



# Infant Exposure to Dolutegravir Through Placental and Breastmilk Transfer: A Population PK Analysis of DolPHIN-1

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on behalf of the DolPHIN-1 Study Group

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# Background

- Approximately 1.5 million HIV-infected women worldwide become pregnant each year
- Risk of mother-to-child transmission (MTCT) of HIV is particularly high when untreated women enter care later in pregnancy ( $\geq 28$  weeks)
- Safe and effective treatment that can quickly reduce viral load is paramount to prevent peripartum transmission
- Use of dolutegravir (DTG) late in pregnancy may provide a suitable alternative to efavirenz (EFV)-based standard of care (SoC):
  - *rapid reduction of viral load*
  - *high genetic barrier to resistance*
  - *good tolerability*

# Background

- Physiological changes induced during pregnancy may influence drug PK

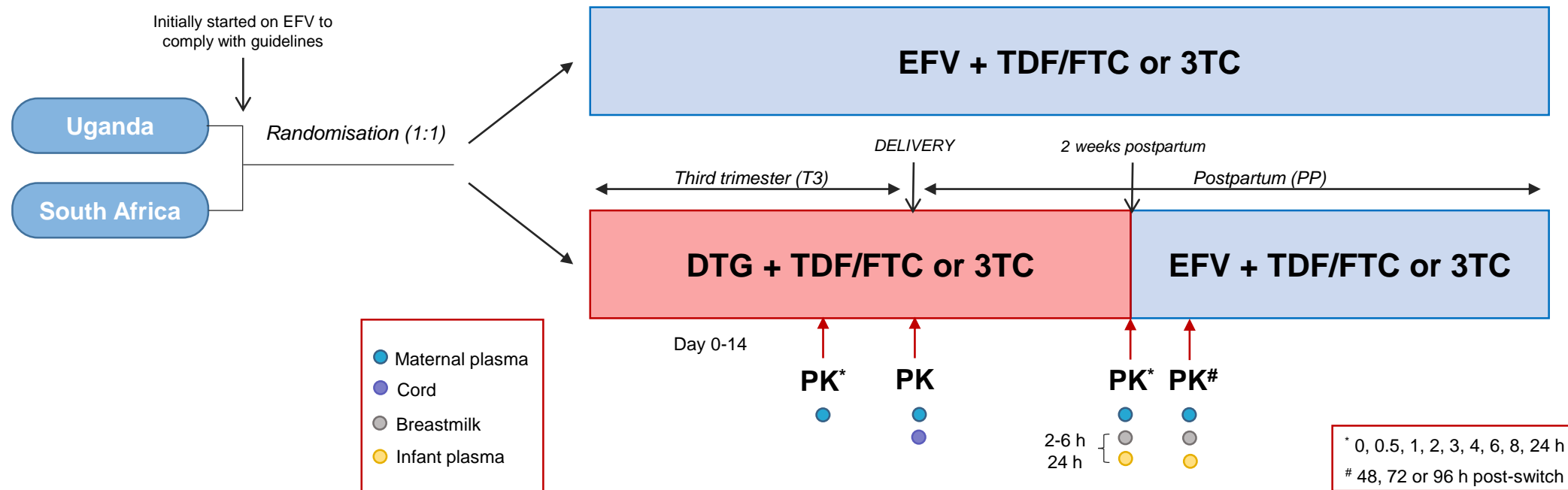
DTG Parameter	IMPAACT P1026s <sup>1</sup> [n=22 paired; 10 (6-32) weeks PP]		PANNA <sup>2</sup> [n=5 paired; 6 (3-7) weeks PP]	
	<i>GMR (90% CI), T3/PP</i>	<i>P value</i>	<i>GMR (90% CI), T3/PP</i>	<i>P value</i>
AUC <sub>0-24</sub>	0.71 (0.63-0.81)	0.0003	0.95 (0.60-1.48)	-
C <sub>max</sub>	0.75 (0.64-0.88)	0.0025	1.07 (0.78-1.47)	-
C <sub>24</sub>	0.66 (0.52-0.84)	0.0062	0.66 (0.32-1.26)	-

- Transplacental (and breastmilk) passage of drug has the potential to provide prophylactic coverage to the infant

DTG Parameter	IMPAACT P1026s <sup>1</sup>		PANNA	
	<i>Median (IQR)</i>	<i>n</i>	<i>Median (IQR)</i>	<i>n</i>
Cord:plasma	1.25 (1.07-1.40)	18	1.40 (0.35-1.60) <sup>2</sup>	5
Breastmilk:plasma	-	-	0.02 <sup>3</sup>	1

# Methods: Study Design & PK Sampling

**DoIPHIN-1** (Do)lutegravir in P(renant) HIV mothers and their N(eonates; NCT02245022) investigated the PK and PD of DTG in pregnant women and their infants presenting with untreated HIV late in pregnancy (28-36 weeks gestation) In comparison to EFV-based SoC the DTG-based regimen was significantly more likely to achieve maternal viral load <50 copies/mL by day 14 of treatment <sup>1</sup>



