Poster # 807

DolPHIN-1: Dolutegravir vs Efavirenz when Initiating Treatment in Late Pregnancy – An Interim Analysis

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Background

~1.4 million HIV-positive women become pregnant each year, 90% in low-resource settings, where women continue to present with untreated HIV in the third trimester of pregnancy

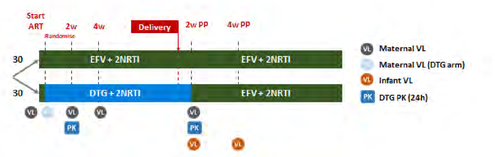
Suppression of maternal HIV viral load by delivery is critical to prevent mother to child transmission of HIV (PMTCT). Currently recommended first-line ART (EFV based) takes a median of 84 days to attain virological suppression, compared to 28 days for dolutegravir (DTG)-based ART*

Study Design

DolPHIN-1 (NCT02245022) was an open-label randomised trial of DTG+2NRTI (vs standard of care [SoC] EFV+2NRTI) in women with women presenting to routine antenatal clinics in Kampala and Cape Town with untreated HIV at ≥28-36 weeks gestation (N=60).

Due to the need for women to commence ART on the day of diagnosis, before laboratory results (Hb, eGFR, LFT, Hep BsAg) to determine eligibility were available, all participants commenced SoC EFV-based ART with randomisation to continue SoC or switch to DTG+2NRTI a median of 3 (range 1-8) days later.

After 2 weeks on DTG, samples were collected pre-dose and at 0.5, 1, 2, 3, 4, 6, 8 and 24h post-dose, with the same sampling schedule at 2 weeks postpartum. DTG was measured using LC-MS/MS^ with a calibration range of 10-4000 ng/mL. Participants on DTG were switched to SoC at 2 weeks postpartum, and followed up to six months.



Primary Endpoint

AUC_{0-24} of DTG in the third trimester (T3) and at two weeks postpartum

Secondary Endpoints

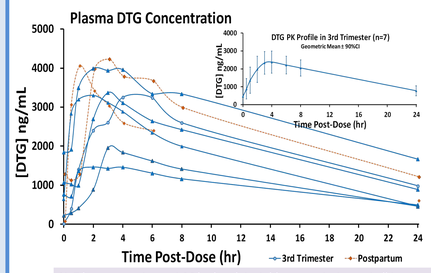
- Safety and tolerability of DTG in pregnant women and their infants
- Proportion in each arm with HIV VL <50 copies/ mL at delivery

Timing of Analysis

This poster reports on a scheduled interim analysis after first 16 women (8 on DTG) delivered to evaluate safety and ensure DTG exposure in T3 is not insufficient

* SINGLE STUDY, N Engl J Med. 2013 Nov 7;369(19):1807-18 ^Else *et al.* 2016, J Chrom B

Results 1: Pharmacokinetics



DTG PK Parameters	
T3 [N=7, Geometric Mean (95%CI)]	
C_{max} (ng/mL)	2645 (1965 - 3325)
C_{24} (ng/mL)	778 (447-1108)
AUC_{24} (ng.h/mL)	39415 (28296 - 50534)
Postpartum (N=2)	
C_{max} (ng/mL)	4224, 4055
C_{24} (ng/mL)	1211, 603
AUC_{24} (ng.h/mL)	59633, 44305

N=7 because participant 14 had undetectable concentrations at all time points, was deemed to be non-adherent and was excluded from PK analysis

Reference data from non-pregnant population (SPRING-1 and SPRING-2) AUC_{24}=53600 ng.h/mL, C_{max}=3670 ng/mL, C_{min}=1110 ng/mL

Results 2: Safety

Four SAEs were reported, two in one participant in the DTG arm and two in the EFV arm:

1. JU9 (DTG arm): Fresh stillbirth attributed to asphyxia resulting from cord around the neck. Unrelated
2. JU9 (DTG arm): Liver event (ALT 5 x ULN, total bili 2.3 x ULN). Resolved after discontinuation of DTG. Had ingested *physalis minima Linn* (herbal medication) prior to event. Possibly related
3. VR0 (EFV arm): Pregnancy induced hypertension necessitating induction of labour. Unrelated.
4. EK6 (EFV arm): Infant polydactyly left foot (9 digits) and sydactyly of 2nd, 3rd and 4th digits. Unrelated (occurred prior to 3rd trimester drug exposure)

Table 2. Adverse events. All were of mild or moderate severity and either not related, possibly related or probably related to ART. In bold are events that occurred more than once. All events that were either possibly or probably related to study drug recovered/resolved before the end of the study except for one case of diarrhoea and the case of hyponatraemia.

