Long-acting injectable formulations for children and adolescents using PBPK modelling

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Background

- Current antiretroviral (ARV) formulations necessitate lifelong, daily dosing
- Suboptimal adherence in the clinical setting leads to high risk of treatment failure and ranges from 50 to 70 %
- Additional care and monitoring is necessary in special populations such as paediatric patients
- Injectable long-acting nano-formulations could represent a pharmacological option
- NIH funding call has been recently published to highlight the relevance of long-acting formulations in infants, children, young adults and pregnant women

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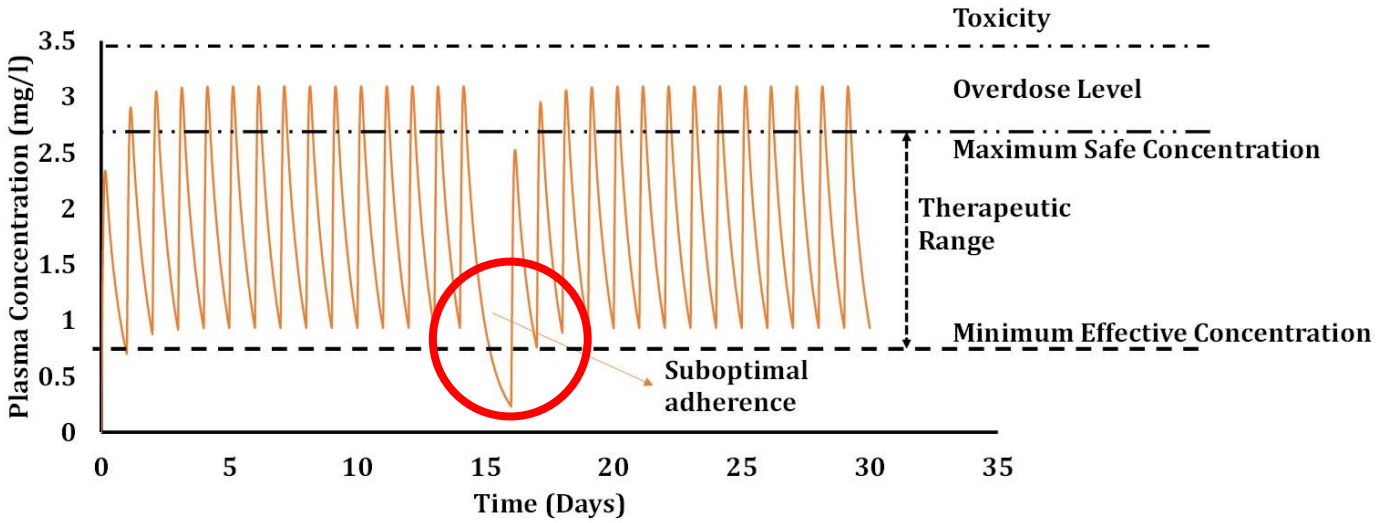
Conventional vs Nanoformulation

