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- *Aggregate data will be included; with any direct reference to individual patients excluded*

**Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered*

TITLE PAGE

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Author(s): PPD
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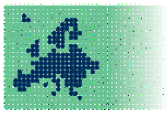

neatid

Pregnancy and Neonatal Outcomes following Antenatal Exposure to Dolutegravir

Final Report, August 2017

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Introduction

Dolutegravir (DTG), marketed as a single agent as Tivicay©, and also Triumeq©, a fixed dose combination (FDC) tablet containing DTG/abacavir (ABC)/lamivudine (3TC), received market authorization for use in the European Union for the treatment of HIV in adults and adolescents aged 12 years and older in combination with other antiretroviral drugs in 2014 (January 2014 for Tivicay© and September 2014 for Triumeq©). DTG belongs to the class of integrase strand transfer inhibitors. Tivicay© and Triumeq© are indicated for use in HIV-infected patients who are treatment naïve or previously treated. In adults, the use of DTG includes those with suspected or documented resistance to integrase inhibitors.

There has been a lack of studies evaluating the use and safety of DTG in pregnant women. In animal studies, DTG was shown to cross the placenta and the current summary of product characteristics (SmPC) states that DTG-containing regimens should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. Preliminary results on DTG pharmacokinetics in pregnancy from the IMPAACT P1026s study suggested that DTG exposure may be lower in the third trimester than 6-12 weeks post-partum, but was based on small numbers; the authors noted that the area under the curve (AUC) and trough values in pregnancy were similar to those seen in non-pregnant adults (Mulligan et al 2016).

Owing to its effectiveness, high barrier to resistance, tolerability and once-daily dosing, DTG-based regimens are now recommended as first-line adult regimens in some countries, including Botswana. Recently, data were presented from the Tsepamo Study in Botswana that compared birth outcomes in 4593 pregnant women starting efavirenz+tenofovir+emtricitabine (EFV+TDF+FTC) between August 2014 and August 2016

and 845 women starting DTG+TDF+FTC between November 2016 and April 2017. The authors found similar risk of adverse birth outcomes in women initiating these two regimens in pregnancy in adjusted analyses, but underscored the need for more data, including first trimester exposure (Zash et al 2017). The Antiretroviral Pregnancy Registry (APR) has also recently presented data on risk of adverse pregnancy outcomes in 142 pregnant women receiving DTG-based regimens, with 90% having live births, 2.1% induced abortions and 7.7% spontaneous abortions; of 133 live births, there were 4 congenital abnormalities (Vannappagari et al 2017).

The current study involved an individual patient data meta-analysis using prospective data collected in clinical sites participating in cohort and other observational studies in order to assess maternal, fetal and neonatal outcomes following DTG use during pregnancy in real-world European settings.

Methods

We conducted a pooled analysis of prospectively followed HIV-positive pregnant women and their newborns from cohorts and studies participating in the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) (http://penta-id.org/hiv/eppicc/), the Pharmacokinetics of newly developed ANtiretroviral agents in HIV-infected pregNAnt women (PANNA) study (www.pannastudy.com) and NEAT-ID (a European treatment network for HIV, hepatitis and global infectious diseases)(www.neat-id.org).

All pregnancies with any exposure to DTG (Tivicay© or Triumeq©) at any time reported to participating studies by December 2016 were eligible for inclusion in this study, regardless of pregnancy outcome; pregnancies that had been reported and were still continuing were included. Exposure data were collected prospectively (i.e. before pregnancy outcome was known). Participating EPPICC cohorts were: the Italian Group on Surveillance of Antiretroviral Treatment in Pregnancy; NENEXP Study PPD European Collaborative Study on HIV-infected pregnant women & their children; Swiss Mother and Child HIV Cohort Study (MoCHiV); UK / Ireland National Study of HIV in Pregnancy and Childhood (NSHPC).

Anonymous individual-level patient data were pooled using a standard operating procedure based on HIV Cohorts Data Exchange Protocol (hicdep.org) data specification. Variables included sociodemographic, clinical and treatment factors, and pregnancy and neonatal outcomes.

Definitions

Maternal age was the age at conception. Undetectable viral load (viral suppression) was defined as HIV RNA <50 copies/mL. Trimesters were defined as follows: first, <13 completed gestational weeks; second, between 13 and 24 completed gestational weeks; and third, ≥25 completed gestational weeks. An elective caesarean section (CS) delivery was defined as taking place prior to labour onset or rupture of membranes, and an emergency CS as any CS taking place with ruptured membranes or during labour. Preterm delivery was defined as that occurring before 37 completed gestational weeks. Low birth weight in term infants was defined as <2500g birth weight and very low birth weight as <1500g. Small for gestational age (SGA) was defined according to sex-specific US standards (ref). An induced abortion was defined as voluntary termination of pregnancy before 22 weeks gestation and a spontaneous abortion as the death of a fetus or expulsion of the products of conception before 22 weeks gestation. The death of a fetus occurring at 22 weeks of gestation or more was considered a stillbirth.

Infant HIV infection status was classified as uninfected or infected on the basis of reported polymerase chain reaction test results or indeterminate for infants whose infection status had not yet been reported. Birth defects were classified according to the World Health Organization's International Classification of Diseases, Tenth Revision and EUROCAT classification.

Statistical analysis

Standard descriptive statistics were used to summarize the data. For continuous variables, the sample size, median and interquartile range (IQR) were provided, with frequency distributions

for categorical variables. For rates, 95% confidence intervals (CI) were calculated. Statistical analyses were carried out using STATA® v12.0 software (StataCorp, College Station, Texas).

