# TITLE PAGE

**Information Type:** ViiV Healthcare Non-Interventional Study Protocol

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|---|---|
| **Title:** | Pregnancy and Neonatal Outcomes following Prenatal Exposure to Cabotegravir: Data from The Antiretroviral Pregnancy Registry (APR) |

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**Development Phase** IV

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**Author(s):**
PPD : ViiV Healthcare
PPD : Syneos Health
PPD : ViiV Healthcare
PPD : Syneos Health
PPD : Syneos Health

# TABLE OF CONTENTS

**PAGE**

1. LIST OF ABBREVIATIONS ..... 3

2. RESPONSIBLE PARTIES: SPONSOR INFORMATION PAGE ..... 4

3. ABSTRACT ..... 7

4. AMENDMENTS AND UPDATES ..... 8

5. MILESTONES ..... 8

6. BACKGROUND AND RATIONALE ..... 9
   6.1. Background ..... 9
   6.2. Rationale ..... 9

7. RESEARCH QUESTION AND OBJECTIVE(S) ..... 10

8. RESEARCH METHODS ..... 10
   8.1. Study Design ..... 10
   8.2. Study Population and Setting ..... 10
   8.3. Variables ..... 11
      8.3.1. Outcome definitions ..... 11
   8.4. Data sources ..... 12
   8.5. Study size ..... 13
   8.6. Data analysis ..... 14
   8.7. Limitations ..... 15

9. PROTECTION OF HUMAN SUBJECTS ..... 15
   9.1. Ethical approval and subject consent ..... 15
   9.2. Subject confidentiality ..... 15

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS ..... 16

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS ..... 16

12. REFERENCES ..... 16

# 1. LIST OF ABBREVIATIONS

| | |
|---|---|
| AEs | Adverse Events |
| APR | Antiretroviral Pregnancy Registry |
| ARV | Antiretroviral |
| CAB | Cabotegravir |
| CD4 | Cluster of Differentiation 4 |
| CDC | Centers for Disease Control and Prevention |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human Immunodeficiency Virus |
| INSTI | Integrase Strand Transfer Inhibitor |
| IRB | Institutional Review Board |
| LBW | Low Birth Weight |
| MACDP | Metropolitan Atlanta Congenital Defects Program |
| NNRTI | Non-Nucleoside Reverse Transcriptase Inhibitor |
| PHI | Protected Health Information |
| SmPC | Summary of Product Characteristics |
| TBDR | Texas Birth Defects Registry |
| US | United States |
| VLBW | Very Low Birth Weight |
| WIRB | Western Institutional Review Board |

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## 2. **RESPONSIBLE PARTIES:** SPONSOR INFORMATION PAGE

ViiV Healthcare UK Limited

**Sponsor Legal Registered Address:**

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

**SPONSOR SIGNATORY:**

| | |
|---|---|
| Vani Vannappagari<br>Global Head, Epidemiology and Real World Evidence | **Date** |
| Nassrin Payvandi<br>VP & Head, Safety and Pharmacovigilance | **Date** |
| Jens-Ulrich Stegmann<br>ViiV QPPV | **Date** |

# INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: PPD

Investigator Signature

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. There are no adequate and well-controlled studies evaluating the use of cabotegravir Long Acting (CAB LA) in pregnant women. Therefore, this analysis aims to assess the frequency of birth defects and non-defect pregnancy outcomes of the prospectively reported pregnancies exposed to CAB prenatally and reported to the APR.

Study Objectives: Among women becoming pregnant while receiving CAB containing ARV regimen, initiating CAB containing regimen during pregnancy, or have received one or more CAB LA injection(s) in the 12 months prior to estimated date of conception:

1. To describe maternal characteristics by timing of first exposure to CAB in relation to estimated date of conception (e.g. 0-6 months prior to conception, 6-12 months prior to conception and by each trimester)
    i. demographic, clinical and immunological characteristics, co-infections, timing of CAB LA initiation, other ARVs used in the regimen

2. To estimate the frequency of birth defects among neonates, with prenatal exposure to CAB, by timing of first exposure

3. To estimate frequency of non-defect adverse pregnancy and neonatal outcomes, by timing of first exposure
    i. stillbirth, spontaneous abortion, induced abortion
    ii. preterm delivery, low birth weight

**Study design:** This is a non-interventional study involving analysis of prospectively (exposure to CAB reported to the registry before pregnancy outcome is known) collected data in pregnant women living with HIV (Human Immunodeficiency Virus), reported to the APR.