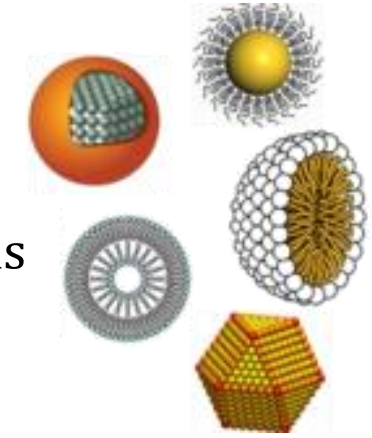
Existing ARVs

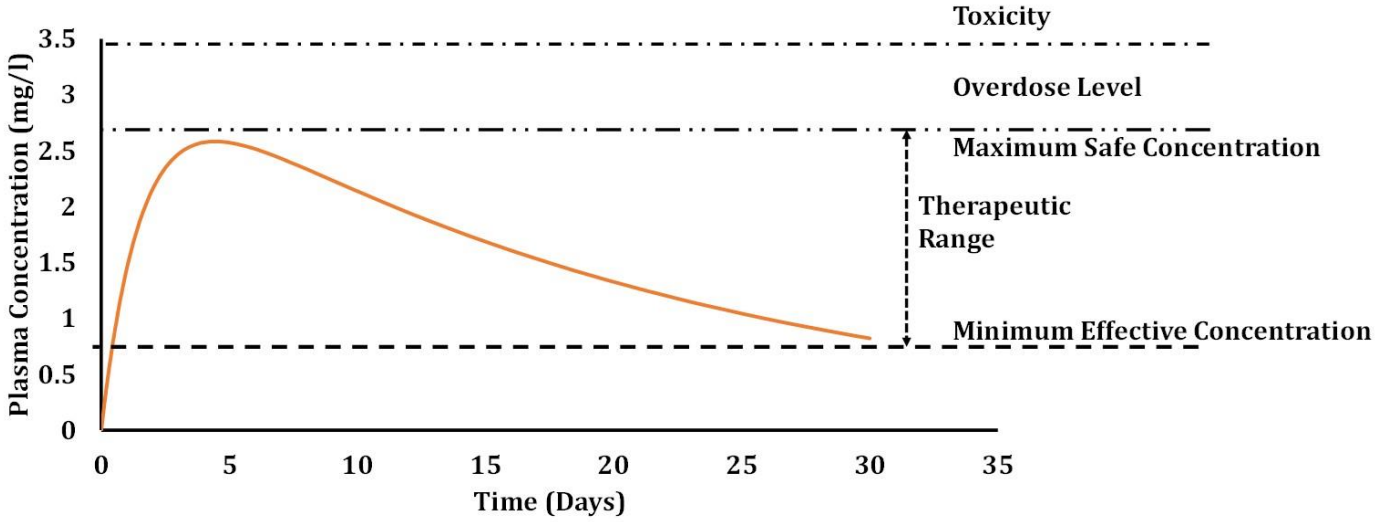
Conventional tablets



Long-acting

Nanoformulations





Paediatric patients