Results

A total of 101 pregnancies to 100 women were included in the pooled analysis (Figure 1). The woman lost to follow-up (LTFU) was reported to the NSHPC in the UK and moved abroad whilst her pregnancy was continuing. There were 61 pregnancies reported from the UK and Ireland, 19 from Germany, 9 from Spain, 5 from Italy, 3 from Switzerland and 2 each from Belgium and the Netherlands. Of the 84 pregnancies with outcomes, 81 pregnancies ended in live births, of which two were twin pregnancies, giving a total of 83 newborns.

Maternal characteristics

Maternal socio-demographic and clinical characteristics for the 101 pregnancies are provided in Table 1. The majority of women were of Black African ethnicity, had acquired HIV infection heterosexually, were aware of their HIV status prior to conception and had conceived whilst receiving ART. Among the 101 pregnancies, date of initiation of DTG was missing for one pregnancy ending in a live birth. Nearly 60% of pregnancies had the earliest exposure to DTG in the first trimester, although this proportion was somewhat lower when restricting to pregnancies ending in livebirths (Table 2). The majority (72) of the pregnancies were conceived in 2015, reflecting the date of marketing authorization for TIVICAY© and TRIUMEQ© and the timing of study data collection.

Birth outcomes

Of the 84 pregnancies with outcomes there was one spontaneous abortion, one induced abortion, one stillbirth, with the remaining 81 pregnancies ending in livebirths (Figure 1). The spontaneous abortion occurred at 10 weeks gestation to a woman who conceived on a DTG-containing regimen. The induced abortion was a personal decision, with no fetal abnormality present; the woman conceived whilst receiving a regimen including DTG. The stillbirth was an intrauterine death to a vertically-infected woman, not on ART at conception, who started a DTG-based regimen in the second trimester.

Data was available on mode of delivery for 79 of the 82 pregnancies ending in a live birth or a stillbirth, with 45 (57.0%) delivered vaginally, 21 (26.6%) by elective CS, 9 (11.4%) by emergency CS and four with CS unspecified (5.1%). The two twin pregnancies were delivered at 33 weeks (both infants with birthweight 1.9-2.0kg) and at 38 weeks gestation (both infants with birthweight 2.8kg).

Birth outcomes (gestational age at delivery, birthweight and SGA) were assessed for the 79 singleton live-born infants and the one stillborn infant. Overall, 11 of these 80 infants (13.8%) were delivered preterm, nine of whom were born at 34-36 weeks gestation and two before 34 weeks gestation (one at 31 weeks and the other at 23 weeks (23+6)). The very preterm infant born at 23 weeks gestation died after withdrawal of care on the second day of life; earliest exposure to DTG was in the second trimester, no congenital abnormalities were reported and birthweight was missing.

With respect to birthweight, 16.7% (13/78; two infants missing birthweight) of newborns had LBW and 18.7% (24/75) were SGA. Distribution of gestational age at delivery, birthweight and SGA classification by earliest DTG exposure is presented in Table 3 for the 79 infants with DTG start dates available; the one infant with missing DTG start date was born at term and had a birthweight >2500g. The proportion of infants born preterm was 7.6% (3/40), 27.3% (6/22) and 11.8% (2/17) for those with earliest DTG exposure in the first, second and third trimesters respectively. The median birthweight was 3120g (IQR 2750-3470).

The presence of congenital abnormalities was assessed in 81 of the 84 live-born and stillborn infants (twins and singletons) with available data. Abnormalities were reported in four infants overall (4.9%, 95% CI 1.4, 12.2%); one infant had two abnormalities reported and the remaining three had one abnormality. The proportion of infants with abnormalities reported by timing of DTG exposure was 7.1% (3/42) for those with earliest exposure in the first trimester, 4.2% (1/24) for the second trimester and none of the 14 infants with earliest exposure in the third trimester. Detailed information on the congenital abnormalities is presented in Table 4. According to the EUROCAT classification, isolated tongue-tie and hyperpigmentation on back are not considered birth defects; excluding these defects, the proportion of infants with abnormalities would decrease to 2.5%.

Maternal viral suppression and MTCT

Of the 40 pregnancies ending in live or stillbirths where the woman started a DTG-based regimen before conception or during the first trimester, 34 (85.0%) achieved an undetectable viral load during pregnancy. No infant was reported to have vertically acquired HIV

infection, but 42 of the 82 surviving infants had indeterminate status at the time of this analysis.

Discussion

This pooled analysis brings together data on the largest number of pregnancies with DTG use in Europe to date, although numbers remain quite small, reflecting the relatively recent licensing of DTG and the SmPC for Tivicay© and Triumeq©. Of note, nearly 60% of the included pregnancies had first trimester DTG exposure, which provides important information on the safety of DTG-based regimens used from conception to complement the data recently presented from Botswana, which included small numbers of women with first trimester exposure, and no data on pregnancies conceived on DTG-based regimens (Zash et al 2017).

The rates of preterm delivery (14%) and SGA (19%) in this small cohort of women exposed to DTG-containing regimens are similar to those reported in UK, which contributed about 60% of all the participants. To illustrate, in a recent analysis of around 1900 pregnant women on boosted protease inhibitor-based or non-nucleoside reverse transcriptase inhibitor-based regimens from the UK and Ireland NSHPC delivering 2007-2015, the preterm delivery rate was 14% among women on ART at conception with CD4 counts below 350 cells/mm^3 at the start of pregnancy and 11% among women starting ART during pregnancy, irrespective of CD4 count (Favarato et al 2017); in the same analysis, the SGA rate was 20%.

