Population pharmacokinetics of emtricitabine in human immunodeficiency virus type 1-infected pregnant women and their neonates.

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Population Pharmacokinetics of Emtricitabine in HIV-1 infected Pregnant Women and their neonates (ANRS 12109).

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Abstract.

Objectives: To evaluate emtricitabine (FTC) pharmacokinetics (PK) in pregnant women and their neonates and to determine the optimal prophylactic dose for neonates after birth to prevent mother-to-child transmission of HIV (PMTCT).

Methods: 38 HIV-infected pregnant women were administered Tenofovir Disoproxyl Fumarate (TDF, 300mg)- emtricitabine (FTC, 200mg) tablets: 2 at the initiation of labour and 1 daily for 7 days postpartum. By pair, 11 maternal, 1 cord blood and 2 neonatal FTC concentrations were measured using an HPLC MS MS validated method and analyzed by a population approach.

Results: Model and mean estimates (inter-patient variability) were a 2-compartment model for mother with absorption rate constant 0.54 h^{-1} (61%), apparent elimination and intercompartmental clearance 23.2 (17%) and 6.04 $L.h^{-1}$ and apparent central and peripheral volume 127 and 237L; an effect compartment linked to maternal circulation for cord and a neonatal compartment disconnected, after delivery, with a 10.6 hours half life (30%). After the 400 mg FTC administration, median population AUC, C_{max} and C_{min} in pregnant women were 14.3 $mg.L^{-1}.h$, 1.68 and 0.076 mg/L respectively. At delivery, median (range) FTC predicted maternal and cord concentrations were respectively 1.16 (0.14–1.99) and 0.72 (0.05–1.19) $mg.L^{-1}$.

Conclusion: The 400 mg FTC administration in pregnant women produces higher exposition than the 200 mg administration to adults, at steady state. FTC was shown to have good placental transfer (80%). Administering FTC 1 mg/kg as soon as possible after birth or 2 mg/kg 12 hours after birth should produce neonatal concentrations comparable to those observed in adults.

Introduction

To prevent mother-to-child transmission of HIV around the delivery, a single-dose administration of nevirapine (sdNVP) administered at start of labour is the most common antiretroviral regimen used in resource-limited settings, as recommended by the World Health Organization in the antiretroviral drugs for treating pregnant women and preventing HIV infection in infants report (http://www.who.int/hiv/pub/guidelines/pmtctguidelines3.pdf). However, the use of sdNVP results in resistance mutations in 15 to 70% of women, at 4 to 6 weeks postpartum, compromising the success of subsequent treatments with NVP in mother and child (7, 9). A recent clinical study suggests that adding a single dose of TDF and FTC at delivery may reduce those resistances by half (6).

Emtricitabine is a potent, once daily (QD) nucleoside reverse transcriptase inhibitor approved for the treatment of human immunodeficiency virus (HIV) in adults and children older than 3 months in combination with other antiretroviral agents. The physiological changes associated with pregnancy can lead to significant variations in pharmacokinetics (10, 12, 14). However, few pharmacokinetic data on emtricitabine in pregnant women (3) and no data on placental transfer are available. Only one study reports pharmacokinetic of emtricitabine in neonates exposed to HIV in utero; apparent elimination clearance was 13 mL/min in 5 to 21 days-old neonates and 22 mL/min in 23 to 42 days-old neonates (5). This suggests that the youngest neonates have the lowest elimination clearance. The neonatal pharmacokinetics just after birth is still unknown.

In the present work, a population pharmacokinetic study was performed on mother, cord and neonatal plasma samples in order i) to describe the concentration-time courses of FTC in mothers, the transfer of FTC from maternal plasma to cord plasma and the neonatal elimination, ii) to study the influence of covariates (such maternal bodyweight, gestational age, type of delivery, maternal creatinine, neonatal bodyweight, height and body surface area)

on FTC pharmacokinetics and iii) to model various dosing strategies to determine optimal dosing scheme for newborn.

Methods

Patients.

The TEmAA (Tenofovir/Emtricitabine in Africa and Asia) - ANRS 12-109 study was an open, phase I/II trial evaluating the pharmacokinetics, the safety and toxicity of the Tenofovir-Emtricitabine combination in HIV infected pregnant women and their neonates. This trial was conducted in Abidjan, Côte d'Ivoire, Phnom Penh, Cambodia and Soweto, South Africa. Pregnant women (between 28 and 38 weeks of gestation), older than 18 years, infected by HIV-1 or HIV-2, naïve to all antiretroviral treatment, who had an indication for antiretroviral prophylaxis for Prevention of Mother-To-Child-Transmission (PMTCT) during pregnancy (in line with international or national recommendations: WHO's clinical stage 1, 2 and CD4≥200/mm3 or stage 3 and CD4≥350/mm3) were eligible. Neonates with a gestational age greater than 32 weeks and a birth weight greater than 2000 grams were eligible. This study protocol was approved by the national ethics committees of Côte d'Ivoire, South Africa and Cambodia and by each country health authorities. The mother and the father of the child to be born provided signed informed-consent.

Treatments

Mothers were administered ZDV (300 mg twice a day) from enrolment to delivery date, one tablet of NVP (200 mg) and two tablets of TDF (300 mg)-FTC (200 mg) at start of labour, and one tablet of TDF (300 mg)-FTC (200 mg) per day during 7 days at postpartum. Children

were given NVP syrup (2 mg/kg) as a single-dose on the first day of life and ZDV syrup (4 mg/kg every 12 hours during 7 days).

Sampling

All women received FTC and underwent blood samplings for pharmacokinetic analysis: at delivery, 1, 2, 3, 5, 8, 12 and 24 hours after the administration of FTC 400 mg and before the 2^{nd} , 3^{rd} and 7^{th} administration of FTC 200 mg. A cord blood sample was obtained at delivery, the neonate had sampling on days 1 and 2 of life. Time elapsed between administrations and sampling time, maternal, fetal bodyweight and gestational age were recorded.

