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

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INTRODUCTION

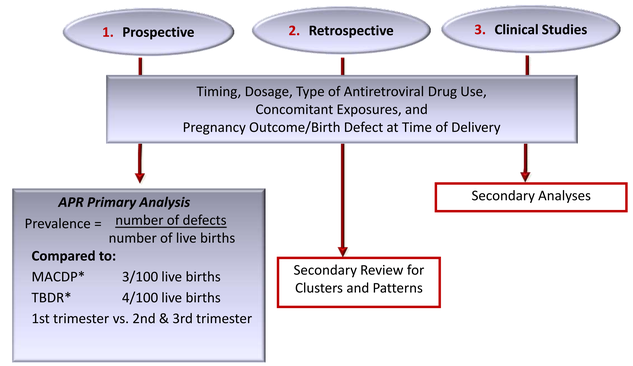
- Preliminary data from the NIH-supported Botswana birth defects surveillance project (Tsepamo study) reported a potential increased risk of neural tube defects (NTD) in infants born to HIV-positive women receiving periconception dolutegravir (DTG)-based antiretroviral therapy (ART) compared to periconception non-DTG ART or to uninfected women (data as of July 2018: 0.67%, 0.12% , and 0.09%, respectively).[1]
- DTG (TIVICAY) is an HIV-1 integrase strand transfer inhibitor (InSTI) with once-daily dosing, rapid viral load decrease and good viral efficacy, high barrier to resistance, and good tolerability.
  - Indicated in combination with other ARV drugs for HIV-1 treatment in adults and children aged ≥6 years and weight ≥30 kg
  - DTG crosses the placenta in humans (DolPHIN-1: DTG cord/maternal blood ratio 1.21)[2]
  - There are to date limited data on pregnancy outcome with periconception exposure outside of Tsepamo
  - Because encephalocele may occur slightly after neural tube closure and because the date of conception may not be determined with precision, the DTG label, per FDA guidance, was updated to recommend avoiding the use of DTG at the time of conception through the first trimester of pregnancy[3]

METHODS

Registry Design

- The Antiretroviral Pregnancy Registry (APR) is a voluntary, international, prospective exposure-registration cohort study[4]
  - Monitors prenatal exposures to ARV drugs to detect a potential increase in the risk of birth defects
  - Ongoing since 1989
  - Currently 29 sponsoring ARV manufacturers
  - Monitors 153 ARV drugs: 55 brand-name single-entity drugs or fixed-dose combinations; 98 generic versions
- **Primary Prospective Cohort**: Clinicians register pregnant women with prenatal ARV exposures before pregnancy outcome is known, report data on exposure throughout pregnancy, and provide birth outcome data
- Registration is voluntary and confidential; patient data is pseudonymised
- Birth defects are reviewed by a dysmorphologist, coded according to modified Metropolitan Atlanta Congenital Defects Program (MACDP) criteria, and classified by organ system
- Birth outcomes at ≥20 weeks estimated gestational age are included
- 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])
  - Earliest timing of exposure was assigned to each InSTI:
    - Periconception – exposure started before conception and continued into the first trimester
    - First trimester – initial exposure started later 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

Statistical Analysis



** MACDP = Metropolitan Atlanta Congenital Defects Program; TBDR = Texas Birth Defects Registry*

- **Retrospective Reports**: Women with prenatal ARV exposures registered before after pregnancy outcome is known; data are reviewed to assist with signal detection but are not included in the primary analysis due to the potential bias associated with these reports

RESULTS

Primary 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%).

Table 1. Maternal Demographics and Clinical Characteristics of Pregnant Women in the APR, Primary Prospective Enrollments with Outcome through July 2018

Total Pregnancies, N	20,064
Maternal age at conception, years	
Median	29.0
Range, min-max	13 - 55
CD4+ T-cell category at time of reporting, n (%)	
≥500 cells/µL	6,252 (31.2)
200-499 cells/µL	7,865 (39.2)
<200 cells/µL	2,810 (14.0)
Unknown/Missing	3,137 (15.6)

- There were 1,193 live births with an InSTI exposure at any time during pregnancy, of which 604 had periconceptional exposure, including 174 DTG, 186 EVG, and 244 RAL live birth outcomes (**Table 2**).
- A total of 2 CNS defect cases were reported with InSTI exposure at any time (both DTG, one 1st trimester, one 2nd/3rd trimester) (**Table 3**).
- There were **no NTD** among **prospective cases** for any InSTI drug.