In this "first-wave" of DTG-exposed pregnancies in Europe, description of maternal characteristics has demonstrated that these women differ somewhat from the larger population of pregnant women living with HIV in Western Europe from which they are drawn. For example, 10% of the women included here were vertically infected themselves. Although the proportion of pregnant women living with HIV in Europe with vertical acquisition of infection is increasing, the percentage is <2% of all pregnancies in European cohorts (Calitri et al 2014, Sconza et al 2017). Similarly, 9% of the women were HIV/HCV co-infected, which is also higher than expected for a contemporary cohort of pregnant women, particularly given the low proportion with an injecting drug use history (Floridia et al 2010).

Around two-fifths of women had CD4 counts below 350 cells/mm^3 at the start of pregnancy. It is difficult to make comparisons between our study (with most conceptions in 2015 and 2016) with other published data because CD4 counts at conception have been increasing over time and few published studies provide maternal CD4 count data for the most recent time period. In an EPPICC analysis of women (Western and Eastern European) delivering in 2008-2014 (restricted to women on ART who did not switch regimens during pregnancy), the median CD4 count at the start of pregnancy was 395 cells/mm^3 (IQR 260, 559) in nearly 6500 women and 60% had a CD4 count >350 cells/mm^3 (Bailey et al 2016). However, in the NSHPC, the median CD4 count at pregnancy start among women delivering in 2013-2015 was 490 cells/mm^3 (IQR, 260, 559) (Sconza et al 2017), which suggests that our study population may be more immunosuppressed than the HIV-infected pregnant population as a whole.

We found that there were four infants with five congenital abnormalities, with an overall congenital abnormality rate of 4.9%. The 95% confidence intervals around this estimate were wide, reflecting the small sample size. Three of the four infants with abnormalities had earliest ART and DTG exposure in the first trimester. When applying the EUROCAT classification, the birth defect rate decreased to 2.5%, underscoring the need to consider the classification system in use when comparing data on birth defects. The findings from this study were consistent with those recently published by the APR (Vannappagari et al 2017).

Limitations of this study include some missing data, as can be the case for observational studies, as well as the small sample size. There were 16 pregnancies that were continuing to term at the time the analysis was conducted, and there will be ongoing work to collect the birth outcome data for these. Similarly, owing to the reporting lag that exists in many cohorts and the recent delivery date for many of the included women, HIV infection status was indeterminate at the time of analysis for the majority of the infants.

These findings contribute to the evidence base on the real-world safety of DTG in pregnancy, but the small numbers preclude firm conclusions. In the UK and Ireland, of around 4500 pregnancies in women living with HIV with estimated dates of delivery between 2013 and 2016, the number of pregnancies receiving a DTG-containing regimen increased >10-fold from 0.3% in 2015 to 3.3% in 2016 (Rasi et al 2017). This expanding use highlights the need for further prospective monitoring of pregnant women receiving DTG-containing regimens and their infants.

Acknowledgements

We would like to thank the women who participated in the contributing studies and cohorts.

The following cohorts / studies / networks participated in this study:

- Italian Group on Surveillance of Antiretroviral Treatment in Pregnancy
- NENEXP Study (PPD
- European Collaborative Study on HIV-infected pregnant women & their children
- Swiss Mother and Child HIV Cohort Study (MoCHiV)
- UK / Ireland National Study of HIV in Pregnancy and Childhood (NSHPC)
- PANNA Study
- NEAT-ID Network

Figure 1: Flow chart of included pregnancies and outcomes

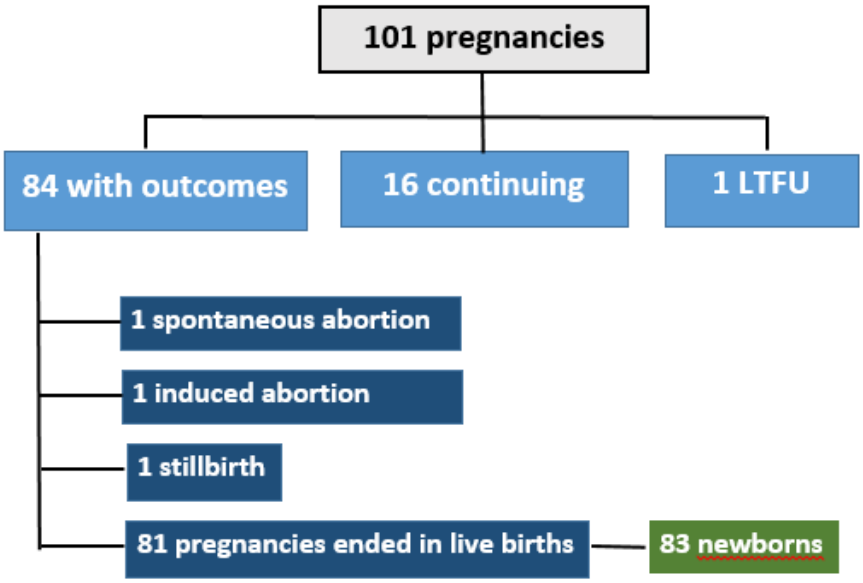

Table 1: Maternal characteristics (101 pregnancies)

Characteristic		N (%)
Ethnicity N=100	Black	71 (71%)
	White	22 (22%)
	Other	7 (7%)
Region of origin N=93	sub-Saharan Africa	62 (67%)
	Europe	22 (24%)
	Other	9 (10%)
Age at conception N=101	<25 years	16 (16%)
	25-34 years	46 (46%)
	≥ 35 years	39 (39%)
Mode of HIV acquisition N=94	Heterosexual	81 (86%)
	Injecting drug use	3 (3%)
	Vertical	9 (10%)
	Other	1 (1%)
Timing of HIV diagnosis N=101	Pre-pregnancy	86 (85%)
	Antenatal	15 (15%)
History of AIDS N=89	Yes	10 (11%)
	No	79 (89%)
HCV status N=91	Seropositive	8 (9%)
	Seronegative	83 (91%)
HBV status N=91	HBsAg positive	4 (4%)
	HBsAg negative	87 (96%)
CD4 count (first in pregnancy) N=89	≤350 cells/mm^3	38 (43%)
	>350 cells/mm^3	51 (57%)
ART at conception N=92	Yes	55 (60%)
	No	37 (40%)

