Division: Worldwide Development
Information Type: Worldwide Epidemiology Study Protocol

Title:	A Prospective Observational Cohort Study to Monitor and Compare the Occurrence of Hypersensitivity Reaction and Hepatotoxicity in Patients Receiving Dolutegravir (with and without Abacavir) or other Integrase Inhibitors (with or without Abacavir).

Compound Number:	GSK1349572
Development Phase	IV
Effective Date:	[DD-MMM-YYYY]

Subject: Dolutegravir vs. other Integrase Inhibitors, hypersensitivity reaction, hepatotoxicity

Author(s):

1. [redacted], MBBS, MPH, PhD; GlaxoSmithKline
2. [redacted], MA, BM BCh, MRCP; GlaxoSmithKline
3. [redacted]; EuroSIDA, statistician
4. [redacted]; EuroSIDA, Co-PI
5. [redacted]; EuroSIDA, Coordination
6. [redacted]; EuroSIDA Coordination
7. [redacted]; EuroSIDA, Senior statistician
8. [redacted], EuroSIDA; Co-PI
9. [redacted]; EuroSIDA, Senior Advisor
10. [redacted], MD, MS; GlaxoSmithKline

PASS information

Title	A Prospective Observational Cohort Study to Monitor and Compare the Occurrence of Hypersensitivity Reaction and Hepatotoxicity in Patients Receiving Dolutegravir (with or without Abacavir) or other Integrase Inhibitors (with or without Abacavir).
Protocol version identifier	v2.2
Date of last version of protocol	[DD Month YYYY]
EU PAS register number	Study not registered
Active substance	Dolutegravir, Dolutegravir/Abacavir sulfate/Lamivudine FDC, Raltegravir, and Elvitegravir
Medicinal product	Proposed invented name: TIVICAY and Proposed invented name: TRIUMEQ
Product reference	[Reference number(s) of centrally authorised products and/or, if possible, of nationally authorised products subject to the study]
Procedure number	TIVICAY: EMEA/H/C/002753/0000 TRIUMEQ: H0002754
Marketing authorisation holder(s)	ViiV Healthcare UK Limited
Joint PASS	No
Research question and objectives	Following initiation of one of the below antiretroviral regimens: a. Dolutegravir (as Triumeq™, the fixed dose combination of DTG/abacavir sulfate/lamivudine) or;

	b. Dolutegravir (Tivicay™) based antiretroviral regimen without abacavir or; c. Other Integrase Inhibitor (raltegravir or elvitegravir) in combination where abacavir sulfate sulfate is a component or; d. Other Integrase Inhibitor (raltegravir or elvitegravir) where abacavir sulfate is not a component the study will aim to: 1. Monitor and compare hypersensitivity reaction to: • Determine the incidence of HSR among DTG exposed treatment naïve and treatment experienced HIV patients with and without abacavir. • Determine the incidence of HSR among treatment naïve and treatment experienced HIV patients on other integrase inhibitors with and without abacavir. • Determine the risk factors for HSR among DTG exposed treatment naïve and treatment experienced HIV patients • Determine the risk factors for HSR among treatment naïve and treatment experienced patients on other integrase inhibitors with and without abacavir. • Collect blood samples from suspected HSR cases for future pharmacogenetic evaluation 2. Monitor for hepatotoxicity • To estimate the incidence of liver chemistry test elevations among DTG exposed treatment naïve and treatment experienced HIV patients with and without abacavir • To estimate the incidence of liver chemistry test elevations among treatment naïve and treatment experienced HIV patients exposed to other integrase inhibitors with and without abacavir

	• To estimate the incidence of cases of combined ALT and total bilirubin liver chemistry test elevations among DTG users with and without abacavir • To estimate the incidence of cases of combined ALT and total bilirubin liver chemistry test elevations among users of other integrase inhibitors with and without abacavir • To determine risk factors for liver chemistry test elevations amongst DTG-exposed treatment naïve and treatment experienced populations with and without abacavir • To determine risk factors for liver chemistry test elevations amongst treatment naïve and treatment experienced populations exposed to other integrase inhibitors with and without abacavir 3. Monitor for severe skin rash • To estimate the incidence of severe rash to the extent this is possible based on the data captured in the bi-annual data capture and a subsequent data collection form completed for all patients with a suspected clinical event in EuroSIDA (detail of follow-up forms in Appendix 1). The above monitoring will be done in accordance with the case definition and screening criteria as defined in protocol section 8.3.1.

Country(-ies) of study	Argentina, Austria, Belarus, Belgium, Bosnia & Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, , Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Ukraine, United Kingdom.
Author	[redacted], MBBS, MPH, PhD Worldwide Epidemiology, GSK R&D Five Moore Dr, 17.2131 Research Triangle Park, NC, 27709-3398, USA Tel: [redacted] Fax: [redacted]

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	ViiV Healthcare UK Limited 980 Great West Road Brentford Middlesex TW8 9GS United Kingdom
MAH contact person	Dr. [redacted] GlaxoSmithKline R&D Limited Stockley Park West Uxbridge Middlesex UB11 1BT United Kingdom

TABLE OF CONTENTS

PAGE

1. LIST OF ABBREVIATIONS

ABC	Abacavir sulfate
ACE	Angiotensin-converting Enzyme
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ART	Antiretroviral Therapy
ARV	Antiretroviral
AST	Aspartate aminotransferase
ATV	Atazanavir
cART	Combination Antiretroviral Therapy
CI	Confidence Interval
CPV	Capravirine
CRF	Clinical Report Form
ddC	Zalcitabine
ddI	Didanosine
DILI	Drug-induced liver injury
DLV	Delavirdine
DRV	Darunavir
DTG	Dolutegravir
d4T	Stavudine
eGFR	Estimated Glomerular Filtration Test
EFV	Efavirenz
EGV	Elvitegravir
EMA	European Medicines Agency
ERC	Event Review Committee
ETV	Etravirine
fAPV	Fosamprenavir
FDC	Fixed-dose combination
FTC	Emtricitabine
GI	Gastrointestinal
GSK	GlaxoSmithKline
GSS	Genotypic Susceptibility Score
GWAS	Genome-wide Association Scan
HbA1c	Glycated hemoglobin or glycosylated hemoglobin
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High-density lipoprotein
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HSR	Hypersensitivity Reaction
IDU	Injecting Drug User
IDV	Indinavir
II	Integrase Inhibitor
INR	International Normalized Ratio

INSTI	Integrase Strand Transfer Inhibitor
IQR	Interquartile Range
IRR	Incidence Rate Ratio
KM	Kaplan-Meier
LCT	Liver Chemistry Tests
LPV	Lopinavir
LVR	Loviride
MSM	Men who have sex with men
MVC	Maraviroc
NFV	Nelfinavir
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
OR	Odds Ratio
PASS	Post-authorization Safety Study
PGx	Pharmacogenetic
PI	Protease Inhibitor
PSA	Prostrate-specific antigen
PYFU	Person-years of follow-up
RAL	Raltegravir
RAM	Resistance-associated Mutation
RIL	Rilpivirine
RNA	Ribonucleic acid
RTV	Ritonavir
SCARS	Severe Cutaneous Adverse Reactions
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SNP	Single Nucleotide Polymorphism
SOP	Standard Operating Procedure
SQV	Saquinavir
TB	Mycobacterium Tuberculosis
TDF	Tenofovir
TEN	Toxic Epidermal Necrolysis
TPV	Tipranavir
T-20	Enfuvirtide
ULN	Upper limit of normal
VCV	Vicriviroc
ZDV	Zidovudine
3TC	Lamivudine
/r	Ritonavir-boosted

Trademark Information

Trademarks of the ViiV Healthcare group of companies	Trademarks not owned by the ViiV Healthcare group of companies
Kivexa	
Proposed invented name: TIVICAY	
Proposed invented name: TRIUMEQ	

2. RESPONSIBLE PARTIES: SPONSOR INFORMATION PAGE

MARKETING AUTHORISATION HOLDER

ViiV Healthcare UK Limited

Sponsor Legal Registered Address:

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

Sponsor Medical Monitor Contact Information:

