Raltegravir (RAL) Pharmacokinetics (PK) and Safety in HIV-1 Exposed Neonates at High Risk of Infection: IMPAACT P1110

Clarke DF, Acosta EP, Chain A, Cababasay M, Wang J, Calabrese K, Spector SA, Bryson YJ, Teppler H, Popson S, Graham B, Smith B, Hazra R, Homony B, Murray R, Mirochnick M, and the P1110 Protocol Team

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Quantitative Solutions

MSD

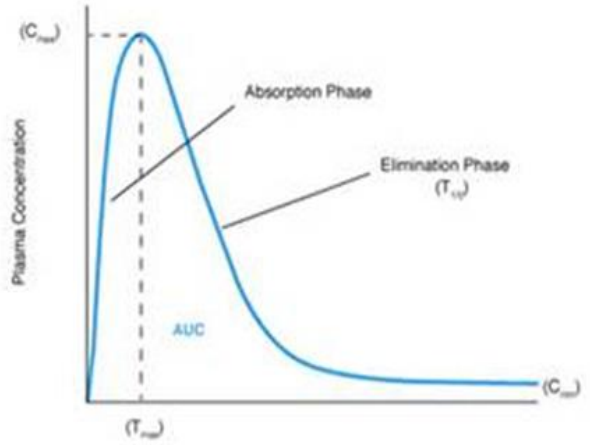
IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

ARVs in Neonates

- Safety and dosing information for antiretroviral drugs (ARVs) in neonates are limited
  - Prophylaxis and early treatment
- RAL first INSTI to be studied in young infants
- Study design for this unique patient population
  - Population PK and simulations to facilitate drug development in neonates
  - Design is being adapted for additional ARVs to be used in neonates
- Collaboration between IMPAACT and industry for pediatric drug development

Population PK Approach to Neonatal-Dose Finding

- Pharmacokinetic analysis that uses sophisticated statistical techniques
- Sparse sampling data sets
- Estimates the population average and variance of PK parameters



Background and Rationale

- RAL has good safety and tolerability
- RAL is primarily metabolized by UGT1A1 enzyme
  - UGT activity low at birth and increases exponentially over the first weeks to months of life
  - High RAL plasma concentrations in vitro displace unconjugated bilirubin from albumin, potentially increasing neonatal risk of kernicterus (Clarke, et.al. PIDJ 2013)
    - RAL concentrations 50-100 X greater than typical peak concentrations (~ 5000 ng/mL)

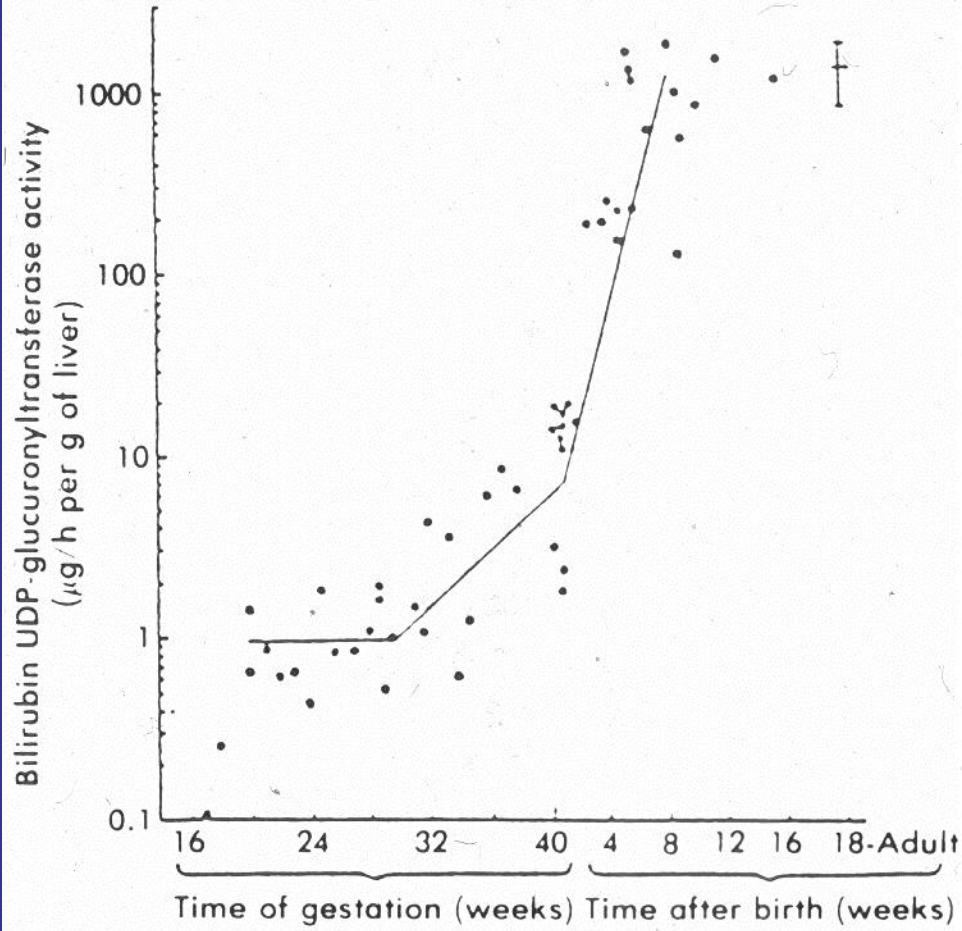
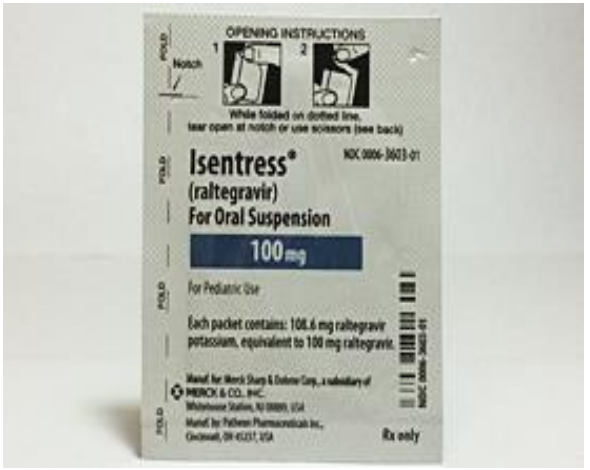


