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Population PK of Dolutegravir in Plasma, Cord and Breastmilk: Results from DolPHIN-1

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INTRODUCTION

- Risk of mother-to-child transmission (MTCT) of HIV is particularly high when untreated HIV-infected women enter care late in pregnancy (≥28 weeks)
- Safe and effective treatment that can quickly reduce viral load is paramount to prevent peripartum transmission in this patient population
- Dolutegravir (DTG)-based therapy may provide a suitable alternative to efavirenz-based standard of care (SoC) due to rapid onset of viral load reduction, high genetic barrier to resistance and good tolerability
- DolPHIN-1 (NCT02245022) investigated the PK and safety of DTG in pregnant women and their infants presenting with untreated HIV late in pregnancy (≥28-36 weeks gestation)[1-2]

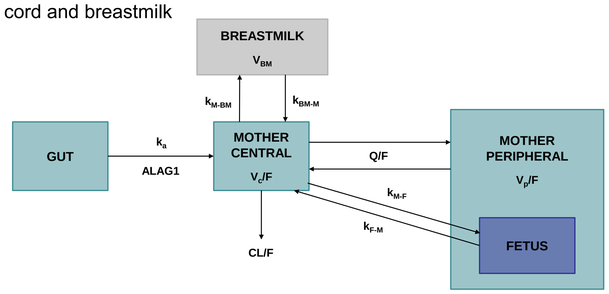
OBJECTIVES

- Develop a population PK model to describe DTG concentrations over time in maternal plasma (ante and postpartum), umbilical cord and breastmilk using data collected during DolPHIN-1
- Assess the impact of covariates on DTG PK parameters and placental and breastmilk transfer and estimate infant exposure to DTG via breastmilk

METHODS

- ***Patients:*** HIV-infected women diagnosed late in pregnancy were recruited from antenatal clinics associated with two study sites:
  1. Infectious Disease Institute, Kampala, Uganda
  2. University of Cape Town, Cape Town, South Africa
- Women were randomised (1:1) to DTG-based therapy (50 mg once daily) or efavirenz-based SoC (NRTI backbone: lamivudine or emtricitabine + tenofovir disoproxil fumarate)
- ***PK Sampling:*** DTG *plasma* PK sampling was performed 14 days after therapy initiation during the third trimester and within 2 weeks of delivery (postpartum) at pre-dose (0 h), 0.5, 1, 2, 3, 4, 6, 8 and 24 h post-dose
- Where possible paired maternal *plasma* and *cord* samples were taken at delivery. *Breastmilk* was obtained postpartum (2-6 h and 24 h post-dose). Patients then switched to SoC and a paired *plasma* and *breastmilk* sample taken 1-3 days post-switch
- DTG was measured by LC-MS/MS[3,4] with a lower limit of quantification of 0.01 mg/L for all matrices
- ***Population PK Modelling:*** Nonlinear mixed effects (NONMEM v. 7.3) was used to describe DTG PK in maternal plasma, umbilical cord and breastmilk
- A sequential approach was applied whereby the maternal plasma was modelled first then PK parameters fixed to the individual estimates for the simultaneous analysis of the cord and breastmilk data
- Covariates included maternal age, weight, pregnancy (third trimester *vs.* postpartum), gestational age, delivery (vaginal *vs.* C-section) and weeks postpartum
- Model evaluation was by means of visual predictive check (VPC)

Figure 1. Schematic of the population PK model to describe DTG in maternal plasma, umbilical cord and breastmilk



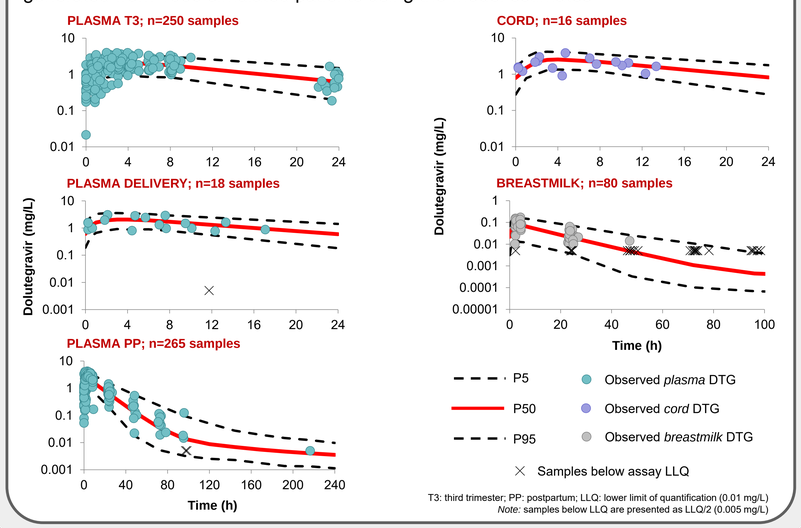
k_a: absorption rate constant; ALAG1: absorption lag time; CL/F, Q/F: maternal apparent oral and intercompartmental clearance; V_c/F, V_p/F: maternal apparent volume of distribution of the central and peripheral compartments; k_{M-F}, k_{F-M}: mother-to-fetus and fetus-to-mother transfer rate constants; k_{M-BM}, k_{BM-M}: mother-to-breastmilk and breastmilk-to-mother transfer rate constants

