Report #2

A Prospective Observational Cohort Study to Monitor Occurrence of Hypersensitivity Reaction and Hepatotoxicity in Patients Receiving Dolutegravir

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1 Background

This data analysis is being conducted by the EuroSIDA Study Group in a scientific collaboration with GSK/ViiV Healthcare.

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 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 with less than 1% of clinical trial patients experiencing 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 to possibly determine associated risk factors. In addition, the post-authorization safety study will monitor for hepatotoxicity and severe skin rash following initiation of DTG based antiretroviral regimen.

This is the second report from a five year-long prospective cohort study nested within the EuroSIDA study. The study population includes HIV positive patients over the age of 16 years from EuroSIDA clinical sites, who are new users of DTG. Following initiation of DTG (as Tivicay or Triumeq, the fixed dose combination of DTG/abacavir sulfate/lamivudine) based antiretroviral regimen, the study will aim to a) Monitor for hypersensitivity reaction, b) Monitor for hepatotoxicity, and c) Monitor for severe skin rash among all patients discontinuing DTG for any reason. This strategy would maximise the capture of discontinuation events, as all 3 reactions would lead to the discontinuation of DTG.

Subsequent to the European Medicines Agency's (EMA) approval of DTG, the study collected prospective data on patients treated with DTG based ARV regimen and will continue collection over the course of 5 years. Blood samples from suspected HSR cases from consenting persons were collected at the participating EuroSIDA centres and processed/stored for future pharmacogenetic assessments. The study protocol was approved by the EuroSIDA steering committee and relevant authorities in the participating countries. Participating EuroSIDA sites adhere to their appropriate local ethics approval procedures as required and additional ethics committee approvals were obtained prior to collecting blood sample from suspected HSR cases from consenting persons for future pharmacogenetic evaluation.

The EuroSIDA study is a prospective, observational cohort of 18,295 HIV-1 infected patients in 105 centres across 31 European countries, Israel and Argentina. The patients included are enrolled to be representative of the patients followed in the various clinical centres that participate in the cohort. EuroSIDA is one of the largest pan-European cohorts and has collected data since 1993. Information is collected on a standardised data collection form every 6 months. Details of the study and its publications can be found at www.chip.dk.

While the study population remains limited at this point in time, the data in this report serve as an outline of what to expect in future reports when more data on DTG usage

has accrued. Data presented at this time should be treated very cautiously due to the limited study population size.

It is important to note that these data are from an observational cohort study and hence need to be interpreted realistically and with full knowledge of its limitations and inherent biases. While there are extensive data quality programs in place within EuroSIDA, it remains an observation of routine clinical practice across Europe. As a consequence, whatever statistical methods are used, we will not be able to exclude confounding by indication that can only be truly accounted for in a randomised clinical trial.

Since the 2015 report, the number of people included has increased by more than 2-fold from 579 people in 2015 (with 250 person years of follow-up [PYFU]) to 1217 in 2016 (with 700 PYFU). There were 130 people who discontinued during follow up in 2016, which is a 2.2 fold increase since the 2015 report (2015 N=58 people discontinued). The number of people who discontinued due to HSR remained at 2.

2 Summary

NOTE: Discontinuations are presented from two sources in tables I and 1; (1) The HSR CRF form and (2) the EuroSIDA follow-up form. The EuroSIDA follow-up form contains reasons for discontinuations which are originally reported to EuroSIDA by the participating clinics. The HSR CRF form contains specific reasons for discontinuation that are HSR specific and are considered to be more refined than standard EuroSIDA reporting. All possible HSRs are examined internally as to whether a HSR is likely, and possible HSR are sent out for review by multiple clinicians for validation. Therefore, it is possible that a stopping event is reported as HSR in the EuroSIDA follow-up form, but may be ruled out as a possible HSR later. Validated discontinuations as reported in the HSR CRF form are presented in all other analyses unless otherwise specified.

Table I: Summary of cohort for first integrase inhibitor started after 16 January 2014

			Overall	A[1]	B[2]	C[3]	D[4]
Persons (at first regimen)		N (%)	1217 (100.0%)	301 (24.7%)	356 (29.3%)	79 (6.5%)	481 (39.5%)
Treatment naïve		N (%)	87 (7.1%)	15 (5.0%)	15 (4.2%)	5 (6.3%)	52 (10.8%)
Integrase inhibitor Naïve		N (%)	962 (79.0%)	249 (82.7%)	229 (64.3%)	73 (92.4%)	411 (85.4%)
Person years of follow-up		Total	674	134	198	46	296
		Median [IQR]	0.5 (0.3,0.8)	0.4 (0.2,0.6)	0.5 (0.3,0.8)	0.5 (0.3,0.9)	0.5 (0.3,0.9)
Date of first ARV (mon-yy)		Median [IQR]	OCT00 (MAR96,JUL08)	OCT01 (DEC96,SEP08)	SEP97 (MAR95,NOV06)	DEC97 (JUL94,JAN08)	JAN02 (JUL96,MAR09)
Date of first II (mon-yy)		Median [IQR]	AUG14 (FEB14,JAN15)	NOV14 (MAY14,MAR15)	JUN14 (OCT11,DEC14)	JUN14 (APR14,DEC14)	JUL14 (FEB14,DEC14)

			Overall	A[1]	B[2]	C[3]	D[4]
Discontinuations[5]							
HSR CRF form[6]	Total	N (%)	130 (10.7%)	23 (7.6%)	26 (7.3%)	15 (19.0%)	66 (13.7%)
	HSR[7]	N (%)	2 (0.2%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.2%)
	Hepatotoxicity	N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Severe Skin Rash (Not HSR)	N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Other	N (%)	97 (8.0%)	19 (6.3%)	21 (5.9%)	10 (12.7%)	47 (9.8%)
	Unknown	N (%)	31 (2.5%)	4 (1.3%)	4 (1.1%)	5 (6.3%)	18 (3.7%)
EuroSIDA data capture[8]	Total	N (%)	130 (10.7%)	23 (7.6%)	26 (7.3%)	15 (19.0%)	66 (13.7%)
	Treatment failure	N (%)	3 (0.2%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	2 (0.4%)
	Hypersensitivity reaction	N (%)	2 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
	Toxicity-predominantly from abdomen/G-I tract	N (%)	8 (0.7%)	1 (0.3%)	2 (0.6%)	0 (0.0%)	5 (1.0%)
	Toxicity, predominantly from nervous system	N (%)	8 (0.7%)	1 (0.3%)	3 (0.8%)	1 (1.3%)	3 (0.6%)

			Overall	A[1]	B[2]	C[3]	D[4]
	Toxicity, predominantly from kidneys	N (%)	3 (0.2%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
	Toxicity, predominantly from the endocrine system	N (%)	4 (0.3%)	2 (0.7%)	1 (0.3%)	0 (0.0%)	1 (0.2%)
	Toxicity, not mentioned above	N (%)	9 (0.7%)	2 (0.7%)	2 (0.6%)	0 (0.0%)	5 (1.0%)
	Patient's wish/decision, not specified above	N (%)	25 (2.1%)	7 (2.3%)	6 (1.7%)	2 (2.5%)	10 (2.1%)
	Physician's decision, not specified above	N (%)	25 (2.1%)	5 (1.7%)	7 (2.0%)	5 (6.3%)	8 (1.7%)
	Other causes, not specified above	N (%)	24 (2.0%)	3 (1.0%)	3 (0.8%)	3 (3.8%)	15 (3.1%)
	Unknown	N (%)	19 (1.6%)	1 (0.3%)	2 (0.6%)	3 (3.8%)	13 (2.7%)

[1]DTG with ABC
[2]DTG without ABC
[3]ELV/RAL with ABC
[4]ELV/RAL without ABC
[5] Discontinuations are presented from two sources. The HSR CRF form and the EuroSIDA follow-up form. The EuroSIDA follow-up form contains reasons for discontinuations which are originally reported to EuroSIDA. The HSR CRF form contains specific reasons for stopping

that are HSR specific and are considered to be more refined than standard EuroSIDA reporting. Discontinuations as reported in the HSR CRF form only are presented from this point onwards.

[6] Reasons for discontinuation as reported on HSR CRF

[7] Includes: Hypersensitivity reaction incl. rash, Hypersensitivity reaction – Allergic reaction, Drug allergy related to DTG or another integrase inhibitor, Hypersensitivity reaction - Anaphylactic reaction.

[8] Reasons for discontinuation as reported on EuroSIDA follow-up form.

Overview of cohort

There were 1217 people who started an integrase inhibitor based regimen over a total of 700 person years of follow-up (PYFU), with a median follow-up of 0.5 (Interquartile range [IQR]: 0.3 – 0.8) years per person between 16 January 2014 – 31 December 2015 (**TABLE I**).

Of the 1217, 87 were treatment naive, 962 were integrase inhibitor naive and 255 patients were integrase inhibitor experienced. Of the 1217, 657 started DTG, including 301 with ABC (treatment group A), 356 without ABC (B). There were 560 people who started RAL/EVG, of which 79 with ABC (C) and 481 without ABC (D). Overall 130 /1217 (11%) people discontinued (accounting for 139 discontinuation events), 23/301 (8%) from A, 26/356 (7%) from B, 15/79 (19%) from C and 66/481 (14%) from D. Only 2 discontinuations were due to HSR (from B and D). Both HSR discontinuations were in treatment experienced patients, and one was also integrase inhibitor experienced (**TABLE 10**). One received DTG at 50 mg once daily for 5 days, the other received RAL at 400 mg twice daily for 43 days.

There were no discontinuations due to hepatotoxicity or severe skin rash (not HSR). The rate of discontinuation in DTG treated patients (A and B combined) was 15.0 (95%CI: 11.4, 19.7)/100 PYFU (N=52, PYFU = 346) and the rate in the RAL/EVG treated group (C and D) combined was 24.6 95%CI: 19.9, 30.3 /100 PYFU (N=87, PYFU = 354). There were too few events within the treatment groups of interest for independent analysis according to reason of discontinuation (i.e. HSR, hepatotoxicity or severe skin rash (not HSR)).

Characteristics of cohort:

Those who started an integrase inhibitor had a median age of 50 (IQR: 44 – 56) at date of initiation, 75% were male, 86% were white, 41% were homosexual, 25% IDU and 26% Heterosexual **(TABLE 2)**. The majority were from Central Europe (33%), followed by North (32%), South and Argentina (24%), East central (11%), and East (1%). More than half had a CD4 of 500 cells/mm^3 or more and only 11% had a CD4 of <200 cells/mm3, whereas 11% had a HIV viral load of ≥400 copies/mL **(TABLE 3)**. Just over one quarter had an AIDS event (26%, includes AIDS-defining conditions listed in the 1993 CDC clinical definition [1]), 15% had a non-AIDS defining event (Non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, NADM [2]). 37% and 4% had a diagnosis of HCV or HBV respectively to starting an integrase inhibitor. The majority of people were treatment experienced (93%), and 21% had prior experience of the integrase inhibitor class **(TABLE 4**). There was a higher proportion of people that were INSTI experienced starting DTG (A: 17% and B: 36%) compared to RAL/ELV(C: 8% D: 15%). At baseline, people had been exposed to a median of 7.0 (4.0,11.0) antiretroviral agents, and had been on treatment for a median of 14.1 (6.3,18.6) years. There were 365 (30%) people with a prior resistance test of which 235 (64%) had any resistance, 195 (53%) had NRTI resistance, 148 (41%) had NNRTI resistance and 107 (29%) had PI major resistance. According the ANRS GSS, the median percentage of drugs within the regimen that were active was 100% (IQR: 70% - 100%).

Those of non-white ethnicity, who acquired HIV through IDU transmission mode (relative to homosexual), living in Argentina, South, East or East central Europe (relative to central Europe), and who were treatment Naïve were less likely to start DTG (A and B) than RAL/EVG (C and D) **(TABLE 12)**.

Those who started DTG with ABC compared to without ABC (A vs B) were less likely to be aged 41 years or older, were more likely to be from central Europe, and less likely to be former smokers **(TABLE 13).**

Those who started RAL or EVG with ABC compared to without ABC (C vs D) were more likely to be from Argentina, South, East or East central Europe **(TABLE 14).**

Interim conclusion

The frequency of discontinuation due to HSR, hepatotoxicity and severe skin rash in users of integrase inhibitors is low, 0.2%, 0.0% and 0.0%, respectively. However this is based on a limited number of study participants receiving DTG (n=657) or RAL or EVG (n=560) and could potentially change as the study progresses and more data are accrued. **The data presented in this report are preliminary, for illustration and further follow-up on all regimens will accrue data over the coming years which will allow more detailed analyses.**

3 Content

3.1 List of Tables

3.2 List of Figures

3.3 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

4 Overview of Research Outcome 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 investigated three questions as outlined below:

4.1 Monitor and compare hypersensitivity reaction

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 was established (**TABLE 1 and SUPPLEMENTARY TABLE 1**):

There were no new discontinuations of DTG or other integrase inhibitor regimens (with or without ABC) due to HSR since the last report.

A. Patients that start DTG and ABC based ARV regimen: There were no cases of discontinuation due to HSR.
B. Patients that start DTG based ARV regimen but without ABC: There was 1 case of discontinuation due to HSR. Fever and gastro intestinal (nausea) symptoms were indicated, however no rash, eosinophilia or respiratory symptoms were reported. Levels of ALT and Bilirubin were not elevated.
C. Patients that start other integrase inhibitor based regimen (RAL and EGV) and with ABC: There were no cases of discontinuation due to HSR.
D. Patients that start other integrase inhibitor based regimen (RAL and EGV) but without ABC: There was 1 case of discontinuation due to HSR. Mild skin rash, gastro intestinal (diarrhoea) were indicated, but fever, eosinophilia, and respiratory symptoms were not present. Levels of ALT and Bilirubin were not elevated.

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 will be determined once the number of events exceeds 20 in each group.

Blood samples from suspected HSR cases for future pharmacogenetic evaluation will be collected from consenting persons. Of the two suspected HSR cases, one will not be included in the blood sample analysis as the site is not able to send blood samples out of the country and the other is awaiting ethics approval.

4.2 Monitor for hepatotoxicity

There were no instances of discontinuation due to hepatotoxicity for DTG or other integrase inhibitors (with or without ABC). The incidence in each group and risk factors will be provided when the number of events exceeds 20 in each group.

The incidence of cases of combined alanine aminotransferase (ALT) and total bilirubin liver chemistry test elevations (ALT>2xULN (ULN=40 U/L) and Bilirubin>2 xULN (ULN=1.2 mg/dL)) among DTG users or users of other integrase inhibitors (with or without ABC) was estimated (**SUPPLEMENTARY TABLE 2**):

A. Patients that start DTG and ABC based ARV regimen: of the 166/301 people who had a test, 3 (2%) were elevated.
B. Patients that start DTG based ARV regimen but without ABC: of the 240/356 people who had a test, 6 (3%) were elevated.
C. Patients that start other integrase inhibitor based regimen (RAL and EGV) and with ABC: of the 50/79 people who had a test, 1(2%) were elevated.
D. Patients that start other integrase inhibitor based regimen (RAL and EGV) but without ABC: of the 299/481 people who had a test, 5(2%) were elevated.

Of the two discontinuations due to HSR, neither had elevated ALT or Bilirubin levels.

4.3 Monitor for severe skin rash.

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 sample follow-up forms and case definitions at: http://www.chip.dk/Ongoing-Studies/EuroSIDA/Study-documents).

There were no discontinuations due to severe skin rash. Presence of mild skin rash was indicated in one discontinuation of RAL without ABC due to HSR. In addition, mild skin rash was indicated in one discontinuation of DTG without ABC not due to HSR, and two discontinuations of EVG without ABC not due to HSR.

5 RESEARCH METHODS

5.1 Study Design

This is the second report from a five year-long prospective cohort study nested within the EuroSIDA study. Potential HSR, hepatotoxicity and severe skin rash cases were and 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 follow 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, hepatotoxicity and severe skin rash cases were and will be identified as described below. In order to collect data beyond the routine data capture, the protocol was submitted for local Ethical approval at EuroSIDA sites where the potential HSR or hepatotoxicity patients were located. After Ethical clearance, clinics with potential cases

performed informed consent for additional data and blood sample collection from consenting persons. A specific data collection form was developed for ascertainment of HSR, hepatotoxicity and severe skin rash case. (see sample HSR form at http://www.chip.dk/Ongoing-Studies/EuroSIDA/Study-documents).
For this non-interventional study, treatment decisions are 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.

5.2 Data Sources

Study Population: The study population includes 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 were monitored among all those who discontinued 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 is 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 32 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 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 Centres for Disease Control and Prevention. Members of the coordinating office visit all centres to ensure correct patient selection and accuracy of data provided.

Data Collection: Following the EMA's approval of DTG, the study collects 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 centre receives data from the clinical sites biannually.

- All suspected HSR cases were identified through screening criteria described below, and review of potential data clarification items collected at a specific HSR event form (see sample HSR form at http://www.chip.dk/Ongoing-Studies/EuroSIDA/Study-documents); screen-positive cases were 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 collection.

5.3 Variables

5.3.1 Outcome definitions:

HSR case definition: All patients discontinuing DTG or other integrase inhibitor regimens (RAL and EGV) for any reason were assessed for potential HSR. Each patient that discontinues DTG (or other integrase inhibitor regimens (RAL and EGV)) had an additional HSR specific data clarification form completed by the site regarding the circumstances surrounding discontinuation. The specific HSR data form (sample displayed at http://www.chip.dk/Ongoing-Studies/EuroSIDA/Study-documents) incorporates 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 were 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 were 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 laboratory biomarkers collected in EuroSIDA were part of the data basis for the current report

5.3.2 Identifying HSR cases

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

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

OR

DTG or another integrase inhibitor was 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 sample HSR form at: http://www.chip.dk/Ongoing-Studies/EuroSIDA/Study-documents) to clarify the circumstances around the HSR event were collected to clarify the case and allow an adjudication process by the independent case review committee.

In addition, the clinical report form (CRF) collected 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 established a case of DTG or other integrase inhibitor HSR as one in which conditions in A or B were fulfilled and where the exclusion criteria did not apply.

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

OR

B. Two or more events were 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. ii. AST elevations (AST is also called serum glutamic oxaloacetic transaminase (SGOT))
    iii. iii. Alkaline phosphatase (ALP) elevations
    iv. iv. Total bilirubin elevations
    v. v. Albumin

Definite DTG-related HSR or definite HSR related to another integrase inhibitor were 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 were 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.

5.3.3 Hepatotoxicity

The above mentioned 6-monthly data collected routinely in EuroSIDA was used to identify potential cases of possible drug-induced liver injury (DILI). Possible data clarification items were addressed in the HSR specific event form (see sample HSR form at http://www.chip.dk/Ongoing-Studies/EuroSIDA/Study-documents).

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

- More than or equal to fivefold elevation above the upper limit of normal (ULN) for ALT[1]
- More than or equal to threefold elevation in ALT concentration and simultaneous elevation of total bilirubin concentration exceeding 2× ULN

[1] 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 were highlighted for special cautious evaluation of drug relatedness by the independent adjudication committee.

5.3.4 Skin rash

Clarifying case data on severe skin rash 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 were 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 good since it is reported directly by the clinic using clinical report forms. All discontinuation cases were reviewed for potential DTG or other integrase inhibitor HSR and further detailed data captured in the HSR CRF, which resulted in HSR and skin rash data that are more valid than usually seen in observational studies.

5.3.5 Exposure definitions

Any exposure to DTG, other integrase inhibitors or DTG or other integrase inhibitor containing products was 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 patients infected with HIV with resistance to INSTIs.

5.3.6 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 below presents 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 it was possible. However, results from observational studies should always be interpreted with caution due to the potential for confounding.

The effect of the following potential confounders and effect modifiers on the risk for outcomes of interest were examined

- ARV status (ARV naïve, treatment experienced)
- Prior AIDS defining illness and/or nadir CD4 count (<50, <200, >200 cells/mm^3)
- 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

5.4 Data Management

Data collection, submission, clarification, keying and quality assurance followed 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.

5.4.1 Data handling conventions

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

In addition, all data were fully anonymised before transfer to Copenhagen and is held securely. Data was transferred to the statistical team in London via secure download and password encrypted file. The data is held on password secured computers in London. EuroSIDA have the relevant data protection clearance, Data Protection Agency No: 2012-54-0035

5.4.2 Timings of Assessment during follow-up

All sites completed the follow-up forms within the two month period, after which the forms were sent to the coordinating centre for data entry. An updated version of the database was 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 was requested on all consenting patients every six months.

6 Data Analysis and Results

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 were monitored among all patients who discontinued DTG or another integrase inhibitor for any reason in 4 subgroups of patients:

The following groups were 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.

6.1 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 (Not HSR),

  which lead to treatment discontinuation as defined within the study protocol

6.2 Statistical methods

A DTG (or other integrase inhibitor)-based regimen were regimens consisting of at least 3 ARVs combined from any class, of which at least one was DTG (or other integrase inhibitor).

New users of DTG (or other integrase inhibiotrs RAL and EGV) were 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 of the patient characteristics of the 4 treatment groups follows below. Baseline in all groups was defined as the date of starting the DTG (or other integrase inhibitor). Patients were not eligible to join treatment groups C-D (i.e. the comparator groups containing EGV or RAL) until after the proposed start date of these analyses when DTG was routinely available to ensure the comparison group has contemporary patients.

Display of 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 was 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 <200/mm3) or with uncontrolled viremia (HIV RNA VL > 400 copies.ml) was also summarised. ARV history summarised included 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[2] 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

[2] 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 broadly followed that of this previous work.

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 results comparing those starting a DTG-based regimen (treatment groups A-B) with those starting another integrase inhibitor (Groups C-D): depending on the exact combinations of regimens used, 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 included baseline demographics and whether the patients were antiretroviral naïve. Patient characteristics at the time of primary event were 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 were 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 also compared those who are antiretroviral naïve at starting each regimen with those who were antiretroviral experienced. The CRF collected information on dose of DTG or other integrase inhibitor which enabled a descriptive analysis of whether those taking higher doses are more likely to discontinue due to HSR compared to other reasons for discontinuation.