Table 2: Earliest exposure to DTG, by trimester

	Trimester 1 N (%)	**Trimester 2** N (%)	**Trimester 3** N (%)	**Missing** N (%)
All pregnancies, N=101	58 (57.4)	24 (23.8)	18 (17.8)	1 (1.0)
Pregnancies ending in livebirths, N=81	42 (51.9)	21 (25.9)	17 (21.0)	1 (1.2)
Stillbirth	0	1	0	0
Induced abortion	1	0	0	0
Spontaneous abortion	1	0	0	0

Table 3: Gestational age, birthweight and SGA outcomes for singleton livebirths and stillbirth, by earliest DTG exposure in pregnancy

		Earliest DTG exposure in trimester 1	Earliest DTG exposure in trimester 2	Earliest DTG exposure in trimester 3	Total
Gestational age N=79	**≥37 weeks**	37/40 (92.5%)	16/22 (72.7%)	15/17 (88.2%)	68/79 (86.1%)
	34-36 weeks	2/40 (5.0%)	5/22 (22.7%)	2/17 (11.8%)	9/79 (11.4%)
	<34 weeks	1/40 (2.5%)	1/22 (4.6%)	0/17 (0.0%)	2/79 (2.5%)
Birthweight N=77	**≥2500g**	35/39 (89.7%)	15/21 (71.4%)	14/17 (82.3%)	64/77 (83.1%)
	1500-2499g	4/39 (10.3%)	6/21 (28.6%)	3/17 (17.7%)	13/77 (16.9%)
	<1500g	0/39	0/21	0/17	0/77
SGA N=75	**No**	34/39 (87.1%)	13/20 (65.0%)	14/16 (87.5%)	61/75 (81.3%)
	Yes	5/39 (12.8%)	7/20 (35.0%)	2/16 (12.5%)	14/75 (18.7%)

Table 4: Details of reported congenital abnormalities

	Abnormality	Earliest DTG exposure	Infant sex	Maternal details	Other ARV exposures	Country
Infant 1	Patent Foramen Ovale, with small left-to-right interatrial shunt	From conception	Male	Black African, aged 38 at delivery	3TC, ABC	Italy
Infant 2	Bilateral hexadactyly, hands (father has the same defect) Hypospadias	Week 3	Male	White, aged 40 at delivery	3TC/ABC, FTC/TDF in T1	Italy
Infant 3	Ankyloglossia (tongue-tie)	Week 12	Male	White, vertically infected, aged 31 at delivery	DRV/r, FTC/TDF, ATZ/r, RAL, TDF in T1	Italy
Infant 4	Hyperpigmentation on back	Week 14	Male	Black African, aged 34 at delivery	3TC, ABC	Switzerland

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INVESTIGATOR SIGNATORY PAGE

I have read this report and confirm that to the best of my knowledge this report accurately describes the conduct and results of study 206254.

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PPD	Date
Investigator Signature	28/09/17

TITLE PAGE

Information Type: ViiV Healthcare Epidemiology Study Protocol

Title:	Pregnancy and Neonatal Outcomes following Prenatal Exposure to Dolutegravir: Data from the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC)

Compound Number:	GSK1349572, GSK2619619
Development Phase	IV
Effective Date:	[DD-MM-YYYY]
Subject:	Dolutegravir, Pregnancy, HIV
Author(s):	1. PPD ViiV Healthcare 2. PPD 3. PPD

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1. LIST OF ABBREVIATIONS

AEs	adverse events
ARV	antiretroviral
DTG	dolutegravir
ECS	European Collaborative Study on HIV-infected pregnant women & their children
EPPICC	European Pregnancy and Paediatric HIV Cohort Collaboration
HICEP	HIV Cohorts Data Exchange Protocol
HIV	human immunodeficiency virus
INSTI	integrase strand transfer inhibitor
MoCHiV	Swiss Mother and Child HIV Cohort Study
MTCT	mother-to-child transmission
NRTI	nucleoside reverse transcriptase inhibitor
NSHPC	National Study of HIV in Pregnancy and Childhood
PANNA	Pharmacokinetics of newly developed antiretroviral agents in HIV-infected pregnant women
SmPC	Summary of Product Characteristics
SOP	standard operating procedure
UCL	University College London
UK	United Kingdom

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Nassrin Payvandi VP, Safety and Pharmacovigilance	**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: **Dr. Claire Thorne**

Investigator Signature | Date

Investigator Name: **Dr. Carlo Giaquinto**

Investigator Signature | Date

3. ABSTRACT

Dolutegravir (DTG) is a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI) indicated in combination with other antiretroviral (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.

Objectives:

1. To describe patterns of prenatal use of DTG-containing regimens, including timing of initiation, nucleoside reverse transcriptase inhibitor (NRTI) backbone and geographic/calendar time trends
2. To describe maternal characteristics (e.g. demographics, clinical and immunological) of women taking DTG-based regimens –by trimester of exposure
3. To describe frequency of adverse pregnancy outcomes in women using DTG in pregnancy including birth defects, stillbirths, spontaneous abortions, induced abortions, preterm births, low birth weight infants, and very low birth weight infants –by trimester of exposure
4. To describe the proportion of women on DTG who achieve viral suppression by the end of pregnancy by trimester of exposure
5. To describe mother-to-child transmission (MTCT) rates in mother-infant pairs with prenatal DTG use

This will be a retrospective analysis of prospectively collected data from the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC). The study will utilize observational data collected in EPPICC cohort and surveillance studies of pregnant women living with HIV and their infants primarily from countries in Europe, Thailand, and Argentina.