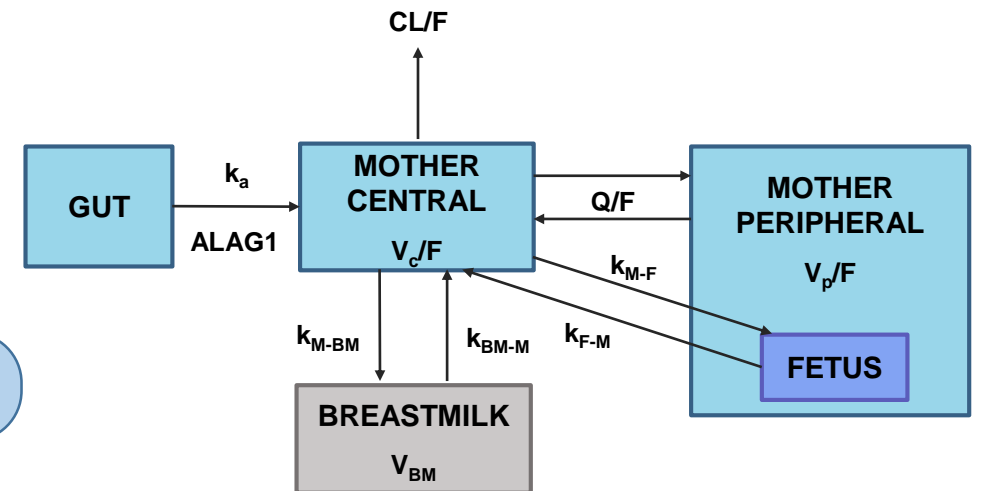
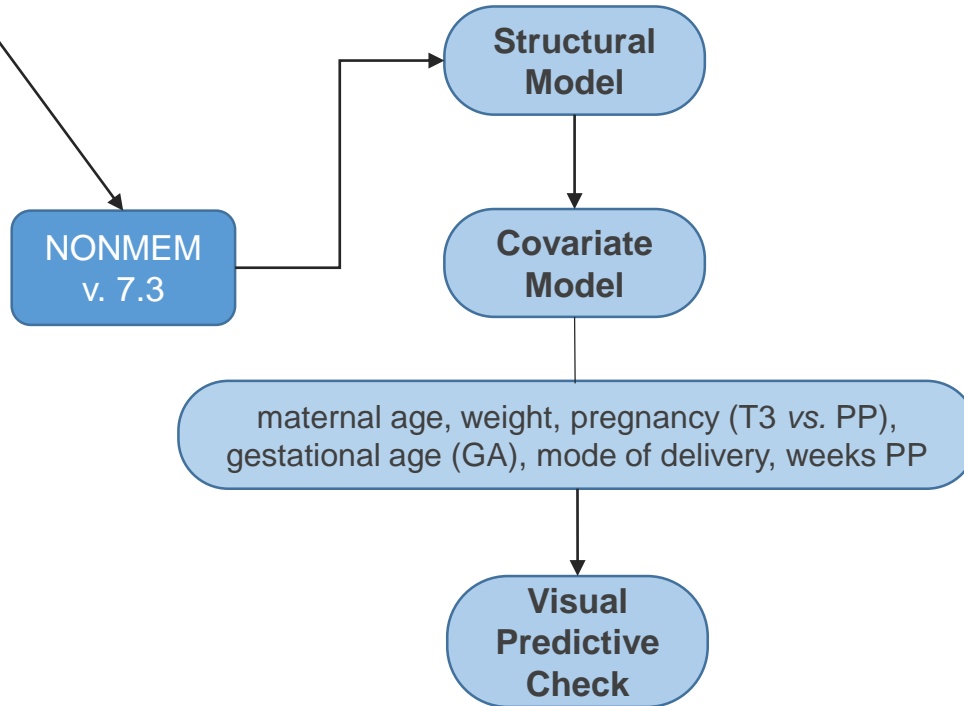
## OBJECTIVES:

1. Develop a population PK model to describe DTG in maternal plasma (ante & postpartum), umbilical cord, breastmilk and in breastfeeding infants following DTG cessation and evaluate potential covariate effects
2. Estimate time to DTG protein adjusted (PA) IC<sub>90</sub> (0.064 mg/L) in breastfed infants

