



# DoIPHIN-2 : RCT OF DOLUTEGRAVIR VS EFAVIRENZ-BASED THERAPY INITIATED IN LATE PREGNANCY

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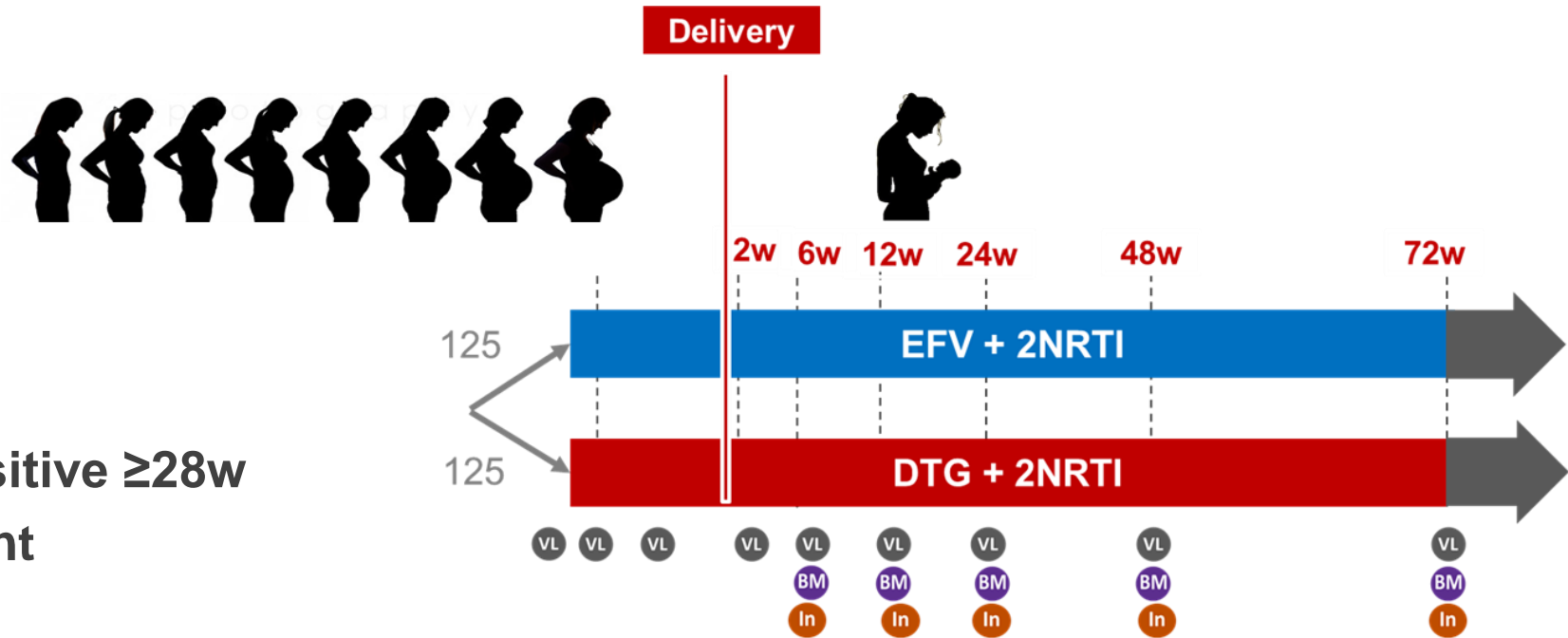
# Background