**Outcomes of Interest**: Outcomes of interest are birth defects, live births, still births, induced abortion, spontaneous abortion, 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 |
|---|---|---|---|---|
| v1.0 | June 2021 | 5,7, 8 and 11 | Milestones, Objectives, variable definitions, analysis and communication | Address EMA comments |
| v2.0 | October, 2021 | 8.7 | Data Analysis | Address EMA comments |

# 5. MILESTONES

| **Milestone** | **Planned date** |
|---|---|
| Draft Protocol Submission | Dec 31, 2020 |
| Register with EU PAS Register | Estimated -November, 2021 |
| Study Start (Protocol Approval) | Estimated - November, 2021 |
| End of Data Reporting Period | Estimated - July, 2022 |
| 1st Interim Report (N=25) | Estimated - Dec, 2022 |
| End of Data Reporting Period | Estimated - January, 2024 |
| 2nd Interim Report (N=100) | Estimated - June, 2024 |
| End of Data Reporting Period | Estimated - July, 2025 |
| 3rd Interim Report (N=200) | Estimated - Dec, 2025 |
| End of Data Reporting Period | Estimated - January, 2027 |
| Final Study Report | Estimated - June, 2027 |

# 6. BACKGROUND AND RATIONALE

## 6.1. Background

Cabotegravir (CAB), a human immunodeficiency virus type-1 (HIV-1) integrase strand transfer inhibitor (INSTI), in combination with rilpivirine (RPV), an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI), is indicated as a complete regimen for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA <50 copies /mL) on a stable antiretroviral regimen with no prior treatment failure with agents of the NNRTI and INI class, and have no known or suspected resistance to either cabotegravir or rilpivirine. Prior to the initiation of cabotegravir long acting (LA) injection, oral cabotegravir together with oral rilpivirine should be taken for approximately one month (at least 28 days) to assess tolerability to cabotegravir and rilpivirine. CAB tablets and injection are not recommended during pregnancy unless the expected benefit justifies the potential risk to the fetus. It is approved in Canada and currently under review by other global regulatory authorities.

There are limited amount of data from the use of cabotegravir in pregnant women. The effect of CAB on human pregnancy is unknown. CAB reproductive and developmental toxicity studies did not demonstrate any effects on fertility or fecundity. CAB was not teratogenic when studied in pregnant rats and rabbits but, exposures higher than the therapeutic dose showed reproductive toxicity in animals. The relevance to human pregnancy is unknown. There is no anticipated risk in humans based on the non-clinical study findings.

No studies have been conducted with CAB in pregnant women. Pregnant and breastfeeding women were excluded from the CAB clinical studies. Women of childbearing potential were required to use highly effective measures to avoid pregnancy. Subjects that became pregnant were required to discontinue the study medication and discontinue the study, regardless of termination status of pregnancy. Clinical experience of CAB use during pregnancy is therefore limited. Thus, the safety of CAB during human pregnancy has not been established. The proposed SmPC states that CAB should be used during pregnancy and by women planning pregnancy only if the expected benefit justifies the potential risk to the fetus and additionally prescribers are reminded of long acting exposure following injection. Most women on ART are of reproductive age and over half of pregnancies in women living with HIV are unplanned[6,7] underlying the importance of carefully considering the exposure period relevant to conception with a long acting injectable ARV, such as CAB LA.

## 6.2. Rationale

There are no adequate and well-controlled studies evaluating the use of CAB in pregnant women. Cabotegravir has been detected in systemic circulation for up to 12 months or longer after an injection. Due to the long acting nature of the CAB injection, exposure

could occur at the time of conception and throughout the duration of the pregnancy even if injections were stopped as soon as pregnancy was identified. So, assessing maternal and fetal outcomes following CAB use during pregnancy is critical for informed ARV prescribing decisions during pregnancy & maternal/fetal health.