Fig. 42-8. Developmental pattern of hepatic bilirubin UDP glucuronyl transferase activity in humans. (From Kawade N and Onishi S: Biochem J 196:257, 1981. Reprinted by permission of The Biochemical Society, London, 1981.)

Study Objectives

- To evaluate the PK, safety and tolerability of RAL oral granules for suspension when administered to HIV-1 exposed infants



Infant Inclusion/Exclusion Criteria

- Full-term infant aged ≤ 48 hours of age
- Infant gestational age at birth at least 37 weeks and weight ≥ 2 kg
- Exclusion criteria:
  - Elevated bilirubin requiring phototherapy
  - Receipt of disallowed medications - phenytoin, phenobarbital, rifampin

P1110 Study Design

Neonates enrolled into 2 sequential cohorts:

- Cohort 1 (n=16): Infants received 2 single RAL doses one week apart (Clarke, et al. IAS 2015)
- Cohort 2 (n=30): Two groups of infants receive daily RAL dosing for first 6 weeks of life
  - Initial group: Infants born to mothers not receiving RAL
  - Subsequent group: Infants born to mothers who received RAL during pregnancy up through delivery

Determination of Cohort 2 Daily RAL Dose

- Population PK modeling and simulations using NONMEM
  - Data set included RAL concentration data from Cohort 1 and from infants and children enrolled in IMPAACT P1066
  - Developmental changes in absorption and clearance explored, with best fit if:
    - Absorption rate changed from 16% of max at birth to 90% at 2 weeks
    - Clearance changed from almost nil to a max at ~ 6 months of age

