

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

Déborah Hirt, Saik Urien, Elisabeth Rey, Elise Arrivé, Didier Ekouévi, Patrick Coffié, Sim Krui Leang, Sarita Lalsab, Divine Avit, Eric Nerrienet, et al.

► **To cite this version:**

Déborah Hirt, Saik Urien, Elisabeth Rey, Elise Arrivé, Didier Ekouévi, et al.. Population pharmacokinetics of emtricitabine in human immunodeficiency virus type 1-infected pregnant women and their neonates.. *Antimicrobial Agents and Chemotherapy*, American Society for Microbiology, 2009, 53 (3), pp.1067-73. 10.1128/AAC.00860-08 . inserm-00348223

HAL Id: inserm-00348223

<https://www.hal.inserm.fr/inserm-00348223>

Submitted on 15 Mar 2013

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

Déborah Hirt*^{a, b}, Saik Urien^{a, b}, Elisabeth Rey^c, Elise Arrivé^d, Didier K. Ekouévi^e, Patrick Coffié^e, Sim Kruey Leang^f, Sarita Lalsab^g, Divine Avit^e, Eric Nerrienet^h, James McIntyre^g, Stéphane Blancheⁱ, François Dabis^d, Jean-Marc Tréluyer^{a, b, c}.

^a EA3620, Université Paris - Descartes, France, ^b Unité de Recherche clinique, AP-HP, Hôpital Tarnier, Paris, France, ^c Service de Pharmacologie Clinique, AP-HP, Hôpital Cochin-Saint-Vincent-de-Paul, Université Paris – Descartes, France, ^d INSERM U897, ISPED, Université Victor Segalen, Bordeaux, France, ^e Programme PAC-CI, ANRS Abidjan, Côte d’Ivoire, ^f Service Gynécologie-obstétrique de l’Hôpital Calmette, Phnom Penh, Cambodia, ^g Perinatal HIV Research Unit (PHRU), University of the Witwatersrand, Chris Hani Baragwanath Hospital, Johannesburg, South Africa, ^h Institut Pasteur du Cambodge, Phnom Penh, Cambodia, ⁱ Service d’Immunologie et Hématologie Pédiatrique, Hôpital Necker Enfants Malades, Université Paris-Descartes, Paris, France

Short title: Mother - neonate emtricitabine pharmacokinetics

Corresponding author: Déborah Hirt

Unité de Recherche Clinique, Hôpital Tarnier, 89 rue d’Assas, 75006 Paris, deborah.hirt@univ-paris5.fr, tel : +33158412884 Fax : +33158411183

Abstract: 250 words, **Manuscript:** 3367 words

Number of figures: 4, **Number of tables:** 4, **Number of references:** 18

Key words: Population pharmacokinetics, Prevention of Mother-to-child transmission of HIV, Emtricitabine, placental transfer, neonatal prophylactic dose.

1 **Abstract.**

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

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

10 Results: Model and mean estimates (inter-patient variability) were a 2-compartment model for
11 mother with absorption rate constant 0.54 h^{-1} (61%), apparent elimination and
12 intercompartmental clearance 23.2 (17%) and 6.04 L.h^{-1} and apparent central and peripheral
13 volume 127 and 237L; an effect compartment linked to maternal circulation for cord and a
14 neonatal compartment disconnected, after delivery, with a 10.6 hours half life (30%). After
15 the 400 mg FTC administration, median population AUC, C_{\max} and C_{\min} in pregnant women
16 were $14.3 \text{ mg.L}^{-1}.\text{h}$, 1.68 and 0.076 mg/L respectively. At delivery, median (range) FTC
17 predicted maternal and cord concentrations were respectively 1.16 (0.14–1.99) and 0.72
18 (0.05–1.19) mg.L^{-1} .

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

24 **Introduction**

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

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

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

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

51

52 **Methods**

53

54 *Patients.*

55 The TEmAA (Tenofovir/Emtricitabine in Africa and Asia) - ANRS 12-109 study was an
56 open, phase I/II trial evaluating the pharmacokinetics, the safety and toxicity of the
57 Tenofovir-Emtricitabine combination in HIV infected pregnant women and their neonates.