- 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

# Study Design



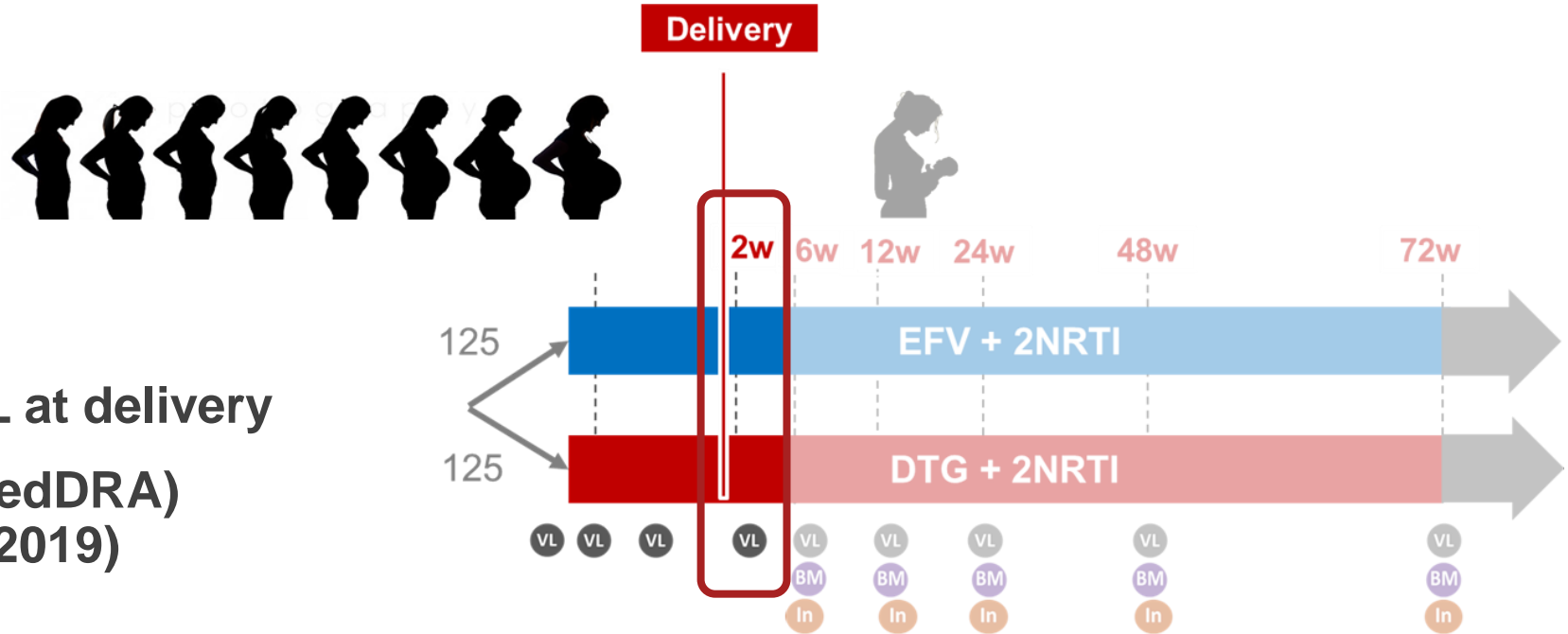
## Inclusions

- Women aged  $\geq 18$  years
- HIV+ and pregnancy test positive  $\geq 28$ w
- Evidence of informed consent

## Exclusions:

- Previous ART within 12 months, or previous integrase inhibitor
- Previous NNRTI failure or EFV intolerance
- eGFR  $< 50$  ml/min, or Hb  $< 8.0$  g/dL, abnormal LFTs or decompensated liver disease
- Medical, psychiatric or obstetric condition that might affect participation
- Drug interaction (anti-epileptic drugs, TB therapy, etc) with EFV or DTG within 2 weeks

