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

Kenneth Kintu, Thoko Malaba, Jesca Nakibuka, Christiana Papamichael, Angela Colbers, Kay Seden, Victoria Watson, Helen Reynolds, Duolao Wang, Catriona Waitt, Catherine Orrell, Mohammed Lamorde, Landon Myer, Saye Khoo, for the DolPHIN-2 Study Group

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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 3rd 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
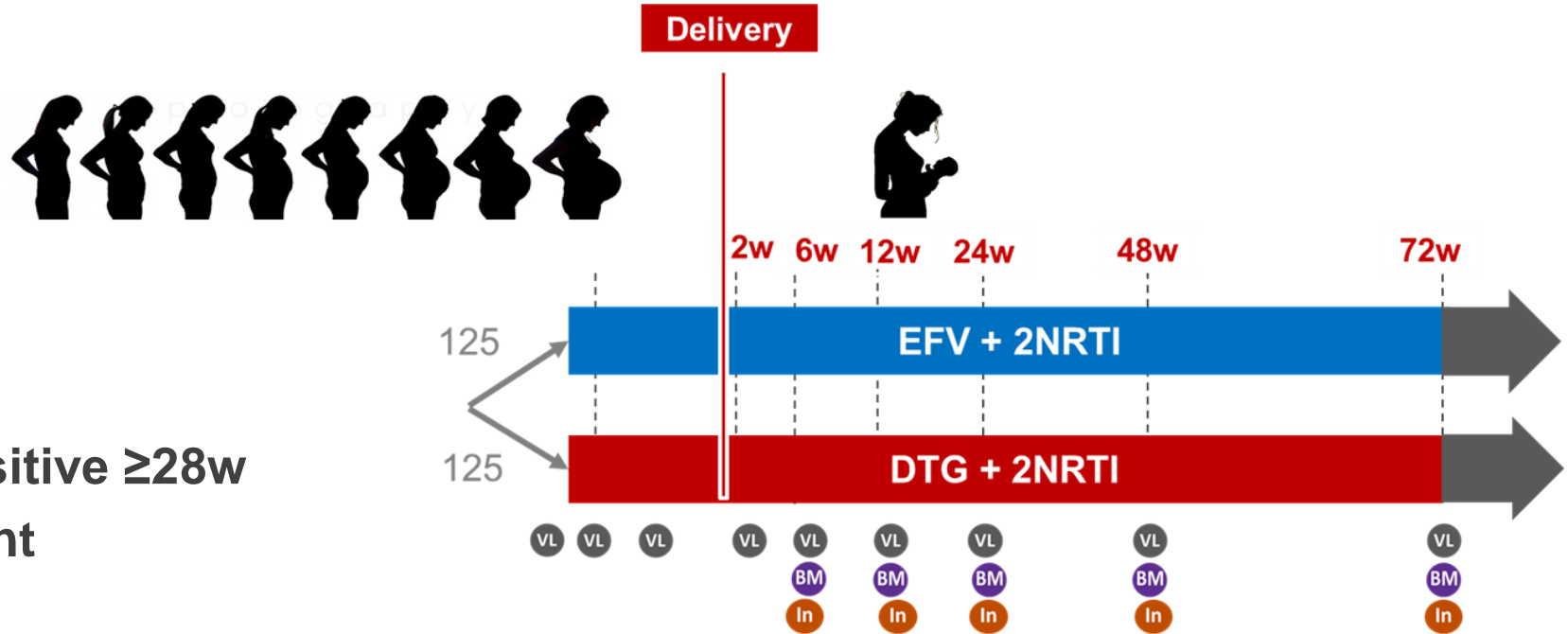
Inclusions