Analytical method

The emtricitabine essay was performed according to the previously published method (11) with a limit of quantification (LOQ), intra- and inter-assay precision of 0.01 mg/L, 3.6 % and 7.9 %. The biais between observed and theoretical concentration range from 0.7 to 14.9 %.

Modeling strategy and population pharmacokinetic model.

Data were analyzed using the nonlinear mixed effect modeling software program NONMEM (version VI, level 1.0) with the DIGITAL FORTRAN compiler (2). The first-order conditional estimation (FOCE) with interaction method was used. A 2-compartment model with first order absorption and elimination best described maternal data. For cord concentrations, an “effect” compartment model of negligible volume and negligible drug accumulation linked to the maternal circulation was used. The effect compartment is modeled as a virtual compartment linked to the maternal plasma compartment by a first-order process which does not modify the compartmental model in the mother. After delivery, this fetal compartment is disconnected, time is reset to zero and the neonate has his own elimination

(Fig 1). Parameters of the model were the absorption rate constant (k_a), maternal elimination clearance from the central compartment (CL), volume of the central maternal compartment (V_1), maternal intercompartmental clearance (Q_2), volume of the peripheral maternal compartment (V_2), maternal to fetal rate constant (k_{1F}), fetal to maternal rate constant (k_{F1}) and neonate elimination rate constant (k_{FO}). Since emtricitabine was orally administered, only k_a, CL/F, V_1/F, Q_2/F, V_2/F, k_{1F}, k_{F1} and k_{FO} were identifiable, where F is the unknown bioavailability. Analytical equations were used in a $PRED section in NONMEM to estimate these pharmacokinetic parameters. When FTC concentrations were below the LOQ, we set them to half of the LOQ. Several error models were investigated (i.e. multiplicative and additive error models) to describe residual variability. Exponential model was used for inter-subject variability (ISV). Only significant ISVs on pharmacokinetic were kept. The effect of each patient covariate was systematically tested via generalized additive modeling on the basic model. Continuous covariates (CO), as bodyweight, gestational age, creatinine, height and body surface area were tested according to the following equation, using CL for example, $CL = \theta_{CL} \times (\frac{CO}{median(CO)})^{\beta_{CO}^{CL}}$, where θ_{CL} is the typical value of clearance for a patient with the median covariate value and β_{CO}^{CL} is the estimated influential factor for the continuous covariate. When a covariate was missing, it was set to the median value from all the other women. Categorical covariates (CA =0 or 1) were tested according to $CL = \theta_{CL} \times (1 + \beta_{CA}^{CL} \times CA)$ for inducing effect or $CL = \theta_{CL} / (1 + \beta_{CA}^{CL} \times CA)$ for inhibitory effect. The type of delivery (TD) was tested according to $CL = \theta_{CL} \times (1 + \beta_{TD}^{CL} \times TD \times DEL)$, where DEL = 1 before delivery and DEL = 0 after delivery. A covariate was kept if its effect was biologically plausible; it produced a minimum reduction of 6.63 in the objective function value (OFV) and a reduction in the variability of the pharmacokinetic parameter, assessed by the associated inter-subject variability. An intermediate model with all significant covariates

was obtained. A backward elimination phase was finally performed by deleting each covariate from the intermediate model, to obtain the final model, using a likelihood ratio test.

Evaluation and validation

For evaluation of the goodness-of-fit, the following graphs were performed: observed and predicted concentrations versus time, observed concentrations vs population predictions, weighted residuals vs time and weighted residuals vs predictions. Similar graphs using individual predictive POSTHOC estimation were displayed. The diagnostic graphs were performed using RfN (S. Urien, RFN-831-20070911, https://sourceforge.net/project/showfiles.php?group_id=29501&package_id=140129&release_id=538680) with the R program (8).

Emtricitabine concentration profiles were simulated and compared with the observed data thanks to visual predictive check in order to validate the model. More precisely, the vector of pharmacokinetic parameters from 1000 patients was simulated using the final model. Each vector parameter was drawn in a log-normal distribution with a variance corresponding to the ISV previously estimated. A simulated residual error was added to each simulated concentration. The simulations were performed using NONMEM. The 5^{th}, 50^{th} and 95^{th} percentiles of the simulated concentrations at each time were then overlaid on the observed concentration data using the R program and a visual inspection was performed.

Maternal concentrations after 400 mg FTC administration to the mother before delivery and placental transfer.

After the 400 mg administration to each pregnant woman, FTC minimal (C_{min}) and maximal (C_{max}) plasma concentration and area under the concentration curve (AUC) were derived from the estimated individual pharmacokinetic parameters. Median values and ranges were

147 calculated and compared to data from adults, in literature. At delivery cord (i.e. fetal) and
148 maternal plasma concentrations were determined. The ratio between fetal and maternal
149 concentrations was calculated and its variation as a function of the delay between drug uptake
150 and delivery was followed. In order to better evaluate placental transfer, for a 400 mg dose
151 administered to the mother, maternal and neonatal areas under the curve were estimated and
152 the ratio between neonatal and maternal AUC was calculated.
153
154 *Determination of the optimal dosing scheme for the newborn.*
155 The optimal timing for FTC administration to the newborns was determined in order to obtain
156 a similar exposure to that observed in adults, (i.e. $\left(AUC_{0\rightarrow 24h}\right)_{neonates}$ = 10.4 mg/L.h) and to
157 guarantee newborn FTC concentration above 0.077 mg/L (i.e. residual adult concentration),
158 before the administration to the neonate and as long as possible after administration to the
159 neonate. The target minimal concentration of 0.077 mg/L corresponds to the mean minimal
160 concentration for FTC 200 mg QD in adults from 3 previous studies (0.071 mg/L for Zhong et
161 al. (18), 0.075 mg/L for Blum et al.(5) and 0.085 mg/L for Ramanathan et al. (15) study). The
162 following hypotheses were necessary: neonate has same bioavailability and absorption rate as
163 his mother and neonatal volume of distribution V_F is proportional to maternal volume of
164 distribution on a bodyweight (BW) basis: $V_F = (V_1+V_2)* BW_{neonate}/BW_{Mother}$. Neonatal AUC
165 was calculated taking into account both neonatal administration and mother-to-fetus drug
166 transfer. As adults receive 200 mg doses or 3 mg/kg, a 3 mg/kg administration was simulated
167 and this dose was modified in order to obtain a neonatal AUC_{0-24h} close to 10.4 (median
168 adults AUC after a 200 mg dose). Different administration schemes were simulated in the
169 neonates: 1, 2, 3 mg/kg, 1 hour after birth and 2 mg/kg 12 hours after birth.
170
171