# Study Design



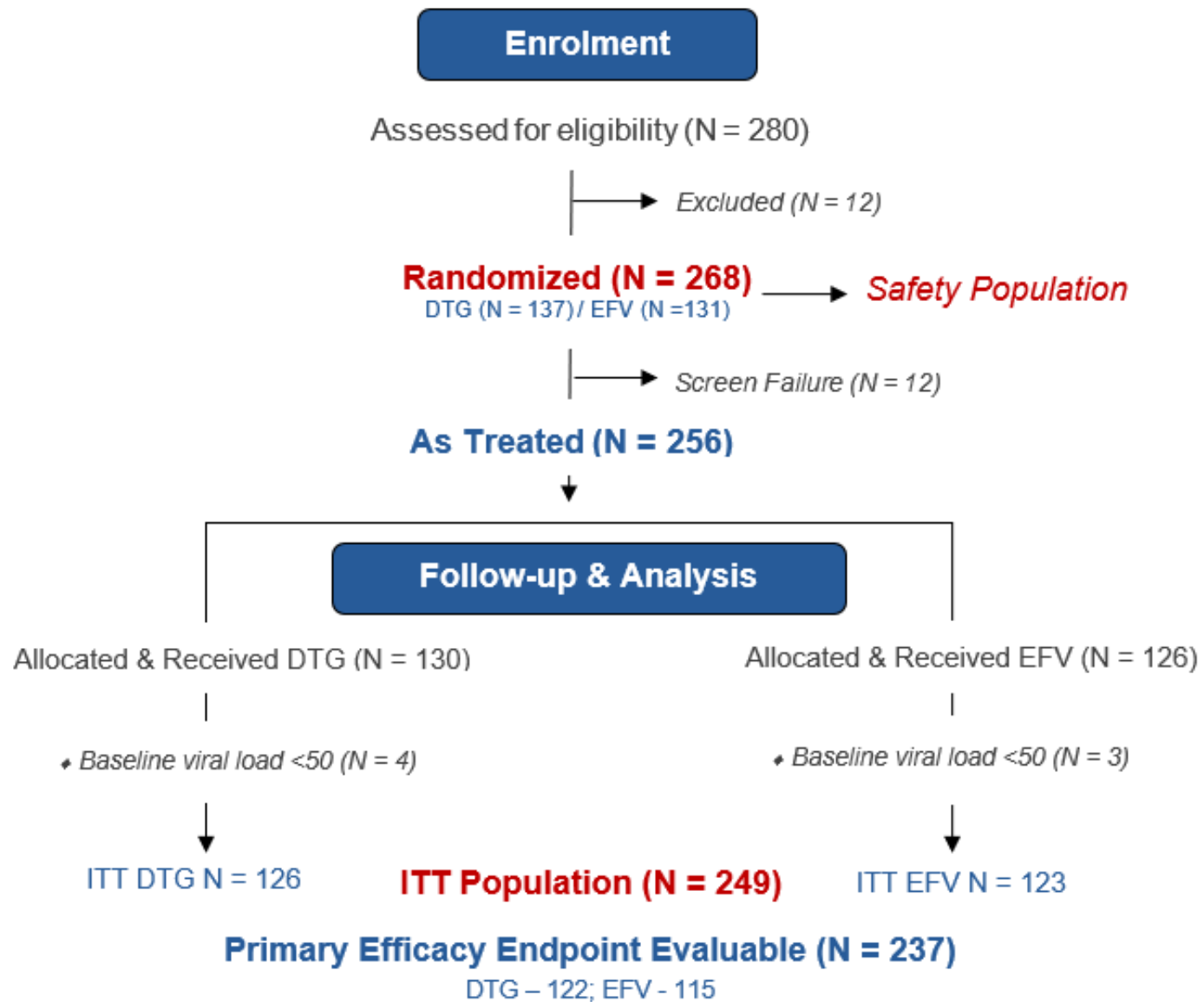