- Women aged ≥18 years
- HIV+ and pregnancy test positive ≥28w
- 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
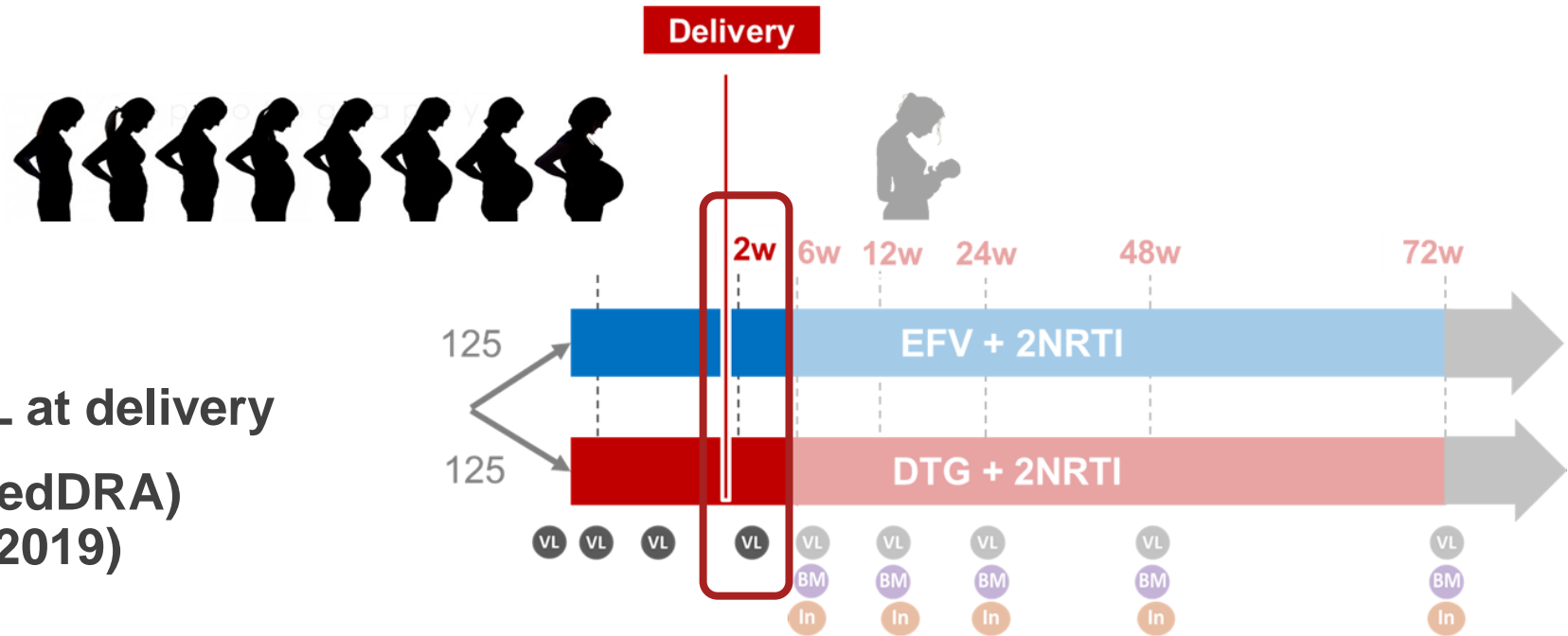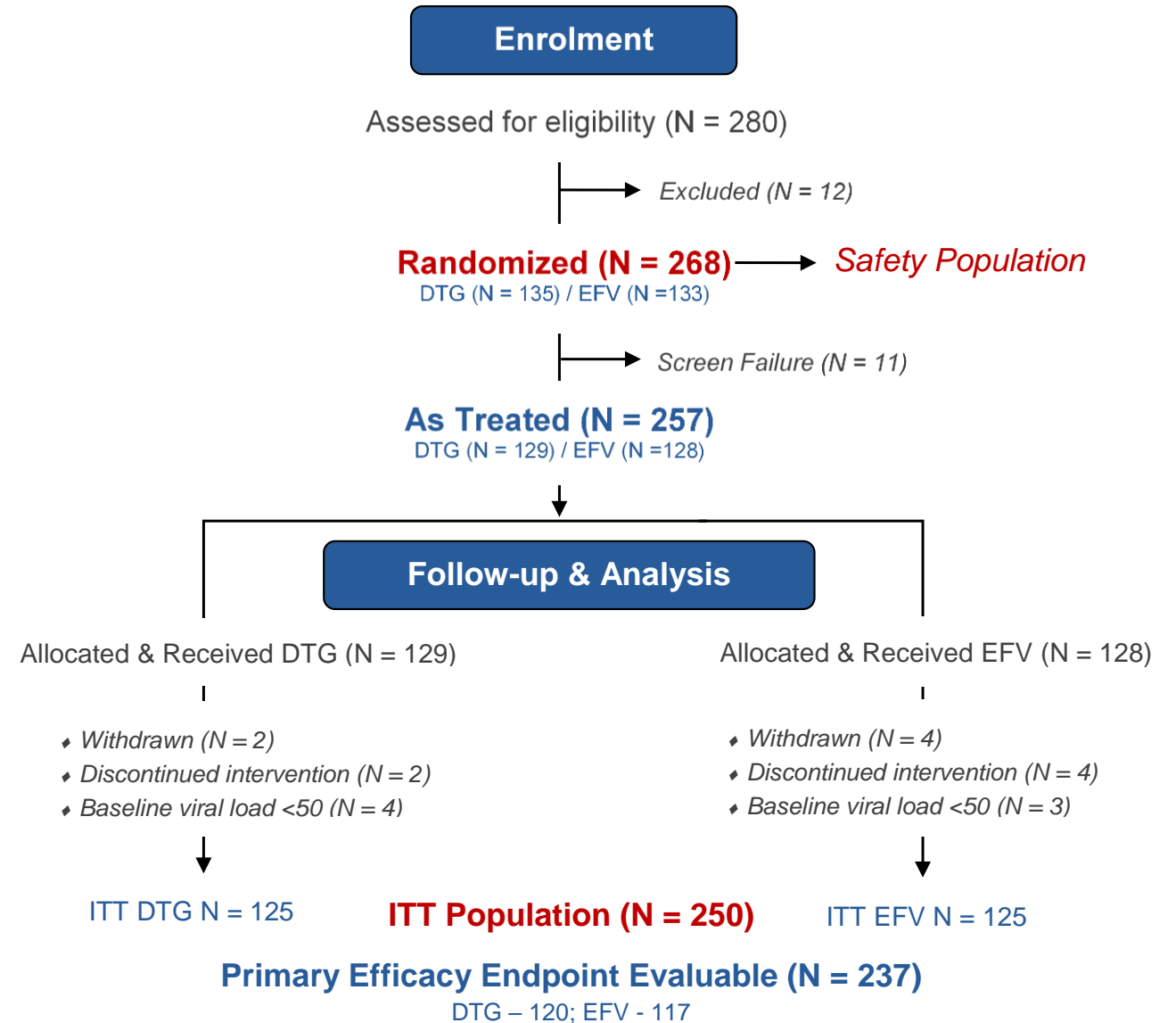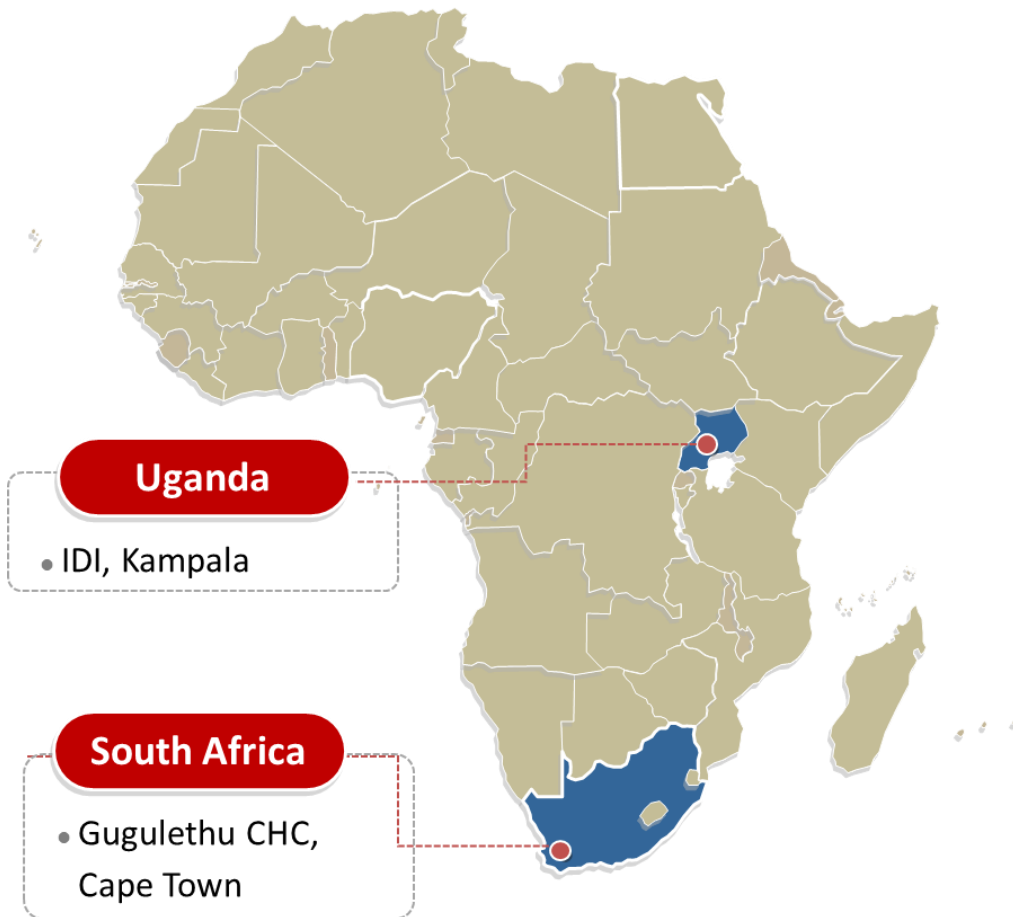
Study Design