# Methods: Population PK Modelling

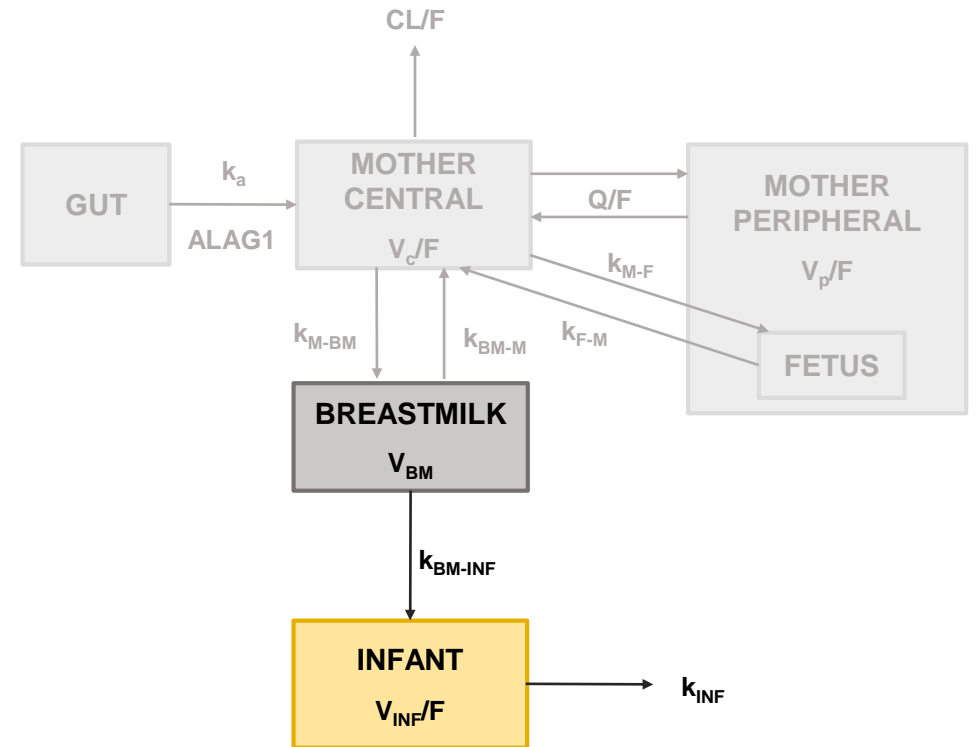
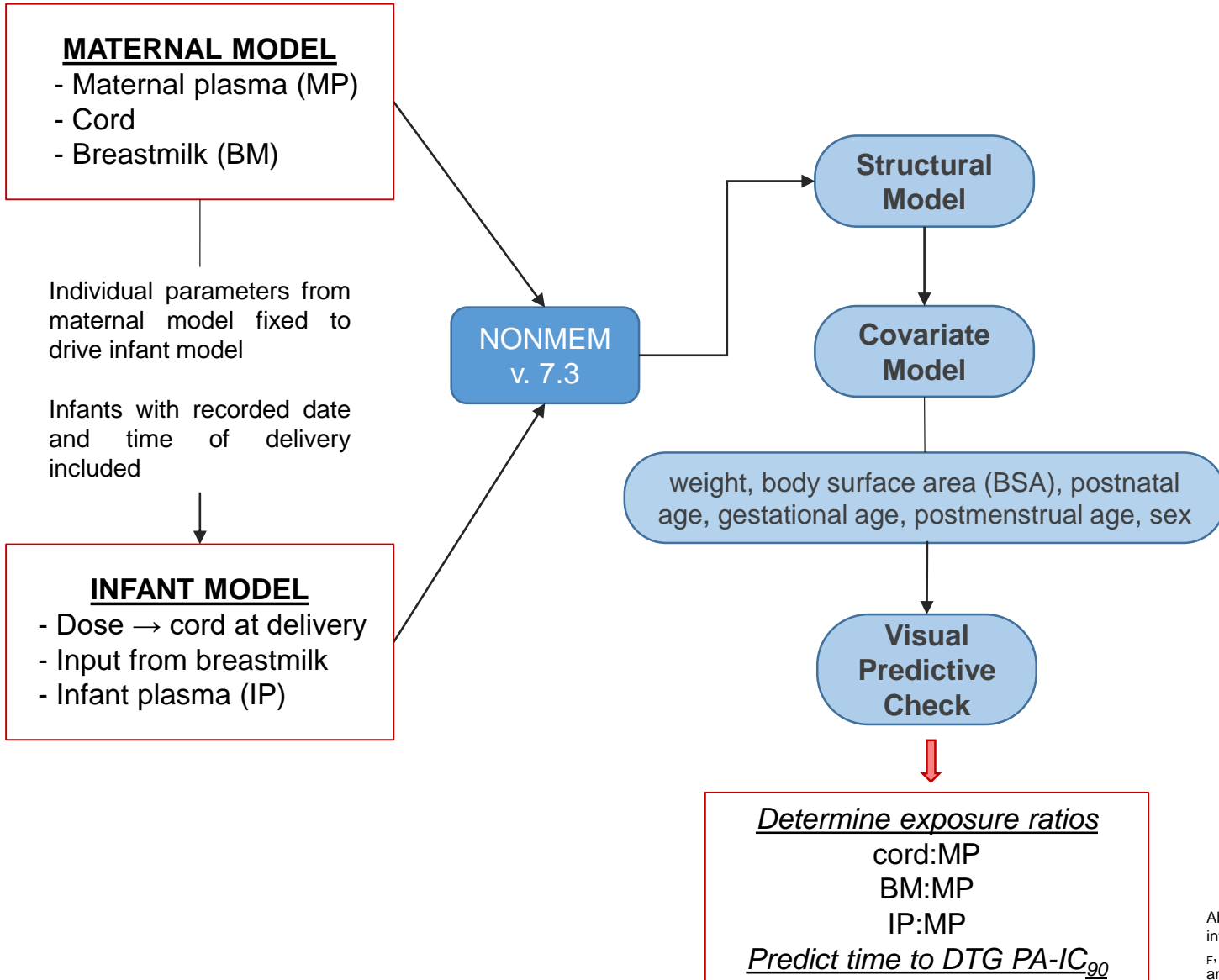
## MATERNAL MODEL

