Outcomes Following Prenatal Exposure to Raltegravir: A Multi-Cohort European Study

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BACKGROUND

- **Raltegravir** (RAL) is an **HIV integrase strand-transfer inhibitor (INSTI)**, first approved for use in Europe in 2008
- **RAL is recommended for use during pregnancy** for maternal viral suppression and prevention of vertical transmission, though **safety is not fully understood**
- **Large samples** with sufficient periconception RAL exposures are needed **to rule out increased risk of rare birth defects**, e.g., neural tube defects (NTDs)
- We aimed to **assess risk of birth defects and other adverse outcomes following prenatal exposure to RAL** using pooled prospectively collected individual patient data from studies in the European Pregnancy and Paediatric Infections Cohort Collaboration (**EPPICC**)

Our study found that **3.9%** of infants with prenatal exposure to *raltegravir* had a reported **birth defect**, with **one NTD** reported.

METHODS

- EPPICC includes **cohort/surveillance studies** with national or sub-national coverage
- Data specification: modified HIV Data Exchange Protocol (www.hicdep.org)
- Analyses included pregnancies in people living with HIV with **any documented prenatal exposure to RAL** and outcomes in **2008-2020**
- Earliest **prenatal RAL exposure timing** was classified as:
  - Periconception (**PC**): exposure at ≤6 completed gestational weeks (GWs)
  - Later first trimester (**Later T1**): exposure in T1 at >6 GWs
  - Second/third trimester (**T2/T3**): exposure at >12 GWs
- **Key outcomes** assessed: birth defects, preterm delivery (PTD) as <37 completed GWs, very PTD as <34 completed GWs, low birthweight (LBW) as <2500 grams, very LBW as <1500 grams, small for gestational age (SGA) as birthweight <10th percentile*
- **9 cohorts** were included, representing Belgium, Italy, the Netherlands, Romania, Russian Federation, Spain, Switzerland, Thailand, and UK/Ireland (Figure 1)

* Using INTERGROWTH-21ST standards

RESULTS

- **1499 RAL-exposed pregnancies** were included (1463 singleton pregnancies, 35 twin pregnancies, 1 triplet pregnancy)
  - 79.7% from the UK/Ireland
  - Median **maternal age** at conception: **32** years (IQR: 27-36)
  - **Maternal ethnicity**: 60.7% Black, 31.5% White
  - **Half** (51.3%) were **conceived on ART**
- **Pregnancy outcomes** are shown in the Table



Figure 1. Countries represented, excluding Thailand

Table 1. Pregnancy outcomes and timing of earliest RAL exposure (*n*=1499)

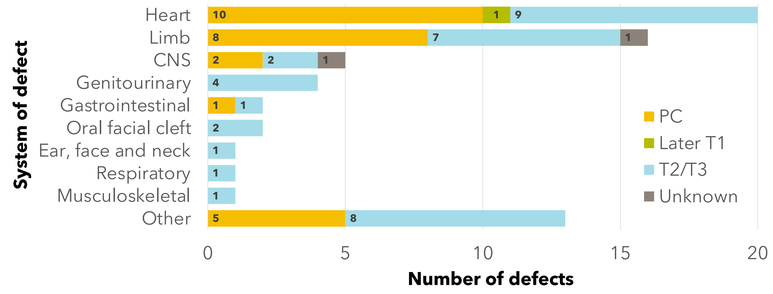
	Timing of earliest RAL exposure				
Pregnancy outcome	**PC**	**Later T1**	**T2/T3**	**Unknown**	**Total**
Live birth	452 (31.6%)	61 (4.3%)	871 (60.9%)	45 (3.2%)	1429
Stillbirth	3 (30.0%)	1 (10.0%)	6 (60.0%)	-	10
Spontaneous abortion	35 (85.4%)	2 (4.9%)	1 (2.4%)	3 (7.3%)	41
Induced abortion	15 (78.9%)	1 (5.3%)	1 (5.3%)	2 (10.5%)	19

- **1466 live-born infants** (1393 singletons, 70 twins, 3 triplets)
- Among live-born infants, earliest RAL exposure was PC in 466 (31.8%), later T1 in 62 (4.2%), T2/T3 in 892 (60.9%), and unknown in 46 (3.1%)
- There were **5 neonatal deaths** (2 with PC, 3 with T2/T3 exposure)

BIRTH DEFECTS

- The overall **prevalence of birth defects** among live-born infants was **3.9%** (56/1443) **(95% CI 2.9, 5.0)**
- Birth defect prevalence **by earliest RAL exposure**:
  - **PC**: 5.0% (95% CI 3.2, 7.4) (23/461)
  - **Later T1**: 1.6% (95% CI 0.0, 8.8) (1/61)
  - **T2/T3**: 4.1% (95% CI 2.3, 4.9) (30/875)
- Figure 2 shows defect systems; **9 infants had 2 defects**
- 38 (2.6%, 95% CI 1.9, 3.6) had defects per EUROCAT
- 2 of the 5 neonatal deaths had birth defects
- **One NTD observed**: spina bifida with PC exposure
- There were no defects among stillbirths

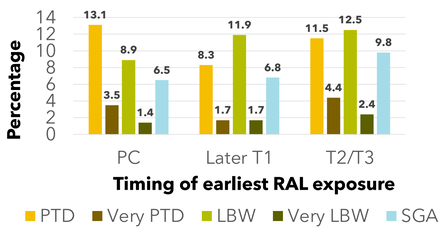
Figure 2. Birth defects by system and timing of RAL exposure (live-born infants)



OTHER OUTCOMES

- Birth outcomes of live-born singleton infants (*n*=1393) are presented in Figure 3

Figure 3. Birth outcomes of live-born singleton infants



CONCLUSIONS

- The birth defect rate in EPPICC is consistent with and contributes to the current evidence-base on safety of periconception RAL use
- As 2000 exposures would be needed to rule out a 3-fold increase for rare events (≈0.1% birth prevalence), ongoing surveillance of birth outcomes is needed

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