Primary Endpoint

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

DolPHIN-2 Enrolment

Enrolment

Assessed for eligibility (N = 280)

→ *Excluded (N = 12)*

Randomized (N = 268) → *Safety Population*
DTG (N = 135) / EFV (N =133)

→ *Screen Failure (N = 11)*

As Treated (N = 257)
DTG (N = 129) / EFV (N =128)

Follow-up & Analysis

Allocated & Received DTG (N = 129)

- *Withdrawn (N = 2)*
- *Discontinued intervention (N = 2)*
- *Baseline viral load <50 (N = 4)*

Allocated & Received EFV (N = 128)

- *Withdrawn (N = 4)*
- *Discontinued intervention (N = 4)*
- *Baseline viral load <50 (N = 3)*

ITT DTG N = 125   **ITT Population (N = 250)**   ITT EFV N = 125

Primary Efficacy Endpoint Evaluable (N = 237)
DTG – 120; EFV - 117

Uganda
- IDI, Kampala

South Africa
- Gugulethu CHC, Cape Town

Baseline

Variable	Statistics	DTG (N=125)	EFV (N=125)	Total (N=250)
Age (years)	Mean (SD)	28.0 (5.3)	27.4 (5.1)	27.7 (5.2)
Estimated gestation age (weeks)	Median(IQR)	31 (29 -34)	31 (29 -33)	31 (29 -34)
Gravidity	Median(IQR)	3 (2 – 4)	3 (2 – 4)	3 (2 – 4)
Previous live births	Median (IQR)	2 (1-3)	1 (1-2)	2 (1-3)
Primigravida	Number (%)	16 (12.8%)	14 (11.2%)	30 (12.0%)
Previous stillbirths	Yes	2 (1.6%)	2 (1.6%)	4 (1.6%)
Use of herbal/ traditional medicine	Yes	42 (33.6%)	45 (36.0%)	87 (34.8%)
Use of supplements & vitamins	Yes	48 (38.4%)	46 (36.8%)	94 (37.6%)
Other comedications	Yes	31 (24.8%)	38 (30.4%)	69 (27.6%)
CD4 Count (cells/mm3)	Median (IQR)	464 (329 – 664)	414 (265 – 581)	446 (296 – 633)
Log_{10} Viral Load	Median (IQR)	4.4 (3.6 - 4.7)	4.6 (3.9 - 4.8)	4.4 (3.8 - 4.8)