[redacted], MD, MS
GlaxoSmithKline ID Discovery and Development
Five Moore Drive, 5.3743
Research Triangle Park,
NC, 27709-3398, USA
Phone: [redacted]
Mobile: [redacted]

Sponsor Serious Adverse Events (SAE) Contact Information:

Email for clinical safety mailbox = [redacted] (preferred)
Fax = [redacted]

Regulatory Agency Identifying Number(s): "Include all numbers that are applicable for the study and if available at the time the protocol is finalized (e.g. IND number, European Drug Regulatory Authorities Clinical Trials (EudraCT) Number, or Both

SPONSOR SIGNATORY:

[redacted] Primary Author/ Project officer	**Date**
[Name] VP, WorldWide Epidemiology	**Date**
[Name] Clinical VP, ViiV Healthcare	**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: [redacted] and [redacted]

Investigator Signature	Date
Investigator Signature	Date

3. ABSTRACT

Dolutegravir (DTG) is recommended for both treatment-naïve and treatment-experienced, HIV infected adults and paediatric patients aged 12 years and older and weighing at least 40 kg. One case of suspected DTG hypersensitivity (HSR) reaction from among over 1500 patients exposed to the drug at the time of submission in 4Q2012, has been identified; this subject experienced a diffuse maculopapular rash with fever and elevated liver enzymes. Isolated rash was uncommon in the DTG programme with less than 1% of clinical trial patients experienced treatment related rash. The pharmacovigilance strategy for DTG and DTG-containing products is to implement a post-marketing risk management program to further quantify the risk of HSR and compare it to that of other integrase inhibitors, and to possibly determine associated risk factors. In addition, the post-authorization safety study will monitor and compare hepatotoxicity and severe skin rash following initiation of DTG or other integrase inhibitor (raltegravir (RAL) or elvitegravir (EGV) based antiretroviral regimens. Further to be able to distinguish the above symptoms and reactions caused by DTG or the other integrase inhibitor regimen from that of abacavir (ABC), known to cause hypersensitivity reaction, the integrase inhibitor groups will be compared in combinations with and without ABC.

This five year-long safety study will be conducted through collaboration with EuroSIDA, a well established prospective observational cohort study of more than 18,200 patients followed in 107 hospitals in 31 European countries, plus Israel and Argentina.

This is a five year-long prospective cohort study nested within the EuroSIDA study. The study population will include HIV positive patients over the age of 16 years from EuroSIDA clinical sites, who are new users of DTG or other integrase inhibitors with and without ABC. Following initiation of DTG with ABC based antiretroviral regimen (DTG as Triumeq™, the fixed dose combination of DTG/ABC/lamivudine) or DTG without ABC (DTG as Tivicay™) or regimens containing other integrase inhibitors (RAL, EGV) with or without ABC, the study will aim to a) Monitor and compare hypersensitivity reaction, b) Monitor and compare hepatotoxicity, and c) Monitor and compare severe skin rash among all patients discontinuing DTG or other integrase inhibitor regimens for any reason.

4. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason

5. MILESTONES

Mile Stone	**Planned Date**
Draft Protocol Submission	August 2013
Study Start	June 2014 or Date DTG is commercially available, whichever is earlier
1st Annual Update	Draft report, Dec 2015 Revised final interim report with major comments addressed Jan 2016 (minor comments not interfering with report conclusions or interpretation to be included in next annual update)
2nd Annual Update	Draft report, Dec 2016 Revised final interim report with major comments addressed Jan 2017 (minor comments not interfering with report conclusions or interpretation to be included in next annual update)
Interim Report	Draft report Dec 2017 Revised final interim report with major comments addressed Jan 2018 (minor comments not interfering with report conclusions or interpretation to be included in next annual update)
3rd Annual Update	Draft report, Dec 2018 Revised final interim report with major comments addressed Jan 2019 (minor comments not interfering with report conclusions or interpretation to be included in next annual update)

Study Completion	June 2019 or 5 years following commercial availability of DTG
Final Report	April 2020 or 10 months after study completion (extended time to allow for bio specimen collection from suspected HSR cases, data analysis and final report writing).

6. BACKGROUND AND RATIONALE

Dolutegravir (Tivicay™) 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. It is recommended for both treatment-naïve and treatment-experienced, HIV infected adults and paediatric patients aged 12 years and older and weighing at least 40 kg. The usual recommended dose of dolutegravir is 50 mg (one tablet) once daily for patients infected with HIV-1 without resistance to the integrase class, and 50mg twice daily in patients infected with HIV-1 that has resistance to the integrase class.

One case of suspected Dolutegravir (DTG) hypersensitivity reaction (HSR) from among over 1500 patients exposed to the drug at the time of submission in 4Q2012, has been identified; this subject experienced a diffuse maculopapular rash with fever and elevated liver enzymes. Isolated rash was uncommon in the DTG programme - less than 1% of clinical trial patients also experienced treatment related rash. The warnings and precautions section of draft label (pending regulatory approval) for DTG includes the following information about hypersensitivity reactions *"Hypersensitivity reactions have been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. The events were reported in 1% or fewer subjects receiving TIVICAY in Phase 3 clinical trials. Discontinue TIVICAY and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema). Clinical status, including liver aminotransferases, should be monitored and appropriate therapy initiated. Delay in stopping treatment with TIVICAY or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction. TIVICAY should not be used in patients who have experienced a previous hypersensitivity reaction to TIVICAY"*.

The pharmacovigilance strategy for DTG and DTG-containing products is to implement a post-marketing risk management program to further quantify the risk of HSR, and to possibly determine associated risk factors. In addition, the post-authorization safety study (PASS) will monitor for hepatotoxicity and severe skin rash following initiation of DTG based antiretroviral (ARV) regimens with or without ABC and compare to that of other integrase inhibitors (RAL or EGV) with or without ABC.

This safety study will be conducted through collaboration with EuroSIDA, a well established, prospective observational cohort study of more than 18,200 patients followed in 107 hospitals in 31 European countries, plus Israel and Argentina. The study protocol as detailed below will be implemented by the EuroSIDA coordinating center.

7. RESEARCH QUESTION AND OBJECTIVES

Following initiation of one of the below regimens:

A. DTG [as Triumeq™, the fixed dose combination of DTG/ABC/lamivudine (3TC)] based antiretroviral regimen, or;
B. DTG [as Tivicay™] based regimen without ABC, or;
C. Other integrase inhibitor based regimens (RAL, EGV) with ABC, or;
D. Other integrase inhibitor regimens without ABC

the study will aim to:

1. Monitor and compare hypersensitivity reaction
    - Determine the incidence of discontinuation of DTG or other integrase inhibitor regimens (with or without ABC) due to HSR among exposed treatment naïve and treatment experienced HIV patients
    - Determine the risk factors for discontinuation of DTG or other integrase inhibitor regimens (with or without ABC) due to HSR among exposed treatment naïve and treatment experienced HIV patients
    - Collect blood samples from suspected HSR cases for future pharmacogenetic evaluation

2. Monitor for hepatotoxicity
    - To estimate the incidence of discontinuation of DTG or other integrase inhibitors (with or without ABC) due to liver chemistry test elevations among exposed treatment naïve and treatment experienced HIV patients
    - To estimate the incidence of cases of combined alanine aminotransferase (ALT) and total bilirubin liver chemistry test elevations among DTG users or users of other integrase inhibitors (with or without ABC)
    - To determine risk factors for liver chemistry test elevations amongst patients exposed to DTG or other integrase inhibitors (with or without ABC) for both treatment naïve and treatment experienced populations

3. Monitor for severe skin rash.
    a. To estimate the incidence of discontinuation of DTG or other integrase inhibitors (with and without ABC) due to severe rash to the extent this is possible based on the data captured in the bi-annual data capture and a subsequent data collection form completed for all patients with a suspected clinical event in EuroSIDA (detail of follow-up forms in Appendix 1).

For study aims 1, 2 and 3 the following groups will be used to compare event rates and risk factors

A. Patients that start DTG and ABC based ARV regimen
B. Patients that start DTG based ARV regimen but without ABC
C. Patients that start other integrase inhibitor based regimen (RAL and EGV) and with ABC.

