In February 2013, GlaxoSmithKline (GSK) announced a commitment to further clinical transparency through the public disclosure of GSK Clinical Study Reports (CSRs) on the GSK Clinical Study Register.

The following guiding principles have been applied to the disclosure:

- *Information will be excluded in order to protect the privacy of patients and all named persons associated with the study*
- *Patient data listings will be completely removed* to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the* ***GSK Clinical Study Register****.*
- *Aggregate data will be included; with any direct reference to individual patients excluded*

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

TITLE PAGE

Information Type: ViiV Healthcare Epidemiology Final Study Report

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

Development Phase:	IV
Compound Number:	GSK1349572 (Tivicay), GSK2619619 (GSK1349572+GR109714+GI265235, Triumeq), GSK3365791 (GSK1349572+GSK1329758, Juluca), GSK 3515864 (GSK1349572+GR109714, Dovato)
Effective Date:	01-Apr-2020
Subject:	Dolutegravir; integrase strand-transfer inhibitor (INSTI); hypersensitivity reaction; hepatotoxicity; observational cohort study; abacavir.
Keywords:	Dolutegravir; integrase strand-transfer inhibitor (INSTI); Abacavir; Hypersensitivity reaction; hepatotoxicity.

Author(s):

PPD [1],
PPD [1],
PPD [1],
PPD [1],
PPD [2],
PPD [2],
PPD [1],
PPD [2],
PPD [2],

PPD [3],
PPD [3],

[1] PPD
UK.
Tel: PPD
Fax: PPD

[2] PPD
Denmark
Tel: PPD
Fax: PPD

[3] ViiV Healthcare Company, Research Triangle Park, North Carolina, USA

SPONSOR SIGNATORY PAGE

I have read this report and confirm that to the best of my knowledge this report accurately describes the conduct and results of study 201177.

Name: Vani Vannappagari

Title: Global Head, Epidemiology and Real World Evidence

Signature: PPD

Date: 01Apr2020

Name: Nassrin Payvandi

Title: VP & Head, Safety & Pharmacovigilance

Signature: _____

Date: _____

Name: Jens-Ulrich Stegmann

Title: ViiV QPPV

Signature: PPD

Date: 01Apr2020

SPONSOR SIGNATORY PAGE

I have read this report and confirm that to the best of my knowledge this report accurately describes the conduct and results of study 201177.

Name: Vani Vannappagari

Title: Global Head, Epidemiology and Real World Evidence

Signature: _____

Date: _____

Name: Nassrin Payvandi

Title: VP & Head, Safety & Pharmacovigilance

Signature: PPD _____

Date: 1 April 2020

Name: Jens-Ulrich Stegmann

Title: ViiV QPPV

Signature: _____

Date: _____

INVESTIGATOR SIGNATURE PAGE

I have read this report and confirm that to the best of my knowledge Study 201177 was carried out as described in this Report

Name of Investigator: Amanda Mocroft

Affiliation:

Signature of Investigator: PPD

Date: 26 March 2020

TABLE OF CONTENTS

PAGE

List of Results Tables

List of Figures

1 LIST OF ABBREVIATIONS

ABC	Abacavir sulfate
ACE	Angiotensin-converting Enzyme
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
aIRR	Adjusted Incidence Rate Ratio
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 Rate
EFV	Efavirenz
EVG	Elvitegravir
EMA	European Medicines Agency
ERC	Endpoint Review Committee
ERCC	Endpoint Review Committee Coordinator
ESCO	EuroSIDA Coordinating Office
ETV	Etravirine
fAPV	Fosamprenavir
FDC	Fixed-dose combination
FTC	Emtricitabine
GI	Gastro-intestinal
GSK	GlaxoSmithKline
GSS	Genotypic Susceptibility Score
GWAS	Genome-wide Association Study
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
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
NADM	Non-AIDS-defining malignancy
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	Prostate-specific antigen
PYFU	Person-years of follow-up
RAL	Raltegravir
RAM	Resistance-associated Mutation
RPV	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
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate
TEN	Toxic Epidermal Necrolysis
TPV	Tipranavir
T-20	Enfuvirtide
ULN	Upper limit of normal
VCV	Vicriviroc
ZDV	Zidovudine
3TC	Lamivudine
/c	Cobicistat-boosted
/r	Ritonavir-boosted

Trademark Information

Trademarks of the GlaxoSmithKline group of companies	Trademarks not owned by the GlaxoSmithKline group of companies
KIVEXA	
TIVICAY	
TRIUMEQ	
JULUCA	
DOVATO	

2 RESPONSIBLE PARTIES

INVESTIGATORS

The EuroSIDA study group is listed in **Annex 1**.

3 ABSTRACT

Title

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

Rationale and background

Hypersensitivity reaction (HSR) is a rare but potentially fatal side-effect of antiretroviral treatment. This study aimed to establish the incidence of discontinuation due to HSR among users of dolutegravir (DTG) or other integrase inhibitors (raltegravir, RAL, and elvitegravir, EGV).

Research questions and objectives

The objectives of the study were to:

a) Monitor and compare hypersensitivity reactions in users of DTG with or without abacavir (ABC) and compare the incidence to that among users of other integrase inhibitors.
b) Monitor for hepatotoxicity
c) Monitor for severe skin rash

Study design

Prospective observational cohort study

Setting

A five year-long non-interventional prospective observational cohort study nested within EuroSIDA, a cohort study of over 23,000 HIV-1 positive individuals in over 100 centres across 35 European countries, Israel and Argentina. The patients included in EuroSIDA are enrolled to be representative of the individuals 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 1994(1).

Subjects and study size, including dropouts

Individuals included were HIV-positive, over the age of 16 years old and started antiretroviral therapy (ART) containing DTG or another integrase inhibitor (RAL or EVG), with or without ABC, between 16/01/2014 and 23/01/2019. Overall 4819 individuals with at least one episode of integrase inhibitor use were included, of whom 3164 started a DTG-containing regimen and 1655 started another integrase inhibitor (RAL or EVG). Individuals were followed until they discontinued the integrase inhibitor, their last visit in EuroSIDA or 23/01/2019. Baseline was the date of first use of an integrase inhibitor after 16/01/2014.

Variables and data sources

Exposure variables: Individuals using integrase inhibitors were divided into five groups:

A. DTG with an ABC-based anti-retroviral regimen (including TRIUMEQ™, the fixed-dose combination of DTG/ABC/3TC)
B. DTG as (TIVICAY™) without ABC
C. Other integrase inhibitors (RAL or EVG) with an ABC-based anti-retroviral regimen
D. Other integrase inhibitors (RAL or EVG) without ABC
E. DTG taken as monotherapy or part of a two-drug regimen and without ABC (Juluca, the fixed-dose combination of DTG/RPV and Dovato, the fixed-dose combination of DTG/3TC)

Outcomes: Discontinuation of integrase inhibitor regimen. All discontinuations and reasons for discontinuation were recorded and discontinuation reasons were reviewed and sent for independent validation. Specific outcomes of interest were integrase inhibitor-related hypersensitivity reactions (HSR), hepatotoxicity or severe skin rash.

Associated variables included baseline demographic variables, clinical characteristics and ARV treatment history.

Results

During this five-year study overall 4819 individuals started an ART regimen containing DTG or another integrase inhibitor (RAL or EVG) with or without ABC. Of these, 1545 (32.1%) started DTG with ABC, 1166 (24.2%) started DTG without ABC and 453 (9.4%) used DTG mono- or two-drug ART. 239 (5.0%) individuals started RAL or EVG with ABC and 1416 (29.4%) used RAL or EVG without ABC. There were altogether 5608 episodes of INSTI use over 9990

person-years of follow-up (PYFU), with median duration of follow-up of 1.6 (interquartile range, IQR, 0.7-2.8) years per episode per person.

Overall 1101 (22.8%) of individuals discontinued DTG or another integrase inhibitor during follow-up to 23/01/2019, and there were altogether 1336 discontinuations of an INSTI, of which 724 (54.2%) were discontinuations of DTG (with or without ABC) and 612 (45.8%) were discontinuations of other integrase inhibitors (RAL or EVG). The rate of discontinuation for any reason in individuals on DTG-containing cART (treatment groups A and B combined) was 11.5 (95% CI: 10.7, 12.5)/100 PYFU and in those on RAL/EVG containing cART (treatment groups C and D combined) was 17.3 (95% CI: 16.0, 18.8)/100 PYFU. The rate of discontinuation among those on DTG as monotherapy or two-drug regimens (treatment group E) was 8.7 (95% CI: 6.9, 10.9)/100 PYFU

After review there were five discontinuations due to definite or probable HSR, of which one was in an individual taking DTG with ABC (group A), one in an individual taking DTG without ABC (group B), and three among individuals taking RAL or EVG without ABC (group D). The rate of discontinuations due to HSR overall was 0.05 (95% CI: 0.02, 0.12)/100 PYFU. There was one discontinuation for hepatotoxicity in group A (DTG with ABC). There were no discontinuations due to severe skin rash.

Discussion

Integrase inhibitor use was common in EuroSIDA and increased in recent years. Overall around 23% of individuals who started an integrase inhibitor-containing ART regimen discontinued. However, the frequency of discontinuation due to HSR or hepatotoxicity in users of integrase inhibitors was low, and no discontinuations due to severe skin rash were observed. Therefore, risk factors for discontinuation of DTG or other integrase inhibitor regimens due to HSR or hepatotoxicity could not be evaluated.

3.1 Update from the last interim report (#4, January 2019)

This final report covers 5 years of follow-up from 16th January 2014 until 23rd January 2019, adding two further years of follow-up since the fourth interim report which included data until 16th January 2017.

The number of individuals included has increased by approximately 1.7-fold from 2855 individuals in interim report #4 to now 4819 individuals in this final report, and the number of INSTI episodes among these individuals increased 1.8-fold from 3144 in interim report #4 to now 5608 in this final report.

The number of individuals who discontinued an integrase inhibitor at least once increased 2.4-fold from 455 in interim report #4 to now 1101 in this final report. Overall there were 1336 discontinuations of INSTI over 9990 PYFU (note that some individuals had more than one discontinuation of an INSTI-containing ARV regimen), up from 516 discontinuations of INSTI over 3237 PYFU in interim report #4. This represents 3-fold increase in follow-up time on INSTIs.

The number of discontinuations due to HSR increased from two in the fourth interim report to now five in the final report. Of the five cases of HSR, two were among individuals taking DTG (one with ABC, group A, and one without ABC in Group B), and three were in individuals on other integrase inhibitors (without ABC, in group D: one individual on RAL and two individuals who were taking EVG). There was also a new discontinuation for hepatotoxicity in Group A (DTG with ABC).

