Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Memo

Date:	June 13, 2018
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Product Names:	All integrase strand transfer inhibitor (INSTI) containing products
Subject:	Neural tube defects and other congenital spinal malformations
Drug/NDA Number/Sponsor:	Tivicay (dolutegravir) / NDA 204790 / ViiV Healthcare Juluca (dolutegravir/rilpivirine) / NDA 210192 / ViiV Healthcare Triumeq (dolutegravir/abacavir/lamivudine) / NDA 205551 / ViiV Healthcare Dutrebis (raltegravir/lamivudine) / NDA 206510 / Merck Sharp Dohme Isentress (raltegravir) / NDA 203045, 205786 / Merck Sharp Dohme Isentress HD (raltegravir) / NDA 022145 / Merck Sharp Dohme Vitekta (elvitegravir) / NDA 203093 / Gilead Sciences, Inc. Genvoya (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate) / NDA 207561 / Gilead Sciences, Inc. Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) / NDA 203100 / Gilead Sciences, Inc. Biktarvy (bictegravir) / NDA 210251 / Gilead Sciences, Inc.
OSE RCM #:	2018-983
TSI #:	1898 (Dolutegravir only)

1 INTRODUCTION

The purpose of this memo is to present summary data describing FDA Adverse Event Reporting System (FAERS) reports of neural tube defects (NTDs) and other congenital spinal malformations following transplacental exposure to any integrase strand transfer inhibitor (INSTI) or INSTI-containing regimen at any time during pregnancy.

On May 8, 2018, the Division of Antiviral Products (DAVP) became aware of a serious safety signal of NTDs in neonates born to women exposed to dolutegravir (DTG) from conception. The signal was identified during a preliminary unscheduled analysis of a birth outcomes surveillance study in Botswana (Tsepamo study, see **Appendix A**). On May 11, 2018, DAVP consulted the Division of Pharmacovigilance (DPV) II to review the FAERS database for reports of NTDs following transplacental exposure to any INSTI (including dolutegravir, raltegravir, elvitegravir, and bictegravir).

This is one of several anticipated reviews, from various disciplines, evaluating a novel safety signal in support of tracked safety issue (TSI) 1898. The safety team consists of members from DAVP, OSE [DPV, Division of Epidemiology (DEPI), and Drug Use] and the Division of Pediatric and Maternal Health (DPMH), and may include others as future needs arise. The team will consider this review, along with other data, to make decisions for regulatory action.

1.1 BACKGROUND

1.1.1 Public communications about this safety issue

FDA issued a Drug Safety Communication on May 18, 2018 regarding the preliminary findings of the Tsepamo study.[1] The European Medicines Agency[2] and the World Health Organization[3] also issued individual statements on May 18, 2018.

1.1.2 Tsepamo study

The Tsepamo study (see **Appendix A**) is an ongoing observational surveillance study of birth outcomes among neonates born to HIV-infected and HIV-uninfected women in Botswana. The study has two purposes: 1) to evaluate adverse birth outcomes by HIV-status and ART regimen, and 2) to determine if there is an increased risk of NTDs among infants exposed to efavirenz (EFV) from conception. Each neonate delivered (including live-born and still-born) is examined by a midwife for NTDs, including myelomeningocele, meningocele, encephalocele, anencephaly with or without "craniorischesis[1]", and iniencephaly.

An unplanned interim analysis in April 2018 identified a safety signal for NTDs among neonates born to HIV-infected women exposed to DTG from the time they conceived. At the time of the analysis, 4 of 385 (1.04%) neonates born to women exposed to DTG from the time they conceived developed NTD, including one case each of frontal encephalocele, anencephaly, lumbar myelomeningocele, and iniencephaly. For comparison, the percentage of neonates born

[1] "craniorischesis" is the term used in the Tsepamo study interim analysis memo in **Appendix A**, and "craniorischesis is assumed to be craniorachischisis

with NTDs to non-DTG exposed mothers in the Tsepamo study as of April 2018 were as follows:

- Exposure to any non-DTG antiretroviral therapy = 0.13%
- Exposure to EFV = 0.05%
- HIV-negative patients = 0.09%

The interim analysis memo (see **Appendix A**) also notes that no neonate born to a woman who started DTG "during pregnancy" had an NTD (zero NTD events out of 2749 births), although the term "during pregnancy" is not defined in the memo. The Tsepamo study is ongoing with an additional 600 births exposed to DTG from conception expected through February 2019.

1.1.3 NTD and other congenital spinal malformations

NTDs are congenital malformations of the spinal column and central nervous system.[4] There are approximately 300,000 births with an NTD each year worldwide.[4] Anencephaly and spina bifida (which includes meningocele, meningomyelocele, or myelocele) are the two most common forms of NTDs in the United States (U.S.).[5] Other less frequently observed NTDs include encephalocele, craniorachischisis, and iniencephaly.[5] The U.S. began cereal fortification with folic acid in 1998 as a public health initiative to prevent NTDs.[6] From 1999 to 2000, reductions in spina bifida and anencephaly cases were observed, and since that time, the prevalence of spina bifida and anencephaly in the U.S. has remained relatively stable although racial disparities persist.[6]

The Centers for Disease Control and Prevention (CDC) estimated the annual number of cases of the three most commonly reported NTDs (anencephaly, spina bifida, and encephalocele) using data from 14 birth defect tracking programs in the U.S. from 2004 to 2006. NTD cases per births include[7]:

- Anencephaly
  - 1 in 4859 births;
  - Estimated annual number of cases = 859
- Spina bifida (without anencephaly)
  - 1 in 2,858 births;
  - Estimated annual number of cases = 1,460
- Encephalocele
  - 1 in 12,235 births
  - Estimated annual number of cases = 341

Data for iniencephaly and craniorachischisis were not reported; these two NTDs are rare relative to anencephaly, spina bifida, and encephalocele, and epidemiologic estimates of prevalence are not available.[7,8]

Multiple genetic and environmental factors increase the risk for NTDs. Risk factors for NTDs include female sex and maternal factors including Hispanic ethnicity, folate insufficiency, obesity, pre-gestational diabetes, hyperthermia, family history of NTDs, and certain medication use.[4,9] Additional variables such as chromosomal abnormalities and gene mutations can also play a role in NTD development.[5] Neural tube development occurs within the first 28 days of pregnancy, and environmental exposures during this time can also incite NTDs.[4] For example,

medications that impede or reduce folate status, such as valproate and carbamazepine, increase the risk for NTDs when taken during the early stages of pregnancy.[4]

There is inconsistency in defining the spectrum of NTDs in the literature.[10] In an effort to present comprehensive data, cases describing congenital spinal malformations such as hemivertebra and butterfly vertebra were included in this memo.

