Outcomes following Prenatal Exposure to Dolutegravir: the Dolomite-EPPICC study

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Background

- Dolutegravir (DTG) is an integrase strand inhibitor approved for treatment of HIV in adults and adolescents since 2013
- In 2018, **Tsepamo Study, Botswana** reported a significantly increased neural tube defect (NTD) risk in women conceiving on DTG (0.94%)[1], leading to a safety alert.
- Updated analysis of NTD prevalence (August 2014 to March 2019)[2]
  - 5 NTDs among 1,683 deliveries (**0.30%**, 95% CI 0.13-0.69) in women on DTG at conception
  - **0.10%** 95% CI 0.06-0.17 in women on non-DTG ART at conception
  - **0.08%**, 95% CI 0.06-0.10 in HIV-uninfected women
  - prevalence difference for DTG vs. non-DTG at conception remained statistically significant
- **Antiretroviral Pregnancy Registry** reported 1 NTD with 312 periconception DTG exposures (NTD prevalence of 0.3% for DTG; overall risk of defects with periconception DTG was 3.2% (data to July 2019)[3]

[1]Zash et al, NEJM 2018; [2]Zash et al, NEJM 2019; [3]Vannappagari et al EACS 2019

Aim

- To assess pregnancy and neonatal outcomes following DTG use during pregnancy in real-world European settings

Our objectives were to describe:

- the characteristics of pregnant women receiving DTG-based regimens
- the frequency of adverse pregnancy and birth outcomes, by earliest timing of DTG exposure

