TITLE PAGE

Information Type: ViiV Healthcare Epidemiology Study Protocol

Title:	DOLOMITE NEAT ID Network Study: A prospective, multi-site observational study to define the safety and effectiveness of Dolutegravir use in HIV positive pregnant women
Compound Number:	GSK1349572 (Tivicay), GSK2619619 (GSK1349572+GR109714+GI265235, Triumeq), GSK3365791 (GSK1349572+GSK1329758, Juluca), GSK 3515864 (GSK1349572+GR109714, D3)
Development Phase:	IV
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Subject: Safety and effectiveness of DTG use in pregnancy.

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MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	ViiV Healthcare UK Limited 980 Great West Road Brentford Middlesex TW8 9GS United Kingdom

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1. LIST OF ABBREVIATIONS

AE	Adverse Event
ADRs	Adverse Drug Reactions
APGAR	Appearance, Pulse, Grimace, Activity, Respiration
AR	Adverse Reaction
ARV	Antiretroviral
APR	Antiretroviral Pregnancy Registry
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CROI	Conference on Retroviruses and Opportunistic Infections
CTA	Clinical Trial Authorisation
DMC	Data Monitoring Committee
DTG	Dolutegravir
EACS	European AIDS Clinical Society
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraVIGILANCE	European Database for Pharmacovigilance
EUROCAT	European Surveillance of Congenital Anomalies
FDC	Fixed Dose Combination
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HR	Hazard Ratio
HIV	Human Immunodeficiency Virus
IAS	International AIDS Society
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IECs	Independent Ethics Committees
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IRBs	Institutional Review Boards
ISF	Investigator Site File
ISRCTN Number	International Standard Randomised Controlled Trials Number
3TC	Lamivudine
MA	Marketing Authorisation
MHRA	Medicines and Healthcare Products Regulatory Agency
MS	Member State
NEAT ID	The European AIDS Treatment Network
NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product
OR	Odds Ratio
PASS	Post-authorization Safety Study
PI	Principal Investigator

PIC	Participant Identification Centre
PIS	Participant Information Sheet
PENTA	Paediatric European Network for Treatment of AIDS
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
RNA	Ribonucleic Acid
RPV	Rilpivirine
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAS	Statistical Analysis Software
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SPSS	Statistical Package for the Social Sciences
SSI	Site Specific Information
SSCR	St Stephen's Clinical Research
sPVP	Study-specific Pharmacovigilance Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File
VL	Viral Load

Trademark Information

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TIVACAY
TRIUMEQ
JULUCA

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2. RESPONSIBLE PARTIES: SPONSOR INFORMATION PAGE

MARKETING AUTHORISATION HOLDER

ViiV Healthcare UK Limited

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Sponsor Medical Monitor Contact Information:

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SPONSOR SIGNATORY:

Vani Vannappagari Primary Author/ Project Officer	**Date**
Harmony Garges VP, Global Medical Sciences	**Date**
Nassrin Payvandi VP, Head of Safety and Pharmacovigilance	**Date**

CHIEF 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: Justyna Kowalska

Investigator Signature **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 at this site. 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.
- I agree to permit any monitoring, auditing and inspection at this site and to retain all trial related essential documentation for the duration of the study as required according to ICH-GCP.

Investigator Name:

Investigator Signature	**Date**

3. ABSTRACT

In 2014, the European Commission recommended the authorisation of Dolutegravir (DTG) an integrase strand transfer inhibitor, marketed as a single agent as Tivicay©, and also Triumeq©, a fixed dose combination (FDC) tablet containing DTG/abacavir (ABV)/lamivudine (3TC), for use in the European Union for the treatment of adults and adolescents aged 12 years and older with HIV-1 in combination with other antiretroviral agents. In clinical trials including adult patients, the most commonly reported adverse drug reactions (ADRs) to Tivicay were nausea, diarrhoea and headache. A more serious but less common side effect is hypersensitivity reaction with rash and possible effects on the liver.

There are no adequate and well-controlled studies evaluating the safety and efficacy of DTG in pregnant women. Hence currently, DTG-containing regimens are recommended during pregnancy only if the potential benefit outweighs the potential risk to the fetus as per the summary of product characteristics (SmPC).