1.2 INSTI USE IN PREGNANCY

On May 30, 2018, the U.S. Department of Health and Human Services (DHHS) updated recommendations for the use of DTG in adults and adolescents with HIV who are of child-bearing potential and for those who are pregnant. The updated recommendations vary based on patient characteristics (e.g., stage of pregnancy, history of antiretroviral therapy use, HIV resistance, etc.), but the overall principles include[11]:

> *For treatment of adults and adolescents with HIV who are pregnant or of child-bearing potential, we recommend the following:*
> - *For individuals not known to be pregnant, documentation of a negative pregnancy test is recommended prior to initiating DTG.*
> - *Those who are currently receiving DTG as a component of their ART or who wish to be started on DTG should be counseled about the potential risk of NTDs when DTG is taken near the time of conception. NTDs occur within the first 28 days after conception or 6 weeks from the last menstrual period.*
> - *Those who are pregnant, taking DTG, and within 8 weeks from last menstrual period should discuss the risks and benefits of their current regimens with their health care providers. If there are other good options to replace DTG, then switching to a non-DTG ART regimen is recommended (see Table 2).*
> - *Those who are pregnant and 8 weeks or greater from last menstrual period may initiate or continue DTG-based regimens. Discontinuing DTG-based regimens is unlikely to confer any benefits after the neural tube has formed, and medication changes during pregnancy could increase the risk of viremia and transmission of HIV to the infant.*
> - *Currently, it is not clear if DTG is the only integrase strand transfer inhibitor (INSTI) with the potential to cause NTDs, or if other INSTIs also carry this risk (i.e., a class effect). Although there have been no reports of NTDs associated with taking DTG or other INSTIs near the time of conception in the prospective portion of the U.S. Antiretroviral Pregnancy Registry, the Registry is based on voluntary reporting and the number of reported INSTI exposures near the time of conception is relatively small.*

1.3 REGULATORY HISTORY: INSTI

Four INSTIs are currently marketed in the U.S. as individual dosage forms or as part of a combination product[12]:

INSTI name and brand name for individual formulation(s)	Indication for individual formulation(s)	U.S. approval date	Other single-tablet combination products containing the INSTI
Dolutegravir (DTG) Tivicay[13]	TIVICAY is a human immunodeficiency virus type 1 (HIV-1) INSTI indicated in combination with: • other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 30 kg. • rilpivirine as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure or known substitutions associated with resistance to either antiretroviral agent	8/12/2013	Triumeq (DTG, Abacavir, Lamivudine) Juluca (DTG, rilpivirine)
Elvitegravir (EVG) Vitekta – discontinued Stribild[14] (first combination product for EVG on U.S. market)	STRIBILD is a four-drug combination of EVG, an HIV-1 INSTI, cobicistat, a CYP3A inhibitor, and emtricitabine (FTC) and tenofovir DF, both HIV nucleoside analog reverse transcriptase inhibitors (HIV NRTI) and is indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older weighing at least 35 kg who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of STRIBILD.	Vitekta - 9/24/2014 Stribild – 8/27/2012	Stribild (EVG, cobicistat, emtricitabine, tenofovir disoproxil fumarate) Genvoya (EVG, cobicistat, emtricitabine, tenofovir alafenamide)
Raltegravir (RAL) Isentress[15] (400 mg) Isentress HD (600 mg dose)	Adult Patients: ISENTRESS and ISENTRESS HD are HIV-1 INSTI indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adult patients. Pediatric Patients: ISENTRESS is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients weighing at least 2 kg. ISENTRESS HD is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients weighing at least 40 kg.	10/12/2007	Dutrebis (RAL, lamivudine)
Bictegravir (BIC) Biktarvy[16]	BIKTARVY is a three-drug combination of BIC, a HIV-1 INSTI, and FTC and tenofovir alafenamide (TAF), both HIV-1 NRTIs, and is indicated as a complete regimen for the treatment of HIV-1 infection in adults who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of BIKTARVY.	2/07/2018	n/a

2 METHODS AND MATERIALS

2.1 CASE DEFINITION

2.1.1 Inclusion

2.1.1.1 INSTI Exposure Criteria

For the purpose of presenting comprehensive summary data, this series includes FAERS cases of NTDs and other congenital spinal malformations in the setting of transplacental exposure to an INSTI. Although NTDs occur early in embryogenesis, cases in which transplacental exposure to an INSTI started before conception, at conception, post-conception, or at an unspecified time during pregnancy were included.

2.1.1.2 NTD and Other Congenital Spinal Malformation Definition

There were no diagnostic criteria required for inclusion; as such, the NTDs vary in diagnostic certainty. A report of an NTD identified during prenatal screening, at birth, or at the end of a pregnancy was sufficient for inclusion. Identification of the specific type of NTD (e.g., encephalocele, iniencephaly, etc.) was not a requirement for inclusion. Of note, myelomeningocele is a type of spina bifida; however, in this memo we cited the exact NTD term used in the FAERS narrative for each case instead of classifying NTDs into higher-level groups. In addition, congenital spinal malformations such as hemivertebra and butterfly vertebra were included in this case series.