D. Patients that start other integrase inhibitor based regimen (RAL and EGV) but without ABC.

The above monitoring will be done in accordance with the case definition and screening criteria as defined in protocol section 8.3.1.

8. RESEARCH METHODS

8.1. Study Design

This is a five year-long prospective cohort study nested within the EuroSIDA study. Potential HSR and hepatotoxicity cases will be identified among those discontinuing DTG or other integrase inhibitor regimens in EuroSIDA's dynamic database of medical information. The study design and analysis follows that of previously published work looking at hypersensitivity reactions in those persons exposed to ABC [Bannister et al. 2008]. Based on data routinely captured in EuroSIDA in accordance with the currently approved general EuroSIDA protocol, potential HSR and hepatotoxicity cases will be identified as described in this PASS protocol. In order to collect data beyond the routine data capture, this PASS protocol will be submitted for local Ethical approval at EuroSIDA sites where the potential HSR or hepatotoxicity patients are located. After Ethical clearance, clinics with potential cases will perform informed consent for additional data and blood sample collection. A specific data collection form has been developed for ascertainment of HSR and hepatotoxicity case data, see Appendix 2.

For this non-interventional study, treatment decisions will be made by the treating physician according to standard practice, taking into account the treatment history, patient characteristics and local guideline or recommendations. Dosage of DTG will be selected by the treating physician.

8.2. Data sources

Study Population: The study population will include HIV positive patients over the age of 16 years from EuroSIDA clinical sites, who are new users of DTG or users of other integrase inhibitor regimens (RAL and EGV).

HSR events will be monitored among all those who discontinue DTG or other integrase inhibitor for any reason in the following subgroups of patients:

A. Patients that start DTG and ABC based ARV regimen
B. Patients that start DTG based ARV regimen but without ABC
C. Patients that start other integrase inhibitor based regimen (RAL and EGV) and with ABC.
D. Patients that start other integrase inhibitor based regimen (RAL and EGV), but without ABC.

The above monitoring will be done in accordance with the case definition and screening criteria as defined in protocol section 8.3.1.

EuroSIDA Cohort description: The EuroSIDA study was initiated in 1994, and is a prospective observational cohort study of more than 18,200 patients followed in 107 hospitals in 34 European countries, plus Israel and Argentina. The main objective of the study is to assess the impact of antiretroviral drugs on the outcome of the general population of HIV-positive patients living in Europe.

In EuroSIDA, the biannual data collection is performed directly from clinics on individuals using comprehensive standardized clinical record forms. For each patient, the date of starting and stopping each antiretroviral drug is recorded, as is the use of drugs for prophylaxis against opportunistic infections. Dates of diagnosis of all AIDS defining diseases are recorded, using the 1993 clinical definition of AIDS from the Centers for Disease Control and Prevention. Members of the coordinating office visit all centers to ensure correct patient selection and that accurate data were provided.

Data Collection: Following the European Medicines Agency (EMA) approval of DTG, the study will collect prospective data on patients treated with DTG [as Tivicay or DTG/ABC/3TC fixed-dose combination (FDC)] based ARV regimen as well as prospective data on patients on other integrase inhibitors with or without ABC over the course of 5 years. The coordinating center receives data from the clinical sites biannually.

- All suspected HSR cases will be identified through screening criteria described below, and review of potential data clarification items collected at a specific HSR event form (see Annex 3); screen-positive cases will be reviewed by an independent adjudication committee for final determination of drug-associated causality

- Causality assessment for hepatotoxicity will be done by the independent adjudication committee.

Following ethical clearance of this PASS protocol at the sites where the potential cases are located, the participant will be asked for informed consent to obtain whole blood samples for potential future pharmacogenetic analysis. The coordinating centre will work with the clinical site, using this PASS protocol and informed consent to enable the collection of this blood sample. The collection of whole blood samples will thus occur only from subjects who have suspected HSR events, and only after ethics approval and patient consent have been obtained. In cases where the pharmacogenetic sample collection is not approved, the patient does not consent, or the patient has died or is lost-to-follow-up, whole blood samples would not be available for analysis.

8.3. Variables

8.3.1. Outcome definitions:

HSR case definition: All patients discontinuing DTG or other integrase inhibitor regimens (RAL and EGV) for any reason will be assessed for potential HSR. Each patient that discontinues DTG (or other integrase inhibitor regimens (RAL and EGV))

will have an additional HSR specific data clarification form completed by the site regarding the circumstances surrounding discontinuation. The specific HSR data form displayed in Appendix 2 incorporate existing information within the database as well as the necessary data items to allow determination of whether the discontinuation was due to HSR (see case definition below). A grading scale is applied (definite, probable etc). The specific HSR forms will be reviewed by an independent adjudication committee for final determination of drug-associated causality.

In the standard follow-up data collection in EuroSIDA reasons for discontinuation are recorded as

1: Treatment failure (i.e. virological, immunological and/or clinical failure)
2: Abnormal fat redistribution
3: Concern of cardiovascular disease
3.1: Dyslipidaemia
3.2: Cardiovascular disease
4: Hypersensitivity reaction
5: Toxicity, predominantly from abdomen/gastrointestinal (GI) tract
5.1: Toxicity - GI tract
5.2: Toxicity - Liver
5.3: Toxicity - Pancreas
6: Toxicity, predominantly from nervous system
7: Toxicity, predominantly from kidneys
8: Toxicity, predominantly from the endocrine system
8.1: Diabetes
9: Haematological toxicity
10: Hyperlactataemia/ lactic acidosis
90: Toxicity, not mentioned above
91: Patient's wish/decision, not specified above
92: Physician's decision, not specified above
93: STI - Structured Treatment Interruption
94: Other causes, not specified above
94.1: Out of stock
99: Unknown

Apart from HIV and hepatitis virology/serology and ART therapy data, the following laboratory biomarkers are collected, on average, every 6 months, if measured in the individual patient.

- Urine dipstick for proteinuria, 24h total urine protein, urine-protein-creatinine (or separate protein and creatinine) ratio, 24h total urine albumin (or urine-albumin-creatinine (or separate albumin and creatinine) ratio.

- Most recently measures S-total cholesterol, S- high-density lipoprotein (HDL) cholesterol, S-triglycerides, glycated hemoglobin or glycosylated hemoglobin (HbA1c), Peak glucose, All serum creatinine measurements, Haemoglobin, Platelet count, Albumin, ALT, aspartate aminotransferase (AST), International Normalized Ratio (INR), Bilirubin, Alkaline phosphatase, Parathyroid hormone, Prostate-specific antigen (PSA), Peak serumamylase.

In addition, the data on opportunistic diseases and drugs used to treat them are captured.

- Opportunistic Infections

DEM: AIDS dementia complex
BCNE: Bacterial pneumonia, recurrent (>2 episodes within 1 year)
CANO: Candidiasis, oesophageal
CRCO: Cryptococcosis, extrapulm.
CRSP: Cryptosporidosis (duration > 1 month)
CMVR: Cytomegalovirus (CMV) chorioretinitis
CMVO: CMV - other location, specify
HERP: Herpes simplex virus ulcers (duration >1 month) or pneumonitis/ esophagitis
HIST: Histoplasmosis, extrapulm.
WAST: HIV wasting syndrome
ISDI: Isosporiasis diarrhoea (duration >1 month)
LEIS: Leishmaniasis, visceral
MCDI: Microsporidosis diarrhoea (duration >1 month)
MC: Mycobact. avium complex (MAC) or Kansasii, extrapulm.
MCP: Mycobact. tuberculosis, pulm.
MCX: Mycobact. tuberculosis, extrapulm.
MCPO: Mycobact. pulm., other type, specify
MCXO: Mycobact. extrapulm., other type, specify
PCP: Pneumocystis jiroveci pneumonia (PCP)
LEU: Progressive multifocal leucoencephalopathy
SAM: Salmonella bacteriaemia (non-typhoid) (>2 episodes)
TOX: Toxoplasmosis, brain
FBLS: Focal brain lesion

