# Predicting Utility of Long-Acting Injectables in Paediatric Patients With PBPK Models

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## Overview

- Long-acting (LA) sustained release ARVs in children and adolescents could represent a valuable pharmacological option, to simplify regimens, reduce drug costs and improve adherence for treatment and PrEP [1].
- Dose optimisation in paediatric patients is complicated due to the differences in anatomical and physiological process compared to adults [2].
- Physiologically-based pharmacokinetic (PBPK) modelling represents a mathematical approach to predict pharmacokinetics, through the description of molecular and physiological processes defining drug distribution.
- The aim of this study was to simulate the pharmacokinetics (PK) of LA intramuscular (IM) ARVs in children and adolescents and to identify optimal doses using PBPK modelling.

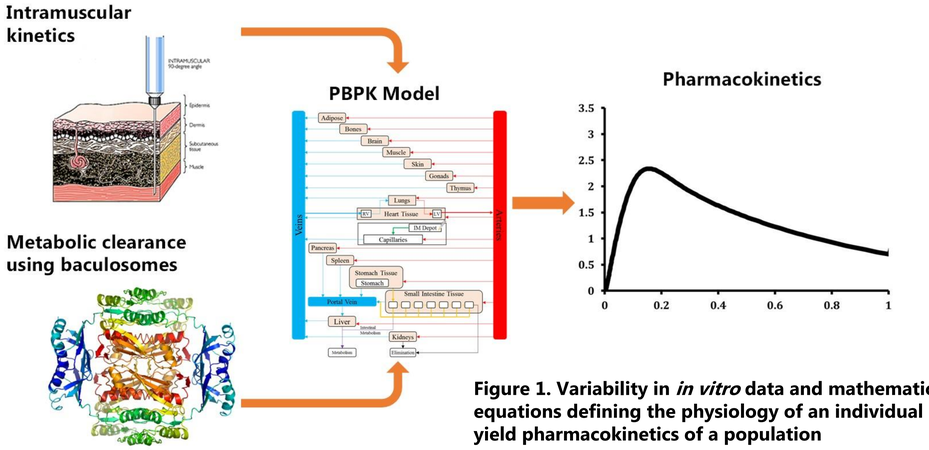


**Figure 1. Variability in *in vitro* data and mathematical equations defining the physiology of an individual yield pharmacokinetics of a population**

## Methods

- *In vitro* PK data for rilpivirine (RPV) and cabotegravir (CBV) was integrated into PBPK models using MATLAB, R2013b.
- The models were validated against available clinical data (800 mg CBV and 900 mg RPV) for the LA formulations in adults. Drug release rate from the site of injection for RPV and CBV was derived from the clinical data in adults during the validation process.
- The anatomy and physiology of children aged between 3-18 years was also validated against data available in literature [2-4].
- The weight band categories were selected according to the World Health Organisation recommendations [5].
- ARV PK was simulated for 200 paediatric patients for each weight band following IM administration of LA CBV and RPV.

**Table 1. Physicochemical and metabolic characteristics of simulated drugs**

| | Cabotegravir | Rilpivirine |
|---|---|---|
| logP | 2.2 | 4.32 |
| pKa | 4.14 | 3.26 |
| Fu | 0.007 | 0.003 |
| B/P | 0.441 | 0.67 |
| Vss (L) | - | - |
| Clint CYP3A4 (µL/min/pmol) | - | 2.04 |
| Clint UGT1A1 (µL/min/pmol) | 4.5 | - |
| Clint UGT1A9 (µL/min/pmol) | 2.2 | - |
| IM Release rate ($h^{-1}$) | 0.000454 | 0.009 |

