



## **DoIPHIN-1 : Randomised controlled trial of dolutegravir (DTG)- versus efavirenz (EFV)-based therapy in mothers initiating antiretroviral treatment in late pregnancy**

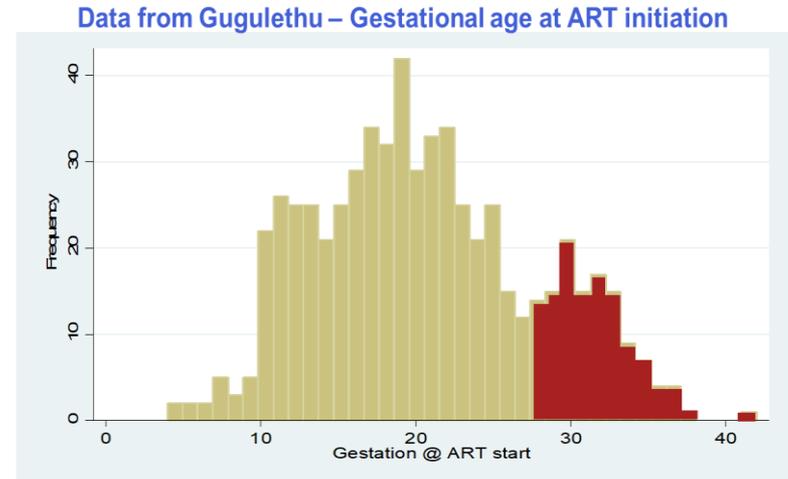
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on behalf of the DoIPHIN-1 Study Group

*\*\* Research funding and drug donation for DoIPHIN-1 was provided by ViiV Healthcare*



# Background

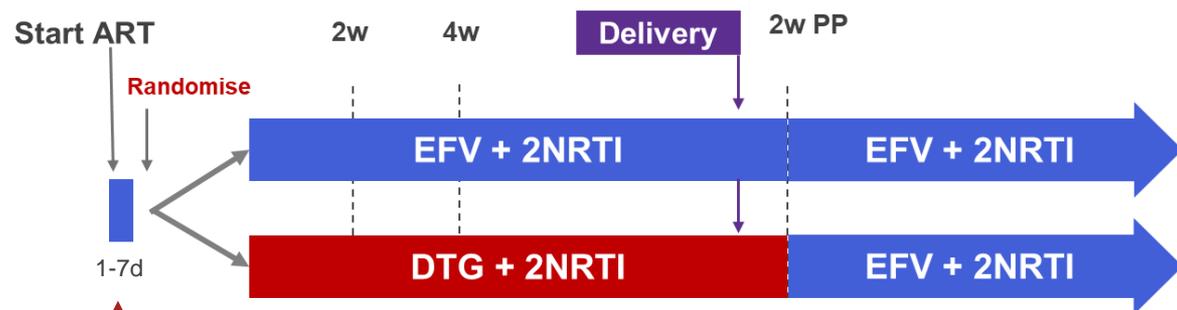
- Around **1.5M HIV+ women become pregnant each year**
- **Effective and timely ART has averted 1.6M infant infections**
- In S Africa, around a **fifth of HIV+ pregnant women initiate ART late, in 3<sup>rd</sup> trimester (T3)**
- Late initiation associated with **7-fold increased risk of MTCT**, and **doubling of infant mortality** in first year



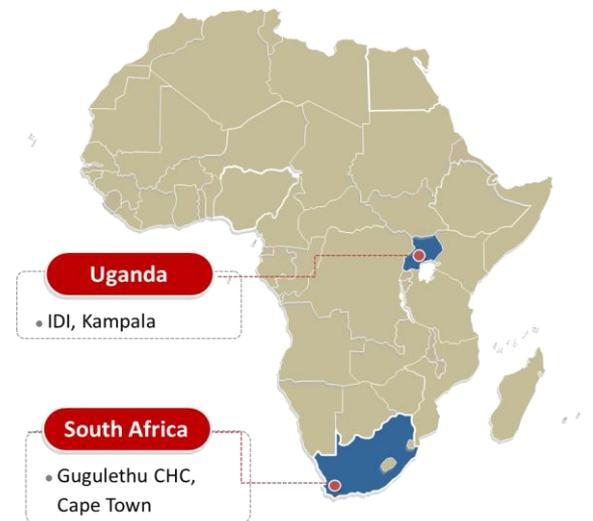
## Hypothesis:

