PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODELLING OF LONG-ACTING RILPIVIRINE IN PREGNANCY

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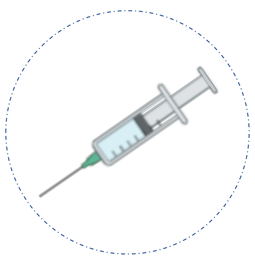
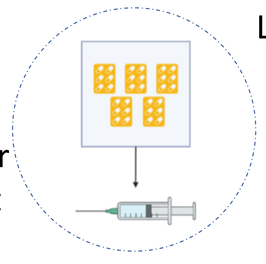
INTRODUCTION



Long-acting injectable (LAI) rilpivirine has been approved for HIV management in adults.



LAI rilpivirine reduces pill burden and promotes drug adherence.

Potentially, an ideal alternative for patients with nausea and vomiting as in pregnancy.

Limited data to guide the dosing of LAI rilpivirine during pregnancy.

PBPK models can simulate the disposition of drug in complex populations.

Are therapeutic concentrations maintained with the approved doses of long-acting injectable rilpivirine in pregnant adults?

METHOD

- A whole-body adult physiologically-based pharmacokinetic (PBPK) model was developed in SimBiology (MATLAB R2019a).

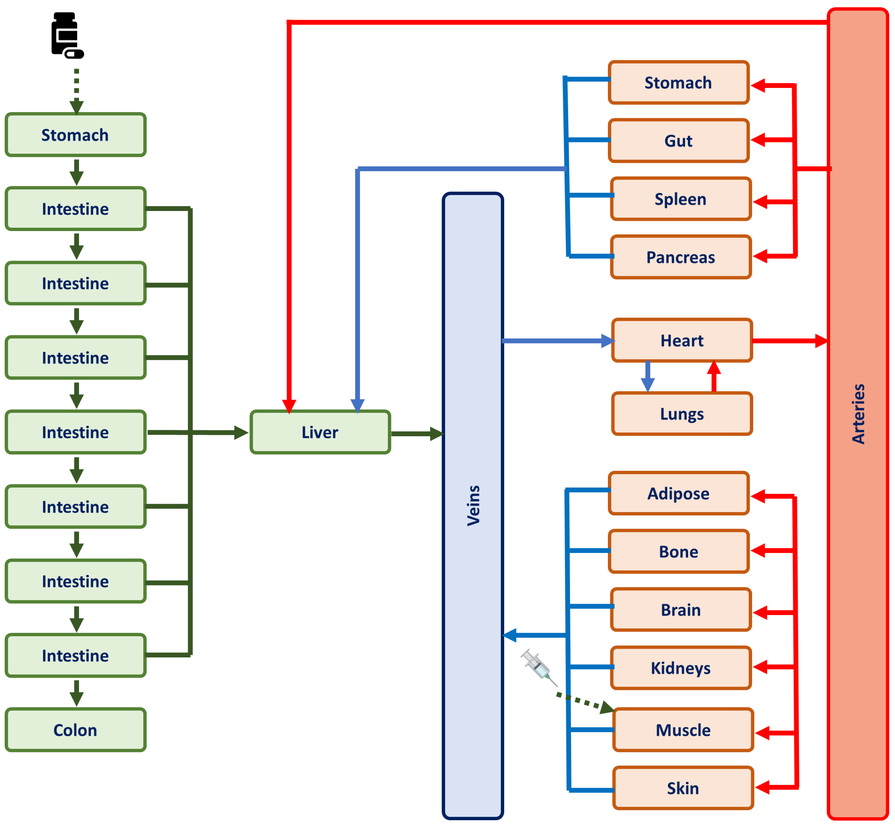


Figure 1: Schematic adult PBPK model diagram illustrating organs and tissues as compartments, and blood flows as (blue/red) arrows.

- Each simulation generated 100 healthy virtual individuals with demographic characteristics similar to the clinical data.
- Relevant drug parameters for rilpivirine from literature were incorporated into the adult PBPK model.
- The adult PBPK model was qualified with available clinical PK data of oral and long-acting intramuscular (IM) doses of rilpivirine in adults.
- Absolute average-fold errors (AAFE) approach was used for the qualification of the models (equation 1).

$$Absolute\ average-fold\ error = 10^{\left|\frac{\sum \log\frac{Predicted}{Reported}}{N}\right|} \quad -----equation\ 1$$

- The PBPK models were considered qualified if the simulated values were within 2-fold of the reported clinical pharmacokinetic data.
- Pregnancy-induced physiological and metabolic changes (e.g. organ blood-flow rates, gestational age-defined CYP3A4 activity levels etc) known to influence drug PK were incorporated into the qualified adult model.
- The pregnancy PBPK model was qualified with available clinical PK data of oral rilpivirine in 2nd and 3rd trimesters of pregnancy.
- The qualified pregnancy PBPK model was used to simulate the PK of 900 mg LAI rilpivirine followed by 600 mg LAI rilpivirine monthly for 12 weeks (initiated at different stages of pregnancy).