Table 1. DTG model estimates and corresponding relative standard errors (RSE%)

Parameter	Estimate (RSE%)	IIV% (RSE%)	IOV% (RSE%)	Parameter	Estimate (RSE%)
Maternal Plasma				***Umbilical cord***	
CL/F(L/h)	1.52 (4)		24.7 (20)	k_{M-F} (h^{-1})	2.74 (2)
V_c/F (L)	22.9 (6)	18.9 (53)		k_{F-M} (h^{-1})	2.22 (4)
Q/F (L/h)	0.0135 (59)			Residual error (%)	25.7 (48)
V_p/F (L)	2.11 (6)				
k_a (h^{-1})	0.700 (15)		85.1 (26)	***Breastmilk***	
Lag time (h)	0.133 (31)			k_{M-BM} (h^{-1})	0.0027 (10)
Residual error (%)				k_{BM-M} (h^{-1})	14.5 (14)
Uganda	35.6 (16)			V_{BM} (L)	0.125 *fixed*
South Africa	27.6 (20)			Residual error (%)	63.7 (30)

IIV: interindividual variability; IOV: interoccasion variability
RSE% = $SE_{ESTIMATE}$/ESTIMATE * 100

Figure 2. DTG 90% prediction interval in maternal plasma, umbilical cord and breastmilk generated from 1000 simulated patients using the model estimates



T3: third trimester; PP: postpartum; LLQ: lower limit of quantification (0.01 mg/L)
Note: samples below LLQ are presented as LLQ/2 (0.005 mg/L)

RESULTS

- ***Patients:*** Twenty-eight women (14 Uganda, 14 South Africa) were included in the analysis; 27 had paired ante/postpartum visits [gestational age: 39 weeks (35-43)]
- Median (range) age and weight was 27 years (19-42) and 67 kg (44-160), respectively. Postpartum sampling was performed within 1, 2 and 3 weeks of delivery for 15, 9 and 3 women, respectively
- ***Population PK Modelling:*** A total of 533 plasma (250 antepartum, 18 delivery, 265 postpartum), 16 cord and 80 breastmilk samples were included
- The small proportion of plasma samples below the assay LLQ (3/533; 0.6%) were included as LLQ/2. The 39% of breastmilk samples <LLQ were included using the M3 method of NONMEM[5]
- A 2-compartment model described DTG in plasma, linked to a fetal compartment of negligible volume (which does not alter the maternal plasma compartment) and a breastmilk compartment of fixed volume (0.125L[6,7]) by first-order processes (Figure 1; Table 1)
- Apparent oral clearance (CL/F) was higher than previously reported for HIV-infected, treatment-naïve patients (1.52 *vs.* 0.90L/h[8]) but not significantly different between the third trimester and 1-3 weeks postpartum. None of the other covariates were significantly associated with DTG parameter estimates
- Covariate effects could not be assessed for cord or breastmilk as interindividual variability could not be estimated for the transfer rate constants
- VPCs (90% prediction intervals) are presented (Figure 2) and indicated a satisfactory description of the data
- ***DTG cord (foetal) and breastmilk transfer:*** Median (range) simulated cord AUC_{0-24} was 41.2 mg.h/L (34.0-59.3) and was 123.4% (123.3-123.6) that of maternal plasma at delivery (n=18)
- Breastmilk AUC_{0-24} was 1.20 mg.h/L (0.71-2.45; n=27) and was consistently 3.3% (2.5-5.2) that of plasma when simulated 1-3 days post-switch to SoC
- ***DTG relative infant dose (RID) via breastmilk:*** Average DTG breastmilk concentration (C_{av}) over 24 h post-switch was 0.050 mg/L (0.029-0.10; n=27) corresponding to an absolute infant dose of 2.2 µg/kg/day (1.2-4.3; n=26; assuming 150 ml/kg/day of milk ingested[7,9,10])
- Over the same time period RID to that of the mother was 0.27% (0.13-0.80; n=26), which is below the suggested safety threshold of 10%[7,10]

CONCLUSIONS

- Rich and sparse data collection allowed estimation of DTG disposition in maternal plasma, cord and breastmilk through population PK modelling
- Model estimation of AUC ratios could provide a better evaluation of placental/milk transfer in the event of variable drug transfer over time
- Although DTG breastmilk RID was within the safety threshold of 10%, accumulation was observed in the infants[2]. Infant DTG placental and breastmilk exposure will be evaluated using a population PK approach

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