Faster VL declines with DTG may reduce MTCT at birth & during breastfeeding (BF) in HIV+ mothers initiating ART in T3

# DolPHIN-1: Dolutegravir in Pregnant HIV mothers and their Neonates NCT02245022

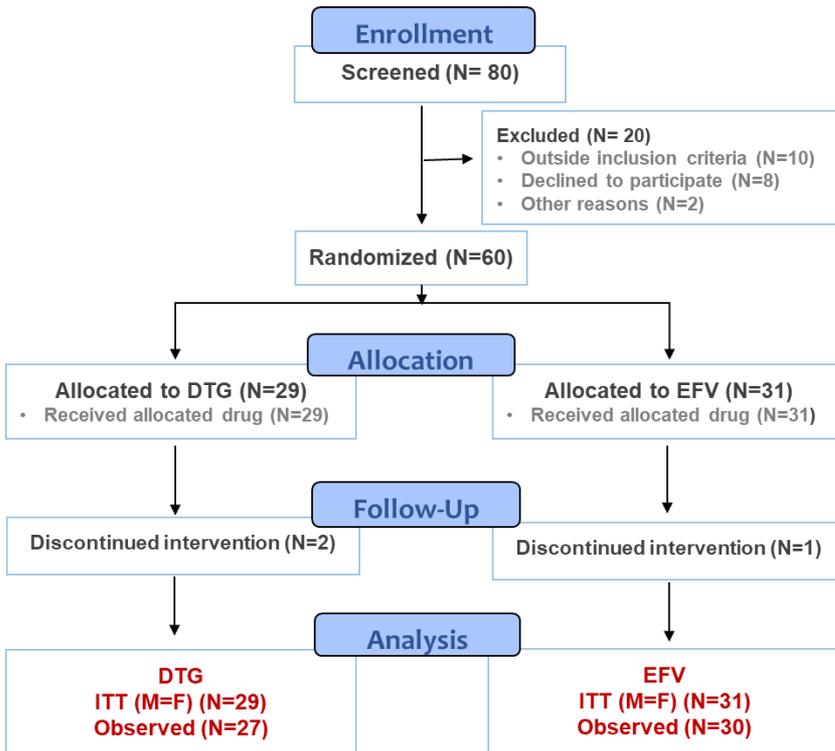


*To comply with guidelines, all subjects start EFV pending randomisation*



- **HIV+ pregnant mums initiating ART in T3 (28-36w gestation)**  
≥18y, no ARVs in preceding 6m (no previous INSTIs), no depression, Hb ≥ 8g/dL, eGFR ≥ 50, ALT ≤ 5xULN, no active HBV
- **Randomised 1:1 to receive DTG vs EFV until 2w PP**  
plus TDF/3TC (Uganda) or TDF/FTC (S Africa). DTG (50mg/d), EFV (600mg/d)
- **Primary endpoint: maternal PK of DTG**
- **Secondary endpoints:** plasma VL <50 copies (or undetectable) at PP visit (0-2w PP), safety and tolerability, PK in cord blood and BM