No significant differences between arms in:
maternal smoking (5.6%), alcohol use (19.6%), psychiatric disorders (4.4%), mean maternal weight 73.4 kg (SD 16.0)
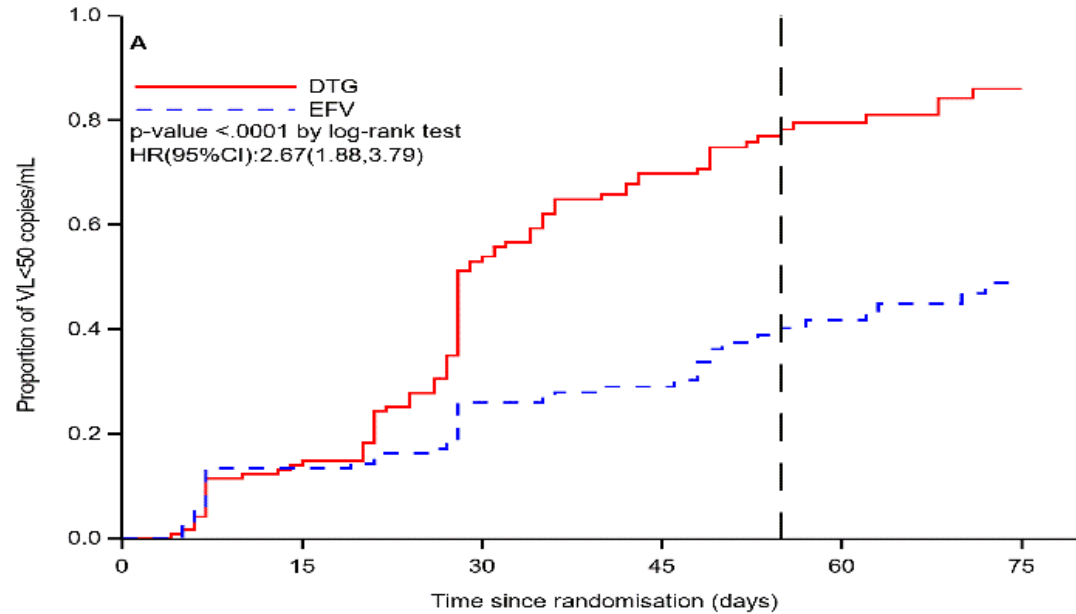
DolPHIN-2 Primary Endpoint: VL <50 copies (ITT)

P <0.0001

74.2 DTG

42.7 EFV

% VL <50 copies

OVERALL

237
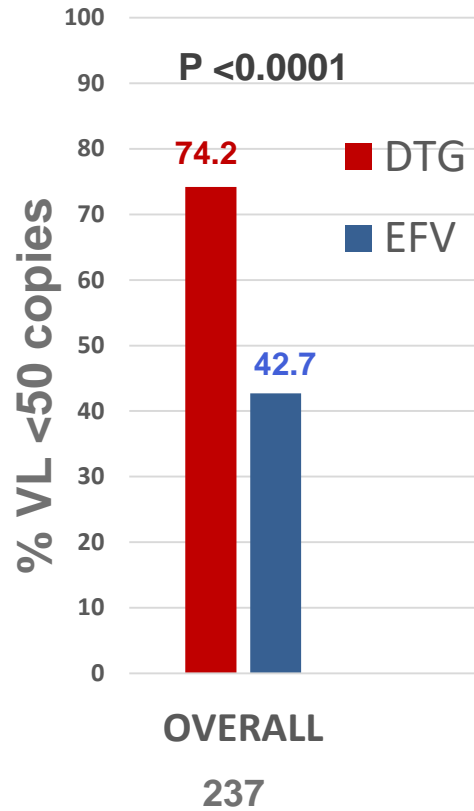
VL <50 copies by ITT

- **DTG (89/120) 74.2% vs EFV (50/117) 42.7%**
- **RR 1.64 (95%CI 1.31 – 2.06; P<0.0001)**

DolPHIN-2 Endpoint: VL <50 copies (ITT)