Only in 2016 there were 34 179 new HIV infections among women 20-39 years old[1]. With the average European growth rate of 0.1 in 2015-2060 approximately 3 400 deliveries annually could be expected only in this population of HIV positive women[2].

In the light of recent EACS guideines it is expected that as DTG use increases in Europe, there will be a growing proportion of pregnant women who either conceive on DTG-regimens or start a DTG-containing regimen in pregnancy[6.]

This multi-site observational study is expected to enrol approximately 250 HIV positive pregnant women recieving DTG, at least 200 starting or on DTG in first trimester and the rest starting in second/third trimester. The data collected will be that obtained during routine standard of care assessments; and the participant will not undergo any interventional study procedures. The study will aim to define the safety profile and effectiveness of DTG in this patient population by:

- Reporting pregnancy and birth outcomes.
- Describing incidence rate of discontinuation of DTG in pregnancy, including reasons and HIV viral load at discontinuation.
- Providing descriptive safety data in relation to DTG (incidence and severity of all drug related adverse events (AEs) and serious adverse events (SAEs)).

4. AMENDMENTS AND UPDATES

Amendment or Update No	Date	Section of Study Protocol	Amendment or Update	Reason

5. MILESTONES

Milestone	**Planned date**
Start of data collection	Jul-2018
End of data collection	Apr-2021
Annual progress reports	Yearly, within 30 days of the anniversary date of EC approvals.
Final report of study results	Oct-2022 or within 12 months after end of study

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6. RATIONAL AND BACKGROUND

Dolutegravir is a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI) indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. 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 for those with suspected or documented resistance to integrase inhibitors. In clinical trials including adult patients, the most commonly reported adverse drug reactions (ADRs) to Tivicay were nausea, diarrhoea and headache. A more serious but less common side effect is hypersensitivity reaction with rash and possible effects on the liver.

There are no adequate and well-controlled studies evaluating the use of DTG in pregnant women. In animal and ex vivo human placenta perfusion studies, DTG has been shown to have a high penetration across the placenta, unlike some other antiretrovirals, where this might protect a developing embryo against vertical HIV transmission, but might also increase the risk of adverse birth outcomes[3,4]. In animal toxicology studies[9], as well as in small observational, retrospective and mostly single centre human studies there has been no evidence for adverse effects from DTG treatment during pregnancy[5]. In view of this, DTG-containing regimens are recommended during pregnancy only if the potential benefit outweighs the potential risk to the fetus as per the summary of product characteristics (SmPC).

It is expected that as DTG use increases in Europe, there will be a growing proportion of pregnant women who either conceive on DTG-regimens or start a DTG-containing regimen in pregnancy[6]. This multi-site prospective observational study, is to look at the usage and assess the safety and effectiveness of DTG use in pregnancy in “real world” settings in Europe.

7. RESEARCH QUESTION AND OBJECTIVE(S)

The aim for this study is to assess the safety and effectiveness of DTG use in HIV positive pregnant women in a “real world” setting.

7.1. Study Objective(s)

7.1.1. Primary Objective

1. To describe pregnancy and birth outcomes; Pregnancy outcomes include spontaneous abortion, induced abortion, still births, multiple births, type of delivery and maternal viral load (VL) at delivery. Birth outcomes include birth defects (to be reported in real-time to the Antiretroviral Pregnancy Registry: http://www.apregistry.com/) and other routinely collected data at birth such as gestational age, birth weight, APGAR score and infant’s HIV status.

7.1.2. Secondary Objectives

1. To provide descriptive analysis of all drug related AEs and SAEs related with the regimen used. These will be categorised by trimester of initiation.
2. To describe rate of DTG discontinuation in pregnant women, including reasons and VL at discontinuation and viral suppression during each of the trimesters where possible.

8. RESEARCH METHODS

8.1. Study Design

This is a 3 year European multi-site prospective observational study, enrolling approximately 250 HIV positive pregnant women. The enrolment period will be over 2 years with follow-up period of 1 year for outcomes across potentially 35 European sites.

Potential NEAT ID investigational sites from across Europe will be contacted for feasibility and selection will be based on sites having DTG as a treatment option for pregnant women or currently using DTG in pregnancy. There will be no additional data collected in this observational study outside of the current routine standard of care at each investigational site.