4 AMENDMENTS AND UPDATES

Number	Date	Section of study report	Amendment or update	Reason
1	06-Oct-2017		Added group E	Also monitor adverse reactions in individuals taking DTG as part of a mono-therapy or 2-drug regimen (DTG/RPV or DTG/3TC)

5 MILESTONES

Milestone	Planned date	Actual date	Comments
Study start	June 2014 or Date DTG is commercially available, whichever is earlier	16 January 2014	*[Text]*
End of data collection	5 years after study start	23 January 2019	*[Text]*
Annual Interim Report #1	December 2015	22 January 2016, and revised 3. February 2017	*[Text]*
Annual Interim Report #2	December 2016	24 January 2017	*[Text]*
Annual Interim Report #3	December 2017	15 December 2017, and revised 5 February 2018	*[Text]*
Annual Interim Report #4	December 2018	11 January 2019, and revised 31 January 2019	*[Text]*
Study Completion	June 2019 or 5 years following commercial availability of DTG	16 January 2019	*[Text]*
Final Report	December 2019	xx March 2020	*[Text]*

6 BACKGROUND AND RATIONALE

Dolutegravir (TIVICAY™) is a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI) indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. It is recommended for both treatment-naïve and treatment-experienced, HIV-infected adults and paediatric patients aged 12 years and older and weighing at least 40 kg. The usual recommended dose of dolutegravir is 50 mg (one tablet) once daily for patients infected with HIV-1 without resistance to the integrase class, and 50 mg twice daily in patients infected with HIV-1 that has resistance to the integrase class.

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

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

This safety study has been conducted through collaboration with EuroSIDA, a well-established, prospective observational cohort study of more than 23,000 patients followed in 100 collaborating clinics across 35 countries covering all European regions, Israel and Argentina(1). The study protocol was implemented by the EuroSIDA coordinating center.

7 RESEARCH QUESTION AND OBJECTIVES

7.1 Research question and objectives

This study applies to individuals initiating of one of the below regimens:

A. cART (≥3 ARVs) with DTG [as TRIUMEQ, the fixed dose combination of DTG/ABC/lamivudine (3TC)], or;
B. cART with DTG [as TIVICAY] without ABC, or;
C. Other integrase inhibitor-based cART regimens (RAL, EVG) with ABC, or;
D. Other integrase inhibitor-based cART regimens (RAL, EVG) without ABC

Following a protocol amendment (see 06 October 2017) in order to include patients on other DTG-based regimens, including JULUCA™ (DTG+RPV) and Dovato (DTG+3TC), a fifth group (group E) was added:

E. Patients that start any other DTG based ARV regimen [including DTG as monotherapy or two-drug regimens]

The study investigated three research questions:

1. Monitor and compare hypersensitivity reaction

- To determine the incidence of discontinuation of DTG or other integrase inhibitor regimens (with or without ABC) due to HSR among exposed treatment naïve and treatment experienced HIV patients
- To determine the risk factors for discontinuation of DTG or other integrase inhibitor regimens (with or without ABC) due to HSR among exposed treatment naïve and treatment experienced HIV patients
- To collect blood samples from suspected HSR cases for potential future pharmacogenetic evaluation

2. Monitor for hepatotoxicity

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

3. Monitor for severe skin rash

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

The above monitoring was be done in accordance with the case definitions and screening criteria as defined in below in section 8.3.2.

7.2 Overview of research outcomes:

7.2.1 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 assessed (**Table 1B and SUPPLEMENTARY TABLE 1**):

There were altogether <u>five</u> cases of discontinuation of DTG or other integrase inhibitor regimens (with or without ABC) due to HSR.

A. Patients that start DTG and ABC based ARV regimen: There was 1 case of discontinuation due to HSR (possible integrase inhibitor-related HSR)[1]. The individual had a mild rash, gastro-intestinal symptoms (nausea) and dyspnoea, but no fever or eosinophilia were reported. Levels of ALT and Bilirubin were not reported.
B. Patients that start DTG based ARV regimen but without ABC: There was 1 case of discontinuation due to HSR. Fever and gastro-intestinal symptoms (nausea) 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 EVG) and with ABC: There were no cases of discontinuation due to HSR.
D. Patients that start other integrase inhibitor-based regimen (RAL and EVG) but without ABC: There were 3 cases of discontinuation due to definite or possible integrase inhibitor-related HSR.
    i. One patient discontinued RAL with severe skin rash, but no gastro-intestinal symptoms, no fever, no eosinophilia, and no respiratory symptoms. Levels of ALT and Bilirubin were not elevated.
    ii. One patient discontinued EVG as Genvoya with gastro-intestinal symptoms (vomiting), but no fever, no eosinophilia, no rash and no respiratory symptoms were reported. Levels of ALT and Bilirubin were not elevated.
    iii. One patient discontinued EVG as Genvoya with mild rash and gastro-intestinal symptoms (nausea), but no fever and no respiratory symptoms were reported. Eosinophilia and levels of ALT and Bilirubin were not reported.

[1] Note: This case of possible integrase inhibitor-related HSR was adjudicated after interim report #4 (January 2019) was finalised. The case was not retrospectively added to report #4 but is now included.

E. Patients that start any other DTG based ARV regimen [including DTG as monotherapy or two-drug regimens]: There were no cases of discontinuation due to HSR.

As only 5 cases of definite or possible integrase inhibitor-related HSR were reported during the 5-year study period, 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 could not be determined[2].

Blood samples from suspected HSR cases for potential future pharmacogenetic evaluation were scheduled to be collected from consenting persons. Of the five suspected HSR cases,

- One individual will not be included in the blood sample analysis as the site is not able to send blood samples out of the country (Norway).
- One individual has moved away and it was not possible to withdraw a blood sample
- For one individual, the site has been asked to apply for PASS protocol ethics approval to be followed by informed consent from the patient and blood sample collection but there has been no response from the site.
- One individual will not be included in the blood sample analysis as the site is not able to send a blood sample at this time due to local regulatory restrictions (Israel).
- One case of HSR was identified recently; the PASS protocol has been submitted to the local IRB, but final ethics approval is pending prior to sending the blood collection kit to the site.

7.2.2 Monitor for hepatotoxicity

There was one instance of discontinuation due to hepatotoxicity for DTG or other integrase inhibitors (with or without ABC).

A. Patients that start DTG and ABC based ARV regimen: There was 1 case of discontinuation due to hepatotoxicity. No fever, eosinophilia, rash, gastro-intestinal or respiratory symptoms were reported. Time to onset was 3 months and 22 days and no concomitant medication was reported. ALT and AST levels were elevated to >10x ULN (ULN=40 U/L), bilirubin was within the normal range. Hepatotoxicity resolved without sequelae.

The incidence of liver chemistry elevations indicative of drug-induced liver injury (DILI, defined as ALT >5x ULN (ULN=40 U/L), or ALT >3x ULN and bilirubin >2x ULN (ULN=1.2 mg/dL), see (2)) among DTG users or users of other integrase inhibitors (with or without ABC) was also estimated and is shown in

[2] This analysis required that the number of events exceeds 30 in each treatment group.

SUPPLEMENTARY TABLE 2. Test data were available for 4300 of the 4819 individuals in the study.

A. Patients that started DTG and ABC based ARV regimen: of the 1372/1545 individuals who had a test, 45 (3.3%) had elevated liver chemistry tests.
B. Patients that started DTG based ARV regimen but without ABC: of the 1063/1166 people who had a test, 39 (3.7%) had elevated liver chemistry tests.
C. Patients that started other integrase inhibitor-based regimen (RAL and EVG) and with ABC: of the 211/239 people who had a test, 10 (4.7%) had elevated liver chemistry tests.
D. Patients that started other integrase inhibitor-based regimen (RAL and EVG) but without ABC: of the 1251/1416 people who had a test, 40 (3.2%) had elevated liver chemistry tests.
E. Patients that started any other DTG based ARV regimen [including DTG as monotherapy or two-drug regimens]: of the 403/453 people who had a test, 9 (2.2%) had elevated liver chemistry tests.

For the 5 discontinuations due to HSR, three did not have elevated ALT or Bilirubin levels, and for two ALT and bilirubin levels were not reported.

7.2.3 Monitor for severe skin rash.

The incidence of discontinuation of DTG or other integrase inhibitors (with and without ABC) due to severe rash was monitored to the extent this is possible based on the data captured in the annual data capture and a subsequent data collection form completed for all patients with a suspected clinical event in EuroSIDA.

A. Patients that started DTG and ABC based ARV regimen: Five individuals were recorded with a mild skin rash. One of these individuals was identified as definite or probable HSR and is described above. In addition, mild skin rash was indicated in two discontinuations of DTG with ABC not due to HSR.
B. Patients that started DTG based ARV regimen but without ABC: no incidence of skin rash was recorded.
C. Patients that started other integrase inhibitor-based regimen (RAL and EVG) and with ABC: no incidence of skin rash was recorded.
D. Patients that started other integrase inhibitor-based regimen (RAL and EVG) but without ABC: Severe skin was indicated in one discontinuation of RAL without ABC due to HSR. In addition, mild skin rash was indicated in two discontinuations of EVG without ABC not due to HSR.
E. Patients that started any other DTG based ARV regimen [including DTG as monotherapy or two-drug regimens]: no incidence of skin rash was recorded.

8 RESEARCH METHODS

8.1 Study design

This is the final report from a five year-long prospective cohort study nested within the EuroSIDA study. Potential HSR, hepatotoxicity and severe skin rash cases were identified among individuals discontinuing DTG or other integrase inhibitor regimens in EuroSIDA's dynamic database of medical information. The study outcome definitions and analysis follow that of previously published work looking at hypersensitivity reactions in those persons exposed to ABC (Bannister et al., 2008(3)) as outlined in the study protocol. 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 identified as described below (section 8.3.2). 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 cases for additional details on the cases. (see sample HSR form at https://www.chip.dk/Studies/EuroSIDA/Study-documents).

For this non-interventional study, treatment decisions were made by the treating physician according to standard practice, taking into account the treatment history, patient characteristics and local guidelines or recommendations. Dosage of DTG and the combination ARVs for the regimen were selected by the treating physician.

8.2 Study Population and Setting

The study population includes HIV positive individuals 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 EVG).

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 a cART regimen with DTG and ABC

B. Patients that start a cART regimen with DTG but without ABC

C. Patients that start a cART regimen with other integrase inhibitors (RAL and EVG) and with ABC.

D. Patients that start a cART regimen with other integrase inhibitors (RAL and EVG), but without ABC.

Following a protocol amendment (see 06 October 2017) in order to include patients on other DTG-based regimens, a fifth group (group E) was added:

E. Patients that start any other DTG-based ARV regimen [including DTG as monotherapy or two-drug regimens]

Monitoring was done in accordance with the case definition and screening criteria as defined in section 8.3.2.

EuroSIDA Cohort description: The EuroSIDA study was initiated in 1994, and is a prospective observational cohort study of over 23,000 HIV-1 infected patients in over 100 centres across 35 European countries, Israel and Argentina(1). The main objective of the EuroSIDA 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 annual 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(4).

8.3 Study variables

8.3.1 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 50 mg twice daily for patients infected with HIV with resistance to INSTIs.

8.3.2 Outcome definitions

8.3.2.1 HSR case definition

All patients discontinuing DTG or other integrase inhibitor regimens (RAL and EVG) for any reason were assessed for potential HSR.

For potential HSR cases, HSR event forms were collected to clarify the circumstances around the HSR event and allow an adjudication process by the independent case review committee.

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. 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

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) including the following, with a focus on alanine aminotransferase elevations and total bilirubin elevations:

i. ALT elevations (ALT is also called serum glutamic pyruvic transaminase (SGPT))

ii. AST elevations (AST is also called serum glutamic oxaloacetic transaminase (SGOT))

iii. Alkaline phosphatase (ALP) elevations

iv. Total bilirubin elevations

v. Albumin

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

8.3.2.2 Hepatotoxicity

The above mentioned annual 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.

