**Integrate Inhibitor Exposure and CNS and Neural Tube Defects: Data from the Antiretroviral Pregnancy Registry (APR)**

Jessica Albanov, Vani Vannappagari, Angela Schueerle, Heath Watts, Claire Thorne, Leslie Ng, Veronica Urdenanta, Lynne Mofenson

**Statistical Analysis**

**Regression**

- **Any InSTI Exposure** 3013
- **Periconception** 688
- **First Trimester** 110
- **Second/Third Trimester** 461
- **Any Dolutegravir Exposure** 401
- **Periconception** 201
- **First Trimester** 61
- **Second/Third Trimester** 139
- **Any Elvitegravir Exposure** 284
- **Periconception** 207
- **First Trimester** 28
- **Second/Third Trimester** 19
- **Any Raltegravir Exposure** 656
- **Periconception** 283
- **First Trimester** 78
- **Second/Third Trimester** 295

**RESULTS**

**Prospective Analysis**

- A total of 20,064 pregnancies resulted in 20,413 fetal outcomes including 19,005 live births (Table 1).
- APR reports come from North America (75%), Europe (8%), Africa (7%), South America (6%) and Asia (4%).

**Future analyses**

- With sufficient numbers of exposed pregnancies, will need to be
- Data on prospectively enrolled pregnancies through July 2018 with birth outcome are summarized:
- Overall, by InSTI drug class and for each specific drug (DTG, elvitegravir [EVG], raltegravir [RAL])
- There were 1,193 live births with an InSTI exposure at any time during pregnancy
- First trimester exposure was assigned to each InSTI:
- Periconception – exposure started before conception and continued into the first trimester
- First trimester – initial exposure started in the first trimester
- Second/Third trimester – initial exposure started after the first trimester-ended
- Data are reviewed semiannually by an independent Advisory Committee
- Birth defects within the central nervous system (CNS) organ system include both NTDs and encephalocele, which is reported separately from NTD

**DISCUSSION**

- The majority of APR reports (83%) come from North America and Europe
- No occurrence of NTDs were observed among 1,193 prospective live birth outcomes with InSTI exposure at any time
- This frequency is consistent with the observed low NTD prevalence (0.01%-0.1%) in developed countries due to reduced NTD occurrence from
- Food folic acid fortification
- Antenatal folic acid supplementation

**CONCLUSIONS**

- The number of pregnancies enrolled in the APR with InSTI periconception exposure are currently insufficient to rule out or confirm any potential association with NTD
- While useful for secondary review for clusters/patterns, retrospective cases (reports after birth with defect) have no denominator and have potential bias in reporting, hence are not included in prospective data analysis
- Future analyses, with sufficient numbers of exposed pregnancies, will need to be stratified based on geographic region
- Healthcare providers are encouraged to continue to report pregnancies with prospective antiretroviral exposures to the APR, especially those involving newer ARVs

**ADVISORY COMMITTEE CONSENSUS**

In reviewing all reported defects from the prospective registry, informed by clinical studies and retrospective reports from antiretroviral exposure, the APR finds no apparent increases in frequency of birth defects with first trimester exposures compared to exposures starting later in pregnancy and no pattern to suggest a common cause. While the Registry was expanded and monitored to date is not sufficient to detect an increase in the risk of relatively rare defects, these findings should provide some assurance when counseling patients. However, potential limitations of registries such as this should be recognized. The Registry is ongoing. Given the use of new therapies about which data are still insufficient, health care providers are strongly encouraged to report eligible patients to the Registry via the data forms available at www.APRregistry.com.