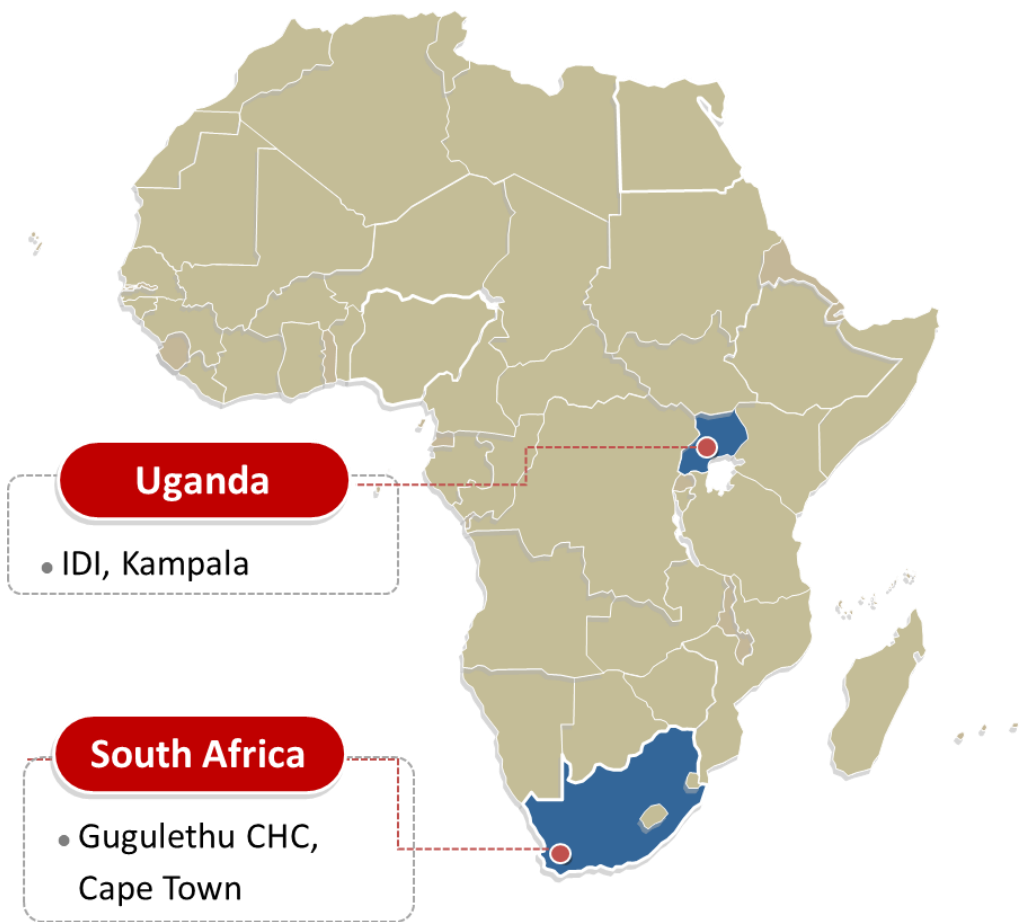
## Primary Endpoint

