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I have read this report and confirm that to the best of my knowledge this report accurately describes the conduct and results of study 208613.

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DOLOMITE EPPICC STUDY

Pregnancy and Neonatal Outcomes Following Prenatal Exposure to Dolutegravir: Data from the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC)

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ABBREVIATIONS

ART	Antiretroviral therapy
CI	Confidence interval
DTG	Dolutegravir
EPPICC	European Pregnancy and Paediatric Infections Cohort Collaboration
EUROCAT	European network of population-based registries for the epidemiological surveillance of congenital anomalies
HBV	Hepatitis B Virus
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C Virus
HIV	Human immunodeficiency virus
IDU	Injecting drug use
IQR	Interquartile range
NRTI	Nucleoside/nucleotide reverse transcriptase inhibitor
NTD	Neural tube defect
PC	Periconception
T1	First trimester
T2	Second trimester
T3	Third trimester
SGA	Small-for-gestational-age

1. Background and rationale

Dolutegravir (DTG) is an integrase strand transfer inhibitor, indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults. DTG was granted a European marketing authorisation from the European Medicines Agency in 2014. An initial study involving European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC) studies along with the NEAT-ID and PANNA networks analysed prospective data on 101 pregnancies with DTG use up to mid-2016, with results presented in a joint publication with the Antiretroviral Pregnancy Registry (Vannappagari et al 2019). Thus, at the time that the DOLOMITE EPPICC Study was developed and initiated in 2017, there were no adequate and well-controlled studies evaluating the use of DTG in pregnancy. The current study was therefore initiated to assess “real-world” maternal and neonatal outcomes following DTG use during pregnancy and increase knowledge of the safety profile of DTG in pregnancy.

In the most recent (March 2022) report from a birth outcome surveillance study in Botswana (Tsepamo Study), there were 10 cases of neural tube defects (NTD) reported out of 9,460 deliveries (0.11%) to patients who were exposed to DTG-containing regimens at the time of conception, which is not statistically different than exposure in any of the comparison groups, including exposure to non- DTG-containing regimens at the time of conception and HIV-uninfected women (Zash et al 2022). This constitutes a further decline in NTD prevalence in deliveries of patients exposed to DTG-containing regimens at the time of conception reported in March 2021 (0.15%). In addition, an ongoing birth surveillance study in Eswatini (Gill et al 2023), with methodology similar to that of the Botswana Tsepamo Study, reported on birth surface defect surveillance conducted September 2021 through September 2022 at five hospitals in four regions of Eswatini that account for 73% of all births in the country in 2021. The study included 7,554 pregnant women living with HIV, 4,832 of whom were receiving DTG regimens at conception, and 17,270 women without HIV infection. NTD prevalence was 0.08% (n=4) in women with HIV receiving DTG at conception and 0.08% (n=13) in women without HIV infection; the prevalence was 0.16% (n=2) in the smaller number of 1,248 women receiving non-DTG regimens at conception. Combined with the Tsepamo Study data, there are now >14,000 births among women on DTG at conception with 14 NTDs identified, giving a weighted NTD prevalence of 0.098%, which is not significantly different than non-DTG regimens at conception or women without HIV infection in either country. These data do not support a causal association between NTD and periconception exposure to DTG.

2. Objectives

The objectives of DOLOMITE: EPPICC were as follows:

1. To describe the trends and patterns of use of DTG-containing regimens in pregnancy in Europe, including timing of initiation, nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) backbone and geographic/calendar time trends

2. To characterize the contemporary population of women taking DTG-based regimens by trimester of exposure

3. To describe frequency of adverse pregnancy outcomes in women using DTG in pregnancy including birth defects, stillbirths, spontaneous abortions, induced abortions, preterm births, low birth weight infants, and very low birth weight infants by trimester of exposure

4. To describe the proportion of women on DTG who achieve viral suppression by the end of pregnancy by trimester of exposure

5. To describe vertical transmission rates in mother-infant pairs with antenatal DTG use

3. Methods

3.1 Study design

This was a non-interventional study involving analysis of observational individual patient data prospectively (exposure data collected before outcome is known) collected in cohort and surveillance studies of pregnant women living with HIV and their infants from several countries participating in EPPICC.

