THE PHARMACOKINETICS AND SAFETY OF DORAVIRINE IN PREGNANT WOMEN LIVING WITH HIV AND THEIR INFANTS

797

Lauren Jennings[1], Laura Else[2], Laura Dickinson[2], Lucy Read[3], Debarpita Choudhury[3], Raymond Monk[2], Duolao Wang[4], Chantel Schreuder[1], Nyiko Mashele[1], Catriona Waitt[5], Thokozile Malaba[6], Landon Myer[6], Catherine Orrell[1,7], Helen Reynolds[2], Saye Khoo[2]

[1]Desmond Tutu HIV Centre, University of Cape Town, [2]Centre for Experimental Therapeutics, University of Liverpool,[3]Global Health Trials Unit, Liverpool School of Tropical Medicine,[4]Department of Clinical Sciences, Liverpool School of Tropical Medicine,[5]Department of Women's and Children's Health, University of Liverpool, [6]Division of Epidemiology and Biostatistics, School of Public Health, University of Cape Town,[7]HIV and other Infectious Diseases Unit, South African Medical Research Council.

Background

- Vertical transmission of HIV remains a major challenge in low- and middle-income countries.
- **Doravirine** (DOR), a 2nd generation NNRTI has a favorable resistance profile but data on safety and pharmacokinetics (PK) in pregnancy are limited.



Objectives

- We sought to determine the steady-state PK parameters of DOR administered in pregnancy and postpartum.
- Secondary objectives include safety and tolerability, PK of DOR in breastmilk and breastfed infants.

Methods

- DoraDO is an ongoing randomised, controlled, open-label study of 76 pregnant South African women initiating ART between 8-26 weeks (wks) gestation.
- Participants are randomized 1:1 to DOR (100 mg in combination with TDF/3TC once daily) or Standard-of-Care (SoC: TDF/3TC/DTG).

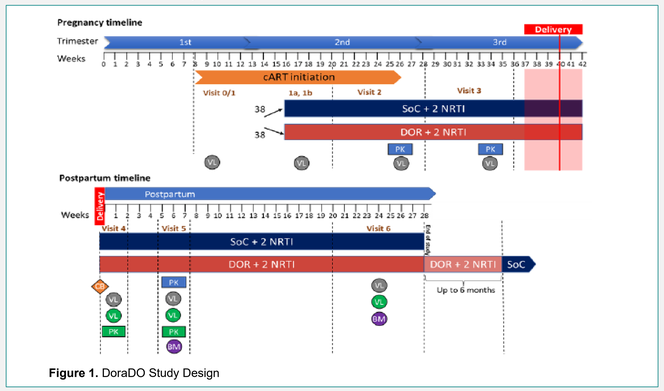


Figure 1. DoraDO Study Design

- Intensive PK sampling (0-24 h) was conducted in the DOR arm at the second (T2; 20-28 wks), third (T3; 32-36 wks) trimesters and 6 wks postpartum (PP).
- Paired maternal plasma (MP), infant plasma (IP) and dried breastmilk spots (DBMS) were collected at delivery (+4 wks) and around 6 and 24 wks PP in breastfeeding mothers receiving DOR or SoC.
- DOR & DTG concentrations were quantified by LC-MS [Plasma|DBMS LLQ = 2.0 | 1.3 ng/mL (DOR); 10 | 6.7 ng/mL (DTG)].
- PK parameters were calculated at intensive sampling visits and changes between visits assessed by linear mixed effects using log-transformed data to determine geometric mean ratios (GMR, 90% CI; Phoenix WinNonlin v. 8.5).
- **Following interim review, additional interventions were triggered if any participant failed to achieve ≥1 log10 drop in VL from baseline at 4 wks on ART or if VL was ≥1000 c/mL at 34 wks GA.**

Doravirine exposure is significantly reduced in trimesters 2 & 3 of pregnancy. Despite moderate transfer of doravirine into breastmilk (~30%), infant levels at postpartum are low.

Results

- This prespecified interim review includes safety and pharmacokinetics of DOR (15 mothers, 11 infants) and DTG (13 mothers, 12 infants); 1 mother-infant pair was excluded for non-adherence.

Maternal Plasma (MP)

- All MP C_{24} values were >33 ng/mL (6x protein adjusted EC_{50}) and were >230 ng/mL (10th percentile) in 38%, 60% and 100% of mothers at T2, T3 & PP, respectively.
- Among mothers with paired visits (n=8), a significant reduction in DOR AUC_{24} at T2 of 40% [0.60 (0.49-0.73)] & T3 of 42% [0.58 (0.44–0.77)] vs. PP was observed (Table 1).

