Predicting human foetal exposure using physiologically based pharmacokinetic models

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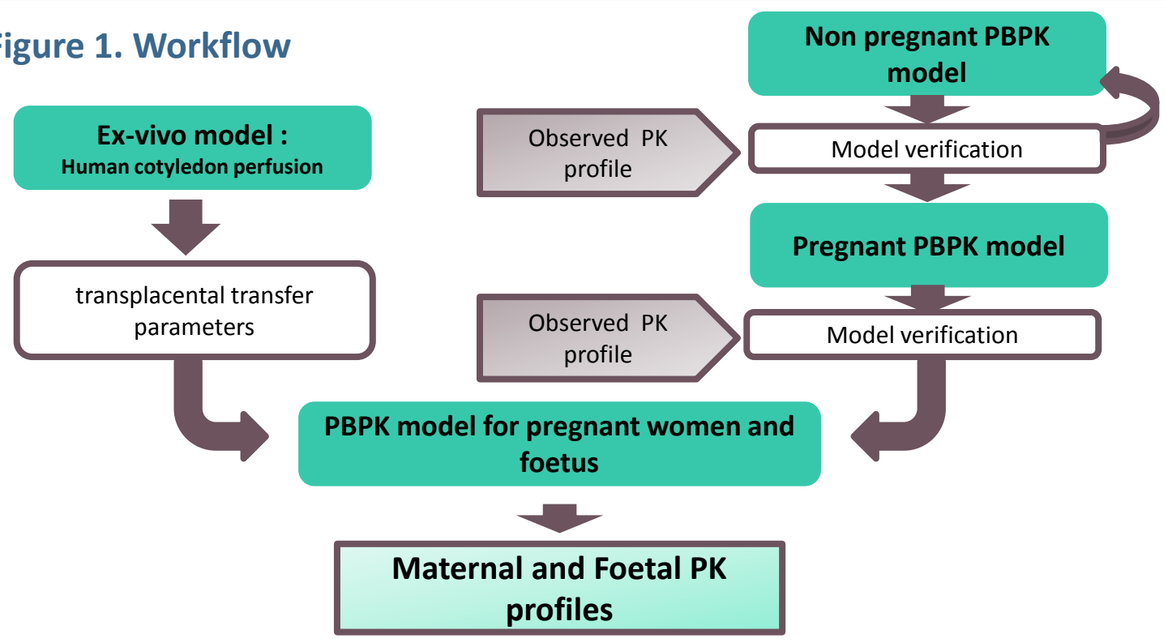
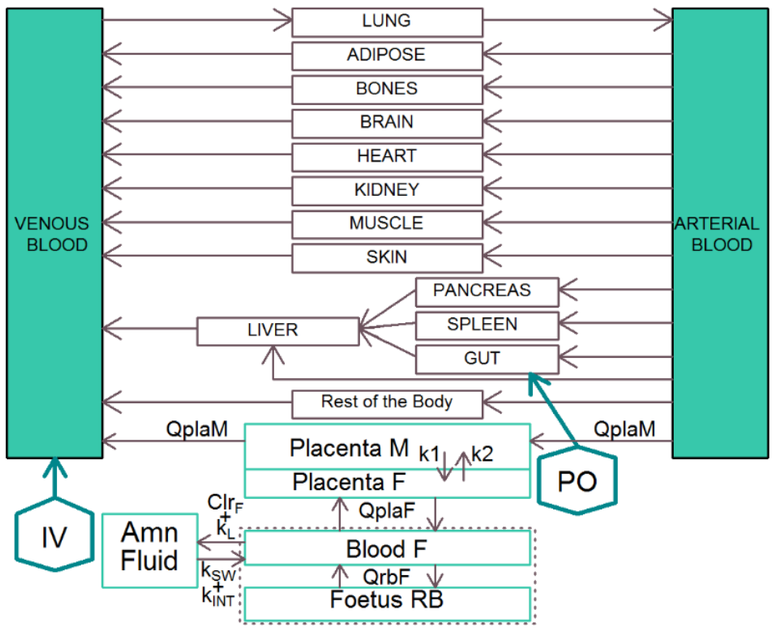
Pregnant women and their foetuses are exposed to numerous drugs. However, due to obvious ethical reasons *in vivo* foetal risk assessment studies related to maternal drugs exposure remain extremely limited. The aim of this work was to develop a novel approach to quantitatively predict drug foetal exposure.

Figure 1. Workflow



Physiologically-based pharmacokinetic (PBPK) models were developed for 3 antiretroviral drugs, tenofovir (TFV), emtricitabine (FTC) and nevirapine (NVP) in Simcyp® for non-pregnant population. All known physiological changes that could impact the drugs PK were taken into account (i.e. change in body weight, glomerular filtration rate, enzymatic activity, plasma volume). It was done in Simcyp and R.