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
Protocol Draft	11-Nov-2016
Registration on the EU PAS register	19-Dec-2016
Start of data analysis	20-Dec-2016
Preliminary results	03-Mar-2017
Draft report of study results	03-Apr-2017
Final report of study results	15-May-2017
Manuscript Draft	30-June-2017

6. BACKGROUND AND RATIONALE

6.1. Background

DTG is an 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. In animal studies, DTG was shown to cross the placenta. Hence, DTG-containing regimens should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus as per the summary of product characteristics (SmPC).

6.2. Rationale

There are no adequate and well-controlled studies evaluating the use of DTG in pregnant women. This analysis aims to assess maternal and fetal outcomes following DTG use during pregnancy.

7. RESEARCH QUESTION AND OBJECTIVE(S)

Specific Aims:

1. To describe patterns of prenatal use of DTG-containing regimens, including timing of initiation, NRTI backbone and geographic/calendar time trends
2. To describe maternal characteristics (e.g. demographics, history of previous pregnancies and outcomes, clinical and immunological) of women taking DTG-based regimens by trimester of exposure
3. To describe frequency of adverse pregnancy outcomes in women using DTG in pregnancy including birth defects, stillbirths, spontaneous abortions, induced abortions, preterm births, low birth weight infants, and very low birth weight infants by trimester of exposure
4. To describe the proportion of women on DTG who achieve viral suppression by the end of pregnancy by trimester of exposure
5. To describe MTCT rates in mother-infant pairs with prenatal DTG use

8. RESEARCH METHODS

8.1. Study Design

This is a retrospective analysis of observational individual patient data prospectively (exposure data collected before outcome is known) collected in cohort and surveillance studies of pregnant women living with HIV and their infants from several countries, primarily those within EPPICC, and supplemented by patient data collected in the NEAT-ID network and obstetric sites participating in the Pharmacokinetics of newly developed antiretroviral agents in HIV-infected pregnant women (PANNA) study.

8.2. Study Population and Setting

All pregnant women with any exposure to DTG (TIVICAY® & TRIUMEQ®) at any time during the pregnancy reported to participating studies by end August 2016 and their infants will be included in the analysis.

8.3. Variables

8.3.1. Outcome definitions

The outcomes assessed in this study will be:

- Pregnancy outcomes (i.e. spontaneous abortion, induced abortion, live birth, still birth) by trimester of exposure to DTG

- Adverse pregnancy outcomes by trimester of exposure to DTG, including birth defects, spontaneous abortion, still birth, preterm births, low birth weight infants,

and very low birth weight infants as defined in Table 1. Birth defects will be classified according to the World Health Organization's International Classification of Diseases, Tenth Revision.

- Maternal virological suppression at the end of pregnancy: viral suppression will be measured as viral load <50 copies/mL. "End of pregnancy viral load" will be considered as the measurement reported closest to delivery, measured up to 28 days before and 7 days after delivery. Viral suppression rates will be assessed separately for patients who were on DTG before pregnancy occurred, and those who started DTG while pregnant (or by trimester of exposure); length of exposure to DTG will be reported where the data is available.

- MTCT: infant HIV infection status will be classified as uninfected or infected on the basis of reported polymerase chain reaction test results or indeterminate for infants whose infection status had not yet been reported.

Table 1. Definitions of pregnancy outcomes –based on consensus from the participating cohorts in the EPPICC.

Pregnancy Outcome	**Definition**
Induced abortion	Voluntary termination of pregnancy before 22 weeks gestation
Spontaneous abortion	Death of a fetus or expulsion of the products of conception before 22 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 22 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

EPPICC is a network of European cohorts of prospectively observed mother-child pairs and children within EuroCoord. Studies that have eligible subjects included in their studies to date are listed here:

- **Italian Group on Surveillance of Antiretroviral Treatment in Pregnancy**

Contact: Dr PPD

- **Spain: PPD Cohort of HIV-Infected Mother-Infant Pairs**

Contact: Dr PPD

- **Spain: NENEXP Study PPD**

Contact: Dr PPD

- **European Collaborative Study** on HIV-infected pregnant women & their children (ECS)

Contacts: Dr PPD (Ukraine: Dr PPD Prof PPD

- **Swiss Mother and Child HIV Cohort Study** (MoCHiV)

Contact: Dr PPD

- **UK / Ireland National Study of HIV in Pregnancy and Childhood** (NSHPC)

Contacts: Dr PPD

- **PANNA Study**

Contacts: Dr PPD; Dr PPD

- **NEAT-ID**

Contacts: Dr PPD

8.5. Study size

On the basis of current estimates, we expect to include between 60 and 70 pregnant women in this study. The small sample size would limit the analysis to descriptive in nature and would be insufficient for detailed statistical analyses.

8.6. Data management

8.6.1. Data handling conventions

PENTA will collect anonymised individual patient data on mother-infant pairs with antenatal DTG use, using a detailed standard operating procedure (SOP) for this study, including a data specification based on a modified HIV Cohorts Data Exchange Protocol (HICDEP) (www.hicdep.org). The HICDEP format is based on a relational structure, and the data for this study will be collected in a series of tables, which are described in the Appendix 1.

Following the merger, data will be reviewed for completeness with logical and consistency checks and any data queries resolved with the participating cohort. This step will also allow de-duplication if the same patient is reported from several sources (e.g. EPPICC and PANNA or NEAT-ID). For example, the European Collaborative Study includes patients from Italian sites, which may also participate in the Italian Group on Surveillance of Antiretroviral Treatment in Pregnancy; the United Kingdom (UK)/Ireland NSHPC is a national surveillance study and thus any pregnant woman delivering in the UK enrolled into a PANNA study would also be included in the NSHPC. De-duplication is facilitated by the Overlap table in the SOP (see Appendix 1).