The study utilised the now well-established framework for individual patient data meta-analysis within EPPICC (EPPICC 2019, EPPICC 2020). EPPICC conducts epidemiological research on pregnant women living with HIV and their children, with a focus on scientific and clinical management-related questions requiring a large sample size of patients which the contributing studies cannot answer individually. Participating studies include multisite cohorts with national or sub-national coverage, single-site cohorts and surveillance studies.

Participating sites/cohorts in EPPICC provided pseudonymised individual patient data prepared according to a detailed standard operating procedure at agreed time-points during the study period. The data specification was based on a modified HIV Data Exchange Protocol (HICDEP) (www.hicdep.org). Variables included sociodemographic, clinical and treatment factors, and

pregnancy and neonatal outcomes. Following merger of these individual cohort/study datasets, analyses were conducted on the pooled dataset to address the study objectives.

3.2 Study population

All pregnant women with any exposure to DTG (TIVICAY® & TRIUMEQ®) at any time during the pregnancy and their infants were included, regardless of pregnancy outcome. Those without known outcome data (including those with continuing pregnancies at time of data collection or lost to follow-up with unknown pregnancy outcome) were excluded. Sequential DTG-exposed pregnancies with known outcomes in the same woman were included.

3.3 Outcome definitions

The outcomes assessed were:

- Pregnancy outcomes (i.e., spontaneous abortion, induced abortion, live birth, stillbirth) by trimester of exposure to DTG
- Adverse pregnancy outcomes by trimester of exposure to DTG, including birth defects, preterm births, low birth weight infants, and very low birth weight infants as defined in Table 1

Table 1 Definitions of pregnancy outcomes, based on consensus from participating studies in EPPICC

Pregnancy 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
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 g

The perinatal mortality rate was expressed as the number of stillbirths and deaths in the first seven days of life per 1000 births, and the extended perinatal mortality rate as stillbirths and deaths before day 28 of life per 1000 births. Infants were classified as small for gestational age (SGA) if their weight centile was below the 10th percentile using INTERGROWTH-21ST standards (Villar et al 2014). Birth

defects were classified according to the World Health Organization's International Classification of Diseases, Tenth Revision. All birth defects were tabulated and reported by organ class affected. In addition, defects were labelled with respect to whether they met EUROCAT (European network of population-based registries for the epidemiological surveillance of congenital anomalies) criteria; defects included in the EUROCAT list of "minor anomalies for exclusion" were included with those not meeting EUROCAT criteria. Participating studies collected data on birth defects apparent / diagnosed at birth or until postnatal discharge, as well as any birth defect reported following postnatal discharge (for example, during initial infant follow-up).

Maternal virological suppression at the "end of pregnancy" was based on the measurement reported closest to delivery, measured up to 28 days before and 7 days after delivery, with suppression defined as viral load <50 copies/mL. This was restricted to pregnancies ending in live births or stillbirths.

Infant HIV infection status was classified as uninfected or infected on the basis of reported polymerase chain reaction (PCR) test results and/or 18-month antibody testing. Infants whose infection status had not yet been reported were classified as having indeterminate status.

3.4 Other definitions

A pregnancy with any documented exposure to DTG was considered "DTG-exposed". Periconception ('PC') DTG exposure was defined as an initial exposure at ≤6 completed gestational weeks, later first trimester ('later T1') DTG exposure as initial exposure in the first trimester at >6 completed gestational weeks and second/third trimester ('T2/T3') DTG exposure as initial exposure at >12 completed gestational weeks. Third trimester ('T3') DTG exposure was defined as initial exposure at >26 completed gestational weeks. Gestational age at earliest DTG exposure was determined using the estimated date of delivery; where unavailable, the date of the last menstrual period was used.

For induced and spontaneous abortions, data were not available on fetal number in some cases; these were considered as singleton pregnancies.

Maternal hepatitis B virus (HBV) co-infection was defined as reported Hepatitis B surface antigen (HBsAg) positivity or reported HBV co-infection. Maternal hepatitis C virus (HCV) co-infection was defined as documented HCV seropositivity or reported co-infection with HCV; it was not possible to classify according to viremic HCV status and some women in the HCV co-infection group may have been non-viremic following HCV treatment or spontaneous clearance.

3.5 Data sources

Participating EPPICC cohorts and studies (i.e., those with pregnancies with DTG use) were the Italian Group on Surveillance of Antiretroviral Treatment in Pregnancy; NENEXP Study (Catalonia, Spain); the

Madrid Cohort of HIV-infected Mother-Infant Pairs (Spain); Swiss Mother and Child HIV Cohort Study (MoCHiV); the Integrated Screening Outcomes Surveillance Service (UK / England) – formerly known as the National Study of HIV in Pregnancy and Childhood; Victor Babes Hospital cohort (Romania) and the St Petersburg City Centre for AIDS and Infectious Diseases cohort.