Clinical chemistry criteria for possible drug-induced liver injury (DILI) included any one of the below(2), 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[3]

[3] 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.

- More than or equal to threefold elevation in ALT concentration and simultaneous elevation of total bilirubin concentration exceeding 2× ULN

8.3.2.3 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)

8.3.2.4 Verification and adjudication of discontinuations to ensure accurate identification of hypersensitivity, hepatotoxicity and severe skin rash

The validity of data on treatment regimens and drug discontinuations 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.

To ensure that cases of discontinuation of hypersensitivity, hepatotoxicity, and severe skin rash were not misclassified as other reasons of discontinuation, an independent adjudication committee was established at the start of the study to review and validate potential discontinuations due to the mentioned adverse events and to ensure minimization of misclassification.

All patients discontinuing DTG or other integrase inhibitor regimens (RAL and EVG) for any reason were assessed for potential HSR.

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.

Each patient that discontinued DTG (or other integrase inhibitor regimens (RAL and EVG)) in September 2015 or later due to a suspected HSR as well as those who discontinue due to “other causes” or “unknown” reasons had an additional HSR specific data clarification CRF form completed by the site regarding the circumstances surrounding discontinuation. Forms were collected on all patients that discontinued an integrase inhibitor regimen prior to September 2015. It is therefore extremely unlikely that any events were missed. The procedures for case finding are described below, as well as the process for reviewing potential HSR cases.

At each EuroSIDA follow up, antiretrovirals started and discontinued in the last five years are collected in a standardized format via REDCap. If the site reports discontinuation of one of the antiretrovirals of interest for one of the following reasons

4: Hypersensitivity reaction

4.1: Hypersensitivity reaction: Allergic reaction

4.2: Hypersensitivity reaction: Anaphylactic reaction

4.9: Drug allergy related to DTG or another integrase inhibitor

5.2: Toxicity – Liver

98: Other causes, not specified above

99: Unknown

then the site is prompted to complete a “Hypersensitivity Reaction/Liver Toxicity event form” in REDCap. This contains information on date of birth, the drug that has been discontinued, start and stop dates, and further information on reasons for discontinuation. If one of the following reasons are chosen:

- Hypersensitivity reaction incl. rash
- Hypersensitivity reaction - Allergic reaction
- Drug allergy related to DTG or another integrase inhibitor
- Hypersensitivity reaction - Anaphylactic reaction
- Toxicity - Liver
- Unknown

Additional information is collected concerning:

- Dosage
- Fever
- Eosinophilia
- Rash
- Gastrointestinal problems
- Respiratory symptoms
- Hepatic lab values related to possible hepatic dysfunction
- Strength of causal relationship between antiretroviral and adverse reaction
- Source documentation where relevant

If the site chooses “Other causes, not specified above”, as reason for discontinuation then they are required to fill out a narrative description of the reason for discontinuation. This narrative is reviewed by both the study coordinator and a clinician to ensure that no HSR is missed. In addition, the EuroSIDA analysis team reviews all the data and discontinuations of antiretrovirals of interest, and this is cross-checked against the data already

reported to the EuroSIDA IT team to ensure discontinuations without all relevant information are prompted to provide the required information.

The process for identifying HSR cases is shown in detail in **Box 1**.

Box 1: The process for identifying HSR events

HSR case identification is carried out by the Coordinating Center in Copenhagen (CHIP). The purpose of the Endpoint Review Committee (ERC) within the DTG-PASS Protocol is to undertake the review and evaluation of potential dolutegravir (DTG), or other integrase inhibitors, hypersensitivity reactions, liver toxicities and rashes. The major objective of the ERC is to determine if the reported event meets the study diagnostic criteria for a confirmed or probable HSR, liver toxicity or rash.

Endpoint Review Committee (ERC)

The ERC consists of 12 experienced clinicians who work independently of the ES Steering Committee and of GSK. The coordination of the review process is managed by the ERC coordinator (ERCC) PPD at CHIP assisted by the hosting ERC member PPD PPD All questions related to the ERC functions and activities should be addressed to the ERC coordinator.

Event Review

Similar to EuroSIDA follow-up forms the HSR Event Form is completed in REDCap, a browser-based data capture system. All completed HSR forms go through a first review by the ERC coordinator and the hosting ERC member at CHIP to determine which HSR forms qualify for ERC review.

Procedures

Pre-review:

Local site: Once a participant has stopped taken DTG or another integrase inhibitor, if the discontinuation reason reported is one of the following:

4 Hypersensitivity reaction;
4.1 Hypersensitivity reaction: Allergic reaction;
4.2 Hypersensitivity reaction - anaphylactic reaction;
4.9 Drug allergy related to DTG or another integrase inhibitor;
5.2 Toxicity – Liver;
98 Other causes, not specified above; or
99 Unknown;

then the local site completes an HSR Event Form in REDCap in order to capture potential case of DTG related HSR/DILI. The local site will also collect and submit additional information on the event if requested by the ESCO.

ERCC: The ERCC reviews the event form for completeness. If key information is missing the ERCC queries the reporting site via the ESCO.

ERCC: Once the pre-review has been completed and the HSR form is clean from queries and an HSR is suspected, then the HSR form is shared with the active ERC reviewers via REDCap. Each ERC member and the ERCC need a personal password to log into REDCap.

Review:

ERC: The major job of the ERC is to determine if the reported event meets the study diagnostic criteria for a confirmed or probable HSR or DILI. The independent review outcome is documented on an ERC review form in REDCap which immediately is available to the ERCC. If needed ERC reviewers can request additional information for a conclusive review. However, each reviewer must provide an initial outcome based on the information available at the time of the initial review of the event.

Reviews should be conducted within two weeks.

Adjudication:

ERC: All ERC reviewers must agree on the classification of an event. Disagreements among reviewers are adjudicated.

ERCC: The ERCC sends to the active ERC reviewers the results of the initial review including all reviewers' comments, and the active ERC reviewers communicate by e-mail until consensus is reached.

ERC: Reviewers should provide their comments on adjudication to the ERCC within one week.

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

8.3.3 Confounders and effect modifiers

Confounding by indication in observational data is a significant issue. This arises whereby persons are chosen to start in any of the treatment groups for reasons that are either unknown or unmeasured within the study, and which cannot therefore be adjusted for as confounders in analyses. The statistical analysis 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

8.4 Data Sources

Following the EMA's approval of DTG, the study collects prospective data on patients treated with cART (≥3 ARVs) including 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. Following the protocol amendment of 06. October 2017, data was also collected on a fifth group, comprising individuals that started any other DTG based ARV regimen [including DTG as monotherapy or two-drug regimens]

The coordinating centre receives data from the clinical sites annually.

- All suspected HSR cases were identified through screening criteria described in section 8.3.2 and review of potential data clarification items collected at a specific HSR event form. Screen-positive cases were reviewed by an independent adjudication committee for final determination of drug-associated causality
- Causality assessment for hepatotoxicity was done by the independent adjudication committee.

Following ethical clearance of the PASS protocol at the sites where the potential cases are located, the participant is asked for informed consent to obtain whole blood samples for potential future pharmacogenetic analysis. The coordinating centre works 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 can therefore 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.

8.5 Study size

Sample size was dependent on the market uptake of DTG following its commercial availability in European countries. Estimates of adverse event rates and number of patients followed, yielding person-years of exposure (PYFU) to DTG or other integrase inhibitors were estimated as shown. As approximately 10,000 patients were under active follow-up in EuroSIDA at the start of the study, contributing approximately 4500 PYFU every 6 months, achieving a sample size between 1,000 and 10,000 PYFU was considered feasible

Person-years follow-up	Incidence of AE/100 PYFU	N Events
1000	0.05	0
	0.10	1
	10.0	10
10000	0.05	5
	0.10	10
	10.0	100

As shown in the results, this 5-year study did accumulate approximately 10,000 PYFU overall.

8.6 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) as well as the Copenhagen HIV Programme Quality Management Plan.

8.7 Data handling conventions

Data handing followed the HICDEP - HIV Collaboration Data Exchange Protocol for data submitted electronically. Data submitted in the online electronic data capture platform REDCap were handled according to current and valid standard operating procedures (SOPs).

In addition, all data were fully anonymised before transfer to Copenhagen and are held securely. Data were transferred to the statistical team in London via

secure download and password-encrypted file. The data are held on password-secured computers in London. EuroSIDA have the relevant data protection clearance, Data Protection Agency No: 2012-54-0035

8.7.1 Timings of Assessment during follow-up

All sites completed the follow-up forms within the two-month period in the online electronic data capture platform REDCap or via electronic download. 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 annually from all consenting patients.

8.8 Statistical methods

8.8.1 Descriptive statistics

DTG (or other integrase inhibitor)-based regimens were regimens consisting of at least 3 ARVs combined from any class, of which at least one was DTG (or other integrase inhibitor). In addition, DTG-based mono- and 2-drug ART therapies were also included.

New users of DTG (or other integrase inhibitors, RAL and EVG) were characterized at baseline, defined as initiation of a DTG- (or other integrase inhibitors) based ARV regimen as specified above, stratified into five treatment groups (A-E).

Descriptive statistics of the patient characteristics of the five treatment groups follow 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 and D (i.e. the comparator groups containing EVG 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 (North, West Central, East Central, East and South/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, (5)], 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 cells/mm^3) 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[4] was 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) were calculated and described. IAS USA integrase mutations currently include: T66/I/A/K, L74M, E92Q/G, T97A, E138A/K G140A/S, Y143R/H/C, S147G, Q148H/K/R, N155H. The number of predicted active drugs included in the initiated DTG-containing regimen (or other integrase inhibitors EVG and RAL) was estimated using the HIVdB genotypic susceptibility score (GSS). Note that most of the genotypic resistance tests in EuroSIDA were from samples collected prior to 2010, and INSTI resistance testing was limited.

All analyses were performed using SAS version 9.4.

8.8.2 Logistic regression modelling

Logistic regression was used to compare those starting cART with DTG (treatment groups A-B[5]) with those starting another integrase inhibitor (Groups C-D). Comparisons are also presented for those starting DTG with or without ABC (treatment group A versus B[5]) and those starting other integrase inhibitors with or without ABC (treatment groups C versus D). The 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 did not develop the endpoint, at last clinic visit, as well as to those who discontinued 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. For HSR and hepatotoxicity events the CRF also 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.

[4] Cross-resistance studies with RAL- and EVG-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 [see 6. Johnson VA, Calvez V, Gunthard HF, Paredes R, Pillay D, Shafer RW, et al. Update of the drug resistance mutations in HIV-1: March 2013. Top Antivir Med. 2013;21(1):6-14.] EuroSIDA has previously published a study considering the incidence of and factors associated with hypersensitivity in persons exposed to ABC(2) and the data analysis broadly followed that of this previous work.

[5] Note: Individuals in group E (DTG mono- and 2-drug therapy) will not be included in these comparisons.