PK Targets and RAL Dose Selection

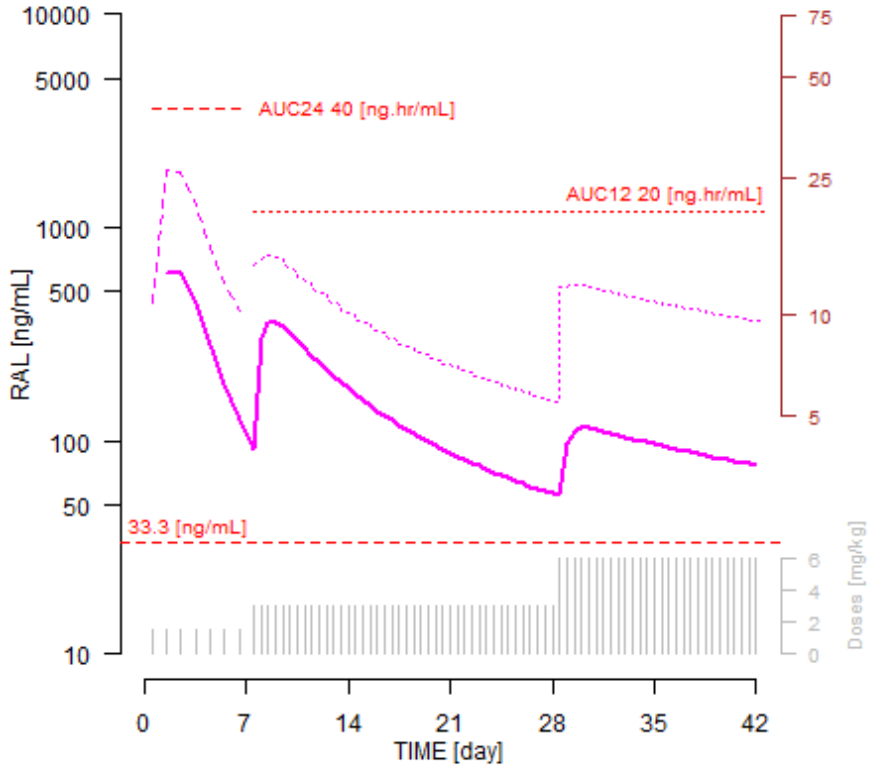
- Simulations used to evaluate potential Cohort 2 dosing regimens (Lommerse, et al. PAGE 2015)
- PK Targets:
  - Cmin > 33 ng/mL; Cmax < 8724 ng/mL
  - AUC12 (BID dosing) 6-20 mg*h/L
  - AUC24 (QD dosing) 12-40 mg*h/L
- Selected Cohort 2 dosing regimen:
  - Birth to day 7 of life: 1.5 mg/kg QD
  - 1 week to 4 weeks of age: Dose 3 mg/kg BID
  - 4 weeks to 6 weeks of age: 6 mg/kg BID

Evaluation of Possible Dosing Regimens

Red – well outside of PK exposure target
Orange – close to PK exposure target
Green – within PK exposure target

Regimen	1-7 (wk-1)	8-14 (wk-2)	15-21 (wk-3)	22-28 (wk-4)	29-35 (wk-5)	36-42 (wk-6)	Trough	Cmax	AUC24 (QD)	AUC12 (BID)
1	2 QD	3 BID					Day42		Day2+3	
2	3 QD	3 BID			4 BID		Day42		Day2+3	
3	2 QD	2 BID			6 BID		Day28		Day2+3	
4	2 QD	2 BID	6 BID						Day2+3	Day14-16
5	3 QD		3 BID		6 BID		Day 14		Day2+3	
6	2 QD	4 QD	6 BID						Day2+3	Day14-16
7	2 QD	3 BID			6 BID				Day2+3	
8	2 QD	6 QD			6 BID		Day 28		Day2+3	
9	3 QD	3 BID			6 BID				Day2+3	
10	1.5 QD	3 BID			6 BID					

Predicted RAL exposure for a typical cohort 2 subject receiving selected regimen during first 6 weeks of life



Cohort 2 PK Sampling

- Intensive PK sampling
  1. Initial dose of 1.5 mg/kg: pre-dose and 1-2, 6-10 and 20-24 hours post-dose
  2. Between 15-18 days of life after dose increased to 3 mg/kg BID: pre-dose and 1-2, 4-6, and 8-12 hours post-dose
- Sparse sampling
  1. After 2nd dose; each dose change; and at week 5-6 of life after dose increased to 6 mg/kg BID: pre-dose and 2 hour post- dose

Cohort 2 Demographics

- 12 infants: 7 from Brazil, 3 from South Africa, 2 from USA
- Infant demographics [n or median (range)]
  - Gender: 4 female/8 male
  - Gestational Age: 38 weeks (37-40)
  - Birth Weight (kg): 2.8 (2.4-3.7)
  - Mode of Delivery: 4 vaginal/ 8 caesarian section