8.2. Study Population and Setting

8.2.1. Inclusion Criteria

The study population will be comprise of:

1. HIV positive pregnant women aged 18 years and over on DTG,
2. With no maternal or birth outcomes yet,
3. Able and willing to provide written informed consent and comply with any safety reporting requirements.

8.2.2. Patient Identification and Consent

We aim to enrol 250 pregnant women from potentially 35 European sites; at least 200 of them with first trimester exposure to DTG, and the rest starting DTG during any trimester. Once all relevant approvals are in place, selected sites will be contacted and asked to identify any pregnant women currently on DTG pending pregnancy outcomes. Consent procedures will be undertaken as required as per protocol and by country specific regulations and local procedures. The participants will not have to attend any additional visits or undergo any additional procedures above their routine standard of care.

8.3. Variables

8.3.1. Exposure Definitions

Duration of exposure to DTG will be expressed in days e.g. 40 days.

- **Exposure on this study**: This is defined as the first day DTG is known to have been taken during pregnancy. A subject may have multiple exposures defined in cases where there is re-intiation of therapy after a period of stoppage during pregnancy; reason for stoppage will be collected.
- **Person time exposed**: This is defined as the number of days that the subject is known to have been exposed to DTG. This will further be categorized by days per trimester.

- Exposure will also be categorised by trimester of exposure for the first time during pregnancy -first trimester, second trimester and third trimester. First trimester exposures will further be stratified into a) conceived while on DTG and b) started DTG after conception.

NOTE: Initiation of pregnancy is measured as gestational age which is taken from the woman's last menstrual period, or the corresponding age of the gestation as estimated by a more accurate method such as ultrasound, if available.

8.3.2. Outcome Definitions

8.3.2.1. Primary Outcomes

a) The primary effectiveness parameters will be maternal VL at delivery and neonatal HIV status.
b) The primary safety parameters will be; spontaneous abortion, induced abortion, still births/live births/, premature births, low birth weight and prevalence of birth defects.

Pregnancy Outcome/ Birth 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
Extermely low birth weight	Birth weight of <1000 gms
Preterm birth	Birth of live infant at <37 weeks gestation
Severely 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 grams
Birth defects	To be classified according to the World Health Organization’s International Classification of Diseases, Tenth Revision

Table 1. Definitions of pregnancy outcomes.

8.3.2.2. Secondary Outcomes

a) All drug related AEs
b) All drug related SAEs
c) Virological failure and development of integrase resistance,
d) Incidence of discontinuation of DTG in pregnancy, reasons and VL at discontinuation
e) Where availale, VL during each of the three trimesters to assess suppression

8.3.3. Confounders

The effect of the following potential confounders on the risk for outcomes of interest will be examined:

- Prior or current AIDS defining illness and/or nadir CD4 count (<50, <200, >200 cells/mm3), if available,
- Concomitant medications (including ARVs and other medications that have been described to be associated with hypersensitivity reaction [HSR], skin reactions, or liver chemistry elevations [LCT] elevations),
- Co-morbidities,
- Race / ethnicity,
- Duration of DTG exposure during pregnancy,
- Trimester of DTG initiation,
- Treatment experience level, switch or naïve,
- Persistent VL during pregnancy,
- Number of prior pregnancies (gravida),
- History of prior abortions, premature births and low weight births,
- History of smoking, alcohol and drug use during pregnancy,
- History of TORCH (Toxoplasmosis, Other [syphilis, varicella-zoster, parvovirus B19], Rubella, Cytomegalovirus [CMV], and Herpes) infections during pregnancy,
- History of birth defects in previous births

8.4. Data Source

Data will be collected from all participating European sites. Following all relevant approvals, selected sites will be contacted and asked to identify any pregnant women currently on DTG and collect data prospectively for any new patients or patients who started on DTG with pending pregnancy outcomes. Data relevant to the study objectives will be abstracted from the patients medical records. The participants will not have to attend any additional visits or undergo any procedure above their routine standard of care. Pseudo anonymised data will be collected either by electronic transfer of datasets from each site. All data will be pseudo-anonymised. Sites will be regularly monitored for data quality and accuracy.

The following data will be collected if available for each participant and updated information included in the 3 monthly data transfer / using data collection systems. The data table is summarised in the flow chart in Appendix 1.

