2nd Long-Acting Treatment and Prevention Conference

29 October 2024 | Johannesburg

Advancements in Neonatal HIV Therapy

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Stellenbosch UNIVERSITY IYUNIVESITHI UNIVERSITEIT

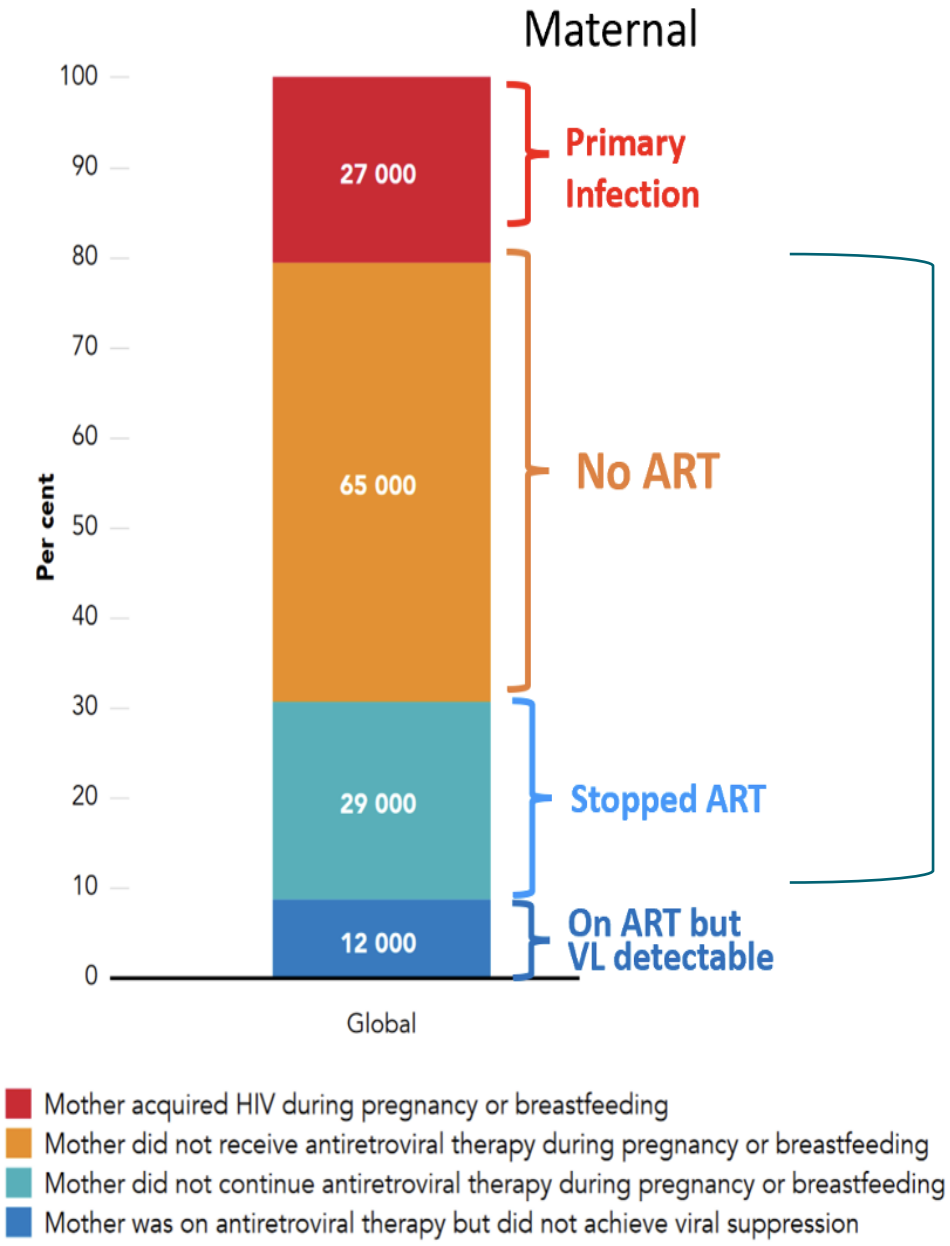
forward together
sonke siya phambili
saam vorentoe

Global Maternal & Pediatric HIV Estimates (2023)

In 2023, approximately **1.2 million women** with HIV were pregnant, resulting in **~ 120 000** new HIV infections among children

Since 2010, there has been a **62%** decline in new pediatric HIV infections, with **~ 3.4 million** vertical and breastmilk transmissions prevented due to antiretroviral therapy (ART) in pregnant and breastfeeding women

Where do these new pediatric HIV transmissions occur?



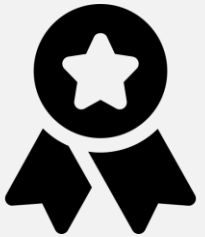
70% of all these HIV transmissions occurred due to ***women not receiving or stopping*** their ARVs during pregnancy

Thus, administering ART to neonates remains a key intervention **if new pediatric HIV infections are to be prevented and early HIV treatment is to be given**

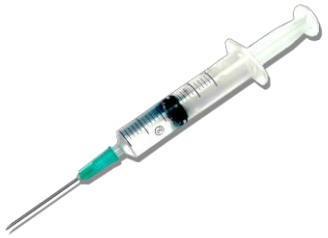
How do we go about to Prevent and Treat Neonatal HIV ?

