TITLE PAGE

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Author(s):	Vannappagari, Vani Albano, Jessica Ragone, Leigh

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1. LIST OF ABBREVIATIONS

APR	Antiretroviral Pregnancy Registry
ARV	Antiretroviral
CROI	Conference on Retroviruses and Opportunistic Infections
DTG	Dolutegravir
FDA	Federal Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
INSTI	Integrase Strand Transfer Inhibitor
IRB	Institutional Review Board
LBW	Low Birth Weight
PHI	Protected Health Information
SPC	Summary of Product Characteristics
US	United States
VLBW	Very Low Birth Weight
WIRB	Western Institutional Review Board

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2. RESPONSIBLE PARTIES: SPONSOR INFORMATION PAGE

MARKETING AUTHORISATION HOLDER

ViiV Healthcare UK Limited

Sponsor Legal Registered Address:

ViiV Healthcare UK Limited
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

SPONSOR SIGNATORY:

[redacted]

14 June 2016

[Vani Vannappagari]
Primary Author/ Project officer

Date

[redacted]

16/June/2016

[Kimberly Smith]
VP, Global Medical Sciences

Date

[Nassrin Payvandi]
VP, Safety & Pharmacovigilance

Date

SPONSOR SIGNATORY:

[redacted]

14 June 2016

[Vani Vannappagari]
Primary Author/ Project officer

Date

[Kimberly Smith]
VP, Global Medical Sciences

Date

[redacted]

21 June 2016

[Nassrin Payvandi]
VP, Safety & Pharmacovigilance

Date

3. ABSTRACT

The Antiretroviral Pregnancy Registry (APR) is a voluntary, international, prospective exposure registration cohort that was established in 1989 to monitor and detect any teratogenic effects of antiretroviral (ARV) drugs used in pregnancy. Each year the registry enrols approximately 1300 pregnant women in the United States (US), which represents approximately 15% of the 8700 Human Immunodeficiency Virus (HIV) positive women who give birth to live infants annually in the US. There are no adequate and well-controlled studies evaluating the use of DTG in pregnant women. So, this analysis aims to assess the frequency of birth defects and non-defect pregnancy outcomes of the prospectively reported pregnancies exposed to DTG prenatally and reported to APR

Objectives:

1. To describe the demographic and clinical characteristics of pregnant women exposed to dolutegravir (DTG) (Tivicay & Triumeq)
2. To assess the frequency of birth defects among neonates, with prenatal exposure to DTG (Tivicay & Triumeq)
3. To describe non-defect pregnancy outcomes among live births for pregnant women exposed to DTG (Tivicay & Triumeq)

Study design: Descriptive analysis of prospectively collected data from the APR on prenatal exposure to DTG.

Outcomes of Interest: Outcomes of interest are live births, still births, induced abortion, spontaneous abortion, birth defects, low birth weight (LBW), very low birth weight (VLBW) and preterm births.

4. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
<1>	<Date>	<Text>	<Text>	<Text>
<2>	<Date>	<Text>	<Text>	<Text>
<n>	<Date>	<Text>	<Text>	<Text>

5. MILESTONES

Milestone	**Planned date**
Start of data Analysis	01 July 2016
Registration in the EU PAS register	30 Jun 2016
Final report of study results	15 December 2016

6. BACKGROUND AND RATIONALE

6.1. Background

DTG is a HIV-1 integrase strand transfer inhibitor (INSTI) indicated in combination with other ARV agents for the treatment of HIV-1 infection in adults and children aged 12 years and older and weighing at least 40 kg.

There are no adequate and well-controlled studies evaluating the use of DTG in pregnant women. Pregnancy was an exclusion criterion in all phase 3 trials evaluating the efficacy and safety of DTG.[1-6] Because animal reproduction studies are not always predictive of human response, and DTG was shown to cross the placenta in animal studies, this drug should be used during pregnancy only if clearly needed. Global Data Sheet (GDS) states that DTG should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

6.2. Rationale

There are no adequate and well-controlled studies evaluating the use of DTG in pregnant women. So, this analysis aims to assess the frequency of birth defects and non-defect pregnancy outcomes of the prospectively reported pregnancies exposed to DTG prenatally and reported to APR.