- Current paediatric doses are scaled down based on weight from adult dose
- Development of anatomy and physiology is not linear with age

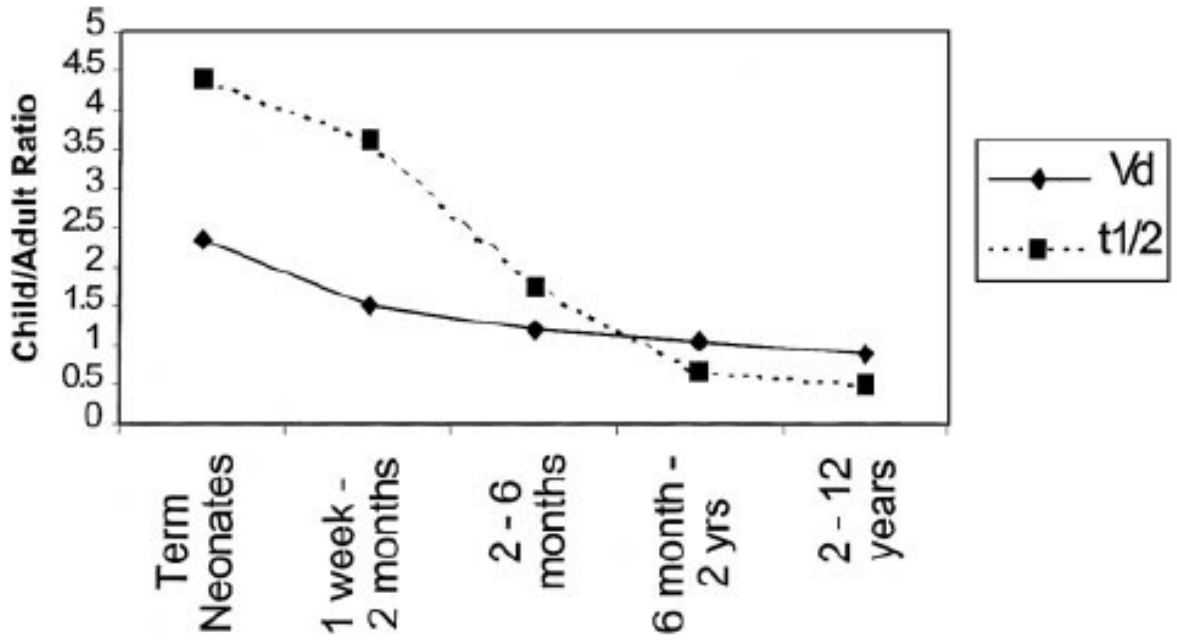
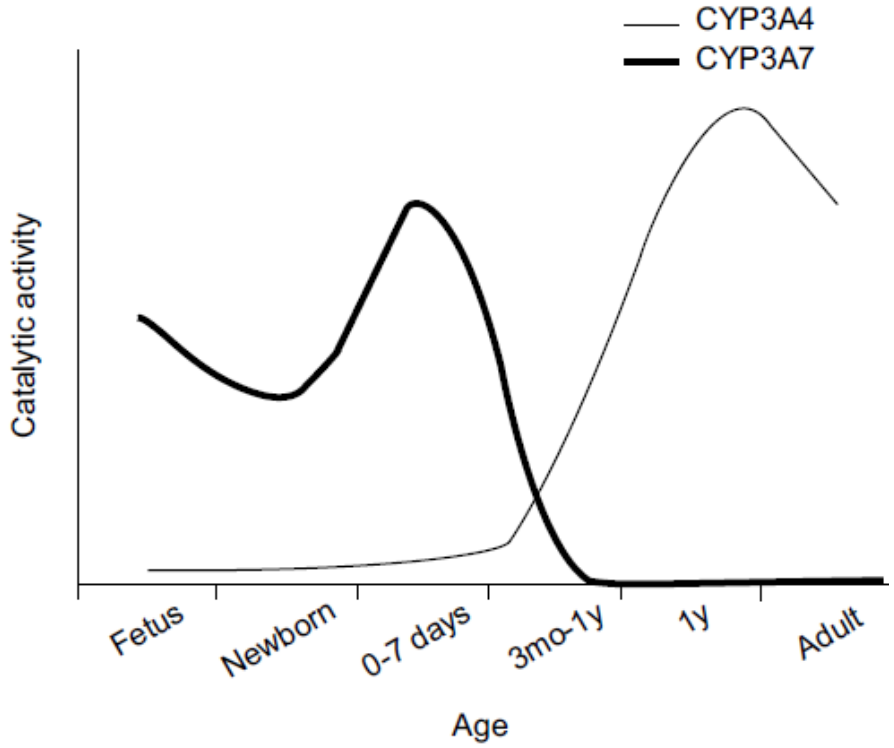