- Maternal plasma (MP)
- Cord
- Breastmilk (BM)



Abbreviations:  $k_a$ : absorption rate constant; ALAG1: absorption lag time; CL/F, Q/F: maternal apparent oral and intercompartmental clearance;  $V_c/F$ ,  $V_p/F$ : maternal apparent volume of distribution of the central and peripheral compartments;  $k_{M-F}$ ,  $k_{F-M}$ : mother-to-fetus and fetus-to-mother transfer rate constants;  $k_{M-BM}$ ,  $k_{BM-M}$ : mother-to-breastmilk and breastmilk-to-mother transfer rate constants

# Methods: Population PK Modelling



Abbreviations:  $k_a$ : absorption rate constant; ALAG1: absorption lag time;  $CL/F$ ,  $Q/F$ : maternal apparent oral and intercompartmental clearance;  $V_c/F$ ,  $V_p/F$ : maternal apparent volume of distribution of the central and peripheral compartments;  $k_{M-F}$ ,  $k_{F-M}$ : mother-to-fetus and fetus-to-mother transfer rate constants;  $k_{M-BM}$ ,  $k_{BM-M}$ ,  $k_{BM-INF}$ : mother-to-breastmilk, breastmilk-to-mother and breastmilk-to-infant transfer rate constants;  $V_{INF}/F$ : infant apparent volume of distribution;  $k_{INF}$ : infant elimination rate constant

# Results: Demographics

## MOTHERS

Parameter	Median (range)*
n total	28
n paired T3/PP	27
Study site [n (%)]	
Uganda	14 (50)
South Africa	14 (50)
Age (years)	27 (19-42)
Weight (kg)	67 (44-160)
Gestational age (wks)	39 (35-43)
Mode of delivery [n (%)]	
vaginal	23 (82)
C-section	3 (11)
missing	2 (7)
PP sampling (days)	7 (2-18)
PP sampling [n (%)]	
within wk 1 PP	15 (56)
within wk 2 PP	9 (33)
within wk 3 PP	3 (11)

## INFANTS

Parameter	Median (range)*
n	22
Sex [n (%)]	
boys	17 (77)
girls	5 (23)
Study site [n (%)]	
Uganda	10 (45)
South Africa	12 (55)
Weight (kg)	3.3 (2.5-4.3)
Postnatal age (days)	7 (3-18)
Gestational age (wks)	39 (35-43)
Postmenstrual age (wks)	40.1 (36.0-43.6)
BSA (m <sup>2</sup> )	0.22 (0.18-0.25)
Simulated DTG dose	
in mg	39.9 (15.5-59.0)
in mg/kg	12.5 (5.0-19.6)

\* Unless stated otherwise

# Results: Population PK Models

## MATERNAL MODEL <sup>1</sup>

- Maternal DTG CL/F *greater* than that reported for treatment-naïve, HIV-infected patients: 1.57 vs. 0.90 L/h<sup>2</sup>
- *No significant difference* in DTG CL/F between T3 and 1-3 weeks PP
- None of the covariates investigated were significant for plasma
- Interindividual variability (IIV) could not be estimated for cord and BM transfer rate constants, therefore covariate effects could not be assessed

## INFANT MODEL

Parameter	Estimate (RSE%)
<i>Fixed effects</i>	
$k_{\text{BM-INF}}$ (h <sup>-1</sup> )	2.5 (8)
$k_{\text{INF}}$ (h <sup>-1</sup> )	0.016 (6%)
$V_{\text{INF}}/F$ (L)	24.9 (11%)
<i>Random Effects</i>	
IIV $k_{\text{INF}}$ (%)	44.4 (67)
Residual error (%)	33.9 (40)