1. Baseline characteristics such as age, ethnicity, medical and social history, nadir CD4 , prior or current AIDs defining illness at time of starting pregnancy.
2. Date of starting pregnancy.
3. Date of starting DTG.
4. Latest data on CD4 count, VL, ARV drug history with dates, within 12 months prior to starting pregnancy, where available.
5. ARV drug history with dates of starting and reasons for stopping during pregnancy.
6. Co-morbidities and all co-medications.
7. Where available, HIV RNA and CD4 count data at time of enrollment and once every 3 months until delivery and also at time of starting DTG.
8. VL at DTG discontinuation during pregnancy, if applicable.
9. Resistance tests results of any HIV resistance tests performed during pregnancy.
10. All drug related AEs and SAEs: timing in pregnancy, incidence and severity.
11. Pregnancy outcomes including spontaneous abortion, induced abortion, still births, multiple births, live births, type of delivery (normal delivery, forceps delivery, or cesarian) and VL at delivery.
12. Birth outcomes including birth defects with date (to be reported in real-time to the Antiretroviral Pregnancy Registry) and other routinely collected data at birth such as gestational age, birth weight, APGAR score.
13. Postpartum CD4 count and VL.
14. HIV status of the newborn infant.

A pooled analysis (individual patient data) on birth outcomes (spontaneous and induced abortions, 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.

8.5. Study Size

This is a non-interventional, prospective, observational study where no formal samples size calculation is to be performed. The Antiretroviral Pregnancy Registry (APR) has estimated that based on the prevalence of birth defects in the general population, 200 first trimester exposures are needed to detect two fold increase in overall birth defect rate [7]. While this is specific to APR, EUROCAT [8] has reported similar or slightly higher birthdefect rates. Thus, it is anticipated that data from 250 participants with at least 200 first trimester exposed pregnancies, should provide sufficient information to meet the study objectives.

8.6. Data Management

8.6.1. Data Collection

8.6.1.1. Source Data

Source data are contained in source documents (original records or certified copies) maintained at site. No additional data will be collected for this study, data will be collected from routine standard of care data only.

8.6.1.2. Source Documents

Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial) will be maintained at site in accordance with usual standard of care.

The subject's number and date of entry into the study, along with a study identifier, should be recorded in the subject's study records.

8.6.1.3. Data Collection Methods

In order to maintain confidentiality, the subject will be identified only by subject number.

Subject data will be collected via extraction from electronic source data by appropriately trained and authorised member(s) of the study team who must be identified and authorised in writing by the Principal Investigator (PI). A delegation of responsibility log will be updated accordingly. Sites will provide / upload data every three months to the data management team who will store the data on a secure network drive with access to authorised personnel of the data management team only, maintained on a log of authorised personnel by the sponsor.

8.6.2. Data Handling Conventions

Data will be handled in accordance with data handling guidelines provided to sites.

The Study Monitor and Data Manager will review data on an on-going basis and raise any discrepancies with site staff as required.

Identified only by subject number, the data are pseudo-anonymised at all times and are transferred securely. All transfers are fully documented.

8.6.3. Resourcing Needs

The study will be overseen by NEAT ID with management, monitoring and data management activities subcontracted to St Stephens Clinical Research (SSCR). SSCR will assign a Project Manager to the study who will oversee the day to day activities of the trial and manage the mutidiscpliary project team.

ViiV, as sponsor will retain all repsonsibilities is relation to regulatory reporting.

8.6.4. Timings of Assessment during Follow-up

Available data will be collected from enrolled participants every 3 months and transferred to the data coordinating centre or updated into a study specific data capture system. Participant involvement in this study will end after the birth and pregnancy outcome data is collected.

8.7. Data Analysis

A detailed statistical analysis plan will be produced during the early stages of the clinical study, after protocol finalization. This statistical analysis plan will describe the rules used for classification of safety data, the primary and secondary analysis and the format of the final tables, figures and listings to be generated.

8.7.1. Essential Analysis

Descriptive report will be generated for the following:

- Characteristics,
- ARV history and concomitant medication,
- Co-morbidities,
- Trimester of DTG initiation and exposure,
- Drug related AEs and SAEs,
- Incidence of DTG discontinuation,
- VL in each trimester, at delivery and at DTG discontinuation,
- Maternal and child outcomes.