Results

Demographic data

Data from the 38 enrolled women and 32 of their neonates were available for FTC pharmacokinetic evaluation. Table 1 summarizes patients' characteristics.

Population pharmacokinetics

A total of 411 maternal, 37 cord blood concentrations and 66 neonatal concentrations were used for pharmacokinetic analysis. Four maternal residual FTC concentrations were excluded because they were seven to 20 times higher than the three other residual concentrations in the same patient. Seven FTC concentrations were lower than the LOQ, so they were set to half of the LOQ (1). The available data were not sufficient to estimate inter-subject variability for V_1/F, Q_2/F, V_2/F, k_{1F} and k_{F1} and fixing the variance of these random effects to zero had no influence on the objective function values (OFV). Variabilities were thus estimated: for k_a, CL/F and k_{FO}. All residual variabilities were best described by a proportional error model. The addition of a correlation between mother and cord residual variabilities, using a L2 item, (r= 0.80 (24%)) decreased OFV by 11.8 units. The effects of maternal bodyweight, serum creatinine, gestational age and type of delivery were tested on CL/F and the effects of neonatal bodyweight, height, body surface area and gestational age were tested on k_{FO}, none of these effects was significant.

Figure 2 displays FTC observed and predicted plasma concentrations as a function of time for the mother, the cord and the neonate. To better visualize neonatal concentrations, cord concentrations were reported on the graph at time zero. Table 2 summarizes the final population pharmacokinetic estimates. Final model performance was appreciated by comparing population predicted and individual predicted to observed plasma concentrations

and population weighted residuals versus predicted concentrations and versus time for FTC (not shown).

Validation

Visual predictive check of the final population pharmacokinetic model (Fig 3) showed the 5th, 50th and 95th predicted percentiles from the 1000 simulations and the observed concentrations of emtricitabine. The visual predictive checking confirmed that the average prediction matched the observed concentrations. The variability was reasonably estimated.

Maternal concentrations after 400 mg administration to the mother before delivery

Table 3 summarizes the maternal C_{min}, C_{max} and AUC obtained after a 400 mg administration to the pregnant woman at the start of the labour, and values previously found after a 200 mg administration to adults, at steady state. In the present study, total elimination clearance was 28 L/h for women at delivery, after a 400 mg dose whereas in previous studies, the mean value was 19.3 L/h in adults after a 200 mg dose. Total elimination clearance increased by 45% in pregnant woman, on the day of delivery.

Placental transfer

Median delay between samples drawn before the first maternal FTC administration and delivery was 5.1 hours (min - max: 0.6 - 20 hours). At delivery, median predicted neonatal and maternal concentrations were respectively 0.72 mg/L (min – max: 0.05 - 1.19) and 1.16 mg/L (min – max: 0.14 - 1.99). The median predicted ratio between cord and maternal concentrations at delivery was 76 % (min – max: 9 - 144), depending on the delay between maternal drug administration and delivery. This range of concentration ratio at delivery suggests that placental transfer depends on the delay between maternal drug intake and

delivery and could not be given as a simple percentage. A more representative measure of placental transfer would be the ratio between neonatal and maternal FTC AUC for 24 hours. Figure 4 represented maternal and neonatal concentrations as a function of time when delivery occured 2, 6 or 12 hours after maternal drug intake. This figure (down) showed the neonatal-to-maternal AUC ratio as a function of the delay between maternal administration and labour.

Determination of the optimal timing for FTC administration to the newborns.

As the median predicted neonatal concentration was relatively high at delivery (0.72 mg/L), with a 10.6 hours half life, this remained above 0.077 mg/L (minimal adult concentrations) for at least 3 half-lives, i.e. 31.8 hours after delivery. Table 4 summarizes neonatal minimal concentration before administration, $AUC_{0\rightarrow 24h}$ and the time during which neonatal concentration remained over 0.077 mg/L for 1, 2 or 3 mg/kg at 1 hour after birth and 2 mg/kg 12 hours after birth. If emtricitabine was only administered to the mother, thanks to placental transfer, it would produce a neonatal $AUC_{0\rightarrow 24h}$ of 8.2 mg/L.h. Administering, as a single dose, 1 mg/kg of emtricitabine 1 hour after birth or 2 mg/kg 12 hours after birth would allow the neonate to obtain same exposition as adults. These results were obtained assuming a neonatal volume of distribution (V_F) proportional to the maternal volume of distribution on a bodyweight basis (mean $V_F = (V_1+V_2)^* BW_{neonate} / BW_{Mother} \approx (127+237)^*2.8/60.3 \approx 16.9$ L). However, 1 mg/kg 1 hour after birth would produce an $AUC_{0\text{-}24h}$ of 9.2 mg/L.h and a concentration above 0.077 mg/L during 34 h if V_F was in reality twice higher than in the assumption. This dose would produce an $AUC_{0\text{-}24h}$ of 12.0 mg/L.h and a concentration above 0.077 mg/L during 40.2 h if the true VF was twice lower than assumed. In both cases, even with a 100% error on neonatal volume of distribution, the $AUC_{0\text{-}24h}$ was close to 10.4 mg/L.h.