2.1.2 Exclusion

Cases were excluded if they were duplicate or if they did not meet the case definition.

2.2 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 2.2.1**.

Table 2.2.1 FAERS Search Strategy*	
Date of Search	May 31, 2018
Time Period of Search	All reports through May 30, 2018
Search Type	Drug Safety Analytics Dashboard – Quick Search
Product Terms	Product Names: Juluca, Tivicay, Triumeq, Isentress, Dutrebis, Genvoya, Stribild, Stribild Access, Vitekta, Biktarvy Product Active Ingredients (PAI): all PAI terms containing dolutegravir, raltegravir, elvitegravir, or bictegravir

Table 2.2.1 FAERS Search Strategy*	
MedDRA Search Terms (Version 20.1)	High Level Term (HLT): *Central nervous system disorders congenital NEC, Musculoskeletal and connective tissue disorders of spine congenital* Preferred Terms (PTs): *Craniorachischisis, Iniencephaly, Encephalocele, Encephalocele repair, Meningoencephalocele repair, Meningocele acquired, Meningocele repair, Meningocele, Spina bifida, Spina bifida cystica, Meningomyelocele, Meningomyelocele repair, Anencephaly, Hydranencephaly, Hemivertebra* Narrative terms: *butterfly vertebra, butterfly vertebrae, hemivertebra, hemivertebrae, dysraphism*
* See **Appendix B** for a description of the FAERS database.	

3 RESULTS

3.1 INCLUSION AND EXCLUSION

The FAERS search retrieved 54 reports. After applying the case definition in **Section 2.1** and accounting for duplicate reports, **13 cases were included** in the case series of NTDs and other congenital spinal malformations reported with transplacental INSTI exposure. The remaining 41 reports were excluded from the final analysis for the following reasons:

- Duplicate reports (n=38)
- Did not meet the case definition (n=3)
  - Report did not provide sufficient information to conclude that the congenital malformation was an NTD (n=2)
  - Report had conflicting information regarding the presence of an NTD (NTD noted prenatally, but not noted at birth), and report noted concurrent aneuploidy, which is a potential explanation for an NTD (n=1)

3.2 FAERS SUMMARY DATA

No reports for BIC were identified in the search. The series of 13 cases included three INSTIs:

- RAL
  - n=7 cases (2 U.S. cases)
- EVG followed by RAL
  - n=1 case (1 U.S. case)
- DTG
  - n=5 cases (0 U.S. cases)
    - Of these 5 cases, 4 were cases from the Tsepamo study (FAERS Case IDs: 14882044, 14882047, 14882048, 14882049)

Transplacental exposure to an INSTI from the time of conception was reported for nine cases. Three cases had transplacental INSTI exposure during pregnancy but the reports did not specify the exact time frame of INSTI exposure relative to the time frame of the pregnancy. One case had transplacental INSTI exposure starting 18 weeks after the mother's last menstrual period.

Ten cases reported NTDs and three cases reported other congenital spinal malformations. NTDs included anencephaly (n=2), encephalocele (n=2), spina bifida (n=2), iniencephaly (n=1), myelomeningocele with hydrocephalus (n=1), spina bifida with possible anencephaly (n=1), and an unspecified NTD (n=1). Congenital spinal malformations included hemivertebra and butterfly vertebra (n=2), and hemivertebra with an unspecified spine malformation (n=1). Of the 13 cases in the series, seven cases had other congenital anomalies[2] in addition to the NTD or congenital spinal malformation.

Table 3.2.1 includes an abbreviated line listing of the 13 FAERS cases of NTDs and other congenital spinal malformations reported with transplacental INSTI exposure for this case series. See **Appendices C and D** for full details of each case, including Reviewer's Comments.

Table 3.2.1. Descriptive characteristics of NTDs and other congenital spinal malformations with transplacental INSTI exposure received by FDA through May 30, 2018

(n=13)

FAERS Case #	Country Derived	Maternal INSTI Start Date	NTD or Congenital Spinal Malformation	Pregnancy Outcome	Additional Congenital Anomalies
RAL, n=7					
11275144	PRI	"At conception"	Encephalocele	Spontaneous abortion	Yes
12103690	USA	Preconception	Myelomeningocele	Live birth	Yes
8915704	DEU	Preconception	Hemivertebra (T9), butterfly vertebra (T10)	Live birth via C-section	Yes
9452383	USA	NR	Hemivertebra, spine malformation	Live birth (per duplicate FAERS report: 9565753)	Yes
11225746	FRA	NR	Hemivertebra (lumbar), cervical butterfly vertebra	Live birth via Caesarean section	Yes
14567908	BRA	NR	Spina bifida	NR	Yes
11105081	GBR	Post-conception, 18 weeks after LMP	Spina bifida and possible anencephaly	Live birth	Yes

[2] Other congenital anomalies include ambiguous genitalia, anal atresia, aplasia of right external auditory canal, bladder agenesis, cloacal exstrophy, esophageal atresia, hydrocephalus, microtia, omphalocele, optic tracts damage, septal agenesis, stenosis of aqueduct of Sylvius, ventricular septal defect. Please see **Appendix D** for full details.