8.8.3 Analysis of event rates

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 occurred first. Time to event 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 exceeded 30 in both treatment groups A-B combined and C-D combined (i.e. allowing a primary comparison between any DTG-based regimen and any other integrase based regimen, with or 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. For analysis of event rates, months of follow-up accumulated in the relevant treatment group A-E and were summed to calculate person-years of follow-up (PYFU). Statistical analyses adjusted for the within patient correlation. Patients could also experience more than one event of interest, and in primary analyses each event was allocated to the treatment group the event occurred in.

8.9 Quality control and quality assurance

Quality control followed the EuroSIDA SOP, EuroSIDA QA checks for data transfer as well as the CHIP Quality Management Plan, related SOPs and the DTG PASS: Quality control processes and Endpoint Review Committee procedures.

8.10 Other aspects: Blood sample collection for potential future pharmacogenetics study

Blood samples from suspected HSR cases have been collected from consenting persons at the participating EuroSIDA centres and processed/stored at the long-term storage facility maintained by the EuroSIDA.

PGx sampling: Quest Laboratories sent out blood collection kits to the EuroSIDA coordinating centre which were distributed to sites with reports of suspected

cases of HSR. The site then attempted to collect the sample and ship to EuroSIDA for processing of genomic DNA and storage.

9 PROTECTION OF HUMAN SUBJECTS

9.1 Ethical approval and subject consent

This study protocol was approved by the EuroSIDA steering committee.

Participating EuroSIDA sites 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 samples 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.

Additional consent and Independent Ethics Committee (IEC) approvals were obtained for blood sample collection for potential future PGx analysis from consenting patients who experienced a potential DTG or other integrase inhibitor related HSR. When applying for IEC approval, it was emphasized that samples would only be used for investigation of any possible genotypic relationship with development of HSR.

9.2 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.

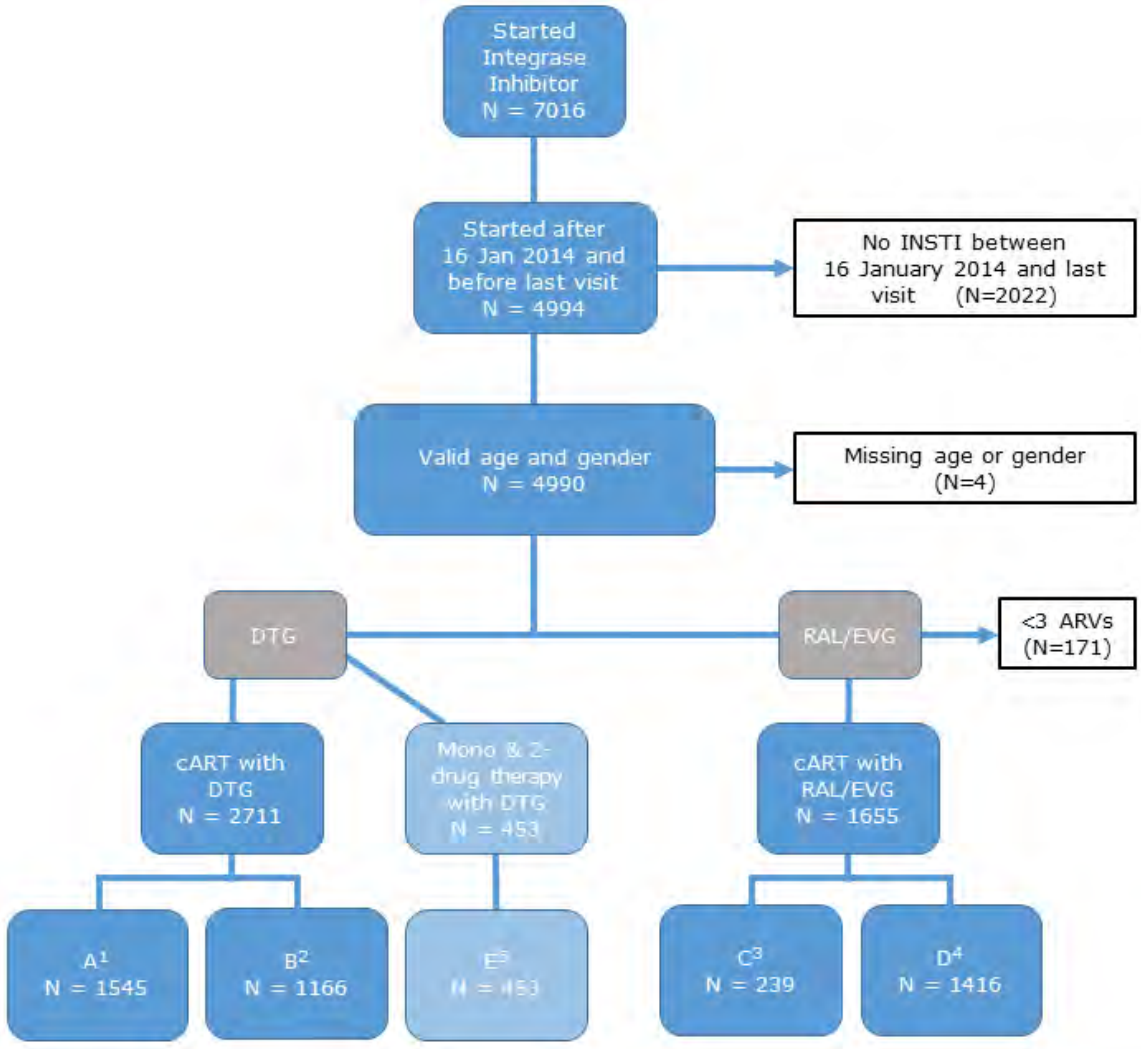
10 RESULTS

10.1 Participants

10.1.1 Summary of study participants

A summary of the study participants included is shown in Figure 1.

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



[1] DTG with ABC
[2] DTG without ABC
[3] EVG/RAL with ABC
[4] EVG/RAL without ABC
[5] Mono- and 2-drug therapy with DTG
Individuals whose only INSTI use was a 2-drug regimen with RAL were excluded.

Altogether 4819 individuals were included, of whom 3164 started a regimen containing DTG: 1545 started a 3-drug regimen including DTG with ABC (Group A), 1166 started a 3-drug regimen including DTG without ABC (Group B) and 453 started DTG as monotherapy or two-drug regimens (Group E). Altogether 1655 individuals started a regimen involving another INSTI (EVG or RAL),

including 239 who started a 3-drug regimen including EVG or RAL with ABC (Group C) and 1416 who started a 3-drug regimen including EVG or RAL without ABC (Group D).

Overall 4179 individuals had only one episode of INSTI use (note that switching between DTG regimens A, B and E, or between EVG/RAL episodes C and D, was allowed within an episode), 523 individuals had two episodes of INSTI use, 98 individuals had three episodes and 19 had more than three episodes of INSTI use (11 had 4 episodes, 4 had 5 episodes, 3 had 6 episodes and one had 7 different episodes of INSTI episodes).

A summary of the individuals included by INSTI use and discontinuation reasons is presented in Table 1A for the first INSTI episodes (one episode for each individual included) and Table 1B for all INSTI episodes.

10.1.2 Overview of cohort

Between 16 January 2014 and 23 January 2019 for an observation period of just over 5 years, there were 4819 individuals who started an integrase inhibitor-based ARV regimen (Table 1A), with around 10,000 person years of follow-up (PYFU) for all integrase inhibitor regimens combined (median follow-up of 1.6 (interquartile range [IQR]: 0.7 – 2.8) years per person, see Table 1B).

Of the 4819, 168 (3.5%) were treatment naïve, 3851 (79.9%) were integrase inhibitor naïve and 968 individuals were integrase inhibitor experienced. Of the 4819, 3164 individuals started DTG, including 1545 on cART (≥3 ARVs) with ABC (treatment group A), 1166 on cART without ABC (treatment group B) and 453 on DTG-containing mono- and 2-drug therapy (treatment group E). There were 1655 individuals who started cART containing RAL/EVG, of which 239 with ABC (treatment group C) and 1416 without ABC (treatment group D) (see Figure 1, Table 1A).

Of the 4819 individuals, 1101 (22.8%) discontinued their first INSTI regimen; of these, 291/1545 (18.8%) had started in treatment group A, 255/1166 (21.9%) in B, 78/239 (32.6%) in C, 412/1416 (29.1%) in D and 65/453 (14.3%) in treatment group E (Table 1A). Six-hundred and forty individuals were treated with more than one INSTI episode during the five-year period, and altogether there were 5608 episodes of INSTI use (1738 episodes starting in treatment group A, 1336 in B, 286 in C, 1758 in D and 492 in E), with 1336 discontinuation events overall (see Table 1B). Of all discontinuations, five were due to HSR (one from group A, one from group B and three from group D). All five HSR discontinuations were in treatment-experienced patients, and three were also integrase inhibitor experienced (see **Table 10**). One individual discontinued due to hepatotoxicity; this individual was treatment-experienced and integrase-inhibitor naïve. The discontinuations by treatment regimen were as follows:

- Group A (DTG with ABC): One individual discontinued due to HSR; this person had received DTG at 50 mg once daily for 40 days.
  Another individual discontinued due to INSTI-related hepatotoxicity; this person had received DTG at 50 mg once daily for 115 days.

- Group B (DTG without ABC): One individual discontinued due to HSR; this person had received DTG at 50 mg once daily for 43 days.
- Group D (EVG or RAL without ABC): There were three discontinuations due to HSR;
    - One individual had received RAL at 400 mg twice daily for 79 days,
    - One individual had received EVG at 150 mg once daily for 7 days
    - One individual had received EVG at 150 mg once daily for 216 days.

There were no discontinuations due to HSR in Group C (EVG or RAL with ABC) and Group E (DTG mono- and 2-drug therapy). There were no other discontinuations due to hepatotoxicity, and no discontinuations due to severe skin rash (not HSR).

Considering all 5608 discontinuation events (**SUMMARY Table 15**) the rate of discontinuation in individuals treated with DTG cART (treatment group A and B combined) was 11.5 (95% CI: 10.7, 12.5)/100 PYFU (653 discontinuations over 5662 PYFU) and the rate of discontinuation in those with DTG on mono- or 2-drug therapy (E) was 8.7 (95% CI 6.9, 10.9)/100 PYFU (71 discontinuations over 820 PYFU). The rate of discontinuation in the RAL/EVG-treated group (C and D) combined was 17.3 (95%CI: 16.0, 18.8)/100 PYFU (612 discontinuations over 3531 PYFU) (**SUMMARY TABLE 15**). There were too few events within the treatment groups of interest for independent analysis according to reason of discontinuation (i.e. HSR or hepatotoxicity).

NOTE: Discontinuations are presented from two sources in Tables 1A and 1B; (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 as well as those who discontinue due to other and unknown reasons 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.

Table 1A: Summary of cohort for first integrase inhibitor started after 16 January 2014, stratified by treatment group at baseline.

