Assessment of maternal and fetal dolutegravir exposure by integrating *ex vivo* placental perfusion data and physiologically-based pharmacokinetic modeling

J.J.M. Freriksen[1], S. Schalkwijk[2], A. Colbers[2], K. Abduljalil[3], F.G.M. Russel[1], R. Greupink[1], D.M. Burger[2]

[1] *Department of Pharmacology and Toxicology, Radboud university medical center, Nijmegen, The Netherlands*

[2] *Department of Pharmacy, Radboud university medical center, Nijmegen, The Netherlands*

[3] *Certara, Sheffield, UK*

14

Background

- In the US, there are ~8500 HIV-infected women giving birth every year
- Antiretroviral therapy during pregnancy reduces the chance of mother-to-child transmission of the virus from 20% to <2%
- Adequate dosing is challenging because of pregnancy-associated physiological and anatomical changes
- Pregnancy physiologically-based pharmacokinetic (p-PBPK) models may be used to predict maternal and fetal drug exposure
- However, to simulate fetal exposure using a p-PBPK model, data on placental drug transfer is necessary

Aim

- Incorporate mechanistic *ex vivo* data that quantitatively describes placental transfer of the antiretroviral agent dolutegravir in a p-PBPK model
- Predict maternal and fetal drug exposure and explore the clinical implications of standard dosing for mother and child

Materials & Methods

Pregnancy-PBPK model development

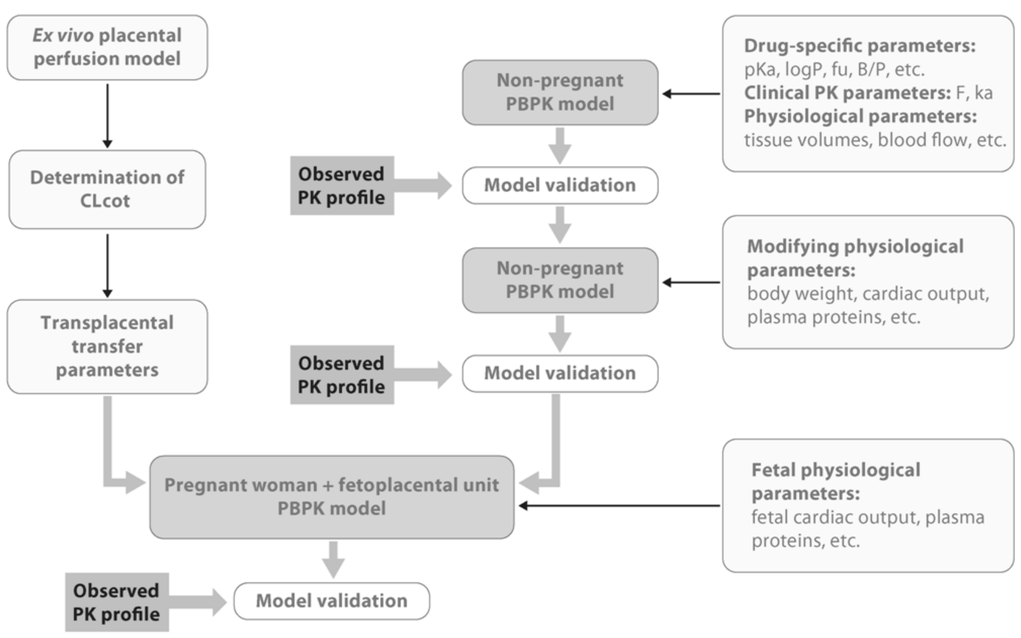

Figure 1. Workflow of p-PBPK model development. *Adapted from De Sousa Mendes et al.* [1]

Ex vivo dual-side placental perfusion experiments

- Placental transfer of dolutegravir (4 µg/mL) was studied by performing bi-directional *ex vivo* dual-side perfusions, using a closed-open set-up
- Intact cotyledons of human term placentas were selected and the fetal and maternal circulations were re-established within 60 minutes after delivery
- Both circulations were sampled at specific time-points for 180 minutes
- HPLC-MS/MS analysis was performed to determine the dolutegravir concentrations