# 7. RESEARCH QUESTION AND OBJECTIVE(S)

Study Objectives: Among women becoming pregnant while receiving CAB containing ARV regimen, initiating CAB containing regimen during pregnancy, or have received one or more CAB LA injection(s) in the 12 months prior to estimated date of conception:

1. To describe maternal characteristics by timing of first exposure to CAB in relation to estimated date of conception (e.g. 0-6 months prior to conception, 6-12 months prior to conception and by each trimester)
    ii. demographic, clinical and immunological characteristics, co-infections, timing of CAB LA initiation, other ARVs used in the regimen

2. To estimate the frequency of birth defects among neonates, with prenatal exposure to CAB, by timing of first exposure to CAB

3. To estimate frequency of non-defect adverse pregnancy and neonatal outcomes, by timing of first exposure to CAB
    iii. stillbirth, spontaneous abortion, induced abortion
    iv. preterm delivery, low birth weight

# 8. RESEARCH METHODS

## 8.1. Study Design

This is a non-interventional study involving analysis of prospectively (exposure to CAB reported to the registry before pregnancy outcome is known) collected data in pregnant women living with HIV, reported to the APR.

## 8.2. Study Population and Setting

All pregnant women with any exposure to CAB at any time during the pregnancy or 12 months prior to the estimated conception period to account for long acting nature of CAB injectable, reported to the APR will be included in the analysis.

## 8.3. Variables

### 8.3.1. Exposure definitions

Timing of first exposure to CAB LA injections will be categorized as follows based on the reported timing of the injections and estimated date of conception.

**Table 1. Exposure Categories**

| | Exposure period |
|---|---|
| 6-12 months prior to conception | 6-12 months prior to estimated date of conception |
| 0-6 months Prior to conception | 0-6 months prior to estimated date of conception |
| 1st trimester | 1 day of last menstrual period to <14 weeks |
| 2nd trimester | ≥14 weeks to <28 |
| 3rd trimester | ≥28 weeks to 40 weeks (or delivery) |

### 8.3.2. Outcome definitions

Demographic and clinical characteristics include maternal age, HIV status, CD4 count, race/ethnicity, and exposure to CAB relative to conception (first trimester, second trimester, third trimester or during the 12 months prior to estimated conception). Outcomes of interest are birth defects, live births, stillbirths, induced abortions, spontaneous abortions, LBWs, very LBWs, extremely LBWs, preterm births and severe preterm births as defined in Table 1.

**Table 2. Definitions of pregnancy outcomes**

| **Pregnancy and neonatal Outcome** | **Definition** |
|---|---|
| Birth Defect | Any major structural or chromosomal defect diagnosed with signs/symptoms, using the CDC MACDP classification (2014) of birth defects |
| Induced abortion | Voluntary termination of pregnancy |
| 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 |
| Extremely low birth weight | Birth weight of <1000 grams |
| Preterm birth | Birth of live infant at <37 weeks gestation |

| | |
|---|---|
| Severe Preterm birth | Birth of live infant at <32 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 |

Birth defects will be classified according to modified MACDP classification[1].

Maternal characteristics:
Age at conception of pregnancy, Indication for ARV use, HIV disease severity, Hepatitis coinfection and CD4 levels are the commonly reported variables. Data on exposure to known teratogenic substances, concurrent medications used and VL is inconsistently reported to the APR. Where data are available the effect of concurrent medications are taken into consideration by the geneticist in the assessment of birth defects.

## 8.4. Data sources

The APR ("Registry") is a voluntary, international, prospective 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 (73%) of the case reports are from the US and its territories. Each year the Registry enrolls approximately 1300-1700 pregnant women exposed to ARV drugs. This number represents approximately 25% of the 5,000 HIV positive women who give birth to live infants annually in the United States and approximately 350 pregnant women from other countries[5].

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. The registry case report form (CRF) will include a data field enquiring about CAB exposure up to 18 months prior to conception. 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 – the Metropolitan Atlanta Congenital Defects Program (MACDP) by Centers for Disease Control and Prevention (CDC) and 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 management

The APR Coordinating Center collects anonymized data on individual pregnancies with antenatal CAB use, using a detailed standard operating procedure (SOP) for the registry. The Registry management and data collected reside at the APR Coordinating Center.

The Registry Coordinating Center staff, project manager, systems staff, biostatisticians, data management staff and statistical programmers have access to the electronic data.

Following the ARV exposed pregnancy report to the registry, case report is reviewed for completeness and any data queries are resolved with further communications with the reporting HCP. All evaluable reports meeting the minimum criteria for evaluation, received by the Registry are reviewed for possible duplicate reporting. Systematic evaluation of duplicates takes into consideration geographic region, maternal characteristics, exposures and timing of exposures, outcomes and gestational age and other supporting available information.