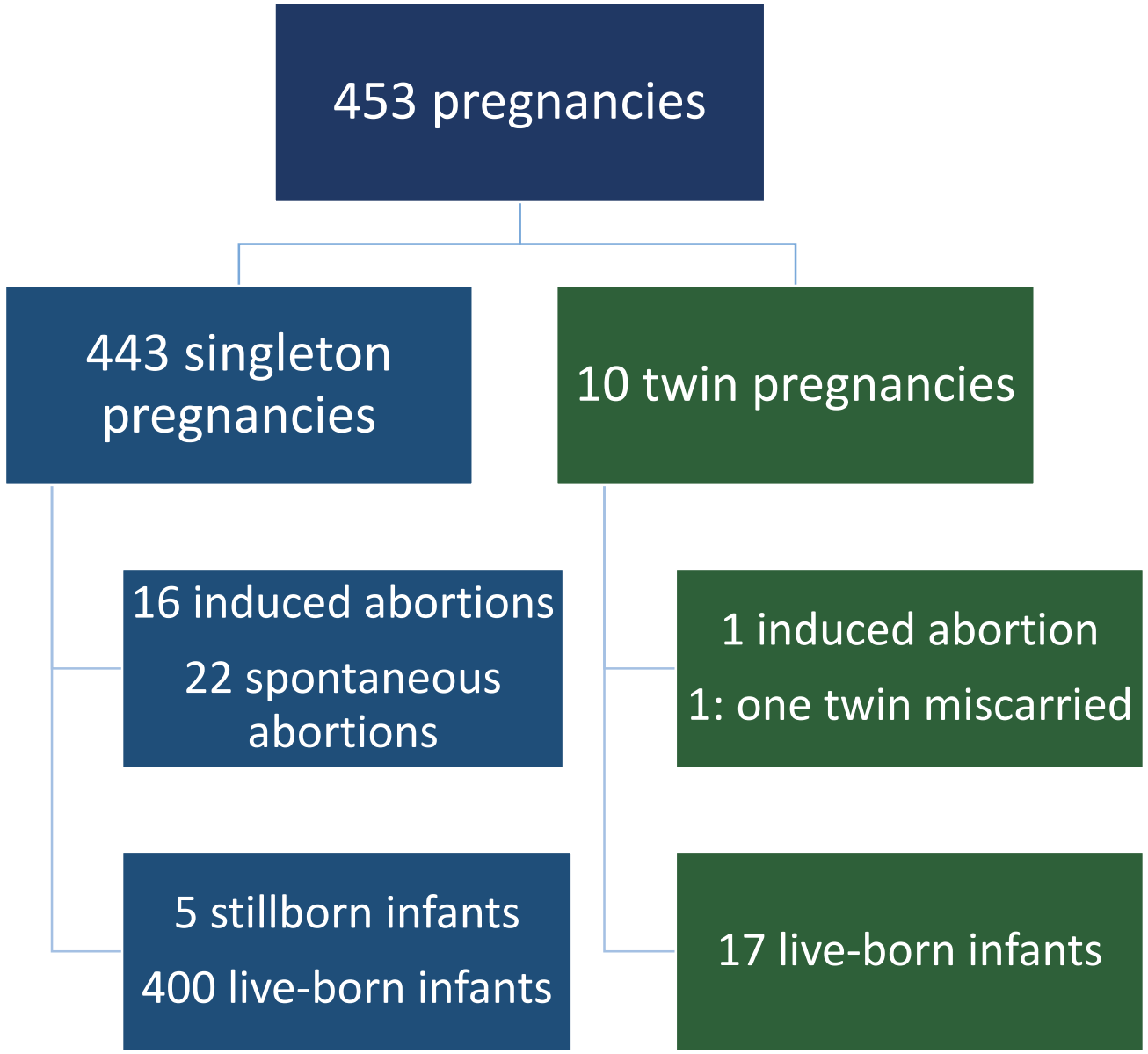
Methods

- The **Dolomite Study** was set up in 2017 to address the use and safety of DTG in pregnant women and exposed infants in Europe and Canada and is conducted within the NEAT-ID network and EPPICC (the European Pregnancy and Paediatric Infections Cohort Collaboration)
- **Dolomite-EPPICC** involves pooled analysis of observational data on DTG-exposed pregnancies from participating studies, following periodic data mergers
- Pseudononymised individual patient data collected from participating studies using a data specification based on a modified HIV Data Exchange Protocol (www.hicdep.org)
- Analysis of prospectively collected individual patient data (i.e. ARV exposure data collected before outcome is known)
- Data merger included
  - All pregnancies with any prenatal DTG exposure
  - With birth outcomes reported by Feb 2019

Definitions

Periconception exposure	Initial exposure within the first 6 weeks of estimated gestational age
Later 1st trimester (T1)	Initial exposure started later in T1 (after 6 weeks estimated gestational age)
2nd / 3rd trimester (T2/T3)	Initial exposure started after 12 weeks estimated gestational age
Induced abortion	Voluntary termination of pregnancy before 22 weeks estimated gestational age
Spontaneous abortion	Death of a fetus or expulsion of the products of conception before 22 weeks gestational age
Low birth weight	Birth weight of <2500 grams
Very low birth weight	Birth weight of <1500 grams
Preterm birth	Birth of live infant at <37 completed weeks gestation
Stillbirth	Death of a fetus occurring at 22 weeks of gestation or more, or for situations in which the gestational age is unavailable, a fetus weighing at least 500 grams

Results


453 pregnancies
443 singleton pregnancies
10 twin pregnancies
16 induced abortions
22 spontaneous abortions
5 stillborn infants
400 live-born infants
1 induced abortion
1: one twin miscarried
17 live-born infants

Pregnancy / maternal characteristics

- 453 pregnancies in 428 women
- Pregnancies reported from 6 countries
  - 347 (76.6%) UK and Ireland
  - 45 (9.9%) Spain
  - 29 (6.4%) Switzerland
  - 29 (6.4%) Italy
  - 3 (0.7%) Romania
- Timing of earliest DTG exposure in 453 pregnancies
  - periconception: 317 (70.0%)
  - later in 1st trimester: 31 (6.8%)
  - 2nd or 3rd trimester: 105 (23.2%)

	428 women	N (%)
Ethnicity N=428	Black African	229 (53.5)
	Black other	35 (8.2)
	White	129 (30.1)
	Other	35 (8.2)
Mode of HIV acquisition N=394	Heterosexual	326 (82.7)
	Injecting drug use	11 (2.8)
	Vertical	42 (10.6)
	Other	15 (3.8)
History of AIDS N=353	Yes	30 (8.5)
HCV status N=395	HCV seropositive	24 (6.1)
HBV status N=393	HBsAg positive	14 (3.6)

Outcomes, by earliest DTG exposure

	Total DTG exposed	Earliest exposure to DTG		
		Periconception	Later T1	T2/T3
Total outcomes, N	463*	325	31	106
Live births	417 (90.1%)	280 (86.1%)	30 (96.8%)	106 (100%)
Stillbirths	5 (1.1%)	5 (1.5%)	0	0
Spontaneous abortions	23 (5.0%)	23 (7.2%)	0	0
Induced abortions	18 (3.7%)	17 (5.2%)	1 (3.2%)	0

*includes outcomes from 10 twin pregnancies

Neonatal Outcomes: 400 singleton, live births

	Total DTG exposed	Earliest exposure to DTG		
		Periconception	Later T1	T2/T3
Total, N	400	266	30	104
Gestational age				
<34 weeks	12 (3.1%)	8 (3.0%)	1 (3.3%)	3 (2.8%)
34-36 weeks	39 (9.7%)	24 (9.0%)	2 (6.7%)	13 (12.5%)
≥ 37 weeks	334 (83.5%)	222 (83.5%)	26 (86.7%)	86 (82.7%)
missing	15 (3.7%)	12 (4.5%)	1 (3.3%)	2 (1.9%)
Birth weight				
<1500g	12 (3.0%)	8 (3.1%)	1 (3.3%)	3 (2.9%)
1500-2499g	36 (9.0%)	23 (8.6%)	2 (6.7%)	11 (10.6%)
≥2500g	342 (85.5%)	230 (86.5%)	26 (86.7%)	86 (82.7%)
missing	10 (2.5%)	5 (1.8%)	1 (3.3%)	4 (3.8%)

Birth defects

- Among the 417 live-born infants there were 17 with reported birth defects (4.1%, 95% CI 2.4, 6.5); one infant had 2 defects.

