Raltegravir dosing in neonates (IMPAACT P1110)

Use of allometry and maturation in PK modeling to develop a daily dosing regimen for investigation during the first weeks of life.

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Objectives

To describe the PK of raltegravir (RAL, Isentress®) in 0-6 week old infants and to determine a prospective daily dosing regimen for the prevention or treatment of HIV infection in IMPAACT P1110 using a two cohort adaptive design where PK data from 2 single doses in Cohort 1 are included in PK modeling to guide daily dosing in Cohort 2.

Background

- 3.2 million children are infected with HIV worldwide; of whom almost 800 die every day because of lack of access to treatment and care
- The World Health Organization (WHO) guidelines include raltegravir as an important product needed for certain pediatric populations
- RAL is metabolized via UGT-1A1, where activity is known to be extremely low immediately after birth followed by a dramatic increase over the first days and weeks of life

Data

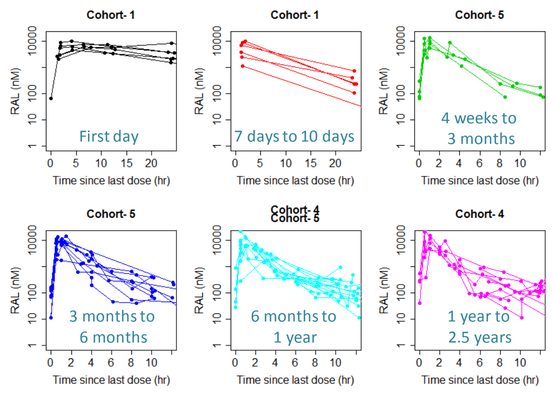
- IMPAACT P1110 is an open label, non-comparative dose-finding study of raltegravir in HIV exposed neonates at high risk of acquiring HIV-1 infection [1,2,5]
- An initial cohort (Cohort-1) of 6 full-term infants received two 3 mg/kg doses of raltegravir:
  - first dose within 48 hours after birth
  - second dose at 7-10 days of life
- Plasma samples for PK profiles were collected around the first dose (intensive) and the second dose
- RAL concentrations were measured by a validated LCMS assay. LLOQ=22.5 nM. Concentrations below LLOQ were imputed as 11.25 nM
- The PK data of Cohort-1 were combined with the pediatric PK data of 24 HIV infected infants and children from the IMPAACT P1066 study (Phase I/II, multi-center, open-label, noncomparative intensive PK study)

Table 1: Overview of PK data used for modeling

	Cohort-1	Cohort-4	Cohort-5
Study	P1110	P1066	P1066
Total number of subjects	6	13	11
Number of data points	48	121	128
Age range (enrollment)	birth	6 months to < 2 years	4 weeks to < 6 months
Weight range (kg)	2.9-3.8	5.5-14	3.7-10.4
Sex (M/F)	3/3	8/5	7/4

Figure 1: RAL conc – time plots of the raw PK data

Age groups have been indicated



Neonate PK model development

Special attention was paid to a number of specific characteristics of raltegravir pharmacokinetics in neonates:

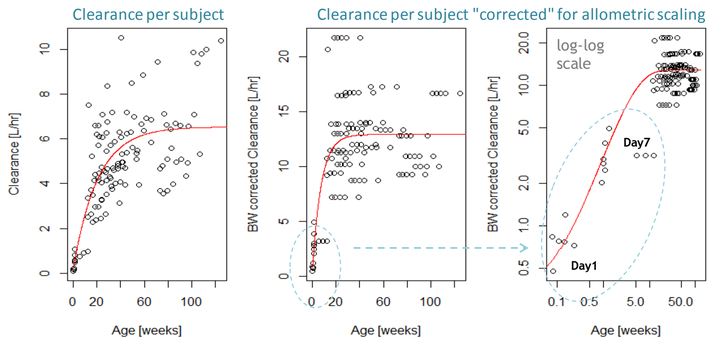
- Raltegravir is metabolized by UGT 1A1, a glucuronosyltransferase known to have very low activity at birth which matures in about 6 months to its full capacity [3,4]
- Important differences in the neonatal gastrointestinal tract that may impact absorption of medications. Feeding was not restricted in the neonates enrolled in P1110. The potential effect of food on absorption cannot be evaluated
- Body weight changes (expressed as %) are significant, even in a relatively short period of time
- The Cohort-1 data alone suggest that the neonates should be modeled using a 1-compartment model, but when combined with the Cohort-4 and 5 data a 2-compartment model is more suitable

Calculations were carried out using PsN/3.7.6, NONMEM/7.3.0 and R/3.1.0

1. Time-dependency of clearance

An existing 2-compartment model describing RAL PK in pediatrics and adults was carefully adjusted using knowledge generated from a initial 1-compartment model for the cohort-1 neonates. The 2-compartment model accounted for body weight changes by standard allometric scaling (Table 2). The individual predictions (EBEs) of the clearance for each individual was plotted against time and was corrected for the allometric scaling as applied in the PK model. An exponential function was fitted (using gnls) to the body-weight corrected data and translated into a time-dependent clearance function in the PK model (Figure 2, Table 2)