The data merger and statistical analyses will be conducted at the APR Coordinating Center.

## 8.6. Study size

At least 200 pregnancies with first trimester exposure to CAB are aimed to be included in this study.

There is no direct comparator arm used in this study and hence no formal sample size estimations are performed. Data from external sources like MACDP, TBDR, the prevalence rates from the APR and EUROCAT (European network of population-based registries for the epidemiological surveillance of congenital anomalies) will be used as reference values for background birth defect rates to put the findings from this study in context.

The APR[1] has estimated that, based on the prevalence of birth defects in the general population of 2.72-4.17 per 100 live births (MACDP[3] and TBDR[8] respectively), 200 first trimester exposures are needed to detect a two-fold increase in overall birth defect rate[2]. While this is specific to the APR, EUROCAT[4] has reported similar birth defect rate (2.59 per 100 live births). APR has reported an overall birth defect rate of 2.83 per 100 live births. Table 3 presents precision estimates for 200 pregnancies and birth defect prevalence rate of 1- 5%

**Table 3. Precision Estimates**

| Confidence Level | Sample Size (N) | CI Width | Prevalence rate (P) | Lower Limit | Upper Limit |
|---|---|---|---|---|---|
| 0.95 | 200 | 0.03 | 1% | 0.0012 | 0.0357 |
| 0.95 | 200 | 0.04 | 2% | 0.0055 | 0.0504 |
| 0.95 | 200 | 0.05 | 3% | 0.0111 | 0.0642 |
| 0.95 | 200 | 0.06 | 4% | 0.0174 | 0.0773 |
| 0.95 | 200 | 0.07 | 5% | 0.0242 | 0.0900 |

## 8.7. Data analysis

We propose to conduct four analyses: the first analyses when the number of pregnant women exposed to CAB containing regimen during first trimester in the cohorts reaches 25, followed by two more analyses when the study population reaches 100 and 200 pregnancies with first trimester exposures to Cab. A final analysis will be done 12 months after the 3rd analysis.

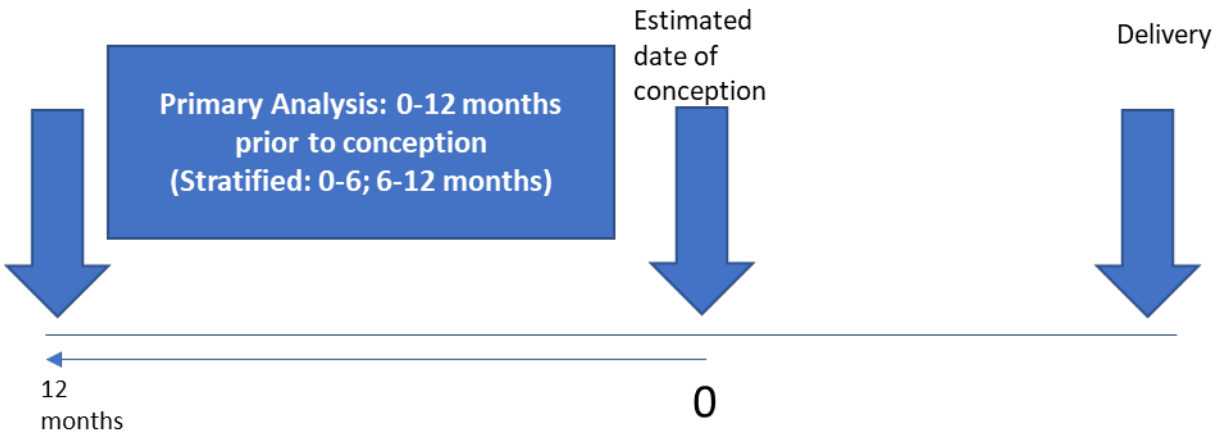
This analysis will be descriptive in nature. Demographic and clinical characteristics of the pregnant women will be tabulated.

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), 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.

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 but will not be included in the primary analysis.

For pregnancies reporting exposure to CAB regimen at conception, exposure is well defined. For pregnancies not on CAB at the time of diagnosis of pregnancy or reporting to APR, history of CAB injection during the past 12 months will be collected and used in the analysis. Analysis for this previous history of exposure to CAB LA will stratify the exposure period by 0-6 months and 6-12 months prior to estimated conception.