Table 3.2.1. Descriptive characteristics of NTDs and other congenital spinal malformations with transplacental INSTI exposure received by FDA through May 30, 2018

(n=13)

FAERS Case #	Country Derived	Maternal INSTI Start Date	NTD or Congenital Spinal Malformation	Pregnancy Outcome	Additional Congenital Anomalies
EVG then RAL, n=1					
14686667	USA	EVG: preconception through week 6 day 7 after LMP RAL: starting from week 6 day 7 after LMP	Anencephaly	NR	NR
DTG, n=5					
13264782	NAM	Preconception	Unspecified NTD	NR; Planning termination	NR
14882044	BWA (Tsepamo study)	Preconception	Anencephaly	Live birth, died shortly after birth	NR
14882047	BWA (Tsepamo study)	Preconception	Iniencephaly	Stillborn (macerated)	NR
14882048	BWA (Tsepamo study)	Preconception	Spina bifida	Live birth, death 4 days later	NR
14882049	BWA (Tsepamo study)	Preconception	Encephalocele	Live birth	NR

BRA = Brazil
BWA = Botswana
DEU = Germany
DTG = Dolutegravir
EVG = Elvitegravir
FRA = France
GBR = Great Britain
INSTI = Integrase strand transfer inhibitor
LMP = Last menstrual period
NAM = Namibia
NTD = Neural Tube Defect
NR = Not reported
PRI = Puerto Rico
RAL = Raltegravir

4 DISCUSSION

We identified 13 FAERS cases of NTDs and other congenital spinal malformations following transplacental exposure to INSTIs. Nine of 13 cases had transplacental exposure to an INSTI from conception, during the time when neural tube development occurs. Some cases appear to be isolated presentations of a single NTD, while other cases may be part of a genetic syndrome. Given the complexity of genetic and environmental factors that may contribute to neural tube development, it can be challenging to definitively attribute an NTD to a single cause, and even more so with reliance on case reports of variable data quality.

In the FAERS case series, three INSTI agents were reported among the 13 cases: RAL, EVG, and DTG. RAL was the most frequently reported INSTI (n=7) among the cases, but RAL was also the first approved INSTI (2007) in the U.S., followed by EVG (Stribild 2012, Vitekta 2014),

DTG (2013), and BIC (2018). The lack of FAERS reports for BIC and NTDs does not exclude the possibility of a causal association between BIC and NTDs or other congenital spinal malformations, particularly given the short time it has been on the market (approximately 4 months).

The FAERS case series has several limitations. In general, the FAERS reports were limited by a lack of complete information on important maternal variables such as past medical history, concurrent medications, and family history. Additionally, reporting adverse events to FAERS is voluntary for consumers and healthcare professionals[17], thus underreporting of adverse events is a recognized limitation.[18,19] Furthermore, because of the background rate of NTDs and complexity of genetic and environmental factors that may contribute to NTDs, there are limitations to assessing causality using FAERS data.

The Tsepamo study identified four cases of NTDs following transplacental DTG exposure (also included in this case series); currently we do not know if other INSTIs were evaluated in this study. The Tsepamo study is ongoing, and an additional 600 births following transplacental exposure to DTG from the time of conception are expected by the end of February 2019. The final results of the Tsepamo study, in conjunction with analyses of postmarketing data and any additional available data, will be essential for evaluating the potential association between transplacental INSTI exposure and NTDs and other congenital spinal malformations.

5 NEXT STEPS

DPV will continue to closely monitor FAERS for new reports of NTDs and other congenital spinal malformations following transplacental exposure to INSTIs. DPV will provide an updated summary of FAERS data after the results of the Tsepamo study are available (after February 2019).

Several other reviews are in progress, including reviews by DEPI (including epidemiologist's review and drug utilization data), and DPMH. The TSI team will jointly assess all available information, including this review, to determine necessary regulatory action.

6 REFERENCES

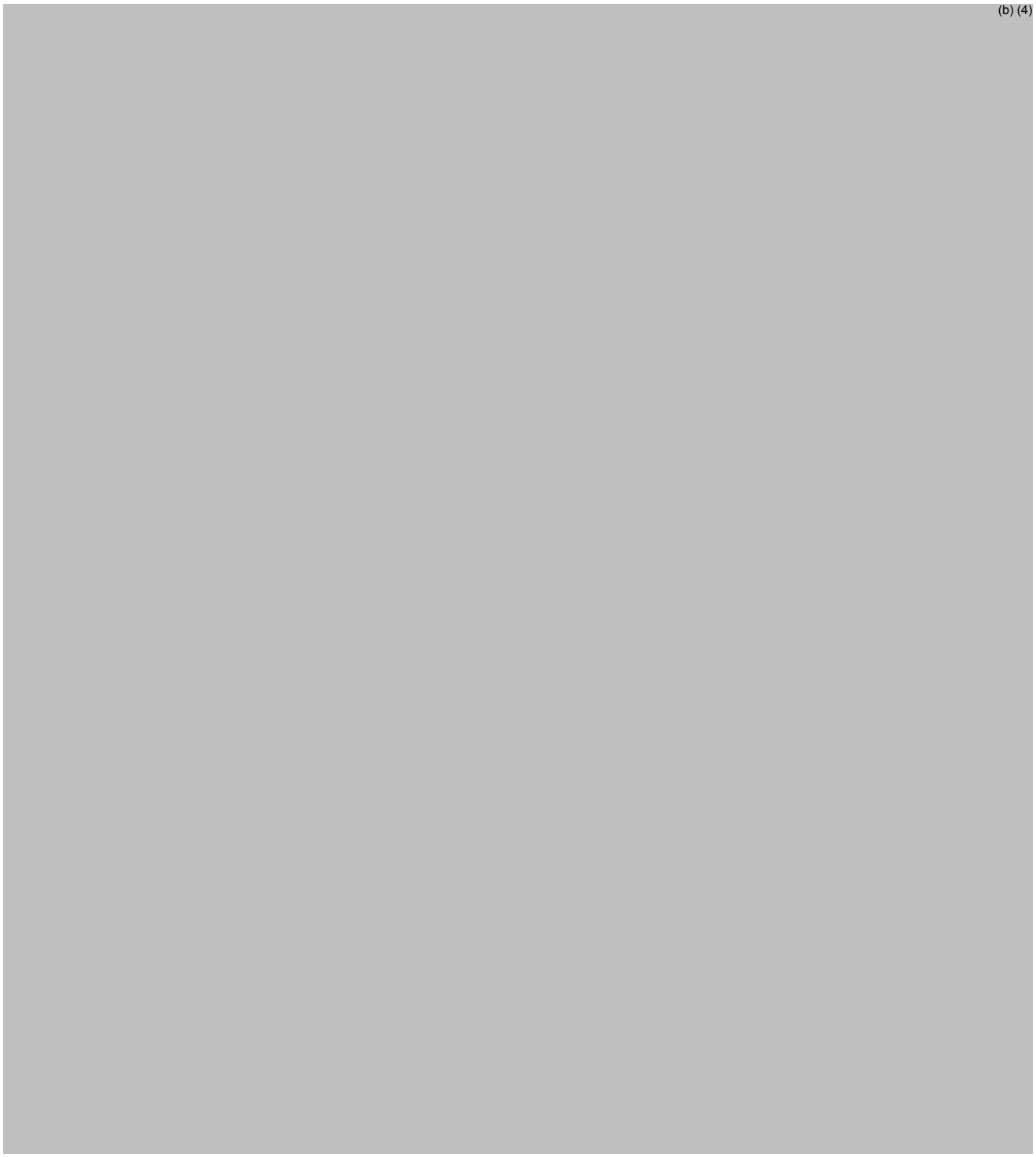
[1] U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA to evaluate potential risk of neural tube birth defects with HIV medicine dolutegravir (Juluca, Tivicay, Triumeq). Available at: https://www.fda.gov/drugs/drugsafety/ucm608112.htm. Accessed on June 2, 2018.
[2] European Medicines Agency. Press release: New study suggests risk of birth defects in babies born to women on HIV medicine dolutegravir. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/05/news_detail_002956.jsp&mid=WC0b01ac058004d5c1. Accessed on June 2, 2018.