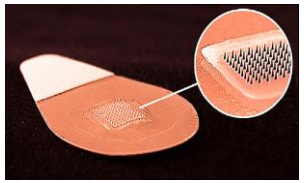
Strategies to be followed:

- To ensure that **women** of reproductive age with HIV are **virally suppressed**
- To **optimize ART in neonates** - both for prevention and treatment of HIV



ARV formulations





*Of the **1.4 million** children worldwide living with HIV,*
*only **57% are receiving ARVs***

Few ARV Options Available to Premature Infants

ARVs with PK and safety data	ZDV IVI	NVP	3TC

**Picture taken with permission*

Factors influencing drug absorption and disposition, include:

- **Gastro-intestinal (GIT) changes**
  - Variable drug absorption
  - Some preterm infants get little or nothing by mouth
  - Impact of ↓gastric acidity and slow GIT motility

- **Extracellular fluid compartment and weight changes**

- **Safety of integrase inhibitors is unclear**
  - as they may displace bilirubin from albumin

Global **preterm rate is 11%**

Infants born to women with **HIV are twice as likely to be preterm**

ARV Formulations - Now to Next

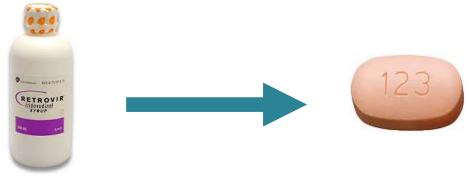
ARV formulations


123

Neonates

Infants, Children and Adults

Why do We Need to Improve?



Few ARV options result in stock-outs	**ARV options aligned with children** may be more readily available
Current neonatal ARV options are from **older drug classes**	New drug classes of ARVs are **more potent and safer**
Liquid formulations have short shelf-lives and are unpalatable	**Dispersible tablets and oral films** have longer expiry dates and are often taste masked
Frequent dosing is difficult (AZT is twice-daily dosing)	Dolutegravir (DTG) dosing is once daily and **may be easier to administer, and possibly improve adherence**

Recent Contributions to Optimizing Neonatal ART

Dosing guidance for **lamivudine (3TC)** liquid in very preterm infants

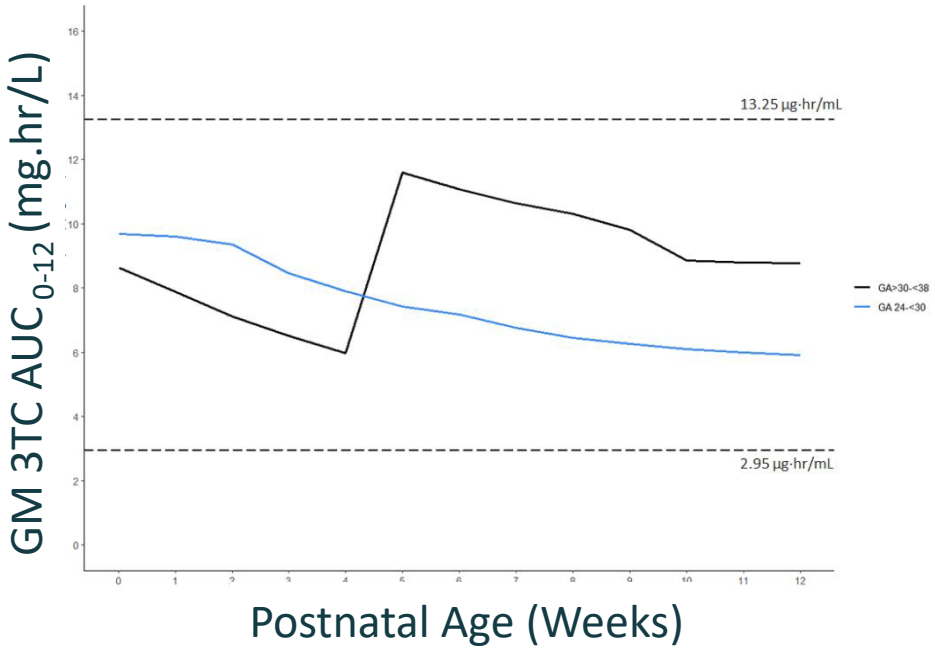
Dosing guidance for **abacavir (ABC)** liquid in term neonates

Dosing guidance for **solid ARV formulations** in term neonates: **PETITE PLATFORM Studies**

3TC: GA-Band Dosing in Very Preterm Infants (<32 weeks)

No 3TC pharmacokinetic (PK) data available in infants <34 weeks GA and 3TC is renally eliminated

Upon WHO request, we combined 3TC concentrations from 8 neonatal and infant PK studies (858 samples; 154 infants) utilizing modeling and simulations **to predict 3TC dosing for preterm infants**



Proposed 3TC Preterm Dosing

Gestational Age Bands	0 - < 4 Weeks of life	≥4 Weeks of life
GA 24 to < 30 weeks	2 mg/kg BID	2 mg/kg BID
GA ≥ 30 to < 36 weeks	2 mg/kg BID	4 mg/kg BID

Infants ≥3kg and aged ≥4 weeks switch to 30mg BID (per WHO)

*Model-based predictions **support twice daily 3TC pragmatic GA band dosing for preterm infants,** but clinical validation is warranted*

