Raltegravir PK in neonates – Modeling rising and declining PK profiles of newborns exposed to raltegravir in-utero

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Introduction

- A daily dosing regimen is used to treat neonates with raltegravir from birth up to 6 weeks to prevent HIV infection [1]
  - As these neonates have not been exposed to raltegravir (RAL) before, we call them raltegravir **naïve neonates**
- Pregnant women can be treated with raltegravir (and other antiviral agents). Raltegravir is readily exchanged between mother and fetus, so their babies will be born with raltegravir in their bodies. These babies are RAL **non-naïve neonates**
- **Main question: Is a different dosing regimen required to treat non-naïve neonates?**
- Dose regimen applied for naïve neonates: Week-1, 1.5 mg/kg QD, weeks 2-4, 3 mg/kg BID and weeks 5-6, 6 mg/kg BID

- Unexpected PK profiles of non-naïve neonates observed in trial P1097 [2] (Figure 1)
  - Mothers dosed raltegravir 400 mg BID up to giving birth
  - Neonates did not receive any dose of raltegravir post-partum
- **Why do some neonates have rising and some have declining PK profiles?**
  - Are rising PK profiles the result of absorption of raltegravir from the gut after break down of conjugated raltegravir glucuronides accumulated in the intestines during the pregnancy [2] ?
- A popPK approach has been undertaken to answer this question

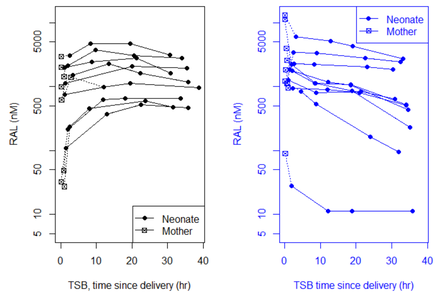


Figure 1. Rising and declining non-naïve neonate PK profiles after birth (P1097):
- 19 mother-neonate pairs
- 1 sample mother after birth
- 4 max. samples per neonate.
- 9 rising PK profiles (left)
- 10 declining PK profiles (right)

Objective

Design of dosing regimen of raltegravir (RAL, Isentress®) for neonates exposed to raltegravir in-utero for the prevention or treatment of HIV infection based on two cohort adaptive design (IMPAACT P1110)

Prior popPK model naïve neonates

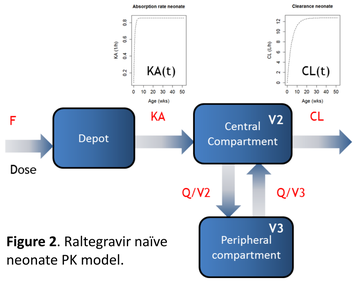


Figure 2. Raltegravir naïve neonate PK model.

A RAL naïve neonate popPK model has been developed previously [1] using:
- Data from 24 infants (P1066) and 18 neonates (P1110)
- 2-compartment model
- Allometric scaling on V2, V3, CL and Q
- Special developed clearance maturation and age-dependent oral absorption rate constant functions:

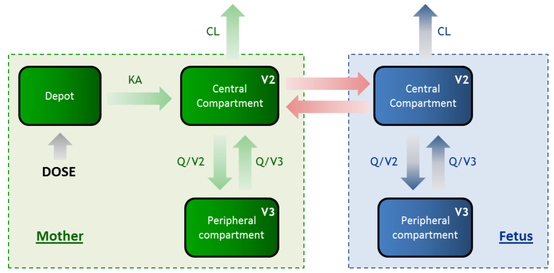
$$CL(t) = CL_{base} + CL_{max}(1 - e^{-\tau_{CL}*Age})$$
$$KA(t) = KA_{base} + KA_{max}(1 - e^{-\tau_{KA}*Age})$$

Dataset: mix of naïve & non-naïve neonates, infants and mothers

Table 1. Data used for non-naïve and naïve neonate PK model development

	Naïve neonates				Non-naïve neonates		Mothers
Study No	P1110		P1066		P1110	P1097	P1097
Cohort No	1	2	4	5	1	-	-
Total number of subjects	10	23	13	11	6	19	19
Number of data points	89	278	121	123	54	75	19
Age range at enrollment	0-2 days	0-2 days	6 months to < 2 years	4 weeks to < 6 months	0-2 days	0-1 day	Unknown
Age range for PK sampling	0-2 weeks	0-6 weeks	6 months to < 2 years	5 weeks to < 6 months	0-2 weeks	0-2 days	Samples < 1 hr postpartum
Weight range (kg)	2.3-4.2	2.2-5.3	5.5-14	3.7-10.4	2.2-3.4	2.2-4.1	Unknown
Sex (M/F)	4/6	13/10	8/5	7/4	4/2	14/5	0/19

