

Outcomes following prenatal exposure to DTG-containing antiretroviral therapy regimens: data from the DOLOMITE-EPPICC study

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BACKGROUND

- Dolutegravir (DTG)** is an HIV integrase strand-transfer inhibitor **recommended for use during pregnancy** for viral suppression and prevention of vertical transmission
- The **DOLOMITE*-EPPICC study** was established in 2017 to assess use and safety of DTG in pregnancy and exposed infants in the European Pregnancy and Paediatric Infections Cohort Collaboration (**EPPICC**), a **network of observational studies** with national or sub-national coverage
 - * Dolutegravir in pregnant women and exposed infants in Europe
- We aimed to **assess pregnancy and neonatal outcomes by earliest prenatal DTG-containing regimen** using real-world European data from DOLOMITE-EPPICC
- DTG-containing regimens assessed:
 - DTG+ABC+3TC
 - DTG+TDF+FTC
 - DTG+TAF+FTC
 - DTG+3TC/RPV

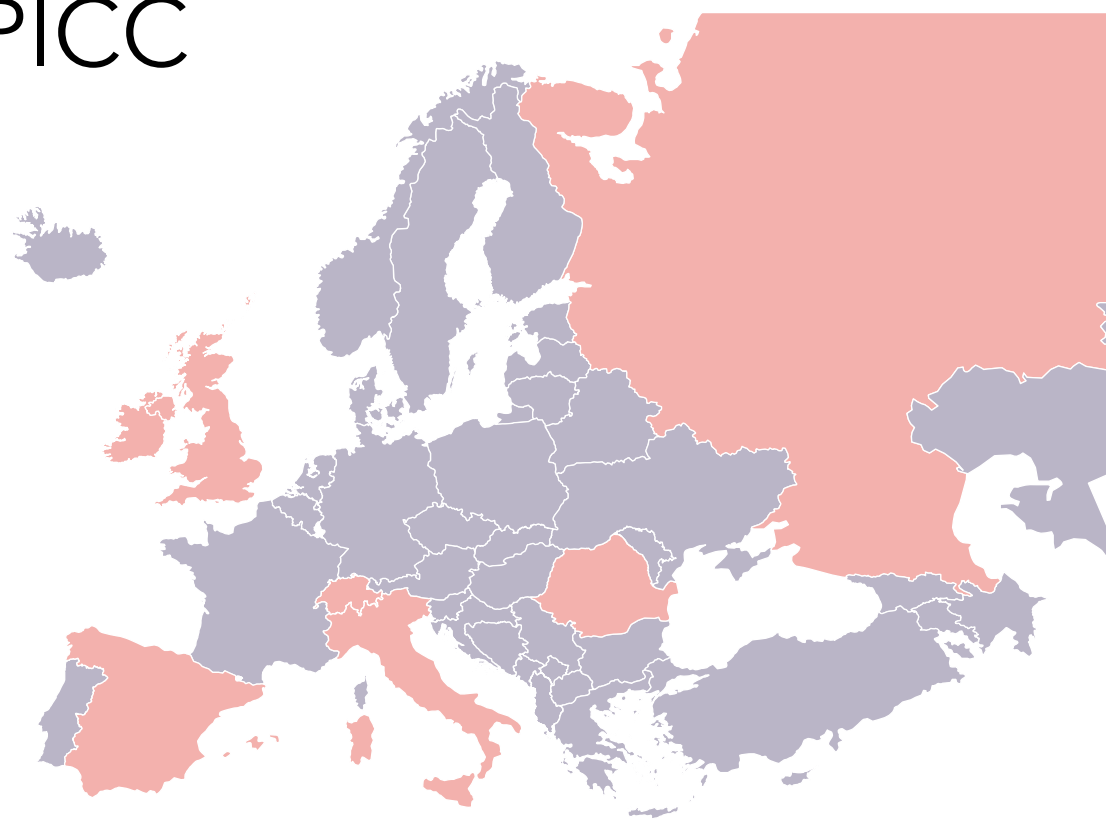


Figure 1. Countries represented in DOLOMITE-EPPICC (Italy, Romania, Russian Federation, Spain, Switzerland, UK/Ireland)