# DoIPHIN-1 Enrolment & Baseline Demographics

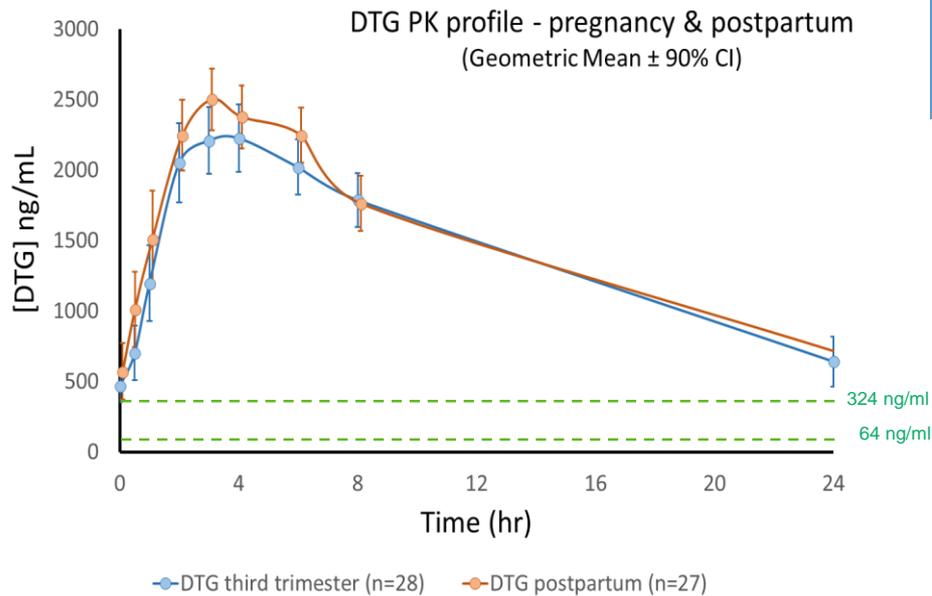


Baseline median (range)	DTG (n=29)	EFV (n=31)	Total (n=60)
Age (y)	27 (19-42)	25 (19-35)	26 (19-42)
Weight (kg)	68 (45-103)	65 (48-119)	66 (45-119)
BMI (kg/m <sup>2</sup> )	26 (19-40)	25 (21-46)	26 (19-46)
Est gestation (w)	31 (27-35)	30 (27-36)	31 (27-36)
HIV VL log <sub>10</sub> copies	4 (2-5)	4 (3-6)	4 (2-6)
CD4 (cells/mm <sup>3</sup> )	343 (41-712)	466 (32-932)	394 (32-932)
HBsAg +ve *	0	2 (6.5%)	2 (3.3%)
Herbal/traditional medicines	5 (17.2%)	8 (25.8%)	13 (21.7%)

\* missing data DTG (2) EFV (1)

- 60 HIV+ mothers enrolled : DTG (29), EFV (31)
- Equally split across both study sites
- Median gestation 31w
- No difference in baseline VL, CD4, previous obstetric history, gestation, BMI
- High use of traditional medicines noted

# Results – Maternal Plasma PK (T3 versus PP)

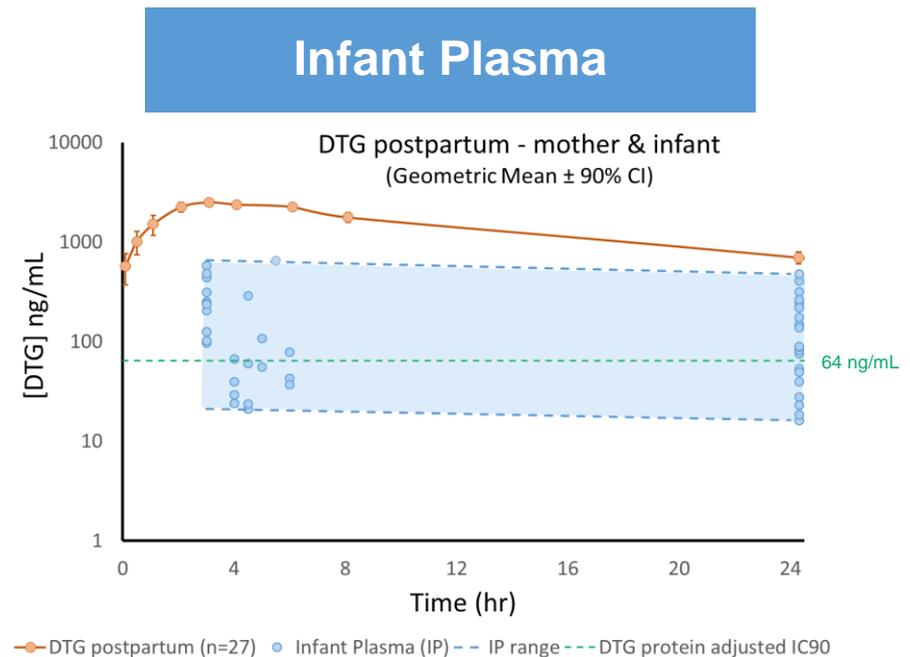
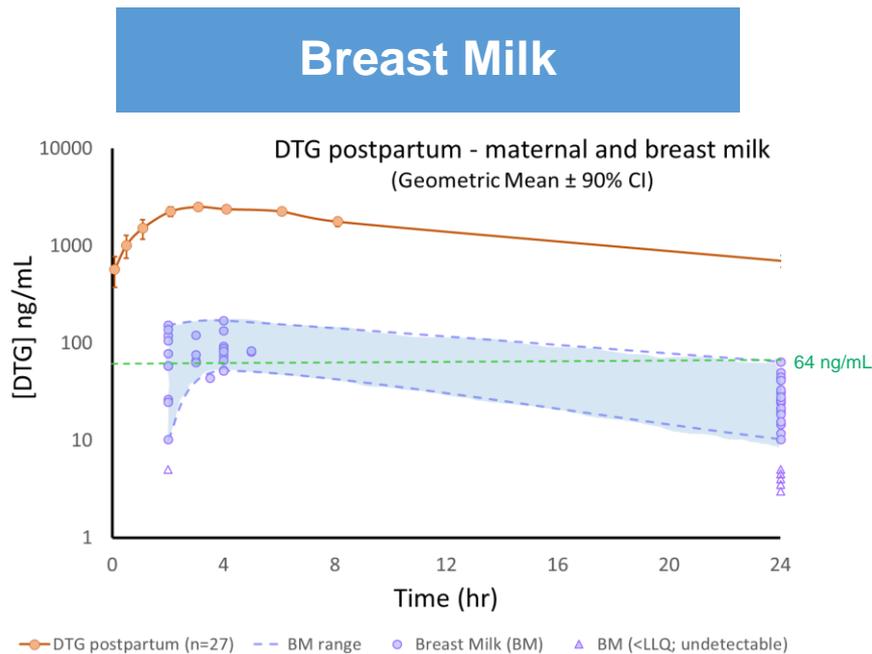


