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

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BACKGROUND

- Dolutegravir (DTG) is recommended and widely used during pregnancy for maternal viral suppression and preventing vertical transmission
- The **Dolomite Study** was set up in 2017 to address use and safety of DTG in pregnancy and exposed infants in Europe and Canada
  - Conducted within the NEAT-ID network and EPPICC (the European Pregnancy and Paediatric Infections Cohort Collaboration) and coordinated by Penta Foundation

OBJECTIVE

- To assess pregnancy and neonatal outcomes including birth defects following prenatal DTG use using real-world European data

METHODS

- **Dolomite-EPPICC** involves pooled analyses of prospectively collected individual patient data on DTG-exposed pregnancies from participating studies
- Data specification based on a modified HIV Data Exchange Protocol (www.hicdep.org)
- Data merger included
  - All pregnancies with any prenatal DTG exposure
  - With birth outcomes reported by end 2019
- Periconception DTG exposure was defined as initial exposure at ≤6 weeks of estimated gestational age (EGA)
- Preterm deliveries (PTD) were those occurring at <37 completed gestational weeks and very PTD at <34 weeks
- Low birth weight (LBW) was <2500g and very LBW was <1500g
- There were seven participating cohorts from Italy, Romania, the Russian Federation, Spain, Switzerland and UK/Ireland

RESULTS

- 550 pregnancies in 428 women were included (**Table 1**)
  - 540 singleton and 10 twin pregnancies
  - Most pregnancies reported from the UK/Ireland (79%)
  - Nearly three-quarters of pregnancies were in parous women (365/506)
- 508 liveborn infants (491 singletons and 17 twins), with singletons delivered at a median (IQR) gestational age of 39 (38, 40) weeks
- Birth outcomes presented in the Figure

Dolomite-EPPICC study found **64%** of 550 enrolled pregnancies had periconception DTG exposure, with **no NTDs** reported**.** Overall **birth defect prevalence was 3.9%.**

Table 1 Pregnancy outcomes

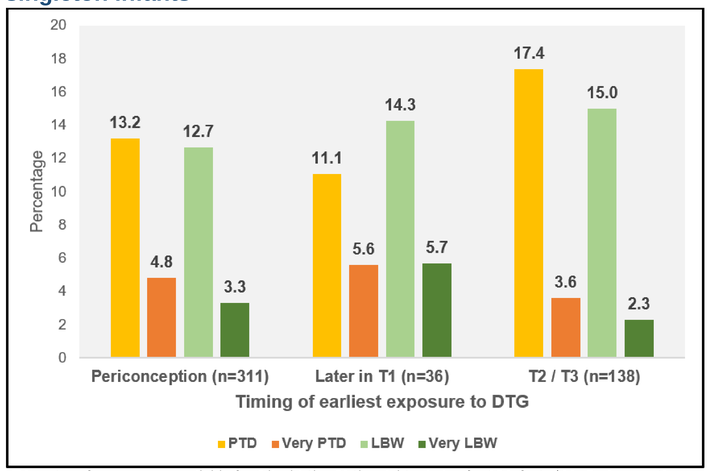
Pregnancies N=550 (including 10 twin pregnancies)	Overall DTG exposed	Earliest exposure to DTG			
		Peri-conception	Later 1st trimester	2nd / 3rd trimester	Unknown
Live born infants	508	326 (64.2%)	36 (7.1%)	140 (27.6%)	6 (1.2%)
Stillbirths	5	5	-	-	-
Spontaneous abortions	27	27	-	-	-
Induced abortions	18	17 (94.4%)	1 (5.6%)	-	-

Table 2 Details of birth defects in live-born infants

Organ system	Exposure	Birth defect	EUroCAT
Heart N=4	PC	Patent foramen ovale	No
	PC	Interatrial communication – ostium secondum	Yes
	PC	Septal defect	Yes
	PC	Unspecified heart defect	Yes
Genitourinary N=7	PC	Congenital hydronephrosis (2 infants)	Yes
	PC	Ectopic Kidney	Yes
	PC	Hypospadias (3 infants*)	Yes
	T2/3	Hypospadias	Yes
Gastrointestinal N=2	T2/3	Duodenal atresia and stenosis	Yes
	PC	Gastroschisis	Yes
Limb N=4	PC	Congenital vertical talus (both feet)	No
	PC	Polydactyly (2 infants*)	Yes
	T2/3	Polydactyly	Yes
Other N=4	Later T1	Ankyloglossia	No
	T2/3	Hyperpigmentation on back	No
	PC	Naevus flammeus	No
	PC	Skin tag	No

*1 infant had hypospadias and polydactyly

Figure: Preterm delivery and low birth weight in 485 live-born singleton infants



Trimester of exposure unavailable for 6 livebirths. Birthweight missing for 10 infants (4 in Periconception, 1 in Later in T1 and 5 in T2/T3 groups)

BIRTH DEFECTS

- 1 of 18 induced abortion was due to identified birth defects
  - neuronal migration disorder and severe microcephaly
- No stillborn infants had a birth defect
- 21 live-born infants had ≥1 birth defect(s) (one infant had two defects, the remainder one). One infant with Down Syndrome was excluded from the defect case count.
- Details of the remaining 21 defects are provided in **Table 2**
- Overall prevalence of birth defects was 3.9% (95% CI 2.4, 6.0)
- Among infants with periconception exposure to DTG, 4.6% (15/326) had a birth defect (95% CI 2.6, 7.5) compared with 2.9% (4/140) of infants with earliest exposure in the 2nd or 3rd trimester (95% CI 0.8, 7.2)

CONCLUSIONS

- The prevalence rate for overall birth defects reported in this updated analysis from Dolomite-EPPICC is the same as recently reported from the Antiretroviral Pregnancy Registry for periconception exposure to DTG
- No NTDs were reported, but 2000 exposures would be needed to rule out a 3-fold increase for these rare events (≈0.1% birth prevalence)
- We will continue to monitor use and safety of DTG-based regimens in pregnancy, noting that our sample size of periconception exposures is currently too small to exclude potential associations with rare birth defects

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