PHARMACOKINETIC AND 4-WEEK SAFETY/EFFICACY OF DOLUTEGRAVIR (S/GSK1349572) DISPERSIBLE TABLETS IN HIV-INFECTED CHILDREN AGED 4 WEEKS TO <6 YEARS: RESULTS FROM IMPAACT P1093

Theodore Ruel, Edward P. Acosta, Rajendra Singh, Carmelita Alvero, Terry Fenton, Kathleen George, Ellen Townley, Rohan Hazra, Stephanie Popson, Ann M. Buchanan, Cindy Brothers, Cindy Vavro, Andrew Wiznia, and the IMPAACT P1093 Team

INTERNATIONAL WORKSHOP ON HIV PEDIATRICS - JULY 20, 2018

IMPAACT International Maternal Pediatric Adolescent AIDS Clinical Trials Network

BACKGROUND

- Dolutegravir (DTG) is a promising agent for children with HIV given its potency, high barrier to resistance, and tolerability.
- IMPAACT P1093 is an ongoing phase 1/2 open-label pharmacokinetic (PK), safety, and dose-finding regulatory study of DTG in children
  - Film-coated tablets approved for older children in the USA and EU.
  - Dispersible tablets (DTG-DT) of 5mg developed for younger children and infants
- *Here we present the intensive PK and 4-week safety (primary outcomes), as well tolerability and efficacy data for DTG-DT in children ages 4 weeks to < 6 years*

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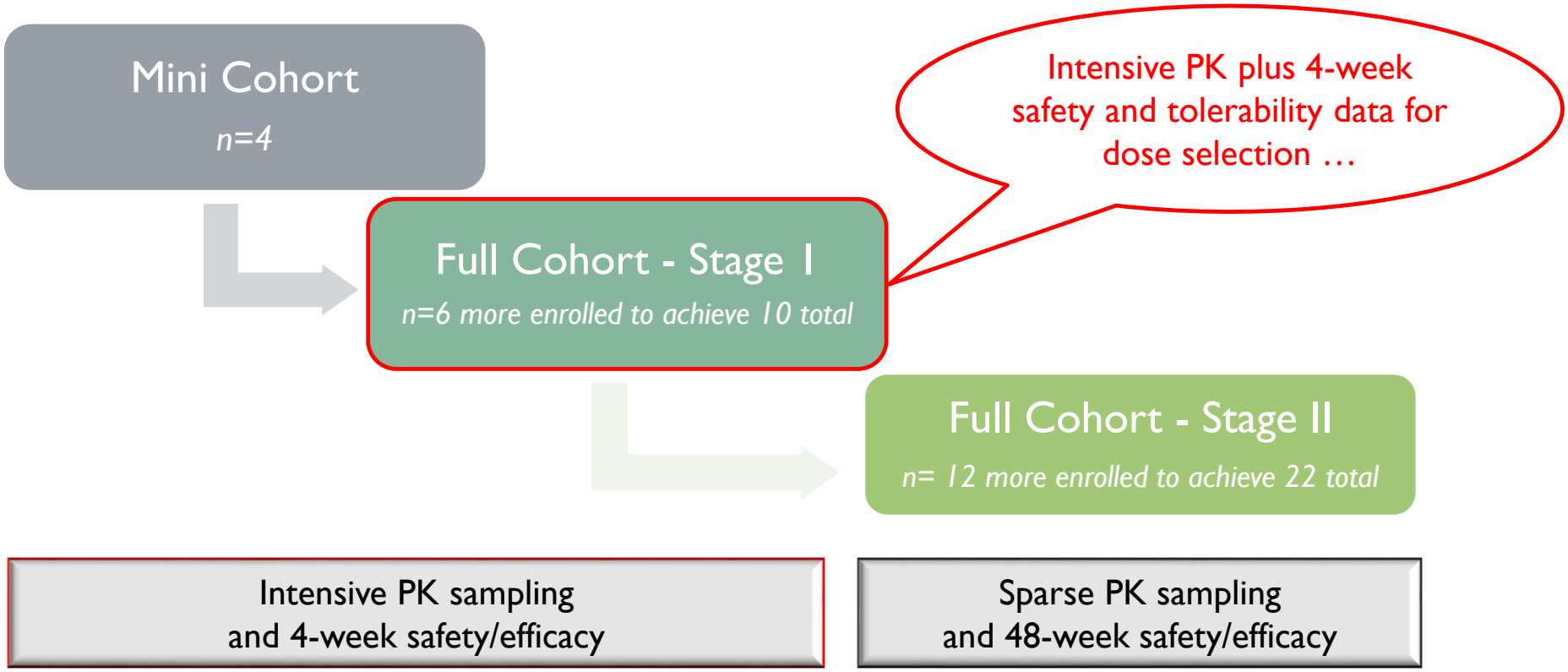
P1093 DESIGN – DOSE DETERMINATION BY AGE COHORTS