	DTG ng/mL (range)		
	T3 * (n=28)	PP * (n=27)	GMR (90%CI)
$AUC_{0-24h}$ (ng*h/mL)	35,322 (19,196 – 67,922)	37,575 (14,933 – 59,633)	0.95 (0.74 – 1.23)
$C_{max}$ (ng/mL)	2,435 (1,462 – 3,986)	2,843 (1,398 – 4,224)	0.91 (0.82 – 1.01)
$C_{trough}$ (ng/mL)	642 (188 – 3,088)	696 (204 – 1,443)	0.93 (0.76 – 1.14)
DTG $\leq$ MEC (324ng/mL)	9/28 (32%)	6/27 (22%)	

\* 1 subject with undetectable levels throughout excluded

- Rich PK sampling in T3 and PP
- PP sampling (2-18d; median 8d) does not reflect return to normal physiology; exposures not significantly different from T3
- All but one [DTG] above 64 ng/mL (PA-IC<sub>90</sub>)
- In T3, 9/28 (32%) of [DTG] at or below 324 ng/mL (MEC)
- Cord:maternal blood ratio = 1.21 (0.51 – 2.11) [median (range)]

# Results – PK in Breast Milk and Breastfeeding Infants



## Breast milk

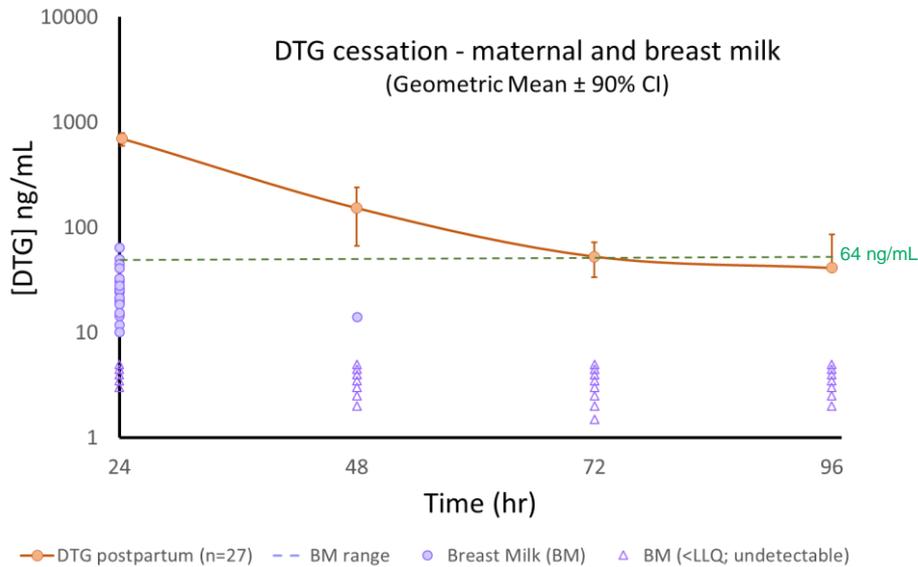
- sampled at maternal plasma  $C_{max}$  and  $C_{trough}$
- Geometric mean  $BM_{max}$  70 (58 – 83) ng/mL;  $BM_{trough}$  24 (19 – 29) ng/mL
- $BM:MP$  at  $C_{max}$  and  $C_{trough}$  = 0.03 (3%)