			Overall	A[1]	B[2]	C[3]	D[4]	E[5]
Persons		N (%)	4819 (100.0%)	1545 (32.1%)	1166 (24.2%)	239 (5.0%)	1416 (29.4%)	453 (9.4%)
Treatment naïve		N (%)	168 (3.5%)	57 (3.7%)	21 (1.8%)	12 (5.0%)	76 (5.4%)	2 (0.4%)
Integrase inhibitor naïve		N (%)	3851 (79.9%)	1331 (86.1%)	830 (71.2%)	226 (94.6%)	1200 (84.7%)	264 (58.3%)
Person years of follow-up[6]		Total	9040	2855	2333	434	2631	787
		Median (IQR)	1.8 (0.7,2.9)	1.8 (0.7,2.8)	1.9 (0.8,3.1)	1.5 (0.6,2.9)	1.6 (0.7,2.9)	1.5 (0.7,2.7)
Date of first ARV (mon-yy)		Median (IQR)	DEC00 (MAY96,JAN08)	JUN01 (OCT96,DEC07)	JUL99 (DEC95,OCT07)	AUG02 (APR97,JUL10)	FEB02 (DEC96,DEC08)	AUG96 (JAN94,OCT01)
Date of first INSTI (mon-yy)		Median (IQR)	AUG15 (MAY14,OCT16)	NOV15 (JAN15,OCT16)	MAY15 (APR13,SEP16)	AUG15 (JUL14,JAN17)	JUL15 (MAY14,NOV16)	APR15 (MAY11,SEP16)
Discontinuations[7]								
HSR CRF form[8]	Total	N (%)	1101 (22.8%)	291 (18.8%)	255 (21.9%)	78 (32.6%)	412 (29.1%)	65 (14.3%)
	HSR[9]	N (%)	4 (0.1%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
	Hepatotoxicity	N (%)	1 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

			Overall	A[1]	B[2]	C[3]	D[4]	E[5]
	Severe Skin Rash (Not HSR)	N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Other	N (%)	744 (15.4%)	191 (12.4%)	184 (15.8%)	51 (21.3%)	267 (18.9%)	51 (11.3%)
	Unknown	N (%)	352 (7.3%)	98 (6.3%)	70 (6.0%)	27 (11.3%)	143 (10.1%)	14 (3.1%)
EuroSIDA data capture[10]	Total	N (%)	1101 (22.8%)	291 (18.8%)	255 (21.9%)	78 (32.6%)	412 (29.1%)	65 (14.3%)
	Treatment failure	N (%)	42 (0.9%)	5 (0.3%)	8 (0.7%)	4 (1.7%)	24 (1.7%)	1 (0.2%)
	Abnormal fat redistribution	N (%)	3 (0.1%)	0 (0.0%)	2 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Concern of cardiovascular disease including dyslipidaemia	N (%)	3 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
	Dyslipidaemia	N (%)	5 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	4 (0.3%)	0 (0.0%)
	Cardiovascular disease	N (%)	3 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
	Hypersensitivity reaction	N (%)	12 (0.2%)	4 (0.3%)	3 (0.3%)	0 (0.0%)	3 (0.2%)	2 (0.4%)
	Toxicity-predominantly from abdomen/G-I tract	N (%)	57 (1.2%)	26 (1.7%)	10 (0.9%)	0 (0.0%)	16 (1.1%)	5 (1.1%)
	Toxicity, predominantly from nervous system	N (%)	105 (2.2%)	43 (2.8%)	32 (2.7%)	3 (1.3%)	19 (1.3%)	8 (1.8%)
	Toxicity, predominantly from kidneys	N (%)	35 (0.7%)	11 (0.7%)	11 (0.9%)	1 (0.4%)	12 (0.8%)	0 (0.0%)

			Overall	A[1]	B[2]	C[3]	D[4]	E[5]
	Toxicity, predominantly from the endocrine system	N (%)	5 (0.1%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	3 (0.2%)	0 (0.0%)
	Haematological toxicity	N (%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
	Toxicity, not mentioned above	N (%)	70 (1.5%)	21 (1.4%)	14 (1.2%)	2 (0.8%)	29 (2.0%)	4 (0.9%)
	Pregnancy-related regimen change	N (%)	2 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
	Patient's wish/decision, not specified above	N (%)	160 (3.3%)	42 (2.7%)	44 (3.8%)	7 (2.9%)	60 (4.2%)	7 (1.5%)
	Physician's decision, not specified above	N (%)	244 (5.1%)	58 (3.8%)	56 (4.8%)	20 (8.4%)	95 (6.7%)	15 (3.3%)
	Availability of more effective treatment (not failure or side effects)	N (%)	12 (0.2%)	1 (0.1%)	8 (0.7%)	0 (0.0%)	3 (0.2%)	0 (0.0%)
	Simplified treatment available	N (%)	115 (2.4%)	23 (1.5%)	24 (2.1%)	19 (7.9%)	34 (2.4%)	15 (3.3%)
	Protocol change	N (%)	31 (0.6%)	2 (0.1%)	11 (0.9%)	2 (0.8%)	16 (1.1%)	0 (0.0%)
	Study-related regimen change	N (%)	10 (0.2%)	1 (0.1%)	0 (0.0%)	3 (1.3%)	6 (0.4%)	0 (0.0%)

			Overall	A[1]	B[2]	C[3]	D[4]	E[5]
	Drug not available	N (%)	9 (0.2%)	3 (0.2%)	0 (0.0%)	2 (0.8%)	3 (0.2%)	1 (0.2%)
	STI - Structured Treatment Interruption	N (%)	6 (0.1%)	0 (0.0%)	2 (0.2%)	1 (0.4%)	3 (0.2%)	0 (0.0%)
	Other causes, not specified above	N (%)	103 (2.1%)	21 (1.4%)	19 (1.6%)	9 (3.8%)	50 (3.5%)	4 (0.9%)
	Unknown	N (%)	68 (1.4%)	25 (1.6%)	10 (0.9%)	5 (2.1%)	26 (1.8%)	2 (0.4%)

[1] DTG with ABC
[2] DTG without ABC
[3] EVG/RAL with ABC
[4] EVG/RAL without ABC
[5] DTG mono- and 2-drug therapy
[6] Note: This refers to the time spent on the first integrase inhibitor episode after 16 January 2014. Precise calculation, based on start and end dates of the INSTI episode

[7] 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.

[8] Reasons for discontinuation as reported on HSR CRF

[9] HSR includes: Hypersensitivity reaction including rash, Hypersensitivity reaction – Allergic reaction, Drug allergy related to DTG or another integrase inhibitor, Hypersensitivity reaction - Anaphylactic reaction.

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

Table 1B: Summary of cohort for <u>all</u> integrase inhibitor episodes started after 16 January 2014, stratified by treatment group at baseline.

			Overall	A[1]	B[2]	C[3]	D[4]	E[5]
Number of INSTI episodes		N (%)	5608 (100.0%)	1738 (31.0%)	1336 (23.8%)	286 (5.1%)	1756 (31.3%)	492 (8.8%)
Person years of follow-up[6]		Total	9990	3100	2537	484	3037	832
		Median (IQR)	1.6 (0.7,2.8)	1.7 (0.7,2.8)	1.8 (0.7,3.0)	1.3 (0.5,2.7)	1.5 (0.7,2.6)	1.5 (0.6,2.6)
Discontinuations[7]								
HSR CRF form[8]	Total	N (%)	1336 (23.8%)	349 (20.1%)	300 (22.5%)	98 (34.3%)	514 (29.3%)	75 (15.2%)
	HSR[9]	N (%)	5 (0.1%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	3 (0.2%)	0 (0.0%)
	Hepatotoxicity	N (%)	1 (0.0%)	1 (0.1%)	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%)	0 (0.0%)
	Other	N (%)	918 (16.4%)	232 (13.3%)	222 (16.6%)	64 (22.4%)	341 (19.4%)	59 (12.0%)
	Unknown	N (%)	412 (7.3%)	115 (6.6%)	77 (5.8%)	34 (11.9%)	170 (9.7%)	16 (3.3%)
EuroSIDA data capture[10]	Total	N (%)	1336 (23.8%)	349 (20.1%)	300 (22.5%)	98 (34.3%)	514 (29.3%)	75 (15.2%)
	Treatment failure	N (%)	46 (0.8%)	7 (0.4%)	8 (0.6%)	4 (1.4%)	26 (1.5%)	1 (0.2%)
	Abnormal fat redistribution	N (%)	3 (0.1%)	0 (0.0%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Concern of cardiovascular disease including dyslipidaemia	N (%)	5 (0.1%)	3 (0.2%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
	Dyslipidaemia	N (%)	5 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	4 (0.2%)	0 (0.0%)

			Overall	A[1]	B[2]	C[3]	D[4]	E[5]
	Cardiovascular disease	N (%)	4 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
	Hypersensitivity reaction	N (%)	18 (0.3%)	5 (0.3%)	3 (0.2%)	0 (0.0%)	7 (0.4%)	3 (0.6%)
	Toxicity-predominantly from abdomen/G-I tract	N (%)	73 (1.3%)	34 (2.0%)	12 (0.9%)	3 (1.0%)	19 (1.1%)	5 (1.0%)
	Toxicity, predominantly from nervous system	N (%)	136 (2.4%)	50 (2.9%)	43 (3.2%)	6 (2.1%)	27 (1.5%)	10 (2.0%)
	Toxicity, predominantly from kidneys	N (%)	39 (0.7%)	12 (0.7%)	12 (0.9%)	2 (0.7%)	13 (0.7%)	0 (0.0%)
	Toxicity, predominantly from the endocrine system	N (%)	5 (0.1%)	1 (0.1%)	1 (0.1%)	0 (0.0%)	3 (0.2%)	0 (0.0%)
	Haematological toxicity	N (%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
	Toxicity, not mentioned above	N (%)	77 (1.4%)	24 (1.4%)	14 (1.0%)	2 (0.7%)	32 (1.8%)	5 (1.0%)
	Pregnancy-related regimen change	N (%)	3 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.2%)	0 (0.0%)
	Comorbidity	N (%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Patient's wish/decision, not specified above	N (%)	221 (3.9%)	57 (3.3%)	60 (4.5%)	11 (3.8%)	82 (4.7%)	11 (2.2%)
	Physician's decision, not specified above	N (%)	278 (5.0%)	64 (3.7%)	63 (4.7%)	21 (7.3%)	115 (6.5%)	15 (3.0%)

			Overall	A[1]	B[2]	C[3]	D[4]	E[5]
	Availability of more effective treatment (not failure or side effects)	N (%)	15 (0.3%)	2 (0.1%)	8 (0.6%)	0 (0.0%)	5 (0.3%)	0 (0.0%)
	Simplified treatment available	N (%)	133 (2.4%)	27 (1.6%)	27 (2.0%)	22 (7.7%)	42 (2.4%)	15 (3.0%)
	Protocol change	N (%)	37 (0.7%)	3 (0.2%)	11 (0.8%)	2 (0.7%)	21 (1.2%)	0 (0.0%)
	Study-related regimen change	N (%)	10 (0.2%)	1 (0.1%)	0 (0.0%)	3 (1.0%)	6 (0.3%)	0 (0.0%)
	Drug not available	N (%)	15 (0.3%)	3 (0.2%)	2 (0.1%)	4 (1.4%)	5 (0.3%)	1 (0.2%)
	STI - Structured Treatment Interruption	N (%)	7 (0.1%)	0 (0.0%)	2 (0.1%)	1 (0.3%)	4 (0.2%)	0 (0.0%)
	Other causes, not specified above	N (%)	120 (2.1%)	23 (1.3%)	19 (1.4%)	10 (3.5%)	64 (3.6%)	4 (0.8%)
	Unknown	N (%)	84 (1.5%)	30 (1.7%)	13 (1.0%)	7 (2.4%)	31 (1.8%)	3 (0.6%)

*Note that switching between DTG regimens A, B and E, or between EVG/RAL regimens C and D, was allowed within an episode

[1] DTG with ABC
[2] DTG without ABC
[3] EVG/RAL with ABC
[4] EVG/RAL without ABC
[5] DTG mono- and 2-drug therapy
[6] Note: This refers to the time spent on the all integrase inhibitor episodes after 16 January 2014, classified according to the first treatment group in each episode. Precise calculation, based on start and end dates of the INSTI episode

[7] 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.