Cohort I:	Adolescents ≥12 to <18 years of age (Tablet formulation)
Cohort IIA:	Children ≥6 to <12 years of age (Tablet formulation)
Cohort IIB:	Children ≥6 to <12 years of age (Granules)
Cohort III - DT:	Children ≥2 to <6 years of age (Dispersible Tablet)
Cohort IV - DT:	Children ≥6 months to <2 years (Dispersible Tablet)
Cohort V - DT:	Infants ≥4 weeks to <6 months (Dispersible Tablet)

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METHODS – ENROLLMENT*

- Inclusion Criteria:
  - Within age range of cohort at time of entry
  - Antiretroviral Therapy (ART) Status:
    - ART-experienced and failing or off ART for ≥ 4 weeks
    - ART-naïve or have started ART < 4 weeks prior to entry (if < 2 years old)
  - HIV RNA > 1,000 copies/ml
- Exclusion Criteria:
  - Current or recent (< 4 weeks) co-morbidity or laboratory abnormality
  - Weight < 3 kg
  - Maternal or participant exposure to integrase inhibitor
  - No receipt of Nevirapine in14 days prior to enrollment (as PMTCT or treatment)

** Per Version 4.0 of the protocol*

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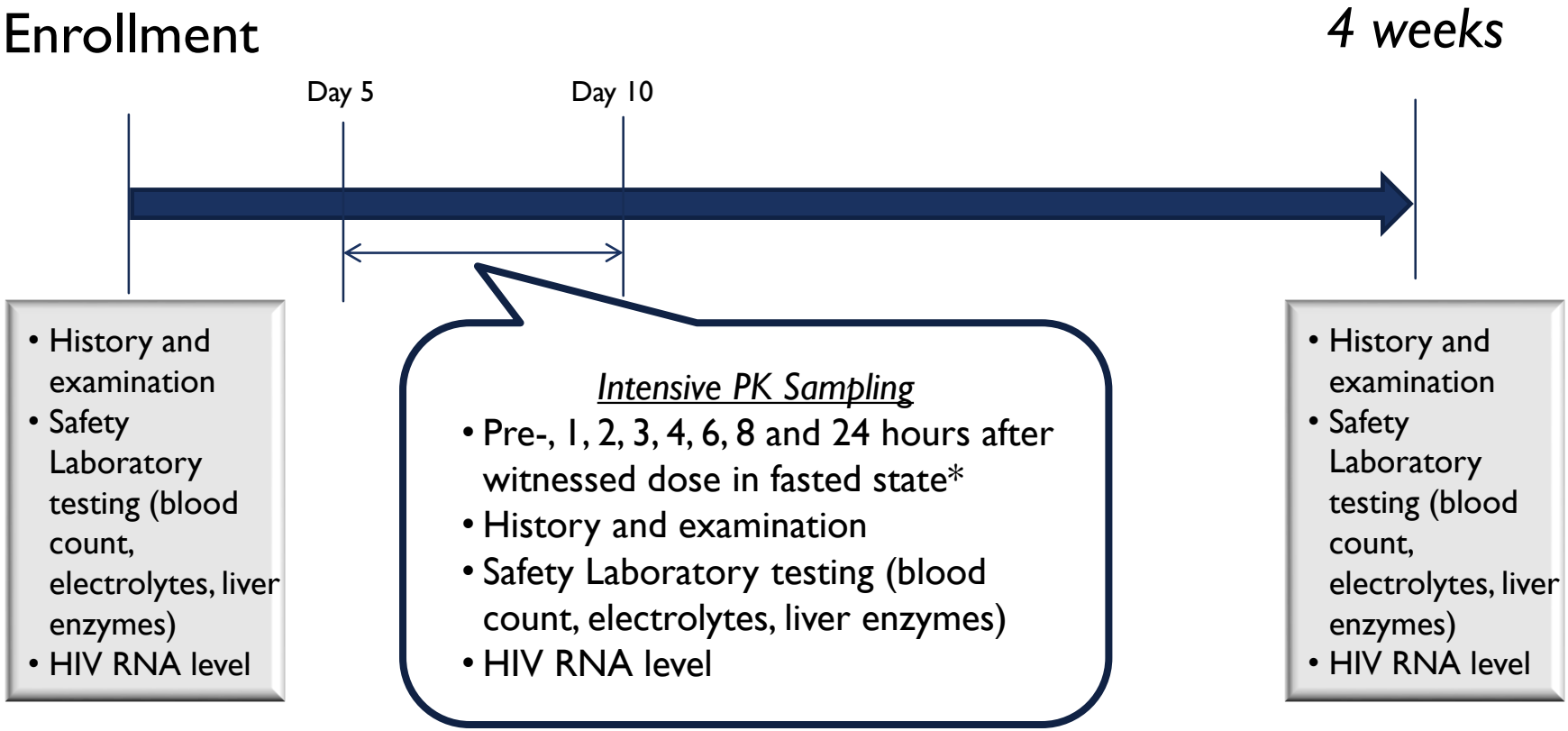
METHODS – STAGE I PK AND MONITORING