- Drugs for OI treatment -

<u>CMV/HSV drugs</u>
CIDO: Cidofovir
CONA: Continous Acyclovir
CONF: Continous Famciclovir
CONV: Continous Valaciclovir
GANC: (Val-)Ganciclovir
FOSC: Foscarnet
<u>Fungal drugs</u>
AMPH: Amphotericin B, i.v.
CASP: Caspofungin
FLUC: Fluconazole
ITRA: Itraconazole
KETO: Ketoconazole
VORI: Voriconazole
<u>HBV drugs</u>
ADEF: Adefovir dipivoxil
ENTE: Entecavir
TELB: Telbivudine

HCV drugs
DACV: Daclatasvir (BMS-790052)
BOCE: Boceprevir
FALV: BI 201335 (Faldaprevir)
PINT: Peg-Interferon
RIBA: Ribavirin
SIMV: TMC-435 (Simeprevir)
TELA: Telaprevir
Immunomodulating therapy
IL2: Interleukin 2
GCSF: G-CSF
INTF: Interferon
PINT: Peg-Interferon
Mycobacterium drugs
CLAR: Clarithromycin/azithromycin
ETHA: Ethambutole
ISON: Isoniazide
PYRA: Pyrazinamide
RIFA: Rifabutine
RIFM: Rifampicine
STRE: Streptomycin
TMC: TMC-207/R207910
PCP/TOXO drugs
ATOV: Atovaquone
BACT: Bactrim (cotrimoxazole)
CLIN: Clindamycin
DAPS: Dapsone
PENT: Pentamidine neb./inj.
PYRI: Pyrimethamine
SULP: Sulphadiazine

A wide variety of other information is captured, including cardiovascular risk modification treatment, start and stop dates -

- Anabolic steroids/appetite stimulants, ACE inhibitors, Other antihypertensive agents, Anti platelets, Insulin or derivatives hereof, Oral anti-diabetic agents, Lipid lowering agents including Statins, Fibrates, and Other/unspecified,

Flu like illness -

- Flu like illness, Influenza A/B, Hospitalised due to severe complications to flu like illness,

Other severe infections requiring hospitalisation -

- Bacteremia, Pneumonia, Meningitis, Peritonitis, Endocarditis, Ostitis, Pyelonephritis or specific full name of any other severe infections,

Clinical events -

- Cardiovascular events: Carotic endarterectomy, Coronary angioplasty/stenting, Coronary artery by-pass grafting, Myocardial infarction, Stroke,

- Metabolic events: Diabetes Mellitus, Lipodystrophy,

- Other organ events: Avascular necrosis in the femural head, Bone fracture, Pancreatitis, End Stage Renal disease, End Stage Liver Disease -

    - For hepatic disease in addition, possible biopsy, fibroscan and signs of hepatic decompensation (Ascites, Hepatorenal syndrome, Spontaneous bacterial peritonitis, Hepatic encephalopathy grade 3 or 4, Oesophageal variceal bleeding)

- Acquired immunodeficiency syndrome (AIDS) defining cancers, date of diagnosis and certainty of diagnosis (definitive, presumptive, autopsy) -

    - Kaposi´s sarcoma, Cervical cancer, Non-Hodgkin lymphoma: (Burkitt (Classical or Atypical), Diffuse large B-cell lymphoma (Immunoblastic or Centroblastic), Primary brain lymphoma (at diagnosis, involvement of the central nervous system without other organ affection - regardless of histology), Unknown/other histology,

- Non-AIDS defining cancers, date of diagnosis and certainty of diagnose (definitive, presumptive, autopsy) -

  ANAL: Anal cancer
  BLAD: Bladder cancer
  BRCA: Breast cancer
  CERV: Cervical dysplasia/carcinoma in situ
  COLO: Colon cancer
  COTC: Connective tissue cancer
  ESOP: Esophagus cancer
  HDL: Hodgkin lymphoma
  GALL: Gallbladder cancer
  KIDN: Kidney cancer
  Leukemia:
  ALL: Acute lymphoid
  AML: Acute myeloid
  CLL: Chronic lymphoid
  CML: Chronic myeloid
  LIPC: Lip cancer
  LIVR: Liver cancer (hepatocellular carcinoma)
  LUNG: Lung cancer
  MALM: Malignant melanoma
  MULM: Multiple myeloma
  Metastasis:

MESC: of squamuos cell carcinoma
MEAC: of adenocarcinoma
MEOC: of other caarcinoma
PANC: Pancreas cance
PENC: Penile cancer
PROS: Prostate cance
RECT: Rectum cancer
STOM: Stomach cance
TESE: Testicular sem
UTER: Uterus cancer

- For fatal cases, the presumed illness causing the terminal condition:
    - Myocardial Infarction, Stroke, Other cardiovascular disease, Symptoms caused by mitochondrial toxicity, Lactic Acidosis, Complications to diabetes mellitus, Pancreatitis, Liver failure, Hepatitis related, Liver failure not related to hepatitis or mitochondrial toxicity, HIV-related, AIDS defining event, Invasive bacterial infection, Non-AIDS malignancy, Renal Failure, Suicide, Drug overdose, Other, specify:, Unknown-.

Identifying HSR cases

Utilising the available data elements described above collected in the 6-monthly EuroSIDA follow-up data collection, the potential cases will be identified as follows:

A potential case of DTG or other integrase inhibitor HSR is one in which DTG or another integrase inhibitor is discontinued due to Hypersensitivity / anaphylactic reaction / allergic reaction / drug allergy related to DTG or another integrase inhibitor.

OR

DTG or another integrase inhibitor is discontinued due to other causes, including unknown or unspecified causes (in order to be certain to capture all potential cases of DTG or other integrase inhibitor HSR).

For potential HSR cases, HSR event forms (see Annex 3) to clarify the circumstances around the HSR event will be collected to clarify the case and allow an adjudication process by the independent case review committee. A charter for the review procedure, selection and rotation of members is included in Annex 4.

In addition, the clinical report form (CRF) will collect the following clarifying event data related to the case of HSR:

- Fever
- Rash criteria
- Gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain)
- Constitutional symptoms (lethargy, fatigue, malaise, myalgia, arthralgia, general ill feeling)
- Respiratory symptoms (dyspnoea, sore throat, cough, chest X-ray changes, predominantly infiltrates, which can be localised).
- Eosinophilia
- Drug causality relation

Case Definition for HSR: The independent review committee establishes a case of DTG or other integrase inhibitor HSR as one in which conditions in ***A*** or ***B*** are fulfilled and where the exclusion criteria do not apply.

A. Hypersensitivity / anaphylactic reaction / allergic reaction / drug allergy to DTG or another integrase inhibitor is reported.

OR

B. Two or more events are reported from two or more of the following groups of signs/symptoms:
    a. rash
    b. fever
    c. gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain)
    d. constitutional symptoms (lethargy, fatigue, malaise, myalgia, arthralgia, general ill feeling)

e. respiratory symptoms (dyspnoea, sore throat, cough, chest X-ray changes, predominantly infiltrates, which can be localised).
f. eosinophilia
g. hepatic dysfunction as indicated by liver chemistry tests (LCT) will include the following, with a focus on alanine aminotransferase elevations and total bilirubin elevations:

    i. ALT elevations (ALT is also called serum glutamic pyruvic transaminase (SGPT))
    ii. AST elevations (AST is also called serum glutamic oxaloacetic transaminase (SGOT))
    iii. Alkaline phosphatase (ALP) elevations
    iv. Total bilirubin elevations
    v. Albumin

Definite DTG-related HSR or definite HSR related to another integrase inhibitor will be defined as category A with a reasonable possibility of causal relationship with DTG or another integrase inhibitor treatment. Possible DTG-related HSR and possible HSR related to other integrase inhibitors will be defined as two or more events in two or more of categories B.a. to B.g. and with a reasonable possibility of causal relationship with DTG treatment.

Hepatotoxicity

The above mentioned 6-monthly data collected routinely in EuroSIDA will be used to identify potential cases of possible drug-induced liver injury (DILI). Possible data clarification items will be addressed in the HSR specific event form (Appendix 2).

Clinical chemistry criteria for possible drug-induced liver injury (DILI) will include any one of the below, under the assumption that a reasonable possibility of causal relationship with DTG or another integrase inhibitor is established by the independent review committee.