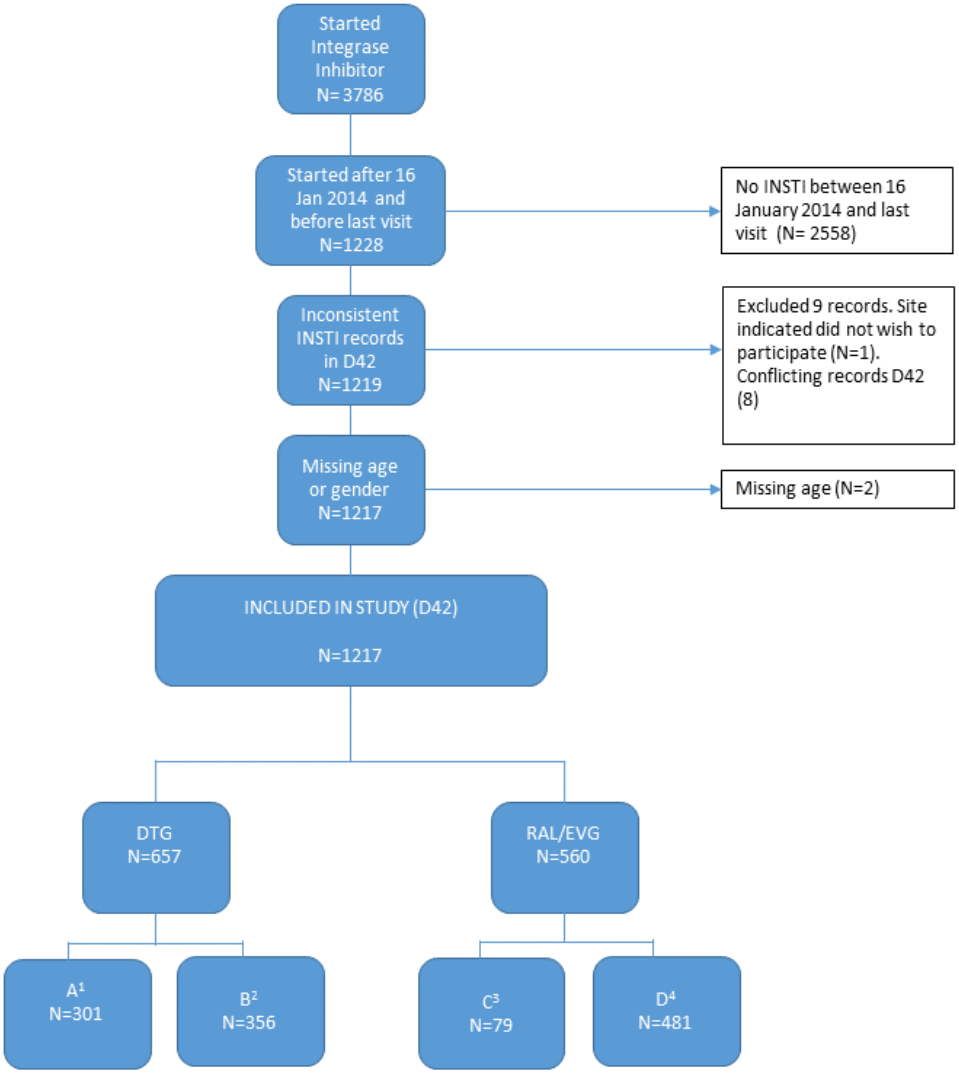
Time to event Kaplan-Meier (KM) estimates describe the cumulative incidence of the primary endpoint. Incidence rates summarized the incidence of the primary endpoint. Primary analysis was on-treatment and persons were followed-up from baseline until discontinuation of DTG (or other integrase inhibitor),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

Multivariable Poisson regression was 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 were significant in univariate analyses ($p<0.1$) were included in multivariate models, as well as treatment group and whether the patients were antiretroviral naïve at starting the regimen Excluded variables were 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 could 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.

6.3 Results of Statistical Analysis

FIGURE 1: Flow chart of patients starting a regimen containing DTG or other integrase inhibitors and their distribution in analysis groups



[1] DTG with ABC
[2] DTG without ABC
[3] ELV/RAL with ABC
[4] ELV/RAL without ABC

NOTE: Discontinuations are presented from two sources in tables I and 1; (1) The HSR CRF form and (2) the EuroSIDA follow-up form. The EuroSIDA follow-up form contains reasons for discontinuations which are originally reported to EuroSIDA by the participating clinics. The HSR CRF form contains specific reasons for discontinuation that are HSR specific and are considered to be more refined than standard EuroSIDA reporting. All possible HSRs are examined internally as to whether a HSR is likely, and possible HSR are sent out for review by multiple clinicians for validation. Therefore, it is possible that a stopping event is reported as HSR in the EuroSIDA follow-up form, but may be ruled out as a possible HSR later. Validated discontinuations as reported in the HSR CRF form are presented in all other analyses unless otherwise specified.

TABLE 1: Summary of cohort for first integrase inhibitor started after 16 January 2014

			Overall	**A[1]**	**B[2]**	**C[3]**	**D[4]**
Persons (at first regimen)		N (%)	1217 (100.0%)	301 (24.7%)	356 (29.3%)	79 (6.5%)	481 (39.5%)
Treatment naïve		N (%)	87 (7.1%)	15 (5.0%)	15 (4.2%)	5 (6.3%)	52 (10.8%)
Integrase inhibitor Naïve		N (%)	962 (79.0%)	249 (82.7%)	229 (64.3%)	73 (92.4%)	411 (85.4%)
Person years of follow-up		Total	674	134	198	46	296
		Median [IQR]	0.5 (0.3,0.8)	0.4 (0.2,0.6)	0.5 (0.3,0.8)	0.5 (0.3,0.9)	0.5 (0.3,0.9)
Date of first ARV (mon-yy)		Median [IQR]	OCT00 (MAR96,JUL08)	OCT01 (DEC96,SEP08)	SEP97 (MAR95,NOV06)	DEC97 (JUL94,JAN08)	JAN02 (JUL96,MAR09)
Date of first II (mon-yy)		Median [IQR]	AUG14 (FEB14,JAN15)	NOV14 (MAY14,MAR15)	JUN14 (OCT11,DEC14)	JUN14 (APR14,DEC14)	JUL14 (FEB14,DEC14)
Discontinuations[5]							
HSR CRF form[6]	Total	N (%)	130 (10.7%)	23 (7.6%)	26 (7.3%)	15 (19.0%)	66 (13.7%)

			Overall	A[1]	B[2]	C[3]	D[4]
	HSR[7]	N (%)	2 (0.2%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.2%)
	Hepatotoxicity	N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Severe Skin Rash (Not HSR)	N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Other	N (%)	97 (8.0%)	19 (6.3%)	21 (5.9%)	10 (12.7%)	47 (9.8%)
	Unknown	N (%)	31 (2.5%)	4 (1.3%)	4 (1.1%)	5 (6.3%)	18 (3.7%)
EuroSIDA data capture[8]	Total	N (%)	130 (10.7%)	23 (7.6%)	26 (7.3%)	15 (19.0%)	66 (13.7%)
	Treatment failure	N (%)	3 (0.2%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	2 (0.4%)
	Hypersensitivity reaction	N (%)	2 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
	Toxicity-predominantly from abdomen/G-I tract	N (%)	8 (0.7%)	1 (0.3%)	2 (0.6%)	0 (0.0%)	5 (1.0%)
	Toxicity, predominantly from nervous system	N (%)	8 (0.7%)	1 (0.3%)	3 (0.8%)	1 (1.3%)	3 (0.6%)
	Toxicity, predominantly from kidneys	N (%)	3 (0.2%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	2 (0.4%)

			Overall	A[1]	B[2]	C[3]	D[4]
	Toxicity, predominantly from the endocrine system	N (%)	4 (0.3%)	2 (0.7%)	1 (0.3%)	0 (0.0%)	1 (0.2%)
	Toxicity, not mentioned above	N (%)	9 (0.7%)	2 (0.7%)	2 (0.6%)	0 (0.0%)	5 (1.0%)
	Patient's wish/decision, not specified above	N (%)	25 (2.1%)	7 (2.3%)	6 (1.7%)	2 (2.5%)	10 (2.1%)
	Physician's decision, not specified above	N (%)	25 (2.1%)	5 (1.7%)	7 (2.0%)	5 (6.3%)	8 (1.7%)
	Other causes, not specified above	N (%)	24 (2.0%)	3 (1.0%)	3 (0.8%)	3 (3.8%)	15 (3.1%)
	Unknown	N (%)	19 (1.6%)	1 (0.3%)	2 (0.6%)	3 (3.8%)	13 (2.7%)

[1]DTG with ABC
[2]DTG without ABC
[3]ELV/RAL with ABC
[4]ELV/RAL without ABC
[5] Discontinuations are presented from two sources. The HSR CRF form and the EuroSIDA follow-up form. The EuroSIDA follow-up form contains reasons for discontinuations which are originally reported to EuroSIDA. The HSR CRF form contains specific reasons for stopping that are HSR specific and are considered to be more refined than standard EuroSIDA reporting. Discontinuations as reported in the HSR CRF form only are presented from this point onwards.
[6] Reasons for discontinuation as reported on HSR CRF

[7]Includes: Hypersensitivity reaction incl. rash, Hypersensitivity reaction – Allergic reaction, Drug allergy related to DTG or another integrase inhibitor, Hypersensitivity reaction - Anaphylactic reaction.
[8] Reasons for discontinuation as reported on EuroSIDA follow-up form.

TABLE 2: Baseline[1] demographic characteristics of new users[2] of DTG with ABC (A), DTG without ABC (B), RAL or ELV with ABC (C) RAL or ELV without ABC (D).

	Overall	A[3]	B[4]	C[5]	D[6]
all					
	1,217 (100)	301 (100)	356 (100)	79 (100)	481 (100)
Age (years)					
≤ 35 years	72 (5.9)	20 (6.6)	17 (4.8)	6 (7.6)	29 (6.0)
36 - 40 years	129 (10.6)	40 (13.3)	24 (6.7)	6 (7.6)	59 (12.3)
41 - 50 years	396 (32.5)	98 (32.6)	102 (28.7)	29 (36.7)	167 (34.7)
51 + years	620 (50.9)	143 (47.5)	213 (59.8)	38 (48.1)	226 (47.0)
Gender					
Male	913 (75.0)	221 (73.4)	272 (76.4)	56 (70.9)	364 (75.7)
Female	304 (25.0)	80 (26.6)	84 (23.6)	23 (29.1)	117 (24.3)
Race					
white	1,040 (85.5)	260 (86.4)	308 (86.5)	71 (89.9)	401 (83.4)
Other/Unknown	177 (14.5)	41 (13.6)	48 (13.5)	8 (10.1)	80 (16.6)
HIV exposure group					
MSM	493 (40.5)	128 (42.5)	159 (44.7)	19 (24.1)	187 (38.9)
IDU	307 (25.2)	51 (16.9)	74 (20.8)	35 (44.3)	147 (30.6)
Heterosexual	320 (26.3)	92 (30.6)	90 (25.3)	17 (21.5)	121 (25.2)
Other/Unknown	97 (8.0)	30 (10.0)	33 (9.3)	8 (10.1)	26 (5.4)

	Overall	A[3]	B[4]	C[5]	D[6]
Region of Europe[7]					
South and Argentina	291 (23.9)	40 (13.3)	74 (20.8)	38 (48.1)	139 (28.9)
North	387 (31.8)	137 (45.5)	119 (33.4)	8 (10.1)	123 (25.6)
Central	397 (32.6)	108 (35.9)	138 (38.8)	15 (19.0)	136 (28.3)
East central	130 (10.7)	16 (5.3)	25 (7.0)	13 (16.5)	76 (15.8)
East	12 (1.0)	0 (0.0)	0 (0.0)	5 (6.3)	7 (1.5)
Body mass index (BMI)					
<18	24 (2.0)	4 (1.3)	9 (2.5)	0 (0.0)	11 (2.3)
18 - 25	431 (35.4)	134 (44.5)	120 (33.7)	23 (29.1)	154 (32.0)
>25	264 (21.7)	66 (21.9)	81 (22.8)	21 (26.6)	96 (20.0)
Unknown	498 (40.9)	97 (32.2)	146 (41.0)	35 (44.3)	220 (45.7)
Smoking status					
Current	363 (29.8)	87 (28.9)	100 (28.1)	27 (34.2)	149 (31.0)
Former	196 (16.1)	43 (14.3)	69 (19.4)	11 (13.9)	73 (15.2)
Never	386 (31.7)	121 (40.2)	113 (31.7)	22 (27.8)	130 (27.0)
Unknown	272 (22.4)	50 (16.6)	74 (20.8)	19 (24.1)	129 (26.8)
Date of baseline[8]					
Median date [IQR]	OCT14 (MAY14,FEB15)	JAN15 (SEP14,APR15)	NOV14 (JUN14,FEB15)	JUL14 (APR14,DEC14)	AUG14 (APR14,JAN15)

[1] Baseline in all groups will be defined as the date of starting the DTG (or other integrase inhibitor).

[2] After the 16 Jan 2014.
[3] DTG with ABC
[4] DTG without ABC
[5] ELV/RAL with ABC
[6] ELV/RAL without ABC
[7] Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; North: Austria, Belgium, France, Germany, Luxembourg, Central: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia; East: Belarus, Estonia, Latvia, Lithuania, Russian Federation, Ukraine.
[8]Baseline in all groups will be defined as the date of starting the DTG (or other integrase inhibitor).

TABLE 3: Baseline[1] clinical characteristics of new users[2] of DTG with ABC (A), DTG without ABC (B), RAL or ELV with ABC (C) RAL or ELV without ABC (D).

	Overall	A[3]	B[4]	C[5]	D[6]
all					
	1,217 (100)	301 (100)	356 (100)	79 (100)	481 (100)
Prior AIDS[7]					
Yes	321 (26.4)	73 (24.3)	109 (30.6)	21 (26.6)	118 (24.5)
No	896 (73.6)	228 (75.7)	247 (69.4)	58 (73.4)	363 (75.5)
Prior non-AIDS[8]					
Yes	187 (15.4)	45 (15.0)	68 (19.1)	13 (16.5)	61 (12.7)
No	1,030 (84.6)	256 (85.0)	288 (80.9)	66 (83.5)	420 (87.3)
Diabetes[9]					
Yes	105 (8.6)	22 (7.3)	36 (10.1)	13 (16.5)	34 (7.1)
No	1,112 (91.4)	279 (92.7)	320 (89.9)	66 (83.5)	447 (92.9)
Hypertension[10]					
Yes	661 (54.3)	177 (58.8)	212 (59.6)	41 (51.9)	231 (48.0)
No	346 (28.4)	94 (31.2)	86 (24.2)	19 (24.1)	147 (30.6)
Unknown	210 (17.3)	30 (10.0)	58 (16.3)	19 (24.1)	103 (21.4)
Anaemia[11]					
severe anaemia/mild anaemia	154 (12.7)	42 (14.0)	45 (12.6)	14 (17.7)	53 (11.0)
normal	480 (39.4)	130 (43.2)	140 (39.3)	33 (41.8)	177 (36.8)

	Overall	A[3]	B[4]	C[5]	D[6]
Other or Unknown	583 (47.9)	129 (42.9)	171 (48.0)	32 (40.5)	251 (52.2)
Prior HCV diagnosis[12]					
Yes	447 (36.7)	89 (29.6)	113 (31.7)	41 (51.9)	204 (42.4)
No	633 (52.0)	185 (61.5)	206 (57.9)	29 (36.7)	213 (44.3)
Unknown	137 (11.3)	27 (9.0)	37 (10.4)	9 (11.4)	64 (13.3)
Prior HBV diagnosis[13]					
Yes	52 (4.3)	15 (5.0)	14 (3.9)	1 (1.3)	22 (4.6)
No	970 (79.7)	241 (80.1)	283 (79.5)	63 (79.7)	383 (79.6)
Unknown	195 (16.0)	45 (15.0)	59 (16.6)	15 (19.0)	76 (15.8)
HIV viral load (copies/mL)[14]					
< 400	884 (72.6)	241 (80.1)	267 (75.0)	57 (72.2)	319 (66.3)
≥ 400	135 (11.1)	28 (9.3)	30 (8.4)	9 (11.4)	68 (14.1)
Unknown	198 (16.3)	32 (10.6)	59 (16.6)	13 (16.5)	94 (19.5)
Peak HIV viral load (copies/mL)[15]					
< 400	111 (9.1)	26 (8.6)	30 (8.4)	7 (8.9)	48 (10.0)
≥ 400	1,072 (88.1)	272 (90.4)	315 (88.5)	68 (86.1)	417 (86.7)
Unknown	34 (2.8)	3 (1.0)	11 (3.1)	4 (5.1)	16 (3.3)
CD4 count (cells/mm^3)[14]					
<200	91 (7.5)	14 (4.7)	30 (8.4)	7 (8.9)	40 (8.3)
200 - 349	112 (9.2)	29 (9.6)	30 (8.4)	10 (12.7)	43 (8.9)

	Overall	A[3]	B[4]	C[5]	D[6]
350 - < 499	184 (15.1)	48 (15.9)	46 (12.9)	19 (24.1)	71 (14.8)
≥500	583 (47.9)	163 (54.2)	174 (48.9)	29 (36.7)	217 (45.1)
Unknown	247 (20.3)	47 (15.6)	76 (21.3)	14 (17.7)	110 (22.9)
CD4 count nadir(cells/mm^3) [16]					
<200	713 (58.6)	166 (55.1)	216 (60.7)	49 (62.0)	282 (58.6)
200 - 349	348 (28.6)	97 (32.2)	103 (28.9)	23 (29.1)	125 (26.0)
350 - < 499	98 (8.1)	28 (9.3)	25 (7.0)	5 (6.3)	40 (8.3)
≥500	42 (3.5)	8 (2.7)	7 (2.0)	1 (1.3)	26 (5.4)
Unknown	16 (1.3)	2 (0.7)	5 (1.4)	1 (1.3)	8 (1.7)
eGFR (ml/min/1.73m^2) [17]					
<60	77 (6.3)	24 (8.0)	20 (5.6)	9 (11.4)	24 (5.0)
≥ 60	940 (77.2)	238 (79.1)	272 (76.4)	56 (70.9)	374 (77.8)
Unknown	200 (16.4)	39 (13.0)	64 (18.0)	14 (17.7)	83 (17.3)
ALT (U/L)					
<40	412 (33.9)	114 (37.9)	124 (34.8)	25 (31.6)	149 (31.0)
≥ 40	217 (17.8)	55 (18.3)	60 (16.9)	21 (26.6)	81 (16.8)
Unknown	588 (48.3)	132 (43.9)	172 (48.3)	33 (41.8)	251 (52.2)
AST (U/L)					
<40	349 (28.7)	97 (32.2)	112 (31.5)	20 (25.3)	120 (24.9)
≥ 40	145 (11.9)	34 (11.3)	40 (11.2)	19 (24.1)	52 (10.8)

	Overall	A[3]	B[4]	C[5]	D[6]
Unknown	723 (59.4)	170 (56.5)	204 (57.3)	40 (50.6)	309 (64.2)
Proportion of follow-up time in EuroSIDA with immunosuppression (defined as a CD4 count <200/cells mm3)[18]					
<20%	933 (76.7)	247 (82.1)	267 (75.0)	58 (73.4)	361 (75.1)
≥ 20%	268 (22.0)	52 (17.3)	84 (23.6)	20 (25.3)	112 (23.3)
Unknown	16 (1.3)	2 (0.7)	5 (1.4)	1 (1.3)	8 (1.7)
Proportion of follow-up time in EuroSIDA with uncontrolled viremia (HIV RNA VL > 400 copies/ml)[19]					
<20%	642 (52.8)	176 (58.5)	182 (51.1)	47 (59.5)	237 (49.3)
≥ 20%	537 (44.1)	122 (40.5)	161 (45.2)	28 (35.4)	226 (47.0)
Unknown	38 (3.1)	3 (1.0)	13 (3.7)	4 (5.1)	18 (3.7)

[1] Baseline in all groups will be defined as the date of starting the DTG (or other integrase inhibitor).
[2] After the 16 Jan 2014.
[3] DTG with ABC
[4] DTG without ABC
[5] ELV/RAL with ABC
[6] ELV/RAL without ABC
[7] Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition[1].
[8] Non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, NADM [2]
[9] Prior diabetes defined as: Prior diagnosis of diabetes mellitus, or taking oral antidiabetic agents or insulin
[10] hypertension defined as: SBP >= 140 mmHg, DBP >= 90 mmHg or taking angiotensin-converting enzyme inhibitors/antihypertensive agents
[11] Severe/mild anaemia defined as: Haemoglobulin < 14 and <12 in males and females respectively. [12] Prior Hepatitis C Virus (HCV) defined as: Prior HCV antibody test Positive (Yes), Negative (No) or no test or inconclusive (Unknown).
[13] Prior Hepatitis B Virus (HBV) defined as: Any hepatitis B surface antigen (HBsAg) positive (Yes), HBsAg negative, with no history of HBsAG positive test (No) or no test or inconclusive (Unknown).
[14] Within 6 months prior to date
[15] Peak Viral-load defined as: the highest HIV-viral load measured prior to date

[16] CD4 nadir defined as: the lowest CD4 cell count measured prior to date
[17] Estimated glomerular filtration rate (eGFR) calculated using: CKD-EPI
[18] Proportion of follow-up time under follow-up with immunosuppression defined as: total time under follow-up with CD4 count <200/cells mm^3 divided by the total time under follow-up, prior to date
[19] Proportion of follow-up time in EuroSIDA with uncontrolled viraemia defined as: total time under follow-up with HIV RNA VL > 400 copies/ml divided by the total time under follow-up, prior to date

TABLE 4: Baseline[1] characteristics of ARV history of new users[2] of DTG with ABC (A), DTG without ABC (B), RAL or ELV with ABC (C) RAL or ELV without ABC (D).