[3] World Health Organization. Statement on DTG – Geneva 18 May 2018. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/05/news_detail_002956.jsp&mid=WC0b01ac058004d5c1. Accessed on June 2, 2018.
[4] Committee on Practice Bulletins-Obstetrics. Practice Bulletin No. 187: Neural Tube Defects. Obstet Gynecol. 2017 Dec;130(6):e279-e290.
[5] Botto LD, Moore CA, Khoury MJ, Erickson JD. Medical Progress (Review Articles): Neural-Tube Defects. N Engl J Med.1999 Nov 11;341(20):1509-1519.
[6] Williams J, Mai CT, Mulinare J, Isenburg J, Flood TJ, Ethen M, Frohnert B, Kirby RS; Centers for Disease Control and Prevention. Updated estimates of neural tube defects prevented by mandatory folic Acid fortification - United States, 1995-2011. MMWR Morb Mortal Wkly Rep. 2015 Jan 16;64(1):1-5.
[7] Centers for Disease Control and Prevention. Birth Defects: Data & Statistics – National estimates for 21 selected major birth defects, 2004-2006. Available at: https://www.cdc.gov/ncbddd/birthdefects/data.html#modalIdString_table-Nattional-Estimates. Accessed on June 2, 2018.
[8] Centers for Disease Control and Prevention. Birth Defects Surveillance Toolkit: Congenital malformations of the nervous system: neural tube defects. Available at: https://www.cdc.gov/ncbddd/birthdefects/surveillancemanual/photo-atlas/nervous.html. Accessed on June 2, 2018.
[9] Agopian AJ, Tinker SC, Lupo PJ, Canfield MA, Mitchell LE, and the National Birth Defects Prevention Study. Proportion of Neural Tube Defects Attributable to Known Risk Factors. Birth Defects Res A Clin Mol Teratol. 2013 Jan:97(1):42-46.
[10] McComb JG. A practical clinical classification of spinal neural tube defects. Child's Nervous System. 2015 Oct;31(10):1641-1657.
[11] U.S. Department of Health and Human Services. Recommendations Regarding the Use of Dolutegravir in Adults and Adolescents with HIV who are Pregnant or of Child-Bearing Potential. Available at: https://aidsinfo.nih.gov/news/2109/recommendations-regarding-the-use-of-dolutegravir-in-adults-and-adolescents-with-hiv-who-are-pregnant-or-of-child-bearing-potential. Accessed on June 2, 2018.
[12] U.S. Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed on June 1, 2018.
[13] Tivicay (dolutegravir) [package insert]. Research Triangle Park, NC: ViiV Healthcare, 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/204790s014lbl.pdf. Updated November 21, 2017. Accessed on June 1, 2018.
[14] Stribild (cobicistat, elvitegravir, emtricitabine, tenofovir) [package insert]. Foster City, CA: Gilead Sciences, Inc., 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/203100s030lbl.pdf. Updated August 30, 2017. Accessed on June 1, 2018.
[15] Isentress (raltegravir) [package insert]. Whitehouse Station, NJ: Merck Share & Dohme Corp., 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022145s038,205786s007,0203045s015lbl.pdf. Updated March 5, 2018. Accessed on June 1, 2018.
[16] Biktarvy (bictegravir) [package insert]. Foster City, CA: Gilead Sciences, Inc.., 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210251s000lbl.pdf. Updated February 7, 2018. Accessed on June 1, 2018.

[17] U.S. Food and Drug Administration. Questions and Answers on FDA's Adverse Event Reporting System (FAERS). Available at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/(updated March 20, 2018, accessed on March 22, 2018).
[18] Hazell, L, and Shakir, SA, 2006, Under-reporting of adverse drug reactions: a systematic review, Drug Saf; 29: 385-96.
[19] Alatawi, YM, and Hansen, RA, 2017, Empirical estimation of under-reporting in the US Food and Drug Administration Adverse Event Reporting System (FAERS), Expert Opinion on Drug Safety; 16: 761-7.