- More than or equal to fivefold elevation above the upper limit of normal (ULN) for ALT*
- More than or equal to threefold elevation in ALT concentration and simultaneous elevation of total bilirubin concentration exceeding 2× ULN

* -As EuroSIDA currently does not store ULN for all involved sites, before the protocol implementation all EuroSIDA sites will be surveyed to obtain or update ULN information.

If the patient has had previous liver injury and hence abnormal LCT at any time prior to starting DTG or other integrase inhibitor, the cases will highlighted for special cautious evaluation of drug relatedness by the independent case review committee.

Skin rash

Clarifying case data on severe skin rash will be based on data collected on the HSR CRF using the Division of AIDS AE toxicity grading scale (December, 2004) & grade 3 and 4 skin rashes will be monitored.

Parameter	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-Threatening)
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)

The validity of data on treatment regimens and drug discontinuation in EuroSIDA is very good since it is reported directly by the clinic using clinical report forms. All discontinuation cases will be reviewed for potential DTG or other integrase inhibitor HSR and further detailed data captured in the HSR CRF, which will give HSR and skin rash data which are more valid than usually seen in observational studies.

8.3.2. Exposure definitions

Any exposure to DTG, other integrase inhibitors or DTG or other integrase inhibitor containing products is of interest. The recommended dose of dolutegravir is 50 mg (one tablet) once daily for patients infected with HIV-1 without resistance to the integrase class, and 50mg twice daily for pateints infected with HIV with resistance to INSTIs.

8.3.3. Confounders and effect modifiers

Confounding by indication in observational data is a significant issue. This arises whereby persons are chosen to start in any of the treatment groups for reasons that are either unknown or unmeasured within the study, and which cannot therefore be adjusted for as confounders in analyses. The statistical analysis will present a detailed overview of the characteristics of patients starting the treatments in question in different groups to assess bias, and adjust for confounders and effect modifiers wherever possible. However, results from observational studies should always be interpreted with caution due to the potential for confounding.

We plan to examine the effect of the following potential confounders and effect modifiers on the risk for outcomes of interest:

- ARV status (ARV naïve, treatment experienced)
- Prior AIDS defining illness and/or nadir CD4 count (<50, <200, >200 cells/mm3)
- Concomitant medications (including ARVs and other medications that have been described to be associated with HSR, skin reactions, or LCT elevations)
- HBV and/or HCV co-infection

- HIV risk factor
- Race / ethnicity

8.4. Study size (sample size or power calculations)

Sample size: Sample size will depend on the market uptake of DTG following its commercial availability in European countries. The Table below provides estimates of adverse event rates and number of patients followed, yielding person-years of exposure (PYFU) to DTG. Approximately 10,000 patients are currently under active follow-up in EuroSIDA and contribute approximately 4500 PYFU every 6 months.

Person-years follow-up	Incidence of AE/1000 PYFU	N Events
250	0.5	0
	1.0	0
	10.0	2
1000	0.5	0
	1.0	1
	10.0	10
10000	0.5	5
	1.0	10
	10.0	100

8.5. Data management

Data collection, submission, clarification, keying and quality assurance follows the Standard Operative Procedures for EuroSIDA (Instructions for follow-up, Information on plasma collection, Sample list, List of diagnoses used in study , List of clinical definitions used in study, EuroSIDA SOP for data transfer, EuroSIDA QA checks for data transfer, HICDEP - HIV Collaboration Data Exchange Protocol) (see http://www.cphiv.dk/EuroSIDA/StudyDocuments/tabid/140/Default.aspx) as well as the Copenhagen HIV Programme Quality Management Plan.

8.5.1. Data handling conventions

Data handing follows the HICDEP - HIV Collaboration Data Exchange Protocol for data submitted electronically. Data submitted on paper based forms are handled according to above mentioned standard operating procedures (SOPs) (http://www.cphiv.dk/EuroSIDA/StudyDocuments/tabid/140/Default.aspx).

In addition, all data is fully anonymised before transfer to Copenhagen and is held securely. Data is transferred to the statistical team in London via secure download and password encrypted file twice yearly. The data is held on password secured computers in

London. EuroSIDA have the relevant data protection clearance, Data Protection Agency No: 2012-54-0035

8.5.2. Timings of Assessment during follow-up

All sites complete the follow-up forms within a two month period, after which the forms are sent to the coordinating centre for data entry. An updated version of the database is usually available 3 months later, allowing the study to provide data on the patients followed up to approximately 6-12 months prior to the close of the database. In addition, a plasma sample is requested on all patients every six months.

8.6. Data analysis

Inclusion criterion: HIV positive persons enrolled in the EuroSIDA study over the age of 16 years who initiate DTG or other integrase inhibitors during prospective follow-up in EuroSIDA.

Primary toxicity events will be monitored among all patients who discontinue DTG* or another integrase inhibitor for any reason in 4 subgroups of patients:

The following groups will be used to compare event rates and risk factors

A. Patients that start DTG and ABC based ARV regimen
B. Patients that start DTG based ARV regimen but without ABC
C. Patients that start other integrase inhibitor based regimen (RAL and EGV) and with ABC.
D. Patients that start other integrase inhibitor based regimen (RAL and EVG), but without ABC.

*Cross-resistance studies with RAL- and EGV-resistant viruses in vitro indicate that mutations Q148H and G140S in combination with mutations L74I/M, E92Q, T97A, E138A/K, G140A,or N155H are associated with 5-fold to 20-fold reduced DTG susceptibility and reduced chance of virological suppression in patients. People in whom at least one among Q148H/K/R, E138A/K, G140S/A were detected will be defined as having reduced susceptibility to DTG [Johnson et al.2013]. EuroSIDA has previously published a study considering the incidence of and factors associated with hypersensitivity in persons exposed to ABC [Bannister et al. 2008], and the data analysis will broadly follow that of this previous work.

Primary objectives

- To describe characteristics of all persons starting DTG or other integrase inhibitors (RAL and EGV) and
- To describe the incidence of and characteristics of those who develop
    - HSR
    - Hepatotoxicity
    - Severe skin rash,

  which lead to treatment discontinuation as defined within the study protocol

Statistical analysis

A DTG (or other integrase inhibitor)-based regimen will be a regimen consisting of at least 3 ARVs combined from any class, of which at least one is DTG (or other integrase inhibitor).

New users of DTG (or other integrase inhibiotrs RAL and EGV) will be characterized at baseline, defined as initiation of DTG (or other integrase inhibitors) based ARV regimen as specified above, stratified into the four treatment groups (A-D). Descriptive statistics will be used to describe the patient characteristics of the 4 treatment groups. Baseline in all groups will be defined as the date of starting the DTG (or other integrase inhibitor). Patients will not be eligible to join treatment groups C-D (ie the comparator groups containing EGV or RAL) until after the proposed start date of these analyses when DTG is routinely available to ensure the comparison group has contemporary patients.

Demographic characteristics include age, gender (male or female), race (white or other), HIV exposure group (MSM, IDU, heterosexual or other) and region of Europe (South, Central, West, East and Argentina), smoking status (current, former, never or unknown). Clinical history will be summarised in terms of baseline CD4 count, viral load, haemoglobin, weight, duration of HIV-infection, eGFR (calculated using CKD-EPI), hepatitis B and C coinfection, prior AIDS or non-AIDS events (including a description of which events have occurred and proximity to baseline), diabetes, hypertension[Mocroft et al. 2010], ALT, AST, CD4 count nadir, and peak viral load. The proportion of follow-up time in EuroSIDA with immunosuppression (defined as a CD4 count $\leq 200/mm^3$) or with uncontrolled viremia (HIV RNA VL > 400 copies.ml) can also be summarised. ARV history will be summarised including the proportion of patients within each treatment group who are treatment naïve, class and number of ARVs previously exposed to, a summary of prior exposure to integrase inhibitors and prior duration of exposure to all ARVs.

