Pregnancy and Neonatal Outcomes following Prenatal Exposure to Dolutegravir

C. Thorne[1], G. Favarato[1], H. Peters[1], A. Soriano-Arandes[2], M. Floridia[3], A. Colbers[4], T. Goetghebuer[5], L. Ragone[6], K. Aebi-Popp[7], M. Sovric[8], D. Burger[4], A. Pozniak[9], C. Giaquinto[10], V. Vannappagari[6]

1. UCL Great Ormond Street Institute of Child Health, London, UK; 2. Hospital Universitari Vall d'Hebron, Barcelona, Spain; 3. Istituto Superiore di Sanità, Rome, Italy; 4. Radboud University Medical Centre, Nijmegen, the Netherlands; 5. Hospital St Pierre, Belgium; 6. ViiV Healthcare; 7. Bern University Hospital, Switzerland; 8. Munich University Hospital, Germany; 9. Chelsea & Westminster Hospital, London, UK; 10. PENTA Foundation, Padua, Italy

BACKGROUND

- Dolutegravir (DTG) is an integrase strand inhibitor approved for the treatment of HIV in adults and adolescents since 2013
- Marketed as a single agent as Tivicay© and as a fixed dose combination tablet as Triumeq© (DTG/abacavir/lamivudine)
- In animal and *ex vivo* human placenta perfusion studies, DTG was shown to cross the placenta
- However, there is minimal information on use and safety of DTG in pregnant women

AIM

- **To assess maternal and fetal 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
- To describe the frequency of adverse pregnancy and birth outcomes, by trimester of DTG-exposure

METHODS

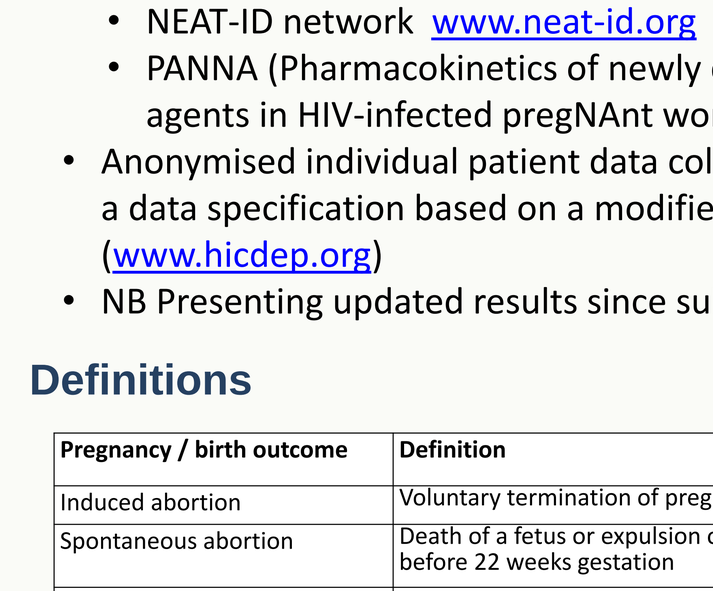
- Analysis of prospectively collected individual patient data (i.e. with ARV exposure data collected before outcome is known) in observational studies of pregnant women living with HIV and their infants in Europe
- Data collection through:
  - European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) http://penta-id.org/hiv/eppicc/
  - NEAT-ID network www.neat-id.org
  - PANNA (Pharmacokinetics of newly developed ANtiretroviral agents in HIV-infected pregNAnt women) www.pannastudy.com
- Anonymised individual patient data collected from studies/sites using a data specification based on a modified HIV Data Exchange Protocol (www.hicdep.org)
- NB Presenting updated results since submission of abstract

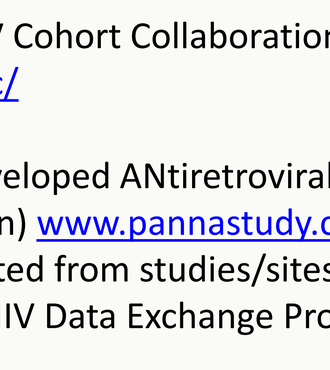
Definitions

Pregnancy / birth outcome	Definition
Induced abortion	Voluntary termination of pregnancy before 22 weeks gestation
Spontaneous abortion	Death of a fetus or expulsion of the products of conception before 22 weeks gestation
Low birth weight	Birth weight of <2500 grams
Very low birth weight	Birth weight of <1500 grams
Small for gestational age	Based on sex-specific US standard[1]
Preterm birth	Birth of live infant at <37 weeks gestation
Stillbirth	Death of a fetus occurring at ≥22 gestational weeks

1. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. Obstetrics and Gynecology. 1996;87(2):163-8.

