UNIVERSITY OF LIVERPOOL

Simulation of long-acting administration of antituberculosis agents using pharmacokinetic modelling

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Background

- Current anti-TB administration strategies are based on long-term oral dosing
- Oral administration is characterised by suboptimal adherence which represents a leading cause of treatment failure
- 20 to 50% of patients fail to complete existing tuberculosis treatment
- Injectable long-acting nano-formulations have been applied in numerous disease areas to simplify drug administration
- Long-acting administration of anti-TB agents could represent a valuable pharmacological strategy

Cuneo WD, Snider DE Jr. Clin Chest Med. 1989 Sep;10(3):375-80.
Munro SA et al. PLoS Med. 2007; 4(7): e238.

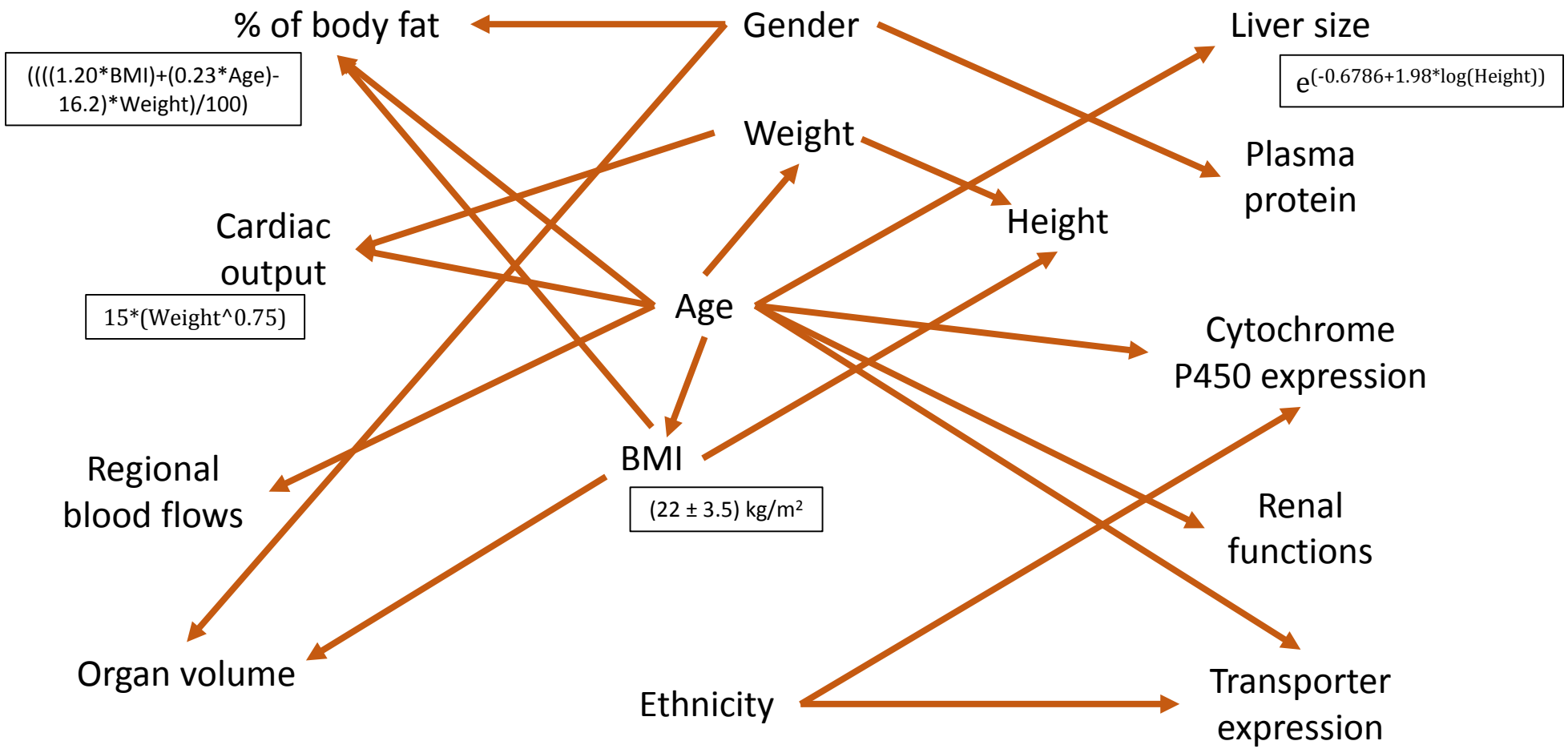
Aims

- Design and validate a physiologically based pharmacokinetic (PBPK) model for existing oral anti-TB agents
- Simulate the pharmacokinetics of long-acting formulations of anti-TB agents in adult individuals