## Infant plasma

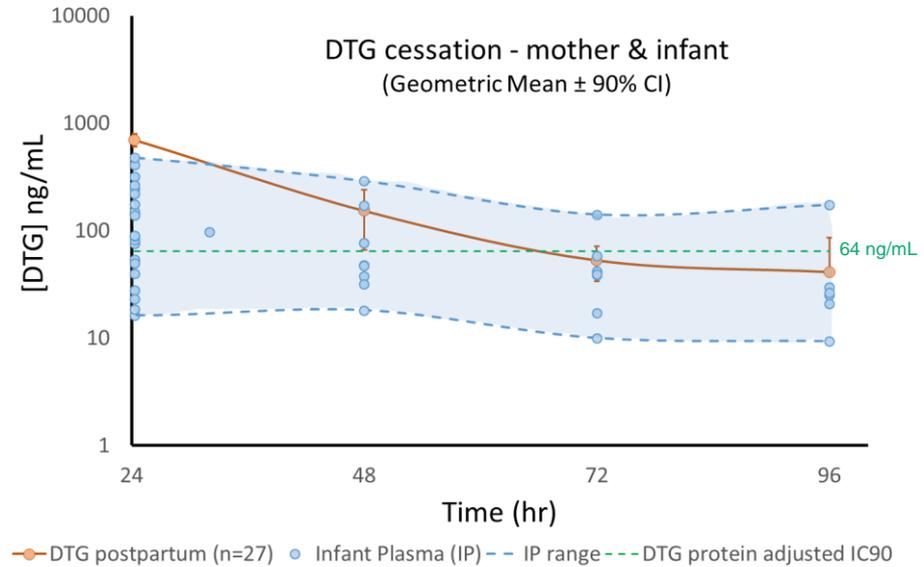
- sampled at maternal plasma  $C_{trough}$ ; feed mandated at  $C_{max}$  and infant sampling 1h later
- Geometric mean  $IP_{max}$  111 (50 – 172) ng/mL;  $IP_{trough}$  87 (47 – 127) ng/mL
- $IP:MP_{max}$  = 0.05 (0.02 – 0.07) ;  $IP:MP_{trough}$  = 0.12 (0 – 0.26)

# Results : DTG Washout following Cessation

## MP vs Breast Milk



## MP vs Infant Plasma



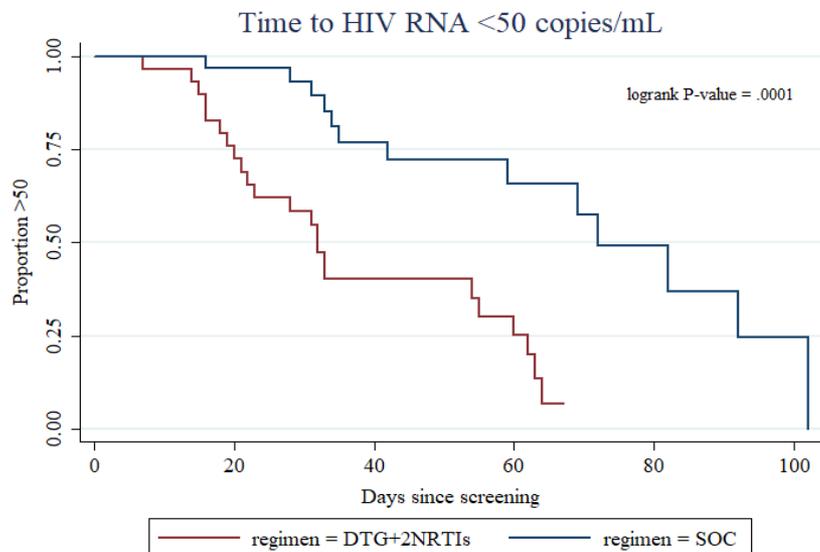
## Breast milk

- Rapid washout following DTG cessation

## Infant plasma

- Slow washout of DTG in infants following cessation of DTG in mother
- Likely reflects accumulation from BF (+/- residual transplacental accumulation) due to decreased glucuronidation in the neonate

# Results – Viral load at Post-partum Visit



ITT (M=F)	DTG (N = 29)	EFV (N = 31)	P value **
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## HIV-1 RNA level at PP visit