$k_{\text{BM-INF}}$ : breastmilk to infant transfer rate constant;  $k_{\text{INF}}$ : infant elimination rate constant;  
 $V_{\text{INF}}/F$ : infant apparent volume of distribution  
RSE% =  $SE_{\text{estimate}}/\text{estimate} * 100$

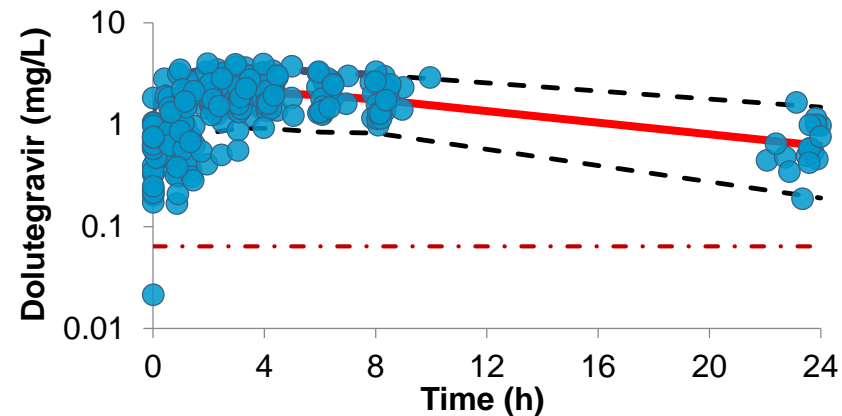
*No significant covariate effects*

Median (range) predicted infant half-life (n=21)  
**38.2 h (23.0-64.1)**

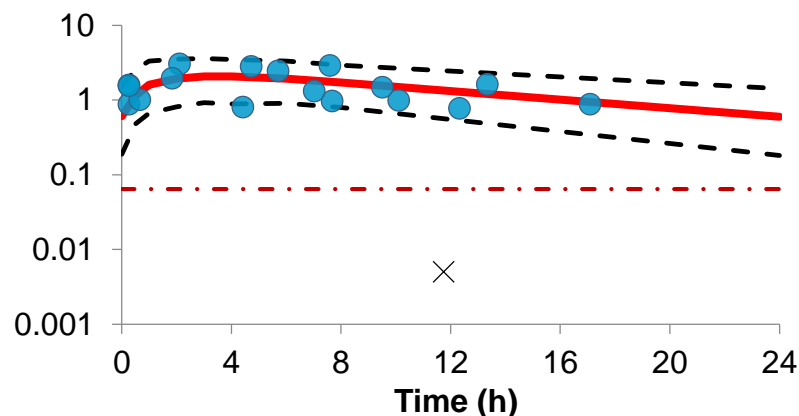


# Results: Population PK Models

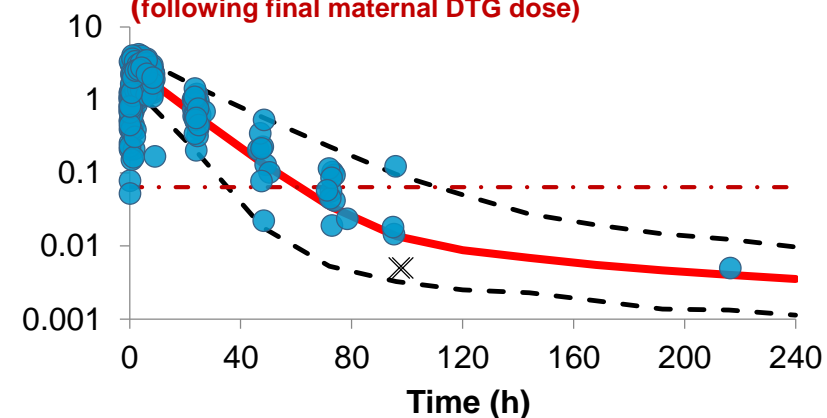
**MATERNAL PLASMA T3; n=250 samples**



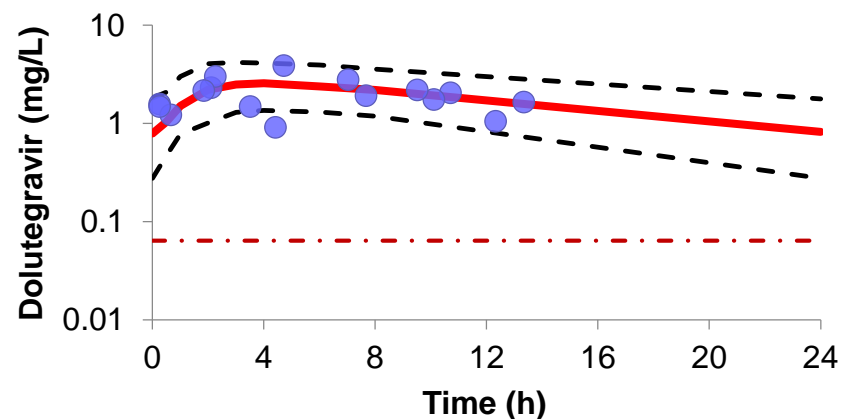
**MATERNAL PLASMA DELIVERY; n=18 samples**