Bekker JAC 2024

Abacavir (ABC) Weight-Band Dosing in Term Neonates

Total blood volume in a neonate ~ 85 mL/kg,
restricting the amount of blood that can be drawn for PK sampling

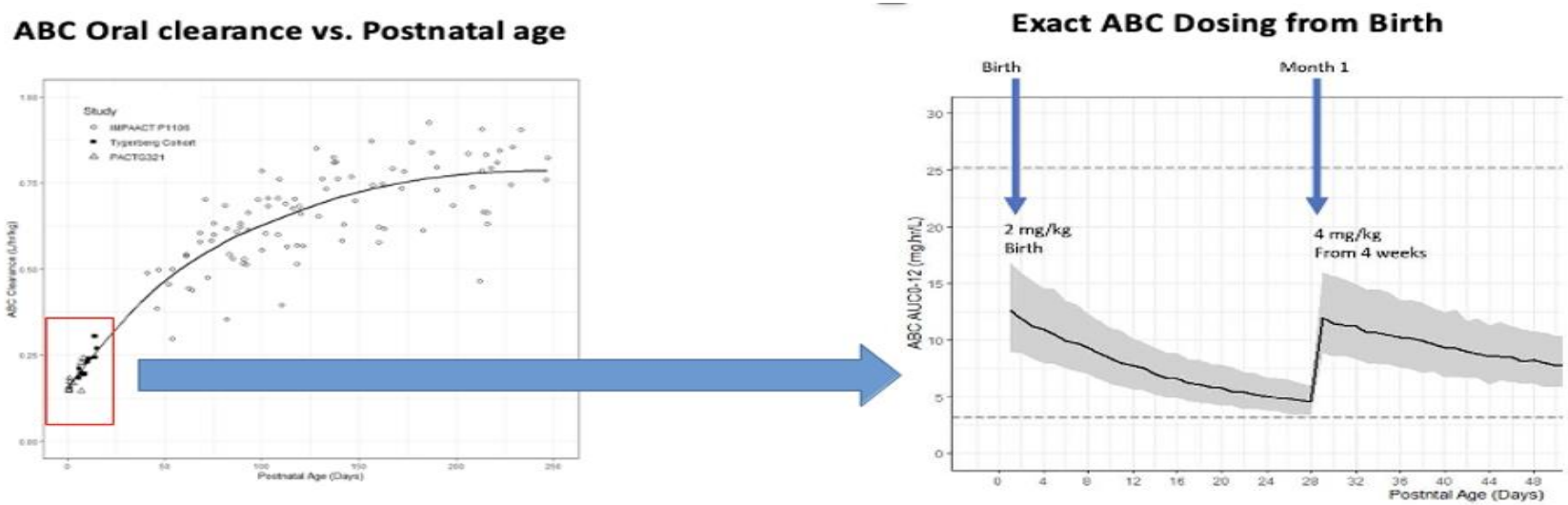
=

Sample limits for clinical research:
For a 3 kg baby, is < 15 mL per day and < 29 mL over 8 weeks

* US National Institutes of Health (NIH) pediatric recommendations

Thus, key strategies for this neonatal study included:

Combining data from 3 neonatal and unfant PK studies & using PK modeling and simulation to derive dosing



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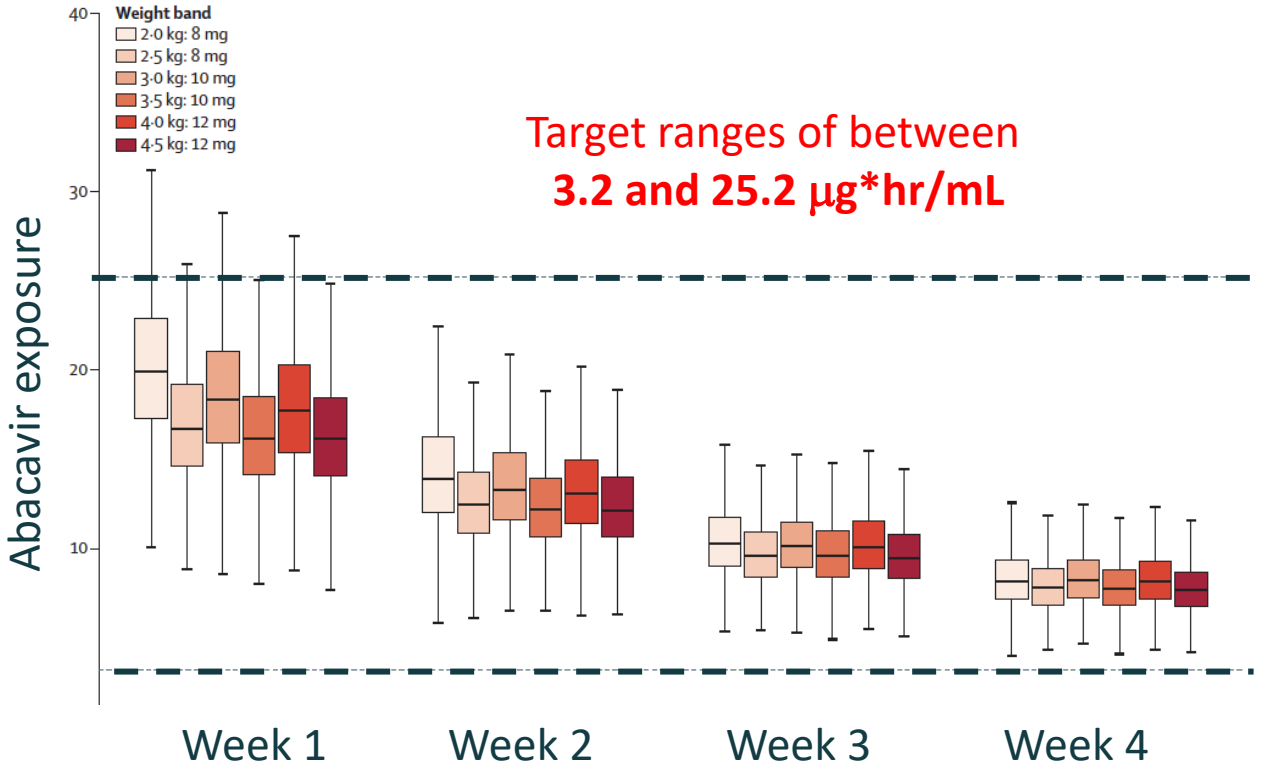
Abacavir (ABC) Weight-Band Dosing in Term Neonates