Time to VL <50 copies/mL

Time to VL <1000 copies/mL

VL <50 copies by ITT

- DTG (89/120) 74.2% vs EFV (50/117) 42.7%
- RR 1.64 (95%CI 1.31 – 2.06; P<0.0001)
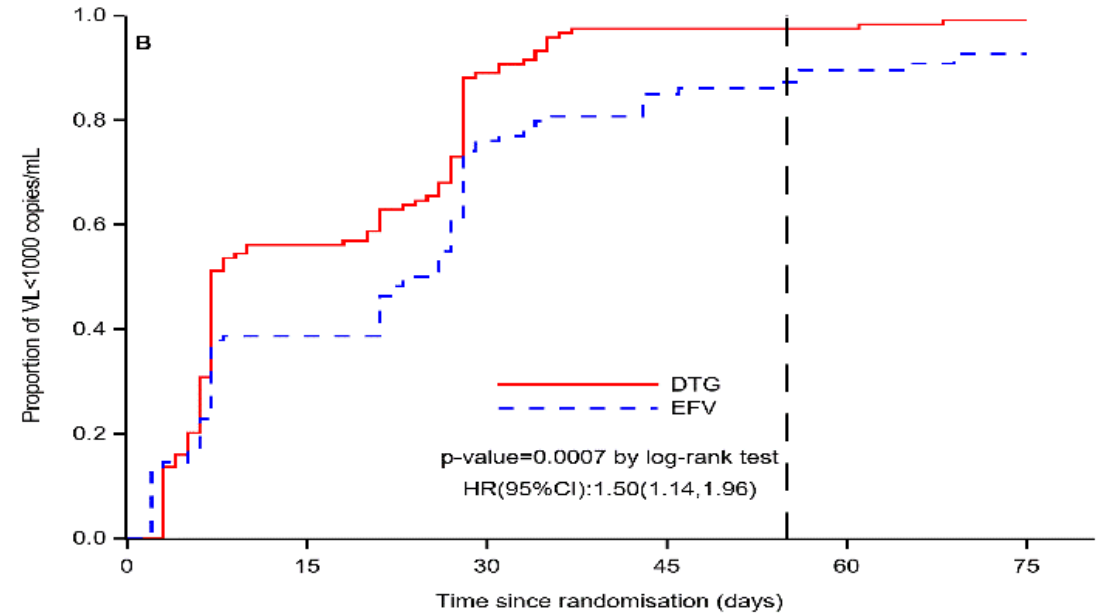
VL <1000 copies by ITT

- DTG (112/120) 93.3% vs EFV (96/117) 82.1%
- RR 1.12 (95%CI 1.00 – 1.25; P=0.042)

Median (IQR) time on ART at delivery: 55 (33 – 77) days (DTG 52 [31 – 75]; EFV 59 [37 – 80])

Infant Transmissions

3 infant transmissions – all in the DTG arm

Study ID	ART pre Delivery (d)	Enrolment Gestation (w)	# + ve PCRs	Delivery to 1st PCR + (d)
10062	35	32	4	5
10143	32	32	3	3
25004	24	30	2	11

SAFETY - Mothers

Mothers	DTG N = 137 (%)	EFV N = 131 (%)	Total N = 268 (%)
Subjects with ≥1 SAE	25 (18.2)	19 (14.5)	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)
SYSTEM ORGAN CLASS			
Blood and lymphatic disorders	2 (1.5)	1 (0.8)	3 (1.1)
Cardiac disorders	**0**	**1 (0.8)**	**1 (0.4)**
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	14 (10.2)	9 (6.9)	23 (8.6)
Stillbirths	3 (2.2)	1 (0.8)	4 (1.5)
Psychiatric disorders			
Suicide ideation / attempt	1 (0.7)	2 (1.5)	3 (1.1)
Renal & urinary disorders	2 (1.5)	0	2 (0.8)
Reproductive system & breast disorders	**0**	**1 (0.8)**	**1 (0.4)**
Social circumstances	2 (1.5)	0	2 (0.8)
Vascular disorders	**0**	**1 (0.8)**	**1 (0.4)**

