Poster
P030

Cumulative Safety Review of Elvitegravir and Bictegravir use During Pregnancy and Risk of Neural Tube Defects

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Introduction

- Preliminary results from the Tsepamo study in Botswana have indicated a potential increased risk of neural tube defects (NTDs) following exposure to the integrase strand transfer inhibitor (INSTI), dolutegravir (DTG), at the time of conception [1].

Background

- Pre-conception and 1st trimester exposures are the vulnerable periods for NTDs as neural tube closure occurs in the 3rd-4th week after conception or the 5-6th week of gestation.
- Tsepamo Study in Botswana [1]
  - Preliminary findings indicate an increased rate of NTDs among babies born to HIV-infected women exposed to DTG at the time of conception
    - **DTG**: 4/426 (**0.94%**; 95% CI: 0.37%, 2.4%)
    - **Non-DTG ART**: 14/11,300 (**0.12%**; 95% CI: 0.07%, 0.21%)
    - **HIV-uninfected**: 61/66,057 (**0.09%**, 95% CI: 0.07%, 0.12%)
- Background rates of NTDs (anencephaly, spina bifida, and encephalocele)
  - The estimated worldwide prevalence of NTDs among live births is 0.18% (95% CI: 0.15, 0.23) [2].
  - The estimated US prevalence of NTDs among live births range from 0.053% to 0.075% [3] – [6].
- Antiretroviral Pregnancy Registry (APR) [7]
  - As of January 2018, there have been no central nervous system (CNS) birth defect cases among the 180 prospectively collected live births among women exposed to elvitegravir (EVG)-containing products during the first trimester.
  - No data are yet available for bictegravir (BIC)-containing products from the APR.
- Nonclinical Toxicology Studies
  - No evidence of CNS toxicity or NTDs was observed with either BIC or EVG in preclinical toxicology studies.

Methods

- The Gilead global safety database was searched from the beginning of clinical development to 31 May 2018.
- The global safety database includes pregnancy exposures and outcomes reported from:
  - Clinical trials
  - Antiretroviral Pregnancy Registry (APR)
  - Postmarketing spontaneous and solicited cases
  - Literature
- All EVG- and BIC-containing products were included:
  - EVG; EVG/cobicistat (COBI)/emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF); EVG/COBI/FTC/tenofovir alafenamide (TAF)
  - BIC; and BIC/FTC/TAF
- Search terms were coded using the Medical Dictionary for Regulatory Activities (MedDRA). All pregnancy exposures and all cases reporting events in the Congenital, familial, and genetic disorders system organ class (SOC) of MedDRA were included.
- Exact timing of medication exposure relative to conception is often unconfirmed in spontaneous reports. All cases of NTDs diagnosed either anatomically or radiologically were included regardless of the trimester of exposure or unavailable timing of exposure.
- Pregnancies were categorised by the initial timing of drug exposure or classified as “unknown” when the timing of exposure was not available. Both retrospective and prospective reports were included.

Results

EVG

- A total of 630 pregnancies were identified with EVG exposure of which 155 were prospectively reported and included preconception or 1st trimester exposure.
- There were no prospectively reported NTD cases.
- One retrospective case of an NTD was reported in a 34 year old woman of African descent with HIV in the US.
  - Obstetric history included 4 pregnancies with 1 spontaneous pregnancy loss. Family history included a maternal cousin with Down syndrome.
  - EVG/COBI/FTC/TAF began prior to conception and was then switched to FTC/TDF + raltegravir 48 days post-LMP.
  - Medications started prior to conception were folate and metronidazole.
  - An initial ultrasound at 15 weeks post-LMP showed no defects; however, a second ultrasound at 19 weeks post LMP showed anencephaly.
  - A medical abortion was performed at 19 weeks. No additional fetal findings or head circumference were reported.
- As of October 10, 2018, one additional retrospective case from 2014 of an NTD was reported for EVG/COBI/FTC/TDF after the data lock point for this analysis.
  - A patient of unknown age with HIV in France began EVG/COBI/FTC/TDF 2 weeks after the LMP.
  - No information on obstetric history, risk factors, or folate supplementation was provided.
  - An event of myelomeningocele was reported at 14 weeks gestational age.
  - A medical abortion was performed 2 weeks later. No fetal findings were provided.