	Overall	A[3]	B[4]	C[5]	D[6]
all					
	1,217 (100)	301 (100)	356 (100)	79 (100)	481 (100)
Treatment naïve at baseline					
Yes vs No	87 (7.1)	15 (5.0)	15 (4.2)	5 (6.3)	52 (10.8)
Integrase inhibitor Naïve at baseline					
Yes vs No	962 (79.0)	249 (82.7)	229 (64.3)	73 (92.4)	411 (85.4)
Current regimen includes PI					
Yes vs No	704 (57.8)	167 (55.5)	238 (66.9)	47 (59.5)	252 (52.4)
Current regimen includes NNRTI					
Yes vs No	368 (30.2)	80 (26.6)	101 (28.4)	23 (29.1)	164 (34.1)
Current regimen includes NRTI					
Yes vs No	1,116 (91.7)	301 (100)	306 (86.0)	79 (100)	430 (89.4)
Prior exposure to PI					
Yes vs No	959 (78.8)	236 (78.4)	305 (85.7)	66 (83.5)	352 (73.2)
Prior exposure to NNRTI					
Yes vs No	744 (61.1)	175 (58.1)	228 (64.0)	47 (59.5)	294 (61.1)
Prior exposure to NRTI					
Yes vs No	1,104 (90.7)	283 (94.0)	334 (93.8)	73 (92.4)	414 (86.1)

Prior exposure to DTG					
Yes vs No	3 (0.2)	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Prior exposure to ELV					
Yes vs No	10 (0.8)	3 (1.0)	4 (1.1)	0 (0.0)	3 (0.6)
Prior exposure to RAL					
Yes vs No	246 (20.2)	49 (16.3)	124 (34.8)	6 (7.6)	67 (13.9)
Number of ARVs previously exposed to					
Median Number [IQR]	7.0 (4.0,11.0)	7.0 (5.0,10.0)	9.0 (5.0,13.0)	8.0 (6.0,11.0)	7.0 (4.0,10.0)
Years since first use of any ARV (years)[7]					
Median years [IQR]	14.1 (6.3,18.6)	13.0 (6.3,17.9)	17.1 (8.0,19.6)	16.7 (6.3,19.7)	12.6 (5.2,18.3)

[1] Baseline in all groups will be defined as the date of starting the DTG (or other integrase inhibitor).
[2] After the 16 Jan 2014.
[3] DTG with ABC
[4] DTG without ABC
[5] ELV/RAL with ABC
[6] ELV/RAL without ABC
[7] Cumulative years since starting at least one ARV prior to date

TABLE 5: Baseline[1] characteristics of resistance history (where available) of new users[2] of DTG with ABC (A), DTG without ABC (B), RAL or ELV with ABC (C) RAL or ELV without ABC (D).

	Overall	A[3]	B[4]	C[5]	D[6]
all					
	365 (100)	88 (100)	128 (100)	17 (100)	132 (100)
Any resistance					
Yes	235 (64.4)	49 (55.7)	86 (67.2)	11 (64.7)	89 (67.4)
No	130 (35.6)	39 (44.3)	42 (32.8)	6 (35.3)	43 (32.6)
Major PI					
Yes	107 (29.3)	19 (21.6)	45 (35.2)	6 (35.3)	37 (28.0)
No	258 (70.7)	69 (78.4)	83 (64.8)	11 (64.7)	95 (72.0)
NNRTI					
Yes	148 (40.5)	29 (33.0)	59 (46.1)	5 (29.4)	55 (41.7)
No	217 (59.5)	59 (67.0)	69 (53.9)	12 (70.6)	77 (58.3)
NRTI					
Yes	195 (53.4)	37 (42.0)	74 (57.8)	9 (52.9)	75 (56.8)
No	170 (46.6)	51 (58.0)	54 (42.2)	8 (47.1)	57 (43.2)
INSTI[7]					
Yes	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
No	365 (100)	88 (100)	128 (100)	17 (100)	132 (100)
Genotypic sensitivity score (GSS)[7]					

<3	160 (43.8)	31 (35.2)	60 (46.9)	9 (52.9)	60 (45.5)
3 or more	205 (56.2)	57 (64.8)	68 (53.1)	8 (47.1)	72 (54.5)
Median score [IQR]	3 (2,3)	3 (2,3)	3 (2,3)	2 (1,4)	3 (2,3)
Proportion of regimen active[8]					
All drugs active	243 (66.6)	56 (63.6)	89 (69.5)	9 (52.9)	89 (67.4)
Not all drugs active	122 (33.4)	32 (36.4)	39 (30.5)	8 (47.1)	43 (32.6)
Median proportion [IQR]	1.0 (0.7,1.0)	1.0 (0.5,1.0)	1.0 (0.8,1.0)	1.0 (0.3,1.0)	1.0 (0.7,1.0)

[1] Baseline in all groups will be defined as the date of starting the DTG (or other integrase inhibitor).
[2] After the 16 Jan 2014.
[3] DTG with ABC
[4] DTG without ABC
[5] ELV/RAL with ABC
[6] ELV/RAL without ABC
[7] will be shown when > 10 patients have resistance data available.
[8] Genotypic sensitivity score calculated using: ANRS algorithm
[9] Proportion of active drugs in regimen calculated as ANRS score/number of ARV in current regimen

TABLE 6 Most recent non-AIDS defining events[2] that occurred prior to baseline[2], with median proximity to baseline [IQR]

Prior non-AIDS events	N	%	Median years (IQR)
Overall	187	100.0	7.2 (3.0,14.4)
cardiovascular	66	35.3	4.2 (1.9,8.2)
liver failure	14	7.5	14.6 (12.6,17.7)
pancreatitis	14	7.5	9.7 (6.7,16.6)
NADM	93	49.7	7.9 (3.8,15.7)

[1]Non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, NADM [2]
[2]Baseline in all groups will be defined as the date of starting the DTG (or other integrase inhibitor)

TABLE 7 Most recent AIDS defining events[2] that occurred prior to baseline[2], with median proximity to baseline [IQR]

Prior AIDS events	N	%	Median years (IQR)
Overall	321	100.0	12.5 (6.9,17.6)
Oesophageal Candidiasis	67	20.9	10.3 (4.5,15.6)
Cryptococcosis	6	1.9	10.7 (6.3,17.0)
Cryptosporidiosis	5	1.6	17.6 (16.9,18.0)
Cervical cancer	3	0.9	4.4 (1.7,14.8)
AIDS dementia complex	11	3.4	13.4 (1.1,18.8)
Focal Brain lesion	1	0.3	19.0 (19.0,19.0)
Herpes simplex virus ulcers (duration > 1 month) or pneumonitis/esophagitis	8	2.5	20.0 (14.2,22.2)

Prior AIDS events	N	%	Median years (IQR)
Isosporiasis diarrhoea (duration > 1 month)	3	0.9	12.3 (9.8,12.6)
Kaposi Sarcoma	37	11.5	10.3 (6.9,18.2)
Leishmaniasis, visceral	2	0.6	11.4 (9.6,13.1)
Progressive multifocal Leucoencephalopathy	2	0.6	12.4 (8.3,16.5)
Pneumocystis carinii pneumonia (PCP)	54	16.8	16.2 (9.7,18.2)
Salmonella septicemia	1	0.3	11.3 (11.3,11.3)
Toxoplasmosis	19	5.9	12.3 (5.4,17.7)
HIV Wasting syndrome	22	6.9	12.2 (7.5,16.8)
Cytomegavirus (CMV)	7	2.2	9.4 (3.5,12.9)
Non-Hodgkin Lymphoma	19	5.9	8.9 (3.8,14.9)
Mycobacterium avium complex (MAC) or Kanasii, extrapulmonary	17	5.3	15.3 (11.2,18.3)
Mycobacterium TB pulmonary	25	7.8	12.8 (7.0,18.3)
Mycobacterium TB extrapulmonary	12	3.7	12.8 (8.3,16.6)

[1]Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition [1].
[2]Baseline in all groups will be defined as the date of starting the DTG (or other integrase inhibitor)

TABLE 8: Demographic characteristics of new users[2] of DTG RAL or ELV who discontinued integrase inhibitors

			Discontinued					
	Overall	**Did not discontinue**	**Total**	**HSR**	**Hepatotoxicity**	**Severe skin rash (Not HSR)**	**Other**	**Unknown**
all								
	1,217 (100.0)	1,087 (100.0)	130 (100.0)	2 (100.0)	0 (0.0)	0 (0.0)	97 (100.0)	31 (100.0)
Integrase inhibitor Regimen								
A[3]	301 (24.7)	278 (25.6)	23 (17.7)	0 (0.0)	0 (0.0)	0 (0.0)	19 (19.6)	4 (12.9)
B[4]	356 (29.3)	330 (30.4)	26 (20.0)	1 (50.0)	0 (0.0)	0 (0.0)	21 (21.6)	4 (12.9)
C[5]	79 (6.5)	64 (5.9)	15 (11.5)	0 (0.0)	0 (0.0)	0 (0.0)	10 (10.3)	5 (16.1)
D[6]	481 (39.5)	415 (38.2)	66 (50.8)	1 (50.0)	0 (0.0)	0 (0.0)	47 (48.5)	18 (58.1)
Age (years)								
≤ 35 years	63 (5.2)	58 (5.3)	5 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	4 (4.1)	1 (3.2)
36 - 40 years	117 (9.6)	103 (9.5)	14 (10.8)	0 (0.0)	0 (0.0)	0 (0.0)	7 (7.2)	7 (22.6)
41 - 50 years	381 (31.3)	352 (32.4)	29 (22.3)	0 (0.0)	0 (0.0)	0 (0.0)	23 (23.7)	6 (19.4)
51 + years	656 (53.9)	574 (52.8)	82 (63.1)	2 (100.0)	0 (0.0)	0 (0.0)	63 (64.9)	17 (54.8)
Gender								
Male	913 (75.0)	822 (75.6)	91 (70.0)	2 (100.0)	0 (0.0)	0 (0.0)	69 (71.1)	20 (64.5)
Female	304 (25.0)	265 (24.4)	39 (30.0)	0 (0.0)	0 (0.0)	0 (0.0)	28 (28.9)	11 (35.5)
Race								
white	1,040 (85.5)	931 (85.6)	109 (83.8)	2 (100.0)	0 (0.0)	0 (0.0)	80 (82.5)	27 (87.1)
Other or Missing	177 (14.5)	156 (14.4)	21 (16.2)	0 (0.0)	0 (0.0)	0 (0.0)	17 (17.5)	4 (12.9)
HIV exposure group								

MSM	493 (40.5)	442 (40.7)	51 (39.2)	2 (100.0)	0 (0.0)	0 (0.0)	35 (36.1)	14 (45.2)
IDU	307 (25.2)	273 (25.1)	34 (26.2)	0 (0.0)	0 (0.0)	0 (0.0)	29 (29.9)	5 (16.1)
Heterosexual	320 (26.3)	284 (26.1)	36 (27.7)	0 (0.0)	0 (0.0)	0 (0.0)	28 (28.9)	8 (25.8)
Other/Missing	97 (8.0)	88 (8.1)	9 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	5 (5.2)	4 (12.9)
Region of Europe[7]								
South and Argentina	291 (23.9)	271 (24.9)	20 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)	14 (14.4)	6 (19.4)
Central	387 (31.8)	327 (30.1)	60 (46.2)	2 (100.0)	0 (0.0)	0 (0.0)	49 (50.5)	9 (29.0)
North	397 (32.6)	363 (33.4)	34 (26.2)	0 (0.0)	0 (0.0)	0 (0.0)	27 (27.8)	7 (22.6)
East central	130 (10.7)	116 (10.7)	14 (10.8)	0 (0.0)	0 (0.0)	0 (0.0)	5 (5.2)	9 (29.0)
East	12 (1.0)	10 (0.9)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.1)	0 (0.0)
Body mass index (BMI)								
<18	25 (2.1)	22 (2.0)	3 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.1)	1 (3.2)
18 - 25	539 (44.3)	492 (45.3)	47 (36.2)	1 (50.0)	0 (0.0)	0 (0.0)	35 (36.1)	11 (35.5)
>25	334 (27.4)	304 (28.0)	30 (23.1)	1 (50.0)	0 (0.0)	0 (0.0)	23 (23.7)	6 (19.4)
unknown	319 (26.2)	269 (24.7)	50 (38.5)	0 (0.0)	0 (0.0)	0 (0.0)	37 (38.1)	13 (41.9)
Smoking status								
Current	459 (37.7)	412 (37.9)	47 (36.2)	1 (50.0)	0 (0.0)	0 (0.0)	32 (33.0)	14 (45.2)
Former	213 (17.5)	196 (18.0)	17 (13.1)	0 (0.0)	0 (0.0)	0 (0.0)	15 (15.5)	2 (6.5)
Never	468 (38.5)	429 (39.5)	39 (30.0)	0 (0.0)	0 (0.0)	0 (0.0)	28 (28.9)	11 (35.5)
Unknown	77 (6.3)	50 (4.6)	27 (20.8)	1 (50.0)	0 (0.0)	0 (0.0)	22 (22.7)	4 (12.9)
Date of baseline[8]								
Median date [IQR]	OCT14 (MAY14,FEB15)	NOV14 (JUN14,FEB15)	JUL14 (APR14,NOV14)	APR14 (APR14,MAY14)	-	-	JUL14 (APR14,NOV14)	AUG14 (APR14,DEC14)

[1]Date of first discontinuation in those who stopped DTG, RAL or ELV, or last clinic visit in those who did not.

[2]After the 16 Jan 2014
[3]DTG with ABC
[4]DTG without ABC
[5]ELV/RAL with ABC
[6]ELV/RAL without ABC
[7]Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; North: Austria, Belgium, France, Germany, Luxembourg, Central: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia; East: Belarus, Estonia, Latvia, Lithuania, Russian Federation, Ukraine.
[8]Baseline in all groups will be defined as the date of starting the DTG (or other integrase inhibitor).

TABLE 9: Clinical characteristics at time of first discontinuation[1] of new users[2] of DTG, RAL, and ELV.

			Discontinued					
	Overall	**Did not discontinue**	**Total**	**HSR**	**Hepatotoxicity**	**Severe skin rash (Not HSR)**	**Other**	**Unknown**
all								
	1,217 (100)	1,087 (100)	130 (100)	2 (100)	0 (0.0)	0 (0.0)	97 (100)	31 (100)
Prior AIDS[3]								
Yes	324 (26.6)	290 (26.7)	34 (26.2)	0 (0.0)	0 (0.0)	0 (0.0)	24 (24.7)	10 (32.3)
No	893 (73.4)	797 (73.3)	96 (73.8)	2 (100)	0 (0.0)	0 (0.0)	73 (75.3)	21 (67.7)
Prior non-AIDS[4]								
Yes	189 (15.5)	171 (15.7)	18 (13.8)	1 (50.0)	0 (0.0)	0 (0.0)	13 (13.4)	4 (12.9)
No	1,028 (84.5)	916 (84.3)	112 (86.2)	1 (50.0)	0 (0.0)	0 (0.0)	84 (86.6)	27 (87.1)
Diabetes[5]								
Yes	105 (8.6)	92 (8.5)	13 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (7.2)	6 (19.4)
No	1,112 (91.4)	995 (91.5)	117 (90.0)	2 (100)	0 (0.0)	0 (0.0)	90 (92.8)	25 (80.6)
Hypertension[6]								
Yes	722 (59.3)	656 (60.3)	66 (50.8)	1 (50.0)	0 (0.0)	0 (0.0)	52 (53.6)	13 (41.9)
No	434 (35.7)	388 (35.7)	46 (35.4)	0 (0.0)	0 (0.0)	0 (0.0)	32 (33.0)	14 (45.2)
Unknown	61 (5.0)	43 (4.0)	18 (13.8)	1 (50.0)	0 (0.0)	0 (0.0)	13 (13.4)	4 (12.9)

Anaemia[7]								
severe anaemia/mild anaemia	154 (12.7)	134 (12.3)	20 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)	14 (14.4)	6 (19.4)
normal	480 (39.4)	441 (40.6)	39 (30.0)	0 (0.0)	0 (0.0)	0 (0.0)	30 (30.9)	9 (29.0)
OtherUnknown	583 (47.9)	512 (47.1)	71 (54.6)	2 (100)	0 (0.0)	0 (0.0)	53 (54.6)	16 (51.6)
Prior HCV diagnosis[8]								
Yes	456 (37.5)	398 (36.6)	58 (44.6)	1 (50.0)	0 (0.0)	0 (0.0)	45 (46.4)	12 (38.7)
No	637 (52.3)	579 (53.3)	58 (44.6)	1 (50.0)	0 (0.0)	0 (0.0)	40 (41.2)	17 (54.8)
Unknown	124 (10.2)	110 (10.1)	14 (10.8)	0 (0.0)	0 (0.0)	0 (0.0)	12 (12.4)	2 (6.5)
Prior HBV diagnosis[9]								
Yes	51 (4.2)	49 (4.5)	2 (1.5)	1 (50.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
No	1,003 (82.4)	900 (82.8)	103 (79.2)	1 (50.0)	0 (0.0)	0 (0.0)	76 (78.4)	26 (83.9)
Unknown	163 (13.4)	138 (12.7)	25 (19.2)	0 (0.0)	0 (0.0)	0 (0.0)	20 (20.6)	5 (16.1)
HIV viral load (copies/mL)[10]								
< 400	1,049 (86.2)	951 (87.5)	98 (75.4)	2 (100)	0 (0.0)	0 (0.0)	75 (77.3)	21 (67.7)
≥ 400	44 (3.6)	34 (3.1)	10 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	6 (6.2)	4 (12.9)
Unknown	124 (10.2)	102 (9.4)	22 (16.9)	0 (0.0)	0 (0.0)	0 (0.0)	16 (16.5)	6 (19.4)
Peak HIV viral load (copies/mL)[11]								
< 400	134 (11.0)	121 (11.1)	13 (10.0)	1 (50.0)	0 (0.0)	0 (0.0)	7 (7.2)	5 (16.1)

≥ 400	1,074 (88.2)	958 (88.1)	116 (89.2)	1 (50.0)	0 (0.0)	0 (0.0)	89 (91.8)	26 (83.9)
Unknown	9 (0.7)	8 (0.7)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
CD4 count (cells/mm3)[10]								
<200	63 (5.2)	59 (5.4)	4 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	4 (4.1)	0 (0.0)
200 - 349	126 (10.4)	114 (10.5)	12 (9.2)	2 (100)	0 (0.0)	0 (0.0)	5 (5.2)	5 (16.1)
350 - < 499	189 (15.5)	171 (15.7)	18 (13.8)	0 (0.0)	0 (0.0)	0 (0.0)	17 (17.5)	1 (3.2)
≥500	648 (53.2)	587 (54.0)	61 (46.9)	0 (0.0)	0 (0.0)	0 (0.0)	44 (45.4)	17 (54.8)
Unknown	191 (15.7)	156 (14.4)	35 (26.9)	0 (0.0)	0 (0.0)	0 (0.0)	27 (27.8)	8 (25.8)
CD4 count nadir(cells/mm3) [12]								
<200	724 (59.5)	655 (60.3)	69 (53.1)	1 (50.0)	0 (0.0)	0 (0.0)	54 (55.7)	14 (45.2)
200 - 349	348 (28.6)	303 (27.9)	45 (34.6)	1 (50.0)	0 (0.0)	0 (0.0)	33 (34.0)	11 (35.5)
350 - < 499	96 (7.9)	86 (7.9)	10 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	7 (7.2)	3 (9.7)
≥500	45 (3.7)	39 (3.6)	6 (4.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.1)	3 (9.7)
Unknown	4 (0.3)	4 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
eGFR (ml/min/1.73m2) [13]								
<60	106 (8.7)	98 (9.0)	8 (6.2)	0 (0.0)	0 (0.0)	0 (0.0)	7 (7.2)	1 (3.2)
≥ 60	1,007 (82.7)	907 (83.4)	100 (76.9)	1 (50.0)	0 (0.0)	0 (0.0)	74 (76.3)	25 (80.6)
Unknown	104 (8.5)	82 (7.5)	22 (16.9)	1 (50.0)	0 (0.0)	0 (0.0)	16 (16.5)	5 (16.1)
ALT (U/L)								

<40	644 (52.9)	600 (55.2)	44 (33.8)	0 (0.0)	0 (0.0)	0 (0.0)	35 (36.1)	9 (29.0)
³ 40	357 (29.3)	333 (30.6)	24 (18.5)	0 (0.0)	0 (0.0)	0 (0.0)	15 (15.5)	9 (29.0)
Unknown	216 (17.7)	154 (14.2)	62 (47.7)	2 (100)	0 (0.0)	0 (0.0)	47 (48.5)	13 (41.9)
AST (U/L)								
<40	544 (44.7)	510 (46.9)	34 (26.2)	0 (0.0)	0 (0.0)	0 (0.0)	23 (23.7)	11 (35.5)
≥ 40	200 (16.4)	188 (17.3)	12 (9.2)	0 (0.0)	0 (0.0)	0 (0.0)	10 (10.3)	2 (6.5)
Unknown	473 (38.9)	389 (35.8)	84 (64.6)	2 (100)	0 (0.0)	0 (0.0)	64 (66.0)	18 (58.1)
Proportion of follow-up time in EuroSIDA with immunosuppression (defined as a CD4 count <200/cells mm3)[14]								
<20%	956 (78.6)	848 (78.0)	108 (83.1)	1 (50.0)	0 (0.0)	0 (0.0)	81 (83.5)	26 (83.9)
≥ 20%	257 (21.1)	235 (21.6)	22 (16.9)	1 (50.0)	0 (0.0)	0 (0.0)	16 (16.5)	5 (16.1)
Unknown	4 (0.3)	4 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Proportion of follow-up time in EuroSIDA with uncontrolled viremia (HIV RNA VL > 400 copies/ml)[15]								
<20%	711 (58.4)	647 (59.5)	64 (49.2)	1 (50.0)	0 (0.0)	0 (0.0)	49 (50.5)	14 (45.2)
≥ 20%	494 (40.6)	430 (39.6)	64 (49.2)	0 (0.0)	0 (0.0)	0 (0.0)	47 (48.5)	17 (54.8)
Unknown	12 (1.0)	10 (0.9)	2 (1.5)	1 (50.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)

[1] Date of first discontinuation in those who stopped DTG, RAL or ELV, or last clinic visit in those who did not.
[2] After the 16 Jan 2014.
[3] Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition[1].
[4] Non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, NADM [2]
[5] Prior diabetes defined as: Prior diagnosis of diabetes mellitus, or taking oral antidiabetic agents or insulin
[6] hypertension defined as: SBP >= 140 mmHg, DBP >= 90 mmHg or taking angiotensin-converting enzyme inhibitors/antihypertensive agents

[7] Severe/mild anaemia defined as: Haemoglobulin < 14 and <12 in males and females respectively.
[8] Prior Hepatitis C Virus (HCV) defined as: Prior HCV antibody test Positive (Yes), Negative (No) or no test or inconclusive (Unknown).
[9] Prior Hepatitis B Virus (HBV) defined as: Any hepatitis B surface antigen (HBsAg) positive (Yes), HBsAg negative, with no history of HBsAG positive test (No) or no test or inconclusive (Unknown).
[10] Within 6 months prior to date
[11] Peak Viral-load defined as: the highest HIV-viral load measured prior to date
[12] CD4 nadir defined as: the lowest CD4 cell count measured prior to date
[13] Estimated glomerular filtration rate (eGFR) calculated using: CKD-EPI
[14] Proportion of follow-up time under follow-up with immunosuppression defined as: total time under follow-up with CD4 count <200/cells mm^3 divided by the total time under follow-up, prior to date
[15] Proportion of follow-up time in EuroSIDA with uncontrolled viraemia defined as: total time under follow-up with HIV RNA VL > 400 copies/ml divided by the total time under follow-up, prior to date

TABLE 10: Characteristics of ARV history at time of first discontinuation[1] of new users[2] of DTG, RAL, and ELV.

