# Evaluation of Neural Tube Defects After Exposure to Raltegravir During Pregnancy

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## BACKGROUND AND OBJECTIVES

- Embryonic neural tube development occurs during the first 28 days after conception
- Failure of neural tube to close leads to neural tube defects (NTDs), which are birth defects of the brain, spine, or spinal cord (eg, spina bifida, anencephaly, myelomeningocele)
- An unplanned interim analysis of a Botswana birth outcomes surveillance study suggests potential risk of NTDs associated with periconception exposure to dolutegravir (DTG)[1]
- Raltegravir (RAL) and DTG are both integrase strand transfer inhibitors
- The objective of this analysis is to evaluate the risk of NTDs after exposure to RAL during pregnancy

## METHODS

- Pregnancy outcome data on HIV-1–infected women who received RAL during pregnancy were reviewed using three sources
  - The Merck Adverse Event Reporting and Review System (MARRS)
  - Two publicly available pregnancy outcome cohorts that have not been submitted to MARRS
    - National Surveillance of HIV in Pregnancy and Childhood (NSHPC)
    - The ANRS French Perinatal Cohort (EPF)
- MARRS contains pregnancy outcomes reported to the company in company-sponsored or -supported investigational clinical trials and in the post-marketing period, including all reports received from the Antiretroviral Pregnancy Registry (APR)
  - APR[2] is a voluntary prospective, exposure-registration, observational study designed to collect and evaluate data on the outcomes of pregnancy exposures to antiretroviral products
- NSHPC[3] is an active national surveillance program in the United Kingdom and Ireland that monitors the prevalence of HIV infection in pregnant women and children and transmission of infection from mother to child
- EPF[4] is a national multicenter prospective cohort that enrolls about 70% of HIV-infected pregnant women in France
- Reports were classified as prospective or retrospective
  - Prospective: report received prior to knowledge of pregnancy outcome or prior to the detection of a congenital malformation at prenatal examination
  - Retrospective: report received after knowledge of pregnancy outcome or after detection of a congenital malformation or any fetal event during prenatal testing
    - Because retrospective reports lack denominator data and are biased toward reporting of more unusual and severe cases, only prospective reports are used to calculate prevalence estimates[5]

**References**

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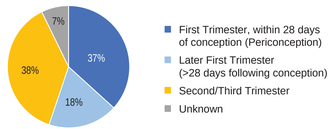
## RESULTS

### MARRS

- As of 31-May-2018, 1256 pregnancy outcomes were reported for 1238 pregnancies in women exposed to 400-mg RAL twice daily (some pregnancies resulted in twins)
- 803 (65%) were reported prospectively and 435 (35%) were reported retrospectively
- Among the 803 prospective reports, 443 (55%) documented first trimester as the earliest exposure, 302 (38%) had second/third trimester exposure, and 58 (7%) had an unknown trimester of exposure (**Figure 1)**
- The majority of first trimester exposures (295/443) were in women receiving RAL during the periconception period (within 28 days of conception)

### Figure 1. Time of Exposure to Raltegravir

**MARRS Prospective Reports (N=803)**




### MARRS Prospective Reports

- Among the 803 prospective reports, no cases of NTDs were identified among infants regardless of the earliest time of RAL exposure
  - Periconception RAL exposure: 0/295
  - Any RAL exposure: 0/803

### MARRS Retrospective Reports

- Among the retrospective reports, the following NTDs were identified: anencephaly, encephalocele, and two cases of myelomeningocele (all from the APR)
- Only one of these NTDs (myelomeningocele) was reported among live births following periconception exposure to RAL. In this case, the mother was also exposed to emtricitabine, tenofovir disoproxil fumarate, ledipasvir/sofosbuvir and valacyclovir during periconception; dietary and family history information was not available

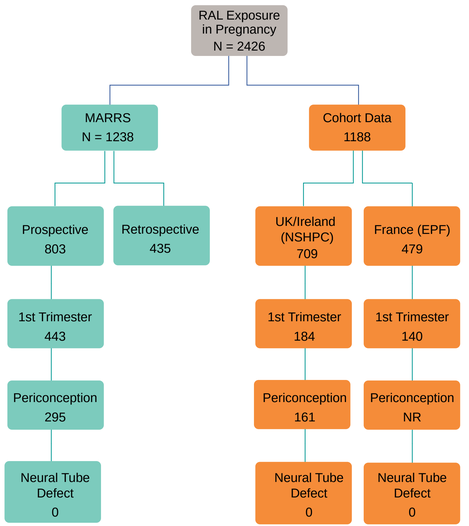
### Summary of NTD Reports in MARRS

| Neural Tube Defect | Initial Exposure to RAL | Outcome |
|---|---|---|
| **Prospective Reports (n=0 reports)** | | |
| N/A | N/A | N/A |
| **Retrospective Reports (n=4 reports)** | | |
| Anencephaly | 6 weeks 6 days | Induced Abortion |
| Myelomeningocele | 19 weeks | Live Birth |
| Myelomeningocele | Preconception | Live Birth |
| Encephalocele | Preconception | Spontaneous Abortion |

### Cohorts – NSHPC and EPF

- NSHPC reported RAL exposure in 709 pregnancies between 2008 and 2016[3]
  - 184 (26.5%) were during the first trimester and 161 (23%) were at conception
  - NTDs were not observed in this cohort
- EPF reported 479 pregnancy exposures to RAL between 2008 and 2015[4]
  - 140 (29%) were during the first trimester (N exposed at conception was not reported)
  - NTDs were not observed in this cohort

### Figure 2. No NTD Cases Among Prospectively Reported Pregnancy Outcomes after RAL Exposure in Pregnant Women with HIV-1

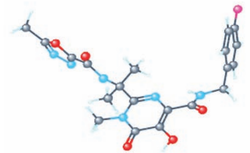



## DISCUSSION

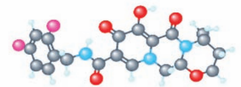
- There is geographic variability in the background rate of NTDs due to dietary and genetic factors. Pregnancy outcome data after RAL exposure are predominantly from Western countries
- Although both RAL and DTG are integrase strand transfer inhibitors, they have distinctly different chemical structures (**Figure 3**) and potentially different effects on neural tube development
- According to HIV treatment guidelines, RAL 400 mg twice daily may be used in women of reproductive potential and during pregnancy if clinically indicated[6,7]

### Figure 3. Chemical Structures

Raltegravir



Dolutegravir



## CONCLUSIONS

- There were no reports of NTDs among 1991 prospective reports of RAL exposure in pregnancy, 456 of which were in the periconception period
- One retrospective report of myelomeningocele was identified among live births following periconception exposure to RAL
- The available data do not indicate an association between RAL exposure and NTDs

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