FIG. 9. Theophylline Vd and $t_{1/2}$ across the age groups.



de Wildt, S., et al.,. Clin Pharmacokinet., 1999. **37**(6): p. 485-505.
Ginsberg, G., et al., Toxicological Sciences, 2002. **66**(2): p. 185-200.

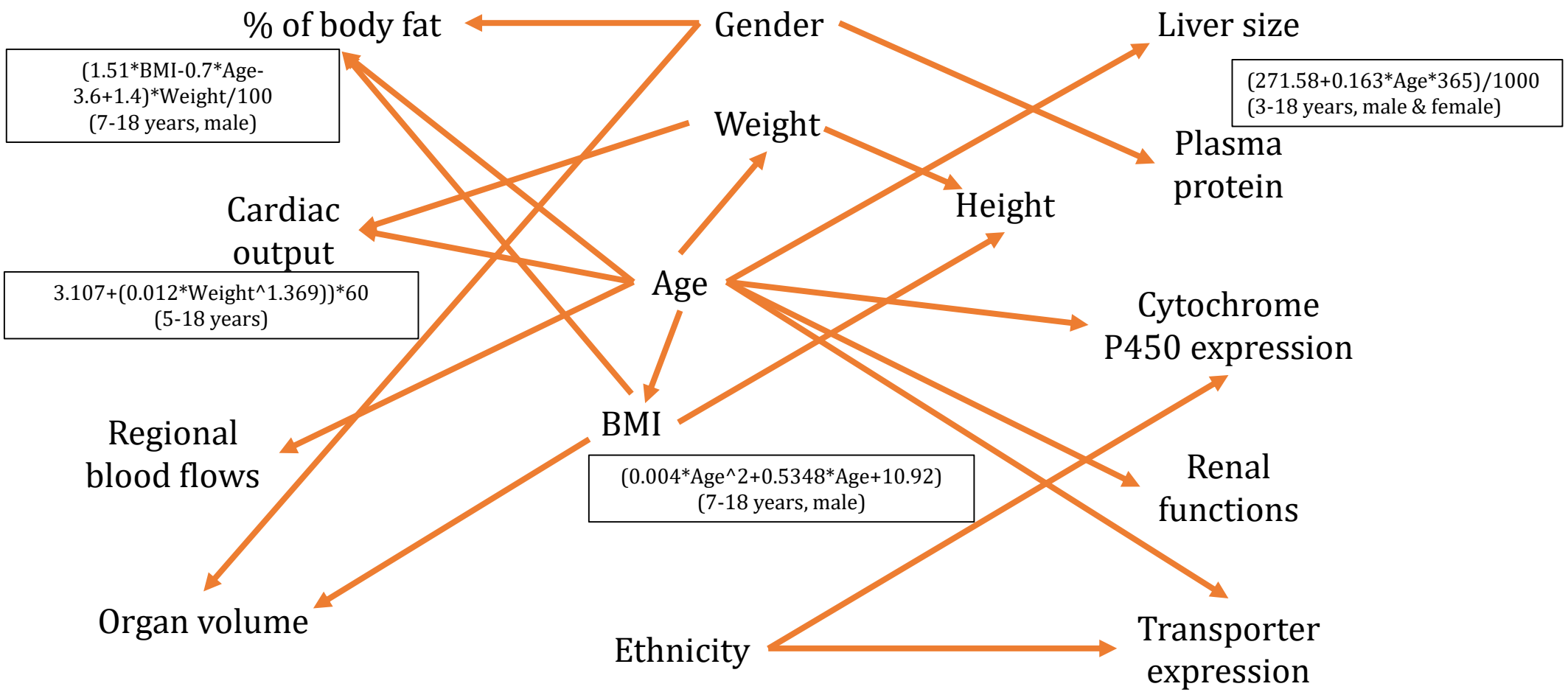
Aims

- Design and validate a paediatric physiologically based pharmacokinetic (PBPK) model
- Identify the optimal doses for existing long-acting formulations of antiretrovirals according to weight categories of paediatric population

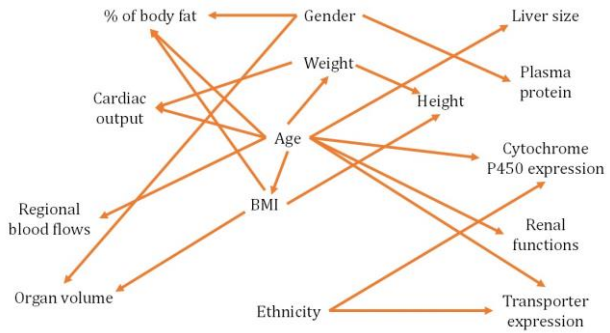
PBPK model

- Physiologically based pharmacokinetic (PBPK) modelling was used to inform the optimal dose of ARVs in children and adolescents
  - Mathematical description of absorption, distribution, metabolism and elimination processes defining pharmacokinetics
  - PBPK modelling integrates *in vitro* data to simulate drug distribution in virtual population