The data merger and statistical analyses will be conducted at University College London (UCL) Great Ormond Street Institute of Child Health.

8.6.2. Timings of Assessment during follow-up

This is a retrospective analysis of prospectively collected observational data from a number of different studies. There are variations across participating studies with regard to the routine variables collected within their standard protocols.

Exposure to ARVs is reported before the pregnancy outcome is known.

8.7. Data analysis

Statistical analysis will be carried out using STATA® v12.0 software (StataCorp, College Station, Texas). Standard descriptive statistics will be used to summarize the data (e.g. socio-demographic variables, history of previous pregnancies and the outcomes and those that describe specific maternal and infant outcomes). For continuous variables, the sample size, median and interquartile range will be provided. Frequency distributions will be provided for categorical variables. For rates, 95% confidence intervals will be calculated.

The unit of analysis (woman, pregnancy, fetus, infant) will vary; multiple gestations will be taken into account if required. Analyses addressing objectives 1 and 2 (patterns of use, time trends, maternal characteristics) will be conducted based on the whole study population. Analyses addressing objective 3 (adverse pregnancy outcomes) will be restricted to pregnancies with an outcome (i.e. excluding continuing pregnancies).

Analyses addressing objective 4 (maternal viral suppression at the end of pregnancy) will be restricted to women delivering live or stillborn infants. MTCT analyses will be limited to live-born infants. While, initial analysis will include any exposure to DTG, duration and timing of exposure (trimester of exposure) will be accounted for in analyses e.g. sensitivity analyses limited to women with a minimum exposure to DTG in pregnancy; exposure for the first time during first trimester versus second/third trimester.

8.8. Quality control and Quality Assurance

Participating studies already have study specific routine processes to assure integrity and quality of their data, for example, during the data entry stage and prior to dataset extractions. An additional level of data integrity and quality checking processes will be provided centrally at the data coordinating centre at UCL Great Ormond Street Institute of Child Health. The SOP includes a comprehensive data specification, which includes clear instructions on: codes to be used (look-up tables for the codes are provided); provision of raw data for numeric values; handling of dates; handling of missing values; data checking processes.

After the submission of data to the data coordinating centre, a comprehensive set of data quality checks will be conducted. These will include validation checks (including data type; range; code), cardinality between tables, consistency checks and logic checks. Identification of any duplicate pregnancies (i.e. reported by more than one study) will form part of these data checks, facilitated by the inclusion of an overlap data table within the SOP. We will be working closely with studies to clean the data. This will involve sending out data quality checks in the form of a discrepancy report to the data manager for each participating study/site, processing their responses and sending further checks where necessary. The study data manager will be responsible for documenting changes to the datasets during the cleaning process. Should exclusion of any specific data item(s) for a mother-infant pair included in the study occur, then this would be fully justified.

Participating studies submit coded anonymised individual patient data with study-specific unique identifiers. For the merged final study database, we will allocate additional unique identifiers to mothers and infants, to ensure a common format for all included mother-infant pairs. Individual study data managers can link the study unique identifiers to the relevant patient records, ensuring traceability of data. This allows data quality queries to be addressed, assists in de-duplication and allows for future reporting of the outcomes of ongoing pregnancies.

8.9. Limitations of the research methods

This study is limited by its observational nature, and thus potential for bias. Only data items collected routinely within the participating studies will be included. Some participating studies' designs may result in under-reporting of early miscarriages and terminations – e.g. in the UK National Study of HIV in Pregnancy and Childhood, where

data are provided by antenatal care providers, this may occur for the group of women who did not receive care from an antenatal care clinic/provider early in their pregnancy.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical approval and subject consent

Participating studies have existing national and/or local ethical approval, and obtain informed subject consent where required within these approvals.

9.2. Subject confidentiality

This analysis will use previously collected, anonymized electronic medical record data. No identifying information will be provided.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves retrospective analysis of previously collected data in an aggregate manner. There is no potential to collect serious and non-serious adverse events (AEs), pregnancy exposures, or incidents related to any ViiV Healthcare product during the conduct of this research, as the minimum criteria needed to report AEs, pregnancy exposures, and incidents are not present in the data source. Specifically, the data are insufficient to establish attribution between a potential safety event and an individual patient using a ViiV Healthcare product.

Therefore, a study specific pharmacovigilance plan will not be developed.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Target Audience

The target audience includes healthcare providers, patient groups (through patient groups like iBase, European AIDS Treatment Group, Positive UK etc.), regulatory and health authorities. The study results will be made available externally through peer reviewed manuscript and conference presentation.

11.2. Study reporting and publications

Final Study results will be included in safety and regulatory reports as appropriate. Results will also be submitted as an abstract to a congress and for publication in peer reviewed journal.

12. REFERENCES

1. Raffi F, Jaeger H, Quiros-Roldan E, et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomized, double-blind, non-inferiority trial. Lancet Infect Dis 2013; 13:927–35.

2. Walmsley S, Antela A, Clumeck N et al. Dolutegravir plus abacavir/lamivudine for the initial treatment of HIV-1 infection. N Engl J Med 2013 ;369:1807–18.

3. Clotet B, Feinberg J, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomized open-label phase 3b study. Lancet 2014;383:2222–31.

4. Castagna A, Maggiolo F, Penco G, et al. Dolutegravir in antiretroviral-experienced patients with raltegravir- and/or elvitegravir- resistant HIV-1: 24-week results of the phase III VIKING-3 study. J Infect Dis 2014;210:354–62.