BIC

- A total of 25 pregnancies were identified with BIC exposure of which 18 were prospectively reported and included preconception or 1st trimester exposure.
- No cases of NTDs were identified for BIC-containing products.

- A prevalence rate could not be derived from these data as many cases originated from retrospective reports and were drawn from a population in which the number of exposed pregnancies is unknown.

Results (cont’d)

Table 1. Pregnancies for EVG-containing Regimens[a]

	Prospective Reports[b] N=264 (41.9%)			Retrospective Reports[c] N=318 (50.5%)			Unknown if Retrospective or Prospective Reports N=48 (7.6%)			Total
	Timing of Exposure in Pregnancy[d]									
	Preconception or 1st Trimester	After 1st Trimester	Unknown	Preconception or 1st Trimester	After 1st Trimester	Unknown	Preconception or 1st Trimester	After 1st Trimester	Unknown	
Total Pregnancy Reports for EVG-containing Products	155 (24.6%)	22 (3.5%)	87 (13.8%)	218 (34.6%)	69 (11.0%)	31 (4.9%)	16 (2.5%)	3 (0.5%)	29 (4.6%)	630

a. Data lock 31 May 2018.
b. Prospective pregnancy data: data acquired prior to the knowledge of pregnancy outcome or prior to the detection of a congenital malformation at prenatal examination (eg, fetal ultrasound, serum markers).
c. Retrospective pregnancy data: data acquired after the outcome of the pregnancy is known or after the detection of a fetal malformation on prenatal test.
d. First trimester exposure = initial drug exposure occurred before conception or during the first trimester; After first trimester = initial drug exposure occurred in the second or third trimester.

Table 2. Pregnancies for BIC-containing Regimens[a]

	Prospective Reports[b] N=20 (80.0%)			Retrospective Reports[c] N=4 (16.0%)			Unknown if Retrospective or Prospective Reports N=1 (4.0%)			Total
	Timing of Exposure in Pregnancy[d]									
	Preconception or 1st Trimester	After 1st Trimester	Unknown	Preconception or 1st Trimester	After 1st Trimester	Unknown	Preconception or 1st Trimester	After 1st Trimester	Unknown	
Total Pregnancy Reports for BIC-containing Products	18 (72.0%)	0	2 (8.0%)	4 (16.0%)	0	0	1 (4.0%)	0	0	25

a. Data lock 31 May 2018.
b. Prospective pregnancy data: data acquired prior to the knowledge of pregnancy outcome or prior to the detection of a congenital malformation at prenatal examination (eg, fetal ultrasound, serum markers).
c. Retrospective pregnancy data: data acquired after the outcome of the pregnancy is known or after the detection of a fetal malformation on prenatal test.
d. First trimester exposure = initial drug exposure occurred before conception or during the first trimester; After first trimester = initial drug exposure occurred in the second or third trimester.

Conclusions

- A search of the global safety database identified 630 pregnancies with EVG exposure.
  - No prospective cases of NTDs were reported.
  - One retrospective case of an NTD was reported in a pregnancy of a woman exposed to EVG prior to conception.
  - After the data lock point for this analysis, one additional retrospective case from 2014 of an NTD was reported in a pregnancy of a women exposed to EVG during the peri-conception period.
  - Viewed in the context of more than 600 EVG-exposed pregnancies, these 2 cases cannot be distinguished from the background rate of NTDs in the general population.
- A review of the limited available data for BIC identified no cases of NTDs among 25 BIC-exposed pregnancies.
- Currently, there is no evidence of an increased risk of NTDs with the use of EVG- or BIC-containing products during pregnancy.
- NTD monitoring through Gilead’s pharmacovigilance process and through the APR is ongoing.

References

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