Parameter correlation

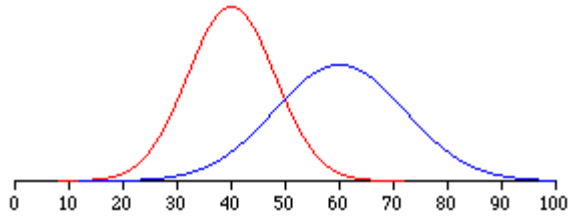


Population variability

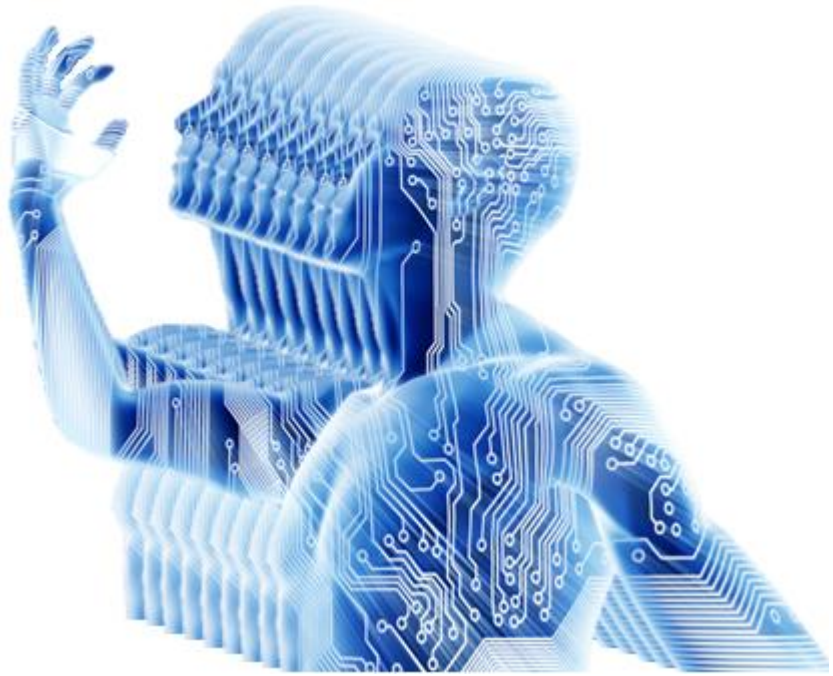


Essential PBPK Parameters

+

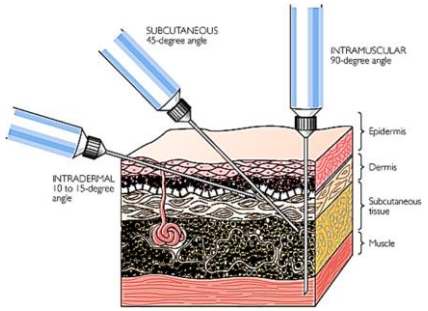


Variability

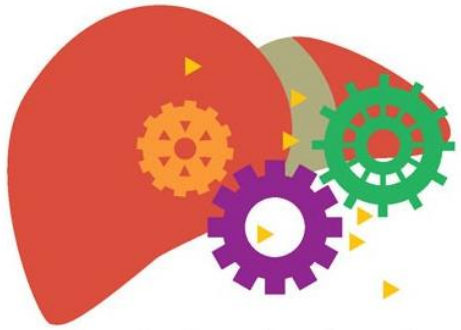


Virtual population

Intramuscular release rate



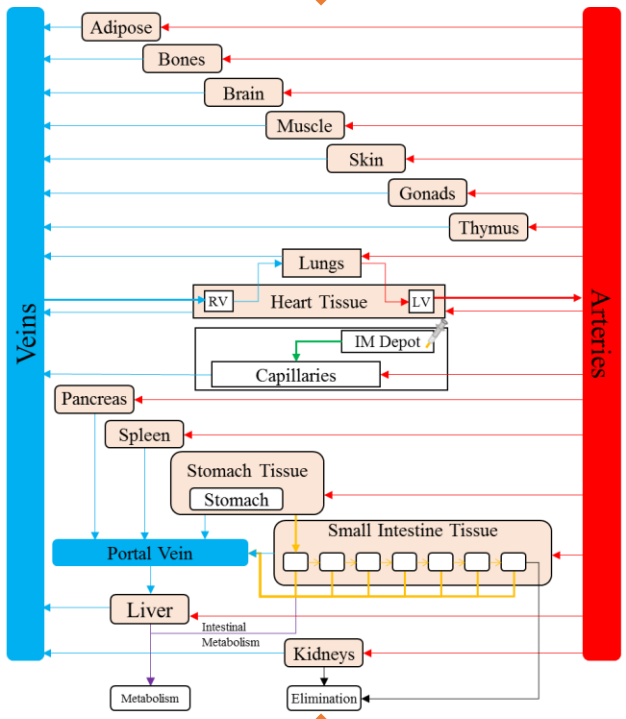
Metabolic clearance



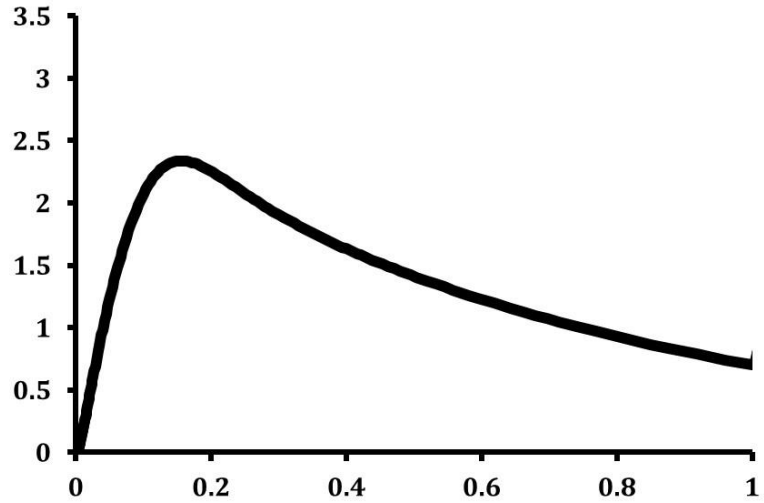
Volume of distribution

$$V_{ss} = (\Sigma V_t^* P_{t:p}) + (V_e^* E:P) + V_p$$

$$P_{t:p\ \text{nonadipose}} = \frac{[P_{o:w} \times (V_{nlt} + 0.3 \times V_{pht})] + [1 \times (V_{wt} + 0.7 \times V_{pht})]}{[P_{o:w} \times (V_{nlp} + 0.3 \times V_{php})] + [1 \times (V_{wp} + 0.7 \times V_{php})]} \times \frac{fu_p}{fu_t}$$



Pharmacokinetics



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ORIGINAL RESEARCH ARTICLE

Physiologically Based Pharmacokinetic Modelling to Inform Development of Intramuscular Long-Acting Nanoformulations for HIV

Rajith K. R. Rajoli · David J. Back · Steve Rannard · Caren L. Freel Meyers · Charles Flexner · Andrew Owen · Marco Siccardi

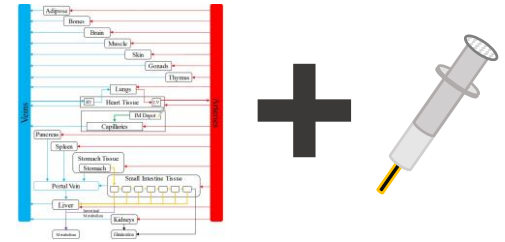
Study design

Validation

- Weights and blood flow rates of children/adolescents at different ages
- Existing available IM formulations of cabotegravir and rilpivirine in adults

