TITLE PAGE

Information Type: ViiV Healthcare Epidemiology Study Protocol

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

Compound Number:	GSK1349572 (Tivicay), GSK2619619 (GSK1349572+GR109714+GI265235, Triumeq), GSK3365791 (GSK1349572+GSK1329758, Juluca), GSK 3515864 (GSK1349572+GR109714, D3)
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Author(s): PPD Fondazione: PENTA ONLUS
PPD ViiV Healthcare
PPD Fondazione PENTA ONLUS

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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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2. RESPONSIBLE PARTIES: SPONSOR INFORMATION PAGE

MARKETING AUTHORISATION HOLDER

ViiV Healthcare UK Limited

Sponsor Legal Registered Address:

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SPONSOR SIGNATORY:

Vani Vannappagari Primary Author/ Project officer	**Date**
Harmony Garges VP, Global Medical Sciences	**Date**
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: Claire Thorne

_____ _____

Investigator Signature Date

Investigator Name: 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 has been approved by the FDA for use among children 6 years and older (weighing at least 30 kg), and by the European Medicines Agency for children weighing more than 15kg. 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 and severely preterm births, low birth weight, very low birth weight and extremely 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 pooled analysis of prospectively collected observational data from the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC), and PANNA network. The first analysis will be done in third quarter of 2018, and final analysis will be done in second quarter of 2020A pooled analysis at the end of the study will include data from EPPICC, PANNA and NEAT-ID Network

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	01-NOV-2017
Registration on the EU PAS register	14-MAR-2018
Start of data analysis	15-MAR-2018
Preliminary results	31-DEC-2022
Draft report of study results	31-MAR-2023
Final report of study results	30-JUN-2023
Manuscript Draft	31-DEC-2023

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 has been approved by the FDA for use among children 6 years and older (weighing at least 30 kg), and by the European Medicines Agency for children weighing more than 15 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)

Pooled analyses of observational data on pregnancy

Aim: To assess "real-world" maternal and fetal outcomes following DTG use during pregnancy and to describe patterns of DTG utilization using data from the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC), NEAT ID Network and PANNA networks in order to increase knowledge of the safety profile of DTG in pregnancy.

Specific objectives

1. To describe trends and patterns of use of DTG-containing regimens in pregnancy in Europe, including timing of initiation, NRTI backbone and geographic/calendar time trends (including future use of DTG-containing two drug regimens)
2. To characterize the contemporary population of DTG-treated women (e.g. demographics, obstetric history, 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 and severely preterm births, low birth weight, very low birth weight and extremely 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 non-interventional study involving analysis of observational individual patient data prospectively (exposure data collected before the pregnancy outcome is known) collected in cohort and surveillance studies of pregnant women living with HIV and their infants from several countries, specifically those within EPPICC. PANNA network sites will include individual patient data to the annual mergers (including any mother-infant pairs from the site meeting our eligibility criteria who did not participate in DOLOMITE PANNA PK study and eligible NEAT ID Network).

This study will follow the pharmacovigilance model implemented for the paediatric studies in EPPICC, which undertakes annual data mergers and pooled analyses of de-identified individual patient data. Participating sites/cohorts in EPPICC and PANNA will provide coded anonymised individual patient data prepared according to a detailed standard operating procedure (SOP) at agreed time-points during the study period.

Following merger of these individual cohort/study datasets, analyses will be conducted on the pooled dataset to address the study objectives.

We would propose to have the first data merger in 2018, with two analyses planned – one in late 2018 and the second in 2020.

8.2. Study Population and Setting

All pregnant women with any exposure to DTG (TIVICAY®, TRIUMEQ®, JULUCA and D3) at any time during the pregnancy and their infants will be included in the analysis.

In the data mergers, we will collect data on any pregnancy reported within the participating studies with any DTG-exposure regardless of pregnancy outcome, including those where the pregnancy is still ongoing at the time of the merger. In addition to individual patient data on eligible mother-infant pairs, participating studies will be required to provide a summary data table at each merger (to include total number of pregnancies reported to their study within the reporting period, pregnancy outcomes, distribution across main treatment groups) in order to provide a context for the interpretation of study results (e.g. rates of adverse birth outcomes) and to allow us to describe trends in use of DTG in pregnancy over time.

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 and severely preterm births, low birth weight, very low birth weight, and extremely 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. Where data is available VL suppression will be assessed during each trimester.

- 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. Where data is available, likely timing of transmission will be explored.

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
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 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: NENEXP Study** PPD

Contact: Dr PPD

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

Contacts: Dr PPD for Western European ECS and Dr PPD Prof PPD for Ukraine ECS

- **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
PPD

In addition, there are a number of other MTCT cohorts in EPPICC that will be able to participate in the study once they start to see DTG use within their cohorts (none to date). These are listed below:

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

Contact: Dr PPD

- **Romania:** PPD **Cohort**

Contact: Dr PPD

- **Russia:** PPD **Cohort** PPD

Contact: Dr PPD

- **Portuguese HIV in Pregnancy Cohort**

Contact: Dr PPD

- **PANNA Study**

Contacts: Dr PPD Dr PPD

8.5. Study size

On the basis of current estimates, we expect to include at least 150 pregnant women in this study in the first year, with larger numbers in subsequent years as use of DTG increases, including in cohorts that to date have not had exposed women enrolled. 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). For example, 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 study involves analysis of prospectively collected observational data from a number of different studies participating in EPPICC and PANNA. 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, thus making this a prospective cohort study.

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, description of backbone used in combination with DTG and the frequency of DTG based 2 drug regimen, 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.

A pooled analysis (individual patient data meta-analysis) on birth outcomes (birth defects, preterm delivery, small-for-gestational age, stillbirth) among mother-infant pairs with first trimester exposure using data collected within DOLOMITE-NEAT ID and DOLOMITE-EPPICC will be conducted at the end of the study period, with appropriate de-duplication for any mother-infant pairs that are in both datasets. The first analysis will be conducted during Q3, 2018 and subsequent analysis in Q2, 2020.

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, coded anonymized electronic medical record data. No identifying information will be provided.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves analysis of previously collected observational 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

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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.

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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 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)
CENTER	Character	Centre name
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_EXP	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) - <u>excluding this reported one</u>
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
AMNIO	0=No 1=Yes 9=Unknown	Was amniocentesis performed in this pregnancy?

AMNIO_DET	Free text	Please give details (reason for amniocentesis and outcome any tests)
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 (please leave blank if continuing)

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

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

Please provide postnatal HIV RNA results for any woman known to have chosen to breastfeed her infant.

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

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 9=unknown	Was there an ultrasound abnormality?
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

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	Mode of delivery

	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	
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	What type of neonatal prophylaxis did the baby receive?

	3 = Combination neonatal prophylaxis with 3 drugs 4 = Prophylaxis was given but type not known 5=sdNVP only 9 = unknown	
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

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

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

Table 13 – CONTEXT table

A summary data table will be completed by each participating study (i.e. based on aggregate and not individual patient data) to include total number of pregnancies reported

to the study within the reporting period, pregnancy outcomes (live births, miscarriages, terminations of pregnancy, stillbirths, pregnancy continuing and loss to follow-up), with distributions across the main treatment groups.