7 APPENDICES

7.1 APPENDIX A TSEPAMO STUDY - PRELIMINARY RESULTS



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7.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM

FDA Adverse Event Reporting System (FAERS)

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

7.3 APPENDIX C. DETAILED CASE SERIES LINE LISTING – PART 1

Table 7.3.1 Descriptive characteristics of NTDs and other congenital spinal malformations with transplacental INSTI exposure received by FDA through May 30, 2018:

Maternal Characteristics
(n=13)

FAERS Case #	Age (yr.)	LMP	EDD	INSTI Dose	INSTI Start Date	INSTI Start Relative to Pregnancy	Other ART	Other Medi-cations	Demographics, PMH	Family History	Country
RAL, n=7											
11275144	39	(b) (6)	(b) (6)	800 mg daily	"At conception"	"At conception"	Emtricitabine and tenofovir disoproxil fumarate (1 tab daily), etravirine 400 mg daily	NR	Hispanic ethnicity, concurrent *Chlamydia,* 1 previous spontaneous abortion (gravida 3 para 1), HIV, hepatitis C (compensated liver disease with Pugh score <7)	No family history of defects	PRI
12103690	NR	NR	NR	NR	12/1/2012	Preconception	12/1/2012 - start Truvada and raltegravir	NR	HIV, hepatitis C	NR	USA
8915704	44	(b) (6)	(b) (6)	400 mg BID	11/29/2008	Preconception	11/29/2008: Trizivir 300-150-300 BID, tenofovir disoproxil fumarate 245mg daily, ritonavir 100mg BID, darunavir 600 mg BID; unspecified antiretroviral	NR	HIV, history of one pregnancy with live birth (no CA)	NR	DEU
9452383	NR	NR	NR	NR	NR	NR	Trizivir, tenofovir (type NR), darunavir, ritonavir	NR	NR (other than HIV)	NR	USA
11225746	28	(b) (6)	(b) (6)	NR	NR	NR	Darunavir, ritonavir	Trandate (labetalol)	HIV, chronic arterial hypertension, "gravida and para were reported as 1"	NR	FRA

Table 7.3.1 Descriptive characteristics of NTDs and other congenital spinal malformations with transplacental INSTI exposure received by FDA through May 30, 2018:

Maternal Characteristics
(n=13)

FAERS Case #	Age (yr.)	LMP	EDD	INSTI Dose	INSTI Start Date	INSTI Start Relative to Pregnancy	Other ART	Other Medi-cations	Demographics, PMH	Family History	Country
14567908	NR	NR	NR	400 mg daily	4/5/2017	NR	4/5/2017 to 8/10/2017 lamivudine/zidovudine 900mg daily	marijuana/cannabis sativa 3 times per week	NR (other than HIV)	NR	BRA
11105081	42	(b) (6)	(b) (6)	400 daily or BID (conflicting)	10/23/2008	Post-conception; 130 days after LMP	Zidovudine during delivery tipranavir 6/5/2007 - 10/23/2008 Truvada 9/5/2006 (APR) - 10/23/2008 ritonavir 6/5/2007 to 10/23/2008 to unknown darunavir 10/23/2008 to unknown etravirine 10/23/2008 - 2/21/2009 raltegravir 10/23/2008 - 2/21/2009	Used prednisolone in 2007 - duration NR, insulin (gestational diabetes), nitrous oxide and oxygen	Race reported as black, HIV 1993, pulmonary and systemic TB 1993, STDs unspecified, herpes zoster 1996, renal vascular disorder NOS, gestational diabetes and insulin, gravida 2 (including current) parity 1 (normal outcome and no spontaneous losses); ALT = 194 on 6/3/2008, ANA = 1:400 and smooth muscle antibody 1:1000 on 6/19/2008, increased ALT/AST, metabolic disorder NOS; no alcohol/smoking/tobacco/recreational drugs; drug induced hepatitis	No family history of CA, hereditary disorder, or significant outcomes	GBR
EVG then RAL, n=1											
14686667	34	(b) (6)	(b) (6)	Genvoya daily, then RAL BID	EVG 10/13/20016 to 12/16/2017 RAL 12/16/2017 to ongoing	EVG: preconception to week 6 day 6 from LMP RAL: week 6 day 6 to ongoing	Truvada once daily	NR	NR (other than HIV), race reported as "of African descent"	NR	USA
DTG, n=5											
13264782	40	NR	NR	NR	"since a few months before falling pregnant"	Preconception	NR	NR	NR (other than HIV)	NR	NAM

Table 7.3.1 Descriptive characteristics of NTDs and other congenital spinal malformations with transplacental INSTI exposure received by FDA through May 30, 2018:

Maternal Characteristics
(n=13)

FAERS Case #	Age (yr.)	LMP	EDD	INSTI Dose	INSTI Start Date	INSTI Start Relative to Pregnancy	Other ART	Other Medi-cations	Demographics, PMH	Family History	Country
14882044	30	Estimated date of conception (b) (6)	NR	NR	6/1/2016	Preconception	NR	(b) (6) (3rd month of pregnancy) started FeFol	HIV, 2 past pregnancies "with one over 20 weeks gestation", no diabetes/insulin, no seizure/AEDs	NR	BWA (Tsepamo study)
14882047	31	(b) (6)	(b) (6)	NR	6/29/2016	Preconception	NR	None	HIV only; no diabetes/insulin, no seizures/AEDs; history of 2 pregnancies of which 1 was past 20 weeks gestation	NR	BWA (Tsepamo study)
14882048	35	(b) (6)	(b) (6)	NR	8/1/2016	Preconception	NR	(b) (6) (6th month of pregnancy) started multivitamin	HIV only; no diabetes/insulin, no seizures/AEDs; history of five pregnancies of which four were over 20 weeks gestation	NR	BWA (Tsepamo study)
14882049	30	(b) (6)	(b) (6)	NR	6/20/2016	Preconception	NR	(b) (6) methyldopa, started during week 22 day 3 from LMP; no MVI or folate	HIV, gestational hypertension, "3 pregnancies with 2 reaching more than 20 weeks gestation"; no diabetes/insulin, no seizures/AEDs	NR	BWA (Tsepamo study)