Prediction

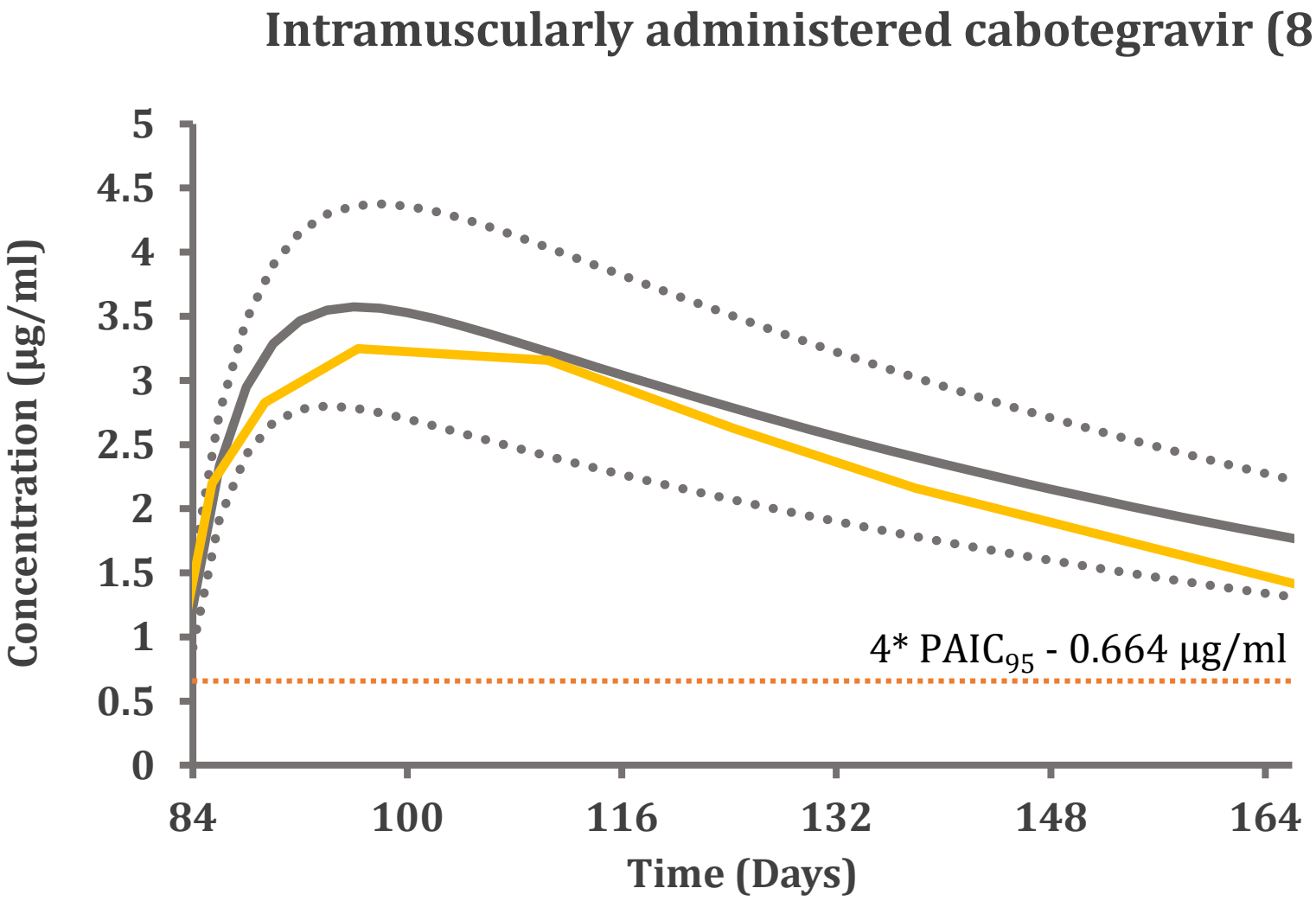
- Release rates were kept similar to clinical formulations
- Pharmacokinetics in children and adolescents according to WHO weight categories



Optimization

- Identify theoretical target dose for once monthly/quarterly administration such that the drug plasma concentrations are above the protein binding adjusted IC_{95} ($PAIC_{95}$) or MEC values