58 This trial was conducted in Abidjan, Côte d'Ivoire, Phnom Penh, Cambodia and Soweto,
59 South Africa. Pregnant women (between 28 and 38 weeks of gestation), older than 18 years,
60 infected by HIV-1 or HIV-2, naïve to all antiretroviral treatment, who had an indication for
61 antiretroviral prophylaxis for Prevention of Mother-To-Child-Transmission (PMTCT) during
62 pregnancy (in line with international or national recommendations: WHO's clinical stage 1, 2
63 and $CD4 \geq 200/mm^3$ or stage 3 and $CD4 \geq 350/mm^3$) were eligible. Neonates with a gestational
64 age greater than 32 weeks and a birth weight greater than 2000 grams were eligible. This
65 study protocol was approved by the national ethics committees of Côte d'Ivoire, South Africa
66 and Cambodia and by each country health authorities. The mother and the father of the child
67 to be born provided signed informed-consent.

68

69 *Treatments*

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

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

75

76 *Sampling*

77 All women received FTC and underwent blood samplings for pharmacokinetic analysis: at
78 delivery, 1, 2, 3, 5, 8, 12 and 24 hours after the administration of FTC 400 mg and before the
79 2nd, 3rd and 7th administration of FTC 200 mg. A cord blood sample was obtained at delivery,
80 the neonate had sampling on days 1 and 2 of life. Time elapsed between administrations and
81 sampling time, maternal, fetal bodyweight and gestational age were recorded.

82

83 *Analytical method*

84 The emtricitabine assay was performed according to the previously published method (11)
85 with a limit of quantification (LOQ), intra- and inter-assay precision of 0.01 mg/L, 3.6 % and
86 7.9 %. The bias between observed and theoretical concentration range from 0.7 to 14.9 %.

87

88 *Modeling strategy and population pharmacokinetic model.*

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

98 (Fig 1). Parameters of the model were the absorption rate constant (k_a), maternal elimination
 99 clearance from the central compartment (CL), volume of the central maternal compartment
 100 (V_1), maternal intercompartmental clearance (Q_2), volume of the peripheral maternal
 101 compartment (V_2), maternal to fetal rate constant (k_{1F}), fetal to maternal rate constant (k_{F1})
 102 and neonate elimination rate constant (k_{FO}). Since emtricitabine was orally administered, only
 103 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
 104 bioavailability. Analytical equations were used in a \$PRED section in NONMEM to estimate
 105 these pharmacokinetic parameters. When FTC concentrations were below the LOQ, we set
 106 them to half of the LOQ. Several error models were investigated (i.e. multiplicative and
 107 additive error models) to describe residual variability. Exponential model was used for inter-
 108 subject variability (ISV). Only significant ISVs on pharmacokinetic were kept. The effect of
 109 each patient covariate was systematically tested via generalized additive modeling on the
 110 basic model. Continuous covariates (CO), as bodyweight, gestational age, **creatinine**, height
 111 and body surface area were tested according to the following equation, using CL for example,

$$112 \quad CL = \theta_{CL} \times \left(\frac{CO}{\text{median}(CO)} \right)^{\beta_{CO}^{CL}}, \text{ where } \theta_{CL} \text{ is the typical value of clearance for a patient with}$$

113 the median covariate value and β_{CO}^{CL} is the estimated influential factor for the continuous
 114 covariate. When a covariate was missing, it was set to the median value from all the other
 115 women. Categorical covariates (CA = 0 or 1) were tested according to
 116 $CL = \theta_{CL} \times (1 + \beta_{CA}^{CL} \times CA)$ for inducing effect or $CL = \theta_{CL} / (1 + \beta_{CA}^{CL} \times CA)$ for inhibitory
 117 effect. The type of delivery (TD) was tested according to $CL = \theta_{CL} \times (1 + \beta_{TD}^{CL} \times TD \times DEL)$,
 118 where $DEL = 1$ before delivery and $DEL = 0$ after delivery. A covariate was kept if its effect
 119 was biologically plausible; it produced a minimum reduction of 6.63 in the objective function
 120 value (OFV) and a reduction in the variability of the pharmacokinetic parameter, assessed by
 121 the associated inter-subject variability. An intermediate model with all significant covariates