Infant Plasma (IP) & Breastmilk (DBMS)

- IP levels were < 33 ng/ml in 8/10 infants at delivery.
- DBMS levels were >230 ng/mL (10th percentile) in 3/8 & 6/6 mothers sampled at maternal pre-dose and T_{max}.
- DBMS:MP ratios were consistent over the sampling period (~18–37%), while IP:MP ratios declined from ~3% at delivery to <1% at 24 wks PP (Table2; Figure 3).

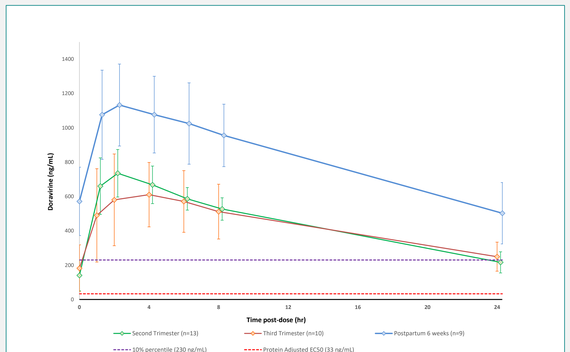


Figure 2. Geometric mean (GM; 90% CI) DOR concentration-time curves.

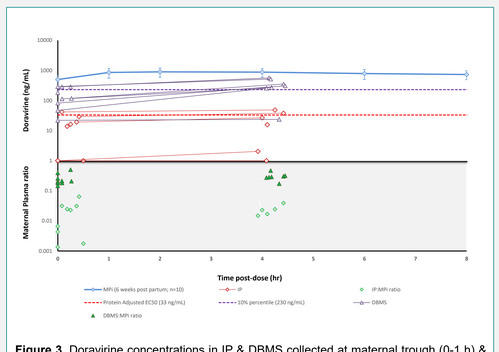


Figure 3. Doravirine concentrations in IP & DBMS collected at maternal trough (0-1 h) & 2 hours post-maternal T_{max} (~4 h), in relation to time-matched intensive MP profiles at 6 weeks PP. Corresponding IP:MP & DBMS:MP ratios are indicated in the grey area.

Intensive PK	T2 (n=13)[1]	T3 (n=10)	6 weeks PP (n=9)[1]	GMR (90% CI) T2 vs. PP (n=8)[1]	GMR (90% CI) T3 vs. PP (n=8)
AUC_{24} ng.h/mL	11074 (9910-12374)	10720 (8158-14085)	20034 (16986-23629)	**0.60** (0.49-0.73)	**0.58** (0.44-0.77)
C_{max} ng/mL	801 (692-927)	728 (528-1004)	1249 (1097-1422)	**0.65** (0.54-0.77)	0.63 (0.45-0.89)
C_{24} ng/mL	216 (170-275)	249 (185-336)	502 (392-645)	**0.55** (0.40-0.74)	**0.56** (0.43-0.72)
CL/F L/h	9.03 (8.08-10.1)	9.33 (7.10-12.3)	4.99 (4.23-5.89)	**1.68** (1.37-2.06)	**1.71** (1.30-2.26)

AUC_{24}: area under the curve from dosing to 24 hours post-dose; C_{max}: maximum concentration; C_{24}: trough concentration 24 hours post-dose; CL/F: apparent oral clearance

Table 1. GM (90%CI) DOR PK parameters at T2, T3 and PP. GMR (90% CI) derived using linear mixed effects analysis with data filtered to include only mothers with paired visits.
[1] one mother and her infant excluded due to suspected non-adherence

Sparse PK	Delivery[1]	6 wks PP[1]		24 wks PP
		predose (0 h)	T_{max} (~4 h)	
MP ng/mL [n]	155 (32-757) [10]	571 (427-765) [9]	1077 (925-1254) [9]	254 (26.8-2405) [6]
IP ng/mL [n]	10.4 (4.57-23.8) [10]	6.93 (2.31-20.8) [8]	15.0 (3.35-67.3) [5]	2.06 (0.80-5.32) [6]
DBMS ng/mL [n]	84.6 (21.5-332) [8]	147 (94.1-231) [8]	360 (274-474) [6]	24.2 (0.67-152) [3]
IP:MP ratio[2] [n]	0.034 (0.017-0.068) [8]	0.012 (0.004-0.031) [8]	0.013 (0.003-0.054) [5]	0.008 (0.001-0.073)
DBMS:MP ratio[2] [n]	0.29 (0.23-0.35) [7]	0.25 (0.19-0.32) [8]	0.32 (0.27-0.37) [6]	0.23 (0.18-0.29) [2]