** Instructed to not ingest breastmilk, formula or other high fat food/liquid 2 hours prior and 1 hour after dosing.*

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PARTICIPANT CHARACTERISTICS

	Cohort V-DT (≥4 wk to <6 mo) (N=10)	Cohort IV-DT (≥6 mo to <2 yr) (N=10)	Cohort III-DT (≥2 yr to <6 yr) (N=10)	Total (N=30)*
Sex				
Female	4	6	3	13 (43%)
Baseline Plasma HIV RNA (copies/mL)				
400 to < 5,000	3	1	2	6 (20%)
5,000 to <10,000	1	1	1	3 (10%)
10,000 to <25,000	0	1	1	2 (7%)
25,000 to <50,000	0	2	1	3 (10%)
≥ 50,000	6	5	5	16 (53%)
Baseline CD4 Cell Count (cells/mm^3)				
≥500	10	10	10	30 (100%)
Baseline CD4 Percent				
≤14	0	1	2	3 (10%)
>14 to <25	5	5	1	11 (37%)
≥25	5	4	7	16 (53%)

Countries	
Botswana	3 (10%)
Brazil	1 (3%)
South Africa	7 (23%)
Tanzania	3 10%)
Thailand	2 (7%)
USA	2 (7%)
Zimbabwe	12 (40%

*Number (%) of participants in each subcategory; * 32 enrolled to achieve 30 evaluable.*

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INITIAL DTG-DT DOSING TABLE

Weight Band (kg)	Dose* (mg)	Dose (mg/kg) for Weight Range	
		Lower Weight	Upper Weight
3 to < 6	5	1.67	0.83
6 to <10	10	1.67	1.00
10 to <14	15	1.50	1.07
14 to <20	15	1.79	1.25
20 to <25	20	1.50	1.20

* Once daily

INTENSIVE PK RESULTS FOR DTG-DT

Cohort (n=10 each)~	Age (yrs)^	Dose (mg/kg)^	AUC_{24h}* (mg x h/L)	C_{24h}* (ng/mL)
≥4 weeks to <6 months *(Cohort V)*	0.34 (0.28-0.39)	1.2 (0.9-1.7)	61 (44%)	1,207 (55%)
≥6 months to <2 years *(Cohort IV)*	1.2 (0.9-1.9)	1.2 (1.0-1.4)	51 (38%)	711 (60%)
≥2 years to <6 years *(Cohort III)*	4.0 (2.1-5.9)	1.1 (0.8-1.6)	40 (36%)	461 (59%)

^ *Median (range);*

* *Geometric mean (arithmetic coefficient of variation %) of 24 hour area under the curve (AUC_{24h}) and trough (C_{24h}).*

Version 4.0 Target (range) for Geometric Mean:

AUC_{24h} : 46 (37-86) mg x h/L

C_{24h} : 750 (500-2260) ng/mL

Note: Dispersible Tablets (DT) are 5mg each.