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 1. LIST OF STAND-ALONE DOCUMENTS

Table 1 - BAS table - Demographic data for each mother

Field name	Format	Description
PATIENT	Character or numeric	Cohort patient ID for the mother (unique and anonymous)
BIRTH_D	yyyy-mm-dd	Birth date of mother
ETHNIC	10 = White 20 = Black 21 = Black African 22 = Black Caribbean 30 = Hispanic 40 = Asian 50 = Indigenous from Americas 60 = Indigenous from other continents 1020 = White/Black 1040 = White/Asian 2030 = Black/Hispanic 3040 = Hispanic/Asian 102040 = White/Black/Asian 97 = other 98 = Prohibited 99 = Unknown	Ethnicity of woman
ORIGIN	Numeric with codes	Country of birth *(if country of birth not available, please provide region)*
HIV_D	yyyy-mm-dd	Date HIV was diagnosed.
AIDS_Y	0=No 1=Yes 9=unknown	Has patient been given an AIDS diagnosis? (i.e. WHO stage 3 or 4, or CDC stage C)
AIDS_D	yyyy-mm-dd	Date AIDS was diagnosed.
HCV_COINF	0=No 1=Yes 9=unknown	Is the woman seropositive for HCV?

HBSAG_Y	0=No 1=Yes 9=unknown	Is the woman hepatitis B surface antigen positive?
HBACTIVE_Y	0=No 1=Yes 9=unknown	Does the woman have detectable HBV DNA and/or is HBeAg positive?
MODE	2 = injecting drug user 5 = transfusion, non-haemophilia related 6 = heterosexual contact 7 = heterosexual contact and injecting drug user 8 = vertical 90 = other (specify) 99 = unknown	Mode of HIV infection
MODE_OTH	Character	Mode of infection – other *Complete if MODE = 90*
TRI_DTG_EXPOSURE	1=1st trimester 2=2nd trimester 3=3rd trimester	Trimester of earliest exposure to DTG

Table 2 - PREG table – Information specific to each pregnancy

Field name	**Format**	**Description**
PATIENT	Character or numeric	Cohort patient ID of mother
PREG_ID	Character or numeric	Unique ID for this pregnancy
MENS	yyyy-mm-dd	Date of last menstrual period If unknown, please put 1911-11-11
EDD	Yyyy-mm-dd	Estimated date of delivery
GESTITY	Numeric	Total number of known pregnancies <u>including this current reported one</u> (including all known miscarriages, terminations, ectopic pregnancies,

		newborns,..etc)
PARITY	Numeric	Total number of prior deliveries after 22 weeks (alive or dead) - excluding this reported one
PREV_DRUG	0=No 1=Yes 9=Unknown	Has the mother used illegal drugs before this pregnancy?
P_TOBACCO	0=No 1=Yes 9=Unknown	Has the mother used tobacco during this pregnancy?
P_ALCOHOL	0=No 1=Yes 9=Unknown	Has the mother used alcohol during this pregnancy?
P_DRUG	0=No 1=Yes 9=Unknown	Has the mother used illegal drugs during this pregnancy?
DTG	0=No 1=Yes 9=Unknown	Was the mother on DTG at conception of this pregnancy?
CARE_D	yyyy-mm-dd	Date pre-natal care was initiated *If unknown, please put 1911-11-11*
N_FETUS	Numeric	Number of embryos/fetuses in this pregnancy
OUTCOME	1=Livebirth > 22 gest wks (even if infant died after birth) 2= miscarriage (<22 wks) 3=termination by choice 4=termination - ultrasound abnormality 5=termination – other/ unknown reason 6=Stillbirth (Intra-uterine death from 22 gest weeks) 9=unknown	Outcome of pregnancy / reason pregnancy was interrupted – where appropriate please put full details in DEFECTS table

OUTCOME_D	yyyy-mm-dd	Date of outcome
INT_DETAILS	Free text	Other details about miscarriage, causes of termination or intra-uterine death, if available

Table 3 -ART table - antiretroviral treatment data

Field name	**Format**	**Description**
PATIENT	Character or numeric	Cohort patient ID of the mother
PREG_ID	Character or numeric	Unique ID for this pregnancy
ART_ID	J05AX12=Dolutegravir J05AR13=Triumeq (Lamivudine, abacavir and dolutegravir)	Code representing the antiretroviral drug
ART_SD	yyyy-mm-dd	Start date
ART_ED	yyyy-mm-dd	Stop date
ART_RS	Numeric with codes	Main reason for stopping
ART_RS_OTH	Character (free text)	If ART_RS=98 (other), please give details here
ART_CONC	0=No 1=Yes 9=unknown	Was this drug being taken at the time of conception?

Table 4 – ZDV_INTRAPART table – intrapartum use of ZDV Field name	**Format**	**Description**
PATIENT	Character or numeric	Cohort patient ID of the mother

PREG_ID	Character or numeric	Unique ID for this pregnancy
ZDV_IP	0=No 1=Yes 9=unknown	Was intrapartum ZDV given during labour?