7. RESEARCH QUESTION AND OBJECTIVE(S)

1. To describe the demographic and clinical characteristics of pregnant women exposed to DTG (Tivicay & Triumeq) and reported to APR

2. To assess the frequency of birth defects among neonates, with prenatal exposure to DTG (Tivicay & Triumeq) and reported to APR

3. To describe non-defect pregnancy outcomes among live births for pregnant women exposed to DTG (Tivicay & Triumeq) and reported to APR

8. RESEARCH METHODS

8.1. Study Design

A descriptive analysis of prospectively collected data from the APR on prenatal exposure to DTG.

8.2. Study Population and Setting

All pregnant women exposed to DTG (Tivicay & Triumeq) and prospectively reported to the APR, from the cumulative APR data through January 2016.

8.3. Variables

8.3.1. Outcome definitions

Demographic and clinical characteristics include maternal age, HIV status, CD4 count, race/ethnicity, and trimester of exposure to DTG. Outcomes of interest are live births, still births, induced abortion, spontaneous abortion, low birth weight (LBW), very low birth weight (VLBW) and preterm births as defined in Table 1.

Table 1. Definitions of pregnancy outcomes

Pregnancy Outcome	Definition
Induced abortion	Voluntary termination of pregnancy before 20 weeks gestation
Spontaneous abortion	Death of a fetus or expulsion of the products of conception before 20 weeks gestation
Low birth weight	Birth weight of <2500 grams
Very low birth weight	Birth weight of <1500 grams
Preterm birth	Birth of live infant at <37 weeks gestation
Stillbirth	Death of a fetus occurring at 20 weeks of gestation or more, or for situations in which the gestational age is unavailable, a fetus weighing at least 500 g

8.4. Data sources

The APR is a voluntary, international, perspective exposure registration cohort that was established in 1989 to monitor and detect any teratogenic effects of ARV drugs used in pregnancy. Although the APR is an international registry with case reports from 70 countries, the majority (77.3%) of the case reports are from the US and its territories. Each year the Registry enrolls approximately 1300 pregnant women in the US exposed to antiretroviral drugs. This number represents approximately 15% of the 8,700 HIV positive women who give birth to live infants annually in the United States [**Error! Reference source not found.**, 2011]. An additional 200 case reports for pregnant women come from other countries.

Clinicians register pregnant women with prenatal exposures to any ARV before the outcome of pregnancy is known, report data on demographic and clinical characteristics, ARV exposure throughout pregnancy, and provide birth outcome data. Registration is voluntary and confidential and all data are reviewed semi-annually by an independent Advisory Committee. Exposure is classified and analyzed by the earliest trimester of exposure to each individual ARV medication. Birth defect prevalence (any pregnancy outcome > 20 weeks of gestation with a defect/live births) is compared to both internal and external comparator groups. The external comparators used are two population-based surveillance systems – Metropolitan Atlanta Congenital Defects Program (MACDP) by Centers for Disease Control and Prevention (CDC) and the Texas Birth Defects Registry (TBDR); and internal comparators include exposures to other drugs and exposures in the 2nd or 3rd trimester of pregnancy relative to 1st trimester exposures when organogenesis occurs.

8.5. Data analysis

Since there are only 51 prospectively reported pregnancies exposed to DTG, this analysis will be descriptive in nature. Demographic and clinical characteristics of the pregnant women will be tabulated. (Table 2)

Frequency assessment of birth defects will be done among all live births. Only singleton births will be included in the analysis of non-defect outcomes; multiple births such as twin and triplet births will be excluded due to the increased risk of adverse outcomes associated with such pregnancies. These outcomes are: spontaneous and induced abortions, stillbirths, premature births (<37 weeks gestation), very premature births (<32 weeks gestation), low birth weight (LBW; <2500g) and very low birth weight (VLBW; <1500g). The APR defines spontaneous abortion as death of a fetus or expulsion of the products of conception prior to 20 weeks gestation. A stillbirth is defined as the death of a fetus occurring at 20 weeks gestation or more, or for situations in which the gestational age is unavailable, a fetus weighing at least 500 grams.