3.6 Data management and analysis

Data were reviewed for completeness with logical and consistency checks and any data queries resolved with the participating cohort.

Standard descriptive statistics were used to summarize the data (e.g. socio-demographic variables, history of previous pregnancies and the outcomes and those that describe specific maternal and infant outcomes). For continuous variables, the sample size, median and interquartile range (IQR) were provided, with frequency distributions provided for categorical variables. For rates, 95% confidence intervals (CI) were calculated.

Analyses of neonatal outcomes were restricted to pregnancies ending in singleton live births.

Statistical analyses were conducted using STATA® v16 and v17 software (StataCorp, College Station, Texas).

3.7 Protection of human subjects

Participating studies obtained ethical approval from local and/or national committees. EPPICC Pregnancy has ethical approval from the University College London Research Ethics Committee (reference 3715.007).

4. Results

4.1 Pregnancy characteristics and outcomes

A total of 848 pregnancies with EDD up to December 2021 in 769 women were reported during the study period up to March 2023 and 15 had unknown pregnancy outcome. A total of 833 pregnancies in 756 women with data on pregnancy outcomes were included in the analysis (Tables 2 and Table 3). The distribution of these pregnancies over calendar time (based on conception year) is presented in Figure 1.

Table 2 Pregnancies with known outcomes (N=833)

	N (%)
Pregnancies resulting in live births	770 (92.4)
Pregnancies resulting in stillbirths	5 (0.6)
Spontaneous abortions	37 (4.4)
Induced abortions	21 (2.5)

Table 3 Number of live born infants

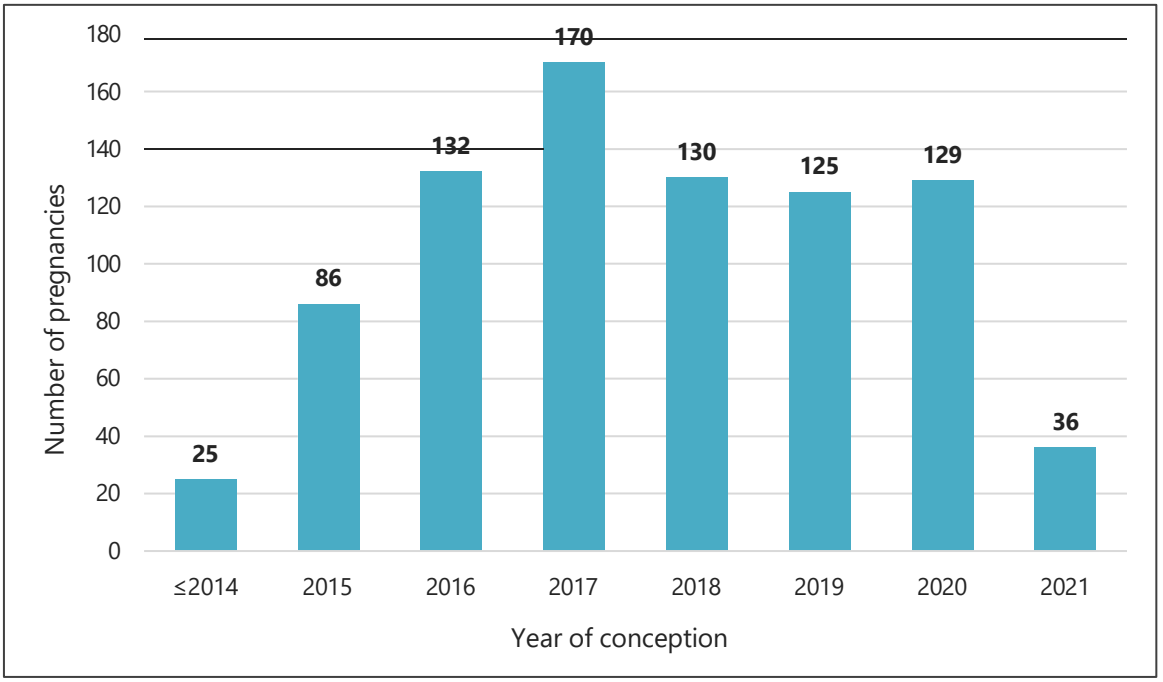
Total live born infants	790
Singletons	750
Twins	37*
Triplets	3

*One miscarried twin

There were 21 twin/triplet pregnancies, one of which ended in an induced abortion and another with the spontaneous abortion of one twin; the discordant outcome twin pregnancy was classified as a live birth for the purposes of these analyses.