Analysis will be conducted to assess if there are any associations between DTG exposure and outcomes for pregnancy and birth. Logistic regression and Cox proportional-hazards models will be used. Potential confounding factors will be included in a step-wise approach to determine whether they change the odds ratio (OR) or the hazard ratio (HR) for DTG exposure by at least 10% in any of the models. Factors modifying the risk for DTG exposure by at least 10% in any of the models will be retained. Final models will be adjusted on the selected confounders.

8.8. Quality Control and Quality Assurance

Electronic data sets will provide an unmonitored subset of existing source data that will be subject to data validation. Site selection and training of site staff will ensure suitably qualified personnel are involved at every stage of the data gathering process. Data will be analysed by a Statistician skilled in population bases analysis using SAS, SPSS or STATA.

SSCR may decide to include this study in the annual audit schedule. The audit conduct and reporting will be preformed by the independent QA personnel and in accordance with Good Clinical Practice (GCP) and the applicable SSCR Standard Operating Procedures

8.9. Limitations of the Research Methods

Limitations of this study are common to non randomized observational studies. Selection bias may be present as the sites may elect to enroll participants that may have a better or worse health status compared to the general HIV positive pregnant population. Channeling bias in prescribing DTG may also be present.

8.9.1. Study Closure/ Uninterpretability of Results

Both the sponsor and the NEAT ID collaboration reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory agencies, Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). In terminating the study, sponsor and the investigator will assure that adequate consideration is given to the protection of the subjects'interests.

Following completion of the study, any study documentation will be retained by the Investigator in accordance with GCP and applicable regulatory requirements.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical Approval

Before the start of data collection, this protocol and any accompanying material to be provided to the patients (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted to Ethics Committee (EC) in the relevant countries. The investigator will not begin any study activities until approval from the EC has been documented and provided as a letter to the investigator.

Any subsequent amendments that require review by EC will not be implemented until the EC grants a Favourable Opinion for the study which will be disseminated to the investigators and sites (**NOTE**: that amendments may also need to be reviewed and accepted by the regulatory agencies and/or local EC departments before they can be implemented in practice at sites).

An annual progress report will be submitted to the EC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. NEAT ID will produce the annual reports as required.

NEAT ID will notify the EC of the end of the study. If the study is ended prematurely, the NEAT ID will notify the EC, including the reasons for the premature termination.

9.2. Subject Confidentiality

All investigators and trial site staff will comply with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Personal information is to be collected, kept secure, and maintained in line with the following requirements:

- the creation of coded, depersonalised data where the participant's identifying information is replaced by an unrelated sequence of characters.
- secure maintenance of the data and the linking code in separate locations using encrypted digital files within password protected folders and storage media.
- limiting access to the minimum number of individuals necessary for quality control, audit, and analysis.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

If during the study, a drug related adverse event (serious or non serious) is identified as being related to any ViiV Healthcare product, this will be reported to the GSK central safety department by email or fax. All drug related SAEs will be reported within 24 hours of first becoming aware of the event to the manufacturer, drug related non-serious AEs or incidents will be reported within 5 days of first becoming aware of the event.

Email for clinical safety mailbox: PPD

Fax (preferred): PPD

Since this is a study of DTG use in pregnancy and outcomes of pregnancy, there is no need to report incident exposures pregnancy as an AE to GSK but adverse pregnancy outcomes deemed related to a ViiV product will be reported.

All drug related serious and non-serious AEs, or incidents associated with any ViiV Healthcare product will be collected and reported as described in the study-specific pharmacovigilance plan (sPVP) and SAE reporting guidelines. This sPVP will include the following elements to ensure a comprehensive approach to safety event collection and reporting:

- Supplier/Vendor staff pharmacovigilance training (RAD-CDV-1281 - online training annually, on the collection and reporting of AEs through external version of myLearning).
- Investigator and site staff pharmacovigilance training (RAD-CDV-1281 - online training annually, on the collection and reporting of AEs through external version of myLearning).
- Safety-specific roles
- ADRs, SAEs, pregnancy outcomes, and incident collection and reporting processes
- Frequency of data review
- Reporting process and timelines
- Interim reports
- Reconciliation process
- Study-specific PVP monitoring process
- Provision of final study report