% of infants with birth defects by timing of earliest exposure to DTG:

Periconception	12/266	4.5%	(95% CI 3.9, 5.1)
Later T1	1/30	3.3%	(95% CI 0.08, 17.2)
T2/T3	4/104	3.8%	(95% CI 1.1, 9.6)

- No defects in stillborn infants
- Of 18 outcomes of induced abortion, there was 1 carried out due to identified birth defects
  - at gestation 29 weeks for neuronal migration disorder and severe microcephaly
  - periconception DTG exposure

Birth defects: details

Organ system	Exposure	Birth defect
Heart	PC	Patent Foramen Ovale
N=3	PC	Interatrial communication – ostium secondum
	PC	Septal defect
Genitourinary	PC	2 x Congenital hydronephrosis
N=7	PC	Ectopic Kidney
	PC	3 x Hypospadias*
	T2/3	Hypospadias
Gastrointestinal	T2/3	Duodenal atresia and stenosis
N=2	PC	Gastroschisis
Limb	PC	2 x Polydactyly*
N=3	T2/3	Polydactyly
Other	Later T1	Ankyloglossia
N=3	T2/3	Hyperpigmentation on back
	PC	Naevus flammeus

*1 infant had hypospadias and polydactyly

PC= periconception

Birth defects: details

Organ system	Exposure	Birth defect	EuroCAT?
Heart	PC	Patent Foramen Ovale	No
N=3	PC	Interatrial communication – ostium secondum	Yes
	PC	Septal defect	Yes
Genitourinary	PC	2 x Congenital hydronephrosis	Yes
N=7	PC	Ectopic Kidney	Yes
	PC	3 x Hypospadias*	Yes
	T2/3	Hypospadias	Yes
Gastrointestinal	T2/3	Duodenal atresia and stenosis	Yes
N=2	PC	Gastroschisis	Yes
Limb	PC	2 x Polydactyly*	Yes
N=3	T2/3	Polydactyly	Yes
Other	Later T1	Ankyloglossia	No
N=3	T2/3	Hyperpigmentation on back	No
	PC	Naevus flammeus	No

*1 infant had hypospadias and polydactyly

PC= periconception

Perinatal mortality

Stillbirths

- 5 Stillbirths: 4 female, 1 unknown sex; 4 preterm, 1 term
- All exposed to periconception DTG
- None with birth defects reported
- Stillbirth rate: 11.8 per 1000 (95% CI 3.9, 27.4)

Neonatal death

- 1 death in an extremely preterm infant
  - born at 23 weeks gestation
- Died on 2nd day of life
- Periconception DTG exposure

Comparative data from National Surveillance of HIV in Pregnancy and Childhood (England & Wales), 2010-2016

	Rate /1000	95% CI
Stillbirth	7.4	(5.7, 9.5)
Neonatal death	4.2	(2.8, 5.7)
Extended perinatal mortality	11.5	(9.3, 14.0)

Perinatal mortality rate: 14.2 per 1000 (95% CI 5.2, 30.7)

perinatal mortality = stillbirths + deaths in first 7 days of life; extended perinatal mortality = stillbirths + neonatal deaths (before 28 days of life)

Conclusions

- This is the largest study to date of DTG use in pregnancy in Europe in which 70% of 453 pregnancies had periconception DTG exposure
- Overall, 4.1% prevalence of birth defects (3.1% if considering only EuroCAT defects)
- No NTDs were reported – but:
  - NTD are rare events (≈0.1% birth prevalence)
  - sample size of <300 pregnancies with periconception DTG exposure
  - cannot rule out or confirm any potential association of DTG with NTD
    - 2000 exposures needed to rule out a 3-fold increase for NTDs
- The birth defect rate and pattern add to the current evidence base on periconception DTG use and safety
- This study is ongoing, in order to provide additional data from European settings

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- NENEXP Study (Catalonia)
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- UK / Ireland National Surveillance of HIV in Pregnancy and Childhood (NSHPC)
- Madrid Cohort of HIV-Infected Mother-Infant Pairs
- Victor Babes Hospital Cohort

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