Timing of earliest DTG exposure was available for all but four pregnancies. Among the 829 pregnancies with timing information, earliest DTG exposure occurred in the periconception period for 527 (63.6%) pregnancies, later in the first trimester for 38 (4.6%) and in the second or third trimester for 264 (31.8%) pregnancies. Use of NRTIs at the time of earliest DTG exposure is presented in Table 4. The "other" group included pregnancies where use of one or three NRTIs was reported. In 3% of pregnancies no NRTI use was reported at the time of earliest DTG exposure.

Figure 1 Included pregnancies* by year of conception, *N*=833



* EDD by 31st December 2021

Table 4 NRTI use at time of earliest DTG exposure in all pregnancies (N=833)

	N (%)
Abacavir + Lamivudine	485 (58.2)
Tenofovir Disoproxil Fumarate + Lamivudine or Emtricitabine (XTC)	262 (31.5)
Tenofovir Alafenamide + XTC	36 (4.3)
Other	24 (2.9)
No NRTI reported	26 (3.1)

Maternal characteristics of the 808 singleton pregnancies are presented in Table 5, stratified by timing of earliest exposure to DTG. Overall, most (64%) pregnancies were in women of Black ethnicity. Heterosexual contact was the most common mode of maternal HIV acquisition; women had vertically-acquired infection in 11% of pregnancies. Overall, 89% of pregnancies were in women whose HIV had been diagnosed before conception. First CD4 count available in pregnancy was below 350 cells/mm^3 in 29% of pregnancies.

Table 5 Maternal characteristics of singleton pregnancies, by timing of earliest exposure to DTG

	Pregnancies, *n* (%)					
	PC/later T1		T2/T3		Total*	
	551 (68.2%)		257 (31.8%)		*N*=808	
Ethnicity						
White	172	(31.2%)	52	(20.2%)	224	(27.7%)
Black	333	(60.4%)	181	(70.4%)	514	(63.6%)
Hispanic/Latinx	10	(1.8%)	9	(3.5%)	19	(2.4%)
Asian	18	(3.3%)	4	(1.6%)	22	(2.7%)
Mixed race	9	(1.6%)	10	(3.9%)	19	(2.4%)
Other race	7	(1.3%)	0	(0.0%)	7	(0.9%)
Not known	2	(0.4%)	1	(0.4%)	3	(0.4%)
Region of birth						
Sub-Saharan Africa	271	(49.2%)	162	(63.0%)	433	(53.6%)
Europe	192	(34.8%)	63	(24.5%)	255	(31.6%)
Other	49	(8.9%)	22	(8.6%)	71	(8.8%)
Not known	39	(7.1%)	10	(3.9%)	49	(6.1%)
Age at conception						
<25 years	69	(12.5%)	41	(16.0%)	110	(13.6%)
25-34 years	290	(52.6%)	142	(55.3%)	432	(53.5%)
≥35 years	192	(34.8%)	74	(28.8%)	266	(32.9%)
Mode of HIV acquisition						
Injecting drug use	9	(1.6%)	4	(1.6%)	13	(1.6%)
Heterosexual contact	407	(73.9%)	193	(75.1%)	600	(74.3%)
Vertical	61	(11.1%)	28	(10.9%)	89	(11.0%)
Other	16	(2.9%)	3	(1.2%)	19	(2.4%)
Not known	58	(10.5%)	29	(11.3%)	87	(10.8%)
Timing of HIV diagnosis						
Before current pregnancy	544	(98.7%)	171	(66.5%)	715	(88.5%)
During current pregnancy	4	(0.7%)	77	(30.0%)	81	(10.0%)
Not known	3	(0.5%)	9	(3.5%)	12	(1.5%)
HCV co-infection						
No	489	(88.7%)	233	(90.7%)	722	(89.4%)
Yes	21	(3.8%)	7	(2.7%)	28	(3.5%)
Not known	41	(7.4%)	17	(6.6%)	58	(7.2%)
HBV co-infection						
No	487	(88.4%)	227	(88.3%)	714	(88.4%)
Yes	17	(3.1%)	12	(4.7%)	29	(3.6%)
Not known	47	(8.5%)	18	(7.0%)	65	(8.0%)
CD4 count (first in pregnancy)						
≤350 cells/mm^3	119	(21.6%)	113	(44.0%)	232	(28.7%)
>350 cells/mm^3	342	(62.1%)	125	(48.6%)	467	(57.8%)
Not known	90	(16.3%)	19	(7.4%)	109	(13.5%)
Any ART at conception						
No	26	(4.7%)	160	(62.3%)	186	(23.0%)
Yes	524	(95.1%)	97	(37.7%)	621	(76.9%)
Not known	1	(0.2%)	0	(0.0%)	1	(0.1%)
Cohort country						
Italy	21	(3.8%)	6	(2.3%)	27	(3.3%)
Romania	5	(0.9%)	1	(0.4%)	6	(0.7%)
Russian Federation	2	(0.4%)	0	(0.0%)	2	(0.2%)
Spain	61	(11.1%)	21	(8.2%)	82	(10.1%)
Switzerland	25	(4.5%)	5	(1.9%)	30	(3.7%)
United Kingdom	437	(79.3%)	224	(87.2%)	661	(81.8%)