- **EFFICACY** - VL < 50 copies/mL at delivery
- **SAFETY** - drug-related AE (MedDRA) (censored 31<sup>st</sup> Jan 2019)

## Secondary Endpoints included:

- viral load < 1000 copies/mL at delivery
- occurrence of MTCT
- maternal response to ART to 72 weeks post-partum (PP)
- safety and tolerability of DTG in mothers and breastfed infants

# DoIPHIN-2 Enrolment



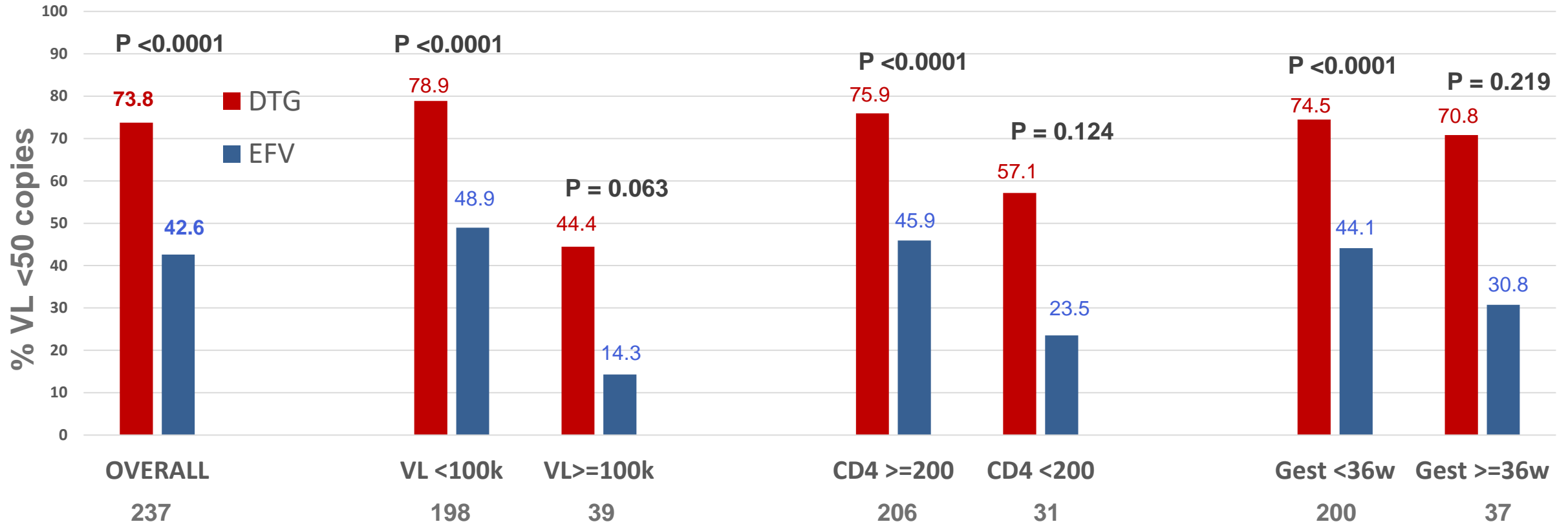
# Baseline

Variable	Statistics	DTG (N=126)	EFV (N=123)	Total (N=249)
Age (years)	Median(IQR)	<b>28 (24 -32)</b>	<b>27 (24 -30)</b>	<b>28 (24 -31)</b>
Estimated gestation age (weeks)	Median(IQR)	<b>31 (29 -34)</b>	<b>31 (29 -33)</b>	<b>31 (29 -34)</b>
Gravidity	Median(IQR)	<b>3 (2 – 4)</b>	<b>3 (2 – 4)</b>	<b>3 (2 – 4)</b>
Previous live births	Median (range)	<b>2 (0 – 9)</b>	<b>2 (0-6)</b>	<b>2 (0-9)</b>
Primigravida	No (%)	<b>16 (12.7%)</b>	<b>14 (11.4%)</b>	<b>30 (12.0%)</b>
Previous stillbirths	Yes	<b>2 (1.6%)</b>	<b>2 (1.6%)</b>	<b>4 (1.6%)</b>
Use of herbal/ traditional medicine	Yes	<b>41 (32.5%)</b>	<b>45 (36.6%)</b>	<b>86 (34.5%)</b>
Use of supplements & vitamins	Yes	<b>48 (38.1%)</b>	<b>46 (37.4%)</b>	<b>94 (37.8%)</b>
Other comedications	Yes	<b>32 (25.4%)</b>	<b>36 (29.3%)</b>	<b>68 (27.3%)</b>
<b>CD4 Count (cells/mm3)</b>	Median (IQR)	<b>463 (327 – 660)</b>	<b>414 (268 – 575)</b>	<b>446 (295 – 633)</b>
<b>Log<sub>10</sub> Viral Load</b>	Median (IQR)	<b>4.4 (3.6 - 4.7)</b>	<b>4.6 (3.9 - 4.8)</b>	<b>4.5 (3.8 - 4.8)</b>

No significant differences between arms in:

*maternal smoking (5.6%), alcohol use (19.7%), psychiatric disorders (4.5%), maternal weight (70kg; IQR 61-83)*