**Fig 1**: Relevant Exposure Period, if not on Cabotegravir at the time of reporting to APR:



All birth defects will be tabulated and reported by organ class affected. At the end of the study period, an evaluation of the birth defects according to the MACDP and EUROCAT classification will be made and a listing of cases appearing in MACDP but not in the EUROCAT categories will be provided in the final study report.

## 8.8. Limitations

The APR is designed to detect teratogenic effects of antiretroviral medications used in pregnancy. The occurrence of other developmental or functional defects is not systematically collected. This study is limited by its observational nature, and thus potential for bias cannot be ruled out. The limitations include, but are not limited to, underreporting (i.e., not every report of an exposure is obtained), differential reporting (i.e., there may be reasons why one report would be provided to the Registry and another would not), under ascertainment of birth defects (i.e., not every birth defect is identified, e.g., reporter may not see the defect at birth), differential ascertainment of birth defects (e.g., variable use of diagnostic tests), and loss to follow-up (e.g., reports where no outcome information is obtained). Despite these limitations, such reports have been useful to supplement animal toxicology studies and clinical trial data, and to assist clinicians in weighing the risks and benefits of antiretroviral treatment during pregnancy and in counseling women with exposure during the first trimester. Moreover, accrual of additional patient experience over time will provide more definitive information regarding risks, if any, of exposure during pregnancy to the antiretroviral therapies followed in the Registry.

# 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 is structured to report all pregnancies and outcomes exposed to any of the ViiV products to GSK case management to facilitate reporting to regulatory agencies. The registry's adverse event management plan provides detailed guidance on the AE reporting requirements for all products monitored by the APR. The APR coordinating center's study team is responsible for reviewing information provided to the Registry to determine if an AE has been indicated, initiating the AE process, and ensuring that all AEs have been reported to the sponsor. For this study, pregnancy will not be defined as an AE. Reports of any AE, including defects identified at pregnancy outcome or during prenatal period, spontaneous or induced abortion, and stillbirth are reported to the appropriate Sponsor(s), regardless of reporter attribution or temporal association with the antiretroviral exposure. all AEs and SAEs are reported to the sponsor within 1 working day of the receiving the information, via fax, mail or electronic data collection system. Since this is a well-established process for all of ViiV healthcare's products, a study specific pharmacovigilance plan for this analysis is not needed.

## 11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The MAH will include summary of data from this study in the CAB Periodic Benefit Risk Evaluation Report (PBRER). Final study results will be included in safety and regulatory reports as appropriate. Results will also be submitted as abstracts to congresses and for publication in a peer reviewed journal.

## 12. REFERENCES

1. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry Interim Report for 1 January 1989 through 31 January 2020. Wilmington, NC: Registry Coordinating Center; 2020. Available from URL: www.APRegistry.com.

2. Covington DL, Tilson H, Elder J, Doi PA, APR Steering Committee. Assessing teratogenicity of antiretroviral drugs: Monitoring and analysis plan of the

Antiretroviral Pregnancy Registry. Pharmacoepidemiology and Drug Safety. 2004;13:537-545

3. Correa A, Cragan J, Kucik J, et al. Metropolitan Atlanta Congenital Defects Program 40th Anniversary Edition Surveillance Report: Reporting Birth Defects Surveillance Data 1968-2003. Birth Defects Research (Part A). 2007;79:65-93. Erratum: 2008;82:41-62.

4. EUROCAT Website Available at:<http://www.eurocat-network.eu/

5. Nesheim SR, FitzHarris LF, Lampe MA, Gray KM. Reconsidering the number of women with HIV infection who give birth annually in the United States. Public Health Reports 2018. DOI: 10.1177/0033354918800466. Available from URL: http://journals.sagepub.com/doi/10.1177/0033354918800466.

6. Salters K, Loutfy M, de Pokomandy A, Money D, Pick N, Wang L, et al. (2017) Pregnancy incidence and intention after HIV diagnosis among women living with HIV in Canada. PLoS ONE 12(7): e0180524. https://doi.org/10.1371/journal.pone.0180524

7. Sutton MY, Patel R, Frazier EL. Unplanned Pregnancies Among HIV-Infected Women in Care-United States. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2014;65(3):350-358

8. Texas Birth Defect Surveillance System. Report of Birth Defects Among 2000 - 2009 Deliveries. Birth Defects Epidemiology & Surveillance, Texas Department of State Health Services. Published February 2012.