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#61

Abacavir Weight-Band Dosing for Infants in the first 4 weeks of life

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Background

- World Health Organization (WHO) recommends abacavir (ABC) from 1 month of age in infants weighing ≥3 kg
- ABC restricted from birth due to limited pharmacokinetic (PK) and safety data in neonates (<28 days old)

Our objective was to determine the optimal weight-band doses for ABC liquid formulation in neonates

Material and Methods

An ABC population PK model was developed by pooling data from **3 studies** administering ABC liquid formulation to neonates and infants:

Study 1
PACTG 321
Term neonates exposed to HIV
Intensive PK after single doses

Study 2
Tygerberg cohort
Term neonates exposed to HIV
Intensive PK after single doses

Study 3
IMPAACT P1106
Low birth weight infants living with HIV
Sparse PK during chronic dosing

PK Model Building

- ABC clearance (CL/F) was allometrically scaled according to infant body weight and maturation linked to post-natal age (PNA) in a non-linear manner
- Monte Carlo simulations were run for neonates to identify the optimal ABC dosing strategy for 3 WHO weight-bands: 2.0-3.0 kg, 3.0-4.0 and 4.0-5.0 kg
- The PK goal was to achieve ABC exposures reported in older children: ***AUC_{0-12} range: 3.2 to 25.2 mcg.hr/mL*** *(based on US FDA submission: Ref ID: 3702679*)

Results

- 45 infants <3 months of age contributed 308 ABC concentrations. Infant characteristics are shown in **Table 1**
- Studies 1 & 2: single ABC dose to 21 term neonates (3 LBW); Study 3: multi-dose of 24 infants living with HIV
- Infants in Study 3 were older at PK sampling than those from the first two studies but the body weight was comparable

Table 1: Characteristics of Infants on ABC (n=45)

	PACTG 321 (Study 1)	Tygerberg (Study 2)	P1106 (Study 3)	Total
Birth weight (kg)	3.1 (2.2-4.0)	3.2 (2.5-4·2)	2.2 (1.4.3.3)	2.6 (1.4-4.2)
LBW (<2500 gm)	3 (27)	0 (0)	18 (75)	21 (47)
GA at birth (weeks)	39 (39-39)	39 (38-42)	35 (27 - 39)	38 (27-42)
ABC Dose	2.0 (1.9-2.1)	8.1 (8.0-8.4)	10.8 (4.1-13.2)	NA
WT 1st PK Visit (kg)	3.1 (2.2-4.0)	3.3 (2.9-4.4)	3.8 (2.4-5.8)	3.5 (2.2-5.8)
PNA 1st PK Visit (days)	1 (1-8)	9.5 (6-15)	73 (41-190)	46 (1-190)

Number (%) or Median (range); *LBW= low birth weight; GA = gestational age; WT= weight; PNA= postnatal-age*

ABC Population PK Model

- PK model: 1-compt. with 1st-order absorption and elimination.
- Maturation of ABC CL/F described using an exponential model as a function of PNA). ABC CL/F was low at birth but increased ~2-fold by 4 weeks of age

ABC Safety

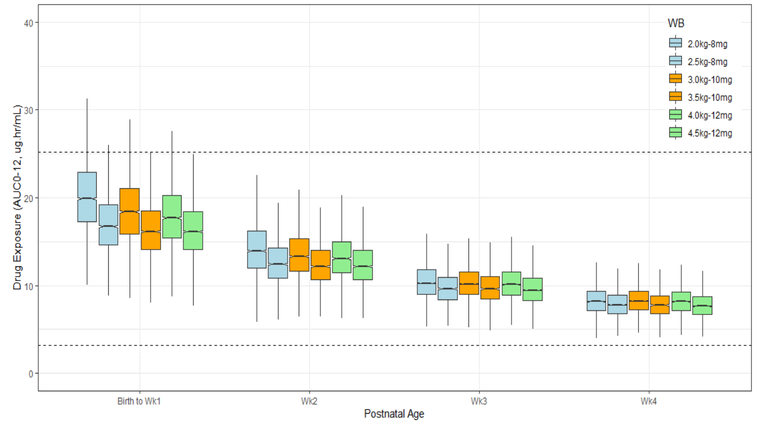
- No hypersensitivity reactions reported
- ABC Single Dose: 2 Grade 3 neutropenia, possibly related to ZDV (resolved)
- ABC Multi-dose : 15 infants met the composite safety endpoint of death and Grade 3 and 4 AE - none considered related to ART
  - One Grade 2 ALT event was possibly related to ABC, but infant had history of hepatotoxic traditional medicine ingestion. ART was stopped and re-started within 2 weeks after ALT normalization

Neonatal ABC Dosing Per WHO-Weight Bands

- ABC exposures simulated for neonates with birth weights of 2.0, 2.5, 3.0, 3.5, 4·0 and 4.5 kg receiving 8, 10 and 12 mg BID are shown in **Figure 1**

Drug	ABC Liquid	2-3 kg		3-4 kg		4-5 kg	
		AM	PM	AM	PM	AM	PM
ABC	**20 mg/mL**	**0.4 ml**	**0.4 ml**	**0.5 ml**	**0.5 ml**	**0.6 ml**	**0.6 ml**

Figure 1: Predicted ABC AUC_{0-12} for neonates birth to 4 weeks of life



- ABC AUC_{0-12} were within the expected range, except for a small proportion (<15%) with higher exposures during the first week of life
- ABC AUC_{0-12} decreased rapidly across all weight bands by ~25% at Week 2 and 55% at Week 4, consistent with the expected maturation of the enzymes that metabolize ABC

Conclusions

- ABC weight-band dosing of 8 mg (2-3 kg), 10 mg (3-4 kg) and 12 mg (4-5 kg) twice daily in infants less than 4 weeks of age provides therapeutic exposures for both treatment/prophylaxis
- Using ABC from birth aligns with current WHO 1st-line ART guidelines

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