Discussion

In the present work, emtricitabine mother and child pharmacokinetics were satisfactorily described by the proposed compartmental model. The following observations support the validity of this model:

Population predicted maternal, cord and neonatal concentrations were well correlated with observed concentrations. The population model was validated thanks to the visual predictive check method.

In pregnant women, the AUC obtained from our population model was decreased (14.3 mg/L.h for a 400 mg dose, i.e. 7.15 mg/L.h for a 200 mg) compared to non pregnant adult value (10.7 mg/L.h for a 200 mg dose). This is in agreement with the PATCG/IMPAACT P1026 study which reports, during the third trimester of pregnancy, a median AUC of 8.6 mg/L.h for a 200 mg dose (3).

As shown in table 3, despite a higher elimination clearance in pregnant women than in non pregnant adults, the 400 mg emtricitabine administration before delivery produces higher exposure than the 200 mg administration in others adults at steady state. Calculating emtricitabine clearance as a dose to AUC ratio, we found 28.0 L/h for pregnant women (our study) compared to 18.7 L/h (4, 18) and 20.4 L/h for adults (15). FTC clearance was increased by 37 or 50 %. FTC is primarily excreted by the kidney by both glomerular filtration and tubular secretion with 86% recovery of the dose achieved in urine, as described in the full prescribing information for Truvada® (http://www.gilead.com/pdf/truvada_pi.pdf). During pregnancy, renal plasma flow increases by 25 to 50% and glomerular filtration rate by 50% which should have enhanced emtricitabine elimination (13). The lowest FTC clearance increase in the PATCG/IMPAACT P1026 study (23.3 vs 28.0 L/h in our study) may be due the sampling time during pregnancy (third trimester vs the day of delivery in our study). None of the covariates tested had an effect on maternal absorption or elimination clearance.

No data were reported on emtricitabine placental transfer. In this study, from one sample at delivery (at various times after drug administration) in each mother – cord pairs, we could draw maternal and cord concentrations curves as a function of the delay and estimate inter subject and residual variabilities. Placental transfer was estimated as fetal to maternal exposure ratio to the drug. We found a relatively constant ratio of 80% for a delivery occurring at least 4 hours after maternal drug administration. This transfer seems to be mainly due to a passive diffusion of the drug through the placenta. Data about active transport are missing.

Cord concentrations were relatively high (0.72 mg/L) compared to the minimal adult concentrations previously reported (0.07 mg/L). This was due to both a good placental transfer of the drug and a higher exposure in mothers; with 400 mg of emtricitabine at delivery time, maternal exposure was higher than the exposure with 200 mg in non pregnant adults. So, even if women delivered a long time after drug intake, cord concentrations should remain over the adult minimal concentration. However re-administering 2 tablets of Truvada® to the mother after 12 hours of labour (if she did not delivered yet, as suggested for tenofovir, unpublished data) would produce reasonable emtricitabine cord concentrations (similar to cord concentrations of a neonate born 5 hours after maternal first drug intake).

The emtricitabine median neonatal half life was 10.6 hours, in agreement with Blum study reporting half lives of 12.5 hours in neonates from birth to 21 days, 11.5 hours for 22 to 42 days old infants and 11.8 hours for 43 to 90 days old children (5). Moreover these half-lives are comparable to children values (9.3 to 11.7 hours for the 2 – 17 years) (17) and adults values (10.5 h for Blum, 9.4h for Zhong and 8.3 h for Ramanathan) (4, 15, 18).

As the model was validated thanks to the visual predictive check method, it was used to simulate the optimal dosage. For this, it was assumed that the child had the same absorption rate and bioavailability as the mother and its volume of distribution was proportional to the total maternal volume distribution on a bodyweight basis. Accordingly, in our model, the mean volume of distribution was 16.9 L for a children weighting 2.7 kg at birth, which is close to the volume of distribution of 14 L ($t_{1/2}$=12.5 h and CL=13mL/min) found in the 18 children from 0 to 21 days of Blum's study (5). Moreover, even with a 100% error on neonatal volume of distribution, the $AUC_{0\text{-}24h}$ and the time during which the concentration was above 0.077 mg/L showed a less than 20% change. The optimal single neonatal dose was determined in order to obtain an exposure in neonates similar to the known exposure in adults (i.e. 10.4 mg/L.h) and concentrations above the residual adult concentration (=0.077 mg/L) before, and as long as possible after neonatal administration. Criteria were based on plasma emtricitabine concentrations although intracellular emtricitabine triphosphate concentrations would have been more appropriate to follow the pharmacologically active part of FTC. It was also supposed that the enzymes of phosphorylation were matures in the neonates (16). For practical reasons, we suggest that FTC should be administered to the neonate at the same time as tenofovir (unpublished data). As previously shown, tenofovir should be administered quickly after birth, i.e. one hour after delivery, so we simulated concentrations obtained with 1, 2 or 3 mg/kg of emtricitabine given one hour after birth to the neonate. A 2 mg/kg FTC dose given 12 hours after birth was also simulated. Taking into account the high exposure of the fetus to the drug due to maternal administration ($AUC_{0\text{-}24h}$ =8.2 mg/L.h), only 1 mg/kg of emtricitabine was needed one hour after birth to reach an $AUC_{0\text{-}24h}$ of 10.1 mg/L.h. However if the neonate could only be administered FTC 12 hours after birth, the dose would increase to 2 mg/kg. This dosage is recommended for a single administration following birth and not for repeated doses as in the Blum study (5).

In conclusion, the maternal 400 mg emtricitabine administration before delivery produces higher exposure than the 200 mg administration in others adults at steady state. Emtricitabine placental transfer, described by neonatal to maternal exposure ratio was around 80%. Finally, neonates should receive FTC 1 mg/kg as soon as possible after birth or 2 mg/kg 12 hours after birth to have concentrations comparable to those observed in adults. The second step of TEmAA trial will validate these recommendations.