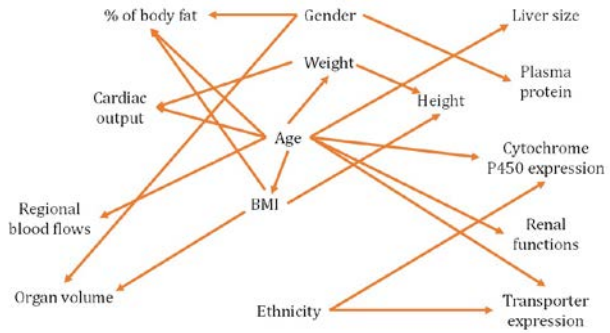
PBPK model

- Physiologically based pharmacokinetic (PBPK) modelling was used to inform the pharmacokinetics of anti-TB agents in adults
  - Mathematical description of absorption, distribution, metabolism and elimination processes defining pharmacokinetics
  - PBPK modelling integrates *in vitro* and clinical data to simulate drug distribution in virtual population

Parameter correlation



Population variability



Essential PBPK Parameters

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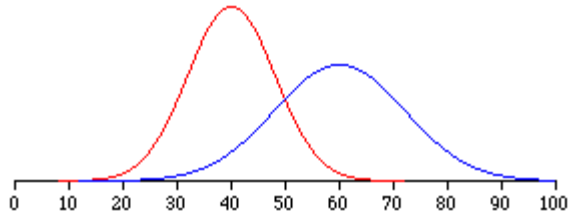
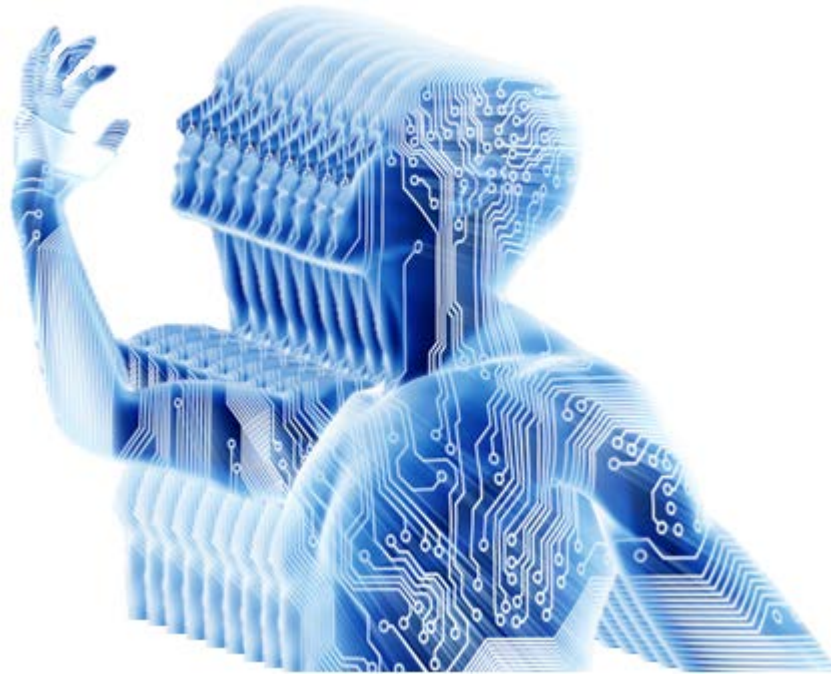
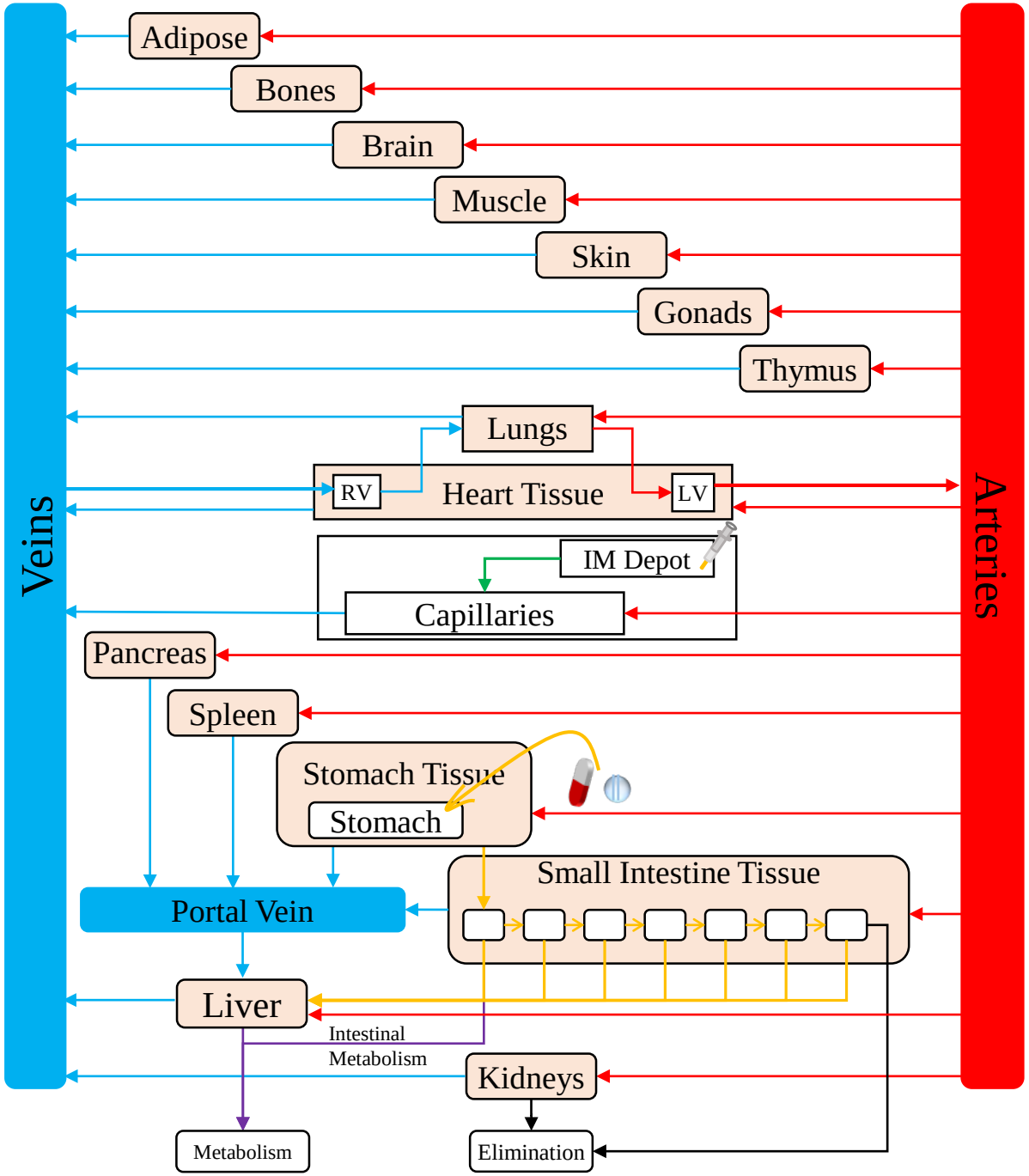


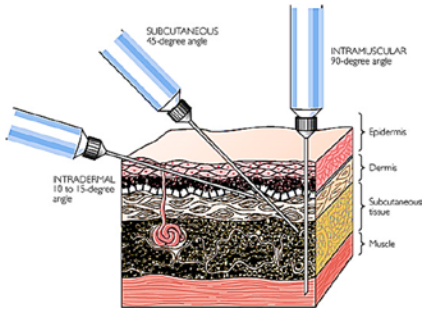
Variability



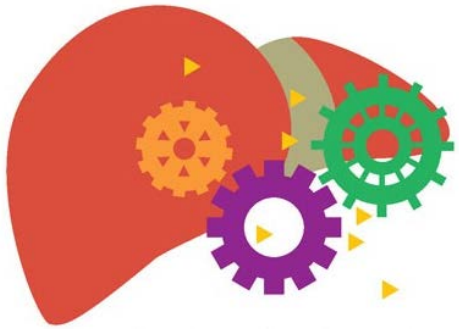
Virtual population


Veins
Arteries
Adipose
Bones
Brain
Muscle
Skin
Gonads
Thymus
Lungs
RV
Heart Tissue
LV
IM Depot
Capillaries
Pancreas
Spleen
Stomach Tissue
Stomach
Small Intestine Tissue
Portal Vein
Liver
Intestinal
Metabolism
Kidneys
Metabolism
Elimination