Combined mother-neonate model



- Raltegravir quickly exchanged between the central circulations of mother and fetus via the placenta/umbilical cord
- Prior adult and neonate popPK models are linked via fast exchange rates between the central compartments and removal of the neonate absorption compartment. This represent the situation at pregnancy
- Mother PK model based on Du et al. [5], adjusted for pregnant women using reports of Watts et al. [3] and Blonk et al. [4]
- Fetus/neonate PK model [1] assumed identical for naïve and non-naïve neonates
- At birth the raltegravir exchange is broken, both mother and neonate continue as two independent models
- Drug disposition non-naïve neonate at birth determined by dose administration pregnant mother before birth

Examples PK fits of mothers and their non-naïve babies

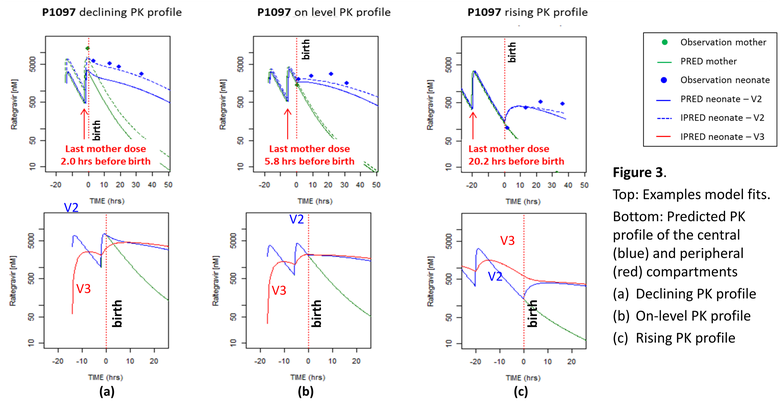


Figure 3.
Top: Examples model fits.
Bottom: Predicted PK profile of the central (blue) and peripheral (red) compartments
(a) Declining PK profile
(b) On-level PK profile
(c) Rising PK profile

Model correctly predicts rising and declining neonate PK profiles! How?

- Before birth: raltegravir in fetus is cleared via the mother only
- At birth: neonate cannot (yet) metabolize raltegravir (immature UGT 1A1)
- **(a) Birth is shortly after the last dose mother :** Concentration peripheral compartment neonate is **lower** than in central compartment. Raltegravir flows to peripheral compartment: concentration central compartment will decrease
- **(b) Birth about 6 hrs after the last dose mother**: central and peripheral concentrations neonate are about **equal** and will initially remain on level
- **(c) Birth is relatively late after the last dose mother**: concentration peripheral compartment neonate is **higher** central compartment. Raltegravir flows back from peripheral to the central compartment. As the clearance is almost zero, the concentration of central compartment will rise

Dosing non-naïve neonates

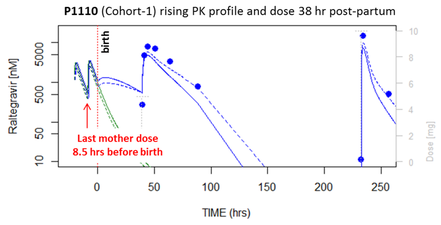


Figure 4. Example non-naïve neonate dosed 38 hrs post-partum. The model predicts rising PK profile shortly after birth (not verified by data).