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Figures

Figure 1

Population pharmacokinetic model for the simultaneous prediction of emtricitabine concentrations in the mother, the cord (top) and the neonate (bottom). A 2-compartment model with first-order absorption and elimination best described maternal data. For cord concentrations, an "effect" compartment is modeled as a virtual compartment linked to the maternal plasma compartment by a first-order process. After delivery, the fetal compartment is disconnected and the neonate has his own elimination. F denotes for bioavailability, D the emtricitabine maternal dose, k_a the absorption rate constant, CL the maternal elimination clearance from the central compartment, V_1 the volume of the central maternal compartment, Q_2 the maternal intercompartmental clearance, V_2 the volume of the peripheral maternal compartment, k_{1F} maternal-to-fetal rate constant, k_{F1} the fetal-to-maternal rate constant, k_{FO} neonate elimination rate constant, V_F the fetal volume of distribution, BW_M the maternal bodyweight and BW_{FPA} the sum of neonatal bodyweight, placenta and amniotic fluid weight.

Figure 2

Left: Observed (points) and population predicted (lines) maternal emtricitabine concentrations versus time. Right: Observed (points) and population predicted (lines) emtricitabine concentrations in cord blood (up) and neonatal plasma (bottom) versus time.

Figure 3

Evaluation of the final model: comparison between the 5^{th} (dash line), 50^{th} (full line) and 95^{th} (dash line) percentile obtained from 1000 simulations and the observed data (points) for emtricitabine concentrations in mother (left), cord blood (middle) and neonate (right).

Figure 4

Up: Population predicted emtricitabine concentrations in the mother (full line) and her neonate (dashed line; cord equation before delivery and neonatal equation after) versus time: for a 2 hours (left), 6 hours (middle) or 12 hours (right) delay between drug administration and delivery time. Down: Neonatal-to-maternal emtricitabine AUC ratio as a function of the delay between drug administration and delivery time.

Table 1. Characteristics of the HIV-infected pregnant women (N=38) enrolled in the pharmacokinetic study of the TEmAA ANRS 12109 trial, Step 1

Covariates	Median (Min-Max)
Maternal bodyweight at delivery (kg)	58.3 (46.5 – 88.1)
Gestationnel age (weeks)	39 (33 – 42)
Delivery : vaginal, caesarian section (n)	24 , 14
Maternal creatinine clearance at enrolment (µmol/L)	42.2 (26 – 88)
Neonatal bodyweight at birth (kg)	2.7 (2.3 – 3.6)
Neonatal height at birth (cm)	48.5 (46 – 53)
Body surface area at birth (m^2)	0.20 (0.18 – 0.23)

Table 2. Population pharmacokinetic parameters of emtricitabine from the final model for HIV-infected pregnant women (N=38) after receiving 400 mg of emtricitabine at the start of the labour and for their neonates (N=32) enrolled in the TEmAA ANRS 12109 trial, Step 1

Structural model		Statistical model	
Parameter	Estimate (RSE %)	Parameter	Estimate (RSE %)
k_a (h^{-1})	0.54 (11)	ω_{ka} (%)	61 (29)
CL/F (L/h)	23.2 (4)	$\omega_{CL/F}$ (%)	17 (34)
V_1/F (L)	127 (7)	ω_{KF0} (%)	30 (35)
Q/F (L/h)	6.04 (10)	σ_{MOTHER} (%)	45 (14)
V_2/F (L)	237 (15)	σ_{CORD} (%)	43 (24)
k_{1F} (h^{-1})	0.289 (13)	$\sigma_{NEONATE}$ (%)	33 (27)
k_{F1} (h^{-1})	0.383 (13)		
k_{F0} (h^{-1})	0.0653 (7)		

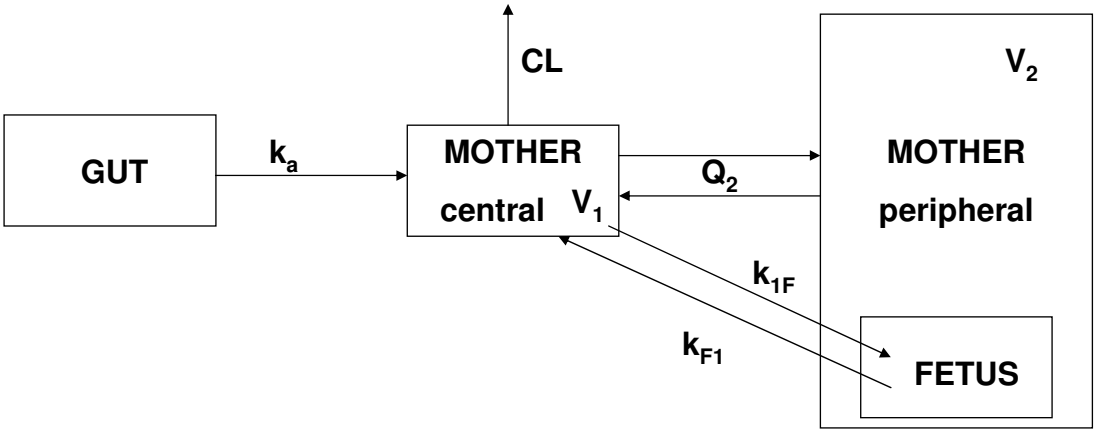
Key: RSE%, relative standard error (standard error of estimate / estimate*100); ka absorption rate constant, CL/F maternal apparent elimination clearance from the central compartment, V_1/F apparent volume of distribution of the central maternal compartment, Q_2/F apparent maternal intercompartmental clearance, V_2/F apparent volume of distribution of the peripheral maternal compartment, k_{1F} maternal-to-fetal rate constant, k_{F1} fetal-to-maternal rate constant and k_{F0} neonate elimination rate constant. σ residual variability estimates (CV of residual variability, %) and ω, interindividual variability estimates (CV of intersubject variability, %).