Intramuscular release rate



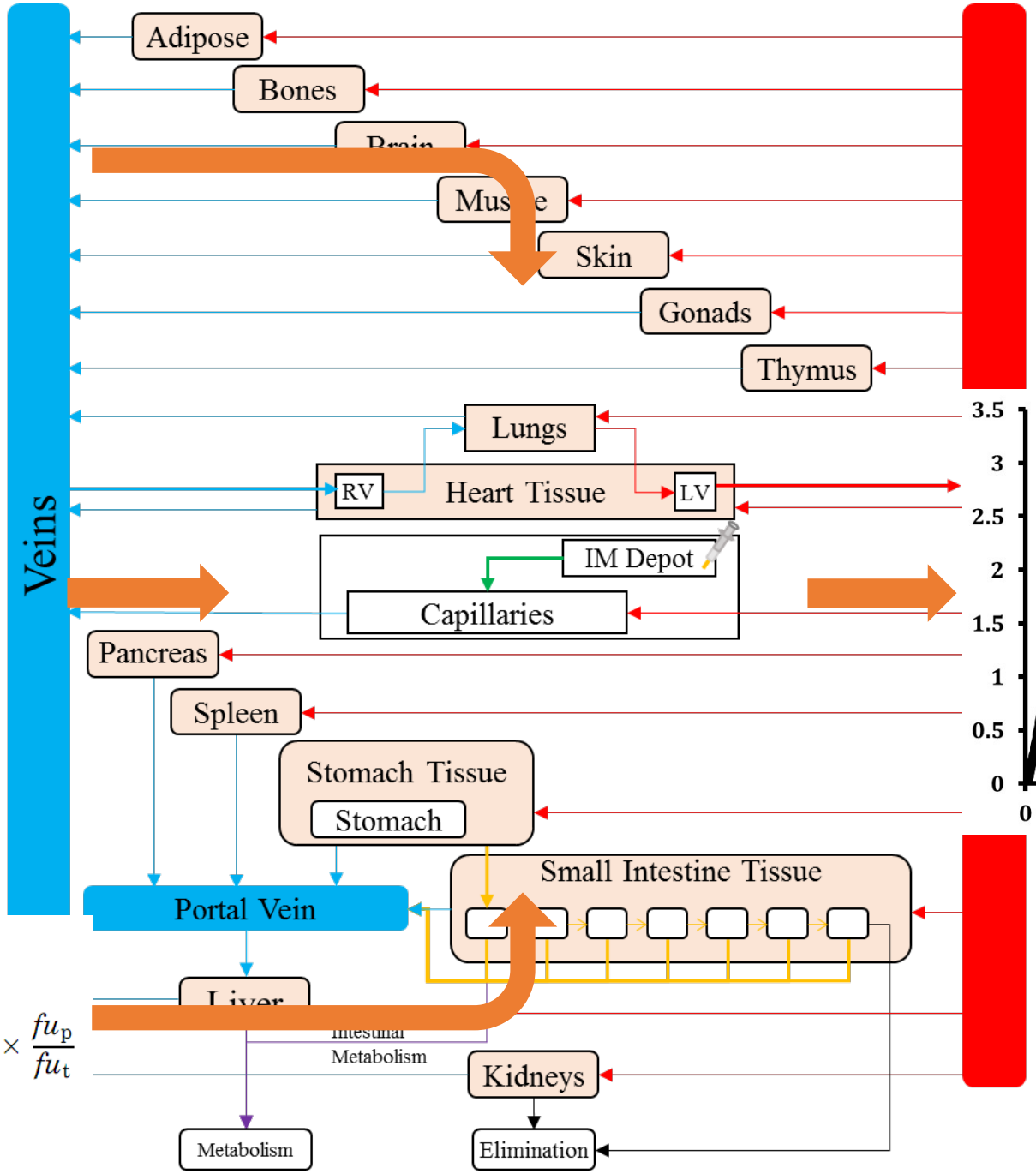
Metabolic clearance



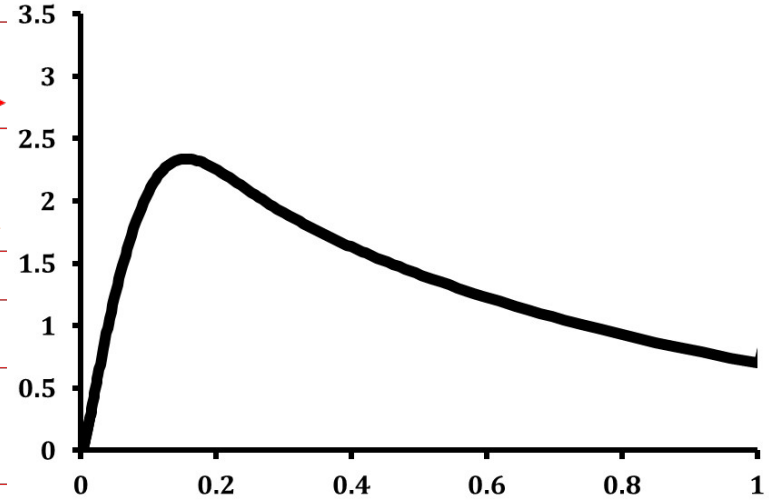
Volume of distribution

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

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



Pharmacokinetics



Clin Pharmacokinet (2015) 54:639–650
DOI 10.1007/s40262-014-0227-1

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

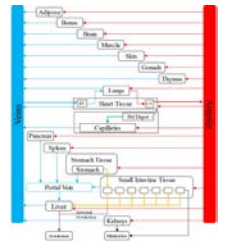
Study design

Validation