# DoIPHIN-2 Primary Endpoint: VL <50 copies (ITT)



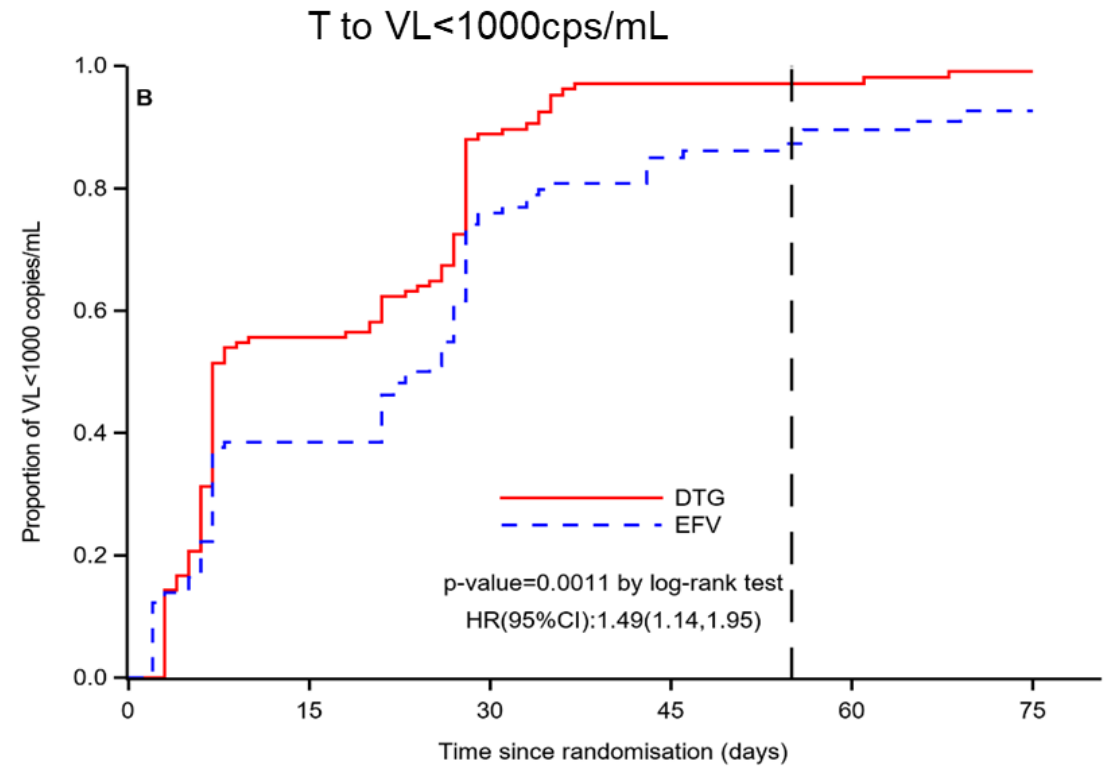
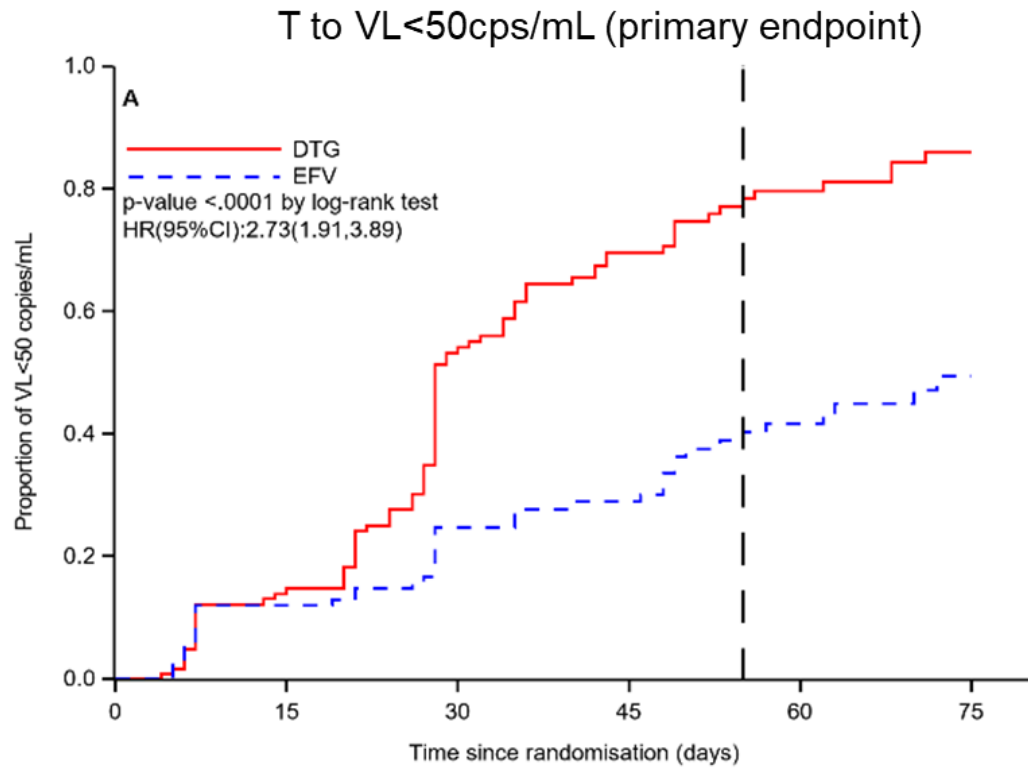
## VL <50 copies by ITT