Table 3. Maternal minimal, maximal concentrations (C_{min} and C_{max}) and area under de curves (AUC), derived from women's individual pharmacokinetic estimates, after a 400 mg FTC dose to the HIV-infected pregnant women (N=38) enrolled in the TEmAA ANRS 12109 trial, Step 1, compared to median adults values after a 200 mg FTC dose at steady state.

Median	**TEMAA Pregnant, 400 mg**	Zhong et al. (18) Adults, 200 mg	Blum et al. (4) Adults, 200 mg	Ramanathan et al. (15) Adults, 200 mg
AUC (mg/L.h)	**14.3 (11.0 – 19.0)**	10.7	10.7	9.8
C_{min} (mg/L)	**0.076 (0.039 – 0.174)**	0.071	0.075	0.085
C_{max} (mg/L)	**1.68 (0.82 – 2.13)**	2.18	1.69	1.68

Table 4. Neonatal parameters estimated for an administration 0, 1, 2 and 3 mg/kg 1 hour after birth and 2 mg/kg 12 hours after birth, TEmAA ANRS 12109 trial, Step 1

Median	0 mg/kg	1 mg/kg at 1h	2 mg/kg at 1h	3 mg/kg at 1h	2 mg/kg at 12 h
$AUC_{0\rightarrow 24}$ (mg/L.h)	8.2	10.1	11.9	13.4	10.5
C_{min} (mg/L)		0.67	0.67	0.67	0.31
T (C>0.077) (h)		36.6	40.2	42.8	33.9



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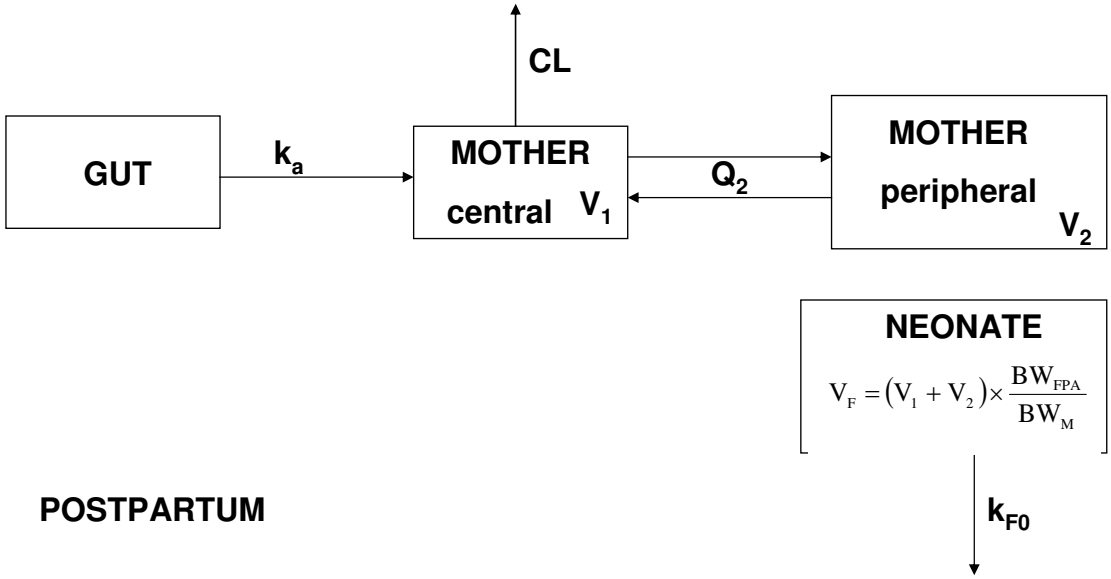