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

124

125 *Evaluation and validation*

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

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

141

142 *Maternal concentrations after 400 mg FTC administration to the mother before delivery and* 143 *placental transfer.*

144 After the 400 mg administration to each pregnant woman, FTC minimal (C_{\min}) and maximal
145 (C_{\max}) plasma concentration and area under the concentration curve (AUC) were derived from
146 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. $(AUC_{0 \rightarrow 24h})_{neonates} = 10.4 \text{ mg/L.h}$) 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

172 **Results**

173 *Demographic data*

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

176

177 *Population pharmacokinetics*

178 A total of 411 maternal, 37 cord blood concentrations and 66 neonatal concentrations were
179 used for pharmacokinetic analysis. Four maternal residual FTC concentrations were excluded
180 because they were seven to 20 times higher than the three other residual concentrations in the
181 same patient. Seven FTC concentrations were lower than the LOQ, so they were set to half of
182 the LOQ (1). The available data were not sufficient to estimate inter-subject variability for
183 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
184 influence on the objective function values (OFV). Variabilities were thus estimated: for k_a ,
185 CL/F and k_{FO} . All residual variabilities were best described by a proportional error model.
186 The addition of a correlation between mother and cord residual variabilities, using a L2 item,
187 ($r= 0.80$ (24%)) decreased OFV by 11.8 units. The effects of maternal bodyweight, serum
188 **creatinine**, gestational age and type of delivery were tested on CL/F and the effects of
189 neonatal bodyweight, height, body surface area and gestational age were tested on k_{FO} , none
190 of these effects was significant.

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

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

198

199 *Validation*

200 Visual predictive check of the final population pharmacokinetic model (Fig 3) showed the 5th,
201 50th and 95th predicted percentiles from the 1000 simulations and the observed concentrations
202 of emtricitabine. The visual predictive checking confirmed that the average prediction
203 matched the observed concentrations. The variability was reasonably estimated.

204

205 *Maternal concentrations after 400 mg administration to the mother before delivery*

206 Table 3 summarizes the maternal C_{\min} , C_{\max} and AUC obtained after a 400 mg administration
207 to the pregnant woman at the start of the labour, and values previously found after a 200 mg
208 administration to adults, at steady state. In the present study, total elimination clearance was
209 28 L/h for women at delivery, after a 400 mg dose whereas in previous studies, the mean
210 value was 19.3 L/h in adults after a 200 mg dose. Total elimination clearance increased by
211 45% in pregnant woman, on the day of delivery.

212

213 *Placental transfer*

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

221 delivery and could not be given as a simple percentage. A more representative measure of
222 placental transfer would be the ratio between neonatal and maternal FTC AUC for 24 hours.
223 Figure 4 represented maternal and neonatal concentrations as a function of time when delivery
224 occurred 2, 6 or 12 hours after maternal drug intake. This figure (down) showed the neonatal-
225 to-maternal AUC ratio as a function of the delay between maternal administration and labour.
226

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

228 As the median predicted neonatal concentration was relatively high at delivery (0.72 mg/L),
229 with a 10.6 hours half life, this remained above 0.077 mg/L (minimal adult concentrations)
230 for at least 3 half-lives, i.e. 31.8 hours after delivery. Table 4 summarizes neonatal minimal
231 concentration before administration, $AUC_{0 \rightarrow 24h}$ and the time during which neonatal
232 concentration remained over 0.077 mg/L for 1, 2 or 3 mg/kg at 1 hour after birth and 2 mg/kg
233 12 hours after birth. If emtricitabine was only administered to the mother, thanks to placental
234 transfer, it would produce a neonatal $AUC_{0 \rightarrow 24h}$ of 8.2 mg/L.h. Administering, as a single
235 dose, 1 mg/kg of emtricitabine 1 hour after birth or 2 mg/kg 12 hours after birth would allow
236 the neonate to obtain same exposition as adults. **These results were obtained assuming a**
237 **neonatal volume of distribution (V_F) proportional to the maternal volume of distribution on a**
238 **bodyweight basis (mean $V_F = (V_1 + V_2) * BW_{neonate} / BW_{Mother} \approx (127 + 237) * 2.8 / 60.3 \approx 16.9$ L).**
239 **However, 1 mg/kg 1 hour after birth would produce an AUC_{0-24h} of 9.2 mg/L.h and a**
240 **concentration above 0.077 mg/L during 34 h if V_F was in reality twice higher than in the**
241 **assumption. This dose would produce an AUC_{0-24h} of 12.0 mg/L.h and a concentration above**
242 **0.077 mg/L during 40.2 h if the true V_F was twice lower than assumed. In both cases, even**
243 **with a 100% error on neonatal volume of distribution, the AUC_{0-24h} was close to 10.4 mg/L.h.**