- Existing available oral anti-TB formulations of bedaquiline, delamanid and rifapentine were validated in adults
- Mean simulated values from 100 virtual individuals (aged 18-60 years) were compared with available clinical data

Prediction

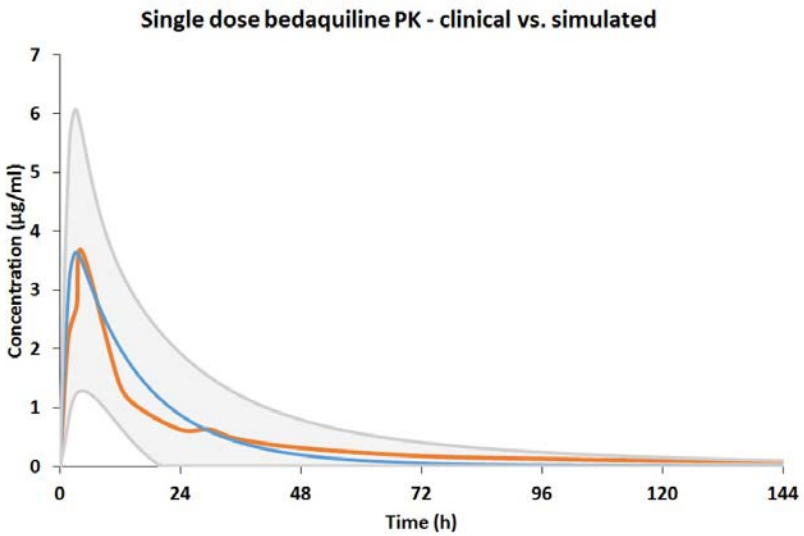
- Virtual IM depot was included in the model to simulate IM administration
- Maximum feasible human IM dose of 2000 mg was assumed for pharmacokinetic predictions in the current study
- Release rate was selected in order to obtain maximal exposure over the dosing interval