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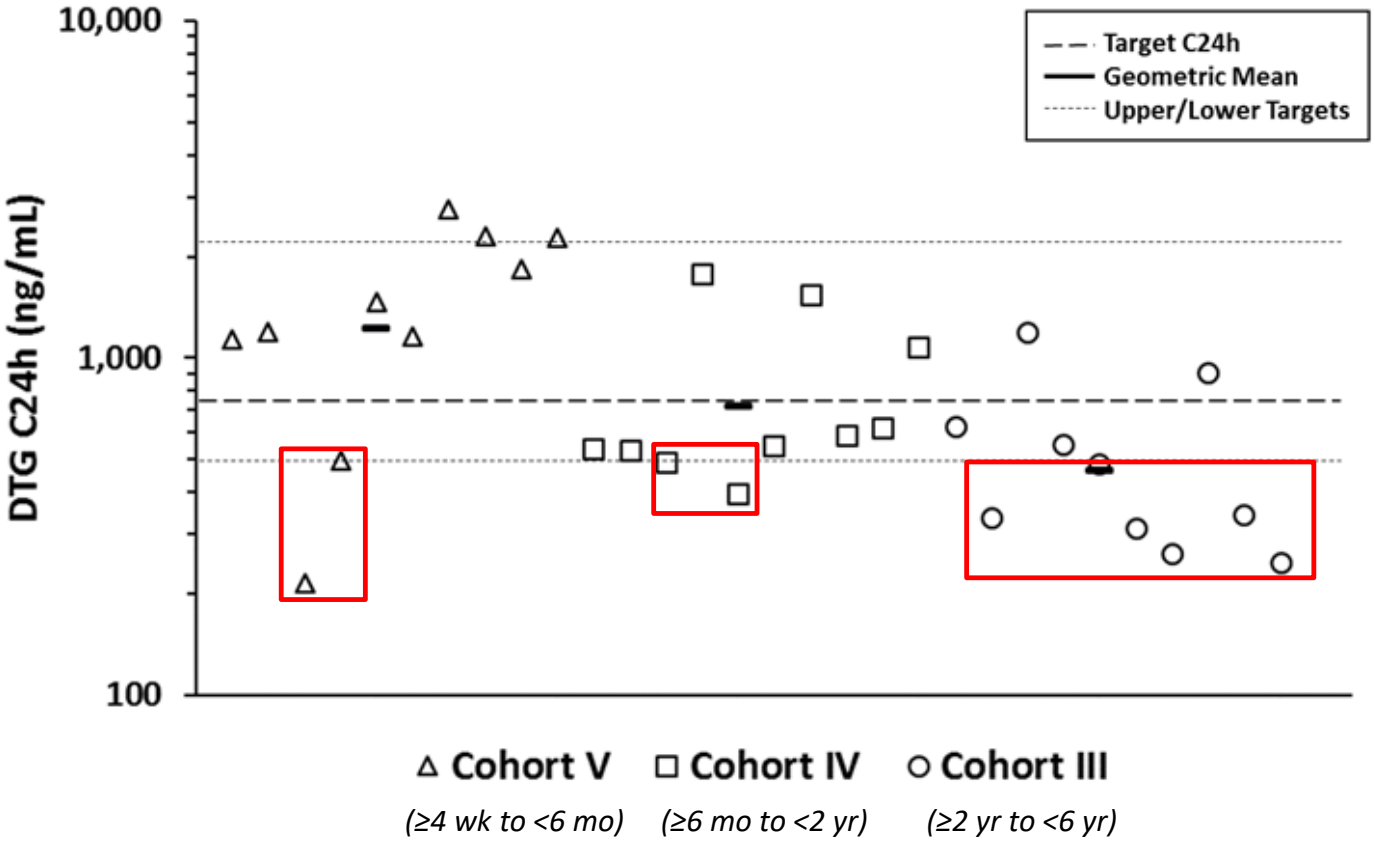
DTG DT : 24 HOUR TROUGH BY COHORT