Drug	*Strength of oral solution*	*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



Target ranges of between
3.2 and 25.2 µg*hr/mL

Optimal drug exposures should **not be too high** (increased risk for toxicity) & **not be too low** (increased risk for resistance)

Bekker *Lancet HIV* 2021

Table A1.4 Drug dosing of liquid formulations for infants younger than four weeks of age[a]

Drug	Strength of oral solution		2–<3 kg		3–<4 kg		4–<5 kg	
			AM	PM	AM	PM	AM	PM
AZT	10 mg/mL		1 mL	1 mL	1.5 mL	1.5 mL	2 mL	2 mL
ABC	20 mg/mL		0.4 mL	0.4 mL	0.5 mL	0.5 mL	0.6 mL	0.6 mL
NVP	10 mg/mL		1.5 mL	1.5 mL	2 mL	2 mL	3 mL	3 mL
3TC	10 mg/mL		0.5 mL	0.5 mL	0.8 mL	0.8 mL	1 mL	1 mL
LPV/r[b]	80 mg/20 mg/mL		0.6 mL	0.6 mL	0.8 mL	0.8 mL	1 mL	1 mL
	Granules 40 mg/10 mg sachet		–	–	2	2	2	2
RAL	10 mg/mL (Oral granules for suspension: 100 mg/ sachet)[c]	<1 week	0.4 mL (once daily)[c]		0.5 mL (once daily)[c]		0.7 mL (once daily)[c]	
		>1 week	0.8 mL	0.8 mL	1 mL	1 mL	1.5 mL	1.5 mL

WHO: Consolidated Guidelines : July 2021

PETITE PLATFORM Studies: PK and Safety of Solid ARV in Neonates

PETITE-4-in-1 ABC/3TC/LPV/r
Completed

ABC/3TC/LPV/r Granules

PETITE-ABC/3TC + LPV/r granules
Completed

ABC/3TC Disp. Tab

LPV/r Granules

PETITE-DTG DT & Oral Dispersible Film
Ongoing

DTG-Oral Film

DTG-Disp. Tab

**Pictures taken with permission*

Co-PIs:
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Tim Cressey

BENEFIT Kids

Unitaid
Innovation in Global Health

Timeline: 2020 → **2024**

Clinical Site
FAMCRU
Cape Town, SA

Lab/Data/Stats
AMS-PHPT
Chiang Mai, TH

AMS CMU

CDISC

ISO:9001/ISO:15189

- ✓ Protocol Writing
- ✓ Regulatory Submissions (e.g. Ethics, local FDA)
- ✓ Trial Implementation, Monitoring
- ✓ Data Management/Statistical Analysis/Reporting
- ✓ Drug Measurement and Pharmacometrics

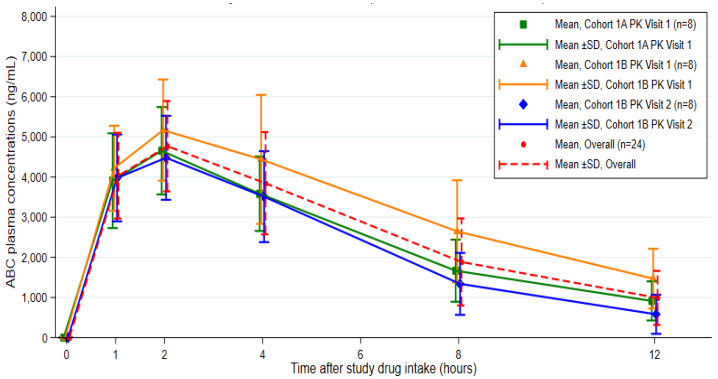
Dissemination to Guideline Committees

PETITE ‘4-in-1’ Study: FDC product of ABC/3TC/LPV/r (n=16)