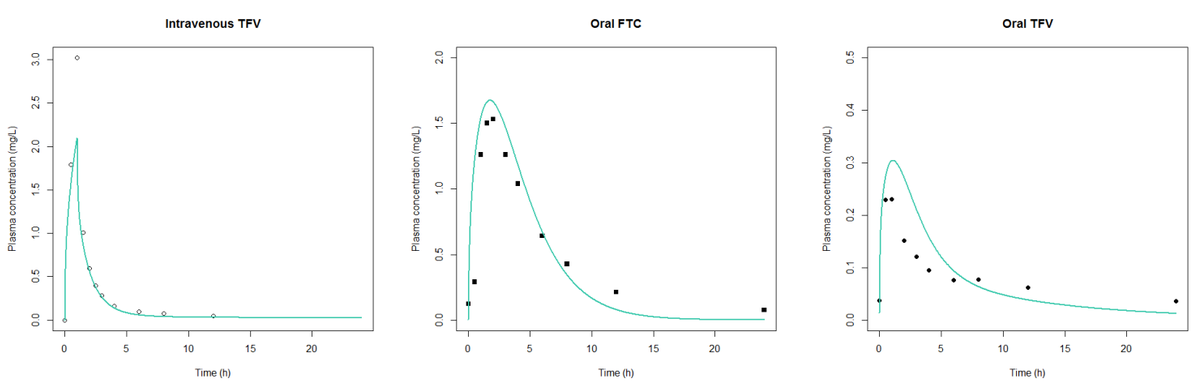
Figure 2 .Full PBPK structure



Transplacental transfer parameters were estimated from the ex-vivo human placenta perfusion experiments and then were implemented in the PBPK models. Model verification was done by comparing observed maternal and cord blood concentrations to predicted concentrations.

Results

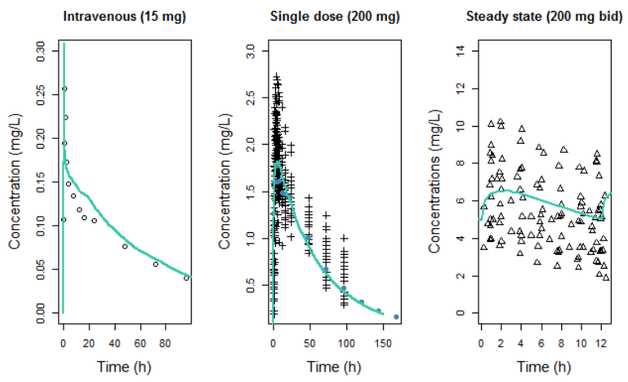
Figure 3. Tenofovir and emtricitabine non pregnant population PK profiles



Results

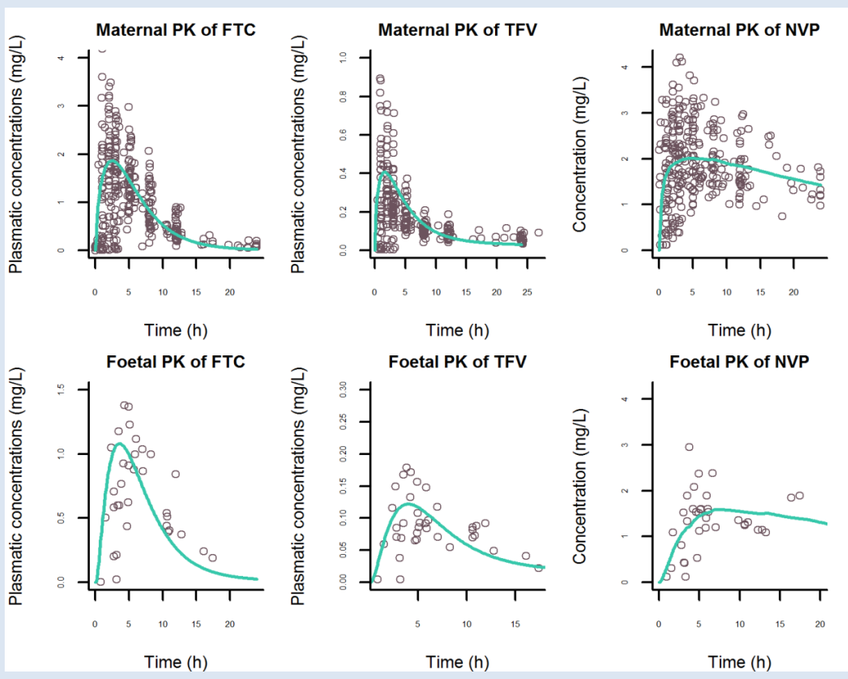
Tenofovir and emtricitabine are two renally excreted drugs. Simulated concentrations (lines) were compared those observed (1-3) (figure 3).

Figure 4. Nevirapine non pregnant population PK profiles



Nevirapine is metabolised by CYP450 3A4, 2B6 and 2D6. Simulated concentrations (lines) were compared to those observed (4-6).

Figure 4. Maternal and foetal PK profiles



Simulations for an average 35 year old patient with a gestational age of 39 weeks (green lines).

- 400 mg emtricitabine (FTC)
- 600 mg tenofovir (TFV)
- 200 mg nevirapine (NVP)

Observed maternal and cord blood concentrations (dots, 7-9)

Table 1. Predicted maternal clearance increase and foetal exposure

	FTC	TFV	NVP
CL increase in late pregnancy	Approximately 20 %		
Fœtal to maternal AUC ratio	60 %	40 %	75 %

- Predicted concentrations obtained from pregnancy PBPK models are in accordance to observed concentrations
- Placental parameters obtained from the *ex-vivo* experiments allowed good predictions of foetal PK profiles
- Limitation: The placenta structure is changing throughout gestation, so this approach reflects placental barrier only at delivery

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Poster IV