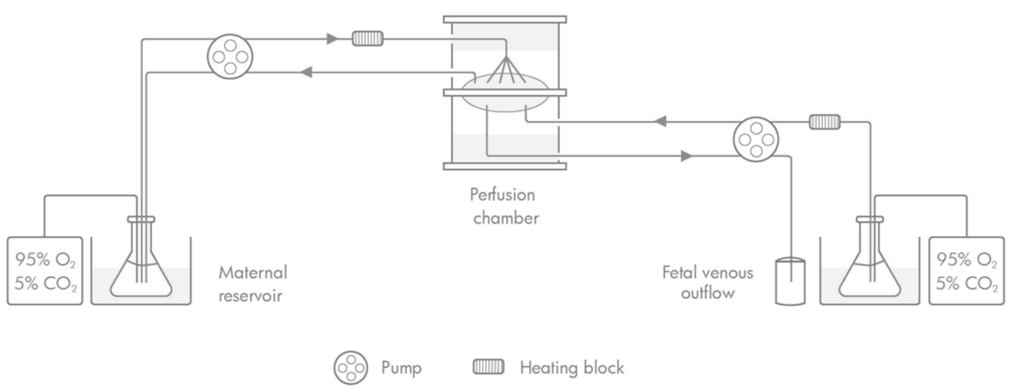

Figure 2. Schematic illustration of placental perfusion model.

Results

Ex vivo dual-side placental perfusion experiments

- Maternal-to-fetal cotyledon clearance (mean ± SD) → 1.03 ± 0.06 mL/min
- Fetal-to-maternal cotyledon clearance (mean ± SD) → 1.03 ± 0.23 mL/min

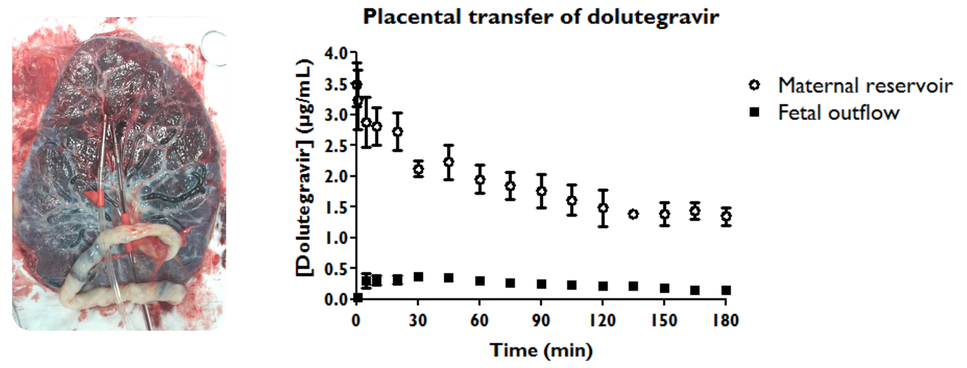

Figure 3. Left: Cannulation of a fetal artery-vein pair. Right: Dolutegravir levels in maternal reservoir decreased during 180 min of perfusion with a constant concentration ending up in the collected fetal outflow. Results are depicted as mean ± SD (n=3).

Simulation of maternal and fetal exposure via a p-PBPK modeling approach

Maternal exposure

Simulated C_{24h} → 0.98 mg/L

Observed C_{24h} [2] (mean, %CV) → 0.7 mg/L (109%)