Cohort 2 Intensive PK results

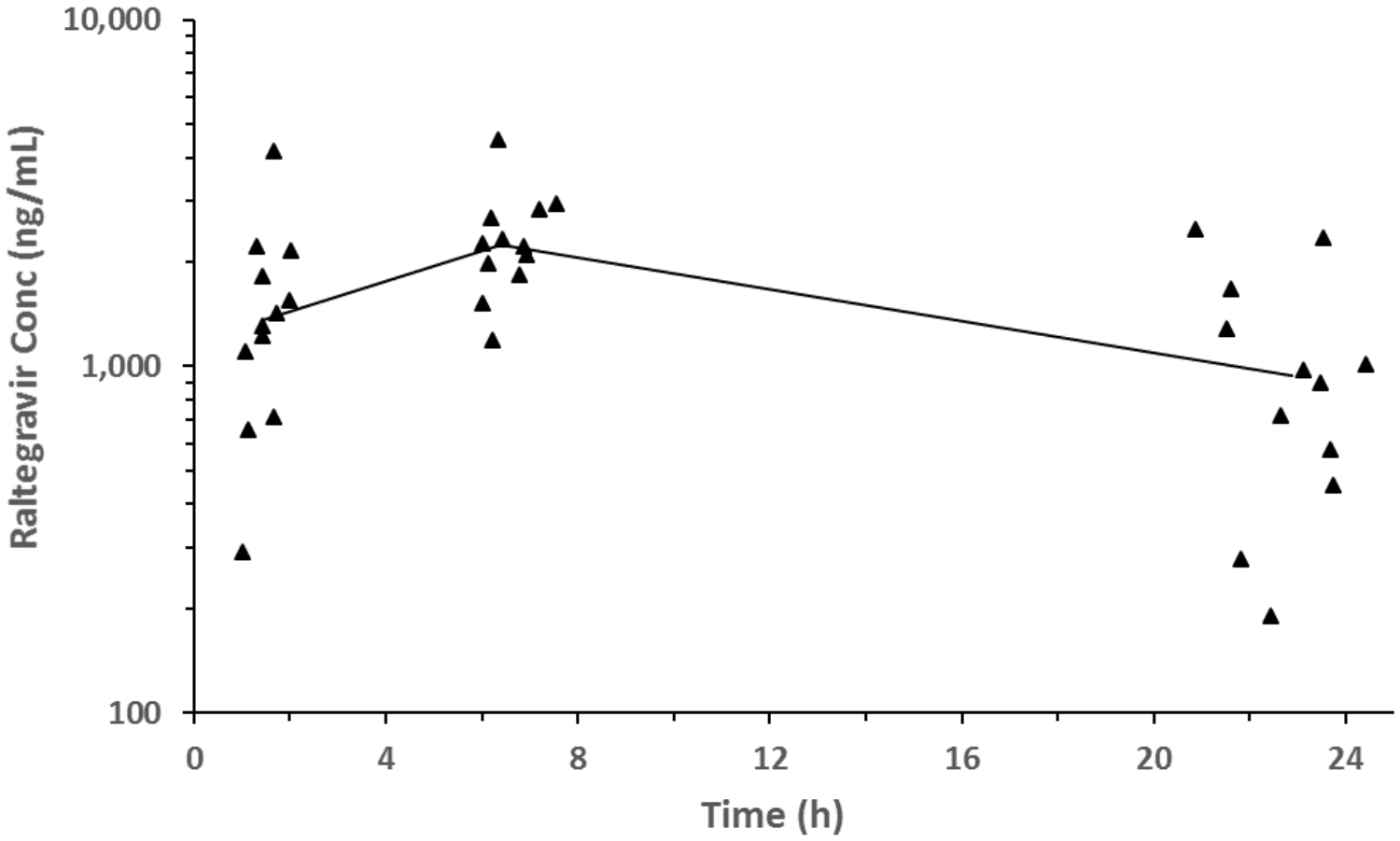
	AUC		Trough	
	Mean (range)	Met target	Mean (range)	Met target
Initial dose – 1.5 mg/kg QD (n=12)	37.0 (18.6-78.3) mg*h/L	8/12	833 (191-2493) ng/mL	12/12
Increased dose - 3.0 mg/kg BID (n=12)	11.8 (4.7-24.5) mg*h/L	9/12	120 (11-666) ng/mL	11/12

PK targets: AUC24: 12-40 mg*h/L, AUC12: 6-20 mg*h/L, Trough concentration >33 ng/mL