Stem Organ Class	Preferred Term (n)	Total	ITT		As Treated	
			DTG	EFV	DTG	EFV
Blood and lymphatic system disorders	Anaemia (1)	1	1	0	1	0
Cardiac disorders	Tachycardia (1)	1	0	1	0	1
Gastrointestinal disorders	**Nausea (6)**, **Vomiting (6)**, **Diarrhoea (3)**, Abdominal pain lower (1), Dyspepsia (1),	17	13	4	7	10
Infections and infestations	**Upper respiratory tract infection (3)**, **Urinary tract infection (6)**, Gastroenteritis (1), Lower respiratory tract infection (1), Nasopharyngitis (1), Oral candidiasis (1), Streptococcal urinary tract infection (1), Vulvovaginal candidiasis (1), Wound sepsis (1)	16	7	9	5	11
Injury, poisoning and procedural complications	Laceration (1)	1	0	1	0	1
Investigations	Blood pressure increase (1)	1	1	0	1	0
Metabolism and nutrition disorders	Decreased appetite (1), hypoglycaemia (1), hyponatraemia (1)	3	1	2	1	2
Musculoskeletal and connective tissue disorders	Arthralgia (1)	1	1	0	1	0
Nervous system disorders	**Dizziness (6)**, **Headache (4)**, Syncope (1)	11	9	2	4	7
Pregnancy, puerperium and perinatal conditions	**Premature labour† (2)**, Gestational hypertension(1)	3	1	2	1	2
Psychiatric disorders	Abnormal dreams, nightmare	2	2	0	1	1
Renal and urinary disorders	Proteinuria (1)	1	1	0	0	1
Respiratory, thoracic and mediastinal disorders	**Cough (2)**, Hiccups (1)	3	2	1	2	1
Skin and subcutaneous tissue disorders	Rash (1), Rash papular (1)	2	1	1	0	2
Total		63	40	23	24	39

DTG = dolutegravir + 2 NRTIs; EFV: efavirenz-based standard of care; ITT = intention to treat; n = number of events. † 35 and 36 weeks of gestation.

Results 3: Viral Load

Subj No.	Gestation at Enrolment	Arm	Baseline CD4	Baseline VL	VL at Rand.	Day 7 VL	Day 14 VL	Day 28 VL	2 Weeks Post-partum
1*	32	DTG	277	76721	34506	610	<100	145	2217
2	30	DTG	343	54246	7432	245	207	<100	ND
3	30	DTG	42	69117	2042	ND	<50	<50	<50
5	28	DTG	578	267	140	ND	<50	54	<50
9	31	DTG	469	6374	4147	ND	<50	<50	<50
11	29	DTG	318	13256	293	61	<50	<50	<50
12	28	DTG	296	15342	41209	ND	63169	301	<50
14^	30	DTG	514	1115	1906	3586	5055	17815	ND
4	27	EFV	117	1181787	~	ND	7455	448	292
6	29	EFV	567	143330	~	ND	1313	201	<50
7	28	EFV	605	3572	~	ND	PD	<50	<50
8	28	EFV	32	33147	~	ND	PD	835	180
10	33	EFV	502	5722	~	ND	166	181	ND
13	30	EFV	381	947	~	ND	103	74	<50
15	35	EFV	69	108975	~	ND	ND	ND	941
16	28	EFV	354	765	<50	<50	<50	<50	<50

*Participant 1 had high level resistance (NNRTI, NRTI and PI) from baseline sample, suggesting previous ART exposure
^Participant 14 had not been taking study drug, as evidenced by undetectable concentrations on the day of intensive PK ~Protocol did not initially require a repeat VL at randomization in the EFV arm
ND: not done; PD: protocol deviation

Conclusions

- By days 14 and 28, VL was undetectable in 5/8 and 4/8 participants on DTG and 1/5 and 2/7 participants on EFV, respectively
- At 2 weeks postpartum, VL was undetectable in 5/6 participants on DTG and 4/7 participants on EFV
- Modest reduction in DTG exposure T3 does not warrant dose increase
- There were 2 virological failures among participants on DTG and 0 on EFV
- In keeping with other published studies, DolPHIN-1 indicates that standard dosing of DTG should be used in the third trimester
- Adherence was identified to be a problem across both arms
- DolPHIN-1 confirms that mothers who initiate ART in late pregnancy are a vulnerable group who may have a higher rate of treatment failure
- DolPHIN-1 completed recruitment in Jan 2018; follow-up is ongoing

Declarations and Acknowledgements

- This study was funded through an investigator award by ViiV Healthcare
- Study drug (DTG) was provided by ViiV Healthcare
- We thank the TSC/ IDSMB (Graham Taylor, Mark Mirochnick, Helen McIlleron and Polly Clayden), Andrew Hill and the participants and study teams at both sites