Version 4.0 Target (range) for Geometric Mean:

C_{24h} : 750 (500-2260) ng/mL

Below target range (<500 ng/mL)

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4 WEEK SAFETY – GRADE 3/4 ADVERSE EVENTS

- No Grade 3 or 4 adverse events (AE) attributed to study drug
- No study drug discontinuations

Cohort	AE Grade~	Week	Description	Outcome/explanation
V-DT	3	I	Low Phosphate	Grade 2 at baseline, then resolved
IV-DT*	3	I	Low Bicarbonate	Grade 3 at baseline
IV-DT*	4	4	Low Absolute Neutrophil Count	253 c/mm^3 but normal 2 days later
III-DT	3	I	Elevated Systolic Blood Pressure	Hypertension noted at baseline, providers suggested anxiety
III-DT	3	I	Low Bicarbonate	Grade 2 at baseline

~ DAIDS AE Grading Table, Version 1.0, December 2004, Clarification August 2009
* Same participant

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FEASIBILITY, ACCEPTABILITY AND TOLERABILITY OF DTG DT

Cohort (N=10 participants in each cohort)	Problems with swirling, dispersing or drawing up?	Overall Taste Assessment?	Problems taking?
≥4 wk to <6 mo *(V)* *n=28 assessments*	Never: 28 "Infrequent/ sometimes": 0	Very good: 9 Fair/Pleasant: 18 Acceptable: 2 Very bad: 0	No: 28 Yes: 0
≥6 mo to <2 yr *(IV)* *n=32 assessments*	Never: 29 "Infrequent/ sometimes": 3	Very good: 7 Fair/Pleasant: 15 Acceptable: 8 Very bad: 2	No: 28 Yes: 4
≥2 yr to <6 yr *(III)* *n= 35 assessments*	Never: 34 "Infrequent/ sometimes": 1	Very good: 14 Good: 13 Average: 2 Very bad: 5	No: 33 Yes: 2

** Dispersible tablets were well-tolerated across all ages*

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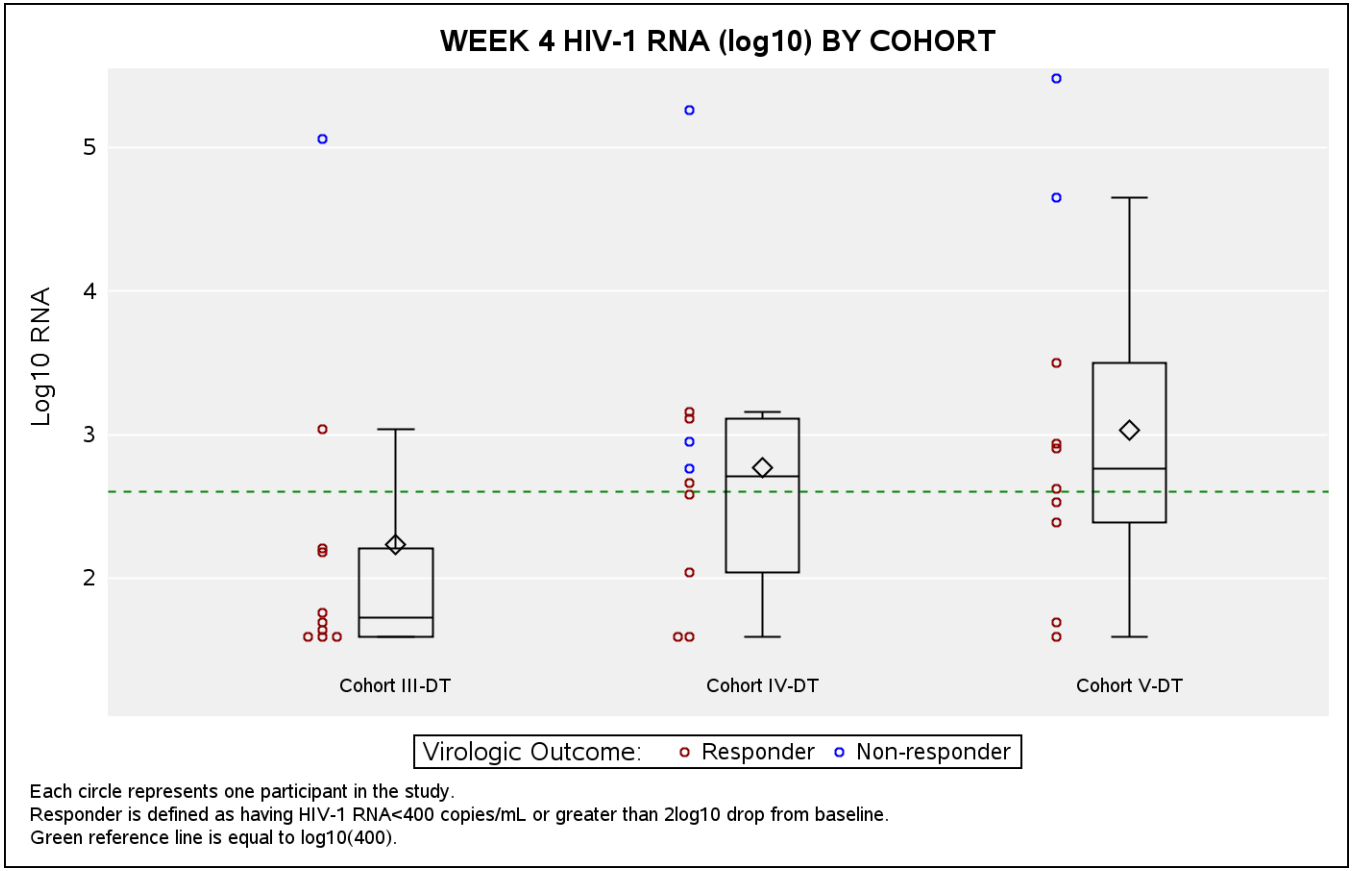
4 WEEK VIROLOGICAL OUTCOMES