RESULTS





Country	Pregnancies
Belgium	2
Germany	19
Italy	5
Netherlands	2
Spain	9
Switzerland	3
UK & Ireland	61
TOTAL	**101**

Table 1: Pregnancies: maternal characteristics

		N (%)
Ethnicity N=100	Black	71 (70%)
	White	22 (22%)
	Other	7 (7%)
Region of origin N=93	sub-Saharan Africa	62 (67%)
	Europe	22 (24%)
	Other	9 (10%)
Age at conception N=101	<25 years	16 (16%)
	25-34 years	46 (46%)
	≥ 35 years	39 (39%)
Mode of HIV acquisition N=94	Heterosexual	81 (86%)
	Injecting drug use	3 (3%)
	Vertical	9 (10%)
	Other	1 (1%)

		N (%)
Timing of HIV diagnosis N=101	Pre-pregnancy	86 (85%)
	Antenatal	15 (15%)
History of AIDS N=89	Yes	10 (11%)
HCV status N=91	HCV seropositive	8 (9%)
HBV status N=91	HBsAg positive	4 (4%)
CD4 count (first in pregnancy) N=89	≤350 cells/mm³	38 (43%)
	>350 cells/mm³	51 (57%)
ART at conception N=92	Yes	55 (60%)

Table 2: Pregnancies, by earliest exposure to DTG

	T1 N (%)	T2 N (%)	T3 N (%)	Missing N (%)	Total
All pregnancies	58 (57.4)	24 (23.8)	18 (17.8)	1 (1.0)*	101 (100%)
Pregnancies ending in livebirths	42 (51.9)	21 (25.9)	17 (21.0)	1* (1.2)	81 (100%)
Stillbirth	0	1	0	0	1
Induced abortion~	1	0	0	0	1
Spontaneous abortion#	1	0	0	0	1

* Missing start date of DTG for 1 pregnancy ending in livebirth; ~ Personal decision, no fetal abnormality; # At 10 weeks gestation

- Of 82 pregnancies ending in live birth or stillbirth, 45 (57%) were vaginally delivered, 21 (27%) were elective CS, 9 (11%) were emergency CS and 4 unspecified CS (4 missing)
- Among 80 infants (79 singleton live births and 1 stillbirth) **13.8%** (11/80) infants were delivered **preterm**, **16.7%** (13/78) had **LBW** and **18.7%** (24/75) were **SGA**

Table 3: Gestational age, birthweight and SGA, by earliest DTG exposure

		Earliest DTG exposure in T1	Earliest DTG exposure in T2	Earliest DTG exposure in T3	Total
Gestational age N=79*	≥37 weeks	37/40 (92.5%)	16/22 (72.7%)	15/17 (88.2%)	68/79 (86.1%)
	34-36 weeks	2/40 (5.0%)	5/22 (22.7%)	2/17 (11.8%)	9/79 (11.4%)
	<34 weeks	1/40 (2.6%)	1/22 (4.6%)	0/17	2/79 (2.5%)
Birthweight N=77~	≥2500g	35/39 (89.7%)	15/21 (71.4%)	14/17 (82.3%)	64/77 (83.1%)
	1500-2499g	4/39 (10.3%)	6/21 (28.6%)	3/17 (17.7%)	13/77 (16.9%)
	<1500g	0/39	0/21	0/17	0/77
SGA N=75	No	34/39 (87.1%)	13/20 (65.0%)	14/16 (87.5%)	62/75 (81.3%)
	Yes	5/39 (12.8%)	7/20 (35.0%)	2/16 (12.5%)	24/75 (18.7%)

* 1 live-born infant excluded due to missing DTG start date (born at term), ~ 2 excluded due to missing BW (DTG exposure in T1)

- Data on congenital abnormalities available for 81 of 84 live-born / stillborn infants
- Abnormalities were reported in 4 live-born infants (4.9%, 95% CI 1.4, 12.2%)
- Abnormality rate was 3/42 (7.1%) among infants with earliest DTG exposure in T1 and 4.2% (1/24) for infants with earliest exposure in T2

Table 4: Congenital abnormalities

	Abnormality	Earliest DTG exposure	Infant sex	Maternal details	Other ARV exposures	Country
Infant 1	Patent Foramen Ovale, with small left-to-right interatrial shunt	From conception	Male	Black African, aged 38 at delivery	3TC, ABC	Italy
Infant 2	Bilateral hexadactyly, hands (father has the same defect)	Week 3	Male	White, aged 40 at delivery	3TC/ABC, FTC/TDF in T1	Italy
	Hypospadias					
Infant 3	Ankyloglossia (tongue-tie)	Week 12	Male	White, vertically infected, aged 31 at delivery	DRV/r, FTC/TDF, ATZ/r, RAL, TDF in T1	Italy
Infant 4	Hyperpigmentation on back	Week 14	Male	Black African, aged 34 at delivery	3TC, ABC	Switzerland

* Abnormalities reported in infants 3 and 4 not considered defects in EUROCAT classification

CONCLUSION

- This is the largest study to date of DTG use in pregnancy in Europe
- Nearly 60% of the included pregnancies had first trimester DTG exposure
- PTD (14%) and SGA (19%) rates were similar to those reported in UK:
  - PTD: 14% among women on ART at conception with CD4<350, 11% not on ART at conception irrespective of CD4; SGA: 20% *(Favarato et al, CROI 2017 and submitted)*
- Maternal characteristics of this "first wave" of DTG-exposed pregnancies differ from the larger population of pregnant women living with HIV
  - 10% vertically infected, 9% HCV co-infected
- Ongoing work to collect outcome data on the 16 continuing pregnancies
- These findings contribute to the evidence base on the real-world safety of DTG in pregnancy, but small numbers preclude firm conclusions
- Further prospective monitoring is required, particularly as DTG use expands

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