			Discontinued					
	Overall	**Did not discontinue**	**Total**	**HSR**	**Hepatotoxicity**	**Severe skin rash (Not HSR)**	**Other**	**Unknown**
All								
	1,217 (100.0)	1,087 (100.0)	130 (100.0)	2 (100.0)	0 (0.0)	0 (0.0)	97 (100.0)	31 (100.0)
Treatment naïve at baseline								
Yes vs No	87 (7.1)	80 (7.4)	7 (5.4)	0 (0.0)	0 (0.0)	0 (0.0)	6 (6.2)	1 (3.2)
Integrase inhibitor Naïve at baseline								
Yes vs No	962 (79.0)	856 (78.7)	106 (81.5)	1 (50.0)	0 (0.0)	0 (0.0)	80 (82.5)	25 (80.6)
Current regimen includes PI								
Yes vs No	519 (42.6)	451 (41.5)	68 (52.3)	1 (50.0)	0 (0.0)	0 (0.0)	48 (49.5)	19 (61.3)
Current regimen includes NNRTI								
Yes vs No	216 (17.7)	176 (16.2)	40 (30.8)	0 (0.0)	0 (0.0)	0 (0.0)	31 (32.0)	9 (29.0)
Current regimen includes NRTI								
Yes vs No	1,090 (89.6)	969 (89.1)	121 (93.1)	2 (100.0)	0 (0.0)	0 (0.0)	93 (95.9)	26 (83.9)
Prior exposure to PI								
Yes vs No	977 (80.3)	875 (80.5)	102 (78.5)	2 (100.0)	0 (0.0)	0 (0.0)	77 (79.4)	23 (74.2)
Prior exposure to NNRTI								
Yes vs No	766 (62.9)	673 (61.9)	93 (71.5)	1 (50.0)	0 (0.0)	0 (0.0)	72 (74.2)	20 (64.5)
Prior exposure to NRTI								
Yes vs No	1,181 (97.0)	1,054 (97.0)	127 (97.7)	2 (100.0)	0 (0.0)	0 (0.0)	96 (99.0)	29 (93.5)
Prior exposure to DTG								

Yes vs No	3 (0.2)	1 (0.1)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (3.2)
Prior exposure to ELV								
Yes vs No	10 (0.8)	7 (0.6)	3 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.1)	0 (0.0)
Prior exposure to RAL								
Yes vs No	246 (20.2)	225 (20.7)	21 (16.2)	1 (50.0)	0 (0.0)	0 (0.0)	15 (15.5)	5 (16.1)
Number of ARVs previously exposed to								
Median Number [IQR]	8.0 (5.0,11.0)	8.0 (5.0,11.0)	8.0 (5.0,12.0)	10.0 (6.0,14.0)	-	-	8.0 (5.0,11.0)	7.0 (5.0,12.0)
Years since first use of any ARV (years)[3]								
Median years [IQR]	14.6 (6.9,19.1)	14.7 (6.9,19.2)	12.8 (6.0,18.7)	16.7 (12.6,20.8)	-	-	12.6 (6.0,18.6)	13.5 (5.7,18.9)

[1] Date of first discontinuation in those who stopped DTG, RAL or ELV, or last clinic visit in those who did not.
[2] After the 16 Jan 2014.
[3] Cumulative years since starting at least one ARV prior to date

TABLE 11: Descriptive analysis of risk of discontinuation due to HSR or hepatotoxicity by dose of integrase inhibitor.

There were 2 discontinuations due to HSR. One received DTG at 50 mg once daily for a duration of 5 days, the other received RAL at 400 mg twice daily for a duration of 43 days.

Note: Table will be completed when >5 discontinuations occur.

Drug	Dosage	Total	Discontinuation									
			HSR		Hepatotoxicity		Severe skin rash (Not HSR)		Other		Unknown	
DTG			n	%	n	%	n	%	n	%	n	%
	50 mg x 1 daily											
	50 mg x 2 daily											
	Unknown											
ELV												
	150 mg x 1 daily											
	Unknown											
RAL												
	400 mg x 2 daily											
	Unknown											
Total												

NOTE: Dose was only collected for those who discontinued an integrase inhibitor due to HSR or hepatotoxicity.

NOTE: Variables had to have 5 or more people receiving each drug to be included in the model. Levels of variables with <5 people receiving each drug were combined if this seemed appropriate (i.e. East and central east, BMI <18 and 18 – 25). These will be presented separately in future reports once the numbers allow.

TABLE 12: Comparison of characteristics of those starting[1] DTG (with or without ABC) vs ELV/RAL (with or without ABC) A[2] or B[3] vs C[4] or D[5]

	Unadjusted		Adjusted	
Variable	**OR**	**P**	**OR[6]**	**P**
Age (years)				
≤ 35 years	1.07 (0.60,1.91)	0.809	1.09 (0.60,2.00)	0.768
36 - 40 years	reference		reference	
41 - 50 years	1.04 (0.70,1.54)	0.860	0.81 (0.53,1.25)	0.345
51 + years	1.37 (0.94,2.00)	0.105	0.94 (0.62,1.43)	0.771
Gender				
Male	reference		reference	
Female	1.00 (0.77,1.29)	0.988	1.07 (0.78,1.48)	0.664
Race				
white	reference		reference	
Other or Missing	0.84 (0.61,1.16)	0.285	0.61 (0.43,0.88)	0.008
HIV exposure group				
MSM	reference		reference	
IDU	0.49 (0.37,0.66)	<.001	0.68 (0.48,0.96)	0.029
Heterosexual	0.95 (0.71,1.26)	0.706	0.99 (0.69,1.42)	0.962
Other/Missing	1.33 (0.84,2.09)	0.218	1.22 (0.76,1.98)	0.412
Region of Europe[7]				
South and Argentina	0.33 (0.24,0.45)	<.001	0.33 (0.23,0.46)	<.001
Central	reference		reference	
North	0.83 (0.62,1.12)	0.222	0.82 (0.60,1.11)	0.195
East and East central	0.21 (0.14,0.32)	<.001	0.19 (0.12,0.30)	<.001
Body mass index (BMI)				
<18, 18 - 25	reference		reference	
>25	0.88 (0.65,1.20)	0.433	0.95 (0.68,1.33)	0.770
Unknown	0.67 (0.52,0.87)	0.002	0.84 (0.62,1.14)	0.262

	Unadjusted		Adjusted	
Variable	**OR**	**P**	**OR[6]**	**P**
Smoking status				
Current	0.69 (0.52,0.92)	0.012	0.74 (0.53,1.02)	0.064
Former	0.87 (0.61,1.23)	0.419	0.91 (0.63,1.34)	0.647
Never	reference		reference	
Unknown	0.54 (0.40,0.75)	<.001	0.67 (0.46,0.99)	0.045
Treatment naïve at baseline				
Yes	0.42 (0.27,0.67)	<.001	0.54 (0.33,0.87)	0.012
No	reference		reference	

[1] After the 16 Jan 2014.
[2] DTG with ABC
[3] DTG without ABC
[4] ELV/RAL with ABC
[5] ELV/RAL without ABC
[6] Models adjusted for all variables shown in table
[7]Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; North: Austria, Belgium, France, Germany, Luxembourg, Central: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia; East: Belarus, Estonia, Latvia, Lithuania, Russian Federation, Ukraine.

NOTE: Variables had to have 5 or more people receiving each drug to be included in the model. Levels of variables with <5 people receiving each drug were combined if this seemed appropriate (i.e. East and central east and BMI <18 and 18 – 25). These will be presented separately in future reports once the numbers allow.

TABLE 13: Comparison of characteristics of those starting[1] DTG with ABC vs DTG without ABC: A[2] vs B[3] only (excluding those on ELV or RAL: C[4] and D[5])

	Unadjusted		Adjusted	
Variable	**OR**	**P**	**OR[6]**	**P**
Age (years)				
≤ 35 years	0.71 (0.31,1.60)	0.406	0.76 (0.33,1.73)	0.508
36 - 40 years	reference		reference	
41 - 50 years	0.58 (0.32,1.03)	0.061	0.54 (0.30,0.97)	0.040
51 + years	0.40 (0.23,0.70)	0.001	0.35 (0.20,0.63)	<.001
Gender				
Male	reference		reference	
Female	1.17 (0.82,1.67)	0.379	0.90 (0.56,1.42)	0.638
Race				
white	reference		reference	
Other or Missing	1.01 (0.65,1.58)	0.959	0.71 (0.42,1.20)	0.204
HIV exposure group				
MSM	reference		reference	
IDU	0.86 (0.56,1.31)	0.475	1.22 (0.73,2.04)	0.439
Heterosexual	1.27 (0.88,1.84)	0.209	1.31 (0.80,2.13)	0.285
Other/Missing	1.13 (0.65,1.95)	0.663	1.17 (0.65,2.09)	0.599
Region of Europe[7]				
South and Argentina	0.47 (0.30,0.74)	0.001	0.43 (0.26,0.70)	<.001
Central	reference		reference	
North	0.68 (0.48,0.97)	0.031	0.57 (0.39,0.83)	0.004
East and East central	0.56 (0.28,1.09)	0.088	0.38 (0.18,0.80)	0.011
Body mass index (BMI)				
<18, 18 - 25	reference		reference	
>25	0.76 (0.51,1.14)	0.187	0.74 (0.48,1.13)	0.162
Unknown	0.62 (0.44,0.88)	0.008	0.63 (0.42,0.94)	0.024
Smoking status				

	Unadjusted		Adjusted	
Variable	**OR**	**P**	**OR[6]**	**P**
Current	0.81 (0.55,1.19)	0.291	0.76 (0.50,1.15)	0.192
Former	0.58 (0.37,0.92)	0.021	0.58 (0.36,0.93)	0.023
Never	reference		reference	
Unknown	0.63 (0.41,0.98)	0.041	0.49 (0.28,0.87)	0.015
Treatment naïve at baseline				
Yes	1.19 (0.57,2.48)	0.638	1.36 (0.60,3.06)	0.461
No	reference		reference	

[1] After the 16 Jan 2014.
[2] DTG with ABC
[3] DTG without ABC
[4] ELV/RAL with ABC
[5] ELV/RAL without ABC
[6] Models adjusted for all variables shown in table
[7] Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; North: Austria, Belgium, France, Germany, Luxembourg, Central: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia; East: Belarus, Estonia, Latvia, Lithuania, Russian Federation, Ukraine.
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NOTE: Variables had to have 5 or more people receiving each drug to be included in the model. Levels of variables with <5 people receiving each drug were combined if this seemed appropriate (i.e. East and central east, BMI <18 and 18 – 25). These will be presented separately in future reports once the numbers allow.

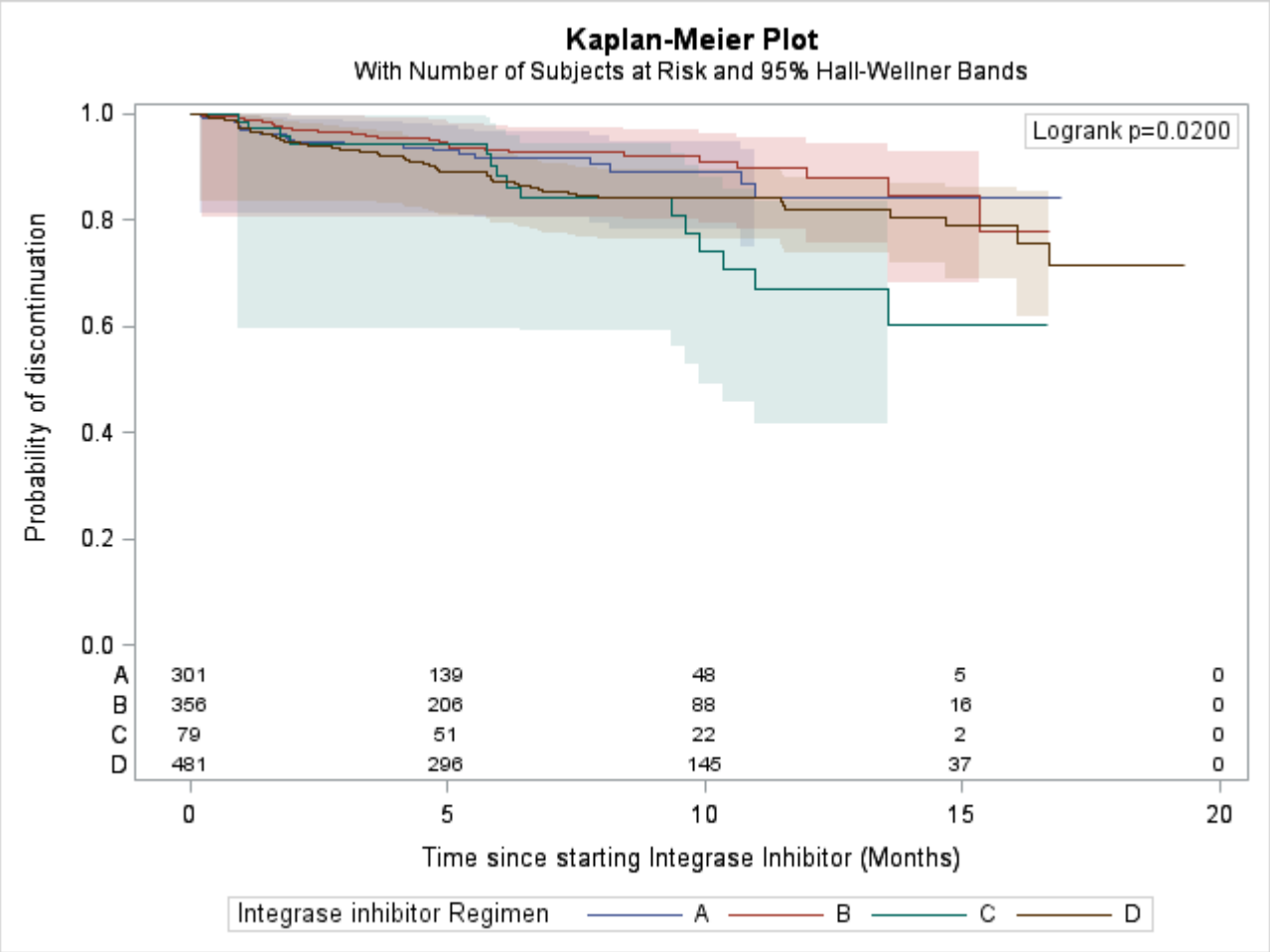
TABLE 14: Comparison of characteristics of those starting[1] ELV/RAL with ABC vs ELV/RAL without ABC: C[2] vs D[3] (excluding those on DTG: A[4] and B[5])

	Unadjusted		Adjusted	
Variable	**OR**	**P**	**OR[6]**	**P**
Age (years)				
≤ 35 years	2.03 (0.60,6.86)	0.252	2.24 (0.65,7.69)	0.202
36 - 40 years	reference		reference	
41 - 50 years	1.71 (0.68,4.32)	0.258	1.66 (0.66,4.19)	0.286
51 + years	1.65 (0.67,4.10)	0.277	1.88 (0.75,4.73)	0.181
Gender				
Male	reference		reference	
Female	1.28 (0.75,2.17)	0.363	1.16 (0.62,2.16)	0.637
Race				
white	reference		reference	
Other or Missing	0.56 (0.26,1.22)	0.146	0.90 (0.40,2.05)	0.803
HIV exposure group				
MSM	reference		reference	
IDU	2.34 (1.29,4.26)	0.005	1.73 (0.90,3.34)	0.100
Heterosexual	1.38 (0.69,2.77)	0.359	1.06 (0.47,2.40)	0.892
Other/Missing	3.03 (1.20,7.62)	0.019	2.47 (0.82,7.43)	0.108
Region of Europe[7]				
South and Argentina	4.20 (1.89,9.36)	<.001	3.55 (1.58,7.98)	0.002
Central	reference		reference	
North	1.70 (0.69,4.14)	0.246	1.59 (0.63,4.06)	0.329
East and East central	3.33 (1.39,8.02)	0.007	3.16 (1.26,7.92)	0.014
Body mass index (BMI)				
<18, 18 - 25	reference		reference	
>25	1.57 (0.83,2.98)	0.169	1.55 (0.73,3.27)	0.250
Unknown	1.14 (0.65,2.01)	0.646	1.11 (0.59,2.10)	0.745
Smoking status				
Current	1.07 (0.58,1.97)	0.826	1.04 (0.53,2.05)	0.916

	Unadjusted		Adjusted	
Variable	**OR**	**P**	**OR[6]**	**P**
Former	0.89 (0.41,1.94)	0.770	0.76 (0.34,1.71)	0.510
Never	reference		reference	
Unknown	0.87 (0.45,1.68)	0.680	0.89 (0.41,1.94)	0.774
Treatment naïve at baseline				
Yes	0.56 (0.22,1.44)	0.228	0.67 (0.24,1.86)	0.439
No	reference		reference	

[1] After the 16 Jan 2014.
[2] DTG with ABC
[3] DTG without ABC
[4] ELV/RAL with ABC
[5] ELV/RAL without ABC
[6] Models adjusted for all variables shown in table
[7]Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; North: Austria, Belgium, France, Germany, Luxembourg, Central: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia; East: Belarus, Estonia, Latvia, Lithuania, Russian Federation, Ukraine.

FIGURE 2: Time to event Kaplan-Meier (KM) estimates of discontinuation by first treatment group (A[1], B[2], C[3], D[4]).



NOTE: FIGURE 3 will be completed once 5 or more HSR, hepatotoxicity events or severe skin rash (Not HSR) have occurred. The blank tables are included to demonstrate the structure of results.

FIGURE 3: Time to event Kaplan-Meier (KM) estimates of discontinuation due to HSR by first treatment group (A[1], B[2], C[3], D[4]).

[FIGURE 3 HERE]

[1] DTG with ABC
[2] DTG without ABC
[3] ELV/RAL with ABC
[4] ELV/RAL without ABC

NOTE: Tables 15 – 24 containing incidence rates and adjusted incidence rates for discontinuation of DTG or other integrase inhibitors will be completed once 30 events or more have occurred in treatment groups A and B combined and C and D combined. Tables 21 and 22 for "other causes" have been included in this report. Blank tables are included to demonstrate the structure of results. The temporary table containing crude incidence rates of discontinuation is included but will be removed once frequency of events improves.

TEMPORARY TABLE: Crude incidence rates of discontinuation by reason for discontinuation as reported on the HSR CRF

Reason for discontinuation	Treatment group	Events	PYFU	Incidence rate/100 PYFU [95% CI][1]
All causes	**Overall**	**139**	**700**	**19.9 (16.8,23.4)**
	A[2] and B[3]	52	346.2	15.0 (11.4,19.7)
	C[4] and D[5]	87	353.8	24.6 (19.9,30.3)
HSR	**Overall**	**2**	**700**	**0.3 (0.1,1.1)**
	A[2] and B[3]	1	346.2	0.3 (0.0,2.1)
	C[4] and D[5]	1	353.8	0.3 (0.0,2.0)
hepatotoxicity	**Overall**	**0**	**700**	**0.0 (0.0,0.0)**
	A[2] and B[3]	0	346.2	0.0 (0.0,0.0)
	C[4] and D[5]	0	353.8	0.0 (0.0,0.0)
Severe skin rash (Not HSR)	**Overall**	**0**	**700**	**0.0 (0.0,0.0)**
	A[2] and B[3]	0	346.2	0.0 (0.0,0.0)
	C[4] and D[5]	0	353.8	0.0 (0.0,0.0)
Other causes	**Overall**	**104**	**700**	**14.9 (12.3,18.0)**
	A[2] and B[3]	42	346.2	12.1 (9.0,16.4)
	C[4] and D[5]	62	353.8	17.5 (13.7,22.5)
Unknown	**Overall**	**33**	**700**	**4.7 (3.4,6.6)**
	A[2] and B[3]	8	346.2	2.3 (1.2,4.6)
	C[4] and D[5]	25	353.8	7.1 (4.8,10.5)

[1] Exact confidence intervals were calculated for all categories with 20 events or less
[2] DTG with ABC
[3] DTG without ABC

[4] ELV/RAL with ABC
[5] ELV/RAL without ABC

NOTE: Table 15 containing incidence rates for discontinuation of integrase inhibitors will be completed once 30 events or more have occurred in treatment groups A and B combined and C and D combined. Blank tables are included to demonstrate the structure of results.