* This table excludes four pregnancies with unknown timing of earliest DTG exposure.

Timing of earliest exposure to DTG for the 808 singleton pregnancies is presented in Table 6, according to pregnancy outcome.

Table 6 Pregnancy outcomes among singleton pregnancies, by timing of earliest exposure to DTG

	Total DTG exposed*	Earliest exposure to DTG		
		Periconception	Later T1	T2/T3
Total outcomes, *N*	808	513	38	257
Live births, *n* (%)	747	453 (60.6%)	37 (5.0%)	257 (34.4%)
Stillbirths, *n* (%)	5	5 (100.0%)	0 (0.0%)	0 (0.0%)
Spontaneous abortions, *n* (%)	36	36 (100.0%)	0 (0.0%)	0 (0.0%)
Induced abortions, *n* (%)	20	19 (95.0%)	1 (5.0%)	0 (0.0%)

* This table excludes four pregnancies with unknown timing of earliest DTG exposure (3 live births, 1 spontaneous abortion).

Of the five stillborn infants, four were female and one had unknown sex. Gestational age at delivery ranged between 24 and 37 weeks, and three of the four infants with available information had low birthweight. These cases were born in the earlier years of the study (one each in 2016 and 2017 and three in 2018). The earliest exposure to DTG was periconception for all five stillbirth cases (Table 6). Thirty-seven singleton pregnancies ended in a spontaneous abortion; all 36 with known timing of DTG use occurred in women on DTG-containing ART regimens from before conception (Table 6). Of the 20 pregnancies ending in induced abortion, all but one had periconception exposure to DTG.

Pregnancy outcomes for the multiple pregnancies, by timing of DTG exposure, are presented in the Appendix. Of the 21 multiple pregnancies, one twin pregnancy was terminated and in another twin pregnancy, one of the twins was miscarried; in both pregnancies, there was periconception DTG exposure.

4.2 Birth and neonatal characteristics

Among the 750 singleton, live-born infants, 383 (51.1%) were male, 349 (46.5%) female, and 18 (2.4%) had unknown sex. Birth outcomes and neonatal deaths by timing of earliest exposure to DTG are summarised in Table 7 for the 747 infants with known timing of DTG exposure. The preterm delivery rate overall was 13.3% (97/727), with 30 (4.1%) infants delivered before 34 completed weeks of gestation. Overall, 12.4% (92/739) of infants had low birthweight, with 2.6% (19/739) having very low birthweight, whilst 61 (8.7%) of the 705 singleton infants with available data were SGA.

The two neonatal deaths among the singleton infants (Table 7) comprised one extremely preterm infant (born at 23 weeks gestation) who died on the second day of life (T2/T3 DTG exposure) and one infant born at 38 weeks gestation with missing cause and date of death (periconception DTG exposure). Among singleton births, the perinatal mortality rate was 7.9 per 1000 births (95% CI 2.9, 17.2) and the extended perinatal mortality rate was 9.3 per 1000 births (95% CI 3.7, 19.0).