[8] Reasons for discontinuation as reported on HSR CRF

[9] HSR includes: Hypersensitivity reaction including rash, Hypersensitivity reaction – Allergic reaction, Drug allergy related to DTG or another integrase inhibitor, Hypersensitivity reaction - Anaphylactic reaction.

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

10.2 Descriptive data including baseline characteristics

Altogether 4819 individuals started an INSTI-containing regimen between 16 January 2014 and 23 January 2019. Characteristics of these 4819 individuals are summarised in **Table 2** to **Table 7**:

Individuals who started an integrase inhibitor had a median age of 51.2 years (IQR: 44.4 – 56.7) at the date of initiation, 73.8% were male, 82.2% were white, 37.7% were infected with HIV through sex between men, 27.7% through injection drug use (IDU) and 26.4% through heterosexual transmission (**Table 2**). The majority were from West Central Europe (33.6%) or South and Argentina (26.3%), followed by North (22.2%), East Central (14.2%) and East Europe (3.7%).

At baseline (the date of starting DTG or other INSTI), approximately 45% of individuals had a CD4 count of 500 cells/mm^3 or more and only 4.4% had a CD4 count of <200 cells/mm^3. Nine percent of individuals had an HIV viral load of ≥400 copies/mL at baseline (**Table 3**). Just over one quarter had experienced an AIDS-defining event (27.2%, includes AIDS-defining conditions listed in the 1993 CDC clinical definition(4)), 14.4% had a prior non-AIDS defining event (non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, NADM(5)). 42.6% and 4.9% had a diagnosis of HCV or HBV respectively prior to starting an integrase inhibitor. The majority of people were antiretroviral (ART) experienced (96.5%), and 20.1% had prior experience of the integrase inhibitor class (**Table 4**).

There was a higher proportion of people that were INSTI experienced starting DTG (A: 13.9%, B: 28.8% and E: 41.7%) compared to RAL/EVG (C: 5.4% D: 15.3%). At baseline, individuals had been exposed to a median of 8.0 (5.0, 11.0) antiretroviral agents, and had been on ART for a median of 15.4 (8.3, 19.8) years (**Table 4**). There were 1529/4819 (31.7%) individuals with a prior resistance test of whom 944 (61.7%) had any resistance, 819 (53.6%) had NRTI resistance, 609 (39.8%) had NNRTI resistance and 473 (30.9%) had major PI resistance (**Table 5**). According the ANRS GSS, the median proportion of drugs within the regimen that were active was 1.0 (IQR: 0.7 - 1.0).

The most recent non-AIDS defining and AIDS-defining events that occurred prior to baseline are summarised in **Table 6** and **Table 7**, respectively.

Table 2: Baseline[1] demographic characteristics of new users[2] of DTG with ABC (A), DTG without ABC (B), RAL or EVG with ABC (C), RAL or EVG without ABC (D) or DTG in a mono- or 2-drug regimen (E).

	Overall	A[3]	B[4]	C[5]	D[6]	E[7]
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
all						
	4,819 (100)	1,545 (100)	1,166 (100)	239 (100)	1,416 (100)	453 (100)
Age (years)						
≤ 35 years	267 (5.5)	88 (5.7)	55 (4.7)	24 (10.0)	96 (6.8)	4 (0.9)
36 - 40 years	413 (8.6)	135 (8.7)	88 (7.5)	38 (15.9)	138 (9.7)	14 (3.1)
41 - 50 years	1,451 (30.1)	461 (29.8)	340 (29.2)	73 (30.5)	461 (32.6)	116 (25.6)
51 + years	2,688 (55.8)	861 (55.7)	683 (58.6)	104 (43.5)	721 (50.9)	319 (70.4)
Gender						
Male	3,555 (73.8)	1,123 (72.7)	875 (75.0)	160 (66.9)	1,057 (74.6)	340 (75.1)
Female	1,264 (26.2)	422 (27.3)	291 (25.0)	79 (33.1)	359 (25.4)	113 (24.9)
Race						
White	3,959 (82.2)	1,285 (83.2)	947 (81.2)	211 (88.3)	1,144 (80.8)	372 (82.1)
Other/Unknown	860 (17.8)	260 (16.8)	219 (18.8)	28 (11.7)	272 (19.2)	81 (17.9)
HIV exposure group						
MSM	1,818 (37.7)	611 (39.5)	456 (39.1)	49 (20.5)	524 (37.0)	178 (39.3)

	Overall	A[3]	B[4]	C[5]	D[6]	E[7]
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
IDU	1,337 (27.7)	404 (26.1)	290 (24.9)	105 (43.9)	422 (29.8)	116 (25.6)
Heterosexual	1,274 (26.4)	395 (25.6)	321 (27.5)	67 (28.0)	367 (25.9)	124 (27.4)
Other/Unknown	390 (8.1)	135 (8.7)	99 (8.5)	18 (7.5)	103 (7.3)	35 (7.7)
Region of Europe[8]						
South and Argentina	1,267 (26.3)	410 (26.5)	188 (16.1)	84 (35.1)	447 (31.6)	138 (30.5)
North	1,070 (22.2)	383 (24.8)	329 (28.2)	19 (7.9)	282 (19.9)	57 (12.6)
West Central	1,620 (33.6)	514 (33.3)	480 (41.2)	30 (12.6)	392 (27.7)	204 (45.0)
East Central	686 (14.2)	186 (12.0)	133 (11.4)	62 (25.9)	254 (17.9)	51 (11.3)
East	176 (3.7)	52 (3.4)	36 (3.1)	44 (18.4)	41 (2.9)	3 (0.7)
Body mass index (BMI)						
<18	77 (1.6)	21 (1.4)	14 (1.2)	4 (1.7)	24 (1.7)	14 (3.1)
18 - 25	1,240 (25.7)	420 (27.2)	246 (21.1)	79 (33.1)	381 (26.9)	114 (25.2)
>25	860 (17.8)	281 (18.2)	209 (17.9)	49 (20.5)	257 (18.1)	64 (14.1)
Unknown	2,642 (54.8)	823 (53.3)	697 (59.8)	107 (44.8)	754 (53.2)	261 (57.6)
Smoking status						
Current	1,821 (37.8)	579 (37.5)	457 (39.2)	96 (40.2)	533 (37.6)	156 (34.4)
Former	773 (16.0)	234 (15.1)	186 (16.0)	32 (13.4)	221 (15.6)	100 (22.1)
Never	1,697 (35.2)	600 (38.8)	403 (34.6)	79 (33.1)	445 (31.4)	170 (37.5)

	Overall	A[3]	B[4]	C[5]	D[6]	E[7]
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Unknown	528 (11.0)	132 (8.5)	120 (10.3)	32 (13.4)	217 (15.3)	27 (6.0)
Age (years)						
Median (IQR)	51.2 (44.4,56.7)	51.2 (44.5,56.5)	51.6 (44.7,57.3)	48.7 (39.6,54.9)	50.2 (43.3,55.6)	53.7 (48.7,59.8)
Date of baseline[1]						
Median date (IQR)	16DEC2015 (26FEB2015,07FEB2017)	17DEC2015 (26MAY2015,15DEC2016)	10NOV2015 (26JAN2015,10FEB2017)	28AUG2015 (10SEP2014,10JAN2017)	05JAN2016 (02DEC2014,14FEB2017)	14APR2016 (14JUL2015,08JUN2017)

[1] Baseline in all groups is 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] EVG/RAL with ABC

[6] EVG/RAL without ABC

[7] DTG mono- and 2-drug therapy

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

Abbreviations:

BMI, body mass index; IDU, injecting drug use; IQR, inter-quartile range; MSM, men who have sex with men.

Table 3: Baseline[1] clinical characteristics of new users[2] of DTG with ABC (A), DTG without ABC (B), RAL or EVG with ABC (C), RAL or EVG without ABC (D) or DTG in a mono- or 2-drug regimen (E).

	Overall	A[3]	B[4]	C[5]	D[6]	E[7]
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
all						
	4,819 (100)	1,545 (100)	1,166 (100)	239 (100)	1,416 (100)	453 (100)
Prior AIDS[8]						
Yes	1,312 (27.2)	391 (25.3)	366 (31.4)	67 (28.0)	342 (24.2)	146 (32.2)
No	3,507 (72.8)	1,154 (74.7)	800 (68.6)	172 (72.0)	1,074 (75.8)	307 (67.8)
Prior non-AIDS[9]						
Yes	696 (14.4)	197 (12.8)	208 (17.8)	33 (13.8)	169 (11.9)	89 (19.6)
No	4,123 (85.6)	1,348 (87.2)	958 (82.2)	206 (86.2)	1,247 (88.1)	364 (80.4)
Diabetes[10]						
Yes	410 (8.5)	115 (7.4)	129 (11.1)	26 (10.9)	91 (6.4)	49 (10.8)
No	4,409 (91.5)	1,430 (92.6)	1,037 (88.9)	213 (89.1)	1,325 (93.6)	404 (89.2)
Hypertension[11]						
Yes	3,040 (63.1)	989 (64.0)	807 (69.2)	115 (48.1)	812 (57.3)	317 (70.0)
No	1,363 (28.3)	460 (29.8)	280 (24.0)	86 (36.0)	426 (30.1)	111 (24.5)
Unknown	416 (8.6)	96 (6.2)	79 (6.8)	38 (15.9)	178 (12.6)	25 (5.5)

	Overall	A[3]	B[4]	C[5]	D[6]	E[7]
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Anaemia[12]						
Severe anaemia/ mild anaemia	511 (10.6)	153 (9.9)	148 (12.7)	32 (13.4)	120 (8.5)	58 (12.8)
Normal	1,964 (40.8)	668 (43.2)	467 (40.1)	92 (38.5)	540 (38.1)	197 (43.5)
Unknown	2,344 (48.6)	724 (46.9)	551 (47.3)	115 (48.1)	756 (53.4)	198 (43.7)
Prior HCV diagnosis[13]						
Yes	2,051 (42.6)	633 (41.0)	487 (41.8)	128 (53.6)	635 (44.8)	168 (37.1)
No	2,335 (48.5)	790 (51.1)	573 (49.1)	82 (34.3)	634 (44.8)	256 (56.5)
Unknown	433 (9.0)	122 (7.9)	106 (9.1)	29 (12.1)	147 (10.4)	29 (6.4)
Prior HBV diagnosis[14]						
Yes	237 (4.9)	48 (3.1)	69 (5.9)	4 (1.7)	101 (7.1)	15 (3.3)
No	4,264 (88.5)	1,398 (90.5)	1,028 (88.2)	215 (90.0)	1,199 (84.7)	424 (93.6)
Unknown	318 (6.6)	99 (6.4)	69 (5.9)	20 (8.4)	116 (8.2)	14 (3.1)
HIV viral load (copies/mL)[15]						
< 400	3,616 (75.0)	1,208 (78.2)	890 (76.3)	158 (66.1)	992 (70.1)	368 (81.2)
≥ 400	433 (9.0)	119 (7.7)	111 (9.5)	29 (12.1)	146 (10.3)	28 (6.2)
Unknown	770 (16.0)	218 (14.1)	165 (14.2)	52 (21.8)	278 (19.6)	57 (12.6)
Peak HIV viral load (copies/mL)[16]						
< 400	580 (12.0)	184 (11.9)	112 (9.6)	32 (13.4)	200 (14.1)	52 (11.5)