TABLE 15 - Crude incidence rates[1] of discontinuation due to HSR

Characteristic	Level	Discontinued due to HSR			
		Persons	Events	PYFU	Incidence rate/100 PYFU [95% CI]
Integrase inhibitor Regimen					
	A[2] and B[3]				
	C[4] and D[5]				
Demographic					
Age (years)					
	[≤35][36-40][41-50][51+]				
Gender					
	Male				
	Female				
Race					
	White				
	Other/Unknown				
HIV exposure group					
	MSM				
	IDU				
	Heterosexual				
	Other/Unknown				
Region of Europe[6]					
	South and Argentina				
	West				
	North				
	East Central				
	East				
Body mass index (BMI)					

Characteristic	Level	Discontinued due to HSR			
		Persons	Events	PYFU	Incidence rate / 100 PYFU [95% CI]
	<18				
	18-25				
	>25				
	unknown				
	Median [IQR]				
Smoking status					
	Current				
	Former				
	Never				
	Unknown				
Clinical history					
Prior AIDS[7]					
	Yes				
	No				
Prior non-AIDS[8]					
	Yes				
	No				
Diabetes[9]					
	Yes				
	No				
	Unknown				
Hypertension[10]					
	Yes				
	No				
	Unknown				
Anaemia					
	severe/mild anaemia				
	normal				
	Unknown				
Prior HCV diagnosis[11]					
	Yes				

Characteristic	Level	Discontinued due to HSR			
		Persons	Events	PYFU	Incidence rate / 100 PYFU [95% CI]
	No				
	Unknown				
Prior HBV diagnosis[12]					
	Yes				
	No				
	Unknown				
HIV viral load (copies/mL)[13]	[<400][≥ 400][Unknown]				
Peak HIV viral load (copies/mL) [14]	[<400][≥ 400][Unknown]				
CD4 count (cells/mm^3)[14]	[< 200][200-349][350-499][500+][Unknown]				
CD4 count nadir(cells/mm^3)[15]	[< 200][200-349][350-499][500+][Unknown]				
eGFR (ml/min/1.73m2) [16]	[<60][≥60][Unknown]				
ALT (U/L)	[<40][≥ 40][Unknown]				
AST (U/L)	[<40][≥ 40][Unknown]				
Proportion of follow-up time in EuroSIDA with immunosuppression (defined as a CD4 count <200/cells mm^3)[17]	[< 20%][≥20%][unknown]				
Proportion of follow-up time in EuroSIDA with uncontrolled viremia (HIV RNA VL > 400 copies/ml)[18]	[< 20%][≥20%][unknown]				
ARV history					
Treatment naïve at baseline					
	Yes				
	No				
Integrase inhibitor Naïve at baseline					
	Yes				
	No				
Current regimen includes PI					
	Yes				
	No				
Current regimen includes NNRTI					

Characteristic	Level	Discontinued due to HSR			
		Persons	Events	PYFU	Incidence rate / 100 PYFU [95% CI]
	Yes				
	No				
Current regimen includes NRTI					
	Yes				
	No				
Prior exposure to PI					
	Yes				
	No				
Prior exposure to NNRTI					
	Yes				
	No				
Prior exposure to NRTI					
	Yes				
	No				
Prior exposure to DTG					
	Yes				
	No				
Prior exposure to ELV					
	Yes				
	No				
Prior exposure to RAL					
	Yes				
	No				
Number of ARVs previously exposed to	Quintiles				
Years since first use of any ARV (years)[19]	Quintiles				

[1]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.

[2] DTG with ABC

[3] DTG without ABC

[4] ELV/RAL with ABC
[5] ELV/RAL without ABC
[6] Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; North: Austria, Belgium, France, Germany, Luxembourg, Central: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia; East: Belarus, Estonia, Latvia, Lithuania, Russian Federation, Ukraine.
[7] Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition[1].
[8] Non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, NADM [2]
[9] Prior diabetes defined as: Prior diagnosis of diabetes mellitus, or taking oral antidiabetic agents or insulin
[10] hypertension defined as: SBP >= 140 mmHg, DBP >= 90 mmHg or taking angiotensin-converting enzyme inhibitors/antihypertensive agents
[11] Severe/mild anaemia defined as: Haemoglobulin < 14 and <12 in males and females respectively.
[12] Prior Hepatitis C Virus (HCV) defined as: Prior HCV antibody test Positive (Yes), Negative (No) or no test or inconclusive (Unknown).
[13] Prior Hepatitis B Virus (HBV) defined as: Any hepatitis B surface antigen (HBsAg) positive (Yes), HBsAg negative, with no history of HBsAG positive test (No) or no test or inconclusive (Unknown).
[14] Within 6 months prior to date
[15] Peak Viral-load defined as: the highest HIV-viral load measured prior to date
[16] CD4 nadir defined as: the lowest CD4 cell count measured prior to date
[17] Estimated glomerular filtration rate (eGFR) calculated using: CKD-EPI
[18] Proportion of follow-up time under follow-up with immunosuppression defined as: total time under follow-up with CD4 count <200/cells mm^3 divided by the total time under follow-up, prior to date
[19] Proportion of follow-up time in EuroSIDA with uncontrolled viraemia defined as: total time under follow-up with HIV RNA VL > 400 copies/ml divided by the total time under follow-up, prior to date
[20] Cumulative years since starting at least one ARV prior to date

NOTE: Table 16 containing adjusted incidence rates for discontinuation of integrase inhibitors will be completed once 30 events or more have occurred in treatment groups A and B combined and C and D combined. Blank tables are included to demonstrate the structure of results.

TABLE 16 - Adjusted incidence rate ratios[1] of discontinuation due to HSR

Characteristic	Level	Discontinued due to HSR			
		Unadjusted IRR	P	Adjusted IRR [2]	P
Integrase inhibitor Regimen					
	A[3] and B[4]				
	C[5] and D[6]				
Demographic					
Age (years)					
	Per 10 years older/[≤35][36-40][41-50][51+]				
Gender					
	Male				
	Female				
Race					
	White				
	Other/Unknown				
HIV exposure group					
	MSM				
	IDU				
	Heterosexual				
	Other/Unknown				
Region of Europe[7]					
	South and Argentina				
	West				
	North				
	East Central				
	East				
Body mass index (BMI)					
	<18				

Characteristic	Level	Discontinued due to HSR			
		Unadjusted IRR	P	Adjusted IRR [2]	P
	18-25				
	>25				
	unknown				
	Median [IQR]				
Smoking status					
	Current				
	Former				
	Never				
	Unknown				
Clinical history					
Prior AIDS[8]					
	Yes				
	No				
Prior non-AIDS[9]					
	Yes				
	No				
Diabetes[10]					
	Yes				
	No				
	Unknown				
Hypertension[11]					
	Yes				
	No				
	Unknown				
Anaemia					
	severe/mild anaemia				
	normal				
	Unknown				
Prior HCV diagnosis[12]					
	Yes				
	No				
	Unknown				

Characteristic	Level	Discontinued due to HSR			
		Unadjusted IRR	P	Adjusted IRR [2]	P
Prior HBV diagnosis[13]					
	Yes				
	No				
	Unknown				
HIV viral load (copies/mL)[14]	Per 10 fold higher/ [<400][≥ 400][Unknown]				
Peak HIV viral load (copies/mL) [15]	Per 10 fold higher/ [<400][≥ 400][Unknown]				
CD4 count (cells/mm^3)[14]	Per 2 fold higher/[< 200][200-349][350-499][500+][Unknown]				
CD4 count nadir(cells/mm^3)[16]	Per 2 fold higher/[< 200][200-349][350-499][500+][Unknown]				
eGFR (ml/min/1.73m2) [17]	Per 10 units higher / [<60][≥60][Unknown]				
ALT (U/L)	Per 10 units higher / [<40][≥ 40][Unknown]				
AST (U/L)	Per 10 units higher / [<40][≥ 40][Unknown]				
Proportion of follow-up time in EuroSIDA with immunosuppression (defined as a CD4 count <200/cells mm^3)[18]	Per 1 year longer / [< 20%][≥20%][unknown]				
Proportion of follow-up time in EuroSIDA with uncontrolled viremia (HIV RNA VL > 400 copies/ml)[19]	Per 1 year longer / [< 20%][≥20%][unknown]				
ARV history					
Treatment naïve at baseline					
	Yes				
	No				
Integrase inhibitor Naïve at baseline					
	Yes				

Characteristic	Level	Discontinued due to HSR			
		Unadjusted IRR	P	Adjusted IRR [2]	P
	No				
Current regimen includes PI					
	Yes				
	No				
Current regimen includes NNRTI					
	Yes				
	No				
Current regimen includes NRTI					
	Yes				
	No				
Prior exposure to PI					
	Yes				
	No				
Prior exposure to NNRTI					
	Yes				
	No				
Prior exposure to NRTI					
	Yes				
	No				
Prior exposure to DTG					
	Yes				
	No				
Prior exposure to ELV					
	Yes				
	No				
Prior exposure to RAL					
	Yes				
	No				
Number of ARVs previously exposed to	Per additional drug/ quintiles				
Years since first use of any ARV (years)[20]	Per 1 year longer / quintiles				

[1]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.

[2] confounding and effect modifying factors that are significant in univariate analyses (p<0.1) were be included in multivariate models, as well as treatment group and whether the patients were antiretroviral naïve at starting the regimen. Excluded variables were then added in turn to determine if their inclusion improved the fit of the model (defined as a significant reduction in the Log-Likelihood). Models adjusted for xxx

[3] DTG with ABC

[4] DTG without ABC

[5] ELV/RAL with ABC

[6] ELV/RAL without ABC

[7] Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; North: Austria, Belgium, France, Germany, Luxembourg, Central: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia; East: Belarus, Estonia, Latvia, Lithuania, Russian Federation, Ukraine.

[8] Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition[1].

[9] Non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, NADM [2]

[10] Prior diabetes defined as: Prior diagnosis of diabetes mellitus, or taking oral antidiabetic agents or insulin

[11] hypertension defined as: SBP >= 140 mmHg, DBP >= 90 mmHg or taking angiotensin-converting enzyme inhibitors/antihypertensive agents

[12] Severe/mild anaemia defined as: Haemoglobulin < 14 and <12 in males and females respectively

[13] Prior Hepatitis C Virus (HCV) defined as: Prior HCV antibody test Positive (Yes), Negative (No) or no test or inconclusive (Unknown).

[14] Prior Hepatitis B Virus (HBV) defined as: Any hepatitis B surface antigen (HBsAg) positive (Yes), HBsAg negative, with no history of HBsAG positive test (No) or no test or inconclusive (Unknown).

[15] Within 6 months prior to date

[16] Peak Viral-load defined as: the highest HIV-viral load measured prior to date

[17] CD4 nadir defined as: the lowest CD4 cell count measured prior to date

[18] Estimated glomerular filtration rate (eGFR) calculated using: CKD-EPI

[19] Proportion of follow-up time under follow-up with immunosuppression defined as: total time under follow-up with CD4 count <200/cells mm^3 divided by the total time under follow-up, prior to date

[20] Proportion of follow-up time in EuroSIDA with uncontrolled viraemia defined as: total time under follow-up with HIV RNA VL > 400 copies/ml divided by the total time under follow-up, prior to date

[21] Cumulative years since starting at least one ARV prior to date

NOTE: Table 17 containing incidence rates for discontinuation of integrase inhibitors will be completed once 30 events or more have occurred in treatment groups A and B combined and C and D combined. Blank tables are included to demonstrate the structure of results.

TABLE 17 - Crude incidence rates[1] of discontinuation due to Hepatotoxicity

Characteristic	Level	Discontinued due to Hepatotoxicity			
		Persons	Events	PYFU	Incidence rate/100 PYFU [95% CI]
Integrase inhibitor Regimen					
	A[2] and B[3]				
	C[4] and D[5]				
Demographic					
Age (years)					
	[≤35][36-40][41-50][51+]				
Gender					
	Male				
	Female				
Race					
	White				
	Other/Unknown				
HIV exposure group					
	MSM				
	IDU				
	Heterosexual				
	Other/Unknown				
Region of Europe[6]					
	South and Argentina				
	West				

Characteristic	Level	Discontinued due to Hepatotoxicity			
		Persons	Events	PYFU	Incidence rate / 100 PYFU [95% CI]
	North				
	East Central				
	East				
Body mass index (BMI)					
	<18				
	18-25				
	>25				
	unknown				
	Median [IQR]				
Smoking status					
	Current				
	Former				
	Never				
	Unknown				
Clinical history					
Prior AIDS[7]					
	Yes				
	No				
Prior non-AIDS[8]					
	Yes				
	No				
Diabetes[9]					
	Yes				
	No				
	Unknown				
Hypertension[10]					
	Yes				
	No				
	Unknown				

Characteristic	Level	Discontinued due to Hepatotoxicity			
		Persons	Events	PYFU	Incidence rate/100 PYFU [95% CI]
Anaemia					
	severe/mild anaemia				
	normal				
	Unknown				
Prior HCV diagnosis[11]					
	Yes				
	No				
	Unknown				
Prior HBV diagnosis[12]					
	Yes				
	No				
	Unknown				
HIV viral load (copies/mL)[13]	[<400][≥ 400][Unknown]				
Peak HIV viral load (copies/mL) [14]	[<400][≥ 400][Unknown]				
CD4 count (cells/mm^3)[14]	[< 200][200-349][350-499][500+][Unknown]				
CD4 count nadir(cells/mm^3)[15]	[< 200][200-349][350-499][500+][Unknown]				
eGFR (ml/min/1.73m2) [16]	[<60][≥60][Unknown]				
ALT (U/L)	[<40][≥ 40][Unknown]				
AST (U/L)	[<40][≥ 40][Unknown]				
Proportion of follow-up time	[< 20%][≥20%][unknown]				

Characteristic	Level	Discontinued due to Hepatotoxicity			
		Persons	Events	PYFU	Incidence rate / 100 PYFU [95% CI]
in EuroSIDA with immunosuppression (defined as a CD4 count <200/cells mm^3)[17]					
Proportion of follow-up time in EuroSIDA with uncontrolled viremia (HIV RNA VL > 400 copies/ml)[18]	[< 20%][≥20%][unknown]				
ARV history					
Treatment naïve at baseline					
	Yes				
	No				
Integrase inhibitor Naïve at baseline					
	Yes				
	No				
Current regimen includes PI					
	Yes				
	No				
Current					

Characteristic	Level	Discontinued due to Hepatotoxicity			
		Persons	Events	PYFU	Incidence rate / 100 PYFU [95% CI]
regimen includes NNRTI					
	Yes				
	No				
Current regimen includes NRTI					
	Yes				
	No				
Prior exposure to PI					
	Yes				
	No				
Prior exposure to NNRTI					
	Yes				
	No				
Prior exposure to NRTI					
	Yes				
	No				
Prior exposure to DTG					
	Yes				
	No				
Prior exposure to ELV					
	Yes				
	No				
Prior exposure to RAL					

Characteristic	Level	Discontinued due to Hepatotoxicity			
		Persons	Events	PYFU	Incidence rate/100 PYFU [95% CI]
	Yes				
	No				
Number of ARVs previously exposed to	Quintiles				
Years since first use of any ARV (years)[19]	Quintiles				

[1]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.

[2] DTG with ABC

[3] DTG without ABC

[4] ELV/RAL with ABC

[5] ELV/RAL without ABC

[6] Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; North: Austria, Belgium, France, Germany, Luxembourg, Central: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia; East: Belarus, Estonia, Latvia, Lithuania, Russian Federation, Ukraine.

[7] Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition[1].

[8] Non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, NADM [2]

[9] Prior diabetes defined as: Prior diagnosis of diabetes mellitus, or taking oral antidiabetic agents or insulin

[10] hypertension defined as: SBP >= 140 mmHg, DBP >= 90 mmHg or taking angiotensin-converting enzyme inhibitors/antihypertensive agents

[11] Severe/mild anaemia defined as: Haemoglobulin < 14 and <12 in males and females respectively.

[12] Prior Hepatitis C Virus (HCV) defined as: Prior HCV antibody test Positive (Yes), Negative (No) or no test or inconclusive (Unknown).

[13] Prior Hepatitis B Virus (HBV) defined as: Any hepatitis B surface antigen (HBsAg) positive (Yes), HBsAg negative, with no history of HBsAG positive test (No) or no test or inconclusive (Unknown).

[14] Within 6 months prior to date

[15] Peak Viral-load defined as: the highest HIV-viral load measured prior to date

[16] CD4 nadir defined as: the lowest CD4 cell count measured prior to date
[17] Estimated glomerular filtration rate (eGFR) calculated using: CKD-EPI
[18] Proportion of follow-up time under follow-up with immunosuppression defined as: total time under follow-up with CD4 count <200/cells mm^3 divided by the total time under follow-up, prior to date
[19] Proportion of follow-up time in EuroSIDA with uncontrolled viraemia defined as: total time under follow-up with HIV RNA VL > 400 copies/ml divided by the total time under follow-up, prior to date
[20] Cumulative years since starting at least one ARV prior to date

NOTE: Table 18 containing adjusted incidence rates for discontinuation of integrase inhibitors will be completed once 30 events or more have occurred in treatment groups A and B combined and C and D combined. Blank tables are included to demonstrate the structure of results.

TABLE 18 - Adjusted incidence rate ratios[1] of discontinuation due to Hepatotoxicity

Characteristic	Level	Discontinued due to Hepatotoxicity			
		Unadjusted IRR	P	Adjusted IRR [2]	P
Integrase inhibitor Regimen					
	A[3] and B[4]				
	C[5] and D[6]				
Demographic					
Age (years)					
	Per 10 years older/[≤35][36-40][41-50][51+]				
Gender					
	Male				
	Female				
Race					
	White				
	Other/Unknown				
HIV exposure group					
	MSM				
	IDU				
	Heterosexual				
	Other/Unknown				
Region of Europe[7]					
	South and Argentina				
	West				
	North				
	East Central				
	East				
Body mass index (BMI)					
	<18				

Characteristic	Level	Discontinued due to Hepatotoxicity			
		Unadjusted IRR	P	Adjusted IRR [2]	P
	18-25				
	>25				
	unknown				
	Median [IQR]				
Smoking status					
	Current				
	Former				
	Never				
	Unknown				
Clinical history					
Prior AIDS[8]					
	Yes				
	No				
Prior non-AIDS[9]					
	Yes				
	No				
Diabetes[10]					
	Yes				
	No				
	Unknown				
Hypertension[11]					
	Yes				
	No				
	Unknown				
Anaemia					
	severe/mild anaemia				
	normal				
	Unknown				
Prior HCV diagnosis[12]					
	Yes				
	No				
	Unknown				

Characteristic	Level	Discontinued due to Hepatotoxicity			
		Unadjusted IRR	P	Adjusted IRR [2]	P
Prior HBV diagnosis[13]					
	Yes				
	No				
	Unknown				
HIV viral load (copies/mL)[14]	Per 10 fold higher/ [<400][≥ 400][Unknown]				
Peak HIV viral load (copies/mL) [15]	Per 10 fold higher/ [<400][≥ 400][Unknown]				
CD4 count (cells/mm^3)[14]	Per 2 fold higher/[< 200][200-349][350-499][500+][Unknown]				
CD4 count nadir(cells/mm^3)[16]	Per 2 fold higher/[< 200][200-349][350-499][500+][Unknown]				
eGFR (ml/min/1.73m2) [17]	Per 10 units higher / [<60][≥60][Unknown]				
ALT (U/L)	Per 10 units higher / [<40][≥ 40][Unknown]				
AST (U/L)	Per 10 units higher / [<40][≥ 40][Unknown]				
Proportion of follow-up time in EuroSIDA with immunosuppression (defined as a CD4 count <200/cells mm^3)[18]	Per 1 year longer / [< 20%][≥20%][unknown]				
Proportion of follow-up time in EuroSIDA with uncontrolled viremia (HIV RNA VL > 400 copies/ml)[19]	Per 1 year longer / [< 20%][≥20%][unknown]				
ARV history					
Treatment naïve at baseline					
	Yes				
	No				
Integrase inhibitor Naïve at baseline					
	Yes				

Characteristic	Level	Discontinued due to Hepatotoxicity			
		Unadjusted IRR	P	Adjusted IRR [2]	P
	No				
Current regimen includes PI					
	Yes				
	No				
Current regimen includes NNRTI					
	Yes				
	No				
Current regimen includes NRTI					
	Yes				
	No				
Prior exposure to PI					
	Yes				
	No				
Prior exposure to NNRTI					
	Yes				
	No				
Prior exposure to NRTI					
	Yes				
	No				
Prior exposure to DTG					
	Yes				
	No				
Prior exposure to ELV					
	Yes				
	No				
Prior exposure to RAL					
	Yes				
	No				
Number of ARVs previously exposed to	Per additional drug/ quintiles				
Years since first use of any ARV (years)[20]	Per 1 year longer / quintiles				

[1]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.

[2] confounding and effect modifying factors that are significant in univariate analyses (p<0.1) were be included in multivariate models, as well as treatment group and whether the patients were antiretroviral naïve at starting the regimen. Excluded variables were then added in turn to determine if their inclusion improved the fit of the model (defined as a significant reduction in the Log-Likelihood). Models adjusted for xxx

[3] DTG with ABC

[4] DTG without ABC

[5] ELV/RAL with ABC

[6] ELV/RAL without ABC

[7] Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; North: Austria, Belgium, France, Germany, Luxembourg, Central: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia; East: Belarus, Estonia, Latvia, Lithuania, Russian Federation, Ukraine.

[8] Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition[1].

[9] Non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, NADM [2]

[10] Prior diabetes defined as: Prior diagnosis of diabetes mellitus, or taking oral antidiabetic agents or insulin

[11] hypertension defined as: SBP >= 140 mmHg, DBP >= 90 mmHg or taking angiotensin-converting enzyme inhibitors/antihypertensive agents

[12] Severe/mild anaemia defined as: Haemoglobulin < 14 and <12 in males and females respectively

[13] Prior Hepatitis C Virus (HCV) defined as: Prior HCV antibody test Positive (Yes), Negative (No) or no test or inconclusive (Unknown).

[14] Prior Hepatitis B Virus (HBV) defined as: Any hepatitis B surface antigen (HBsAg) positive (Yes), HBsAg negative, with no history of HBsAG positive test (No) or no test or inconclusive (Unknown).

[15] Within 6 months prior to date

[16] Peak Viral-load defined as: the highest HIV-viral load measured prior to date

[17] CD4 nadir defined as: the lowest CD4 cell count measured prior to date

[18] Estimated glomerular filtration rate (eGFR) calculated using: CKD-EPI

[19] Proportion of follow-up time under follow-up with immunosuppression defined as: total time under follow-up with CD4 count <200/cells mm^3 divided by the total time under follow-up, prior to date

[20] Proportion of follow-up time in EuroSIDA with uncontrolled viraemia defined as: total time under follow-up with HIV RNA VL > 400 copies/ml divided by the total time under follow-up, prior to date

[21] Cumulative years since starting at least one ARV prior to date

NOTE: Table 19 containing incidence rates for discontinuation of integrase inhibitors will be completed once 30 events or more have occurred in treatment groups A and B combined and C and D combined. Blank tables are included to demonstrate the structure of results.