Table 7 Characteristics of singleton live born infants, by timing of earliest exposure to DTG

	Earliest exposure to DTG		
	Periconception	**Later T1**	**T2/T3**
Gestational age, weeks (*n*=727)			
<34 weeks	19 (4.3%)	3 (8.3%)	8 (3.2%)
34-36 weeks	38 (8.7%)	3 (8.3%)	26 (10.3%)
≥37 weeks	382 (87.0%)	30 (83.3%)	218 (86.5%)
Birthweight, g (*n*=739)			
<1500	13 (2.9%)	1 (2.7%)	5 (2.0%)
1500-2499	43 (9.6%)	8 (21.6%)	22 (8.7%)
≥2500	393 (87.5%)	28 (75.7%)	226 (89.3%)
SGA[*] (*n*=705)			
No	388 (90.0%)	30 (88.2%)	226 (94.2%)
Yes	43 (10.0%)	4 (11.8%)	14 (5.8%)
Neonatal death (*n*=688[#])			
No	416 (99.8%)	33 (100%)	237 (99.6%)
Yes	1 (0.2%)	0 (0%)	1 (0.4%)

[*] Infants were classified as small for gestational age (SGA) if their weight centile was below the 10th percentile using INTERGROWTH standards.
[#] Not known for 59 UK infants as paediatric follow-up not yet complete

4.3 Birth defects

Induced abortions

Of 21 pregnancy outcomes of induced abortion, there was one carried out due to identified birth defects. This was carried out at 29 gestational weeks for neuronal migration disorder and severe microcephaly; this pregnancy had a periconception DTG exposure.

Stillborn infants

There were no defects identified in the five stillborn infants reported.

Live-born infants

A total of 38 infants were reported with at least one birth defect. This included four infants with chromosomal abnormalities. Two infants had Down Syndrome, both with one other defect reported: one with talipes equinovarus (born to a mother who conceived on DTG) and one with septal defects (earliest exposure was in T2/T3). Two further infants were reported with unspecified chromosomal anomalies (one with periconception exposure and one with T2/T3 exposure).

Excluding the infants with chromosomal abnormalities from the defect case count, 34 infants had 37 defects: three infants each had two defects and 31 had one defect. Among 783/790 (99.1%) infants with data available, the overall prevalence of birth defects was 4.3% (95% CI 3.0, 6.0). The proportion of infants with birth defects by timing of exposure to DTG is presented in Table 8.

Table 8 Proportion of live-born infants with birth defects by timing of earliest exposure to DTG

Timing of earliest DTG exposure	n/N*	%	95% CI
Periconception	22/476	4.6	2.9, 6.9
Later T1	1/37	2.7	0.1, 14.2
T2/T3	11/267	4.1	2.1, 7.3

* This table includes all infants (including twins) and excludes three infants where DTG timing was unknown

The majority of birth defects were in the heart and genitourinary systems (Table 9). No NTDs were reported. The infant with CCI and aortic valve stenosis died (after the neonatal

period at 52 days). One of the infants with isomerism of atrial appendages with asplenia was a twin and died on day 15 of life.

Table 9 Details of birth defects among live-born infants with no chromosomal anomalies (37 defects from among 34 infants)

Organ system	Earliest exposure	Birth defect	EuroCAT defect
Heart	PC	Patent Foramen Ovale	No
N=8	PC	Interatrial communication – ostium secondum	Yes
	PC	Septal defect	Yes
	T2/T3	Patent ductus arteriosus	Yes
	PC	Pulmonary valve stenosis	Yes
	PC	Aortic valve stenosis*	Yes
	PC	Unspecified heart defects	
	T2/T3	Septal defect	Yes
Genitourinary	PC	3 x congenital hydronephrosis	Yes
N=9	PC	Ectopic kidney	Yes
	PC	2 x Hypospadias*	Yes
	Later T1	Hypospadias	Yes
	T2/T3	2x Hypospadias*	Yes
Gastrointestinal	T2/T3	Duodenal atresia and stenosis	Yes
N=3	PC	Gastroschisis	Yes
	T2/T3	Omphalocele / exomphalos	Yes
Limb	PC	3 x Polydactyly*	Yes
N=6	T2/T3	Polydactyly	Yes
	T2/T3	Talipes equinovarus*	Yes
	PC	Congenital vertical talus (both feet)	No
Ear, face & neck	PC	Malformation of the ear	No
N=1			
Other syndromes	PC	2 x situs inversus (with dextrocardia)	Yes
N=6	PC	CCI [redacted]	Yes
	T2/T3	Achondroplasia	Yes
	T2/T3	2 x isomerism of atrial appendages with asplenia	Yes
Other anomalies	T2/T3	Ankyloglossia	No
N=4	PC	Hyperpigmentation on back	No
	PC	Skin tag	No
	PC	Naevus flammeus	No

* 1 infant had hypospadias and polydactyly; 1 infant had hypospadias and talipes equinovarus; 1 infant with CCI [redacted] also had aortic valve stenosis.

