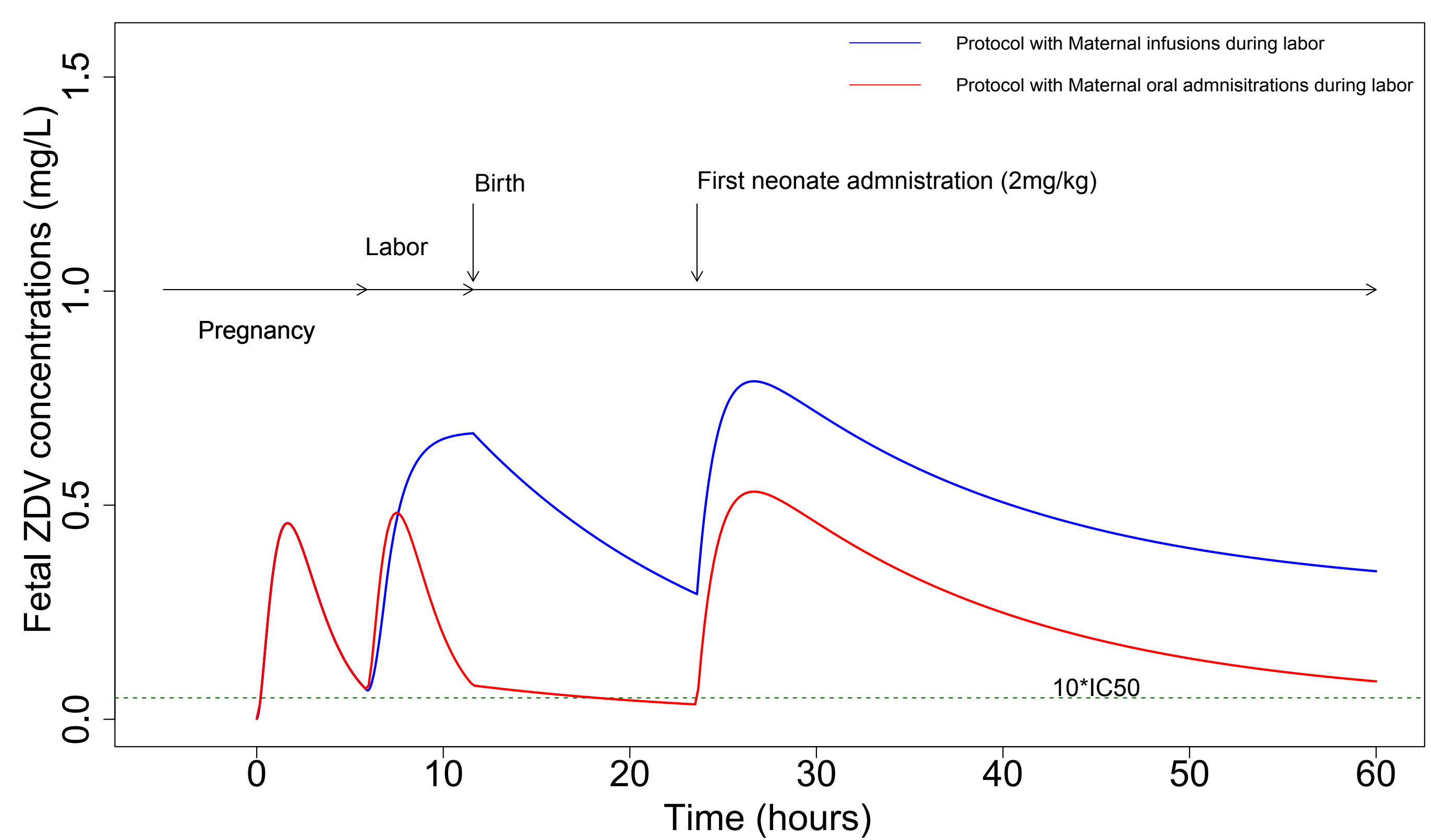


The median fetal exposure (0-24 hours) due to maternal oral administration (3.20 mg/L.h) was higher than the maternal exposure during pregnancy (2.50 mg/L.h)

The median maternal exposure (0-24 hours) due to infusions (3.77 mg/L.h) was higher to those resulting from oral administration (2.50 mg/L.h).

The median fetal exposure resulting from maternal infusions (from start of the infusions up to 24 hours later) was much higher (9.71 mg/L.h) than corresponding median maternal exposure (3.77 mg/L.h)

### SIMULATIONS



The median fetal exposure due to maternal infusions (9.71 mg/L.h) was two times lower than the 0-24 hours exposure (18.5 mg/L.h) estimated in a neonate weighting 3 kg on the first day of life and receiving current French recommendations (2mg/kg).

These exposures were higher than the toxic threshold suggested in a previous study (AUC >8.4 mg/L.h). By maintaining the present protocol, neonates have exposures at higher risk of toxicity. We have simulated different infusions rate (not shown) and maternal dosing regimen during labor.

Thus, to keep a fetal protective concentration (i.e 10\*IC50) and to decrease the toxicity risk, either maternal infusions rate could be decreased by half or the mother could take ZDV orally every 5 hours during labor.

### CONCLUSIONS

This study reports for the first time a model linking the fetal ZDV concentration to the maternal ZDV concentrations. No covariate effect was found (pregnancy, age, bodyweight) on the maternal pharmacokinetics. By maintaining maternal infusions at delivery, neonates have exposures at higher risk of toxicity. Thus, to keep a fetal protective concentration and to decrease the toxicity risk, either maternal infusions rate could be decreased by half or the mother could take ZDV orally every 5 hours during labor.