Validation against clinical formulations



AUC - 4,467 vs. 5,257 µg.h/ml

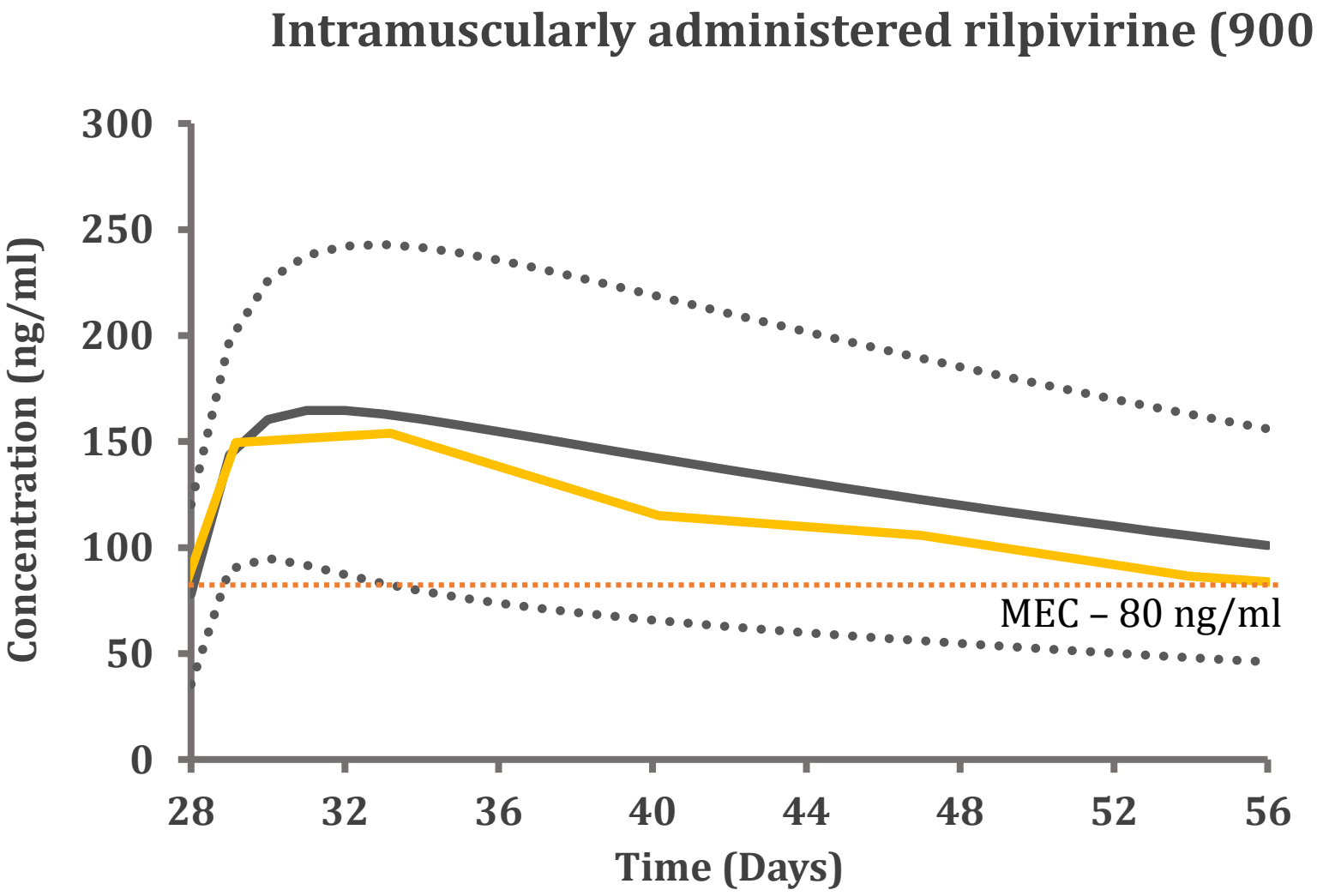
C_{max} - 3.3 vs. 3.54 µg/ml

C_{trough} - 1.1 vs. 1.2 µg/ml

Release rate – 0.00454 h^{-1}

[1] Spreen, W., et al., Jaids, 2014. **67**(5): p. 487-492.

Validation against clinical formulations



AUC - 74,420 vs. 91,087 ng.h/ml

C_{max} - 168 vs. 168.7 ng/ml

C_{trough} - 79.1 vs. 78.3 ng/ml

Release rate – 0.0009 h^{-1}

[1] Spreen, W., et al., Jaids, 2014. **67**(5): p. 487-492.

Prediction - Summary

Weight (kg)	Rilpivirine (1st and 2nd dose in mg)		Cabotegravir (mg)	
14 - 19.9	240, 180	960, 720	30	110
20 - 24.9	250, 190	960, 720	30	130
25 - 29.9	250, 190	970, 730	35	150
30 - 34.9	270, 200	980, 740	35	160
35 - 39.9	270, 200	1025, 770	45	170
40 - 44.9	280, 210	1050, 790	45	180
45 - 49.9	290, 220	1075, 810	50	190
50 - 54.9	300, 230	1100, 830	50	200
55 - 59.9	310, 230	1125, 840	55	210
60 - 64.9	310, 230	1150, 860	55	220
65 - 69.9	320, 240	1175, 880	60	240
Duration	4 weeks		12 weeks	
Cut-off limit (ng/ml)	20.3 ($PAIC_{95}$)	80 (MEC)	166 ($PAIC_{95}$)	664 ($4*PAIC_{95}$)

Limitations

- The ontogeny and activity of transporters can affect distribution and elimination patterns
- Drugs with high lipophilicity tend to diffuse through the lymphatic circulation rather than through blood
- Physiological and metabolic variation of muscle composition in children compared to adults was not accounted

Dotan, R., et al. (2012). Pediatric exercise science **24**(1): 2-21.
Tegenge, M. and R. Mitkus (2013). J. Pharmacokinet. Pharmacodyn. **40**(5): 545-556.

Conclusion

- This data could assist in dose optimisation of long-acting intramuscular antiretrovirals for paediatric patients improving adherence to therapy
- PBPK modelling represents a predictive tool to improve dosing strategies for use in selective population thus potentially simplifying antiretroviral therapy

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