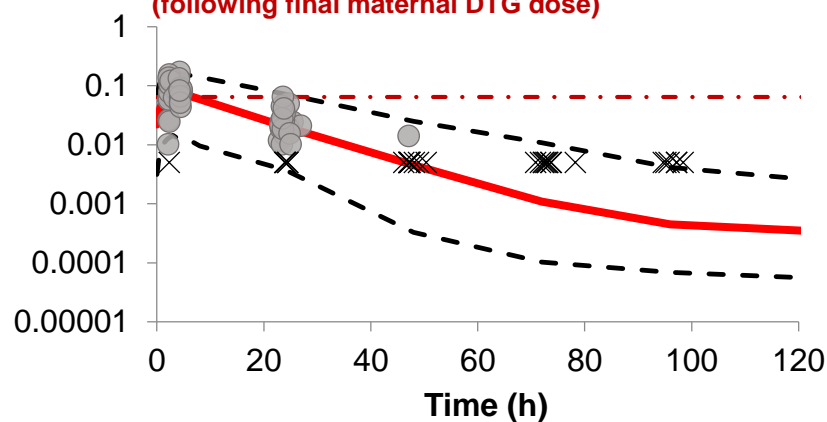
**MATERNAL PLASMA PP; n=265 samples (following final maternal DTG dose)**