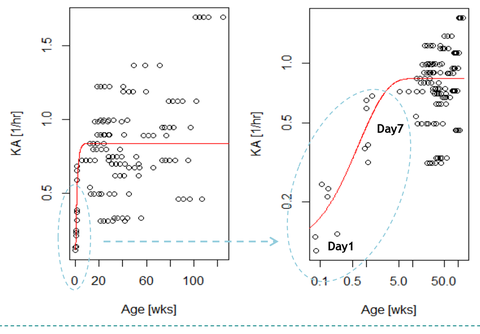
Figure 2: Maturation profiles for clearance



- Based on these PK data only, clearance appeared to change from almost nil to a maximum after about 6 months of life. This is consistent with literature reports [3,4]
- After 6 months, clearance continues to increase due to body weight changes
- $CL = CL_{base} + CL_{max}(1 - e^{-\tau_{CL} * Age})$

Figure 3: Time-dependent absorption rates

Absorption rate per subject



2. Time-dependency of absorption rate

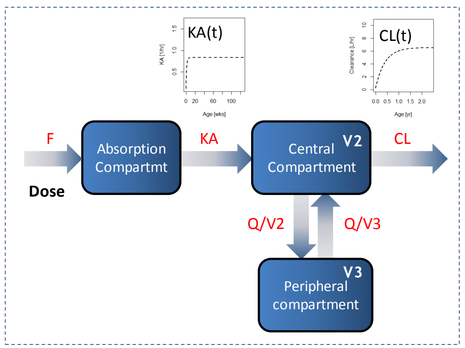
A similar approach was applied to describe the time dependency observed for the absorption rate (Figure 3, Table 2)

- Absorption rate changes from 16% at birth to 90% of the maximum rate within 2 weeks
- The absorption rate is assumed to be independent of body weight, and therefore not allometrically scaled: KA is constant after approximately 6 weeks
- $KA = KA_{base} + KA_{max}(1 - e^{-\tau_{KA} * Age})$

Table 2. Allometric scaling in the RAL PK model for neonates and pediatrics

Parameter	Abbr.	Unit	Allometric Scaling
Volume of distribution (central compartment)	V2	L	$V2 = \theta_{V2} * (BW/25)^1$
Clearance	CL	L/hr	$CL = CL(t) * (BW/25)^{0.75}$ $CL(t) = \theta_{CLbase} + \theta_{CLmax} * (1-exp(-\theta_{CLtau} * AGE))$
Oral absorption rate	KA	1/hr	$KA = KA(t)$ $KA(t) = \theta_{KAbase} + \theta_{KAmax} * (1-exp(-\theta_{KAtau} * AGE))$
Volume of distribution (peripheral comp.)	V3	L	$V3 = \theta_{V3} * (BW/25)^1$
Inter-compartment clearance	Q	L/hr	$CL = \theta_{Q} * (BW/25)^{0.75}$

Figure 4: Final PK model



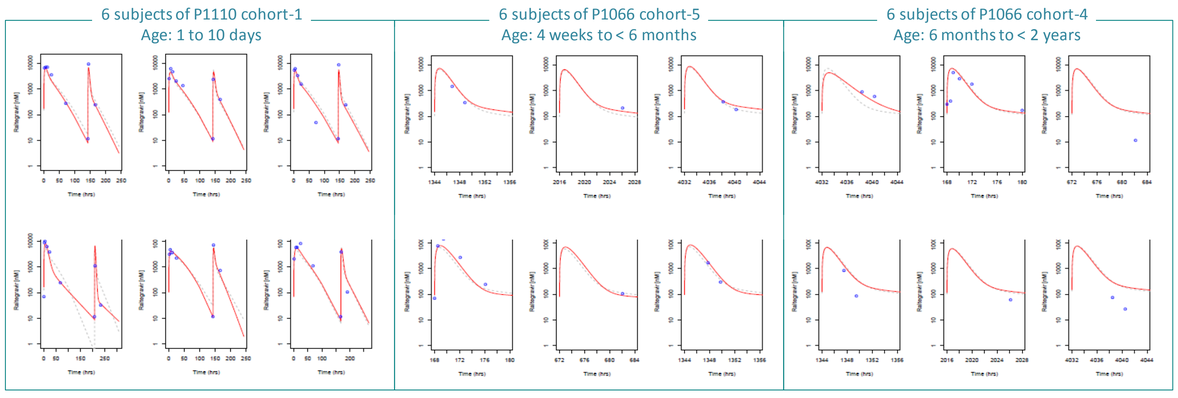
Results

- The time-dependency of PK parameters CL and KA (CLmax, CLbase, CLtau, KAmax, KAbase and KAtau) were re-estimated in the full 2-compartment NONMEM model (Figure 4). CLbase (clearance at time of birth) was estimated to be very small (or negative) and was fixed to zero
- KAtau (the rate to develop to maximum absorption rate) could not be precisely estimated
- PK parameter estimates with confidence intervals are given in Table 3
- Examples of PK profiles of the various age groups are shown in Figure 5. The model very adequately captures the rapid changes in PK properties of the Cohort-1 (1-10 days):
  - 1-compartment-like PK profile on day-1 changes into a 2-compartment profile
  - Clearance increases rapidly
  - Absorption rate also increases day-by-day (see simulated profile, Figure 6)