TABLE 19 - Crude incidence rates[1] of discontinuation due to severe skin rash (Not HSR)

Characteristic	Level	Discontinued due to severe skin rash (Not HSR)			
		Persons	Events	PYFU	Incidence rate/100 PYFU [95% CI]
Integrase inhibitor Regimen					
	A[2] and B[3]				
	C[4] and D[5]				
Demographic					
Age (years)					
	[≤35][36-40][41-50][51+]				
Gender					
	Male				
	Female				
Race					
	White				
	Other/Unknown				
HIV exposure group					
	MSM				
	IDU				
	Heterosexual				
	Other/Unknown				
Region of Europe[6]					
	South and Argentina				
	West				
	North				
	East Central				

Characteristic	Level	Discontinued due to severe skin rash (Not HSR)			
		Persons	Events	PYFU	Incidence rate/100 PYFU [95% CI]
	East				
Body mass index (BMI)					
	<18				
	18-25				
	>25				
	unknown				
	Median [IQR]				
Smoking status					
	Current				
	Former				
	Never				
	Unknown				
Clinical history					
Prior AIDS[7]					
	Yes				
	No				
Prior non-AIDS[8]					
	Yes				
	No				
Diabetes[9]					
	Yes				
	No				
	Unknown				
Hypertension[10]					
	Yes				
	No				
	Unknown				
Anaemia					
	severe/mild anaemia				

Characteristic	Level	Discontinued due to severe skin rash (Not HSR)			
		Persons	Events	PYFU	Incidence rate/100 PYFU [95% CI]
	normal				
	Unknown				
Prior HCV diagnosis[11]					
	Yes				
	No				
	Unknown				
Prior HBV diagnosis[12]					
	Yes				
	No				
	Unknown				
HIV viral load (copies/mL)[13]	[<400][≥ 400][Unknown]				
Peak HIV viral load (copies/mL) [14]	[<400][≥ 400][Unknown]				
CD4 count (cells/mm^3)[14]	[< 200][200-349][350-499][500+][Unknown]				
CD4 count nadir(cells/mm^3)[15]	[< 200][200-349][350-499][500+][Unknown]				
eGFR (ml/min/1.73m2) [16]	[<60][≥60][Unknown]				
ALT (U/L)	[<40][≥ 40][Unknown]				
AST (U/L)	[<40][≥ 40][Unknown]				
Proportion of follow-up time in EuroSIDA with	[< 20%][≥20%][unknown]				

Characteristic	Level	Discontinued due to severe skin rash (Not HSR)			
		Persons	Events	PYFU	Incidence rate/100 PYFU [95% CI]
immunosuppression (defined as a CD4 count <200/cells mm^3)[17]					
Proportion of follow-up time in EuroSIDA with uncontrolled viremia (HIV RNA VL > 400 copies/ml)[18]	[< 20%][≥20%][unknown]				
ARV history					
Treatment naïve at baseline					
	Yes				
	No				
Integrase inhibitor Naïve at baseline					
	Yes				
	No				
Current regimen includes PI					
	Yes				
	No				
Current regimen includes NNRTI					

Characteristic	Level	Discontinued due to severe skin rash (Not HSR)			
		Persons	Events	PYFU	Incidence rate/100 PYFU [95% CI]
	Yes				
	No				
Current regimen includes NRTI					
	Yes				
	No				
Prior exposure to PI					
	Yes				
	No				
Prior exposure to NNRTI					
	Yes				
	No				
Prior exposure to NRTI					
	Yes				
	No				
Prior exposure to DTG					
	Yes				
	No				
Prior exposure to ELV					
	Yes				
	No				
Prior exposure to RAL					
	Yes				
	No				

Characteristic	Level	Discontinued due to severe skin rash (Not HSR)			
		Persons	Events	PYFU	Incidence rate/100 PYFU [95% CI]
Number of ARVs previously exposed to	Quintiles				
Years since first use of any ARV (years)[19]	Quintiles				

[1]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.

[2] DTG with ABC

[3] DTG without ABC

[4] ELV/RAL with ABC

[5] ELV/RAL without ABC

[6] Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; North: Austria, Belgium, France, Germany, Luxembourg, Central: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia; East: Belarus, Estonia, Latvia, Lithuania, Russian Federation, Ukraine.

[7] Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition[1].

[8] Non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, NADM [2]

[9] Prior diabetes defined as: Prior diagnosis of diabetes mellitus, or taking oral antidiabetic agents or insulin

[10] hypertension defined as: SBP >= 140 mmHg, DBP >= 90 mmHg or taking angiotensin-converting enzyme inhibitors/antihypertensive agents

[11] Severe/mild anaemia defined as: Haemoglobulin < 14 and <12 in males and females respectively.

[12] Prior Hepatitis C Virus (HCV) defined as: Prior HCV antibody test Positive (Yes), Negative (No) or no test or inconclusive (Unknown).

[13] Prior Hepatitis B Virus (HBV) defined as: Any hepatitis B surface antigen (HBsAg) positive (Yes), HBsAg negative, with no history of HBsAG positive test (No) or no test or inconclusive (Unknown).

[14] Within 6 months prior to date

[15] Peak Viral-load defined as: the highest HIV-viral load measured prior to date

[16] CD4 nadir defined as: the lowest CD4 cell count measured prior to date

[17] Estimated glomerular filtration rate (eGFR) calculated using: CKD-EPI

[18] Proportion of follow-up time under follow-up with immunosuppression defined as: total time under follow-up with CD4 count <200/cells mm^3 divided by the total time under follow-up, prior to date

[19] Proportion of follow-up time in EuroSIDA with uncontrolled viraemia defined as: total time under follow-up with HIV RNA VL > 400 copies/ml divided by the total time under follow-up, prior to date

[20] Cumulative years since starting at least one ARV prior to date

NOTE: Table 20 containing adjusted incidence rates for discontinuation of integrase inhibitors will be completed once 30 events or more have occurred in treatment groups A and B combined and C and D combined. Blank tables are included to demonstrate the structure of results.

TABLE 20 - Adjusted incidence rate ratios[1] of discontinuation due to severe skin rash (not HSR)

Characteristic	**Level**	**Discontinued due to severe skin rash (not HSR)**			
		Unadjusted IRR	**P**	**Adjusted IRR** [2]	**P**
Integrase inhibitor Regimen					
	A[3] and B[4]				
	C[5] and D[6]				
Demographic					
Age (years)					
	Per 10 years older/[≤35][36-40][41-50][51+]				
Gender					
	Male				
	Female				
Race					
	White				
	Other/Unknown				
HIV exposure group					
	MSM				
	IDU				
	Heterosexual				
	Other/Unknown				
Region of Europe[7]					
	South and Argentina				
	West				
	North				
	East Central				
	East				
Body mass index (BMI)					
	<18				
	18-25				

Characteristic	Level	Discontinued due to severe skin rash (not HSR)			
		Unadjusted IRR	P	Adjusted IRR [2]	P
	>25				
	unknown				
	Median [IQR]				
Smoking status					
	Current				
	Former				
	Never				
	Unknown				
Clinical history					
Prior AIDS[8]					
	Yes				
	No				
Prior non-AIDS[9]					
	Yes				
	No				
Diabetes[10]					
	Yes				
	No				
	Unknown				
Hypertension[11]					
	Yes				
	No				
	Unknown				
Anaemia					
	severe/mild anaemia				
	normal				
	Unknown				
Prior HCV diagnosis[12]					
	Yes				
	No				
	Unknown				
Prior HBV diagnosis[13]					

Characteristic	Level	Discontinued due to severe skin rash (not HSR)			
		Unadjusted IRR	P	Adjusted IRR [2]	P
	Yes				
	No				
	Unknown				
HIV viral load (copies/mL)[14]	Per 10 fold higher/ [<400][≥ 400][Unknown]				
Peak HIV viral load (copies/mL) [15]	Per 10 fold higher/ [<400][≥ 400][Unknown]				
CD4 count (cells/mm^3)[14]	Per 2 fold higher/[< 200][200-349][350-499][500+][Unknown]				
CD4 count nadir(cells/mm^3)[16]	Per 2 fold higher/[< 200][200-349][350-499][500+][Unknown]				
eGFR (ml/min/1.73m2) [17]	Per 10 units higher / [<60][≥60][Unknown]				
ALT (U/L)	Per 10 units higher / [<40][≥ 40][Unknown]				
AST (U/L)	Per 10 units higher / [<40][≥ 40][Unknown]				
Proportion of follow-up time in EuroSIDA with immunosuppression (defined as a CD4 count <200/cells mm^3)[18]	Per 1 year longer / [< 20%][≥20%][unknown]				
Proportion of follow-up time in EuroSIDA with uncontrolled viremia (HIV RNA VL > 400 copies/ml)[19]	Per 1 year longer / [< 20%][≥20%][unknown]				
ARV history					
Treatment naïve at baseline					
	Yes				
	No				
Integrase inhibitor Naïve at baseline					
	Yes				
	No				

Characteristic	Level	Discontinued due to severe skin rash (not HSR)			
		Unadjusted IRR	P	Adjusted IRR [2]	P
Current regimen includes PI					
	Yes				
	No				
Current regimen includes NNRTI					
	Yes				
	No				
Current regimen includes NRTI					
	Yes				
	No				
Prior exposure to PI					
	Yes				
	No				
Prior exposure to NNRTI					
	Yes				
	No				
Prior exposure to NRTI					
	Yes				
	No				
Prior exposure to DTG					
	Yes				
	No				
Prior exposure to ELV					
	Yes				
	No				
Prior exposure to RAL					
	Yes				
	No				
Number of ARVs previously exposed to	Per additional drug/ quintiles				
Years since first use of any ARV (years)[20]	Per 1 year longer / quintiles				

[1]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.

[2] confounding and effect modifying factors that are significant in univariate analyses (p<0.1) were be included in multivariate models, as well as treatment group and whether the patients were antiretroviral naïve at starting the regimen. Excluded variables were then added in turn to determine if their inclusion improved the fit of the model (defined as a significant reduction in the Log-Likelihood). Models adjusted for xxx

[3] DTG with ABC

[4] DTG without ABC

[5] ELV/RAL with ABC

[6] ELV/RAL without ABC

[7] Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; North: Austria, Belgium, France, Germany, Luxembourg, Central: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia; East: Belarus, Estonia, Latvia, Lithuania, Russian Federation, Ukraine.

[8] Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition[1].

[9] Non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, NADM [2]

[10] Prior diabetes defined as: Prior diagnosis of diabetes mellitus, or taking oral antidiabetic agents or insulin

[11] hypertension defined as: SBP >= 140 mmHg, DBP >= 90 mmHg or taking angiotensin-converting enzyme inhibitors/antihypertensive agents

[12] Severe/mild anaemia defined as: Haemoglobulin < 14 and <12 in males and females respectively

[13] Prior Hepatitis C Virus (HCV) defined as: Prior HCV antibody test Positive (Yes), Negative (No) or no test or inconclusive (Unknown).

[14] Prior Hepatitis B Virus (HBV) defined as: Any hepatitis B surface antigen (HBsAg) positive (Yes), HBsAg negative, with no history of HBsAG positive test (No) or no test or inconclusive (Unknown).

[15] Within 6 months prior to date

[16] Peak Viral-load defined as: the highest HIV-viral load measured prior to date

[17] CD4 nadir defined as: the lowest CD4 cell count measured prior to date

[18] Estimated glomerular filtration rate (eGFR) calculated using: CKD-EPI

[19] Proportion of follow-up time under follow-up with immunosuppression defined as: total time under follow-up with CD4 count <200/cells mm^3 divided by the total time under follow-up, prior to date

[20] Proportion of follow-up time in EuroSIDA with uncontrolled viraemia defined as: total time under follow-up with HIV RNA VL > 400 copies/ml divided by the total time under follow-up, prior to date

[21] Cumulative years since starting at least one ARV prior to date

TABLE 21 - Crude incidence rates[1] of discontinuation due to other causes as reported on the HSR CRF form (i.e. not HSR, hepatotoxicity, severe skin rash (not HSR) or unknown)

	Discontinued due to other causes			
Level	**Persons**	**Events**	**PYFU**	**Incidence rate 100 PYFU [95% CI]**
Integrase inhibitor Regimen				
A[2] and B[3]	679	42	346.2	12.1 (9.0,16.4)
C[4] and D[5]	570	62	353.8	17.5 (13.7,22.5)
Demographic				
Age (years)				
≤ 35 years	71	4	41.7	9.6 (3.6,25.6)
36 - 40 years	138	7	72.8	9.6 (4.6,20.2)
41 - 50 years	411	25	224.7	11.1 (7.5,16.5)
51 + years	655	68	360.9	18.8 (14.9,23.9)
Gender				
Male	913	74	533.4	13.9 (11.0,17.4)
Female	304	30	166.6	18.0 (12.6,25.8)
Race				
white	1040	86	596.0	14.4 (11.7,17.8)
Other/Unknown	177	18	104.0	17.3 (10.9,27.5)

	Discontinued due to other causes			
Level	**Persons**	**Events**	**PYFU**	**Incidence rate 100 PYFU [95% CI]**
HIV exposure group				
MSM	493	40	304.2	13.2 (9.6,17.9)
IDU	307	31	176.3	17.6 (12.4,25.0)
Heterosexual	320	28	162.7	17.2 (11.9,24.9)
Other/Unknown	97	5	56.9	8.8 (3.7,21.1)
Region of Europe[6]				
South and Argentina	291	14	156.2	9.0 (5.3,15.1)
North	387	52	235.5	22.1 (16.8,29.0)
Central	397	30	225.8	13.3 (9.3,19.0)
East central	130	6	76.8	7.8 (3.5,17.4)
East	12	2	5.7	35.3 (8.8,141.1)
Body mass index (BMI)				
<18	29	3	13.8	21.8 (7.0,67.6)
18 - 25	522	37	252.8	14.6 (10.6,20.2)
>25	315	22	165.7	13.3 (8.7,20.2)
Unknown	576	42	267.8	15.7 (11.6,21.2)
Smoking status				
Current	415	33	221.1	14.9 (10.6,21.0)
Former	207	15	111.1	13.5 (8.1,22.4)

	Discontinued due to other causes			
Level	**Persons**	**Events**	**PYFU**	**Incidence rate 100 PYFU [95% CI]**
Never	424	31	231.3	13.4 (9.4,19.1)
Unknown	266	25	136.5	18.3 (12.4,27.1)
Clinical history				
Prior AIDS[7]				
Yes	324	26	180.1	14.4 (9.8,21.2)
No	896	78	519.9	15.0 (12.0,18.7)
Prior non-AIDS[8]				
Yes	189	14	104.2	13.4 (8.0,22.7)
No	1030	90	595.7	15.1 (12.3,18.6)
Diabetes[9]				
Yes	105	7	59.3	11.8 (5.6,24.8)
No	1115	97	640.8	15.1 (12.4,18.5)
Hypertension[10]				
Yes	704	55	386.7	14.2 (10.9,18.5)
No	408	33	209.8	15.7 (11.2,22.1)
Unknown	206	16	103.5	15.5 (9.5,25.2)
Anaemia[11]				

	Discontinued due to other causes			
Level	**Persons**	**Events**	**PYFU**	**Incidence rate 100 PYFU [95% CI]**
severe anaemia/mild anaemia	272	19	100.4	18.9 (12.1,29.7)
normal	711	34	303.4	11.2 (8.0,15.7)
OtherUnknown	876	51	296.2	17.2 (13.1,22.7)
Prior HCV diagnosis[12]				
Yes	456	48	254.8	18.8 (14.2,25.0)
No	637	42	368.4	11.4 (8.4,15.4)
Unknown	136	14	76.8	18.2 (10.8,30.8)
Prior HBV diagnosis[13]				
Yes	54	1	29.9	3.3 (0.5,23.7)
No	998	79	557.7	14.2 (11.4,17.7)
Unknown	194	24	112.3	21.4 (14.3,31.9)
HIV viral load (copies/mL)[14]				
< 400	1088	79	555.8	14.2 (11.4,17.7)
≥ 400	153	6	34.1	17.6 (7.9,39.2)
Unknown	371	19	110.1	17.3 (11.0,27.1)
Peak HIV viral load (copies/mL)[15]				
< 400	125	6	60.3	10.0 (4.5,22.2)
≥ 400	1074	96	621.5	15.4 (12.6,18.9)

	Discontinued due to other causes			
Level	**Persons**	**Events**	**PYFU**	**Incidence rate 100 PYFU [95% CI]**
Unknown	33	2	18.3	11.0 (2.7,43.8)
CD4 count (cells/mm^3) [14]				
<200	116	5	44.6	11.2 (4.7,26.9)
200 - 349	179	5	65.9	7.6 (3.2,18.2)
350 - < 499	288	17	101.0	16.8 (10.5,27.1)
≥500	724	47	337.2	13.9 (10.5,18.6)
Unknown	456	30	151.3	19.8 (13.9,28.4)
CD4 count nadir(cells/mm^3) [16]				
<200	723	58	403.7	14.4 (11.1,18.6)
200 - 349	354	35	207.8	16.8 (12.1,23.5)
350 - < 499	102	8	52.1	15.4 (7.7,30.7)
≥500	46	3	28.6	10.5 (3.4,32.5)
Unknown	15	0	7.8	0.0 (0.0,3.7)
eGFR (ml/min/1.73m2) [17]				
<60	127	8	55.2	14.5 (7.3,29.0)
≥ 60	1021	78	548.0	14.2 (11.4,17.8)
Unknown	196	18	96.8	18.6 (11.7,29.5)
ALT (U/L)				
<40	632	35	258.0	13.6 (9.7,18.9)

	Discontinued due to other causes			
Level	**Persons**	**Events**	**PYFU**	**Incidence rate 100 PYFU [95% CI]**
≥ 40	389	17	146.3	11.6 (7.2,18.7)
Unknown	873	52	295.7	17.6 (13.4,23.1)
AST (U/L)				
<40	555	24	235.2	10.2 (6.8,15.2)
≥ 40	258	12	87.2	13.8 (7.8,24.2)
Unknown	961	68	377.7	18.0 (14.2,22.8)
Proportion of follow-up time in EuroSIDA with immunosuppression (defined as a CD4 count <200/cells mm3)[18]				
<20%	954	88	549.3	16.0 (13.0,19.7)
≥ 20%	272	16	142.8	11.2 (6.9,18.3)
Unknown	15	0	7.8	0.0 (0.0,3.7)
Proportion of follow-up time in EuroSIDA with uncontrolled viremia (HIV RNA VL > 400 copies/ml)[19]				
<20%	690	49	385.6	12.7 (9.6,16.8)
≥ 20%	539	53	294.6	18.0 (13.7,23.5)
Unknown	37	2	19.8	10.1 (2.5,40.3)
ARV history				
Treatment naïve at baseline				
Yes	87	6	50.6	11.9 (5.3,26.4)

	Discontinued due to other causes			
Level	**Persons**	**Events**	**PYFU**	**Incidence rate 100 PYFU [95% CI]**
No	1131	98	649.4	15.1 (12.4,18.4)
Integrase inhibitor Naïve at baseline				
Yes	962	80	542.2	14.8 (11.9,18.4)
No	292	24	157.8	15.2 (10.2,22.7)
Current regimen includes PI				
Yes	765	45	309.9	14.5 (10.8,19.4)
No	686	59	390.1	15.1 (11.7,19.5)
Current regimen includes NNRTI				
Yes	430	26	134.0	19.4 (13.2,28.5)
No	994	78	566.0	13.8 (11.0,17.2)
Current regimen includes NRTI				
Yes	1124	100	633.5	15.8 (13.0,19.2)
No	126	4	66.5	6.0 (2.3,16.0)
Prior exposure to PI				
Yes	978	83	562.3	14.8 (11.9,18.3)
No	243	21	137.7	15.3 (9.9,23.4)
Prior exposure to NNRTI				
Yes	765	76	431.8	17.6 (14.1,22.0)
No	454	28	268.2	10.4 (7.2,15.1)

	Discontinued due to other causes			
Level	**Persons**	**Events**	**PYFU**	**Incidence rate 100 PYFU [95% CI]**
Prior exposure to NRTI				
Yes	1181	103	677.3	15.2 (12.5,18.4)
No	38	1	22.7	4.4 (0.6,31.3)
Prior exposure to DTG				
Yes	20	3	9.1	33.0 (10.7,102.4)
No	1214	101	690.9	14.6 (12.0,17.8)
Prior exposure to ELV				
Yes	21	5	11.5	43.5 (18.1,104.5)
No	1207	99	688.5	14.4 (11.8,17.5)
Prior exposure to RAL				
Yes	266	21	145.2	14.5 (9.4,22.2)
No	971	83	554.8	15.0 (12.1,18.6)
Number of ARVs previously exposed to				
1 - lowest quintile	253	17	152.4	11.2 (6.9,17.9)
2	231	20	119.2	16.8 (10.8,26.0)
3	298	29	178.0	16.3 (11.3,23.4)
4	167	15	90.2	16.6 (10.0,27.6)
5 - highest quintile	293	23	160.3	14.4 (9.5,21.6)
Years since first use of any ARV (years)[20]				

	Discontinued due to other causes			
Level	**Persons**	**Events**	**PYFU**	**Incidence rate 100 PYFU [95% CI]**
No history	15	1	9.0	11.1 (1.6,78.9)
1 - lowest quintile	235	19	138.2	13.8 (8.8,21.6)
2	250	24	138.2	17.4 (11.6,25.9)
3	271	24	138.2	17.4 (11.6,25.9)
4	277	19	138.2	13.8 (8.8,21.6)
5 - highest quintile	282	17	138.2	12.3 (7.6,19.8)

[1]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.
[2] DTG with ABC
[3] DTG without ABC
[4] ELV/RAL with ABC
[5] ELV/RAL without ABC
[6] Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; North: Austria, Belgium, France, Germany, Luxembourg, Central: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia; East: Belarus, Estonia, Latvia, Lithuania, Russian Federation, Ukraine.
[7] Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition[1].
[8] Non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, NADM [2]
[9] Prior diabetes defined as: Prior diagnosis of diabetes mellitus, or taking oral antidiabetic agents or insulin
[10] hypertension defined as: SBP >= 140 mmHg, DBP >= 90 mmHg or taking angiotensin-converting enzyme inhibitors/antihypertensive agents
[11] Severe/mild anaemia defined as: Haemoglobulin < 14 and <12 in males and females respectively.
[12] Prior Hepatitis C Virus (HCV) defined as: Prior HCV antibody test Positive (Yes), Negative (No) or no test or inconclusive (Unknown).

[13] Prior Hepatitis B Virus (HBV) defined as: Any hepatitis B surface antigen (HBsAg) positive (Yes), HBsAg negative, with no history of HBsAG positive test (No) or no test or inconclusive (Unknown).
[14] Within 6 months prior to date
[15] Peak Viral-load defined as: the highest HIV-viral load measured prior to date
[16] CD4 nadir defined as: the lowest CD4 cell count measured prior to date
[17] Estimated glomerular filtration rate (eGFR) calculated using: CKD-EPI
[18] Proportion of follow-up time under follow-up with immunosuppression defined as: total time under follow-up with CD4 count <200/cells mm^3 divided by the total time under follow-up, prior to date
[19] Proportion of follow-up time in EuroSIDA with uncontrolled viraemia defined as: total time under follow-up with HIV RNA VL > 400 copies/ml divided by the total time under follow-up, prior to date
[20] Cumulative years since starting at least one ARV prior to date

NOTE: Variables had to have 5 or more events within each category to be included in the model. Levels of variables with <5 people receiving each drug were combined if this seemed appropriate (i.e. East and central east, BMI <18 and 18 – 25). These will be presented separately in future reports once the numbers allow. The following variables were excluded: Prior HBV diagnosis, Peak HIV viral load, CD4 count nadir, Proportion of follow-up time in EuroSIDA with immunosuppression, and HIV-VL, Proportion of follow-up time in EuroSIDA with uncontrolled viremia, prior exposure to DTG, and years since first use of any ARV. The following variables were not considered due to collinearity with other variables: Integrase inhibitor Naïve at baseline, current regimen includes PI, current regimen includes NNRTI, current regimen includes NRTI, prior exposure to PI, prior exposure to NNRTI, prior exposure to NRTI.