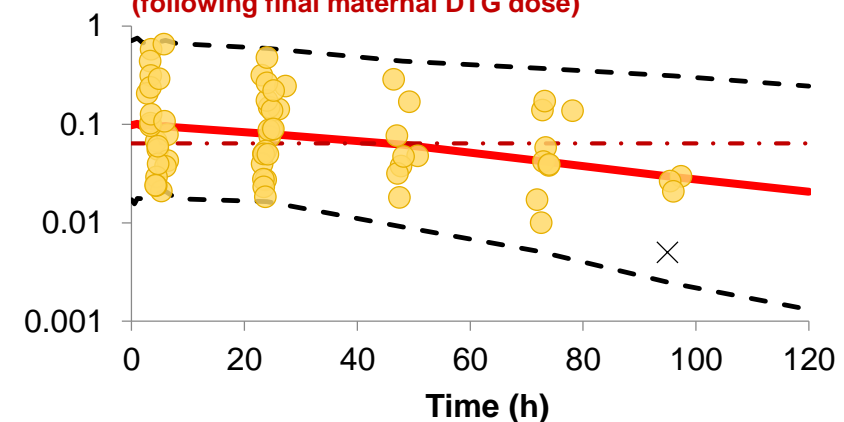
**CORD; n=16 samples**



**BREASTMILK; n=80 samples (following final maternal DTG dose)**



**INFANT PLASMA; n=65 samples (following final maternal DTG dose)**



P5    
  P50    
  P95  
 PA-IC<sub>90</sub>; 0.064 mg/L

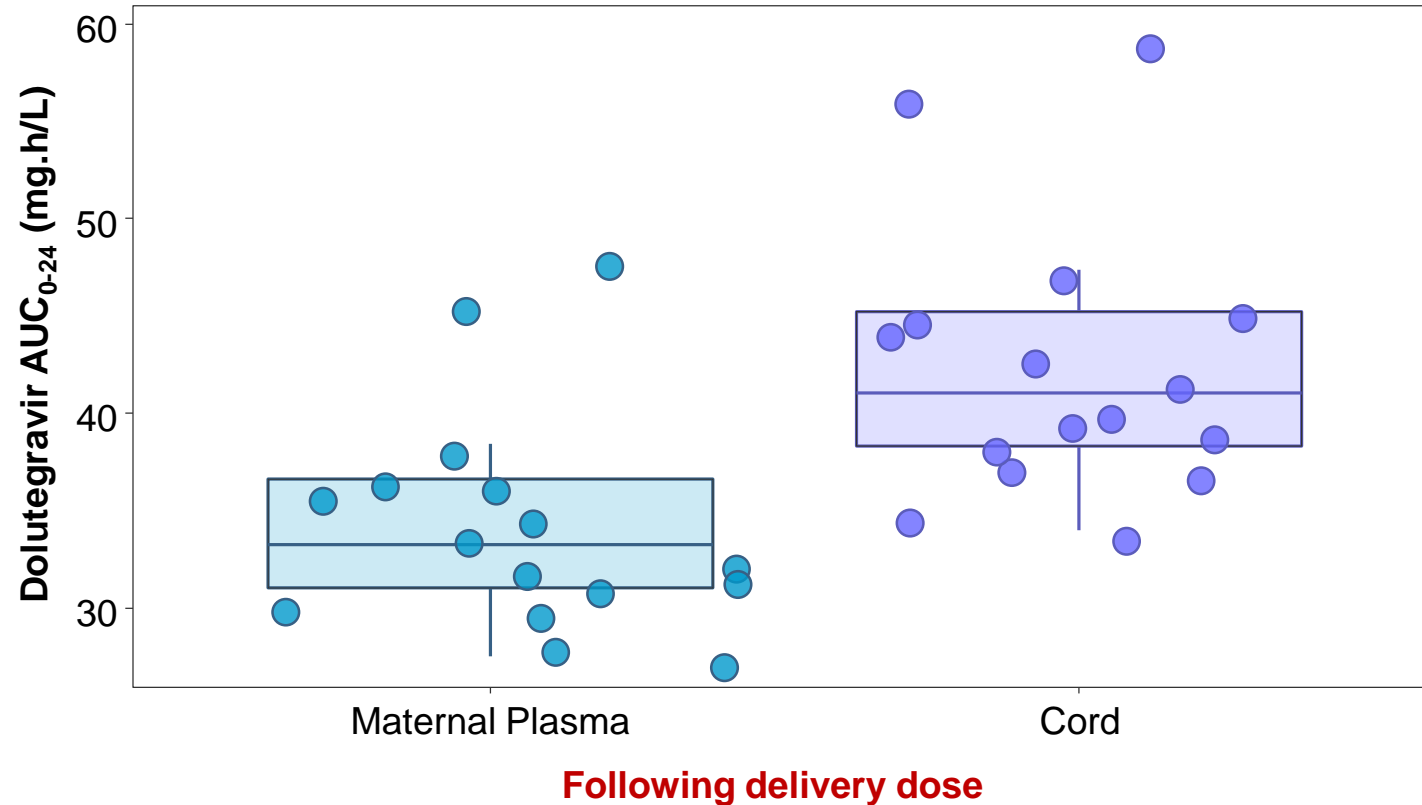
● Observed *maternal plasma*  
● Observed *breastmilk*

● Observed *cord*  
● Observed *infant plasma*

⊗ Samples below assay LLQ

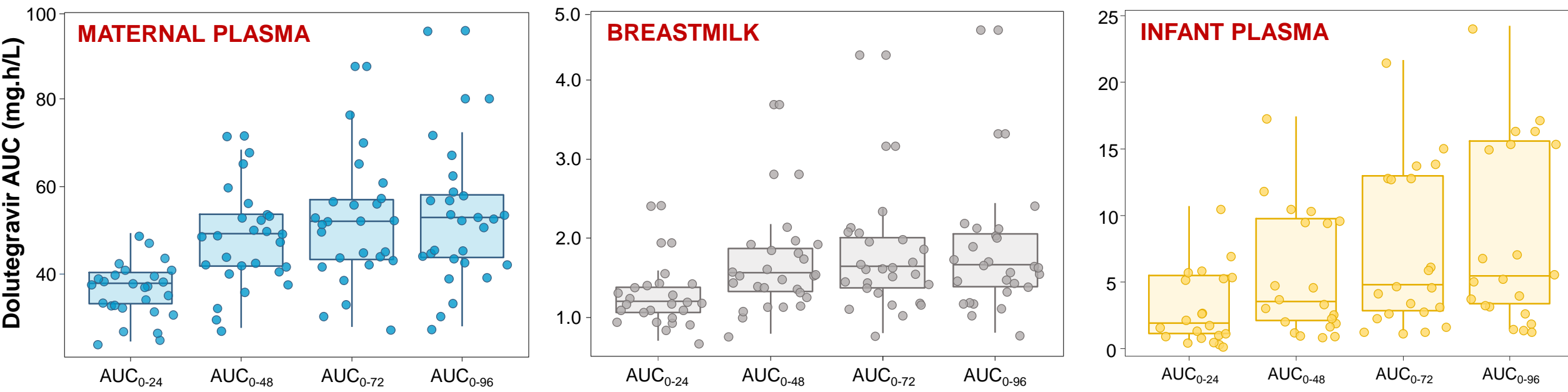
LLQ: lower limit of quantification (0.01 mg/L)  
 samples below LLQ presented as LLQ/2 (0.005 mg/L)

# Results: Cord to Maternal Plasma Ratios



AUC <sub>0-24</sub> MP (mg.h/L), n=18	AUC <sub>0-24</sub> cord (mg.h/L), n=16	Ratio, n=16
33.3 (27.5-48.1)	41.1 (34.0-59.3)	1.23 (1.233-1.236)