4.4 Maternal viral load suppression and vertical transmission

Of the 775 pregnancies resulting in delivery (i.e., live birth or stillbirth), an end of pregnancy viral load measurement (i.e., measured up to 28 days before and 7 days after delivery) was unavailable for 175 (22.6%), with 140 (80.0%) of these women having conceived on ART. Of the 600 deliveries with available viral load at the end of pregnancy, 516 (86%) women had suppressed viral load measures and 79 (13.2%) women had unsuppressed measures at the end of pregnancy. The median maternal viral load among the 79 unsuppressed women was 138 copies/mL (IQR: 69-958; range: 51-615,831). Maternal viral suppression at delivery by timing of earliest DTG exposure (where available) is presented in Table 10.

Table 10 Maternal viral suppression at end of pregnancy, by trimester of earliest exposure to DTG

	Timing of DTG start			Total* *N*=764
	Before pregnancy or in T1	T2	T3	
Viral load <50 copies/mL at end of pregnancy?				
Yes	359 (70.7%)	97 (66.0%)	60 (55.1%)	516 (67.5%)
No	19 (3.7%)	21 (14.3%)	35 (32.1%)	75 (9.8%)
Not available	130 (25.6%)	29 (19.7%)	14 (12.8%)	173 (22.6%)

* This table excludes 11 deliveries where precise timing (i.e., trimester) of earliest DTG exposure was not known.

Among the 591 women with viral load available, the proportion with an undetectable viral load at the end of pregnancy was 95.0% (359/378) for those who started DTG in the first trimester or earlier and 82.2% (97/118) and 63.2% (60/95) for those starting in the second and third trimesters, respectively (p<0.001).

Overall, the vertical transmission rate was 0.29% (95% CI 0.04, 1.06) among all live-born infants and 0.31% (95% CI 0.04, 1.12) if restricted to singleton live-born infants. Some infants had indeterminate HIV status at the time of the data collection, mainly reflecting lags in paediatric data collection within participating studies. Table 11 provides infant infection status, stratified by earliest exposure to DTG. One of the two infected infants was born to a mother who was diagnosed late in the third trimester, when she started on a DTG-based regimen; the other had conceived on a DTG-based regimen. Both mothers had detectable delivery viral loads (13 200 and 91 500 copies/mL).

Table 11 Infant HIV infection status, by trimester of earliest exposure to DTG

	Timing of DTG start			Total*
	Before pregnancy or in T1	T2	T3	
Infant HIV status				
Uninfected	443 (86.0%)	129 (84.3%)	94 (84.7%)	666 (85.5%)
Infected	1 (0.2%)	0 (0.0%)	1 (0.9%)	2 (0.3%)
Indeterminate#	71 (13.8%)	24 (15.7%)	16 (14.4%)	111 (14.2%)

* This table excludes 11 deliveries where precise timing (i.e., trimester) of earliest DTG exposure was not known.
# Two of these infants were neonatal deaths

5. Discussion

In the DOLOMITE-EPPICC study, real world observational data from ongoing cohort and surveillance studies of pregnant women living with HIV and their infants from six European countries were collected and analysed to address questions around the safety and effectiveness of prenatal DTG use. The study included 833 pregnancies in 756 women, the majority of whom had an established HIV diagnosis from before the pregnancy, with only one in ten newly diagnosed following antenatal testing. Around three-quarters of women were on ART at conception, and this group were mainly on a DTG-containing regimen at this time although there were some women who conceived on a regimen with another third agent and switched to a DTG-based regimen. The number of pregnancies with DTG use reported showed an upward trajectory up until 2017, when annual pregnancies peaked at 170, with a subsequent decline and plateauing at around 130 per year from 2018. This most likely reflects the impact of the safety signal in 2018 and subsequent temporary guideline changes regarding use of DTG in women of childbearing potential (WHO 2018, EMA 2018).