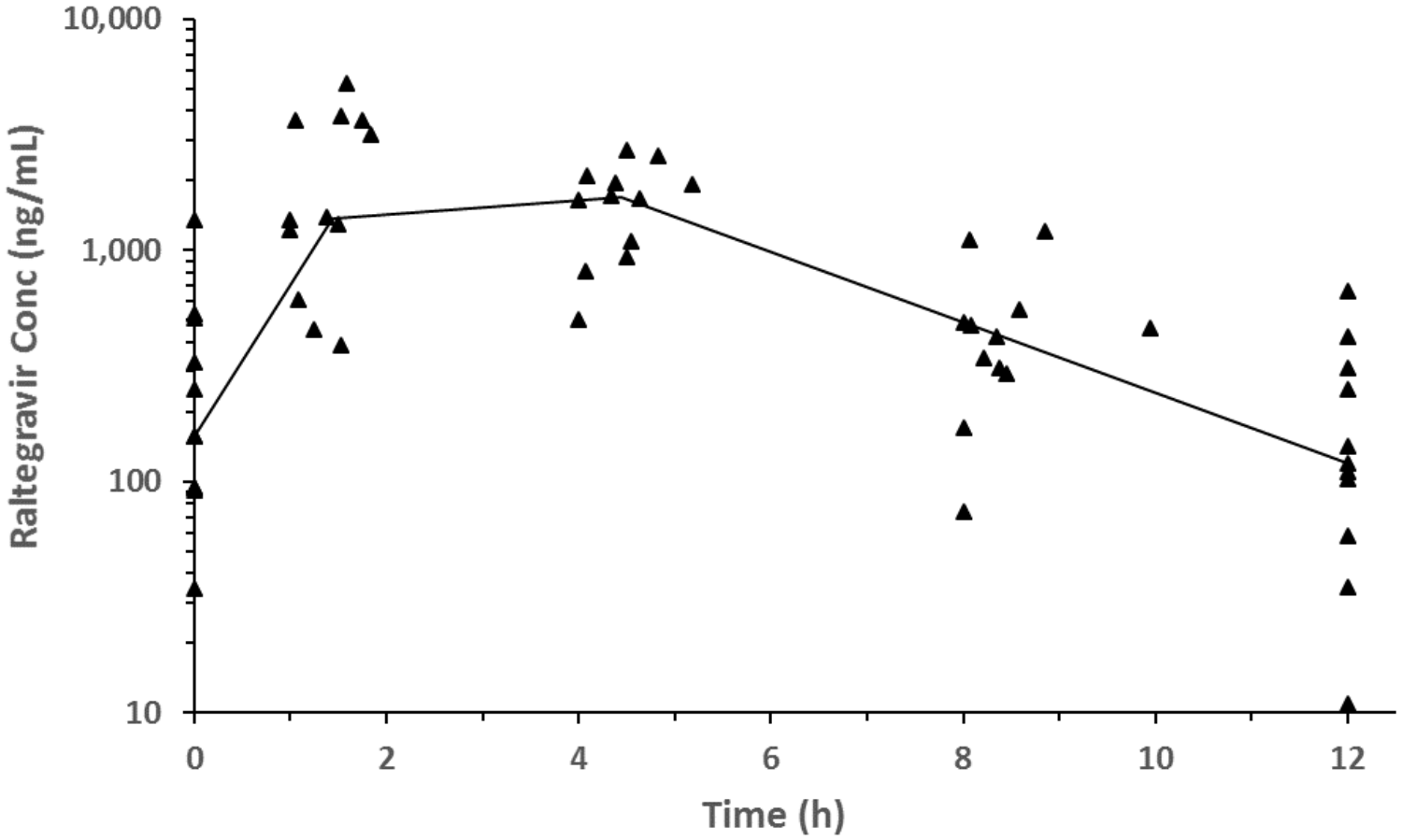
Safety Evaluations

- No safety concerns observed with daily RAL administration through 6 weeks of life
  - Physical Exam
  - Hematology including CBC with differential and platelet count
  - Chemistries including AST, ALT, creatinine, total and direct bilirubin
  - HIV nucleic acid test (HIV NAT)

Initial Dose 1.5 mg/kg QD



3 mg/kg BID



Conclusions

- Population analysis and simulations can be used to facilitate drug development in neonates
- With initial 1.5 mg/kg dose, Cmin within target but AUC24 slightly above target range
  - Given the rapid increase in RAL metabolism over the first week of life, this exposure was considered acceptable
- With 3 mg/kg BID: day 15-18, AUC12 and Cmin within target range
- Daily RAL was well tolerated in infants receiving this regimen during the first 6 weeks of life
- P1110 Cohort 2 RAL-naïve (closed): 26 infants enrolled as of July 7
- Further modeling efforts are ongoing to allow enrollment of infants exposed to RAL in utero.

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