Where available, baseline ARV resistance can be summarised. The prevalence of IAS USA resistance mutations in the three major classes (NRTI, NNRTI and PI) as well as integrase resistance mutations (including INSTI mutations) will be calculated and described. IAS USA integrase mutations currently include: T66/I/A/K, L74M, E92Q/G, T97A, E138A/K G140A/S, Y143R/H/C, S147G, Q148H/K/R, N155H. The number of predicted active drugs included in the initiated DTG-containing regimen (or other integrase inhibitors EGV and RAL) will be estimated using the HIVdB genotypic susceptibility score (GSS).

Logistic regression will be used to compare those starting a DTG-based regimen (treatment groups A-B) with those starting another integrase inhibitor (Groups C-D), and depending on the exact combinations of regimens used, to compare those starting DTG with or without ABC (treatment group A versus B) and those starting other integrase inhibitors with or without ABC (treatment groups C versus D). Such analyses will include baseline demographics and whether the patients are antiretroviral naïve. Patient characteristics at the time of primary event will be described and compared to those of patients who do not develop the endpoint, at last clinic visit, as well as to those who discontinue for reasons other than HSR. They will be compared between DTG treatment groups with and without ABC as well as between the comparator arm in patients not

exposed to DTG but exposed to integrase inhibitors. The analyses will also compare those who are antiretroviral naïve at starting each regimen with those who are antiretroviral experienced. The CRF will collect information on dose of DTG or other integrase inhibitor which will enable a descriptive analysis of whether those taking higher doses are more likely to discontinue for HSR compared to other reasons for discontinuation.

Time to event Kaplan-Meier (KM) estimates will describe the cumulative incidence of the primary endpoint. Incidence rates will summarize the incidence of the primary endpoint. Primary analyses will be on-treatment and persons will be followed-up from baseline until discontinuation of DTG (or other integrase inhibitor), last study visit or event, whichever occurs first. . Time to events and incidence rates will be compared between treatment groups.

Multivariable Poisson regression will be used to determine factors associated with the primary endpoint when the number of cases exceeds 30 in both treatment groups A-B combined and C-D combined (ie allowing a primary comparison between any DTG-based regimen and any other integrase based regimen, with our without ABC); confounding and effect modifying factors that are significant in univariate analyses ($p<0.1$) will be included in multivariate models, as well as treatment group and whether the patients were antiretroviral naïve at starting the regimen Excluded variables will be added in turn to determine if their inclusion improves the fit of the model (defined as a significant reduction in the Log-Likelihood).

Each patient can be included in more than one treatment group over time depending on their exposure to DTG or other integrase inhibitors and ABC. For example, a patient could start RAL without ABC and would be included in group D. A change to the regimen to include ABC would move him to group C. A switch to DTG but remaining on ABC would then include the person in group A. Person years of follow-up will accumulate in the relevant treatment group A-D and statistical analyses will adjust for the within patient correlation. Patients may also experience more than 1 event of interest, and in primary analyses each event would be allocated to the treatment group the event occurred in.

Sensitivity analyses

Primary events will be graded by independent adjudicators as definitive or possible, and analyses will be repeated considering only definitive events.

HSR and hepatotoxicity are potentially serious adverse events directly related to drug administration and are unlikely to develop after long term exposure to DTG (or other integrase inhibitors) or after DTG (or other integrase inhibitors) are stopped. As such, including patients who are exposed to more than one integrase inhibitor and in more than 1 treatment group should not create significant bias. However, sensitivity analyses can be used to assess the robustness of the results when each patient is only included in the first treatment group they are eligible to join. Similarly, rather than censoring at stopping DTG (or other integrase inhibitor), patients can be assumed to stay on the drug for an

additional 4 weeks (lag-time analysis), to ensure that any primary events occurring shortly after discontinuation are included. In this specific lag-time analyses, if patients have switched from one treatment group to another, the event will be assumed to have occurred in the first treatment group.

Completeness of data

Not all variables within EuroSIDA are complete for all persons; missing data is rarely missing at random from observational cohort studies. Data may be categorized, including a category for missing, persons may be completely excluded with missing data, or imputation can be used. None of these approaches is likely to be unbiased, but with a small number of primary endpoints anticipated, excluding those with missing data would not be a reasonable approach to analysis.

8.7. Quality control

Quality control follows the EuroSIDA SOP, EuroSIDA QA checks for data transfer (v1.01) (http://www.cphiv.dk/EuroSIDA/StudyDocuments/tabid/140/Default.aspx) as well as the Copenhagen HIV Programme Quality Management Plan and related SOPs.

8.8. Limitations of the research methods

Because the CRF for full assessment of HSR, serious skin rash, and hepatotoxicity will be completed after the event has occurred (and whole blood sample collection will also be undertaken retrospectively), the completeness of data will vary within centers. While every effort to maximize data collection will be made, data are more likely to be missing from some patient groups compared to others (e.g., from IDUs, or centres within Eastern Europe). Any analysis of the data shall include consideration of the representativeness of the included patients as well as those with missing data.

However, routinely collected data (including treatment status, co-infections, concomitant medication, gender/race/ethnicity, etc) will usually be available for analysis for all patients in order to determine patient characteristic risk factors for the outcomes of interest.

Enrolment of consecutive participants in each of the EuroSIDA cohorts reduces selection bias and uniform criteria for monitoring are applied to all sites.

The majority of the patients included in EuroSIDA are antiretroviral experienced at enrolment to the study (approximately 80% of those on treatment), and this study will not be adequately powered to compare antiretroviral naïve to experienced within treatment groups A-D described above. The statistical analyses will provide a summary and comparison of those who are antiretroviral naïve versus experienced, and adjust for this important confounder.

8.8.1. Study timelines

Data collection is expected to commence mid-2014 (or once DTG is commercially available in European countries) and continue through 2019 for a total of five years of

monitoring. Annual updates and an interim report mid-way through the study, will be submitted per schedule listed in the table below. These reports will include updates on patient recruitment, potential number of HSR cases and adjudication committee decision and final number of HSR cases.

Mile Stones	Approximate Due Dates
Draft Protocol Submission	August 2013
Study Start	June 2014 or Date DTG is commercially available, whichever is earlier
1st Annual Update	Draft report, Dec 2015 Revised final interim report with major comments addressed Jan 2016 (minor comments not interfering with report conclusions or interpretation to be included in next annual update)
2nd Annual Update	Draft report, Dec 2016 Revised final interim report with major comments addressed Jan 2017 (minor comments not interfering with report conclusions or interpretation to be included in next annual update)
Interim Report	Draft report, Dec 2017 Revised final interim report with major comments addressed Jan 2018 (minor comments not interfering with report conclusions or interpretation to be included in next annual update)
3rd Annual Update	Draft report, Dec 2018 Revised final interim report with major comments addressed Jan 2019 (minor comments not interfering with report conclusions or interpretation to be included in next annual update)
Study Completion	June 2019 or 5 years following commercial availability of DTG

Final Report	April 2020 or 10 months after study completion (extended time to allow for bio specimen collection from suspected HSR cases, data analysis and final report writing).

8.8.2. Blood sample collection for future pharamcogentics study

Exploratory pharmacogenetic analysis may be conducted as discussed below.

It is anticipated that pharmacogenetic (PGx) analysis will be conducted for subjects participating in EuroSIDA who experience HSR, where HSR is considered potentially due to treatment with DTG (or other integrase inhibitor). Blood samples from suspected HSR cases will be collected at the participating EuroSIDA centers and processed/stored as described below. Two sources of controls will be considered to provide baseline genotype frequencies for PGx analysis: historical controls from DTG (or other integrase inhibitors) clinical trials, and/or European population controls. The former source of controls would be matched to HSR cases (e.g. by ethnicity, age, gender) and genotyped alongside HSR cases for PGx analysis. Human leukocyte antigen (HLA) and/or single nucleotide polymorphism (SNP) frequency data may be obtained from publically accessible databases for the European population controls.

PGx analysis will be exploratory, as no specific genetic hypothesis is available; the proposed study will take into account evidence implicating HLA variation in other drug-related severe cutaneous adverse reactions (SCARs) [Mallal et al. 2002, Hetherington et al. 2002, Chung et al. 2004, Hung et al.2005]. Consequently, two approaches will be considered for PGx analysis: (1) Genotyping HLA class I (A, B, C) and II (DRB1, DQA1, DQB1) genes, and (2) Single nucleotide polymorphism (SNP) Genome-wide association scan (GWAS). Genotype frequencies for the genetic markers evaluated as part of the study will be compared between HSR cases and controls, and standard statistical approaches will be used to identify any association with specific HLA or SNP alleles.