244

245

246 **Discussion**

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

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

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

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

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

279

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

289

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

295 As the model was validated thanks to the visual predictive check method, it was used
296 to simulate the optimal dosage. For this, it was assumed that the child had the same absorption
297 rate and bioavailability as the mother and its volume of distribution was proportional to the
298 total maternal volume distribution on a bodyweight basis. Accordingly, in our model, the
299 mean volume of distribution was 16.9 L for a children weighting 2.7 kg at birth, which is
300 close to the volume of distribution of 14 L ($t_{1/2}$ =12.5 h and CL=13mL/min) found in the 18
301 children from 0 to 21 days of Blum's study (5). Moreover, even with a 100% error on
302 neonatal volume of distribution, the AUC_{0-24h} and the time during which the concentration
303 was above 0.077 mg/L showed a less than 20% change. The optimal single neonatal dose was
304 determined in order to obtain an exposure in neonates similar to the known exposure in adults
305 (i.e. 10.4 mg/L.h) and concentrations above the residual adult concentration (=0.077 mg/L)
306 before, and as long as possible after neonatal administration. Criteria were based on plasma
307 emtricitabine concentrations although intracellular emtricitabine triphosphate concentrations
308 would have been more appropriate to follow the pharmacologically active part of FTC. It was
309 also supposed that the enzymes of phosphorylation were matures in the neonates (16). For
310 practical reasons, we suggest that FTC should be administered to the neonate at the same time
311 as tenofovir (unpublished data). As previously shown, tenofovir should be administered
312 quickly after birth, i.e. one hour after delivery, so we simulated concentrations obtained with
313 1, 2 or 3 mg/kg of emtricitabine given one hour after birth to the neonate. A 2 mg/kg FTC
314 dose given 12 hours after birth was also simulated. Taking into account the high exposure of
315 the fetus to the drug due to maternal administration (AUC_{0-24h} =8.2 mg/L.h), only 1 mg/kg of
316 emtricitabine was needed one hour after birth to reach an AUC_{0-24h} of 10.1 mg/L.h. However
317 if the neonate could only be administered FTC 12 hours after birth, the dose would increase to
318 2 mg/kg. This dosage is recommended for a single administration following birth and not for
319 repeated doses as in the Blum study (5).

320 In conclusion, the maternal 400 mg emtricitabine administration before delivery
321 produces higher exposure than the 200 mg administration in others adults at steady state.
322 Emtricitabine placental transfer, described by neonatal to maternal exposure ratio was around
323 80%. Finally, neonates should receive FTC 1 mg/kg as soon as possible after birth or 2 mg/kg
324 12 hours after birth to have concentrations comparable to those observed in adults. The
325 second step of TEmAA trial will validate these recommendations.

326

327

328

329

Acknowledgements

We acknowledge the French Agence Nationale de Recherche contre le VIH/SIDA et les hepatitis virales (ANRS) for sponsoring the trial, as well as European and Developing Clinical Trials Partnership (EDCTP) for their additional financial support.

We greatly thank the local investigators and their staff in the Formations Sanitaires Urbaines de Youpougon and Abobo and the Centre Hospitalier Universitaire de Yopougon in Abidjan, in the Calmette Hospital and Pasteur Institute in Phnom Penh, and the Perinatal HIV Research Unit and Lesedi Clinic in Soweto. We also thank the women who accepted to participate in the trial and their infants. We acknowledge Gilead Sciences for providing the study drugs. Didier K Ekouevi was EDCTP Senior fellowship (2005-2007).