Table 2 in Appendix outline the demographic and clinical characteristics that will be described for the pregnant women exposed to DTG. Table 3 will tabulate the pregnancy outcomes for the pregnancies.

Listing 1 will outline the individual pregnancies and outcomes reported to the APR.

For pregnancy outcomes with birth defects, all concurrent medications reported will be listed. Retrospectively reported cases and cases from clinical studies will also be listed separately.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical approval and subject consent

The APR sought and obtained Institutional Review Board (IRB) approval from Western Institutional Review Board (WIRB) in March 2000. With the IRB approval of the protocol, the APR was granted a waiver from having to obtain patient informed consent. The IRB reviews the APR protocol annually with annual status reports required. No additional IRB approval is required when de anonymised data analysis such as this one is conducted. Additionally, the IRB reviews data privacy issues on a regular basis.

9.2. Subject confidentiality

The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule allows covered entities (e.g., health care providers) to disclose protected health information (PHI) without subject authorization if the covered entity obtains documentation that an IRB has waived the requirement for authorization. On April 29, 2003, WIRB approved a request for a waiver of authorization for use and disclosure of PHI below for the APR: Information about subjects on antiretroviral drugs during pregnancy, including dates of services, estimated date of delivery, date of last menstrual period, dates of exposure to antiretroviral drugs and date of pregnancy outcome.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

APR reports all cases of pregnancies to the MAH (case management) as soon as the pregnancies are reported. All AEs and SAEs including birth defects are reported within 24 hours of receiving the notification. Therefore no AEs or SAEs will be reported under this protocol.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Study results will be presented at a conference such as Conference on Retroviruses and Opportunistic Infections (CROI) or International AIDS Society Conference and published in a peer reviewed journal. Additionally, the study results will be included in the regulatory and safety reports as appropriate.

12. REFERENCES

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5. Cahn P, Pozniak A, Mingrone H, et al. Dolutegravir versus raltegravir in antiretroviral-experience, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. Lancet 2013: 382:700–08.

6. Mulligan N, Best BM, Capparelli EV, et al. Dolutegravir pharmacokinetics in HIV-infected pregnant and postpartum women. Presented at the 23rd Conference on Retroviruses and Opportunistic Infections, February 22-25, 2016, Boston, MA. Presentation 438

Appendix

Table 2. Demographic and Clinical Characteristics of Pregnant Women Exposed to Dolutegravir

Characteristic	
Total Pregnancies, N	
Maternal Age at conception (years)	
N	
Mean	
Median	
Range (min-max)	
Missing	
CD4+ T-cell Categories at Start of Pregnancy	
≥ 500 cells/μL	
200-499 cells/μL	
<200 cells/μL	
Unknown	
N/A	
Missing	
Race/Ethnicity	
Black	
White	
Asian	
Hispanic	
Other	
Missing	

HIV status	
Positive	
Negative	
Missing	
Trimester of First Exposure to DTG	
1st	
2nd/3rd	
Missing	

Table 3. Birth Outcomes of Pregnant Women Exposed to Dolutegravir

Birth Outcomes	Overall	Earliest exposure to DTG -1st Trimester	Earliest exposure to DTG -2nd /3rd Trimester
Total Outcomes, N			
Pregnancy Outcomes			
Live Birth			
Stillbirths			
Spontaneous Abortions			
Induced Abortions			
Missing			
Gestational Age*			
≥ 37 weeks			
< 37 weeks (Preterm)			
Missing			

Birth Weight*			
≥ 2500 grams			
< 2500 grams (LBW)			
< 1500 grams (very LBW)			
Missing			

* Among singleton, live births without defect

Listing 1. Maternal characteristics and birth outcomes among infants born to mothers receiving treatment with Dolutegravir based regimen

	Maternal age at conception	CD4 at the start of pregnancy	Country of report	Race/ Ethnicity	Trimester of earliest DTG exposure	other ARV drug exposures and trimesters of exposure	Pregnancy outcome(s)	Birth Defect	Non-defect outcomes*
Pregnancy 1									GA = BW =
Pregnancy 2									GA = BW =
: :									
: :									

*Gestational Age (GA) in weeks; Birth Weight (BW) in grams