Table 5 - LAB_CD4 table - CD4 data **by trimester of earliest exposure to DTG**

Field name	**Format**	**Description**
PATIENT	Character or numeric	Cohort patient ID of the mother
PREG_ID	Character or numeric	Unique ID for this pregnancy
CD4_D	yyyy-mm-dd	Date of CD4 measurement
CD4_V	Numeric	Value of CD4 measurement
CD4_U	1=cells/mm^3 2=%	CD4 cell count or CD4 %

Table 6 -LAB_RNA table – HIV-1 RNA data **by trimester of earliest exposure to DTG**

Field name	**Format**	**Description**
PATIENT	Character or numeric	Cohort patient ID
PREG_ID	Character or numeric	Unique ID for this pregnancy
RNA_D	yyyy-mm-dd	Date of HIV-1 RNA measurement
RNA_V	Numeric For undetectable values, enter -1 in RNA_S	HIV-1 RNA measurement value (copies/ml)
RNA_S	-1 = less than the value in RNA_V 0 = exactly equal to value in RNA_V 1 = greater than value in RNA_V	Sign of result for RNA_V Flag to indicate whether the result in RNA_V is the exact value or whether less or more

RNA_L	Numeric	Lower limit of HIV-1 RNA assay (leave blank if unknown)
RNA_U	Numeric	Upper limit of HIV-1 RNA assay (leave blank if unknown)

Table 7 - LINKAGE table – allows mothers, pregnancies and fetus or babies to be matched

Field name	**Format**	**Description**
PATIENT	Character or numeric	Cohort patient ID of the mother
PREG_ID	Character or numeric	Unique ID for pregnancy. Twins will both have the same values of PATIENT and PREG_ID
FETAL_ID	Character or numeric	Unique ID for fetus delivered at less than 22 weeks. This will be blank for other outcomes
BABY_ID	Character or numeric	Unique ID for baby (delivered at 22 or more weeks). This will be blank for other outcomes

Table 8 - FETAL_LOSS table – data regarding reasons for pregnancy loss or interruption before 22 weeks **by trimester of earliest exposure to DTG**

Field name	**Format**	**Description**
PATIENT	Character or numeric	Cohort patient ID of the mother
PREG_ID	Character or numeric	Unique ID for pregnancy
FETAL_ID	Character or numeric	Unique ID for this fetus.
US_ABN	0=No 1=Yes	Was there an ultrasound abnormality?

	9=unknown	
US_ABN_TYPE	Free Text	Describe ultrasound abnormality
FET_LOSS_D	Free text	Describe reason for miscarriage or termination, if known.

Table 9 - NEWBORN table – data regarding delivery and the baby if born at 22 or more weeks by trimester of earliest exposure to DTG

Field name	**Format**	**Description**
PATIENT	Character or numeric	Cohort patient ID of the mother
PREG_ID	Character or numeric	Unique ID for pregnancy
BABY_ID	Character or numeric	Unique ID for this baby
DELIV_D	Yyyy-mm-dd	Date of delivery (*NB This will be the same date as OUTCOME_D)*
GEST_AGE	Numeric 99=missing	Gestational age (in completed weeks) at delivery
DELIV_M	1=Vaginally, spontaneous 2=Vaginally, forceps 3=Vaginally, vacuum 4=Vaginally, unknown if spontaneous or instrumented 10=Caesarean section, primary/elective (before onset of labour and rupture of membrane) 11=Caesarean section, secondary (“emergency caesarean”) 12=Caesarean section, unspecified 99=unknown	Mode of delivery

GENDER	1=male 2=female 9=unknown	Sex of baby
WEIGHT	Numeric 999 if unknown	Weight of baby at birth in g
HEIGHT	Numeric 999 if unknown	Length of baby at birth in cm
HEAD	Numeric 999 if unknown	Head circumference of baby at birth in cm
NEO_DEATH	1=stillborn 2=neonatal death 3=alive 9=unknown	Has the baby died during the neonatal period (first 4 weeks of life)?
DEATH_D	yyyy-mm-dd	Date of baby's death
DEATH_CAUSE	Free text	Cause of death. If autopsy carried out, please provide results.
BIRTH_DEFECT	0=No 1=Yes 9=unknown	If yes, please provide details in separate DEFECTS table
NEO_PROPH	0 = None 1 = ZDV prophylaxis 2 = Combination neonatal prophylaxis with 2 drugs 3 = Combination neonatal prophylaxis with 3 drugs 4 = Prophylaxis was given but type not known 5=sdNVP only 9 = unknown	What type of neonatal prophylaxis did the baby receive?
NEO_DUR	Numeric 99=unknown	Duration of neonatal prophylaxis in weeks
BRFEED_Y	0=No 1=Yes 9=unknown	Was baby ever breastfed?

BRFEED_DUR	Numeric	How long did breastfeeding last (in days)?
HIV_BABY	0=uninfected 1=infected 2=indeterminate 9=unknown	Infection status of the baby at most recent follow-up

Table 10 - DEFECTS table – data regarding birth defects in newborn and stillborn infants **by trimester of earliest exposure to DTG**

Field name	**Format**	**Description**
PATIENT	Character or numeric	Cohort patient ID of the mother
PREG_ID	Character or numeric	Unique ID for pregnancy
BABY_ID	Character or numeric	Unique ID for this baby – will be blank if delivery < 22 gestational weeks
DIAG_D	yyyy-mm-dd	Date this birth defect was diagnosed
DIAG_DESCRIP	Free text	Details of birth defect
DIAG_ICD	Code with one letter and 2 to 4 digits	ICD 10 code for birth defect if known

Table 11 - BABY_LAB table – HIV DNA PCR and antibody test results by trimester of earliest exposure to DTG

Field name	**Format**	**Description**
PATIENT	Character or numeric	Cohort patient ID of the mother
BABY_ID	Character or numeric	Unique ID for this baby
VS_ID	*HIVA: HIV antibodies* *HIVD: HIV DNA PCR* *HIVR: HIV RNA PCR*	Test identification

VS_R	If antibodies or HIV DNA PCR: 0=negative 1=positive 9=unknown/borderline If HIV RNA PCR: 0=undetectable If detectable provide value (copies/ml)	Test result
VS_D	yyyy-mm-dd	Test date

Table 12 - OVERLAP table – patients overlapping with other cohorts

Field name	**Format**	**Description**
PATIENT	Character or numeric	Cohort patient ID of the mother
COH_OTH	Character	Other cohort who this patient is part of
PAT_OTH	Character	Unique patient ID in the other cohort