RESULTS

- 833 DTG-exposed pregnancies** were included (Figure 2)
 - 81.8% (681) from UK/Ireland, 10.2% (85) from Spain
 - Median age** at conception: **32** years (IQR: 27-36)
 - Maternal ethnicity:** 63.4% (528) Black, 27.7% (231) White
 - 77.2%** (640/829) were **conceived on ART** (4 missing ART timing)
- Earliest DTG exposure timing and regimens**
 - Timing:** PC in 63.6% (527/829), later T1 in 4.6% (38/829), T2/T3 in 31.8% (264/829) (4 missing exposure timing)
 - Regimen:** DTG+ABC+3TC: 56.2% (468/833), DTG+TDF+FTC: 15.8% (132/833), DTG+TAF+FTC: 2.8% (23/833), DTG+3TC/RPV: 0.8% (7/833), other: 24.4% (203/833)
 - Figure 3** shows **pregnancies by regimen and timing**
- Pregnancy and neonatal outcomes by earliest DTG-containing regimen** are shown in **Table 1**

Figure 2. Pregnancies and infants in DOLOMITE-EPPICC

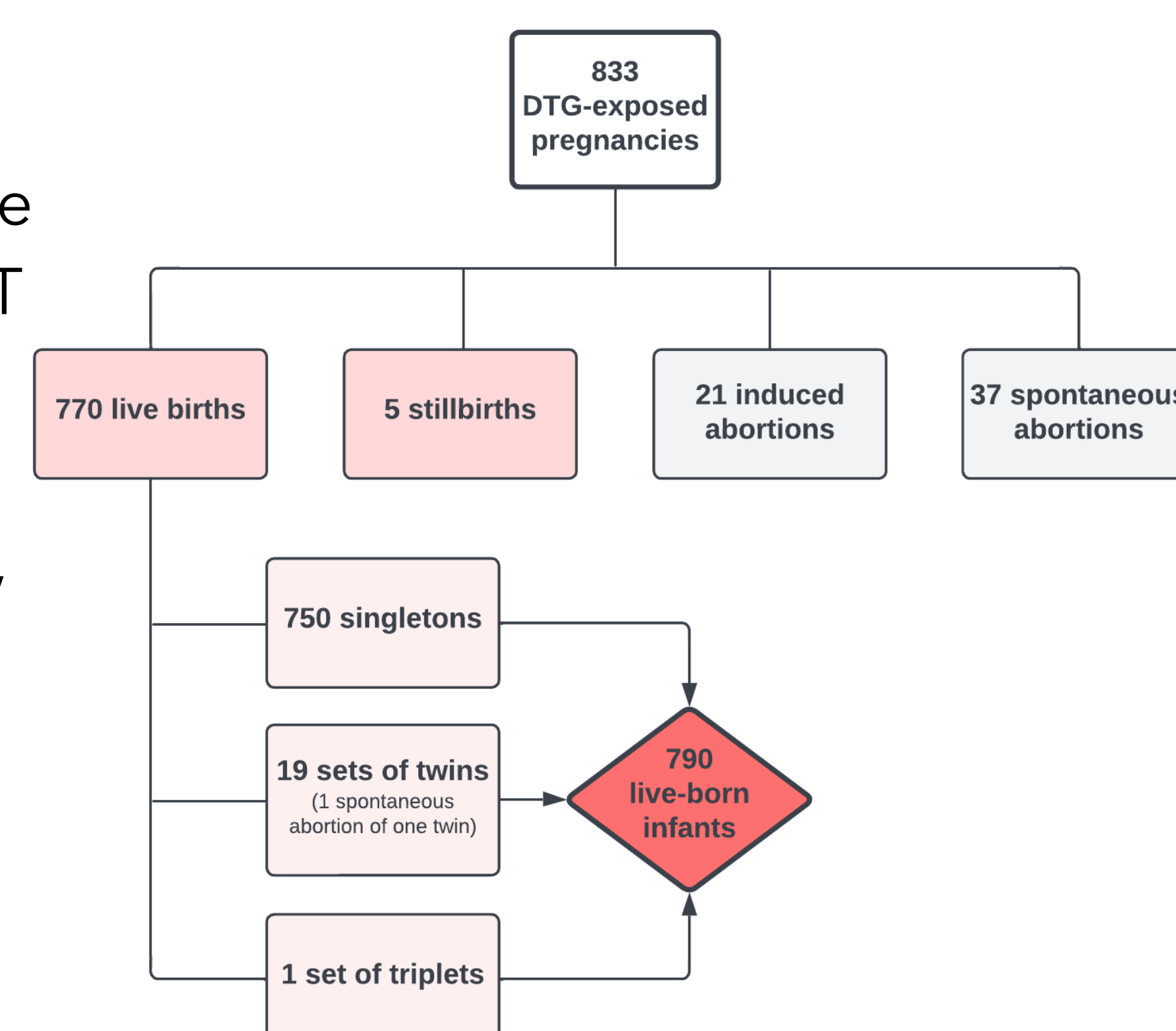


Figure 3. Earliest prenatal DTG-containing regimens by timing of exposure

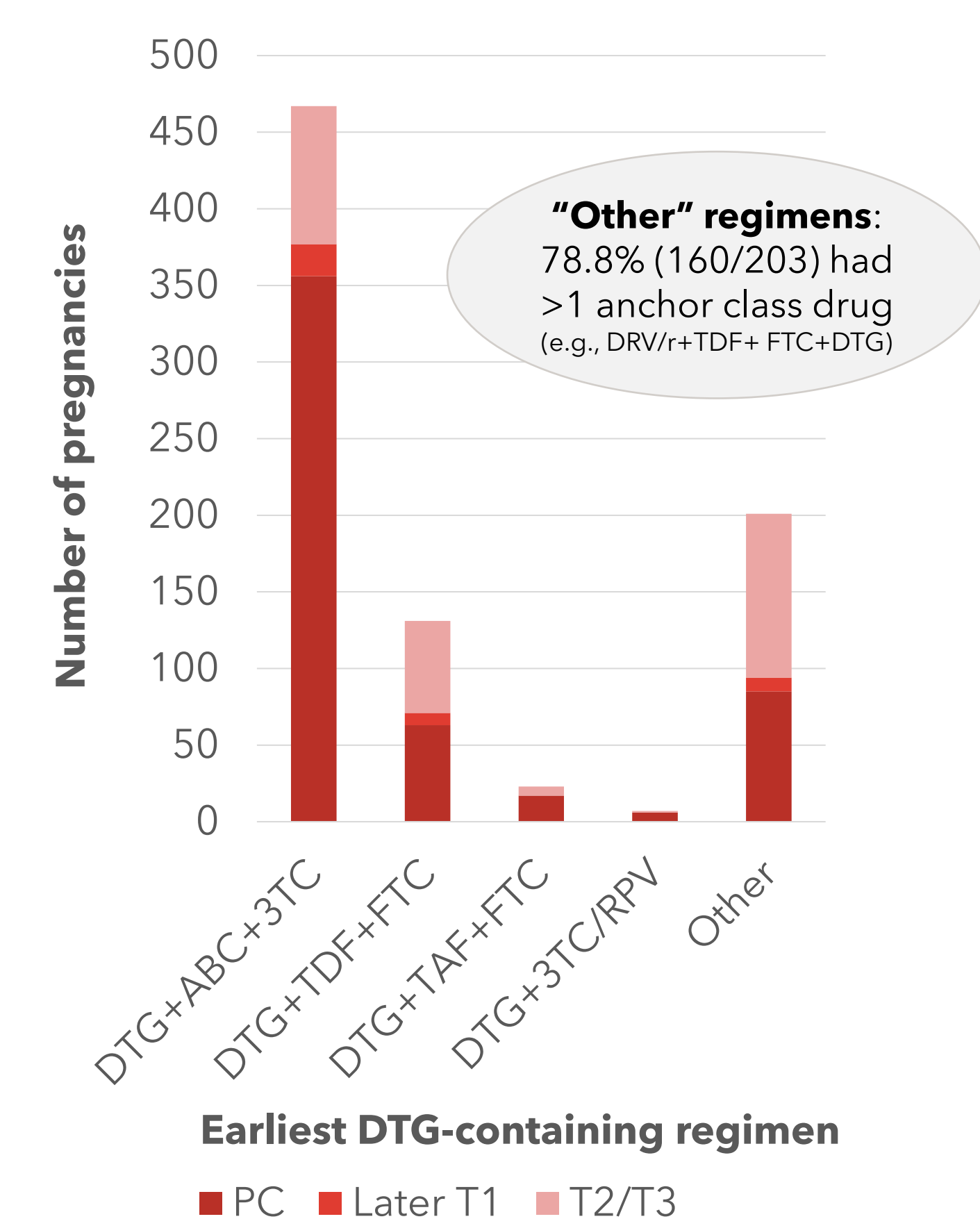


Table 1. Pregnancy and neonatal outcomes by earliest prenatal DTG-containing regimen in DOLOMITE-EPPICC (n=833)