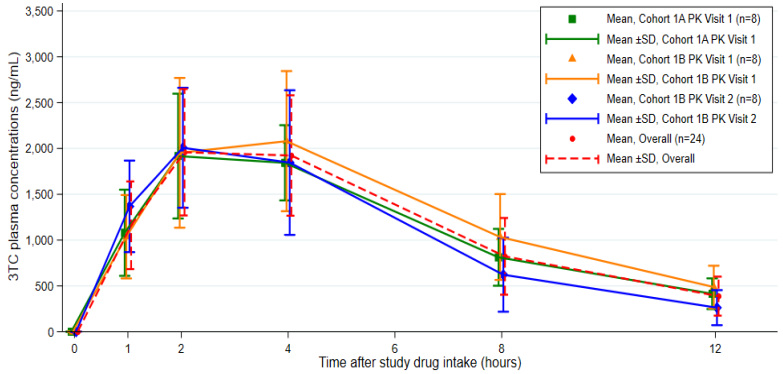
Phase I/II, open-label, single arm, ***two-stage trial*** of HIV-exposed term neonates (≥2500g to ≤4000g)

Stage 1: Single dose(s) of the ‘4-in-1’ in two sequential cohorts: Cohort 1A (n=8) & Cohort 1B (n=8)

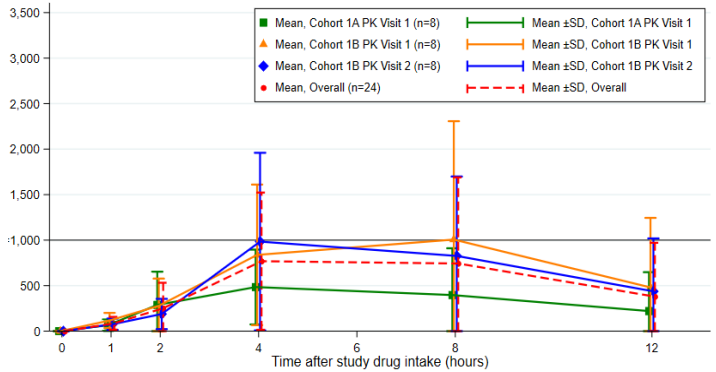
ABC



3TC



LPV



ABC/3TC exposures higher than in children at equivalent dose

Low LPV/r concentrations

In the PETITE ‘4-in-1’ Study: Safety and acceptability data reassuring; first PK data in neonates of solid ABC/3TC drugs; ABC and 3TC plasma concentrations were acceptable, but the very low LPV/r concentrations were of concern

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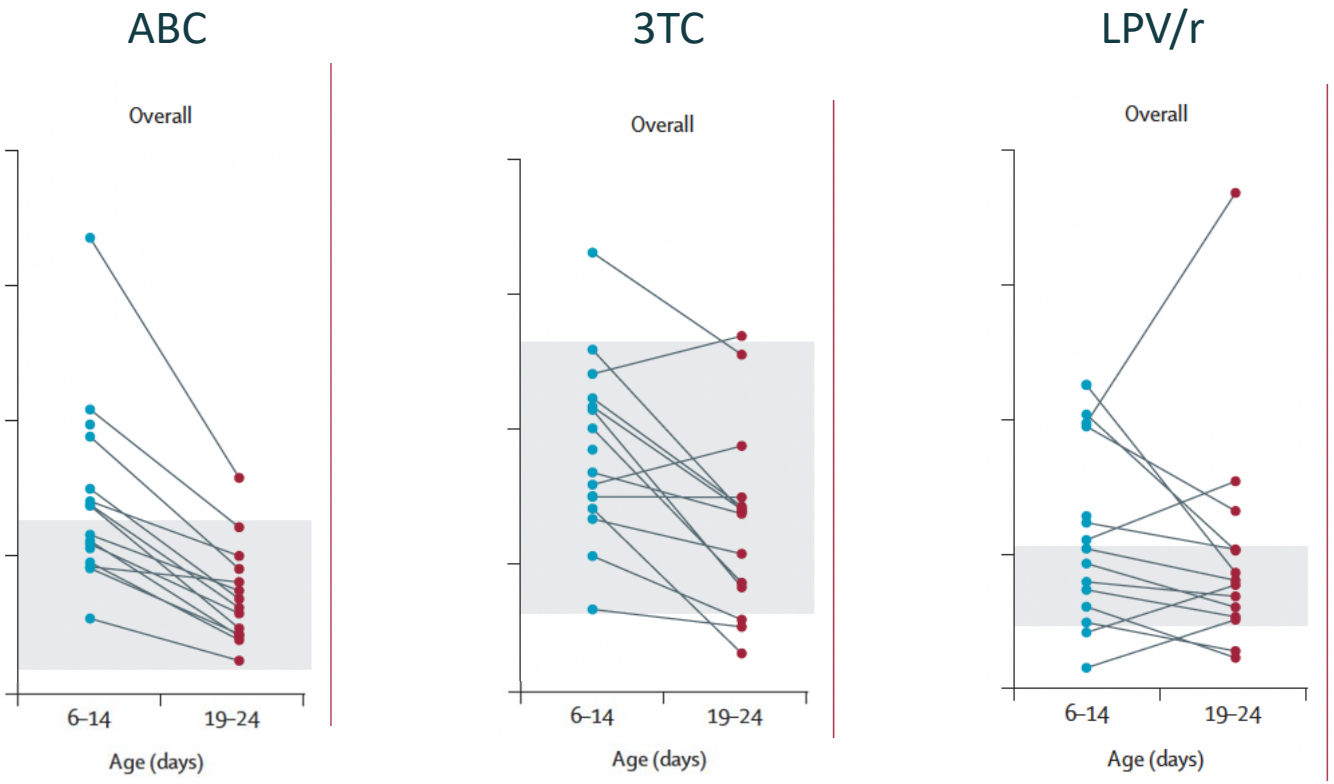
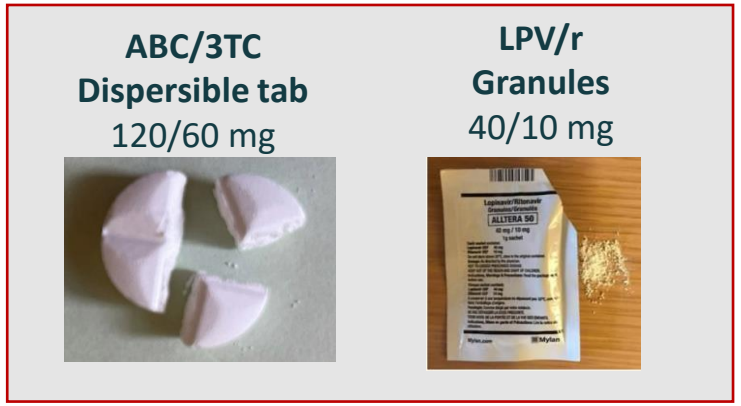
PETITE ABC/3TC + LPV/r granules Study (n=24)