Parameter estimates

Table 2. Parameter estimates and 95% confidence intervals of mother/neonate model

Mother

Param	Unit	Value	95% CI Low	95% CI High
V2	L	3.52		
V3	L	27.03		
CL	L/hr	9.73		
Q	L/hr	0.87		
KA	1/hr	0.197	0.080	0.314
F		0.55	0.41	0.69

Neonate F=0 and CLbase=0

Param	Unit	Value	95% CI Low	95% CI High
V2	L	7.20	5.08	10.21
V3	L	10.77	7.59	15.29
CLMAX	L/hr	9.45	7.26	11.65
Q	L/hr	0.80	0.55	1.18
KAMAX	1/hr	0.42	0.29	0.56
CLTAU	1/year	11.41	7.34	15.48
KABASE	1/hr	0.095	0.033	0.277
KATAU	1/year	65.6	0.0	135.7

Variability

Param	Value	95% CI Low	95% CI High
Residual variability			
ADDI	15.26	8.67	21.85
CCV	0.54	0.49	0.58
Interindividual Variability			
F – Mother	0.47	0.26	0.67
CL - Neonate	0.62	0.43	0.81
KA - Neonate	0.46	0.35	0.57

Assessment dose regimen non-naïve neonates

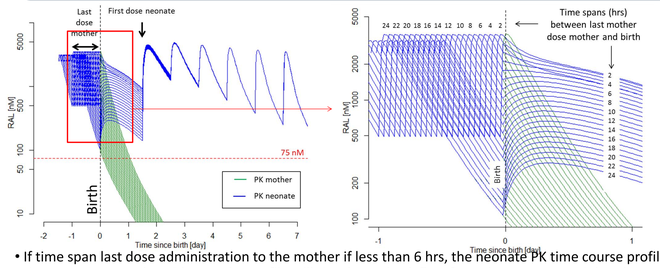
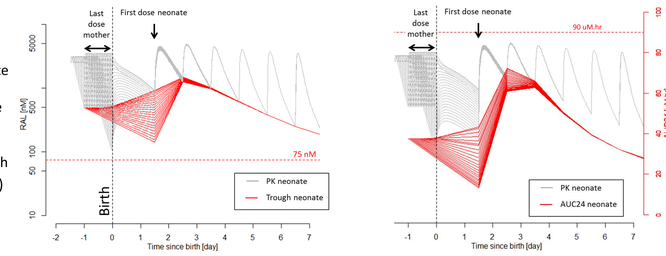


Figure 5: Predicted superimposed PK profiles of both mother (green) and neonate (blue). First dose neonate 36 hrs post-partum, last dose mother in time range 1 - 24 hrs before giving birth

- If time span last dose administration to the mother if less than 6 hrs, the neonate PK time course profile will decline; if the time span is more than 6 hours, the profile will rise due to back flow from the neonate peripheral compartment (see enlargement)
- Neonate PK profile are almost identical after 3 doses

Figure 6: Predicted PK profiles (gray). First dose neonate 36 hrs post-partum, last dose mother in time range 1 - 24 hrs before giving birth
(a) Thoughs (red)
(b) $AUC_{0\text{-}24}$ (red)



(a) Red lines: connected troughs concentrations **(b)** Red lines: connected $AUC_{0\text{-}24}$ levels

- Before birth: neonate trough and AUC levels are identical to mother
- Trough level neonate at first dose 140 nM - 1500 nM (for timespan last dose mother to birth is 24 and 2 hrs, respectively)
- Though >75 nM in all cases, sufficient to suppress on viral replication
- $AUC_{0\text{-}24}$ levels highest after first or second dose but remain well below 90 uM.hr

Conclusions

- An elegant popPK model has been developed describing PK time-course profiles of non-naïve neonates
- Depending on the time interval between the last dose administration to the mother and birth, the PK profile may rise or decline:
  - If the time interval < 6 hours, the neonate will have declining concentrations of raltegravir in the central circulation
  - If the time interval > 6 hours, the will have initial rising concentration due to backflow of raltegravir from peripheral tissue back into the central circulation where the compound is only very slowly cleared due to immature UGT-1A1 enzyme complexes in the liver
- Current practice is to start dosing non-naïve neonates 36 hrs post-partum, subsequently followed by the normal dosing regimen. This is adequate to maintain C-trough concentrations above 75 nM and $AUC_{0\text{-}24}$ levels below 90 uM.hr

References

1. ACoP-2016, Poster S-06/T-33: Jos Lommerse, Diana Clarke, Anne Chain, Han Witjes, Hedy Teppler, Edward P Acosta, Edmund Capparelli, Matthew L. Rizk, Larissa Wenning, Thomas Kerbusch, Stephen Spector, Betsy Smith, Mark Mirochnick. Raltegravir PK in neonates - An adaptive trial design to define an appropriate regimen for neonates from birth to 6 weeks of age.
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