TABLE 22 - Adjusted incidence rate ratios[1] of discontinuation due to other causes as reported on the HSR CRF form (i.e. not HSR, hepatotoxicity, severe skin rash (not HSR) or unknown)

	Discontinued due to other causes			
Variable	**Unadjusted IRR**	**P**	**Adjusted IRR[2]**	**P**
Integrase inhibitor Regimen				
A[3] and B[4]	reference		reference	
C[5] and D[6]	1.44 (0.97,2.14)	0.068	1.62 (1.08,2.43)	0.021
Demographic				
Age (years)				
≤ 35 years	1.00 (0.29,3.38)	0.997	1.13 (0.35,3.64)	0.842
36 - 40 years	reference		reference	
41 - 50 years	1.16 (0.50,2.69)	0.735	1.23 (0.54,2.80)	0.618
51 + years	1.96 (0.90,4.28)	0.092	2.04 (0.94,4.41)	0.070
Gender				

	Discontinued due to other causes			
Variable	**Unadjusted IRR**	**P**	**Adjusted IRR[2]**	**P**
Male	reference			
Female	1.30 (0.85,1.99)	0.232		
Race				
white	reference			
Other/Unknown	1.20 (0.72,1.99)	0.483		
HIV exposure group				
MSM	reference			
IDU	1.34 (0.84,2.14)	0.224		
Heterosexual	1.31 (0.80,2.14)	0.283		
Other/Unknown	0.67 (0.26,1.72)	0.403		
Region of Europe[7]				
South and Argentina	0.67 (0.36,1.28)	0.226	0.55 (0.29,1.06)	0.075
North	1.66 (1.06,2.62)	0.028	1.60 (0.98,2.63)	0.061
Central	reference		reference	
East and East central	0.73 (0.33,1.59)	0.428	0.73 (0.30,1.80)	0.499
Body mass index (BMI)				
<18,18 - 25	reference			
>25	0.88 (0.52,1.49)	0.647		
Unknown	1.04 (0.68,1.61)	0.843		

	Discontinued due to other causes			
Variable	**Unadjusted IRR**	**P**	**Adjusted IRR[2]**	**P**
Smoking status				
Current	reference	0.669		
Former	1.01 (0.54,1.88)	0.980		
Never	reference			
Unknown	1.37 (0.81,2.31)	0.244		
Clinical history				
Prior AIDS[8]				
Yes	0.96 (0.61,1.51)	0.868		
No	reference			
Prior non-AIDS[9]				
Yes	0.89 (0.50,1.58)	0.691		
No	reference			
Diabetes[10]				
Yes	0.78 (0.36,1.70)	0.533		
No	reference			
Hypertension[11]				
Yes	0.90 (0.58,1.40)	0.650		
No	reference			

	Discontinued due to other causes			
Variable	**Unadjusted IRR**	**P**	**Adjusted IRR[2]**	**P**
Unknown	0.98 (0.54,1.79)	0.953		
Anaemia[12]				
severe anaemia/mild anaemia	1.69 (0.96,2.97)	0.069	1.31 (0.75,2.30)	0.347
normal	reference		reference	
Unknown	1.54 (0.99,2.37)	0.053	1.13 (0.69,1.85)	0.625
Prior HCV diagnosis[13]				
Yes	1.65 (1.09,2.50)	0.018	1.91 (1.19,3.05)	0.007
No	reference		reference	
Unknown	1.60 (0.86,2.97)	0.135	1.68 (0.85,3.33)	0.139
HIV viral load (copies/mL)[14]				
< 400	0.81 (0.35,1.85)	0.614		
≥ 400	reference			
Unknown	0.98 (0.39,2.45)	0.966		
CD4 count (cells/mm^3)[14]				
<200	0.80 (0.32,2.05)	0.648		
200 - 349	0.54 (0.21,1.38)	0.200		
350 - < 499	1.21 (0.69,2.11)	0.508		

	Discontinued due to other causes			
Variable	**Unadjusted IRR**	**P**	**Adjusted IRR[2]**	**P**
≥500	reference			
Unknown	1.42 (0.90,2.24)	0.130		
eGFR (ml/min/1.73m2) [15]				
<60	1.02 (0.49,2.11)	0.960		
≥ 60	reference			
Unknown	1.31 (0.78,2.19)	0.311		
ALT (U/L)				
<40	1.17 (0.65,2.09)	0.602		
≥ 40	reference			
Unknown	1.51 (0.88,2.62)	0.138		
AST (U/L)				
<40	0.74 (0.37,1.48)	0.398		
≥ 40	reference			
Unknown	1.31 (0.71,2.41)	0.390		
ARV history				
Treatment naïve at baseline				
Yes	0.79 (0.35,1.78)	0.563	0.93 (0.39,2.26)	0.881
No	reference		reference	

	Discontinued due to other causes			
Variable	**Unadjusted IRR**	**P**	**Adjusted IRR[2]**	**P**
Prior exposure to PI				
Yes	0.97 (0.60,1.56)	0.893		
No	reference			
Prior exposure to NNRTI				
Yes	1.69 (1.09,2.60)	0.018	1.59 (0.97,2.61)	0.066
No	reference		reference	
Prior exposure to ELV				
Yes	3.02 (1.24,7.36)	0.015	2.46 (1.15,5.30)	0.021
No	reference		reference	
Prior exposure to RAL				
Yes	0.97 (0.60,1.57)	0.892		
No	reference			
Number of ARVs previously exposed to				
1 - lowest quintile	reference			
2	1.50 (0.79,2.86)	0.213		
3	1.46 (0.80,2.66)	0.214		
4	1.49 (0.74,3.01)	0.264		
5 - highest quintile	1.29 (0.69,2.42)	0.432		

[1]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.

[2] confounding and effect modifying factors that are significant in univariate analyses ($p<0.1$) were be included in multivariate models, as well as treatment group and whether the patients were antiretroviral naïve at starting the regimen. Excluded variables were then added in turn to determine if their inclusion improved the fit of the model (defined as a significant reduction in the Log-Likelihood). Models adjusted for Integrase inhibitor regimen, age, region of Europe, anaemia, prior HCV, treatment naïve at baseline, prior exposure to NNRTI, prior exposure to ELV.

[3] DTG with ABC

[4] DTG without ABC

[5] ELV/RAL with ABC

[6] ELV/RAL without ABC

[7] Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; North: Austria, Belgium, France, Germany, Luxembourg, Central: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia; East: Belarus, Estonia, Latvia, Lithuania, Russian Federation, Ukraine.

[8] Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition[1].

[9] Non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, NADM [2]

[10] Prior diabetes defined as: Prior diagnosis of diabetes mellitus, or taking oral antidiabetic agents or insulin

[11] hypertension defined as: SBP >= 140 mmHg, DBP >= 90 mmHg or taking angiotensin-converting enzyme inhibitors/antihypertensive agents

[12] Severe/mild anaemia defined as: Haemoglobulin < 14 and <12 in males and females respectively

[13] Prior Hepatitis C Virus (HCV) defined as: Prior HCV antibody test Positive (Yes), Negative (No) or no test or inconclusive (Unknown).

[14] Within 6 months prior to date

[15] Estimated glomerular filtration rate (eGFR) calculated using: CKD-EPI

NOTE: Table 23 containing incidence rates for discontinuation of integrase inhibitors will be completed once 30 events or more have occurred in treatment groups A and B combined and C and D combined. Blank tables are included to demonstrate the structure of results.

TABLE 23 - Crude incidence rates[1] of discontinuation due to unknown causes

Characteristic	Level	Discontinued due to unknown causes			
		Persons	Events	PYFU	Incidence rate/100 PYFU [95% CI]
Integrase inhibitor Regimen					
	A[2] and B[3]				
	C[4] and D[5]				
Demographic					
Age (years)					
	[≤35][36-40][41-50][51+]				
Gender					
	Male				
	Female				
Race					
	White				
	Other/Unknown				
HIV exposure group					
	MSM				
	IDU				
	Heterosexual				
	Other/Unknown				
Region of Europe[6]					
	South and Argentina				
	West				

Characteristic	Level	Discontinued due to unknown causes			
		Persons	Events	PYFU	Incidence rate/100 PYFU [95% CI]
	North				
	East Central				
	East				
Body mass index (BMI)					
	<18				
	18-25				
	>25				
	unknown				
	Median [IQR]				
Smoking status					
	Current				
	Former				
	Never				
	Unknown				
Clinical history					
Prior AIDS[7]					
	Yes				
	No				
Prior non-AIDS[8]					
	Yes				
	No				
Diabetes[9]					
	Yes				
	No				
	Unknown				
Hypertension[10]					
	Yes				
	No				
	Unknown				
Anaemia					

Characteristic	Level	Discontinued due to unknown causes			
		Persons	Events	PYFU	Incidence rate/100 PYFU [95% CI]
	severe/mild anaemia				
	normal				
	Unknown				
Prior HCV diagnosis[11]					
	Yes				
	No				
	Unknown				
Prior HBV diagnosis[12]					
	Yes				
	No				
	Unknown				
HIV viral load (copies/mL)[13]	[<400][≥ 400][Unknown]				
Peak HIV viral load (copies/mL) [14]	[<400][≥ 400][Unknown]				
CD4 count (cells/mm^3)[14]	[< 200][200-349][350-499][500+][Unknown]				
CD4 count nadir(cells/mm^3)[15]	[< 200][200-349][350-499][500+][Unknown]				
eGFR (ml/min/1.73m2) [16]	[<60][≥60][Unknown]				
ALT (U/L)	[<40][≥ 40][Unknown]				
AST (U/L)	[<40][≥ 40][Unknown]				
Proportion of follow-up time in EuroSIDA	[< 20%][≥20%][unknown]				

Characteristic	Level	Discontinued due to unknown causes			
		Persons	Events	PYFU	Incidence rate/100 PYFU [95% CI]
with immunosuppression (defined as a CD4 count <200/cells mm^3)[17]					
Proportion of follow-up time in EuroSIDA with uncontrolled viremia (HIV RNA VL > 400 copies/ml)[18]	[< 20%][≥20%][unknown]				
ARV history					
Treatment naïve at baseline					
	Yes				
	No				
Integrase inhibitor Naïve at baseline					
	Yes				
	No				
Current regimen includes PI					
	Yes				
	No				
Current regimen includes NNRTI					
	Yes				
	No				

Characteristic	Level	Discontinued due to unknown causes			
		Persons	Events	PYFU	Incidence rate/100 PYFU [95% CI]
Current regimen includes NRTI					
	Yes				
	No				
Prior exposure to PI					
	Yes				
	No				
Prior exposure to NNRTI					
	Yes				
	No				
Prior exposure to NRTI					
	Yes				
	No				
Prior exposure to DTG					
	Yes				
	No				
Prior exposure to ELV					
	Yes				
	No				
Prior exposure to RAL					
	Yes				
	No				
Number of ARVs previously exposed to	Quintiles				

Characteristic	Level	Discontinued due to unknown causes			
		Persons	Events	PYFU	Incidence rate/100 PYFU [95% CI]
Years since first use of any ARV (years)[19]	Quintiles				

[1]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.

[2] DTG with ABC

[3] DTG without ABC

[4] ELV/RAL with ABC

[5] ELV/RAL without ABC

[6] Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; North: Austria, Belgium, France, Germany, Luxembourg, Central: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia; East: Belarus, Estonia, Latvia, Lithuania, Russian Federation, Ukraine.

[7] Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition[1].

[8] Non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, NADM [2]

[9] Prior diabetes defined as: Prior diagnosis of diabetes mellitus, or taking oral antidiabetic agents or insulin

[10] hypertension defined as: SBP >= 140 mmHg, DBP >= 90 mmHg or taking angiotensin-converting enzyme inhibitors/antihypertensive agents

[11] Severe/mild anaemia defined as: Haemoglobulin < 14 and <12 in males and females respectively.

[12] Prior Hepatitis C Virus (HCV) defined as: Prior HCV antibody test Positive (Yes), Negative (No) or no test or inconclusive (Unknown).

[13] Prior Hepatitis B Virus (HBV) defined as: Any hepatitis B surface antigen (HBsAg) positive (Yes), HBsAg negative, with no history of HBsAG positive test (No) or no test or inconclusive (Unknown).

[14] Within 6 months prior to date

[15] Peak Viral-load defined as: the highest HIV-viral load measured prior to date

[16] CD4 nadir defined as: the lowest CD4 cell count measured prior to date

[17] Estimated glomerular filtration rate (eGFR) calculated using: CKD-EPI

[18] Proportion of follow-up time under follow-up with immunosuppression defined as: total time under follow-up with CD4 count <200/cells mm^3 divided by the total time under follow-up, prior to date

[19] Proportion of follow-up time in EuroSIDA with uncontrolled viraemia defined as: total time under follow-up with HIV RNA VL > 400 copies/ml divided by the total time under follow-up, prior to date

[20] Cumulative years since starting at least one ARV prior to date

NOTE: Table 24 containing adjusted incidence rates for discontinuation of integrase inhibitors will be completed once 30 events or more have occurred in treatment groups A and B combined and C and D combined. Blank tables are included to demonstrate the structure of results.

TABLE 24 - Adjusted incidence rate ratios[1] of discontinuation due to unknown causes

Characteristic	Level	Discontinued due to unknown causes			
		Unadjusted IRR	P	Adjusted IRR [2]	P
Integrase inhibitor Regimen					
	A[3] and B[4]				
	C[5] and D[6]				
Demographic					
Age (years)					
	Per 10 years older/[≤35][36-40][41-50][51+]				
Gender					
	Male				
	Female				
Race					
	White				
	Other/Unknown				
HIV exposure group					
	MSM				
	IDU				
	Heterosexual				
	Other/Unknown				
Region of Europe[7]					
	South and Argentina				
	West				
	North				
	East Central				
	East				
Body mass index (BMI)					
	<18				

Characteristic	Level	Discontinued due to unknown causes			
		Unadjusted IRR	P	Adjusted IRR [2]	P
	18-25				
	>25				
	unknown				
	Median [IQR]				
Smoking status					
	Current				
	Former				
	Never				
	Unknown				
Clinical history					
Prior AIDS[8]					
	Yes				
	No				
Prior non-AIDS[9]					
	Yes				
	No				
Diabetes[10]					
	Yes				
	No				
	Unknown				
Hypertension[11]					
	Yes				
	No				
	Unknown				
Prior HCV diagnosis[12]					
	Yes				
	No				
	Unknown				
Prior HBV diagnosis[13]					
	Yes				
	No				
	Unknown				

Characteristic	Level	Discontinued due to unknown causes			
		Unadjusted IRR	P	Adjusted IRR [2]	P
HIV viral load (copies/mL)[14]	Per 10 fold higher/ [<400][≥ 400][Unknown]				
Peak HIV viral load (copies/mL) [15]	Per 10 fold higher/ [<400][≥ 400][Unknown]				
CD4 count (cells/mm^3)[14]	Per 2 fold higher/[< 200][200-349][350-499][500+][Unknown]				
CD4 count nadir(cells/mm^3)[16]	Per 2 fold higher/[< 200][200-349][350-499][500+][Unknown]				
eGFR (ml/min/1.73m2) [17]	Per 10 units higher / [<60][≥60][Unknown]				
ALT (U/L)	Per 10 units higher / [<40][≥ 40][Unknown]				
AST (U/L)	Per 10 units higher / [<40][≥ 40][Unknown]				
Proportion of follow-up time in EuroSIDA with immunosuppression (defined as a CD4 count <200/cells mm^3)[18]	Per 1 year longer / [< 20%][≥20%][unknown]				
Proportion of follow-up time in EuroSIDA with uncontrolled viremia (HIV RNA VL > 400 copies/ml)[19]	Per 1 year longer / [< 20%][≥20%][unknown]				
ARV history					
Treatment naïve at baseline					
	Yes				
	No				
Integrase inhibitor Naïve at baseline					
	Yes				
	No				
Current regimen includes PI					
	Yes				
	No				

Characteristic	Level	Discontinued due to unknown causes			
		Unadjusted IRR	P	Adjusted IRR [2]	P
Current regimen includes NNRTI					
	Yes				
	No				
Current regimen includes NRTI					
	Yes				
	No				
Prior exposure to PI					
	Yes				
	No				
Prior exposure to NNRTI					
	Yes				
	No				
Prior exposure to NRTI					
	Yes				
	No				
Prior exposure to DTG					
	Yes				
	No				
Prior exposure to ELV					
	Yes				
	No				
Prior exposure to RAL					
	Yes				
	No				
Number of ARVs previously exposed to	Per additional drug/ quintiles				
Years since first use of any ARV (years)[20]	Per 1 year longer / quintiles				

[1]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.

[2] confounding and effect modifying factors that are significant in univariate analyses ($p<0.1$) were be included in multivariate models, as well as treatment group and whether the patients were antiretroviral naïve at starting the regimen. Excluded variables were then added

in turn to determine if their inclusion improved the fit of the model (defined as a significant reduction in the Log-Likelihood). Models adjusted for xxx

[3] DTG with ABC

[4] DTG without ABC

[5] ELV/RAL with ABC

[6] ELV/RAL without ABC

[7] Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; North: Austria, Belgium, France, Germany, Luxembourg, Central: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia; East: Belarus, Estonia, Latvia, Lithuania, Russian Federation, Ukraine.

[8] Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition[1].

[9] Non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, NADM [2]

[10] Prior diabetes defined as: Prior diagnosis of diabetes mellitus, or taking oral antidiabetic agents or insulin

[11] hypertension defined as: SBP >= 140 mmHg, DBP >= 90 mmHg or taking angiotensin-converting enzyme inhibitors/antihypertensive agents

[12] Severe/mild anaemia defined as: Haemoglobulin < 14 and <12 in males and females respectively

[13] Prior Hepatitis C Virus (HCV) defined as: Prior HCV antibody test Positive (Yes), Negative (No) or no test or inconclusive (Unknown).

[14] Prior Hepatitis B Virus (HBV) defined as: Any hepatitis B surface antigen (HBsAg) positive (Yes), HBsAg negative, with no history of HBsAG positive test (No) or no test or inconclusive (Unknown).

[15] Within 6 months prior to date

[16] Peak Viral-load defined as: the highest HIV-viral load measured prior to date

[17] CD4 nadir defined as: the lowest CD4 cell count measured prior to date

[18] Estimated glomerular filtration rate (eGFR) calculated using: CKD-EPI

[19] Proportion of follow-up time under follow-up with immunosuppression defined as: total time under follow-up with CD4 count <200/cells mm^3 divided by the total time under follow-up, prior to date

[20] Proportion of follow-up time in EuroSIDA with uncontrolled viraemia defined as: total time under follow-up with HIV RNA VL > 400 copies/ml divided by the total time under follow-up, prior to date

[21] Cumulative years since starting at least one ARV prior to date

SUPPLEMENTARY TABLE 1 symptoms recorded in those who discontinued due to HSR or Hepatotoxicity

		Total	A[1]	B[2]	C[3]	D[4]
All discontinuations (N)		**2**	**0**	**1**	**0**	**1**
HSR		2	0	1	0	1
Hepatotoxicity		*0*	*0*	*0*	*0*	*0*
Severe Skin Rash (not HSR)		*0*	*0*	*0*	*0*	*0*
Reported Symptoms (N)						
Fever						
	Yes	1	0	1	0	0
	No	0	0	0	0	0
	Unknown	1	0	0	0	1
Eosinophilia						
	Yes	0	0	0	0	0
	No	1	0	0	*0*	*1*
	Unknown	1	*0*	*1*	0	0
Skin rash						
	Yes	1	0	0	0	1
	Severe	*0*	*0*	*0*	*0*	*0*
	Moderate	*0*	*0*	*0*	*0*	*0*
	Mild	*1*	*0*	*0*	*0*	*1*
	No	1	0	1	0	0
	Unknown	0	0	0	0	0
Gastro intestinal						
	Yes	2	0	1	0	1
	Nausea	*1*	*0*	*1*	*0*	*0*
	Vomiting	*0*	*0*	*0*	*0*	*0*
	Diarrhoea	*1*	*0*	*0*	*0*	*1*
	No	0	0	0	0	0
	Unknown	0	0	0	0	0
Respiratory						
	Yes	0	0	0	0	0
	Dyspnoea	*0*	*0*	*0*	*0*	*0*
	Sore throat	*0*	*0*	*0*	*0*	*0*
	Cough	*0*	*0*	*0*	*0*	*0*
	Chest x-ray changes	*0*	*0*	*0*	*0*	*0*
	No	1	0	1	0	0
	Unknown	1	0	0	0	1
Elevated ALT						
	>5xULN	0	0	0	0	0
Elevated Bilirubin						
	>2xULN	0	0	0	0	0

[1] DTG with ABC

[2] DTG without ABC
[3] ELV/RAL with ABC
[4] ELV/RAL without ABC

SUPPLEMENTARY TABLE 2 signs of hepatotoxicity of in those who started an integrase inhibitor during follow-up.

Treatment group	Total N	≥1 ALT or Bilirubin test during followup N (% of total)	At least 1 test elevated[1] N (% of tested)
A[2]	301	166 (55)	3 (2)
B[3]	356	240 (67)	6 (3)
C[4]	79	50 (63)	1 (2)
D[5]	481	299 (62)	5 (2)
Total	1217	755 (62)	15 (2)

[1] Either alanine aminotransferase (ALT) test >5xULN (ULN=40) and total bilirubin >2xULN (ULN=1.2) liver chemistry test elevations.
[2] DTG with ABC
[3] DTG without ABC
[4] ELV/RAL with ABC
[5] ELV/RAL without ABC

6.4 Sensitivity analyses

Primary events were graded by independent adjudicators as definitive or possible, and analyses were 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 was used to assess the robustness of the results when each patient was only included in the first treatment group they are eligible to join. Similarly, rather than censoring at stopping DTG (or other integrase inhibitor), patients were assumed to stay on the drug for an additional 4 weeks (lag-time analysis), to ensure that any primary events occurring shortly after discontinuation were included. In this specific lag-time analyses, if patients have switched from one treatment group to another, the event was assumed to have occurred in the first treatment group.

