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IN SILICO PREDICTION OF DOLUTEGRAVIR PHARMACOKINETICS & DOSE OPTIMISATION IN NEONATES

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OBJECTIVE

- To model the pharmacokinetics (PK) of DTG to predict optimal dose selection for neonates.

BACKGROUND

- It is important to investigate the PK profile of antiretrovirals (ARVs) in neonates to increase knowledge on alternative treatments for HIV infections.
- Dolutegravir (DTG) is a potent HIV-1 integrase inhibitor and has potential for prophylaxis of perinatal transmission and as part of a regimen for neonatal therapy. [1]
- Safety and PK of DTG have previously been studied in paediatric patients and ongoing studies are seeking to identify the appropriate dose in infants aged > 4 weeks.
- Dose optimisation in neonatal patients is complex and in the absence of empirical data, physiologically-based pharmacokinetic (PBPK) modelling may help inform knowledge gaps and dose selection.

METHODS

- The PBPK model was designed in Simbiology (MATLAB R2018a), incorporating neonatal maturation characteristics and mathematical descriptions of physiological and anatomical growth
- Healthy virtual patients between 0 – 28 days were simulated.
- As DTG is predominantly metabolised by UGT1A1 and CYP3A4, the PBPK model was validated using physicochemical data from the surrogate substrates: raltegravir (UGT1A1) and midazolam (CYP3A4). *(Table 1)*
- Sufficient clinical PK data were available for raltegravir (RAL) and midazolam (MDZ) for comparison against simulated values. [2-3]
- Experimental *in vitro* data for DTG was integrated into the model to aid prediction of DTG PK in the neonatal population.
- Additionally, DTG adult and infant clinical data [4-5] were used for the validation of the PBPK model.
- Due to the difficulty of approximating DTG clearance from *in vitro* experiments, clearance was estimated from adult *in vivo* systemic clearance.
- The clearance was split into three mechanisms, including: UGT1A1, CYP3A4 and renal, with the fraction cleared by each mechanism integrated into the final calculation. Maturation functions for both enzymes were also applied in the equations to account for differences in ontogeny. Renal clearance was allometrically scaled.
- The PBPK model was evaluated by calculating the absolute average fold error (AAFE) and root mean squared error (RMSE) where appropriate.
- AAFE is a useful parameter to assess over or under-prediction of the model, values closer to 1 indicate a closer similarity with observed values.
- RMSE calculates the error between the predicted value and the observed value. RMSE is particularly sensitive to outliers and values closer to zero indicate a reliable prediction.
- The model was assumed to be qualified if the simulated values were within 2-fold of the mean reported values, AAFE <2 and RMSE <1 as per convention for the approach.

RESULTS

- For model qualification, RAL PK data were split into two distinct age ranges: 1-7 days and 8-28 days. The dose for neonates in the first week of life is 1.5 mg/kg once daily (QD), increasing to 3 mg/kg twice daily (BID) from 2-4 weeks [2]. 100 healthy neonates were simulated and the model was adjusted accordingly. Comparisons were made between simulated and clinical PK curves by calculating the AAFE and RMSE. *(Table 2)*
- Clinical PK data for MDZ involved administration of an intravenous bolus of 0.2 $mg.kg^{-1}$ in neonates [3]. AAFE was calculated for each PK parameter (*Table 3).* The model was deemed qualified as all values were within 2-fold of observed data in agreement with accepted norms.
- The qualification of DTG in adults and infants is summarised in Table 4. A combination of different DTG multiple dose strategies were simulated in 100 healthy neonates with the aim of achieving plasma exposure comparable to therapeutic levels observed in paediatric patients **(C_{trough}: 0.99 mg/L and AUC_{24}: 50.1 mg.h/L)** [4]. The PK parameters for each regimen have been listed in Table 5. Regimens 2, 3, 5 and 6 result in PK parameters comparable to those in paediatric patients.

Table 1 Physicochemical parameters of DTG, RAL and MDZ.

	DTG	RAL	MDZ
MW (g/mol)	419.4	444.4	325.8
LogP	2.2	0.58	3.89
pK_a	8.2	6.67	6.57
P_{app} Caco-2 (10^{-6} cm/s)	40.17	6.6	32.4
Fraction unbound	0.011	0.17	0.034
Blood:Plasma	0.535	0.6	0.55
Clearance	0.776[A]	-	1.16[B]
Solubility (mg/L)	95	70000	0.134
Hydrogen Bond Donor	2	3	0
Polar Surface Area (Å²)	99.2	150	30.2
CLint CYP3A4 (uL/min/pmol)	-	-	3.75
CLint UGT1A1 (uL/min/10^6)	-	12.4	-

A- (L/h). B- (ml/min/mg of microsomal protein).

