

# POPULATION PHARMACOKINETICS OF EMTRICITABINE IN HIV-1 INFECTED PREGNANT WOMEN AND THEIR NEONATES (TEmAA - ANRS 12109)

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## INTRODUCTION

Limited number of ARVs and drug regimens are used for PMTCT (zidovudine, lamivudine, nevirapine) (WHO guidelines). A single-dose nevirapine (sdNVP) is the most common ARV regimen used for PMTCT: one 200 mg tablet at the onset of labor and one neonatal dose of syrup on Day 2 (Musoke 1999). However high rate of NVP resistance mutations were observed at 4-8 weeks (Arrivé 2007) in HIV-infected women (36%) and children (52%). Cross resistance to all non nucleoside reverse transcriptase inhibitors (NNRTIs) were also described, having a negative impact on virological response to subsequent ARV therapy including a NNRTI (Lallemant 2004, Lockman 2007). Adding a single dose of Truvada® (=Tenofovir disoproxil + emtricitabine) to nevirapine at delivery was shown to reduce resistance to non-nucleoside reverse transcriptase inhibitors at 6 weeks after delivery by half (Chi 2007).

The objectives of TEmAA was to study the pharmacokinetics of emtricitabine (FTC) and tenofovir disoproxil (TD), contained in Truvada® tablets, in pregnant women and neonates.

Emtricitabine : potent, once daily nucleoside reverse transcriptase inhibitor approved in HIV infected adults and children > 3 months. In adults, FTC is rapidly and extensively absorbed, widely distributed and primarily excreted by the kidneys. There is no FTC pharmacokinetic (PK) data during pregnancy, on placental transfer, and at neonatal birth.

## METHODS

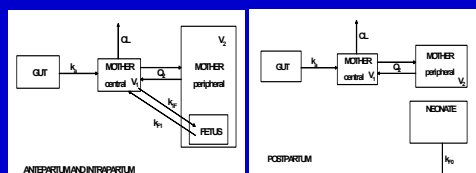
### TREATMENTS AND SAMPLING

|  |   |   |
|--|---|---|
| <b>INCLUSION:</b> W28 to W38 gestation   | <b>START OF LABOUR (DELIVERY)</b>                             | <b>POSTPARTUM</b><br>D1 D2 D3 D4 D5 D6 D7 |
| <b>38 MOTHERS</b><br>ZDV 300 mg BID      | 1) NVP 200 mg<br>2) TRUVADA® (2 tab) = 600 mg TD + 400 mg FTC | TRUVADA® (QD) = 300 mg TD + 200 mg FTC    |
| <b>Maternal PK sampling (n=413)</b>      | H0 H1 H2 H3 H5 H8 H12<br>DEL                                  | H24 H48 H72<br>H168                       |
| <b>32 CHILD</b>                          | D1 : NVP (2 mg/kg)<br>D1→D7: ZDV (4 mg/kg BID)                |   |
| <b>Fetal/Neonatal PK sampling (n=37)</b> | CORD<br>(n=37)  | H24 H48<br>(n=43)                         |

### MOTHER – CHILD PK MODELING

A population pharmacokinetic study was performed on maternal, cord and neonatal plasma samples in order to I) describe the concentration-time courses of FTC in mothers, the transfer of FTC from maternal plasma to cord plasma and the neonatal elimination, II) study the influence of covariates (maternal bodyweight, gestational age, type of delivery, creatinin, neonatal bodyweight and height) on FTC pharmacokinetics.

This model allowed us to determine the optimal dose of emtricitabine and tenofovir disoproxil in women at the start of labour and the optimal single dose in their neonates to prevent mother to child transmission of HIV.



## RESULTS

### POPULATION PK PARAMETERS

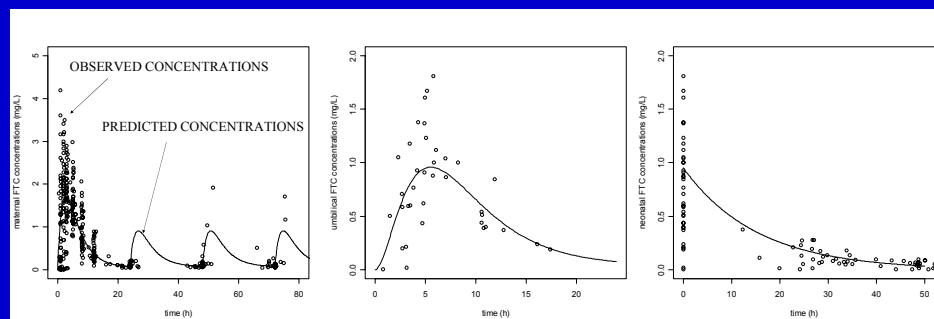
| Structural model            |                  | Statistical model   |                  |
|-----------------------------|------------------|---|------------------|
| Parameter                   | Estimate (RSE %) | Parameter   | Estimate (RSE %) |
| $k_e$ (h <sup>-1</sup> )    | 0.54 (11)        | $\omega_{ka}$ (%)   | 61 (29)          |
| CL/F (L/h)                  | 23.2 (4)         | $\omega_{CL/F}$ (%)   | 17 (34)          |
| $V_1/F$ (L)                 | 127 (7)          | $\omega_{KFD}$ (%)  | 30 (35)          |
| Q/F (L/h)                   | 6.04 (10)        | $\sigma_{MOTHER}$ (%)   | 45 (14)          |
| $V_2/F$ (L)                 | 237 (15)         | $\sigma_{CORD}$ (%)   | 43 (24)          |
| $k_{IF}$ (h <sup>-1</sup> ) | 0.29 (13)        | $\sigma_{NEONATE}$ (%)  | 33 (27)          |
| $k_{EF}$ (h <sup>-1</sup> ) | 0.38 (13)        | Good estimation of the parameters.<br><b>None of the covariate studied had an effect on FTC PK.</b> |                  |
| $k_{FD}$ (h <sup>-1</sup> ) | 0.065 (7)        |   |                  |