Table 3: Final PK parameter estimates

Parameter	Unit	Value	CI-95%		Parameter	Value	CI-95%	
		THETA				**OMEGA**		
V2	L	**11.51**	5.34	24.78	IIV-CLmax	**0.18**	0.08	0.27
V3	L	**26.47**	15.75	44.47	IIV-Q	**0.61**	0.13	1.10
CLMAX	L/hr	**12.73**	10.60	14.86	IIV-KAmax	**0.46**	0.19	0.73
Q	L/hr	**1.22**	0.76	1.97		**SIGMA**		
KAMAX	1/hr	**0.76**	0.32	1.20	RUV-prop	**0.56**	0.49	0.62
F	-	**1**			RUV-add	**4.44**	0	82.21
CLbase	L/hr	**0**						
CLtau	1/wk	**0.20**	0.07	0.34				
KAbase	1/hr	**0.08**	2.66	0.00				
KAtau	1/wk	**0.95**	0	4.21				

Figure 5: Examples of predicted PK profiles with observed RAL concentrations



Prospective dosing regimen design

- The model was used to simulate Cohort-2 subjects in order to design regimens that best meet PK exposure targets (Cmax < 19.63 μM , Cmin > 75 nM, AUC12 (BID) < 45 μM.hr, AUC24 (QD) < 90 μM.hr, Figure 7) as have been defined for safety and efficacy from the studies in older infants, children and adults [5]
- A simulated full PK profile is shown in Figure 6, from which the changing trough levels and AUCs can be derived (Figure 7)
- The simulations demonstrated that Ctrough levels decrease rapidly due to the increase of the clearance especially the first days after birth. Therefore, a change to a higher daily dosing (BID) regimen is needed after about 7 days in order to maintain Ctrough > 75 nM while keeping the AUC within a safe range (Fig. 7)
- The regimen selected for further evaluation was proposed at 1.5 mg/kg once a day from birth to day 7 of life, followed by 3 mg/kg twice a day until 4 weeks of age, then 6 mg/kg twice a day (as depicted in Figures 6 and 7). This aligns with the approved pediatric dosing regimen of 6 mg/kg raltegravir twice a day for children of 4 weeks and older

Figure 6: Simulated full PK profile of a typical subject from Cohort-2

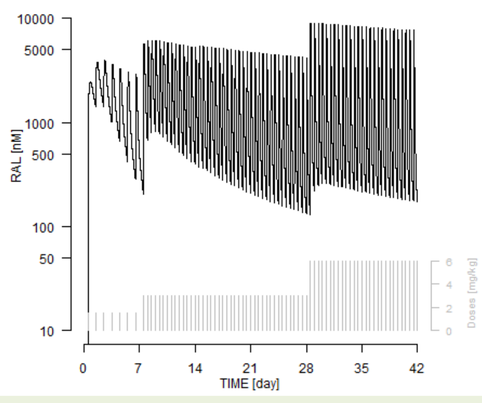
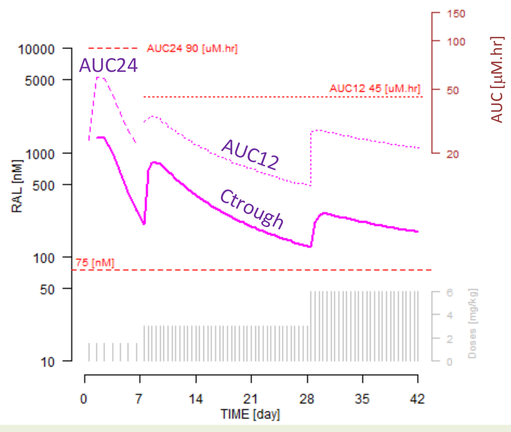


Figure 7: Trough and AUC profile



Summary

RAL is metabolized via UGT-1A1, where activity is known to be extremely low immediately after birth followed by a dramatic increase over the first days and weeks of life until the enzyme is fully matured after about 6 months [3,4]. Using time-dependent clearance and absorption rate relationships, the population PK model shown here described the observed data in neonates well. From our model simulations, we were able to inform a daily dosing regimen for evaluation in Cohort 2 of P1110. Further modeling and simulations will be performed as neonates are enrolled in cohort 2 to verify the proposed dosing regimen.

References and Acknowledgements

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