Consent and ethics:
Additional consent and Independent Ethics Committee (IEC) approvals will be needed for blood sample collection for PGx analysis from patients who experience a potential DTG or other integrase inhibitor related HSR. When applying for IEC approval, it will be emphasized that samples will only be used for investigation of any possible genotypic relationship with development of HSR.

PGx sampling:
It is planned that Quest Laboratories will send out blood collection kits to the EuroSIDA coordinating centre for distribution to sites with reports of suspected cases of HSR. The site would then collect the sample and ship back to EuroSIDA for processing of genomic DNA. Specimens will be stored in the EuroSIDA specimen storage in line with the plasma samples collected 6-monthly in order to have all samples processed and stored at a single facility. Specimens can potentially be used for downstream PGx analysis,

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical approval and subject consent

This PASS study protocol is approved by the EuroSIDA steering committee. Participating EuroSIDA sites will adhere to their appropriate local ethics approval procedures as requirement to be involved in the general EuroSIDA study. Additional ethics committee approvals will be obtained prior to collecting blood sample from suspected HSR cases for future pharmacogenetic evaluation with the specific aim to investigate any possible genotypic relationship with development of HSR.

9.2. Subject confidentiality

Principles of medical confidentiality in relation to Study Subjects are maintained. Personal data shall not be disclosed to third parties save where this is required directly or indirectly to satisfy the requirements of the Protocol or for the purpose of monitoring or Safety Reporting. The identity of Study Subjects shall not be disclosed to third parties without prior written consent of the Study Subject and then only in accordance with the requirements of the applicable data protection act.

Investigators and the EuroSIDA coordinating office shall ensure that only those of their officers and employees directly concerned with carrying out Study related activities are granted access to Confidential Information. All parties undertake not to disclose to any third party Confidential Information save where disclosure is required by a Regulatory Authority or by law, and not to make use of Confidential Information other than in accordance with this Protocol, unless the prior written consent been obtained.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

If, during the study, an adverse event (serious or non serious) is identified as explicitly attributed to any ViiV or GSK product (including products not covered in the specific study objective), this will be reported. The study coordinating centre will include reporting of such events in the 6-monthly report to GSK related to the 6-monthly follow-up data capture in EuroSIDA.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Target Audience

HIV International conferences such as CROI, the Glasgow meeting, EACS or IAS.

11.2. Study reporting and publications

EuroSIDA has the ownership of data collected related to this PASS study and has an interest in publishing and presenting the outcome of the Study and/or data deriving thereof in peer reviewed publications in accordance with the publication rules of the EuroSIDA Steering Committee selected among investigators representing the regions of EuroSIDA.

12. REFERENCES

1. Bannister WP, Friis-Møller N, Mocroft A, Viard JP, van Lunzen J, Kirk O, Gargalianos P, Bánhegyi D, Chiesi A, Lundgren JD; EuroSIDA Study Group. Incidence of abacavir hypersensitivity reactions in euroSIDA. Antivir Ther. 2008;13(5):687-96
2. Chung WH, Hung SI, Hong HS et al.: Medical genetics: a marker for Stevens–Johnson syndrome. Nature 428, 486 (2004).
3. Hetherington S, Hughes AR, Mosteller M et al.: Genetic variation in HLA-B region and hypersensitivity reactions to abacavir. Lancet 359, 1121–1122 (2002).
4. Hung SI, Chung WH, Liou LB et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse drug reactions caused by allopurinol. Proc. Natl Acad. Sci. USA 102, 4134–4139 (2005).
5. Johnson VA, Calvez V, Gunthard HF, Paredes R, Pillay D, Shafer RW, et al. Update of the drug resistance mutations in HIV-1: March 2013. Top Antivir Med 2013 Feb;21(1):6-14.
6. Mallal S, Nolan D, Witt C et al.: Association between presence of HLA-B*5701, HLA-DR7 and HLA-DQ3 and hypersensitivity to HIV-1 reverse transcriptase inhibitor abacavir. Lancet 359, 727–732 (2002).
7. Mocroft A, Reiss P, Gasiorowski J, Ledergerber B, Kowalska J, Chiesi A, et al. Serious fatal and nonfatal non-AIDS-defining illnesses in Europe. J Acquir Immune Defic Syndr 2010 Oct 1;55(2):262-70.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

No.	Document Reference	Date	Title
1.		<Date>	<Text>
2.		<Date>	<Text>

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Section 1: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the formulation of the research question clearly explain:				
1.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	x	☐	☐	17
1.1.2 The objectives of the study?	x	☐	☐	18
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	x	☐	☐	19
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	x	
1.2.3 if applicable, that there is no *a priori* hypothesis?	☐	☐	x	

Comments:

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Is the source population described?	x	☐	☐	19
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	x	☐	☐	18

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.2.2 Age and sex?	x	☐	☐	19
2.2.3 Country of origin?	x	☐	☐	19
2.2.4 Disease/indication?	x	☐	☐	19
2.2.5 Co-morbidity?	☐	☐	x	20
2.2.6 Seasonality?	☐	☐	x	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	x	☐	☐	20

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	x	☐	☐	24
3.2 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	x	☐	☐	18
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	x	☐	☐	29
3.4 Is sample size considered?	x	☐	☐	27
3.5 Is statistical power calculated?	☐	☐	x	

Comments:

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc)	x			19-20
4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc)	x	☐	☐	19-20
4.1.3 Covariates?	x	☐	☐	19-20
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	x	☐	☐	19-20
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	x	☐	☐	19-20
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	x	☐	☐	19-20
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	x	
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☐	☐	x	

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	x	
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	x	☐	☐	27

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	x	☐	☐	26
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	x	☐	☐	26
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	x	☐	☐	28
5.4 Is exposure classified based on biological mechanism of action?	☐	☐	x	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☐	26

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	x	☐	☐	24-26
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☐	24-26

Comments:

Section 7: Biases and Effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address:				
7.1.1 Selection biases?	x	☐	☐	30
7.1.2 Information biases?	x	☐	☐	30
7.2 Does the protocol address known confounders?	x	☐	☐	26
7.3 Does the protocol address known effect modifiers?	☐	☐	☐	26
7.4 Does the protocol address other limitations?	x	☐	☐	30

Comments:

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the plan include measurement of absolute effects?	☐	☐	x	
8.2 Is the choice of statistical techniques described?	x	☐	☐	28-29
8.3 Are descriptive analyses included?	x	☐	☐	28
8.4 Are stratified analyses included?	x	☐	☐	29
8.5 Does the plan describe the methods for identifying:				
8.5.1 Confounders?	x	☐	☐	
8.5.2 Effect modifiers?	x	☐	☐	
8.6 Does the plan describe how the analysis will address:				
8.6.1 Confounding?	x	☐	☐	29
8.6.2 Effect modification?	x	☐	☐	29

Comments:

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	x	☐	☐	27
9.2 Are methods of quality assurance described?	x	☐	☐	30
9.3 Does the protocol describe quality issues related to the data source(s)?	☐	☐	☐	30

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	x	☐	☐	27
9.5 Does the protocol specify timelines for				
9.5.1 Start of data collection?	x	☐	☐	15
9.5.2 Any progress report?	x	☐	☐	15-16
9.5.3 End of data collection?	x	☐	☐	16
9.5.4 Reporting? (i.e. interim reports, final study report)	x	☐	☐	15-16
9.6 Does the protocol include a section to document future amendments and deviations?	x	☐	☐	15
9.7 Are communication methods to disseminate results described?	x	☐	☐	33
9.8 Is there a system in place for independent review of study results?	x	☐	☐	24, 49

Comments:

Section 10: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	x	☐	☐	32
10.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	x	
10.3 Have data protection requirements been	x	☐	☐	27

Section 10: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
described?				