The TEmAA trial group is constituted as follows:

- Co-investigators: Prs Christine Rouzioux, Stéphane Blanche and Jean-Marc Treluyer, Dr Marie-Laure Chaix and Dr Elisabeth Rey (Paris, France), Pr N'dri-Yoman (Abidjan, Côte d'Ivoire), Pr Kruiy Leang Sim and Dr Eric Nerrienet (in

Phnom Penh, Cambodia) and Prs Glenda Gray and James McIntyre (Soweto, South Africa)

- Trial coordinator: Dr Elise Arrivé (Bordeaux, France)
- Other members of the TEmAA ANRS 12109 Study Group (by place and alphabetic order):
 - Paris: Déborah Hirt, Saik Urien
 - Abidjan: Gérard Allou, Clarisse Amani-Bosse, Divine Avit, Gédéon Bédikou, Kouakou Brou, Patrick Coffié, Patrice Fian, Eulalie Kanga, Broulaye Kone, Suzanne Kouadio, Guy César Kouaho, Jeanne Eliam Kouakou, Sidonie Ngatchou, Touré Pety, Zenica Seoue, Mamourou Kone
 - Phnom Penh: Laurence Borand, Pinn Chou, Kearena Chhim, Meng Ly Ek, Viseth Horm Srey, Seng Hout, Sethikar Im, Saroeum Keo, Vannith Lim, Sopheak Ngin, Vara Ouk, Vibol Ung , and the Magna and Maryknoll associations
 - Soweto : Gail Ashford, Promise Duma, Portia Duma, Sarita Lalsab, Shini Legote, Tshepiso Mabena, Joseph Makhura, Modise Maphutha, Selvan Naidoo, Mandisa Nyati
- Scientific Board: Pr Bernard Koffi Ngoran (Abidjan, Côte d'Ivoire), Pr Koum Kanal (Phnom Penh, Cambodia), Pr Lynn Morris (Johannesburg, South Africa), Dr Séverine Blesson (ANRS, Paris, France), Dr Camille Aubron-Olivier (Gilead Sciences, Paris, France), Pr Gilles Peytavin (Paris, France), Pr Koen Van Rompay (Davis, California, USA), Dr Valériane Leroy (Bordeaux, France)

- Independent Committee: Prs John Sullivan (Worcester, Massachusetts, USA), Philippe Lepage (Brussels, Belgium), Laurent Mandelbrot (Paris, France), Marie-Louise Newell (London, UK), Anne-Marie Taburet (Paris, France)

References

1. **Beal, S. L.** 2001. Ways to fit a PK model with some data below the quantification limit. *J Pharmacokinet Pharmacodyn* **28**:481-504.
2. **Beal, S. L., and L. B. Sheiner.** 1998. *NONMEM User's Guide*; NONMEM project group, San Francisco:University of California.
3. **Best, B., A. Stek, C. Hu, S. Burchett, S. Rossi, E. Smith, B. Sheeran, J. Read, E. Capparelli, M. Mirochnick, and a. f. t. P. I. P. s. Team.** 2008. Presented at the 15th Conference on Retroviruses and Opportunistic Infections, Boston, 3-6th of february.
4. **Blum, M. R., G. E. Chittick, J. A. Begley, and J. Zong.** 2007. Steady-state pharmacokinetics of emtricitabine and tenofovir disoproxil fumarate administered alone and in combination in healthy volunteers. *J Clin Pharmacol* **47**:751-9.
5. **Blum, M. R., D. Ndiweni, G. Chittick, N. Adda, D. Kargl, and D. Josipovic.** 2006. Presented at the 13th Conference on Retroviruses and Opportunistic Infections, Denver, 5-8 th of february 2006.
6. **Chi, B. H., M. Sinkala, F. Mbewe, R. A. Cantrell, G. Kruse, N. Chintu, G. M. Aldrovandi, E. M. Stringer, C. Kankasa, J. T. Safrit, and J. S. Stringer.** 2007. Single-dose tenofovir and emtricitabine for reduction of viral resistance to non-nucleoside reverse transcriptase inhibitor drugs in women given intrapartum nevirapine for perinatal HIV prevention: an open-label randomised trial. *Lancet* **370**:1698-705.
7. **Eshleman, S. H., D. R. Hoover, S. Chen, S. E. Hudelson, L. A. Guay, A. Mwatha, S. A. Fiscus, F. Mmiro, P. Musoke, J. B. Jackson, N. Kumwenda, and T. Taha.** 2005. Nevirapine (NVP) resistance in women with HIV-1 subtype C, compared with subtypes A and D, after the administration of single-dose NVP. *J Infect Dis* **192**:30-6.