	Overall	A[3]	B[4]	C[5]	D[6]	E[7]
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
≥ 400	4,171 (86.6)	1,351 (87.4)	1,040 (89.2)	198 (82.8)	1,186 (83.8)	396 (87.4)
Unknown	68 (1.4)	10 (0.6)	14 (1.2)	9 (3.8)	30 (2.1)	5 (1.1)
CD4 count (cells/mm³)[15]						
< 200	212 (4.4)	57 (3.7)	54 (4.6)	12 (5.0)	66 (4.7)	23 (5.1)
200 - 349	411 (8.5)	120 (7.8)	105 (9.0)	29 (12.1)	123 (8.7)	34 (7.5)
350 - 499	623 (12.9)	198 (12.8)	149 (12.8)	38 (15.9)	173 (12.2)	65 (14.3)
≥ 500	2,172 (45.1)	730 (47.2)	464 (39.8)	99 (41.4)	649 (45.8)	230 (50.8)
Unknown	1,401 (29.1)	440 (28.5)	394 (33.8)	61 (25.5)	405 (28.6)	101 (22.3)
CD4 count nadir(cells/mm³) [17]						
< 200	2,812 (58.4)	886 (57.3)	707 (60.6)	135 (56.5)	772 (54.5)	312 (68.9)
200 - 349	1,372 (28.5)	445 (28.8)	314 (26.9)	72 (30.1)	433 (30.6)	108 (23.8)
350 - 499	394 (8.2)	145 (9.4)	85 (7.3)	18 (7.5)	123 (8.7)	23 (5.1)
≥ 500	195 (4.0)	58 (3.8)	39 (3.3)	10 (4.2)	79 (5.6)	9 (2.0)
Unknown	46 (1.0)	11 (0.7)	21 (1.8)	4 (1.7)	9 (0.6)	1 (0.2)
eGFR (ml/min/1.73m²) [18]						
< 60	345 (7.2)	132 (8.5)	77 (6.6)	24 (10.0)	65 (4.6)	47 (10.4)
≥ 60	4,295 (89.1)	1,376 (89.1)	1,054 (90.4)	197 (82.4)	1,267 (89.5)	401 (88.5)
Unknown	179 (3.7)	37 (2.4)	35 (3.0)	18 (7.5)	84 (5.9)	5 (1.1)

	Overall	A[3]	B[4]	C[5]	D[6]	E[7]
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
ALT (U/L)						
< 40	2,407 (49.9)	785 (50.8)	601 (51.5)	87 (36.4)	665 (47.0)	269 (59.4)
≥ 40	1,097 (22.8)	340 (22.0)	283 (24.3)	75 (31.4)	306 (21.6)	93 (20.5)
Unknown	1,315 (27.3)	420 (27.2)	282 (24.2)	77 (32.2)	445 (31.4)	91 (20.1)
AST (U/L)						
< 40	2,246 (46.6)	749 (48.5)	513 (44.0)	93 (38.9)	624 (44.1)	267 (58.9)
≥ 40	756 (15.7)	214 (13.9)	203 (17.4)	62 (25.9)	215 (15.2)	62 (13.7)
Unknown	1,817 (37.7)	582 (37.7)	450 (38.6)	84 (35.1)	577 (40.7)	124 (27.4)
Proportion of follow-up time in EuroSIDA with immunosuppression (defined as a CD4 count <200/cells mm3)[19]						
< 20%	3,826 (79.4)	1,266 (81.9)	899 (77.1)	182 (76.2)	1,119 (79.0)	360 (79.5)
≥ 20%	947 (19.7)	268 (17.3)	246 (21.1)	53 (22.2)	288 (20.3)	92 (20.3)
Unknown	46 (1.0)	11 (0.7)	21 (1.8)	4 (1.7)	9 (0.6)	1 (0.2)
Proportion of follow-up time in EuroSIDA with uncontrolled viremia (HIV RNA VL > 400 copies/ml)[20]						
< 20%	2,908 (60.3)	1,024 (66.3)	656 (56.3)	127 (53.1)	826 (58.3)	275 (60.7)
≥ 20%	1,843 (38.2)	511 (33.1)	496 (42.5)	103 (43.1)	560 (39.5)	173 (38.2)
Unknown	68 (1.4)	10 (0.6)	14 (1.2)	9 (3.8)	30 (2.1)	5 (1.1)

[1] Baseline in all groups is 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] EVG/RAL with ABC
[6] EVG/RAL without ABC
[7] DTG mono- and 2-drug therapy
[8] Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition(4)
[9] Non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, NADM(5)
[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: Haemoglobin <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 viremia 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 EVG with ABC (C), RAL or EVG without ABC (D) or DTG in a mono- or 2-drug regimen (E).

	Overall	A[3]	B[4]	C[5]	D[6]	E[7]
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
all						
	4,819 (100)	1,545 (100)	1,166 (100)	239 (100)	1,416 (100)	453 (100)
Treatment naïve at baseline						
Yes	168 (3.5)	57 (3.7)	21 (1.8)	12 (5.0)	76 (5.4)	2 (0.4)
Integrase inhibitor naïve at baseline						
Yes	3,851 (79.9)	1,331 (86.1)	830 (71.2)	226 (94.6)	1,200 (84.7)	264 (58.3)
Current regimen includes PI						
Yes	2,323 (48.2)	632 (40.9)	716 (61.4)	133 (55.6)	613 (43.3)	229 (50.6)
Current regimen includes NNRTI						
Yes	1,514 (31.4)	380 (24.6)	398 (34.1)	71 (29.7)	511 (36.1)	154 (34.0)
Current regimen includes NRTI						
Yes	4,538 (94.2)	1,545 (100)	1,135 (97.3)	239 (100)	1,400 (98.9)	219 (48.3)
Prior exposure to PI						
Yes	3,836 (79.6)	1,189 (77.0)	1,005 (86.2)	196 (82.0)	1,028 (72.6)	418 (92.3)
Prior exposure to NNRTI						

	Overall	A[3]	B[4]	C[5]	D[6]	E[7]
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Yes	3,168 (65.7)	970 (62.8)	765 (65.6)	142 (59.4)	951 (67.2)	340 (75.1)
Prior exposure to NRTI						
Yes	4,626 (96.0)	1,481 (95.9)	1,140 (97.8)	225 (94.1)	1,334 (94.2)	446 (98.5)
Prior exposure to DTG						
Yes	7 (0.1)	1 (0.1)	4 (0.3)	0 (0.0)	2 (0.1)	0 (0.0)
Prior exposure to EVG						
Yes	25 (0.5)	9 (0.6)	7 (0.6)	1 (0.4)	7 (0.5)	1 (0.2)
Prior exposure to RAL						
Yes	946 (19.6)	207 (13.4)	328 (28.1)	12 (5.0)	211 (14.9)	188 (41.5)
Number of ARVs previously exposed to						
Median number (IQR)	8.0 (5.0,11.0)	7.0 (5.0,10.0)	9.0 (6.0,12.0)	7.0 (5.0,9.0)	7.0 (4.0,10.0)	10.0 (7.0,13.0)
Years since first use of any ARV (years)[8]						
Median years (IQR)	15.4 (8.3,19.8)	14.5 (8.4,19.3)	16.3 (8.4,19.9)	13.9 (6.1,18.5)	13.8 (7.4,19.1)	19.7 (14.7,22.1)

[1] Baseline in all groups was 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] EVG/RAL with ABC
[6] EVG/RAL without ABC

[7] DTG mono- and 2-drug therapy
[8] Cumulative years since starting at least one ARV prior to date

NOTE: INSTI resistance was not reported from the interim report #3 (December 2017) onwards as EuroSIDA does not collect sequencing data for the integrase region of HIV.

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 EVG with ABC (C), RAL or EVG without ABC (D) or DTG in a mono- or 2-drug regimen (E).

	Overall	A[3]	B[4]	C[5]	D[6]	E[7]
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
all						
	1,529 (100)	436 (100)	451 (100)	36 (100)	411 (100)	195 (100)
Any resistance						
Yes	944 (61.7)	228 (52.3)	306 (67.8)	24 (66.7)	235 (57.2)	151 (77.4)
No	585 (38.3)	208 (47.7)	145 (32.2)	12 (33.3)	176 (42.8)	44 (22.6)
Major PI						
Yes	473 (30.9)	101 (23.2)	174 (38.6)	10 (27.8)	103 (25.1)	85 (43.6)
No	1,056 (69.1)	335 (76.8)	277 (61.4)	26 (72.2)	308 (74.9)	110 (56.4)
NNRTI						
Yes	609 (39.8)	146 (33.5)	204 (45.2)	17 (47.2)	151 (36.7)	91 (46.7)
No	920 (60.2)	290 (66.5)	247 (54.8)	19 (52.8)	260 (63.3)	104 (53.3)
NRTI						
Yes	819 (53.6)	184 (42.2)	275 (61.0)	20 (55.6)	197 (47.9)	143 (73.3)
No	710 (46.4)	252 (57.8)	176 (39.0)	16 (44.4)	214 (52.1)	52 (26.7)

	Overall	A[3]	B[4]	C[5]	D[6]	E[7]
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Genotypic sensitivity score (GSS)[8]						
<3	698 (45.7)	156 (35.8)	185 (41.0)	16 (44.4)	146 (35.5)	195 (100)
3 or more	831 (54.3)	280 (64.2)	266 (59.0)	20 (55.6)	265 (64.5)	0 (0.0)
Median score [IQR]	3.0 (2.0,3.0)	3.0 (2.0,3.0)	3.0 (2.0,3.0)	3.0 (1.0,3.0)	3.0 (2.0,3.0)	2.0 (1.5,2.0)
Proportion of regimen active[10]						
All drugs active	942 (61.6)	275 (63.1)	238 (52.8)	19 (52.8)	248 (60.3)	162 (83.1)
Not all drugs active	587 (38.4)	161 (36.9)	213 (47.2)	17 (47.2)	163 (39.7)	33 (16.9)
Median proportion (IQR)	1.0 (0.7,1.0)	1.0 (0.5,1.0)	1.0 (0.7,1.0)	1.0 (0.4,1.0)	1.0 (0.7,1.0)	1.0 (1.0,1.0)

[1] Baseline in all groups was 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] EVG/RAL with ABC
[6] EVG/RAL without ABC
[7] DTG mono- and 2-drug therapy
[8] Genotypic sensitivity score calculated using: ANRS algorithm. For drugs in the regimen, a score of 1=fully active, 0.5=some resistance, 0=no longer active. Since no INSTI resistance data are available, DTG, RAL and EVG are scored as 1.
[9] The GSS score was calculated for the mono- or 2 drug regimens.