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

Birth Outcomes - Pre-term, Premature and Stillbirths

Gestational Age at Delivery

Deliveries	DTG N = 124 (%)	EFV N = 120 (%)	Total N = 244 (%)
Median gestation * (IQR)	39 (37.2 - 40.7)	39 (37.3 - 40.0)	39 (37.3 - 40.3)
Late Pre-term (<37w)	21 (16.9)	19 (15.8)	40 (16.4)
Premature (<34w)	3 (2.4)	5 (4.2)	8 (3.3)

best estimate using recall of LMP, fundal height and ultrasound, modified post-partum by Ballard score

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
101340002	41	EFV	64	Unlikely	Not related	Post-dates, fetal distress	
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

SAFETY – Infants (242 live births evaluable)

Infants (242 Live Births)	DTG N = 123 (%)	EFV N = 119 (%)	Total N = 242 (%)
Infants with at least one SAE	65 (52.8)	58 (48.7)	123 (50.8)
SYSTEM ORGAN CLASS			
Infant Deaths	**5 (4.1)**	**3 (2.5)**	**8 (3.3)**
Congenital, familial and genetic	**47 (38.2)**	**49 (41.2)**	**96 (39.7)**
Ear & labyrinth disorders	1 (0.8)	0	1 (0.4)
General disorders	1 (0.8)	1 (0.8)	2 (0.8)
Hepatobiliary disorders	1 (0.8)	0	1 (0.4)
Infections & infestations	15 (12.2)	11 (9.2)	26 (10.7)
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	3 (2.4)	7 (5.9)	10 (4.1)
Respiratory, thoracic, mediastinal	7 (5.7)	3 (2.5)	10 (4.1)
Skin & subcutaneous tissue disorders	0	1 (0.8)	1 (0.4)
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 (%)
SYSTEM ORGAN CLASS			
Congenital, familial and genetic	**47 (38.2)**	**49 (41.2)**	**96 (39.7)**
Congenital umbilical hernia	37 (30.1)	41 (34.5)	78 (32.2)
Birth mark	20 (16.3)	21 (17.6)	41 (16.9)
Sacral dimple congenital	3 (2.4)	0	3 (1.2)
Congenital acrochordon	2 (1.6)	3 (2.5)	5 (2.1)
Heterochromia iridis	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	Relation to maternal 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)	Disengaged (22d DTG), switched to EFV (17d), fu for safety
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 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.

DolPHIN2

UNIVERSITY OF LIVERPOOL
Catriona Waitt
Helen Reynolds
Eva-Maria Hodel
Kay Seden
Laura Else
Alieu Amara
Laura Dickinson
Justin Chiong
Katie McAllister
Steve Potter

LSTM
Kelly Byrne
Duolao Wang
Miriam Taegetmeyer
Christiana Papamichael
Vicky Watson
Tao Chen
Yusif AlHassan

David Burger
Angela Colbers

University of Cape Town
Landon Myer
Catherine Orrell
Thoko Malaba
Carmen Delport
Lee-Ann Stemmet
Megan Mrubata
Helene Theunissen
Sivuyile Tambula
Ushma Mehta
Phelokazi Tshazibane
Xola Ntilashe

Unitaid
Innovation in Global Health

TSC / IDSMB
Anton Pozniak (TSC)
Tim Peto (IDSMB)
Graham Taylor
Marta Boffito
Polly Clayden

Infectious Diseases Institute
Mohammed Lamorde
Kenneth Kintu
Jesca Nakibuka
Flavia Vivian Najjuma
Annet Onzia
Adelline Twimukye
Julian Kaboggoza
Eva Laker
Daniel Kiiza
Byamugisha Josaphat
Andrew Kambugu
Betty Agwang
Brian Isaaya

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