### FTC PK DURING PREGNANCY, COMPARISON TO NON PREGNANT ADULTS

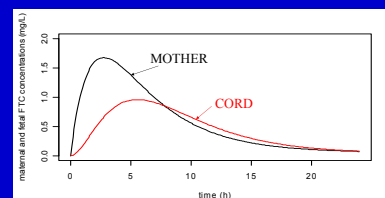
| Median                  | TEmAA Pregnant 400 mg | Zhong 2007 Adults, 200 mg | Blum 2007 Adults, 200 mg | Ramana -than 2007 Adults, 200 mg |
|-------------------------|-----------------------|---------------------------|--------------------------|----------------------------------|
| AUC (mg/L.h)            | 14.3                  | 10.7                      | 10.7                     | 9.8                              |
| C <sub>min</sub> (mg/L) | 0.076                 | 0.071                     | 0.075                    | 0.085                            |
| C <sub>max</sub> (mg/L) | 1.68                  | 2.18                      | 1.69                     | 1.68                             |

The 400 mg FTC administration in pregnant women produces higher exposition than the 200 mg administration to adults, at steady state.

### POPULATION PREDICTION FOR MOTHER – FŒTUS AND NEONATE

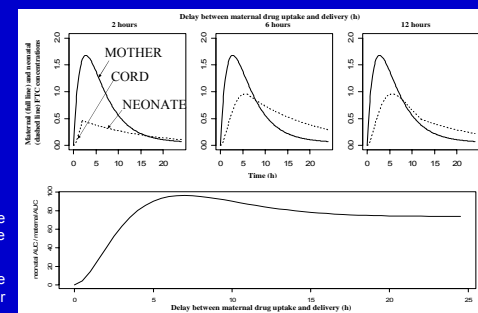


### PLACENTAL TRANSFER



Neonatal to maternal concentrations ratio varies as a function of the delay between emtricitabine drug intake and delivery. This measure is an instantaneous descriptor of the placental transfer.

A neonatal to maternal expositions (AUCs) ratio is more representative of the real placental transfer. From four hours after delivery, this ratio was around 80%.



## PREDICTIONS

### ADMINISTRATION TO THE NEONATE

#### Goals :

- To obtain in neonates an exposition similar to the known exposition in adults, i.e. to have  $(AUC_{0-24h})_{NEONATES} = 10.4$  mg/L.h
- To guarantee newborn FTC concentrations higher than 0.077 mg/L (=residual adult concentration),
  - ✓ before neonatal administration
  - ✓ as long as possible after administration to the neonate

#### Hypothesis for the neonate :

- same bioavailability and absorption rate as his mother
- volume of distribution proportional to the maternal one.

#### Methods :

Using neonatal individual PK parameters: simulation of  $AUC_{0-24h}$ ,  $C_{min}$ ,  $t_{(C_{min}>0.077 \text{ mg/L})}$  for 1 and 2 mg/kg of FTC administered 1h after birth.

|                                 | Dose in mg/kg administered 1 hour after birth |      |      |
|---------------------------------|---|------|------|
| Median                          | 0   | 1    | 2    |
| AUC (mg/L.h)                    | 9.56  | 11.7 | 14.0 |
| C <sub>min</sub> (mg/L)         |   | 0.67 | 0.67 |
| $t_{(C_{min}>0.077 \text{ h})}$ |   | 36.6 | 40.2 |

The major part of the neonatal emtricitabine AUC was due to the maternal administration (i.e. 9.56 mg/L.h). Only a 1 mg/kg dose is needed one hour after birth in order to obtain same neonatal as adult concentrations.

## CONCLUSIONS

The maternal 400 mg emtricitabine administration before delivery produces higher exposition than the 200 mg administration in others adults, at steady state.

Emtricitabine placental transfer, described by neonatal to maternal expositions ratio was around 80%.

To obtain same exposition for a single dose, neonates should receive 1 mg/kg of emtricitabine as soon as possible after birth.

The objectives of TEmAA was to study the pharmacokinetics of emtricitabine and tenofovir disoproxil, contained in Truvada® tablets, in pregnant women and neonates. Results for tenofovir disoproxil were presented at the Mother to child transmission session (Hirt et al. 47LB, Monday, February, 4, 5:30 pm). Conclusions for Truvada® administration of the TEmAA study have to be made on both molecules :

**Mother :** 2 tablets of Truvada®, readminister 2 tablets of Truvada® if time between maternal administration and delivery is higher than 12 hours

**Neonate :** Tenofovir : 13 mg/kg of Tenofovir disoproxil fumarate (= 6 mg/kg tenofovir) and Emtricitabine : 1 mg/kg as soon as possible after birth

These predictions will be validated during the second part of TEmAA.

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