Table 2 RAL validation results including AAFE and RMSE

RAL PK Profile Qualification		
	RAL 1.5 mg/kg Day 1-7 AAFE	RAL 3.0 mg/kg Day 8- 28 RMSE
AAFE	**1.05**	**1.05**
RMSE	**0.21**	**0.17**

Table 3 AAFE values from MDZ validation

MDZ Qualification			
	Clinical	Simulated	AAFE
AUC (mg.h/L)	2.20	2.89	**1.314**
Cmax (mg/L)	0.41	0.42	**1.022**
C_{trough} (mg/L)	0.11	0.11	**1.020**
CL (L/h)	0.41	0.38	**1.063**

Table 4 AAFE values from DTG validation in adults and infants

DTG Adult Qualification			
	Clinical Geometric Mean (%CV)	Simulated ± SD	AAFE
AUC (mg.h/L)	53.6 (27)	54.0 ± 14.02	**1.311**
Cmax (mg/L)	3.67 (20)	2.80 ± 0.69	**1.007**
C_{trough} (mg/L)	1.11 (46)	1.62 ± 0.43	**1.462**
CL (L/h)	0.78 (39)	0.79 ± 0.17	**1.022**
DTG Infants Qualification >4 weeks to <6 months			
	Clinical Geometric Mean (%CV)	Simulated ± SD	AAFE
AUC (mg.h/L)	61 (44)	38.6 ± 15.93	**1.581**
C_{trough} (mg/L)	1.2 (55)	1.25 ± 0.60	**1.040**

Table 5 PK parameters of DTG multiple dose regimens 1-6.

DTG PK Parameters in Neonates							
Regimen	Total Dose (mg)	Dose* (mg/kg)	C_{max}[1] (mg/L)	AUC_{av} (mg.h/L)	C_{max}[2] (mg/L)	AUC (mg.h/L)	C_{trough} (mg/L)
1	5 QD	1.4 (1.7 - 1.1)	3.99 ± 1.1	66.1 ± 22.9	2.3 ± 1.1	47.8 ± 14.3	1.6 ± 1.1
2	4 QD	1.1 (1.3 - 0.9)	3.3 ± 0.6	47.0 ± 14.1	1.7 ± 0.6	35.1 ± 10.5	1.1 ± 0.6
3	3 QD	0.85 (1 - 0.7)	2.4 ± 0.6	35.2 ± 13.4	1.3 ± 0.7	27.3 ± 9.2	0.9 ± 0.7
4	2 QD	0.55 (0.7 - 0.4)	1.6 ± 0.3	23.5 ± 6.6	0.8 ± 0.3	18.0 ± 6.4	0.5 ± 0.2
5	Day 1-7 = 2 QD, Day 8-28 = 3 QD	0.7 (1 – 0.4)	1.8 ± 0.7	30.5 ± 11.7	1.3 ± 0.7	25.9 ± 7.6	0.8 ± 0.7
6	Day 1-7 = 2 QD, Day 8-28 = 3.5 QD	0.8 (1.2 – 0.4)	2.2 ± 1.4	35.4 ± 17.2	1.6 ± 1.1	28.8 ± 8.4	1.1 ± 1.4

*Median(Range), neonate weight range in the model is 3.0 - 4.5kg. Cmax[1], Maximum plasma concentration over 28 day simulations; Cmax[2], Maximum plasma concentration after final dose has been administered; AUC_{av}, Average area under curve over 28 day simulations; AUC, Area under curve after final dose; C_{trough}, Minimum plasma concentration after final dose.

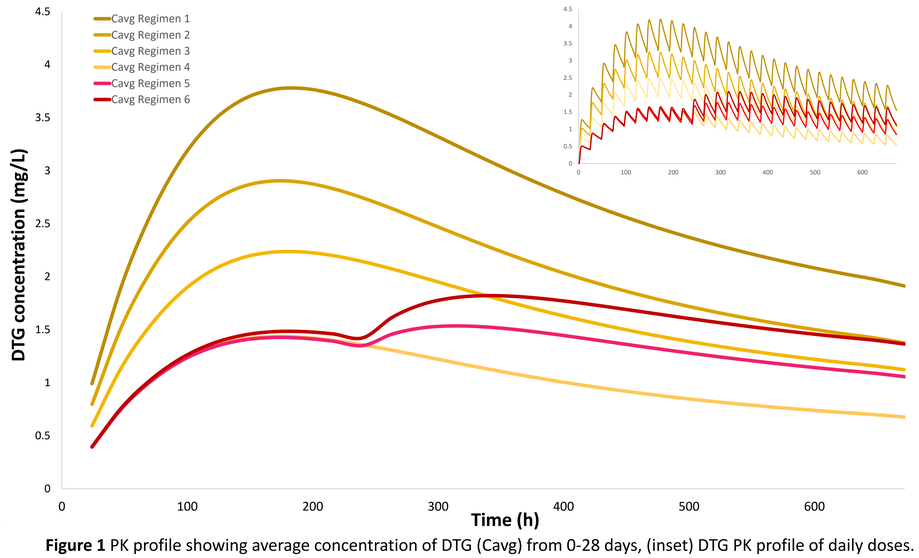

Figure 1 PK profile showing average concentration of DTG (Cavg) from 0-28 days, (inset) DTG PK profile of daily doses.

CONCLUSION

- Neonates represent a vulnerable population and the lack of clinical PK data complicates clinical management. Clinical trials in neonates are extremely difficult to conduct and trial design may be de-risked by sophisticated mathematical dose prediction.
- The combination of rapid development and immature ontogeny complicate a direct scaling of existing doses. PBPK modelling allows these changes to be represented mathematically, and following a comprehensive model validation, can support accurate predictions.
- Based on the presented data, appropriate doses for DTG in neonates range between 2 – 4 mg, resulting in plasma exposure comparable to those observed in paediatric patients.

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