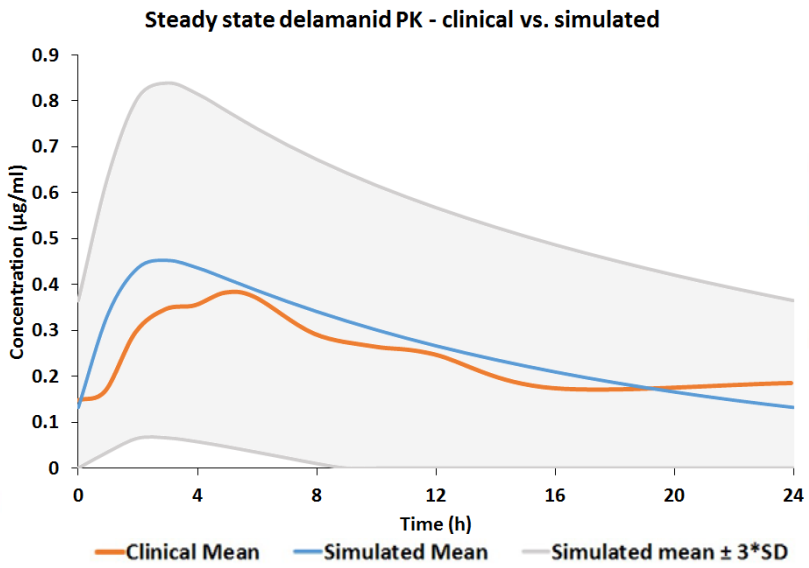


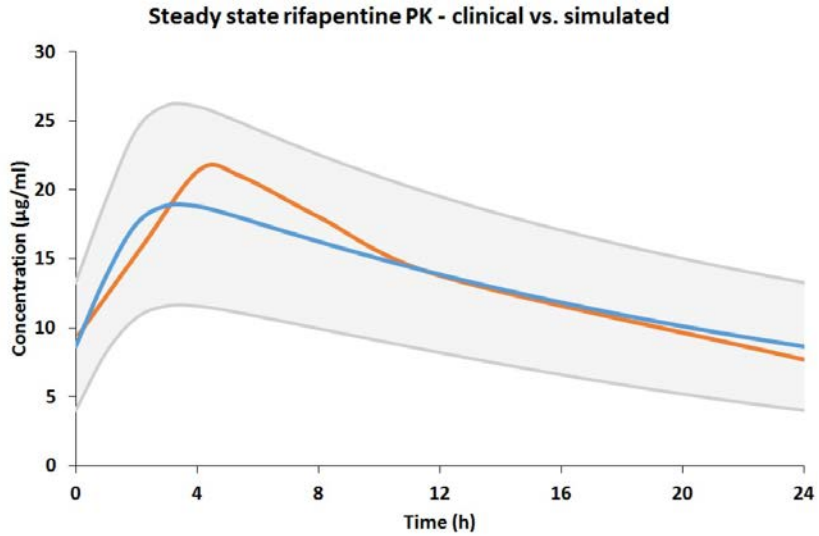
Validation against clinical formulations

	Clinical			Simulated		
Drug	C_{max} (µg/ml)	C_{min} (µg/ml)	AUC (µg.h/ml)	C_{max} (µg/ml)	C_{min} (µg/ml)	AUC (µg.h/ml)
Bedaquiline (450 mg OD, single dose)[1]	3.76 ± 1.17	-	‡64.5 ± 26.9	3.59 ± 0.79	-	‡63.1 ± 15.6
Delamanid (300 mg OD, day 10)[2]	0.41 ± 0.05	0.14 ± 0.04	†5.84 ± 0.99	0.45 ± 0.13	0.13 ± 0.08	†6.57 ± 2.31
Rifapentine (10 mg/kg OD, day 14)[3]	21.7 (21.3-22.2)	-	†330 (284-340)	18.9 ± 2.4	8.6 ± 1.5	†327 ± 44