Results of sensitivity analysis to be included when 30 events or more have occurred in treatment groups A and B combined and C and D combined. The following tables will be provided:

TABLE S1 – S6 : Table 15 – 20 with including DEFINITIVE events only.
TABLE S7 – S16 : TABLE 15 – 24 including results from first treatment group only.
TABLE S17 – S22 : TABLE 15 – 20 Allowing 4 additional weeks of follow-up after discontinuation.

NOTE: Tables S1 – S12, S15 – S22 containing incidence rates and adjusted incidence rates for discontinuation of integrase inhibitors will be completed once 30 events or more have occurred in treatment groups A and B combined and C and D combined.

TABLE S13 - Crude incidence rates[1] of discontinuation due to other causes as reported on the HSR CRF form (i.e. not HSR, hepatotoxicity, severe skin rash (not HSR) or unknown), including results from first treatment group only.

	Discontinued due to other causes			
Level	**Persons**	**Events**	**PYFU**	**Incidence rate 100 PYFU [95% CI]**
Integrase inhibitor Regimen				
A[2] and B[3]	655	34	332.9	10.2 (7.3,14.3)
C[4] and D[5]	562	52	345.0	15.1 (11.5,19.8)
Age (years)				
≤ 35 years	71	3	41.2	7.3 (2.4,22.6)
36 - 40 years	138	6	71.8	8.4 (3.8,18.6)
41 - 50 years	411	21	216.3	9.7 (6.3,14.9)
51 + years	655	56	348.6	16.1 (12.4,20.9)
Demographic				
Gender				
Male	913	60	517.7	11.6 (9.0,14.9)
Female	304	26	160.2	16.2 (11.1,23.8)
Race				
white	1040	72	578.1	12.5 (9.9,15.7)
Other/Unknown	177	14	99.8	14.0 (8.3,23.7)
HIV exposure group				
MSM	493	34	294.3	11.6 (8.3,16.2)
IDU	307	26	171.0	15.2 (10.4,22.3)
Heterosexual	320	25	157.6	15.9 (10.7,23.5)
Other/Unknown	97	1	55.0	1.8 (0.3,12.9)
Region of Europe[6]				
South and Argentina	291	11	152.0	7.2 (4.0,13.1)
North	387	43	227.0	18.9 (14.0,25.5)
Central	397	25	218.3	11.5 (7.7,17.0)
East central	130	5	75.0	6.7 (2.8,16.0)
East	12	2	5.7	35.3 (8.8,141.1)

	Discontinued due to other causes			
Level	**Persons**	**Events**	**PYFU**	**Incidence rate 100 PYFU [95% CI]**
Body mass index (BMI)				
<18	29	2	13.1	15.3 (3.8,61.1)
18 - 25	521	29	244.8	11.8 (8.2,17.0)
>25	314	19	160.7	11.8 (7.5,18.5)
Unknown	572	36	259.3	13.9 (10.0,19.2)
Smoking status				
Current	414	28	214.5	13.1 (9.0,18.9)
Former	207	11	109.3	10.1 (5.6,18.2)
Never	422	25	222.8	11.2 (7.6,16.6)
Unknown	264	22	131.3	16.8 (11.0,25.4)
Prior AIDS[7]				
Yes	324	21	174.6	12.0 (7.8,18.4)
No	896	65	503.3	12.9 (10.1,16.5)
Clinical history				
Prior non-AIDS[8]				
Yes	189	10	101.9	9.8 (5.3,18.2)
No	1030	76	576.0	13.2 (10.5,16.5)
Diabetes[9]				
Yes	105	4	56.8	7.0 (2.6,18.8)
No	1114	82	621.2	13.2 (10.6,16.4)
Hypertension[10]				
Yes	701	44	374.0	11.8 (8.8,15.8)
No	407	29	203.8	14.2 (9.9,20.5)
Unknown	203	13	100.2	13.0 (7.5,22.4)
Anaemia[11]				
severe anaemia/mild anaemia	266	13	95.4	13.6 (7.9,23.5)
normal	707	26	296.9	8.8 (6.0,12.9)
OtherUnknown	870	47	285.6	16.5 (12.4,21.9)

	Discontinued due to other causes			
Level	**Persons**	**Events**	**PYFU**	**Incidence rate 100 PYFU [95% CI]**
***Prior HCV diagnosis*[12]**				
Yes	455	41	245.7	16.7 (12.3,22.7)
No	637	33	358.1	9.2 (6.6,13.0)
Unknown	136	12	74.2	16.2 (9.2,28.5)
***Prior HBV diagnosis*[13]**				
Yes	54	1	29.9	3.3 (0.5,23.7)
No	998	66	541.1	12.2 (9.6,15.5)
Unknown	192	19	106.9	17.8 (11.3,27.9)
***HIV viral load (copies/mL)*[14]**				
< 400	1081	64	537.2	11.9 (9.3,15.2)
≥ 400	151	4	32.7	12.2 (4.6,32.5)
Unknown	369	18	107.9	16.7 (10.5,26.5)
***Peak HIV viral load (copies/mL)*[15]**				
< 400	124	5	57.3	8.7 (3.6,21.0)
≥ 400	1074	79	603.2	13.1 (10.5,16.3)
Unknown	32	2	17.4	11.5 (2.9,45.9)
***CD4 count (cells/mm^3)*[14]**				
<200	116	3	43.8	6.8 (2.2,21.2)
200 - 349	174	3	62.3	4.8 (1.6,14.9)
350 - < 499	285	13	95.7	13.6 (7.9,23.4)
≥500	723	38	328.4	11.6 (8.4,15.9)
Unknown	451	29	147.6	19.6 (13.7,28.3)
***CD4 count nadir(cells/mm^3)* [16]**				
<200	723	47	393.2	12.0 (9.0,15.9)
200 - 349	353	29	198.3	14.6 (10.2,21.0)
350 - < 499	102	7	51.3	13.6 (6.5,28.6)
≥500	46	3	27.2	11.0 (3.6,34.1)
Unknown	15	0	7.8	0.0 (0.0,3.7)
***eGFR (ml/min/1.73m^2)* [17]**				
<60	125	5	53.6	9.3 (3.9,22.4)

	Discontinued due to other causes			
Level	**Persons**	**Events**	**PYFU**	**Incidence rate 100 PYFU [95% CI]**
≥ 60	1014	65	530.4	12.3 (9.6,15.6)
Unknown	196	16	93.9	17.0 (10.4,27.8)
ALT (U/L)				
<40	627	25	249.9	10.0 (6.8,14.8)
≥ 40	381	13	142.9	9.1 (5.3,15.7)
Unknown	867	48	285.1	16.8 (12.7,22.3)
AST (U/L)				
<40	548	16	226.9	7.1 (4.3,11.5)
≥ 40	254	10	85.7	11.7 (6.3,21.7)
Unknown	956	60	365.2	16.4 (12.8,21.2)
Proportion of follow-up time in EuroSIDA with immunosuppression (defined as a CD4 count <200/cells mm3)[18]				
<20%	954	75	530.0	14.2 (11.3,17.7)
≥ 20%	272	11	140.1	7.9 (4.3,14.2)
Unknown	15	0	7.8	0.0 (0.0,3.7)
Proportion of follow-up time in EuroSIDA with uncontrolled viremia (HIV RNA VL > 400 copies/ml)[19]				
<20%	688	41	373.8	11.0 (8.1,14.9)
≥ 20%	539	43	285.9	15.0 (11.2,20.3)
Unknown	36	2	18.2	11.0 (2.8,44.0)
Treatment naïve at baseline				
Yes	87	6	50.3	11.9 (5.4,26.5)
No	1130	80	627.6	12.7 (10.2,15.9)
ARV history				
Integrase inhibitor Naïve at baseline				
Yes	952	73	538.6	13.6 (10.8,17.0)
No	265	13	139.3	9.3 (5.4,16.1)
Current regimen includes PI				
Yes	760	36	302.8	11.9 (8.6,16.5)

	Discontinued due to other causes			
Level	**Persons**	**Events**	**PYFU**	**Incidence rate 100 PYFU [95% CI]**
No	680	50	375.2	13.3 (10.1,17.6)
Current regimen includes NNRTI				
Yes	427	24	131.5	18.3 (12.2,27.2)
No	987	62	546.4	11.3 (8.8,14.6)
Current regimen includes NRTI				
Yes	1124	83	612.2	13.6 (10.9,16.8)
No	126	3	65.7	4.6 (1.5,14.2)
Prior exposure to PI				
Yes	977	66	543.0	12.2 (9.5,15.5)
No	243	20	134.9	14.8 (9.6,23.0)
Prior exposure to NNRTI				
Yes	765	63	415.0	15.2 (11.9,19.4)
No	454	23	262.9	8.7 (5.8,13.2)
Prior exposure to NRTI				
Yes	1181	85	655.5	13.0 (10.5,16.0)
No	38	1	22.4	4.5 (0.6,31.7)
Prior exposure to DTG				
Yes	11	2	4.4	45.3 (11.3,181.1)
No	1206	84	673.5	12.5 (10.1,15.4)
Prior exposure to ELV				
Yes	20	4	10.1	39.7 (14.9,105.7)
No	1197	82	667.8	12.3 (9.9,15.2)
Prior exposure to RAL				
Yes	246	10	130.2	7.7 (4.1,14.3)
No	971	76	547.7	13.9 (11.1,17.4)
Number of ARVs previously exposed to				
1 - lowest quintile	253	17	150.7	11.3 (7.0,18.1)
2	228	13	114.8	11.3 (6.6,19.5)
3	297	24	169.9	14.1 (9.5,21.1)
4	167	14	89.4	15.7 (9.3,26.4)

	Discontinued due to other causes			
Level	**Persons**	**Events**	**PYFU**	**Incidence rate 100 PYFU [95% CI]**
5 - highest quintile	293	18	153.0	11.8 (7.4,18.7)
Years since first use of any ARV (years)[20]				
No history	15	1	8.7	11.4 (1.6,81.1)
1 - lowest quintile	235	16	135.8	11.8 (7.2,19.2)
2	248	20	135.0	14.8 (9.6,23.0)
3	270	19	131.2	14.5 (9.2,22.7)
4	276	14	134.1	10.4 (6.2,17.6)
5 - highest quintile	280	16	133.0	12.0 (7.4,19.6)

[1]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.
[2] DTG with ABC
[3] DTG without ABC
[4] ELV/RAL with ABC
[5] ELV/RAL without ABC
[6] Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; North: Austria, Belgium, France, Germany, Luxembourg, Central: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia; East: Belarus, Estonia, Latvia, Lithuania, Russian Federation, Ukraine.
[7] Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition[1].
[8] Non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, NADM [2]
[9] Prior diabetes defined as: Prior diagnosis of diabetes mellitus, or taking oral antidiabetic agents or insulin
[10] hypertension defined as: SBP >= 140 mmHg, DBP >= 90 mmHg or taking angiotensin-converting enzyme inhibitors/antihypertensive agents
[11] Severe/mild anaemia defined as: Haemoglobulin < 14 and <12 in males and females respectively.
[12] Prior Hepatitis C Virus (HCV) defined as: Prior HCV antibody test Positive (Yes), Negative (No) or no test or inconclusive (Unknown).
[13] Prior Hepatitis B Virus (HBV) defined as: Any hepatitis B surface antigen (HBsAg) positive (Yes), HBsAg negative, with no history of HBsAG positive test (No) or no test or inconclusive (Unknown).
[14] Within 6 months prior to date
[15] Peak Viral-load defined as: the highest HIV-viral load measured prior to date
[16] CD4 nadir defined as: the lowest CD4 cell count measured prior to date
[17] Estimated glomerular filtration rate (eGFR) calculated using: CKD-EPI
[18] Proportion of follow-up time under follow-up with immunosuppression defined as: total time under follow-up with CD4 count <200/cells mm^3 divided by the total time under follow-up, prior to date

[19] Proportion of follow-up time in EuroSIDA with uncontrolled viraemia defined as: total time under follow-up with HIV RNA VL > 400 copies/ml divided by the total time under follow-up, prior to date

[20] Cumulative years since starting at least one ARV prior to date

NOTE: Variables included in this model were consistent with those in table 22 (variables had to have 5 or more events within each category to be included in the model in table 22). Levels of variables with <5 people receiving each drug were combined if this seemed appropriate (i.e. East and central east, BMI <18 and 18 – 25). These will be presented separately in future reports once the numbers allow. The following variables were excluded: Prior HBV diagnosis, Peak HIV viral load, CD4 count nadir, Proportion of follow-up time in EuroSIDA with immunosuppression, and HIV-VL, Proportion of follow-up time in EuroSIDA with uncontrolled viremia, prior exposure to DTG, years since first use of any ARV. The following variables were not considered due to collinearity with other variables: Integrase inhibitor Naïve at baseline, current regimen includes PI, current regimen includes NNRTI, current regimen includes NRTI, prior exposure to PI, prior exposure to NNRTI, prior exposure to NRTI.

TABLE S14 - Adjusted incidence rate ratios[1] of discontinuation due to other causes as reported on the HSR CRF form (i.e. not HSR, hepatotoxicity, severe skin rash (not HSR) or unknown), including results from first treatment group only.

	Discontinued due to other causes			
Variable	**Unadjusted IRR**	**P**	**Adjusted IRR[2]**	**P**
Integrase inhibitor Regimen				
A[3] and B[4]	reference		reference	
C[5] and D[6]	1.48 (0.96,2.28)	0.079	1.49 (0.93,2.39)	0.099
Demographic				
Age (years)				
≤ 35 years	0.87 (0.22,3.43)	0.845		
36 - 40 years	reference			
41 - 50 years	1.16 (0.47,2.90)	0.747		
51 + years	1.92 (0.82,4.49)	0.130		
Gender				
Male	reference			
Female	1.40 (0.88,2.23)	0.155		
Race				
white	reference			
Other/Unknown	1.13 (0.64,1.99)	0.684		
HIV exposure group				
MSM	reference		reference	
IDU	1.32 (0.79,2.19)	0.289	1.17 (0.62,2.22)	0.625

	Discontinued due to other causes			
Variable	**Unadjusted IRR**	**P**	**Adjusted IRR[2]**	**P**
Heterosexual	1.37 (0.81,2.32)	0.236	1.80 (1.01,3.21)	0.046
Other/Unknown	0.16 (0.02,1.16)	0.070	0.17 (0.02,1.27)	0.084
Region of Europe[7]				
South and Argentina	0.63 (0.31,1.29)	0.205	0.44 (0.22,0.89)	0.023
North	1.65 (1.01,2.72)	0.047	1.47 (0.81,2.67)	0.203
Central	reference		reference	
East and East central	0.76 (0.33,1.75)	0.515	0.64 (0.28,1.51)	0.313
Body mass index (BMI)				
<18,18 - 25	reference			
>25	0.98 (0.55,1.75)	0.956		
Unknown	1.16 (0.72,1.87)	0.556		
Smoking status				
Current	reference	0.586		
Former	0.90 (0.44,1.83)	0.764		
Never	reference			
Unknown	1.49 (0.84,2.64)	0.168		
Clinical history				
Prior AIDS[8]				
Yes	0.93 (0.57,1.53)	0.780		
No	reference			
Prior non-AIDS[9]				
Yes	0.74 (0.38,1.46)	0.388		
No	reference			
Diabetes[10]				
Yes	0.53 (0.19,1.47)	0.225		
No	reference			
Hypertension[11]				
Yes	0.83 (0.52,1.33)	0.430		
No	reference			

	Discontinued due to other causes			
Variable	**Unadjusted IRR**	**P**	**Adjusted IRR[2]**	**P**
Unknown	0.91 (0.47,1.75)	0.781		
Anaemia[12]				
severe anaemia/mild anaemia	1.56 (0.80,3.04)	0.195	1.19 (0.58,2.44)	0.642
normal	reference		reference	
OtherUnknown	1.88 (1.16,3.03)	0.010	0.72 (0.18,2.93)	0.651
Prior HCV diagnosis[13]				
Yes	1.81 (1.14,2.87)	0.011	2.06 (1.15,3.70)	0.016
No	reference		reference	
Unknown	1.76 (0.90,3.43)	0.099	1.78 (0.82,3.84)	0.143
HIV viral load (copies/mL)[14]				
< 400	0.98 (0.36,2.67)	0.962		
≥ 400	reference			
Unknown	1.37 (0.46,4.02)	0.571		
CD4 count (cells/mm^3)[14]				
<200	0.59 (0.18,1.93)	0.385	0.51 (0.15,1.74)	0.280
200 - 349	0.42 (0.13,1.35)	0.145	0.34 (0.10,1.16)	0.085
350 - < 499	1.17 (0.62,2.21)	0.620	1.16 (0.61,2.19)	0.657
≥500	reference		reference	
Unknown	1.70 (1.05,2.75)	0.031	1.41 (0.82,2.42)	0.212
eGFR (ml/min/1.73m^2) [15]				
<60	0.76 (0.31,1.88)	0.555		
≥ 60	reference			
Unknown	1.39 (0.80,2.41)	0.239		
ALT (U/L)				
<40	1.10 (0.56,2.15)	0.782	1.11 (0.54,2.27)	0.775
≥ 40	reference		reference	
Unknown	1.85 (1.00,3.41)	0.048	1.98 (0.46,8.53)	0.358
AST (U/L)				
<40	0.60 (0.27,1.33)	0.212		

	Discontinued due to other causes			
Variable	**Unadjusted IRR**	**P**	**Adjusted IRR[2]**	**P**
≥ 40	reference			
Unknown	1.41 (0.72,2.75)	0.315		
ARV history				
Treatment naïve at baseline				
Yes	0.93 (0.41,2.13)	0.872	1.11 (0.44,2.83)	0.824
No	reference		reference	
Prior exposure to PI				
Yes	0.82 (0.50,1.35)	0.436		
No	reference			
Prior exposure to NNRTI				
Yes	1.74 (1.08,2.80)	0.024	2.13 (1.25,3.61)	0.005
No	reference		reference	
Prior exposure to ELV				
Yes	3.23 (1.22,8.56)	0.018	3.30 (1.20,9.09)	0.021
No	reference		reference	
Prior exposure to RAL				
Yes	0.55 (0.29,1.07)	0.079	0.60 (0.30,1.21)	0.155
No	reference		reference	
Number of ARVs previously exposed to				
1 - lowest quintile	reference			
2	1.00 (0.49,2.06)	0.991		
3	1.25 (0.67,2.33)	0.476		
4	1.39 (0.68,2.84)	0.367		
5 - highest quintile	1.04 (0.54,2.03)	0.900		

[1]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.

[2] confounding and effect modifying factors that are significant in univariate analyses ($p<0.1$) were be included in multivariate models, as well as treatment group and whether the patients were antiretroviral naïve at starting the regimen. Excluded variables were then added in turn to determine if their inclusion improved the fit of the model (defined as a significant reduction in the Log-Likelihood). Models adjusted for

Integrase inhibitor regimen, age, region of Europe, anaemia, prior HCV, treatment naïve at baseline, prior exposure to NNRTI, prior exposure to ELV.

[3] DTG with ABC

[4] DTG without ABC

[5] ELV/RAL with ABC

[6] ELV/RAL without ABC

[7] Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; North: Austria, Belgium, France, Germany, Luxembourg, Central: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia; East: Belarus, Estonia, Latvia, Lithuania, Russian Federation, Ukraine.

[8] Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition[1].

[9] Non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, NADM [2]

[10] Prior diabetes defined as: Prior diagnosis of diabetes mellitus, or taking oral antidiabetic agents or insulin

[11] hypertension defined as: SBP >= 140 mmHg, DBP >= 90 mmHg or taking angiotensin-converting enzyme inhibitors/antihypertensive agents

[12] Severe/mild anaemia defined as: Haemoglobulin < 14 and <12 in males and females respectively

[13] Prior Hepatitis C Virus (HCV) defined as: Prior HCV antibody test Positive (Yes), Negative (No) or no test or inconclusive (Unknown).

[14] Within 6 months prior to date

[15] Estimated glomerular filtration rate (eGFR) calculated using: CKD-EPI

6.5 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.

6.6 Quality control

Quality control followed 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.

6.7 Limitations of the research methods

Because the CRF for full assessment of HSR, serious skin rash, and hepatotoxicity were completed after the event occurred (and whole blood sample collection was also undertaken retrospectively for consenting patients), the completeness of data vary within centres. While every effort to maximize data collection was 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 above included 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) were 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 therefore this study will not be adequately powered to compare antiretroviral naïve to experience within treatment groups A-D described above. Below is a summary of statistical analyses and comparison of those who are antiretroviral naïve versus experienced: To be included when data on sufficient number of patients are available.

6.8 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 from consenting persons at the participating EuroSIDA centres 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 applied for blood sample collection for PGx analysis from consenting patients who experienced 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:

Quest Laboratories sent out blood collection kits to the EuroSIDA coordinating centre which will be distributed to sites with reports of suspected cases of HSR. The site will then collect the sample and shipped back to EuroSIDA for processing of genomic DNA. Specimens will be 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,

7 Overall Conclusion

The frequency of discontinuation due to HSR, hepatotoxicity and severe skin rash in users of integrase inhibitors is low, 0.2%, 0.0% and 0.0%, respectively. However this is based on a limited number of study participants receiving DTG (n=657) or RAL or ELV (n=560) and could potentially change as the study progresses and more data are accrued. **The data presented in this report are preliminary, for illustration and further follow-up on all regimens will accrue data over the coming years which will allow more detailed analyses.**

8 Protection of Human Subjects

8.1 Ethical approval and subject consent

This study protocol was 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 from consenting persons for future pharmacogenetic evaluation with the specific aim to investigate any possible genotypic relationship with development of HSR.

8.2 Subject confidentiality

Principles of medical confidentiality in relation to Study Subjects were 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.

9 Management and Reporting of Adverse Events/ Adverse Reactions

If, during the study, an adverse event (serious or non serious) was identified as explicitly attributed to any ViiV or GSK product (including products not covered in the specific study objective), this was reported according to national guidelines and standard operating procedures in place at each participating clinic.

10 Plans for Disseminating and Communicating Study Results

10.1 Target Audience

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

10.2 Study reporting and publications

EuroSIDA has the ownership of data collected related to this 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.

11 References

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