RESULTS

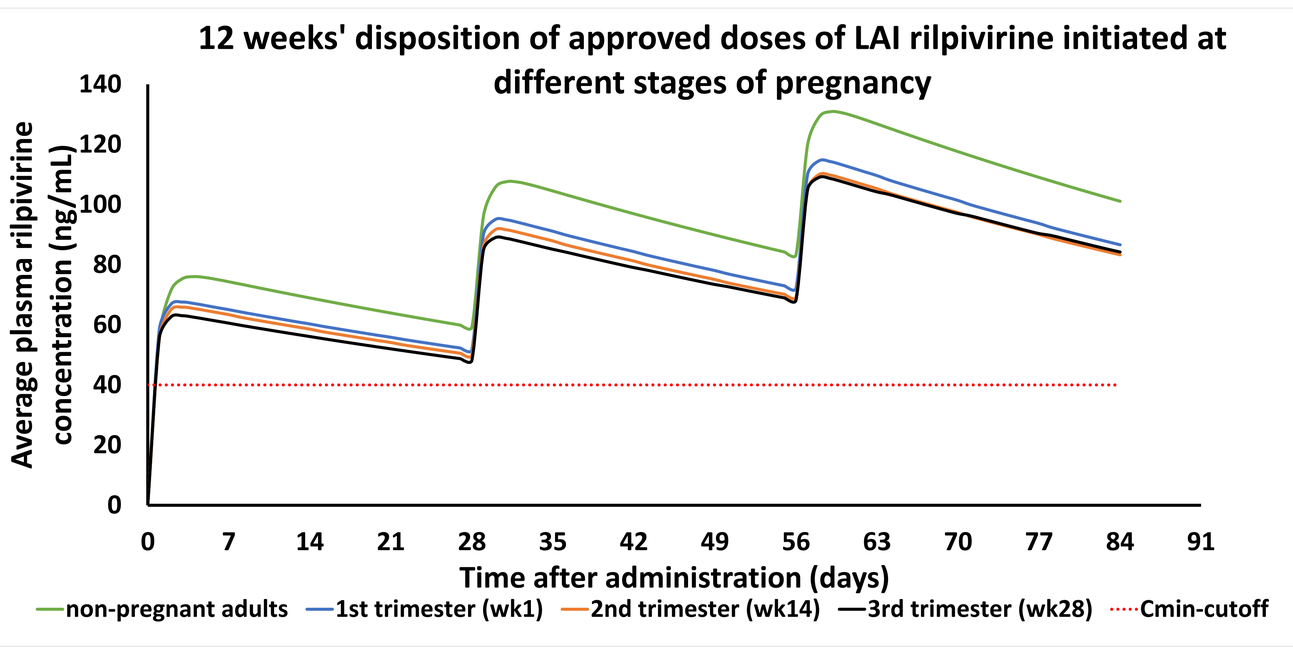
- The adult PBPK model was successfully qualified for both oral and LAI rilpivirine.
- Mean (min-max) AAFE of the PK parameters were 1.32 (1.03-1.68) for LAI rilpivirine (Table 1) and 1.18 (1.04-1.31) for oral rilpivirine.

Table 1: Predicted and reported PK of repeated dosing of LAI rilpivirine in adults.

	1200 mg then 600 mg LAI rilpivirine			1200 mg then 900 mg LAI rilpivirine		
PK Parameter	Reported[β]	Simulated	AAFE	Reported[β]	Simulated	AAFE
$AUC_{0-\tau}$ (ng.h/mL)	63,656	84,685	1.33	74,420	102,489	1.38
C_{max} (ng/mL)	126	143	1.13	168	173	1.03
C_{τ} (ng/mL)	78.9	109	1.39	79.1	133	1.68

Data presented as geometric mean values. LAI – long-acting injectable, C_{τ}– Trough plasma concentration, C_{max} – Maximum plasma concentration, $AUC_{0-\tau}$ - Area under the plasma concentration-time curve between the last dosing interval; β – Spreen et al., 2014

- Mean (min-max) AAFE of the PK parameters for oral rilpivirine in pregnancy were 1.32 (1.03-1.68) for LAI rilpivirine (Table 1) and 1.18 (1.04-1.31) for oral rilpivirine.
- Predicted PK-time profiles of 900 mg followed by 600 mg LAI rilpivirine monthly in non-pregnant and pregnant adults for 12 weeks are shown in Fig 2.



CONCLUSION: The PBPK model predicted that approved doses of long-acting injectable rilpivirine maintain therapeutic concentrations and clinical efficacy in pregnancy without need for dose adjustments. Confirmation of these findings in clinical trials is, however, warranted. In addition, this approach can be used to support the design of future clinical trials in pregnant adults.

ACKNOWLEDGMENT

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- Images on the Introduction section are adapted from BioRender templates.