†AUC_{0-24}, ‡AUC_{0-144}

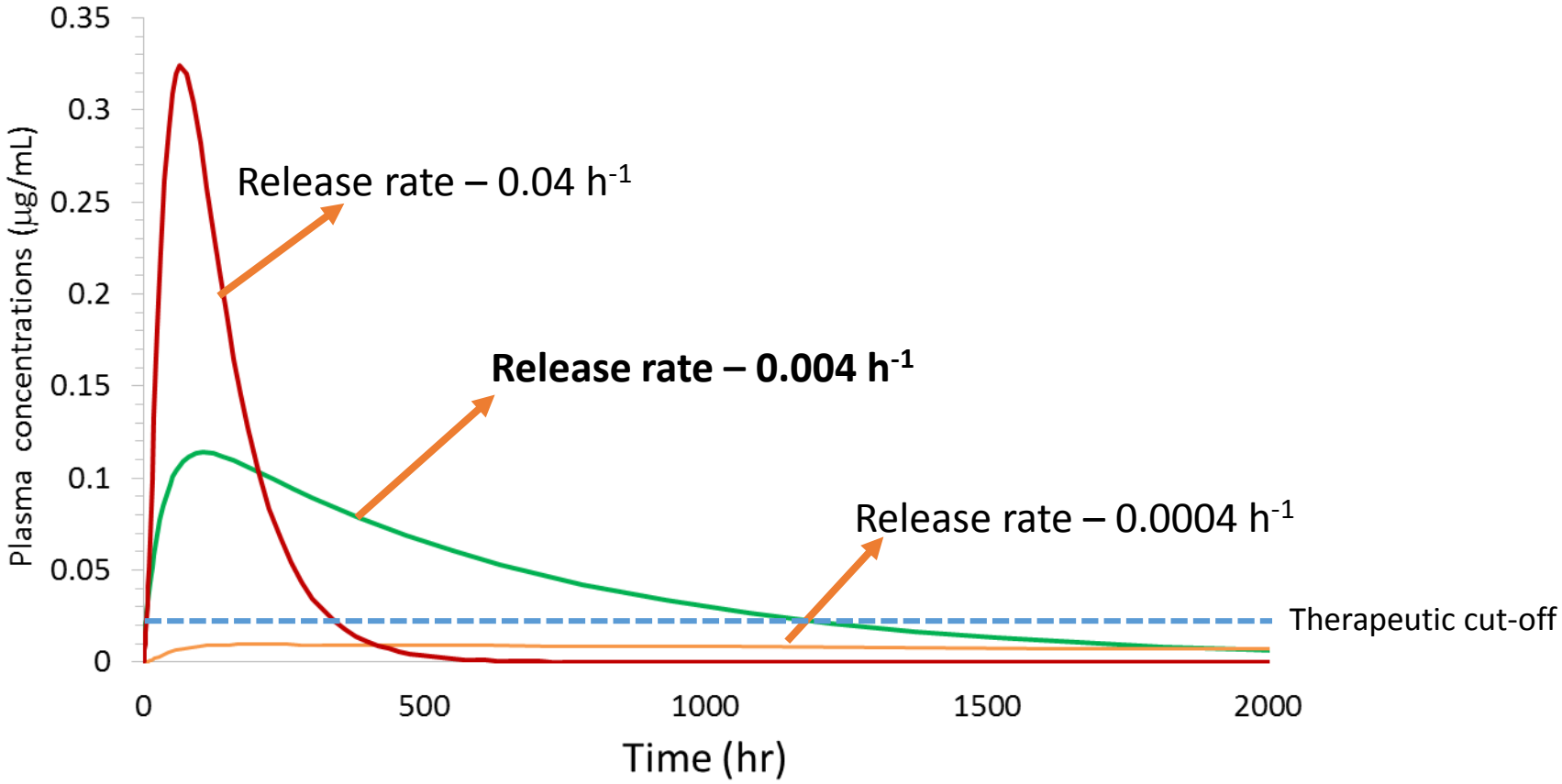






[1]van Heeswijk RP, Dannemann B, Hoetelmans RM., J Antimicrob Chemother. 2014 Sep;69(9):2310-8.
[2]Deltyba, Assessment report, EMA, 2014.
[3]Dooley KE et al. Clin Pharmacol Ther. 2012 May ; 91(5).