Comments:

Name of main author of study protocol: Dr. [redacted]

Date: 05 August, 2013

Signature:_____

ANNEX 3. HSR Event Form

EuroSIDA Hypersensitivity Reaction Event Form Center/patient code: <Bar code>

Completed by (investigator's initials) ⌊____⌋ Date of completion of this form (dd-mm-yyyy) ⌊- - ⌋

In the follow-up form you have indicated that this patient discontinued

Dolutegravir (DTG) ⌊⌋

Elvitegravir (EGV) ⌊⌋

Raltegravir (RAL) ⌊⌋

containing treatment regimen due to:

<Reason for treatment discontinuation, data from follow-up form>

Please give details on the reason for DTG or other integrase inhibitor discontinuation,

Discontinuation was due to:

Hypersensitivity ⌊⌋ | Anaphylactic reaction ⌊⌋ | Allergic reaction ⌊⌋ | Drug allergy ⌊⌋

Other reason ⌊⌋ , please specify:

Please indicate the dose of DTG or other integrase inhibitor prior to discontinuation: Value ⌊_____⌋ Unit ⌊_____⌋

Once Daily ⌊- - ⌋ OR

Twice Daily ⌊- - ⌋

Date of discontinuation recorded in follow-up form (dd-mm-yyyy) ⌊- - ⌋ , confirm data ⌊- - ⌋

Was fever present? Yes ⌊⌋ No ⌊⌋ Unknown ⌊⌋

if yes, date of onset ⌊- - ⌋ and duration (days) ⌊_____⌋

Was eosinophilia present? Yes ⌊⌋ No ⌊⌋ Unknown ⌊⌋

Date of measurement (dd-mm-yyyy)	Value	Unit	ULN
⌊- - ⌋	⌊_____⌋	⌊_____⌋	⌊_____⌋

Details of eosinophilia, please describe:

Was there a rash reaction? Yes ☐ No ☐

If yes, please grade the rash:

Grade 1 ☐ (Mild)	Grade 2 ☐ (Moderate)	Grade 3 ☐ (Severe)	Grade 4 ☐ (Potentially Life-Threatening)
Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)

Please indicate date of onset (dd-mm-yyyy) ☐☐-☐☐-☐☐☐☐ and duration (days) ☐☐☐☐

Was there gastrointestinal symptoms? Yes ☐ No ☐

If yes, please indicate details:

Nausea ☐	Vomiting ☐	Diarrhoea ☐

Other GI symptoms, please describe:

Please indicate date of onset (dd-mm-yyyy) ⌊ - - ⌋ and duration (days) ⌊ ⌋

Was there respiratory symptoms? Yes ⌴ No ⌴

If yes, please indicate details:

Dyspnoea ⌴	Sore throat ⌴	Cough ⌴	Chest X-ray changes ⌴ If yes, please describe

Other respiratory symptoms, please describe:

Please indicate date of onset (dd-mm-yyyy) ⌊ - - ⌋ and duration (days) ⌊ ⌋

Pleas confirm or add hepatic lab values related to possible dysfunction

	Date of measurement (dd-mm-yyyy)	Value	Unit	ULN
ALT	⌊ - - ⌋	⌊ ⌋	⌊ ⌋	⌊ ⌋
AST	⌊ - - ⌋	⌊ ⌋	⌊ ⌋	⌊ ⌋
	⌊ - - ⌋	⌊ ⌋	⌊ ⌋	⌊ ⌋

	Date of measurement (dd-mm-yyyy)	Value	Unit	ULN
ALP	- -			
Total bilirubnin	- -			
Direct (conjugated) bilirubin	- -			
Indirect (unconjugated) bilirubin (total bilirubin minus direct bilirubin)	- -			

Prothrombin Time (PT)

Other please describe:

Please evaluate the causal relationship of the symptoms recorded at this form with DTG/ other integrase inhibitor treatment:

Reasonable possibility of relationship ☐ Not related ☐

For Review Committee use only

Date of review: (dd-mm-yyyy) - -, reviewer initials

The event is evaluated as follows:

Not a HSR ⊔	Definite integrase inhibitor-related HSR ⊔	Possible integrase inhibitor-related HSR, ⊔	Integrase inhibitor-related DILI, ⊔

Other ⊔, please describe

Review comments:

ANNEX 4. Independent Adjudication Committee Charter

HYPERSENSITIVITY EVENT REVIEW COMMITTEE CHARTER
TITLE: Event Review for a Prospective Observational Cohort Study to Monitor Occurrence of Hypersensitivity Reaction and Hepatotoxicity in Patients Receiving Dolutegravir or other integrase inhibitor.

INVESTIGATOR: The EuroSIDA Study Group

EuroSIDA study sponsor: Research Directorate-General of the European Commission under the seventh EC Framework Programme, Network of Excellence: EuroCoord, GA# 260694.

Co-sponsor of Data Analysis: ViiV Healthcare UK Limited

Observational data collection and analyses

EuroSIDA Coordinating Centre, Copenhagen HIV Programme (CHIP)

Panum Institute

University of Copenhagen

Blegdamsvej 3 b, DK 2200, Copenhagen N

A. INTRODUCTION

The Event Review Committee (ERC) is the operational team that undertakes the review and evaluation of potential Dolutegravir (DTG) or other integrase inhibitor hypersensitivity cases in the nested Dolutegravir Post Authorisation Safety Study within EuroSIDA. The major objective of the ERC is to determine if the reported event meets the study diagnostic criteria for a confirmed or probable HSR. The ERC reports to the EuroSIDA Steering Committee and the EuroSIDA study group reports to GlaxoSmithKline (GSK).

B. ROLES AND RESPONSIBILITIES OF THE ERC

Composition of the ERC
The ERC is a scientific committee independent of the EuroSIDA Steering Committee and of GSK. The ERC will always have, as voting members, at least three experienced HIV clinicians of which one is a hepatologist and one is a pharmacogeneticist with no potential conflict of interest. The EuroSIDA coordinating office will appoint a ERC coordinator to manage the ERC process. An experienced physician from the Coordinating centre will join the ECR as non-voting member and will assist assessing the adequacy of the submitted event documentation.

The EuroSIDA Steering Committee approves the ERC members and appoints one of them the chair.

Function
Review: The active ERC reviewers receive event CRFs and supplementary documentation from the ERC-coordinator by e-mail and independently perform their review. The review is documents at an ERC review

form that is returned by e-mail to the ERC Coordinator. Reviewers can request additional information if needed for a conclusive review.

Disagreements among the three active reviewers are adjudicated: if consensus is not obtained in the primary review, the ERC coordinator sends all ERC review forms by e-mail to all reviewers and all ERC reviewers discuss via e-mail to obtain agreement on the classification of an event. Reviewers should provide their comments on adjudications to the ERC Coordinator within one week.

If the reviewers still disagree and consensus cannot be reached, the ERC chair makes the final decision.

Regular meetings: Once quarterly the ERC meets at teleconferences to discuss, agree and document evaluation criteria or coding issues. It needed face-to-face meetings can be arranged. The EuroSIDA coordinating office organises teleconferences and meetings.

Document exchange: Relevant SOPs, Forms and Event evaluation criteria are shared via FTP up-load/down-load in a secure environment. Each ERC member and coordinating office have access to this platform and may upload and download documents.

Details of the review process is described in the ERC SOP001: Event Review in the Dolutegravir PAS Study.

Accountability
The ERC is accountable to:

- the EuroSIDA Steering Committee

Decision making
Whenever possible, decision is reached by a consensus of the active ERC members. When this is not possible, the final decision lies with the chair of the ERC.

Interaction with other Trial Committees
The ERC (represented by the ERC coordinator) informs the EuroSIDA Steering Committee on progress of the event review and the EuroSIDA study group formally reports annually to the GSK on the progress of the event review. The annual report from the ERC should be prepared by the ERC chairperson, mutually agreed upon and signed by the ERC members.

B. CONFLICT OF INTEREST

EuroSIDA Study Group is to contract with the individual members of the ERC. All ERC members will submit to EuroSIDA Study Group a signed statement indicating that they have no potential conflicts of interest. If an ERC member identifies a conflict of interest during the study period and is likely not to be able to continue participating in the ERC, he or she must notify the chairperson and EuroSIDA Study Group as soon as possible so that a substitute member can be selected in a timely manner.