# Results: Breastmilk/Infant Plasma to Maternal Plasma Ratios



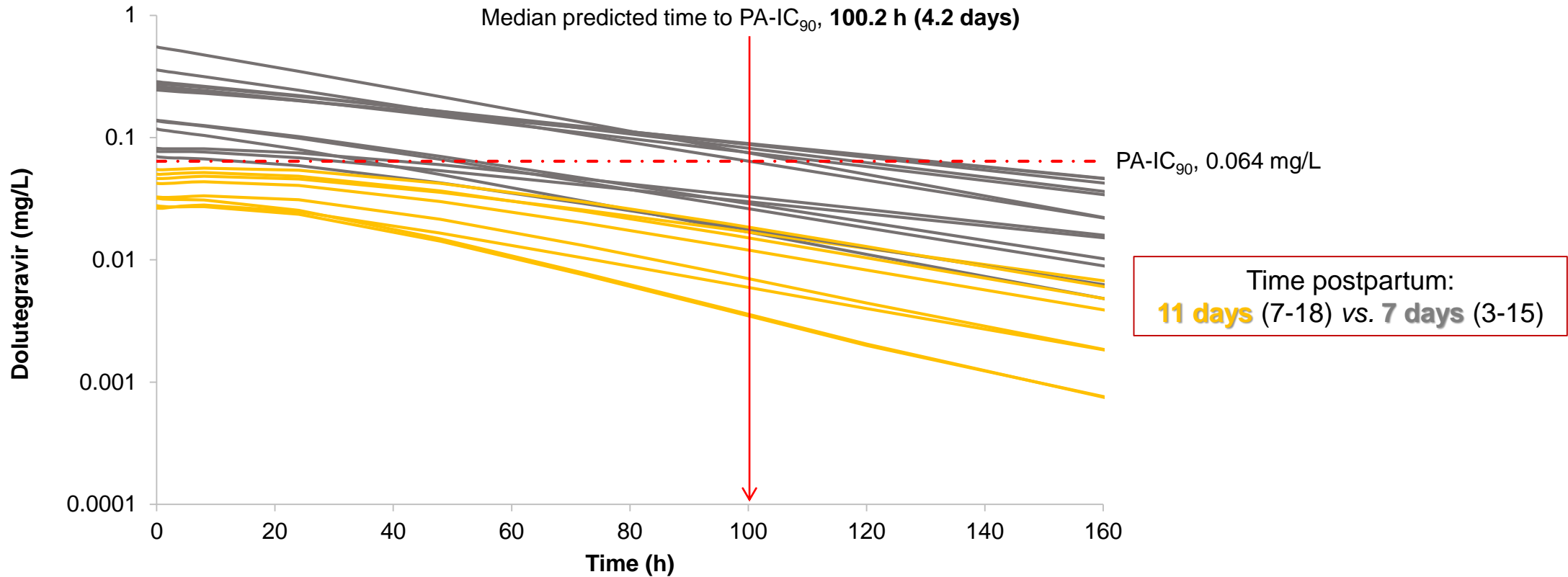
Postpartum following the final dose of DTG

	AUC <sub>0-24</sub> (mg.h/L)	AUC <sub>0-48</sub> (mg.h/L)	AUC <sub>0-72</sub> (mg.h/L)	AUC <sub>0-96</sub> (mg.h/L)
Maternal plasma (MP), n=27	37.9 (24.6-49.4)	49.3 (27.7-72.2)	52.1 (28.0-88.2)	52.9 (28.1-96.2)
Breastmilk (BM), n=27	1.20 (0.71-2.45)	1.56 (0.79-3.73)	1.65 (0.80-4.36)	1.67 (0.81-4.67)
Infant plasma (IP), n=22	1.9 (0.6-10.7)	3.5 (1.1-17.5)	4.8 (1.3-21.7)	5.5 (1.5-24.2)
	RATIO			
BM:MP, n=27	0.033 (0.025-0.062)	0.033 (0.025-0.052)	0.033 (0.025-0.049)	0.033 (0.025-0.049)
IP:MP, n=21	0.055 (0.017-0.279)	0.085 (0.022-0.363)	0.108 (0.025-0.430)	0.121 (0.027-0.474)

Data expressed as median (range)

# Results: Time to DTG PA-IC<sub>90</sub>

Predicted infant profiles following the final maternal postpartum DTG dose



Median (range) predicted time to PA-IC<sub>90</sub>: 100.2 h (15.5-130.8; n=13)

# Conclusion

- Model adequately predicted DTG exposures in maternal plasma, cord and breastmilk, and plasma of breastfed infants (DoIPHIN-1)
- Transplacental and breastmilk transfer of DTG and infant plasma half-life were consistent with previously reported values (IMPAACT, PANNA)
- Elimination of DTG in infants was prolonged, likely due to immaturity of metabolic pathways (UGT1A1)
- Breastfeeding contributed relatively little to infant exposures; breastfeeding alone is unlikely to provide adequate post-exposure prophylaxis
- High transplacental transfer of DTG offers additional infant post-exposure prophylaxis, which wanes with time postpartum
- Infants whose mothers discontinue DTG in the first week postpartum may have an additional 1-4 days of protection, whereas those whose mothers discontinue later are unlikely to have additional protection

# Acknowledgements

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