- DTG (90/122) 73.8% vs EFV (49/115) 42.6%
- RR 1.66 (95%CI 1.32 – 2.08; P<0.0001)

## Multivariable model (GLM)

- Findings unaltered by baseline VL (</≥100k), CD4 (</≥200), gestation at enrolment (</≥36w), maternal age, country

# DoIPHIN-2 Primary Endpoint: VL <50 copies (ITT)



## VL <50 copies by ITT

- DTG (90/122) 73.8% vs EFV (49/115) 42.6%
- RR 1.66 (95%CI 1.32 – 2.08; P<0.0001)

## VL <1000 copies by ITT

- DTG (113/122) 92.6% vs EFV (95/115) 82.6%
- RR 1.11 (95%CI 1.00 – 1.23; P=0.05)

**Median (IQR) time on ART at delivery: 55 (33 – 77) days (DTG 52 [30 – 74]; EFV 59 [38 – 82])**



# Infant Transmissions

## 3 infant transmissions – all in the DTG arm

Study ID	ART pre Delivery (d)	Enrolment Gestation (w)	# + ve PCRs	Delivery to 1 <sup>st</sup> PCR + (d)	Study visit (infant PCR)			
					BL screening	Day +7 confirm	Day +28	Delivery to 14d
10062	35	32	4	5				+
10143	32	32	3	3				+
25004	24	30	2	11				+
					Maternal VL			
					48969	5211	53	29
					32844	210	100	20
					31354	258		200

# SAFETY - Mothers

Mothers	DTG N = 137 (%)	EFV N = 131 (%)	Total N = 268 (%)
Subjects with ≥1 SAE	26 (19.0)	18 (13.7)	44 (16.4)
Subjects with ≥1 drug-related SAE	2 (1.5)	5 (3.8)	7 (2.6)
Subjects with ≥1 IRIS-related SAE	1 (0.7)	2 (1.5)	3 (1.1)
<b>SYSTEM ORGAN CLASS</b>			
Blood and lymphatic disorders	2 (1.5)	1 (0.8)	3 (1.1)
Gastrointestinal disorders	1 (0.7)	0	1 (0.4)
Infections & infestations	5 (3.6)	2 (1.5)	7 (2.6)
Abnormal Investigations	0	3 (2.3)	3 (1.1)
Pregnancy, puerperium, perinatal	15 (10.9)	8 (6.1)	23 (8.6)
<i>Stillbirths</i>	<i>4 (2.9)</i>	<i>0</i>	<i>4 (1.5)</i>
Psychiatric disorders			
<i>Suicide ideation / attempt</i>	1 (0.7)	2 (1.5)	3 (1.1)
Renal & urinary disorders	2 (1.5)	0	2 (0.8)
Social circumstances	2 (1.5)	0	2 (0.8)

*No difference in laboratory tests, other than creatinine (change from BL 6.2 vs 1.8umol/L; P<0.0001)*

# Stillbirths

Infant ID	Gestation (w)	Arm	Maternal ART (d)	Relation to maternal ART	IRIS	Primary Cause	Notes
100320002	40	DTG	33	Unlikely	Unlikely	Maternal Syphilis,	Macerated stillbirth
100460003	36	DTG	33	Not related	Not related	Uterine Rupture & hemoperitoneum	Maternal syphilis
100810003	41	DTG	34	Unlikely	Unlikely	Maternal fever, respiratory illness, empirical TB treatment, preceded ART (16w gestation) but worsened	Antimalarials at 16w Herbal use  Macerated stillbirth
101340002	41	DTG	64	Unlikely	Not related	Post-dates, fetal distress	