Performed PK and safety in the PETITE ABC/3TC + LPV/r Study: Single dose (n=8) and Multi-dose (n=16):

Dose: ¼ tablet of ABC/3TC once daily and 2 sachets of LPV/r twice daily





In the PETITE ABC/3TC + LPV/r Study:

- **¼ tablet of ABC/3TC OD** resulted in high initial exposures which rapidly decreased
- **2 sachets of LPV/r BID** led to exposures comparable to infants receiving LPV/r liquid
- Data in small cohort supports the use from birth

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Pediatric DTG oral formulations available

- Original 5 mg DTG dispersible tablet

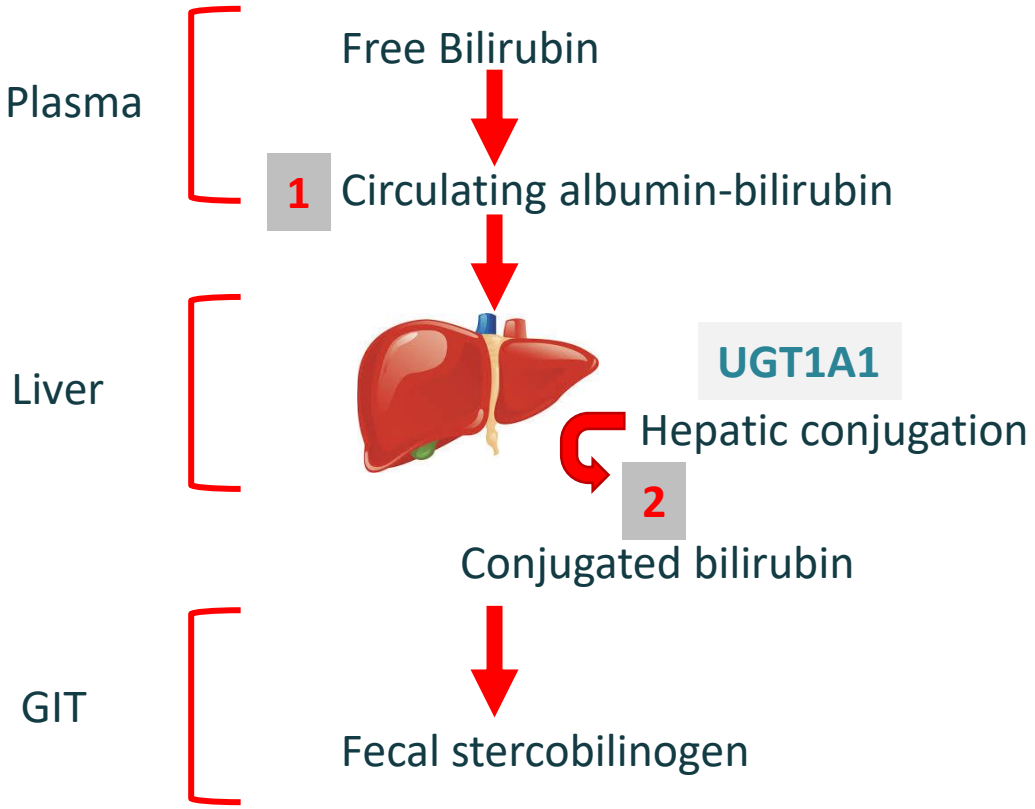
- Generic 10 mg scored dispersible tablet

- DTG oral film (5 mg, 10 mg): thin strip (mint flavoured)

  - To be placed on tongue for rapid disintegration (10 sec) in the saliva prior to swallowing
  - Adult bioequivalent study – with 2 tablets of 5 mg DTG as ref range – US FDA submission

INSTIs and Risk of Hyperbilirubinemia in Neonates

Potential safety concerns of ***severe unconjugated jaundice*** with INSTIs (↑free bilirubin)



Mechanisms by which free bilirubin levels can be increased among high INSTI concentrations:

1. DTG or RAL can displace bilirubin from albumin

2. UGT1A1 enzyme activity is slow at birth, with less effective conjugation of free bilirubin, and less effective DTG metabolism