## Results

- Weights and blood flow rates of children/adolescents at different ages were validated against available anthropometric and anatomical data. [2]. Parameters of existing available adult IM formulations of cabotegravir and rilpivirine were validated against available clinical data [3].
- The mean values of AUC were 4467 vs. 5257 µg.h/ml, $C_{max}$ 3.3 vs. 3.54 µg/ml and $C_{trough}$ 1.1 vs. 1.2 µg/ml for 800 mg CBV quarterly intramuscular administration (Figure 2b) [5,6].
- The mean values of AUC for 900 mg IM RPV monthly administration were 74,420 vs. 91,087 ng.h/ml, $C_{max}$ 168 vs. 168.7 ng/ml and $C_{trough}$ 79.1 vs. 78.3 ng/ml (Figure 2a) [3].
- The summary of the predicted doses for CBV and RPV for all weight categories (according to WHO guidelines) are shown in Table 2.
- Optimal ARV doses resulting in at least 95 % of the patients achieving $C_{trough}$ over the cut-off values for quarterly or monthly administration of CBV or RPV were predicted.

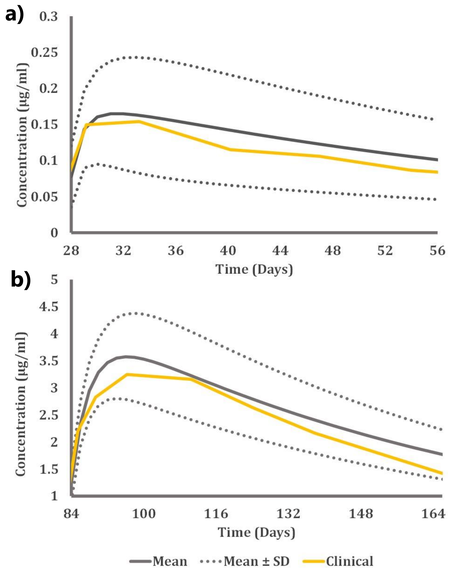


**Figure 2. Validation of PBPK model against against available clinical data a) 800 mg CBV and 900 mg RPV for the LA formulations in adults [3]**

**Table 2. Optimised doses of Rilpivirine and Cabotegravir long-acting formulations for various weights categories of children and adolescents**

| Age (years) | Weight (kg) | Rilpivirine | | Cabotegravir | |
|---|---|---|---|---|---|
| Duration | | 1 month | | 3 months | |
| Cut-off limit (ng/ml) | | 20.3 ($PAIC_{95}$) | 80 (MEC) | 166 ($PAIC_{95}$) | 664 (MEC) |
| 3 - 5.75 | 14 - 19.9 | 180 | 720 | 30 | 110 |
| 5.75 - 7.75 | 20 - 24.9 | 190 | 720 | 30 | 130 |
| 7.75 - 9.4 | 25 - 29.9 | 190 | 730 | 35 | 150 |
| 9.4 - 10.75 | 30 - 34.9 | 200 | 735 | 35 | 160 |
| 10.75 - 11.9 | 35 - 39.9 | 200 | 770 | 45 | 170 |
| 11.9 - 12.8 | 40 - 44.9 | 210 | 790 | 45 | 180 |
| 12.8 - 13.7 | 45 - 49.9 | 220 | 810 | 50 | 190 |
| 13.7 - 14.75 | 50 - 54.9 | 225 | 825 | 50 | 200 |
| 14.75 - 15.75 | 55 - 59.9 | 230 | 840 | 55 | 210 |
| 15.75 - 17.25 | 60 - 64.9 | 230 | 860 | 55 | 220 |
| 17.25 - 19.5 | 65 - 69.9 | 240 | 880 | 60 | 240 |

## Conclusion

- The validated PBPK models predicted the *in vivo* pharmacokinetics of CBV and RPV in children and adolescents.
- This data could assist in the dose optimisation of LA IM ARVs for paediatric patients.
- Modelling approach could be an innovative way to optimise dose requirements in special population, broadening usage in ARV therapy.
- Role of transporters, immune system, drug diffusion through the lymphatic system during long term therapy represent potential limitations which have not been considered in these PBPK models.
- PBPK model represents a predictive tool to improve dosing strategies thus potentially simplifying antiretroviral therapy.

## References


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