The proportions of infants born preterm and SGA were broadly consistent with earlier analyses from EPPICC (EPPICC 2019, EPPICC 2020), and there was no pattern observed with respect to timing of DTG exposure. The prevalence rate for birth defects among infants with periconception exposure to DTG was 4.6% (95% CI 2.9, 6.9) and 4.1% (2.1, 7.3) for those with earliest exposure in the first trimester and second/third trimesters respectively. These are consistent with rates reported from the Antiretroviral Pregnancy Registry for DTG-exposed pregnancies: 3.1% (2.0, 4.5) and 5.0% (3.2, 7.4) for infants with earliest exposure in the first trimester and those with earliest exposure in the second or third trimesters, respectively (APR 2023).

No specific pattern of birth defects was observed. There were no NTDs, nor any central nervous system defects, reported among the live-born infants. For a rare defect such as an NTD (with around a 0.1% birth prevalence), at least 2000 periconception exposures would be required to rule out a three-fold increased risk (and there were just over 500 periconception exposures in our study) (Watts et al 2007). Our finding is consistent with the surveillance data from Botswana and Eswatini, incorporating more than 14,000 infants, that showed no evidence for an increased risk of NTD associated with periconception DTG use (Zash et al 2022, Gill et al 2023).

High proportions of women in this study had suppressed viral loads by the time of delivery, as expected given the timing of HIV diagnosis and ART initiation in the study population, and there was a very low rate of vertical transmission. This reflects the overall picture among pregnant women living with HIV in Europe. For example, the vertical transmission rate in the Madrid Cohort in 2014-2020 was 0.3%, with 91% of women having undetectable HIV RNA (<50 copies/mL) at delivery (Illan Ramos et al

2022). Similarly, in the UK, the vertical transmission rate has been below 0.4% since 2012, with the proportion of women delivering with suppressed viral loads also around 90% (ISOSS 2022), whilst an Italian study reported a vertical transmission rate of 0.35% in 2012-2017 with 88% of women who delivered having viral load below 50 copies/mL in the third trimester (Tibaldi et al 2019).

There were 20 singleton pregnancies ending in induced abortion and one twin pregnancy, with one of the singleton pregnancies terminated following identifications of fetal abnormalities as a result of ultrasound scanning. Thirty-seven pregnancies (assumed to be singleton pregnancies) ending in spontaneous abortion were included in the study, as well as one twin pregnancy where one of the fetuses was miscarried. With respect to the data included on spontaneous abortions, it should be noted that women are only included in EPPICC studies when they enter antenatal care and therefore this study was not designed to capture early pregnancy loss or early terminations of pregnancy (i.e., due to undesired pregnancy). There were five stillbirths overall in the study, representing a rate of 6.6 per 1000 births, which is consistent with an earlier study in the UK which reported a stillbirth rate of 6.1 per 1000 births in 2013-2015 among women living with HIV, a decrease from 8.3 per 1000 in 2010-2012 (Favarato et al 2019). An Italian study reported a stillbirth rate of 10 per 1000 births among women living with HIV delivering between 2001 and 2018, with no temporal trends observed (Floridia et al 2019).

A limitation of the study was the missing data for some variables, reflecting the real-world nature of the included studies. Under-reporting of birth defects cannot be ruled out, but the included studies involved paediatric follow-up (i.e., for ascertaining infant HIV infection status) and thus this is expected to be minimal.

This study contributes to the growing evidence base on the effectiveness and safety of DTG-containing regimens in pregnancy, providing data on the outcomes of pregnancies in women delivering in a range of European countries and on neonatal outcomes following in utero exposure in their infants.

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Appendix

Supplementary table. Pregnancy outcomes among multiple birth pregnancies, by earliest DTG exposure

	Total DTG exposed	Earliest exposure to DTG		
		Periconception	Later T1	T2/T3
Twin / triplet pregnancies, *N*	21	14 (66.7%)	0 (0.0%)	7 (33.3%)
Fetuses, *N*	43	28 (65.1%)	0 (0.0%)	15 (34.9%)
Live births, *n* (%)	40	25 (62.5%)	0 (0.0%)	15 (37.5%)
Stillbirths, *n* (%)	0	-	-	-
Spontaneous abortions, *n* (%)	1	1 (100.0%)	0 (0.0%)	0 (0.0%)
Induced abortions, *n* (%)	2	2 (100.0%)	0 (0.0%)	0 (0.0%)