Retrospective Reports

- Reported to APR after birth outcome has occurred; there is no denominator for number of exposures and not included in prospective data review.
- There were 7 NTD plus 2 encephalocele cases reported with InSTI exposure reported **after** delivery with defect that has occurred (**Table 4**).

Table 4. Summary of Retrospective NTD and Encephalocele Cases with InSTI Drug Exposure through July 2018

Dolutegravir [timing of exposure, country, year reported]	Raltegravir [timing of exposure, country, year reported]
Anencephaly [P, BW, 2018]	Myelomeningocele [P, US, 2013]
Iniencephaly [P, BW, 2018]	Myelomeningocele [T2, UK, 2013]
Myelomeningocele [P, BW, 2018]	Myelomeningocele [unk, US, 2016]
Meningocele [P, US, 2018]	- - -
Encephalocele [P, BW, 2018]	Encephalocele [P, US, 2015]

P = periconception, T2 = second trimester, unk = unknown; BW = Botswana, PR = Puerto Rico, UK = United Kingdom, US = United States

Table 2. Frequency of CNS and NTD Defect Cases by InSTI Drug and Timing of Earliest Exposure, Primary Prospective Enrollments with Outcome through July 2018

	Total Outcomes (N)	Live Births	Defect Cases	Central Nervous System[1,2]	Neural Tube[1]
Any InSTI Exposure[3]	1301	1193	37	2	0
Periconception	688	604	16	1	0
First Trimester	150	135	4	0	0
Second/Third Trimester	461	452	17	1	0
Any Dolutegravir Exposure[3]	401	366	12	2	
Periconception	201	174	6	1	0
First Trimester	61	55	2	0	0
Second/Third Trimester	139	137	4	1	0
Any Elvitegravir Exposure[3]	294	270	5	0	
Periconception	207	186	5	0	0
First Trimester	28	27	0	0	0
Second/Third Trimester	59	57	0	0	0
Any Raltegravir Exposure[3]	656	605	55	0	
Periconception	280	244	2	0	0
First Trimester	78	68	4	0	0
Second/Third Trimester	295	290	13	0	0

[1]Neural tube are a subset of CNS defects and are counted in both columns: no cases have been reported
[2]Encephalocele are a subset of CNS defects and are counted separately from neural tube defects: no cases have been reported
[3]Includes cases with missing trimester of exposure

Table 3. Details of CNS Defect Cases with InSTI Drug Exposure, Primary Prospective Enrollments with Outcome through July 2018

	Case A	Case B
Country of Report	United Kingdom	United States
Maternal Age	28 years	28 years
CD4+ T-cell	≥500 cells/µL	200-499 cells/µL
Race	Black	Black
Pregnancy Outcome	Induced abortion	Live birth
InSTI Drug Exposure – earliest timing	Dolutegravir – P	Dolutegravir – T3
Other ARV Exposures – earliest timing	Abacavir – P Lamivudine – P	Atazanavir – P Emtricitabine – P Ritonavir – P Tenofovir Disoproxil Fumarate – P
Verbatim Defect Term	a) lissencephaly b) ventriculomegaly	a) bilateral ventriculomegaly
Preferred Defect Term	a) structural defect of the CNS – other specified b) hydrocephalus not otherwise specified	a) hydrocephalus not otherwise specified
Temporality Assessment	Cannot rule out a possible association	Cannot rule out a possible association

P = periconception; T1 = first trimester; T2 = second trimester; T3 = third trimester

DISCUSSION

- The majority of APR reports (83%) come from North America and Europe
- No occurrence 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 of antiretroviral exposure, the Registry 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 population exposed 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.APRegistry.com.

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