8. **Ihaka, R., and R. Gentleman.** 1996. R: a language for data analysis and graphics. *J Comput Graph Stat* **5**:299.
9. **Jackson, J. B., G. Becker-Pergola, L. A. Guay, P. Musoke, M. Mracna, M. G. Fowler, L. M. Mofenson, M. Mirochnick, F. Mmiro, and S. H. Eshleman.** 2000. Identification of the K103N resistance mutation in Ugandan women receiving nevirapine to prevent HIV-1 vertical transmission. *AIDS* **14**:F111-5.
10. **Krauer, B., F. Krauer, and F. E. Hytten.** 1980. Drug disposition and pharmacokinetics in the maternal-placental-fetal unit. *Pharmacol Ther* **10**:301-28.
11. **Le Saux, T., S. Chhun, E. Rey, O. Launay, L. Weiss, J. P. Viard, G. Pons, and V. Jullien.** 2008. Quantification of seven nucleoside/nucleotide reverse transcriptase inhibitors in human plasma by high-performance liquid chromatography with tandem mass-spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci* **865**:81-90.
12. **Loebstein, R., A. Lalkin, and G. Koren.** 1997. Pharmacokinetic changes during pregnancy and their clinical relevance. *Clin Pharmacokinet* **33**:328-43.
13. **Mirochnick, M.** 2000. Antiretroviral pharmacology in pregnant women and their newborns. *Ann N Y Acad Sci* **918**:287-97.
14. **Parry, E., R. Shields, and A. C. Turnbull.** 1970. Transit time in the small intestine in pregnancy. *J Obstet Gynaecol Br Commonw* **77**:900-1.
15. **Ramanathan, S., G. Shen, A. Cheng, and B. P. Kearney.** 2007. Pharmacokinetics of emtricitabine, tenofovir, and GS-9137 following coadministration of emtricitabine/tenofovir disoproxil fumarate and ritonavir-boosted GS-9137. *J Acquir Immune Defic Syndr* **45**:274-9.
16. **Rodman, J. H., P. M. Flynn, B. Robbins, E. Jimenez, A. D. Bardeguetz, J. F. Rodriguez, S. Blanchard, and A. Fridland.** 1999. Systemic pharmacokinetics and

cellular pharmacology of zidovudine in human immunodeficiency virus type 1-infected women and newborn infants. *J Infect Dis* **180**:1844-50.

17. **Wang, L. H., A. A. Wiznia, M. H. Rathore, G. E. Chittick, S. S. Bakshi, P. J. Emmanuel, and P. M. Flynn.** 2004. Pharmacokinetics and safety of single oral doses of emtricitabine in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother* **48**:183-91.
18. **Zong, J., G. E. Chittick, L. H. Wang, J. Hui, J. A. Begley, and M. R. Blum.** 2007. Pharmacokinetic evaluation of emtricitabine in combination with other nucleoside antivirals in healthy volunteers. *J Clin Pharmacol* **47**:877-89.

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 5th (dash line), 50th (full line) and 95th (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 ($\mu\text{mol/L}$)	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_{k_a} (%)	61 (29)
CL/F (L/h)	23.2 (4)	$\omega_{CL/F}$ (%)	17 (34)
V_1/F (L)	127 (7)	$\omega_{k_{F0}}$ (%)	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)		