	All DTG-containing regimens	DTG+ABC+3TC	DTG+TDF+FTC	DTG+TAF+FTC	DTG+3TC/RPV*	Other†
Total pregnancies	833	468	132	23	7	203
Live birth	770 (92.4%)	425† (90.8%)	124 (93.9%)	21 (91.3%)	6 (85.7%)	194 (95.6%)
Spontaneous abortion	37 (4.4%)	25 (5.3%)	4 (3.0%)	2 (8.7%)	1 (14.3%)	5 (2.5%)
Induced abortion	21 (2.5%)	14 (3.0%)	4 (3.0%)	0	0	3 (1.5%)
Stillbirth	5 (0.6%)	4 (0.9%)	0	0	0	1 (0.5%)
Total live-born infants	790	438	127	21	6	198
With birth defects	34/783 (4.3%, 95% CI 3.0%-6.0%)	22/434 (5.1%, 95% CI 3.2%-7.6%)	4/125 (3.2%, 95% CI 0.9%-8.0%)	0	0	8/197 (4.1%, 95% CI 1.8%-7.8%)
Total singleton live-born infants	750	412	121	21	6	190
Preterm (<37 weeks)	97/729 (13.3%)	52/407 (12.8%)	12/118 (10.2%)	5 (23.8%)	2 (33.3%)	26/177 (14.7%)
Very preterm (<34 weeks)	30/729 (4.1%)	16/407 (3.9%)	5/118 (4.2%)	2 (9.5%)	1 (16.7%)	6/177 (3.4%)
Low birthweight (<2500g)	92/742 (12.4%)	48/408 (11.8%)	16/118 (13.6%)	3 (14.3%)	1 (16.7%)	24/189 (12.7%)
Very low birthweight (<1500g)	19/742 (2.6%)	11/408 (2.7%)	3/118 (2.5%)	3 (14.3%)	0	2/189 (1.1%)
Small-for-gestational-age‡	61/706 (8.6%)	34/396 (8.6%)	12/111 (10.8%)	3 (14.3%)	0	12/172 (7.0%)

Note: amended denominator indicated where data incomplete.

*DTG+3TC (n=3) or DTG+RPV (n=4)

†Includes DTG-containing regimens containing drugs of additional anchor classes

‡Includes one twin pregnancy with discordant outcome (one miscarried twin)

§Classified using INTERGROWTH-21st standards.

- One termination of pregnancy was carried out due to identified birth defects: neuronal migration disorder and severe microcephaly (PC DTG exposure)
- There were no defects reported among stillborn infants

Abbreviations | 3TC: lamivudine; ABC: abacavir; ART: antiretroviral therapy; ATV/r: atazanavir/ritonavir; CI: confidence interval; DOLOMITE: Dolutegravir in pregnant women and exposed infants in Europe; DRV/r: darunavir/ritonavir; DTG: dolutegravir; EPPICC: European Pregnancy and Paediatric Infections Collaboration; FTC: emtricitabine; GW: gestational weeks; ICD-10: International Classification of Diseases: Tenth Revision; IQR: interquartile range; LBW: low birthweight; PTD: preterm delivery; RPV: rilpivirine; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate

METHODS

- Prospectively-collected individual patient data** from **7 cohorts** were **pooled** according to a modified HIV Data Exchange Protocol (www.hicdep.org) (Figure 1)
- Included pregnancies in individuals living with HIV with:
 - Any prenatal exposure to DTG-containing ART
 - Outcome up to 2022
- Outcomes assessed:** birth defects classified using WHO's ICD-10, preterm delivery (PTD) as <37 completed gestational weeks (GWs), very PTD as <34 completed GWs, low birthweight (LBW) as <2500 grams, very LBW as <1500 grams, small-for-gestational-age as birthweight <10th percentile using INTERGROWTH-21st standards
- Birth defect prevalence was calculated among live-born infants; analysis of other neonatal outcomes was restricted to singleton live-born infants
- Earliest prenatal DTG exposure timing** was classified as:
 - Periconception (**PC**): exposure at ≤6 GWs
 - Later first trimester (**Later T1**): exposure in T1 at >6 GWs
 - Second/third trimester (**T2/T3**): exposure at >12 GWs

CONCLUSIONS

- The birth defect prevalence reported in this updated DOLOMITE-EPPICC analysis is consistent with rates reported for DTG-exposed pregnancies in the Antiretroviral Pregnancy Registry (3.96%)
- Monitoring of use and safety of DTG-containing regimens in pregnancy is ongoing in EPPICC, as sample size for some groups is too small to exclude association with rare outcomes

- The overall **prevalence of birth defects** among live-born infants was **4.3% (95% CI 3.0%-6.0%)**
- Birth defect systems:** heart (8), genitourinary (9), gastrointestinal (3), limb (6), ear, face and neck (1), other syndromes (6), other anomalies (4) (3 infants had 2 defects)