Note: This possible jaundice risk has *not been* observed in the ~ **74** term neonates enrolled thus far in 2 DTG PK studies

PETITE-DTG Study Design: (n=56)

A **Phase I/II**, open-label, single arm, **two-stage** trial of **56** HIV-exposed neonates (**≥2000**g)

Stage 1: Single dose of the DTG 5 mg dispersible tablet in two **sequential** cohorts:

- Cohort 1A (n=8) ≥14 days and <28 days of life
- Cohort 1B (n=8) <14 days of life

Safety Criteria to move from Cohort 1A to 1B — Fail → DSMB

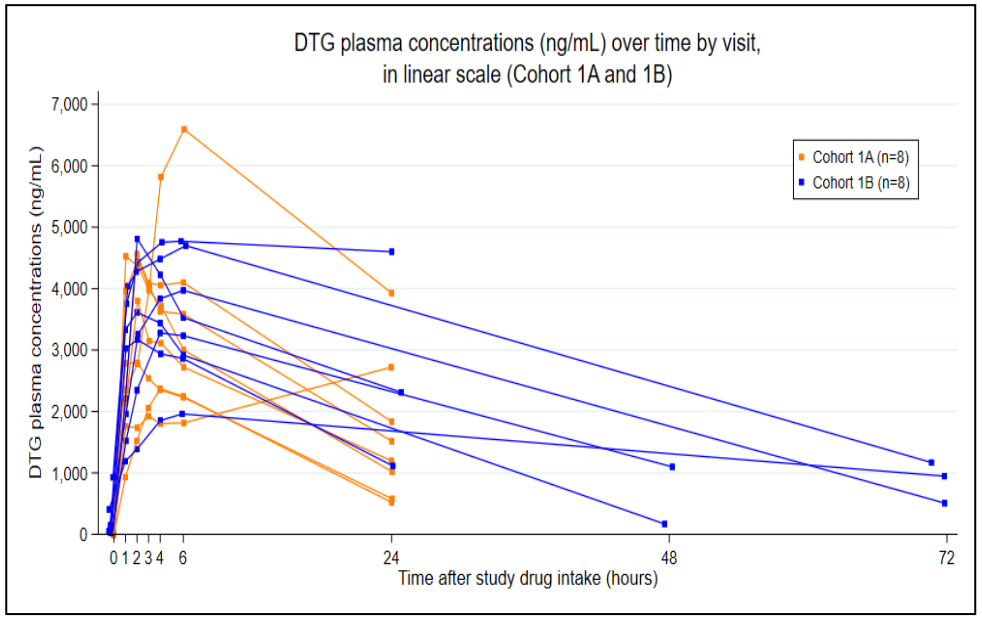
DSMB Review: Interim Analysis: Review Safety/PK data: **SELECT Multi-DTG DOSE**

Stage 2: Multi-doses of DTG 5 mg in two parallel cohorts:

- Cohort 2A: (n=20) neonates
- Cohort 2B: (n=20) neonates

Stage 1 PK/Safety: Single 5 mg DTG-DT Dose in Neonates (n=16)

DTG Conc. vs Time Curves



Cohort 1A (n=8): PK at 17 (16 – 22) days of life

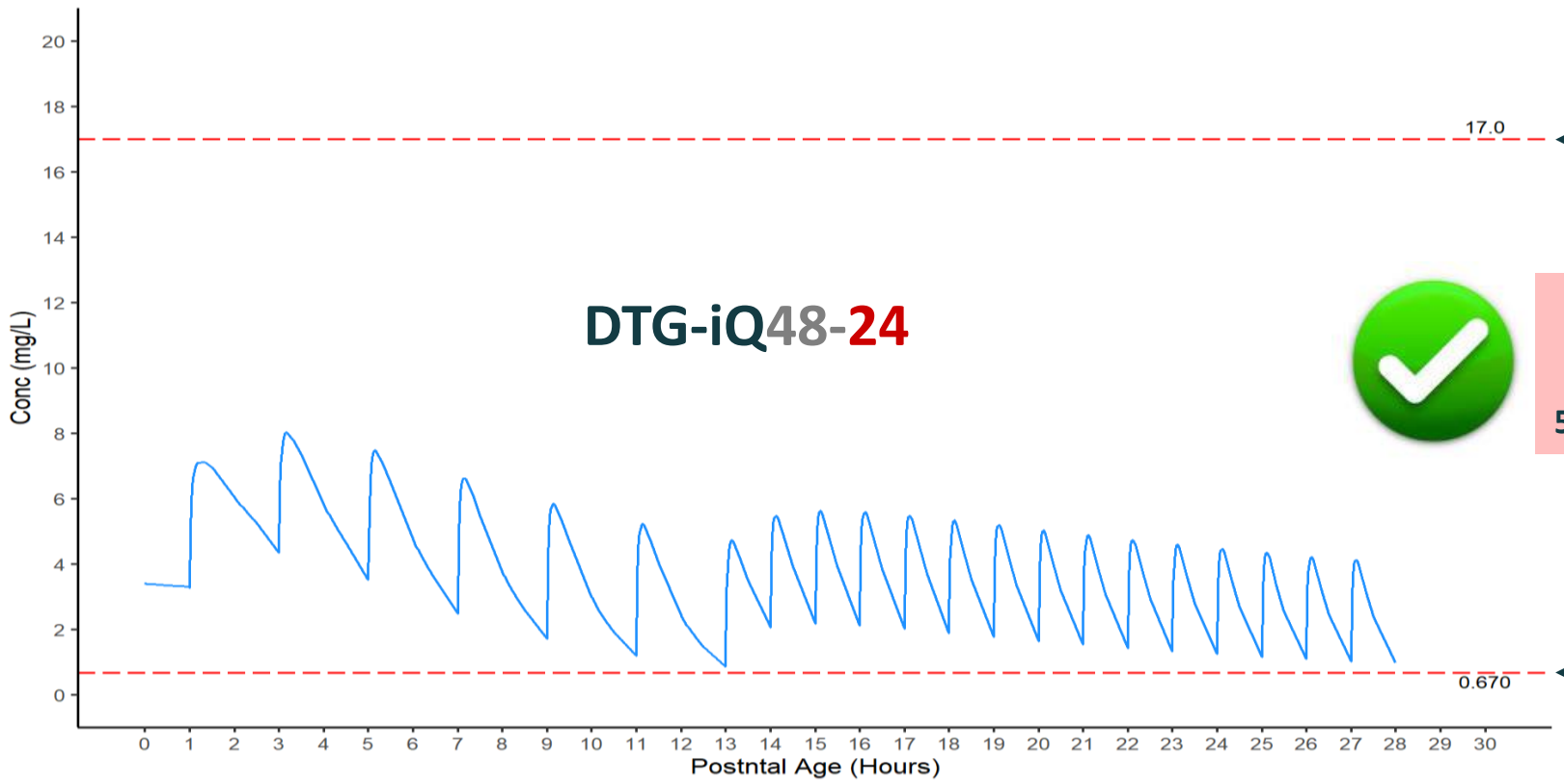
Cohort 1B (n=8): PK at 6 (4 – 8) days of life