Each circle represents one participant in the study.
Responder is defined as having HIV-1 RNA<400 copies/mL or greater than 2log10 drop from baseline.
Green reference line is equal to log10(400).

Diamond is mean, box is quartiles, whiskers are 1.5x interquartile range.

At 4 weeks, 24/30 (80%) attained HIV-1 RNA of <400 copies/ml or a >2 log_{10} decrease

Background Regimens*

ZDV/3TC	15
ABC/3TC	4
LPV/r + ZDV/3TC	6
LPV/r + ABC/3TC	3
LPV/r + D4T/3TC	1
LPV/r + 3TC	1
LPV/r + TDF	1

** Optimized to ensure ≥ genotype-documented active agent*

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KEY PK FINDINGS AND NEXT STEPS DTG DT FOR AGES 4 WEEKS TO 6 YEARS

- This dosing of DTG-DT resulted in geometric mean AUC_{24h} and C_{24h} generally within target ranges
- However children 6 mos to < 6 yrs of age demonstrated moderate inter-subject variability and some low individual C_{24h}
  - *Higher doses now under study for those ages*
- Next protocol version allows for additional enrollments to ensure data adequate for WHO weight-band and age-based dosing

CURRENT DTG-DT DOSING TABLE: P1093

Age	Weight Band (kg)	Dose (mg)	Dose Range (mg/kg)	
			low weight	high weight
≥ 4 weeks to < 6 months of age	3 to < 6	5	1.67	0.83
	6 to < 10	10	2.50	1.50
≥ 6 months of age	3 to < 6	10	3.33	1.67
	6 to < 10	15	2.50	1.50
	10 to < 14	20	2.00	1.43
	14 to < 20	25	1.79	1.25
	≥ 20	30	1.50	

** Due to greater bioavailability, the 30mg dispersible tablet is approximately equivalent to the 50mg film-coated tablets.*

CONCLUSIONS: DTG DT FOR AGES 4 WEEKS TO 6 YEARS IN P1093

- Drug Exposures similar to adults can be achieved with the dispersible tablet formulation of dolutegravir in children aged 4 weeks to 6 years.
- The dispersible tablet formulation was well tolerated and easily administered by participants and their families
- Week 4 virologic outcomes suggest that DTG-DT plus standard background regimens will provide safe and potent treatment for children with HIV

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- P1093 Protocol Team
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