<50 copies/mL *	<b>20 (69.0%)</b>	<b>12 (38.7%)</b>	<b>0.02</b>
≥50 copies/mL	9 (31%)	19 (61.3%)	

\* <50 copies/mL or UD (Roche Ampliprep Cobas Taqman HIV-1 2.0)

\*\* Pearson Chi-squared

Includes individuals missing or discontinued by visit

- By ITT, significantly greater proportion of DTG subjects achieved virological suppression at PP (2w) visit
- Median time to HIV-1 RNA <50 copies was approximately halved with DTG compared to EFV
- 1 mother in the DTG arm had UD DTG concentrations, with no VL response; another with [DTG] < 64 ng/mL experienced virological rebound (3 class drug resistance from baseline sample)

NRTI: M41L, L210W, T215Y, M184V

NNRTI: Y188L

PI: M46I, I84V, I54V, V32I, V82A, L33F, K43T

## Safety – Maternal outcomes

	DTG (N = 29)	EFV (N = 31)	Total (N = 60)
Given birth	29 (100.0%)	31 (100.0%)	60 (100.0%)
Mode of delivery, N (%)			
Normal	25 (86.2%)	21 (67.7%)	46 (76.7%)
C-section	4 (13.8%)	10 (32.3%)	14 (23.3%)
Experiencing at least 1 adverse event Grade $\geq$ 3	2 (6.9%)	0	2 (3.3%)
Experiencing at least 1 serious adverse event	2 (6.9%) <sup>§</sup>	1 (3.2%)*	3 (5.0%)

Maternal AEs and SAEs since starting ART (i.e. includes initial EFV-based ART in mothers subsequently randomised to DTG)

<sup>§</sup> 1 case of Haemoglobin decreased (not related);

1 case with Malaria + Urinary tract infection (possibly related), Stillbirth (not related), and ALT+ bilirubin increased + Hypokalaemia + Hyponatraemia (possibly related)

\* 1 case of Hypertension + Pre-eclampsia (unlikely related)

# Safety – Infant outcomes

	DTG (N = 29)	EFV (N = 31)	Total (N = 60)
<b>Outcome of delivery</b>			
Normal healthy baby	28 (96.6%)	29 (93.5%)	57 (95.0%)
Stillbirth <sup>§</sup>	1 (3.4%)	-	1 (1.7%)
Congenital malformation	-	2 (6.5%)	2 (3.3%)
<i>of which syndactyly</i> <sup>§</sup>	-	1 (3.2%)	1 (1.7%)
<i>Multiple</i> <sup>*</sup>	-	1 (3.2%)	1 (1.7%)
<b>Gestation age at birth, weeks</b>			
median (range)	39 (35-43)	38 (34-42)	38 (34-43)
<b>Length of baby, cm</b>			
median (range)	51 (44-58)	50 (33-55)	50 (33-58)
<b>Weight of baby, kg</b>			
median (range)	3 (2-4)	3 (2-4)	3 (2-4)
<b>Experiencing at least 1 serious adverse event</b>	-	3 (9.7%) <sup>†</sup>	3 (5.0%)

<sup>§</sup> Not related

<sup>\*</sup> Not related.

**Multiple skeletal and limb defects** (talipes, multiplex arthrogyposis, developmental hip dysplasia, limb hyperextension)

**Cardiac defects** (Atrial septal defect, Persistent left superior vena cava) + cleft palate, hyporeflexia (? Larsen or TARP syndrome)

Note: The infant was also pre-term/small for gestational age, and had congenital syphilis.

<sup>†</sup> 2 cases with congenital malformations and 1 case of neonatal sepsis (not related)

## **DolPHIN-1 Conclusions**

- In this pilot study, a significantly greater proportion of mothers initiating ART late in pregnancy achieved HIV-1 RNA <50 copies/mL with DTG- compared to EFV- based regimens
- DTG exposures in T3 were relatively low. *In-utero* accumulation of DTG was high (121%).
- Breast milk accumulation of DTG was 3% with higher exposures in breastfed infants, likely due to reduced drug clearance
- Upon cessation, DTG was rapidly eliminated from breast milk; however infant washout was prolonged.
- Safety of DTG and EFV was comparable; however evaluation is limited by small sample size, relatively short follow-up and by prior EFV use in all DTG mothers initiating ART
- DolPHIN-2 (NCT03249181) is a randomised comparison of DTG vs EFV initiation in third trimester (28w – labour; N = 250).

# Acknowledgements

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