## SAFETY – Infants (242 live births evaluable)

Infants (242 Live Births)	DTG N = 123 (%)	EFV N = 119 (%)	Total N = 242 (%)
Gestation at delivery (median; IQR)	39.9 (37.6 - 41.9)	39.9 (38.3 - 41.4)	39.9 (37.9 - 41.6)
Pre-term (<37w)	21 (17.1)	18 (15.1)	39 (16.1)
Pre-term (<34w)	6 (4.9)	6 (5.0)	12 (5.0)
<b>Infants with at least one SAE</b>	<b>65 (52.8)</b>	<b>55 (46.2)</b>	<b>120 (49.6)</b>
<b>SYSTEM ORGAN CLASS</b>			
<b>Infant Deaths</b>	<b>5 (4.1)</b>	<b>3 (2.5)</b>	<b>8 (3.3)</b>
<b>Congenital, familial and genetic</b>	<b>47 (38.2)</b>	<b>45 (37.8)</b>	<b>92 (38.0)</b>
General disorders	1 (0.8)	1 (0.8)	2 (0.8)
Hepatobiliary disorders	1 (0.8)	0	1 (0.4)
Infections & infestations	14 (11.4)	11 (9.2)	25 (10.3)
Injury, poisoning and procedures	1 (0.8)	0	1 (0.4)
Metabolism and nutrition	2 (1.6)	1 (0.8)	3 (1.2)
Nervous system disorders	2 (1.6)	1 (0.8)	3 (1.2)
Pregnancy, puerperium, perinatal	2 (1.6)	7 (5.9)	9 (3.7)
Respiratory, thoracic, mediastinal	8 (6.5)	3 (2.5)	11 (4.5)
Social circumstances	1 (0.8)	0	1 (0.4)

# SAFETY – Congenital, Familial, Genetic

Infants (Live Births)	DTG N = 123 (%)	EFV N = 119 (%)	Total N = 242 (%)
<b>SYSTEM ORGAN CLASS</b>			
<b>Congenital, familial and genetic</b>	<b>47 (38.2)</b>	<b>45 (37.8)</b>	<b>92 (38.0)</b>
Congenital umbilical hernia	37 (30.1)	35 (29.4)	72 (29.8)
Birth mark	18 (14.6)	18 (15.1)	36 (15.3)
Sacral dimple congenital	3 (2.4)	0	3 (1.2)
Congenital acrochordon	2 (1.6)	3 (2.5)	5 (2.1)
Corneal opacity congenital	1 (0.8)	0	1 (0.4)
Craniosynostosis	1 (0.8)	1 (0.8)	2 (0.8)
Laryngomalacia	1 (0.8)	0	1 (0.4)
Sickle cell anaemia	1 (0.8)	0	1 (0.4)
Strabismus congenital	1 (0.8)	1 (0.8)	2 (0.8)
Talipes	1 (0.8)	2 (1.7)	3 (1.2)
Cleft palate	0	1 (0.8)	1 (0.4)
Polydactyly	0	2 (1.7)	2 (0.8)
Neural Tube Defects	0	0	0

# Infant deaths to 31/01/2019

Infant ID	Gestation (w)	Age (d)	Arm	Maternal ART (d)	Relation to maternal ART	IRIS	Primary Cause	Other factors
10135-01-01	28	1	EFV	0	Not related	Not related	Premature (28w) twin pregnancy	
10091-01-01	32	19	DTG	30	Unlikely	Not related	Premature infant (32w)	Antepartum haemorrhage
25118-01-02	35	14	EFV	7	Unlikely	Not related	Respiratory distress	Neonatal sepsis/grunting 10d before
10040-01-02	37	88	DTG	13	Unlikely	Not related	Sudden Infant Death (nasal discharge 1w)	
25025-01-01	38	47	DTG	28	Not related	Not related	Infant choking	
10042-01-01	38	256	DTG	4	Not related	Not related	Bronchopneumonia	
10037-01-01	39	2	DTG	52	Not related	Not related	Neonatal asphyxia	
25077-01-01	40	77	EFV	83	Unlikely	Not related	Infectious diarrhoea	

# Conclusion

- DolPHIN-2 designed to evaluate VL responses between DTG and EFV regimens in third trimester initiation of ART.
- DTG achieves more rapid virological suppression before delivery compared to EFV when initiated in late pregnancy and is well tolerated.
- Three infant infections were likely *in-utero* transmissions.
- Four stillbirths in the DTG arm were associated with known risk factors, and considered unlikely to be related to study medication.
- Infant deaths, stillbirths and infant infections attest to the poor outcomes previously reported in this group of mothers.



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