10.1. Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE does not include the following: • Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE. • Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)

	• Any medical condition or clinically significant laboratory abnormality with an onset date before baseline are considered to be preexisting conditions and should be documented as medical history.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between the drug and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the drug qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation unless hospitalization is for: o Routine treatment or monitoring of the studies indication, not associated with any deterioration in condition. o Elective or pre-planned treatment for pre-existing condition that is unrelated to the indication under study and has not worsened since the start of the study drug. o Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of SAE given above and not resulting in hospital admission. o Social reasons and respite care in the absence of any deterioration in the patient's general condition. • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect • Is medically significant, i.e. defines as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above. • All events of possible drug-induced liver injury with hyperbilirubinemia defined as ALT 3xULN and bilirubin 2xULN (>35% direct*) *Note: bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥2xULN, then the event is still reported as an SAE. INR elevations of >1.5 suggest severe liver injury. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.

"Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

10.2. Assessment of Adverse Events and Serious Adverse Events (SAE)

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and for final review and confirmation of accuracy of event information and assessments.

10.3. Assessment of Causality for Study Drugs

The relationship to study drug of each adverse event will be assessed taking into consideration the following:

- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator/subinvestigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The approved Product Information (SmPC) for marketed products should be used in consideration of this assessment

A causality assessment should be provided on all AE/SAE forms reported to ViiV/GSK.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Target Audience

The target audience includes healthcare providers, patient groups, regulatory and health authorities.

Interim and final study results will be presented annually at conferences such as but not limited to Conference on Retroviruses and Opportunistic Infections (CROI) and/or International AIDS Society (IAS), and followed by a publication in relevant peer-reviewed medical scientific journal and relevant newsletters.

11.2. Study Reporting and Publications

Within one year after the end of the study, NEAT ID will submit a final report with the results, including any publications/abstracts, to the EC.

12. REFERENCES

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13. APPENDICES

13.1. APPENDIX 1: DATA ASSESSMENT TABLE

Data Collected	Timepoints			
	Pre-pregnancy	**Pregnancy**	**Partum**	**Post-partum**
Informed Consent	Prior to collection of any data as per local requirements			
Age	X			
Ethnicity	X			
Country of birth (if available)	X			
Mode of HIV infection	X			
HIV medical history including: -Antiretroviral treatment history[1] -Nadir CD4 -HIV resistance test dates and results	X	X(ARV and resistance tests)		
Gynecological history (previous pregnancies and outcomes, methods of delivery, Cervical cancer surgical treatment)	X			
Health risk factors (i.e. Smoking, alcohol, psychoactive substance use (if intravenously or not))	X	X		
HIV diagnosis date/confirmatory test date	X			
Any prior or current AIDS defining illness	X			
AIDS diagnosis date	X			
CD4 count	X	X[3]		X[6]
HIV RNA test[4]	X	X	X	X[6]
Pregnancy diagnosis method & date		X		
Estimated date of delivery		X		
Concomitant medication (exc cART)	X	X		
Co-morbidities[2]	X	X		
TORCH infections		X		
Side effects/ toxicity		X		
*Pregnancy outcome - Date - Type of delivery: normal, forceps or cesarian - Spontaneous or induced abortion - Multiple births - Still or live birth(s) - Birth defects			X	
*Newborn data[5] - Gestational age - Birth weight - APGAR score - HIV status				X

*Essential data

Footnotes:

1. ARV history to include start date, stop date and reasons for discontinuation
2. Any chronic disease diagnosis before pregnancy (if possible year of diagnosis), other co-morbidities diagnosed before pregnancy (for example cervical dysplasia, NAD cancers, co-infections).
3. Ideal time points for this data: at pregnancy start, prior to starting DTG treatment, every 3 months during pregnancy
4. Additionally, HIV RNA data to be collected at time of DTG discontinuation
5. Within 6 months of birth
6. Within 3-12 months of giving birth

Point of DTG exposure to be calculated in-house

13.2. APPENDIX 2: DIVISION OF AIDS (DAIDS) TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS GRADING SCALE

division-of-aids-(daids)-table-for-grading-t