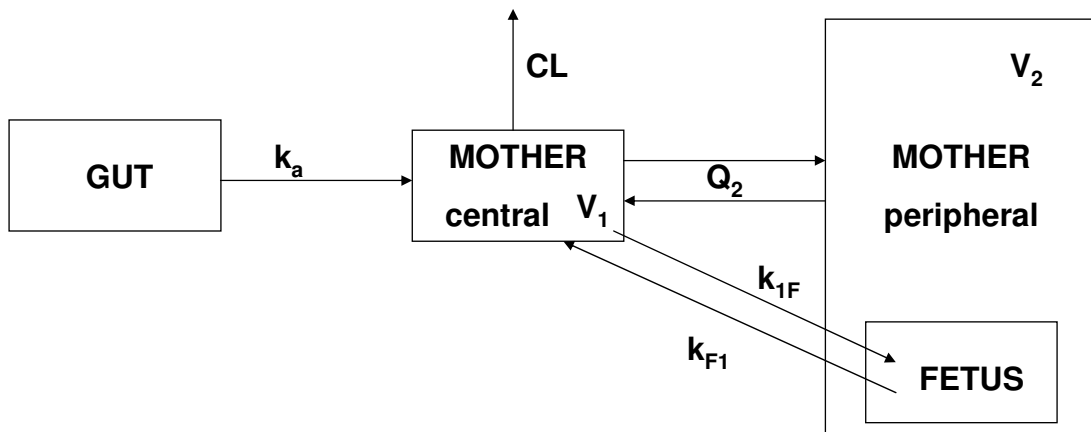
Key: RSE%, relative standard error (standard error of estimate / estimate*100); k_a absorption rate constant, CL/F maternal apparent elimination clearance from the central compartment, V_1/F apparent volume of distribution of the central maternal compartment, Q₂/F apparent maternal intercompartmental 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.**

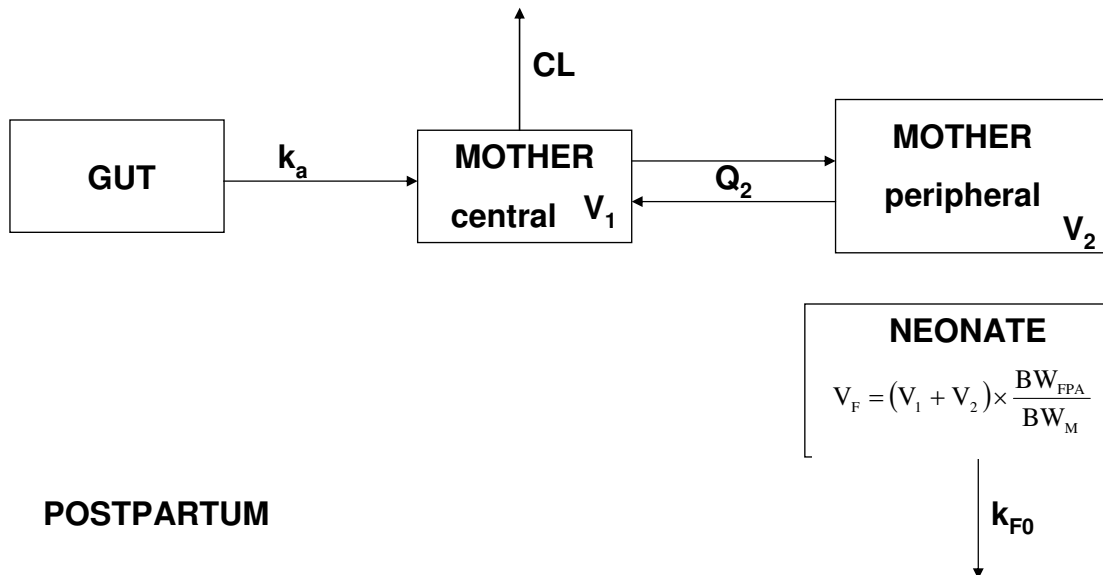
Median	TEMAA Pregnant, 400 mg	Zhong et al. (18) Adults, 200 mg	Blum et al. (4) Adults, 200 mg	Ramanathan et al. (15) Adults, 200 mg
AUC (mg/L.h)	14.3 (11.0 – 19.0)	10.7	10.7	9.8
C_{\min} (mg/L)	0.076 (0.039 – 0.174)	0.071	0.075	0.085
C_{\max} (mg/L)	1.68 (0.82 – 2.13)	2.18	1.69	1.68

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



ANTEPARTUM AND INTRAPARTUM



POSTPARTUM