[1] one mother and her infant excluded due to suspected non-adherence
[2] ratios excluded if any paired samples were <LLQ

Table 2. GM (90%CI) DOR concentrations in MP, IP & DBMS at delivery & PP (6wks PP collected at maternal pre-dose & ~2 h post T_{max}).

We would like to thank all DoraDO participants for their involvement in this study. This study was funded by Merck, Sharp and Dohme (MSD).

Results (cont.)

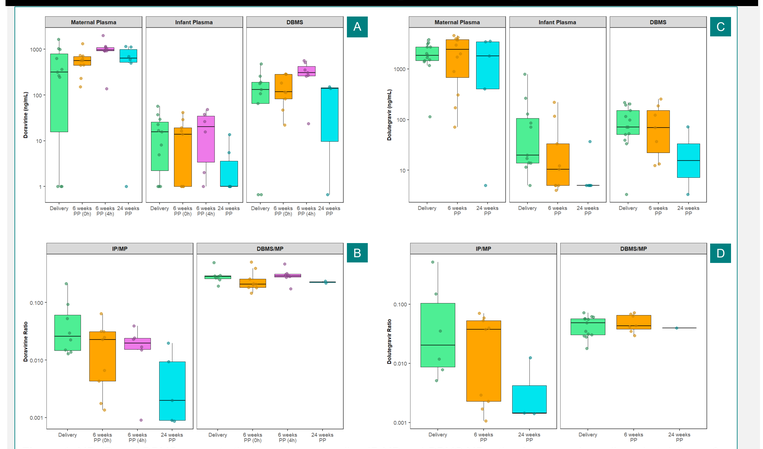


Figure 4. MP, IP, and DBMS concentrations and corresponding IP:MP and DBMS:MP ratios from samples collected at delivery, 6 weeks postpartum, and ~24 weeks postpartum in mothers receiving DOR (A, B) or DTG (C, D). The total of DTG MP, IP, DBMS analysed at delivery | 6 wks PP | ~24 wks PP were 13, 11, 13 | 12, 9, 7 | 5, 6, 2, respectively.

Dolutegravir PK

- All randomly sampled MP were above the protein-adjusted (PA) IC_{90} (64 ng/mL) at all visits except for one mother ~24 wks PP (<LLQ; Figure 4).
- Paired IP were above the PA-IC_{90} in 5/11, 2/9 and 1/6 at delivery, 6 wks PP and ~24 wks PP (5/6 <LLQ ~24 wks PP) with concentrations ranging between <LLQ-787 ng/mL at delivery and <LLQ-220 ng/mL at 6 wks PP.
- DTG transfer into breastmilk was consistently 4-5% (1.8-7.2% across visits) but only 1 of 2 DBMS samples quantifiable at 24 wks.
- IP:MP ratios declined from ~3% at delivery to <1% at ~24 wks PP (Figure 4).

Safety Data

- In 46 mothers enrolled to date, there have been 15 maternal and 6 infant serious adverse events. No trial stopping criteria were met to date.
- In both arms, no birth defects were detected and there have been no HIV transmissions.
- 1/14 and 1/7 participants required adherence interventions for insufficient VL reductions at 4 wks post-initiation and 34 wks GA, respectively.

Conclusions

1. **Doravirine exposure is reduced in T2 & T3 of pregnancy, but trough concentrations remain above target (>33 ng/mL).**
2. **Despite moderate transfer of doravirine into breastmilk (~30%), infant levels at postpartum are low and may predominantly reflect breastmilk transfer as well as maturation of CYP3A4-mediated metabolism.**
3. **There were no HIV transmissions or birth defects observed.**
4. **One participant required intervention for VL at 4 wks and 34 wks.**
5. **Ongoing follow-up will inform clinical recommendations during pregnancy and lactation.**

PLAIN LANGUAGE SUMMARY

Doravirine levels decrease in the later stages of pregnancy. Although some of the drug passes into breastmilk, babies are exposed to very small amounts.