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

932

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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)

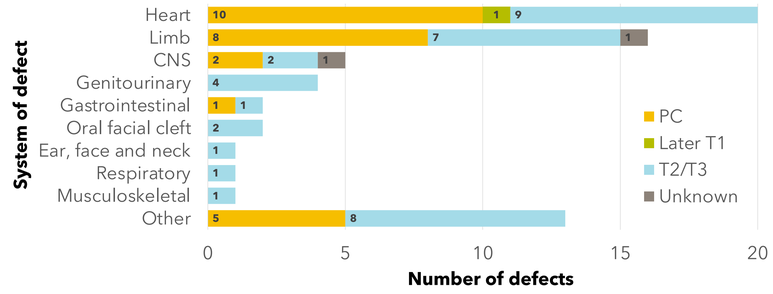
	Timing of earliest RAL exposure				
Pregnancy outcome	**PC**	**Later T1**	**T2/T3**	**Unknown**	**Total**
Live birth	452 (31.6%)	61 (4.3%)	871 (60.9%)	45 (3.2%)	1429
Stillbirth	3 (30.0%)	1 (10.0%)	6 (60.0%)	-	10
Spontaneous abortion	35 (85.4%)	2 (4.9%)	1 (2.4%)	3 (7.3%)	41
Induced abortion	15 (78.9%)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

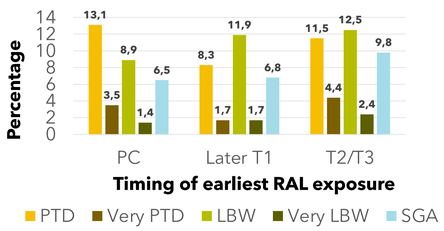
Figure 2. Birth defects by system and timing of RAL exposure (live-born infants)



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

Acknowledgements: Thanks to participating cohorts/studies (European Collaborative Study, NENEXP Study (Catalonia), Swiss Mother and Child HIV Cohort Study (MoCHiV), the Integrated Screening Outcomes Surveillance Service (ISOSS), Madrid Cohort of HIV-Infected Mother-Infant Pairs, St Petersburg City Centre for AIDS and Infectious Diseases Cohort, Thailand Perinatal HIV Prevention Trials (PHPT) Cohort, Victor Babes Hospital Cohort), the Italian Register for HIV Infection in Children, and all participants included.

Funding: This study was supported by Merck Sharpe & Dohme (MSD).