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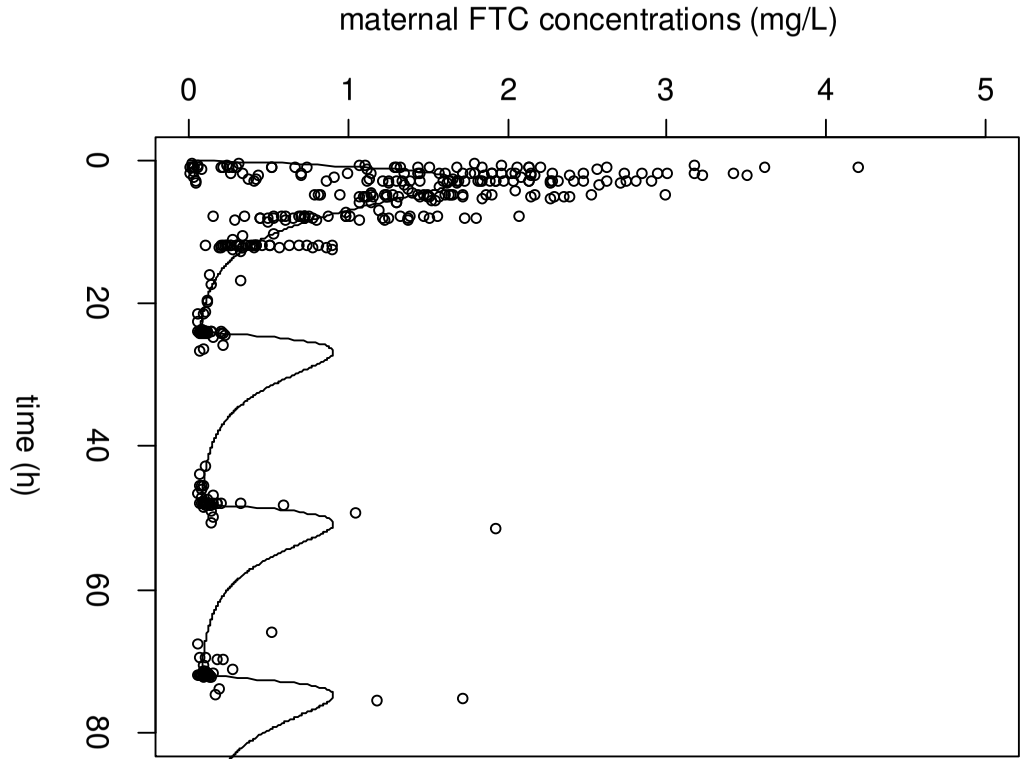
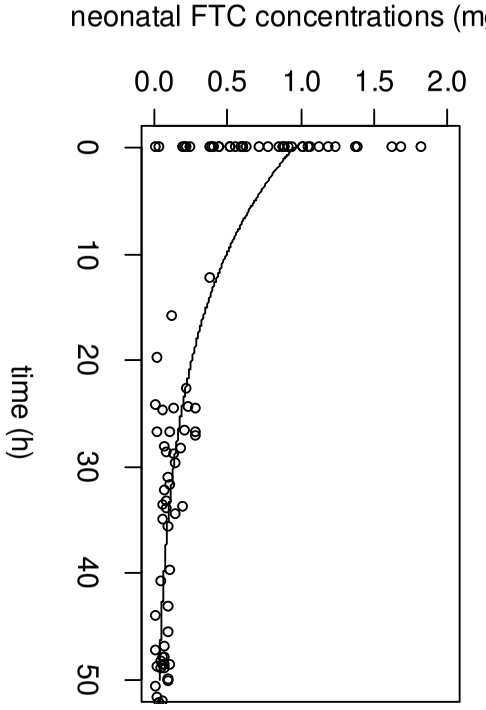
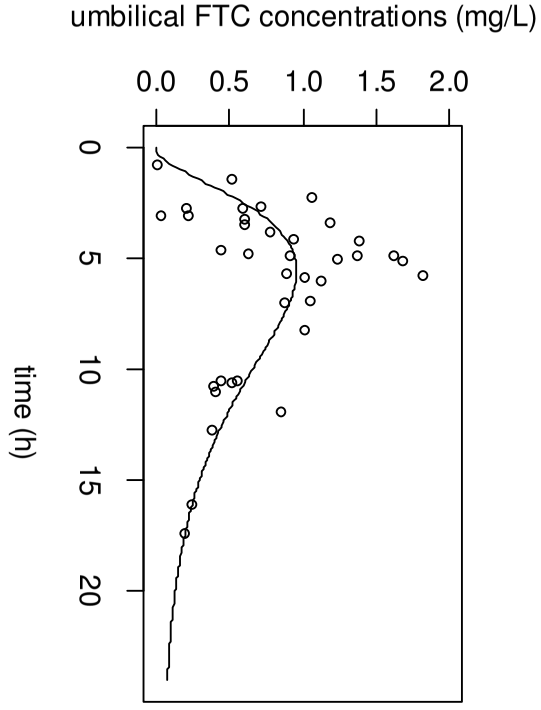
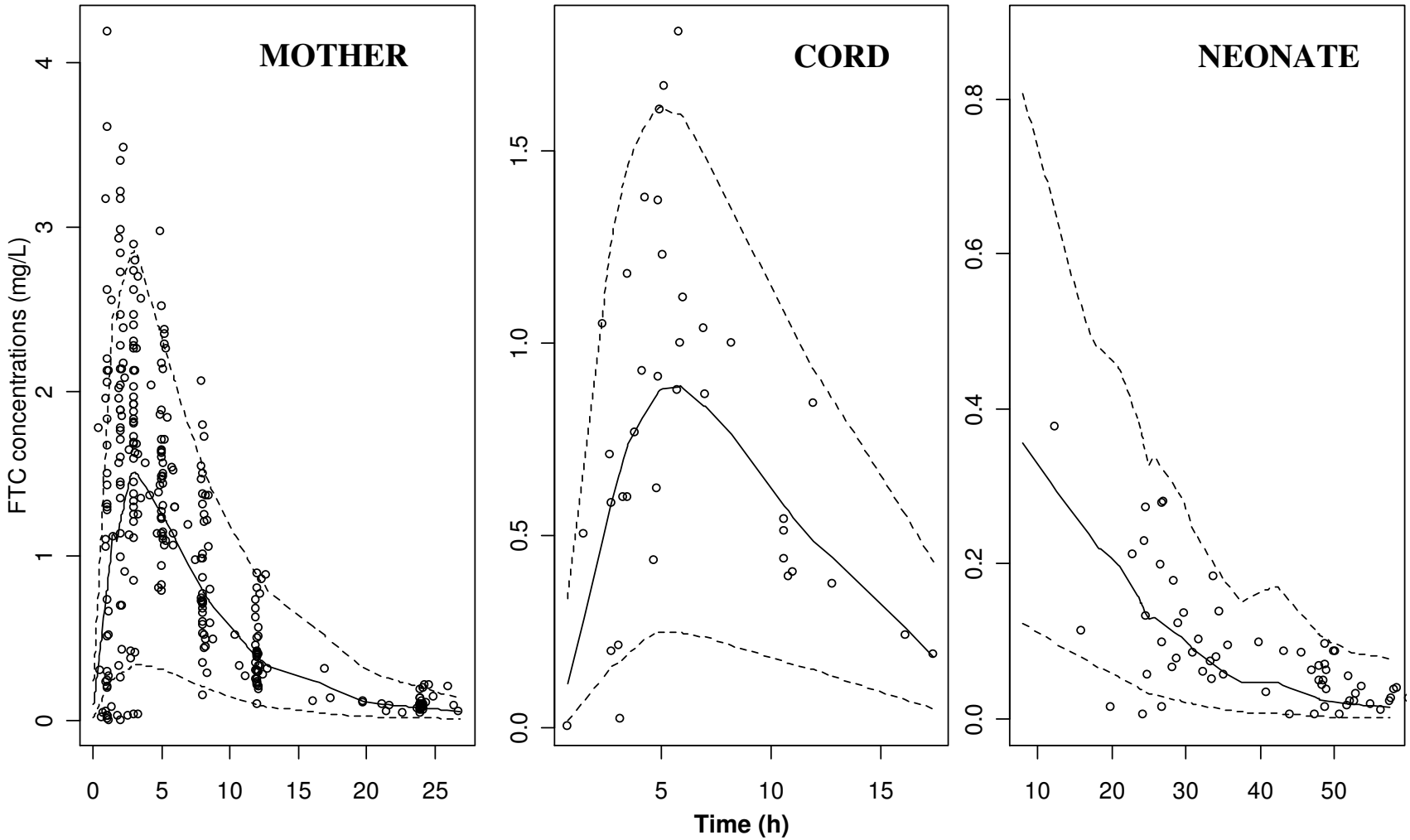
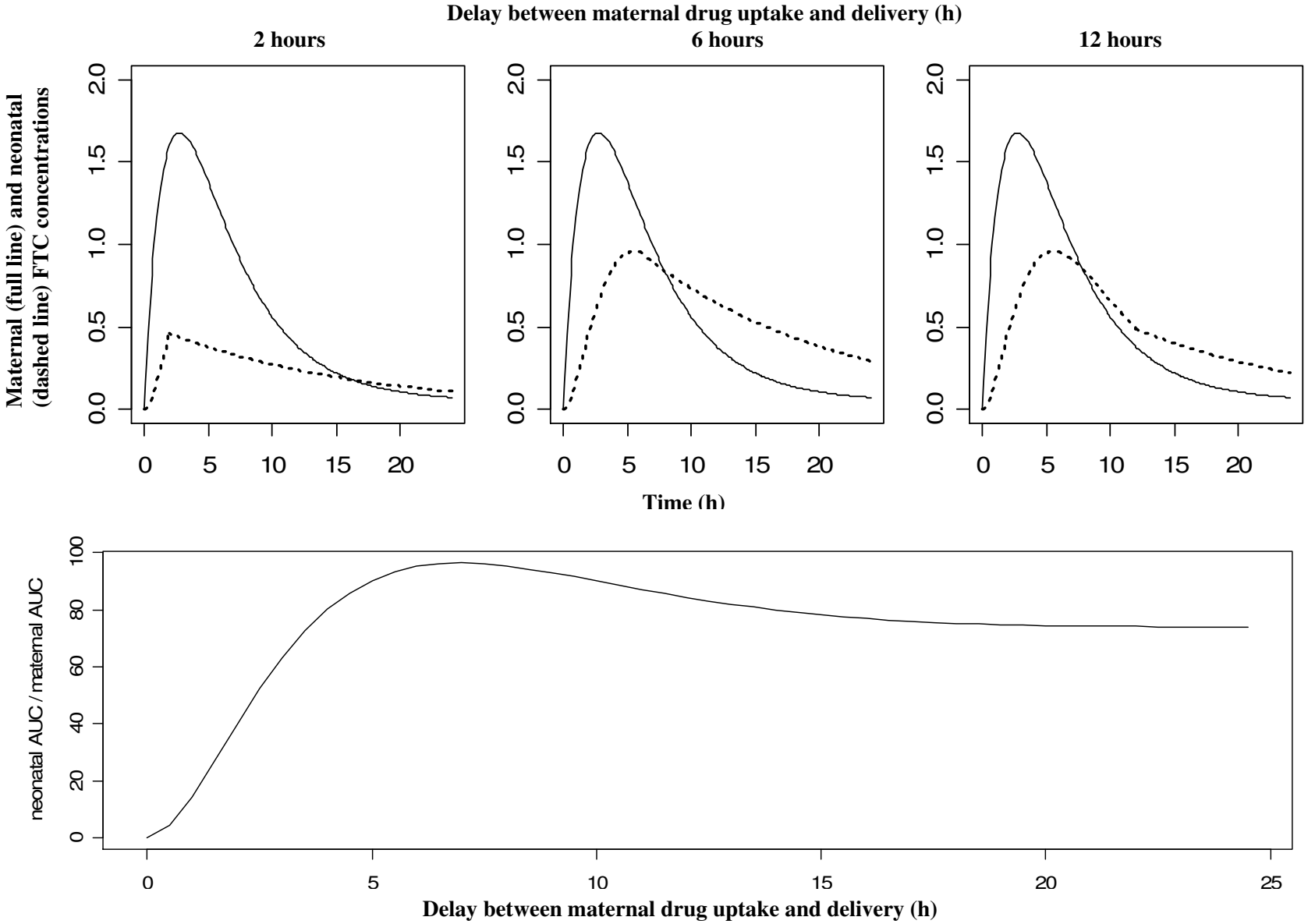

maternal FTC concentrations (mg/L)
0
1
2
3
4
5
time (h)
0
20
40
60
80


neonatal FTC concentrations (mg/L)
0.0
0.5
1.0
1.5
2.0
time (h)
0
10
20
30
40
50


umbilical FTC concentrations (mg/L)
0.0
0.5
1.0
1.5
2.0
time (h)
0
5
10
15
20


MOTHER
CORD
NEONATE
FTC concentrations (mg/L)
Time (h)
0
1
2
3
4
0.0
0.5
1.0
1.5
0.0
0.2
0.4
0.6
0.8
0
5
10
15
20
25
5
10
15
10
20
30
40
50


Delay between maternal drug uptake and delivery (h)
2 hours
6 hours
12 hours
Maternal (full line) and neonatal (dashed line) FTC concentrations
0.0
0.5
1.0
1.5
2.0
0
5
10
15
20
Time (h)
neonatal AUC / maternal AUC
0
20
40
60
80
100
25
Delay between maternal drug uptake and delivery (h)