Release rate optimisation

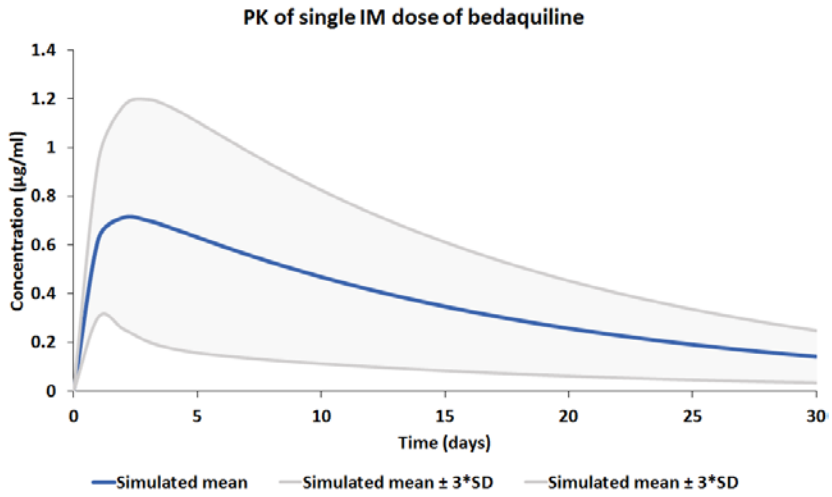


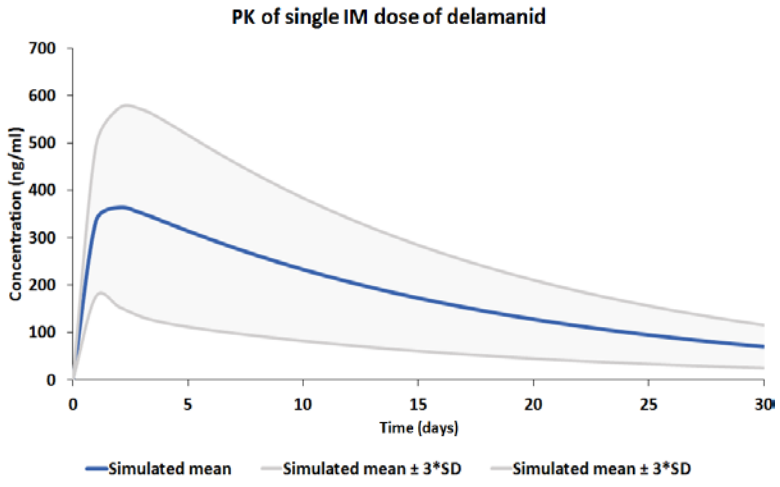
representative

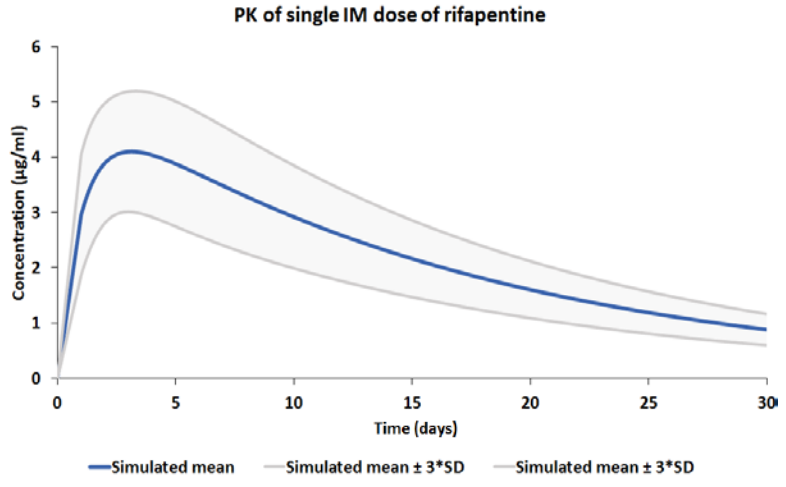
Prediction - Summary

IM Dose – 2000 mg/30 days IM release rate – 0.0025 h^{-1}

Drug	AUC (Mean ± SD) (µg.h/ml)	C_{max} (Mean ± SD) (µg/ml)	C_{trough} (Mean ± SD) (µg/ml)	Cut-off limit (µg/ml)
Bedaquiline	271 ± 65	0.72 ± 0.16	0.14 ± 0.04	1.6 (ECOFF)
Delamanid	89 ± 16	0.23 ± 0.04	0.05 ± 0.01	0.04 (ECOFF)
Rifapentine	1639 ± 160	4.12 ± 0.38	0.88 ± 0.09	0.06 (MIC)







Limitations

- Activity of transporters can affect distribution and elimination patterns
- Drugs with high lipophilicity tend to diffuse through the lymphatic circulation rather than through blood
- The technological complexities associated with reformulation may constitute a barrier for some anti-TB agents
- Long term stability of anti-TB agents in potential long-acting formulations is unknown

Conclusion

- This theoretical approach could assist in informing the design of long-acting formulation for IM administration of anti-TB agents
- PBPK modelling represents a predictive tool to rationalise anti-TB agent pharmacokinetics and hypothesise potential applications of long-acting anti-TB therapy
- Lack of clear pharmacodynamics cut-offs and clinical validation of alternative combinations complicates the selection of suitable long-acting candidates
- Long-acting formulations could also find potential application in the treatment of latent TB or chemoprophylaxis

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Long-Acting/Extended Release Antiretroviral Resource Program

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