AED = anti-epileptic drugs
ALT = Alanine Aminotransferase
ART = Antiretroviral therapy
AST = Aspartate Aminotransferase
BRA = Brazil
BWA = Botswana
CA = Congenital anomaly
DEU = Germany
DTG = Dolutegravir
EDD = Estimated delivery date
EVG = Elvitegravir
FeFol = Iron, Folate
FRA = France
GBR = Great Britain
INSTI = Integrase strand transfer inhibitor
LMP = Last menstrual period
MVI = multivitamin
NAM = Namibia
NOS = not otherwise specified
NTD = Neural Tube Defect
NR = Not reported
PMH = Past medical history
PRI = Puerto Rico
RAL = Raltegravir
TB = Tuberculosis

7.4 APPENDIX D. DETAIL CASE SERIES LINE LISTING – PART 2

Table 7.4.1 Descriptive characteristics of NTDs and other congenital spinal malformations with transplacental INSTI exposure received by FDA through May 30, 2018:

NTD Characteristics
(n=13)

FAERS Case #	1st trimester screening (weeks 0-13*)	2nd trimester screening (weeks 14-26)	3rd trimester screening (weeks 27+)	DOB/Date of other outcome	Sex	Gestational age at DOB/Date of other outcome	Weight at DOB/Date of other outcome	Pregnancy Outcome	NTD or Other Congenital Spinal Malformation Description	Other CAs and concurrent conditions	Reviewer's Comments
RAL, n=7											
11275144	NR	NR	NR	NR	Male	17 weeks	83 grams	Spontaneous abortion	Encephalocele	2 vessel cord	Temporal association present; Hispanic ethnicity is risk factor for NTDs
12103690	ultrasound on (b) (6) (date may be incorrect) during unknown trimester showed myelomeningocele with hydrocephalus			(b) (6) (DOB may be wrong because ultrasound date reported as (b) (6))	Female	NR	NR	Live birth	Myelomeningocele with hydrocephalus (lower lumbar and sacral lumbar open NTD)	Hydrocephalus; possibly hepatitis C based on concurrent medications of cefazolin, acetaminophen, hydrocodone, docusate, simethicone, ledipasvir, sofosbuvir, valacyclovir	Temporal association present
8915704	pregnancy identified at end of 1st tri; "no prenatal tests were done"			(b) (6)	Male	33 weeks	1.6 kg	Live birth via C-section	Hemivertebra (T9), butterfly vertebra (T10)	Esophageal atresia (IIIb), "small for dates baby" (length 44 cm, head circumference 33 cm)	Temporal association present
9452383	NR	NR	NR	NR	NR	NR	NR	Live birth (per duplicate FAERS Case: 9565753)	Hemivertebra, spine malformation	Esophageal atresia	INSTI exposure at conception cannot be confirmed

Table 7.4.1 Descriptive characteristics of NTDs and other congenital spinal malformations with transplacental INSTI exposure received by FDA through May 30, 2018:

NTD Characteristics
(n=13)

FAERS Case #	1st trimester screening (weeks 0-13*)	2nd trimester screening (weeks 14-26)	3rd trimester screening (weeks 27+)	DOB/Date of other outcome	Sex	Gestational age at DOB/Date of other outcome	Weight at DOB/Date of other outcome	Pregnancy Outcome	NTD or Other Congenital Spinal Malformation Description	Other CAs and concurrent conditions	Reviewer's Comments
11225746	NR	NR	NR	(b) (6)	Male	"37 weeks amenorrhea plus 4 days"	2.44 or 2 5 kg (conflicting)	Live birth via C-section	Hemivertebrae, butterfly vertebra	Tri-ventricular hydrocephalus with a 4th non dilated ventricle with short stenosis of aqueduct of Sylvius and septal agenesis, suspected ventricular septal defect (VSD), esophageal atresia without tracheoesophageal fistula, right microtia with aplasia of right external auditory canal and absence of the handle of the malleus, bilateral optic tracts damage	INSTI exposure at conception cannot be confirmed ; clinical picture consistent with VACTERL syndrome
14567908	NR	NR	NR	(b) (6)	Male	NR	2.92 kg	NR	Spina bifida	NR	INSTI exposure at conception cannot be confirmed
11105081	Identified pregnancy (b) (6) (week 10+3 days); possible screening at week 11 ultrasound showing "no abnormalities" (timing unclear)	week 21 ultrasound showed "no abnormalities"	week 28 ultrasound showed "no abnormalities"	(b) (6)	Female	APR update in FAERS says 37 weeks which fits LMP dates (FAERS reported also says 28 weeks)	2.5 kg per FAERS; 2.2kg per APR in FAERS	Live birth	Spina bifida myelomeningocele with low-lying spinal cord tethering, anencephaly, butterfly vertebra	Cloacal exstrophy, exomphalos (omphalocele), ambiguous small bifid genitalia, anal atresia, bladder agenesis, umbilical cord abnormality, acquired lipodystrophy, erythema	Post-conception exposure to INSTI; Gestational diabetes is potential risk factor for NTDs; clinical findings consistent with caudal regression syndrome and OEIS syndrome,
EVG then RAL, n=1											

Table 7.4.1 Descriptive characteristics of NTDs and other congenital spinal malformations with transplacental INSTI exposure received by FDA through May 30, 2018:

NTD Characteristics
(n=13)