DTG PK Parameters

Single Dose PK	Cohort 1A		Cohort 1B	
	N	GM (%CV)	N	GM (%CV)
C_{last} (µg/mL)				
- 24h	8	1.35 (80.0)	3	2.28 (80.9)
- 48h		-	2	0.43 (218.4)
-72h		-	3	0.83 (45.3)
C_{max} (µg/mL)	8	3.78 (35.3)	8	3.65 (30.8)
AUC_{0-24} (µg.h/mL)	7	55.77 (46.3)	8	65.53 (34.8)

SAFETY RESULTS: AEs not related to DTG: Of 11 AEs: 8 were Grade 1 & 3 were Grade 2; 1 SAE: hospitalization for a NVP skin rash (Grade 2) not related to study drug

PETITE-DTG: Multi-dose DTG selection and 2 DTG formulations

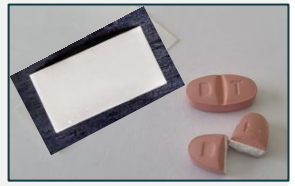


Maximum Conc. Target
C_{max} 17.0 µg/mL

Dosing Agreed by DSMB
5 mg DTG every 48 hrs for the 1st 14 days
5 mg DTG every 24 hrs from day 14 to Day 28

Minimum GM Target
C_{24} 0.697 µg/mL

This dosing strategy was taken forward in Stage 2 (multi-dose)
Thus far, we have enrolled 40 neonates in the multi-dose
(20 receiving 'DTG 5 mg dispersible tablet' and 20 receiving 'DTG-Oral Film"



PETITE-DTG: Multi-dose DTG selection and 2 DTG formulations

- IMPAACT 2023 team presented their Stage 1 (single dose) results at the Pediatric HIV Workshop at IAS 2024 and proposed the same DTG dosing regimen to be evaluated in Stage 2 (multi-dose)
- In June 2024, we completed enrolment of the 1st 20 neonates in Stage 2, who received 5 mg DTG at Q48hr (Day 0 – 13), followed by 5 mg DTG Q24hr (Day 14 – 28).
- An abstract on the interim analysis from the multi-dose PETITE-DTG study was submitted to CROI 2025…

If we could look into the future of Long-Acting ARVs for Neonates

***Panel 1:* PADO-HIV 5 priority list**

PADO-HIV 5 priority list: medium term, 3–5 years

- Dolutegravir/lamivudine/abacavir (5/30/60 mg dispersible)
- Ritonavir–boosted darunavir (20/120 mg)
- Lamivudine/emtricitabine combined with tenofovir alafenamide, with or without dolutegravir
- Cabotegravir for postnatal prophylaxis

PADO-HIV 5 watch list (products of potential interest for paediatric treatment in the longer term)

- Islatravir
- Broadly neutralising antibodies
- Microarray patches (with potent antiretroviral identified after appropriate matching)
- Lenacapavir

PADO-HIV=Paediatric Drug Optimization for HIV.

WHO PADO 5 meeting 2021

PADO 5 - PRIORITY LIST

Cabotegravir (CAB) for PNP

PADO 5 - WATCH LIST

Monoclonal Antibodies (bNAbs)

Lenacapavir (LEN)

"It always seems impossible until it's done"– *Nelson Mandela*

Acknowledgements

All our mothers and babies who participated in the studies

Tim Cressey and PHPT team in Thailand

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Anneke Hesseling and Tony Garcia-Pratz from DTTC at SU