Fetal exposure

Simulated C_{24h} → 0.65 mg/L

Simulated C_{max} → 2.66 mg/L

Observed cord blood concentrations [2] (median, range) → 1.29 (0.79-2.63) mg/L

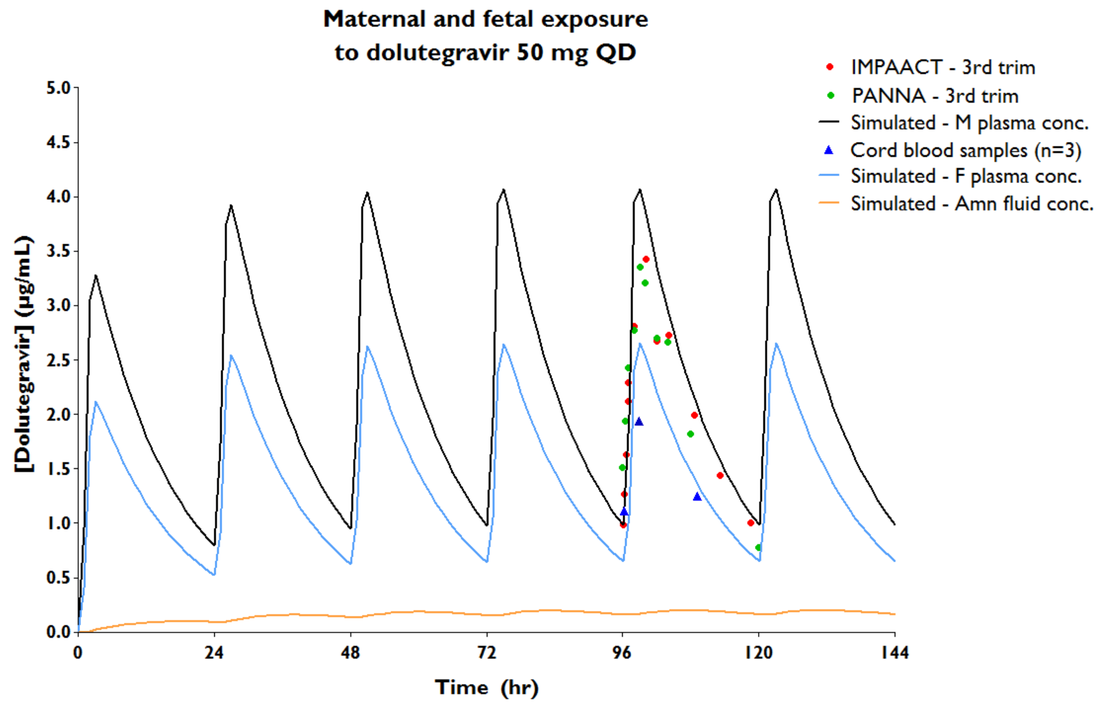

Figure 4. Simulations of maternal and fetal exposure via a p-PBPK modeling approach and compared with 3rd trimester pharmacokinetic data from the PANNA network and the IMPAACT group [2,3]

Conclusion & Future perspectives

- Dolutegravir crosses the placenta during 180 minutes of *ex vivo* placental perfusion
- Scaled placental transfer data were incorporated into the established p-PBPK model and simulations were able to adequately capture clinical dolutegravir pharmacokinetics
- The predicted fetal C_{24h} is above the EC90 for viral inhibition (0.064 µg/L) and may therefore have potential for fetal pre-exposure prophylaxis

***In silico* simulation of maternal and fetal drug exposure using *ex vivo* data provides a tool to guide maternal dosing and ensure safety of its use during pregnancy**

[1] De Sousa Mendes et al. *Prediction of human fetal pharmacokinetics using ex vivo human placenta perfusion studies and physiologically based models*. Br J Clin Pharmacol. 2016 Apr;81(4):646-57.

[2] Bollen et al. A *Comparison of the Pharmacokinetics of Dolutegravir in Pregnancy and Postpartum*. Presented at the 18th International Workshop on Clinical Pharmacology of Antiretroviral Therapy, 14-16 June 2017, Chicago, USA. www.pannastudy.com

[3] Mulligan et al. *Dolutegravir pharmacokinetics in pregnant and postpartum women living with HIV*. AIDS 2018, 32:729–737.

Jolien.Freriksen@radboudumc.nl

Institute for Molecular Life Sciences

Radboudumc