FAERS Case #	1st trimester screening (weeks 0-13*)	2nd trimester screening (weeks 14-26)	3rd trimester screening (weeks 27+)	DOB/Date of other outcome	Sex	Gestational age at DOB/Date of other outcome	Weight at DOB/Date of other outcome	Pregnancy Outcome	NTD or Other Congenital Spinal Malformation Description	Other CAs and concurrent conditions	Reviewer's Comments
14686667	NR 10-29--17	1st pregnancy visit ((b) (6)) week 14 day 2 from LMP - ultrasound showed no defects; (b) (6) week 18 day 4 from LMP ultrasound - anencephaly	NR	NR	NR	NR	NR	NR	Anencephaly	NR	Temporal association present for EVG at time of conception; RAL exposure after conception (~6 weeks after LMP)
DTG, n=5											
13264782	NR	NR	NR	planning termination	NR	planning termination	n/a	Planning termination	Unspecified NTD	NR	Temporal association present
14882044	NR	NR	NR	(b) (6)	NR	39 weeks	NR	Live birth; died shortly after birth	Anencephaly	NR	Temporal association present; no folate supplementation at conception
14882047	NR	NR	NR	(b) (6)	NR	39 weeks	NR	Stillborn macerated	Iniencephaly	NR	Temporal association present; no folate supplementation at conception
14882048	NR	NR	NR	(b) (6)	NR	38 weeks	NR	Live birth; death 4 days later	Spina bifida	NR	Temporal association present; no folate supplementation at conception

Table 7.4.1 Descriptive characteristics of NTDs and other congenital spinal malformations with transplacental INSTI exposure received by FDA through May 30, 2018:

NTD Characteristics
(n=13)

FAERS Case #	1st trimester screening (weeks 0-13*)	2nd trimester screening (weeks 14-26)	3rd trimester screening (weeks 27+)	DOB/Date of other outcome	Sex	Gestational age at DOB/Date of other outcome	Weight at DOB/Date of other outcome	Pregnancy Outcome	NTD or Other Congenital Spinal Malformation Description	Other CAs and concurrent conditions	Reviewer's Comments
14882049	NR	NR	NR	(b) (6)	NR	33 weeks from LMP	NR	Live birth	Encephalocele	NR	Temporal association present; no folate supplementation at conception

*Week of pregnancy was based on reported information or calculated using reported date of LMP as the start of week 0

APR = Antiretroviral Pregnancy Registry
CA = Congenital Anomaly
DOB = Date of birth
DTG = Dolutegravir
EVG = Elvitegravir
INSTI = Integrase strand transfer inhibitor
LMP = Last menstrual period
NTD = Neural Tube Defect
NR = Not reported
RAL = Raltegravir

7.5 APPENDIX E. FAERS LINE LISTING OF NTDS AND OTHER CONGENITAL SPINAL MALFORMATIONS WITH TRANSPLACENTAL INSTI EXPOSURE

	Initial FDA Received Date	FAERS Case #	Duplicate FAERS Case #	Version #	Manufacturer Control #	Case Type	Gestational Age (weeks)	Sex	Country Derived	Serious Outcomes *
1	2015-05-11	11105081	9560568, 11114726, 9617547, 7064207, 7229428, 9471300, 9537993, 9547517, 9549097, 11089525, 7151595, 9452837, 7080988, 9455309, 9534245, 9802193, 9537014, 9537033, 9540414, 10421287, 7169554	9	GB-GILEAD-2015-0152641	Expedited	APR notes 37 weeks (FAERS says 28 weeks)	Female	GBR	HO, LT, CA, DS, OT
2	2015-07-16	11275144	11308388	3	PR-009507513-1507PER007282	Expedited	17 weeks	Male	PRI	DE, CA
3	2016-02-23	12103690	n/a	3	US-009507513-1602USA010104	Expedited	NR	Female	USA	CA
4	2018-03-27	14686667	n/a	1	US-GILEAD-2018-0328964	Expedited	NR	NR	USA	CA, OT
5	02/23/2017	13264782	n/a	1	NA-VIIV HEALTHCARE LIMITED-NA2017GSK023909	Expedited	NR	NR	NAM	OT
6	2018-02-23	14567908	n/a	2	BR-MYLANLABS-2018M1012363	Expedited	NR	Male	BRA	CA, OT

	Initial FDA Received Date	FAERS Case #	Duplicate FAERS Case #	Version #	Manufacturer Control #	Case Type	Gestational Age (weeks)	Sex	Country Derived	Serious Outcomes *
7	2018-05-11	14882044	n/a	1	US-VIIV HEALTHCARE LIMITED-BW2018GSK083088	Expedited	39 weeks	NR	BWA	DE, CA, OT
8	2018-05-11	14882047	n/a	1	US-VIIV HEALTHCARE LIMITED-BW2018GSK083124	Expedited	39 weeks	NR	BWA	DE, CA, OT
9	2018-05-11	14882048	n/a	1	US-VIIV HEALTHCARE LIMITED-BW2018GSK083116	Expedited	38 weeks	NR	BWA	DE, CA, OT
10	2018-05-11	14882049	n/a	1	US-VIIV HEALTHCARE LIMITED-BW2018GSK083007	Expedited	33 weeks	NR	BWA	CA, OT
11	2012-11-19	8915704	7638368, 7696785, 7660221, 7629932, 7617998, 7624984	1	DE-009507513-1009DEU00132B1	Expedited	33 weeks	Male	DEU	CA, OT, HO
12	2013-08-12	9452383	9587450, 9595917, 9565753, 9605172	2	US-JNJFOC-20130802277	Expedited	NR	NR	USA	CA, OT

	Initial FDA Received Date	FAERS Case #	Duplicate FAERS Case #	Version #	Manufacturer Control #	Case Type	Gestational Age (weeks)	Sex	Country Derived	Serious Outcomes *
13	2015-06-29	11225746	11219063, 11359307, 11224782, 11216977	5	FR-MERCK-1506FRA011547	Expedited	"37 weeks amenorrhea plus 4 days"	Male	FRA	CA, OT

APR = Antiretroviral Pregnancy Registry
BRA = Brazil
BWA = Botswana
DEU = Germany
FRA = France
GBR = Great Britain
NAM = Namibia
NR = Not Reported
PRI = Puerto Rico

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. This outcome should not be confused with the clinical outcome of the reported adverse drug experience. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A report may have more than one serious outcome.

Abbreviations: DE=Death, HO=Hospitalization, LT= Life-threatening, DS= Disability, CA= Congenital Anomaly, OT=Other medically significant

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