[10]Proportion of active drugs in regimen calculated as ANRS score/number of ARVs in current regimen

Table 6: Most recent non-AIDS defining events[1] that occurred prior to baseline[2], with median proximity to baseline [IQR] in years

Prior non-AIDS events	N	%	Median (IQR)
Overall	696	100.0	5.2 (1.5,10.0)
cardiovascular	290	41.7	4.6 (1.5, 9.1)
Renal disease	8	1.1	4.0 (0.5,12.3)
liver failure	87	12.5	5.5 (1.1,13.9)
pancreatitis	46	6.6	6.7 (4.5,13.1)
NADM	265	38.1	5.2 (1.3, 9.9)

[1]Non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, and non-aids defining malignancies (NADM) (5)
[2]Baseline in all groups is defined as the date of starting the DTG (or other integrase inhibitor)

Table 7: Most recent AIDS defining events[1] that occurred prior to baseline[2], with median proximity to baseline [IQR] in years

Prior AIDS events	N	%	Median (IQR)
Overall	1312	100.0	14.6 (8.4,19.1)
Bacterial pneumonia, recurrent (>2 episodes within 1 year)	47	3.6	16.0 (6.7,20.2)
Candidiasis, oesophageal, bronchi, trachea, or lungs	259	19.7	13.4 (8.0,18.4)
CMV – other location	25	1.9	11.6 (9.3,14.5)
Cytomegalovirus (CMV) chorioretinitis	34	2.6	18.2 (13.0,20.1)
Cryptococcosis, extrapulmonary	30	2.3	16.9 (10.4,19.5)
Cryptosporidiosis (duration > 1 month)	23	1.8	19.8 (17.2,22.5)
AIDS dementia complex	36	2.7	9.9 (4.2,17.3)
Focal Brain lesion	3	0.2	16.1 (4.0,19.0)

Prior AIDS events	N	%	Median (IQR)
Herpes simplex virus ulcers (duration > 1 month) or pneumonitis/esophagitis	42	3.2	12.3 (9.4,17.1)
Histoplasmosis, extrapulmonary	1	0.1	7.4 (7.4,7.4)
Isosporiasis diarrhoea (duration > 1 month)	4	0.3	11.1 (6.4,12.5)
Kaposi Sarcoma	137	10.4	16.4 (8.4,19.6)
Progressive multifocal leucoencephalopathy	23	1.8	15.5 (12.1,18.5)
Mycobacterium avium complex (MAC) or Kanasii, extrapulmonary	34	2.6	17.8 (12.2,19.9)
Mycobacterium tuberculosis pulmonary	138	10.5	14.2 (7.3,19.2)
Mycobacterium pulmonary, other	5	0.4	4.4 (3.9,11.0)
Mycobacterium tuberculosis extrapulmonary	63	4.8	14.7 (8.4,20.0)
Mycobacterium extrapulmonary, other	16	1.2	12.0 (6.1,15.7)
Non-Hodgkin Lymphoma	67	5.1	10.8 (4.9,16.1)
Pneumocystis carinii pneumonia (PCP)	209	15.9	15.9 (9.6,19.2)
Salmonella bacteriaemia (non-typhoid) (recurrent)	5	0.4	19.9 (18.7,23.1)
Toxoplasmosis, brain	58	4.4	13.3 (9.0,18.5)
HIV Wasting Syndrome	53	4.0	15.1 (9.8,18.6)

[1] Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition(4)
[2] Baseline in all groups is defined as the date of starting the DTG (or other integrase inhibitor)

10.3 Characteristics of individuals at the time of INSTI discontinuation

Characteristics of participants at the time of discontinuation of the INSTI regimen are summarised in **Table 8** – **Table 10** and stratified by discontinuation reason according to the HSR form. **Table 8** shows the demographic characteristics at time of INSTI discontinuation, **Table 9** lists clinical characteristics and **Table 10** shows the ARV treatment history at time of the discontinuation. Data are shown for all discontinuations; therefore, the characteristics of individuals who discontinued more than one INSTI episode are included for each INSTI episode. Tables showing the breakdown of characteristics by the first INSTI episode only are presented in the Appendix (**APPENDIX Table 8** to **APPENDIX Table 10**).

There were 1336 discontinuations reported for 5608 episodes of INSTI use for the 4819 individuals (1101 discontinued their first INSTI episode) (**Table 8**). Most discontinuations were among individuals who started in treatment group D (38.5%), followed by Group A (26.1%) and B (22.5%); 7.3% of discontinuations were from individuals in treatment group C and 5.6% in Group E (**Table 8**). Of the discontinuations, 63% were in individuals >50 years old, 73% were in men and 79.8 in individuals of white ethnicity. 41.3% of discontinuations were in West Central Europe, 27.5% in North, 20.6% in South and 10.5% in Central East or East Europe.

Altogether there were 5 discontinuations for definite or probable HSR, one in treatment group A, one in group B and three in group D and there was one discontinuation due to hepatotoxicity in treatment group A. There were no discontinuations due to severe skin rash (not HSR). Altogether 918 discontinuations were for other reasons, and for 412 the discontinuation reason was unknown.

Of the discontinuations due to HSR, one was for an individual aged between 40 and 50 years and four were in individuals >50 years old, three were in men and two in women. Four discontinuations were among individuals of white ethnicity; two resided in South and Argentina, two in North Europe and one in West Central Europe, while the hepatotoxicity event occurred in East Europe (**Table 8**). For the discontinuations due to HSR, two individuals had prior AIDS and two prior non-AIDS clinical conditions, three had hypertension, three had a prior HCV diagnosis and one had an HBV diagnosis (**Table 9**).

Table 11 summarises the risk of discontinuation due to HSR or hepatotoxicity by dose of integrase inhibitor.

Table 8: Demographic characteristics at time of discontinuation[1] for individuals using DTG, RAL, and EVG[2].

			Discontinued					
	Overall	Did not discontinue	Total	HSR	Hepato-toxicity	Severe skin rash (Not HSR)	Other	Unknown
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
All								
	5,608 (100.0)	4,272 (100.0)	1,336 (100.0)	5 (100.0)	1 (100.0)	0 (0.0)	918 (100.0)	412 (100.0)
Integrase inhibitor Regimen[3]								
A[4]	1,738 (31.0)	1,389 (32.5)	349 (26.1)	1 (20.0)	1 (100.0)	0 (0.0)	232 (25.3)	115 (27.9)
B[5]	1,336 (23.8)	1,036 (24.3)	300 (22.5)	1 (20.0)	0 (0.0)	0 (0.0)	222 (24.2)	77 (18.7)
C[6]	286 (5.1)	188 (4.4)	98 (7.3)	0 (0.0)	0 (0.0)	0 (0.0)	64 (7.0)	34 (8.3)
D[7]	1,756 (31.3)	1,242 (29.1)	514 (38.5)	3 (60.0)	0 (0.0)	0 (0.0)	341 (37.1)	170 (41.3)
E[8]	492 (8.8)	417 (9.8)	75 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	59 (6.4)	16 (3.9)
Age (years)								
≤ 35 years	223 (4.0)	163 (3.8)	60 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	45 (4.9)	15 (3.6)
36 - 40 years	348 (6.2)	245 (5.7)	103 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	62 (6.8)	41 (10.0)
41 - 50 years	1,437 (25.6)	1,106 (25.9)	331 (24.8)	1 (20.0)	0 (0.0)	0 (0.0)	234 (25.5)	96 (23.3)
51 + years	3,600 (64.2)	2,758 (64.6)	842 (63.0)	4 (80.0)	1 (100.0)	0 (0.0)	577 (62.9)	260 (63.1)
Gender								
Male	4,124 (73.5)	3,149 (73.7)	975 (73.0)	3 (60.0)	0 (0.0)	0 (0.0)	671 (73.1)	301 (73.1)
Female	1,484 (26.5)	1,123 (26.3)	361 (27.0)	2 (40.0)	1 (100.0)	0 (0.0)	247 (26.9)	111 (26.9)
Race								
White	4,578 (81.6)	3,512 (82.2)	1,066 (79.8)	4 (80.0)	1 (100.0)	0 (0.0)	741 (80.7)	320 (77.7)
Other/Unknown	1,030 (18.4)	760 (17.8)	270 (20.2)	1 (20.0)	0 (0.0)	0 (0.0)	177 (19.3)	92 (22.3)

			Discontinued					
	Overall	Did not discontinue	Total	HSR	Hepato-toxicity	Severe skin rash (Not HSR)	Other	Unknown
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
HIV exposure group								
MSM	2,136 (38.1)	1,588 (37.2)	548 (41.0)	2 (40.0)	0 (0.0)	0 (0.0)	363 (39.5)	183 (44.4)
IDU	1,575 (28.1)	1,191 (27.9)	384 (28.7)	1 (20.0)	0 (0.0)	0 (0.0)	274 (29.8)	109 (26.5)
Heterosexual	1,447 (25.8)	1,142 (26.7)	305 (22.8)	1 (20.0)	1 (100.0)	0 (0.0)	210 (22.9)	93 (22.6)
Other/Missing	450 (8.0)	351 (8.2)	99 (7.4)	1 (20.0)	0 (0.0)	0 (0.0)	71 (7.7)	27 (6.6)
Region of Europe[9]								
South and Argentina	1,432 (25.5)	1,157 (27.1)	275 (20.6)	2 (40.0)	0 (0.0)	0 (0.0)	208 (22.7)	65 (15.8)
North	1,292 (23.0)	924 (21.6)	368 (27.5)	2 (40.0)	0 (0.0)	0 (0.0)	229 (24.9)	137 (33.3)
West Central	1,933 (34.5)	1,381 (32.3)	552 (41.3)	1 (20.0)	0 (0.0)	0 (0.0)	366 (39.9)	185 (44.9)
East Central	762 (13.6)	647 (15.1)	115 (8.6)	0 (0.0)	0 (0.0)	0 (0.0)	92 (10.0)	23 (5.6)
East	189 (3.4)	163 (3.8)	26 (1.9)	0 (0.0)	1 (100.0)	0 (0.0)	23 (2.5)	2 (0.5)
Body mass index (BMI)								
<18	85 (1.5)	63 (1.5)	22 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	14 (1.5)	8 (1.9)
18 - 25	1,368 (24.4)	1,059 (24.8)	309 (23.1)	1 (20.0)	0 (0.0)	0 (0.0)	203 (22.1)	105 (25.5)
>25	1,124 (20.0)	917 (21.5)	207 (15.5)	2 (40.0)	1 (100.0)	0 (0.0)	138 (15.0)	66 (16.0)
Unknown	3,031 (54.0)	2,233 (52.3)	798 (59.7)	2 (40.0)	0 (0.0)	0 (0.0)	563 (61.3)	233 (56.6)
Smoking status								
Current	2,319 (41.4)	1,783 (41.7)	536 (40.1)	2 (40.0)	0 (0.0)	0 (0.0)	374 (40.7)	160 (38.8)
Former	952 (17.0)	735 (17.2)	217 (16.2)	0 (0.0)	0 (0.0)	0 (0.0)	160 (17.4)	57 (13.8)
Never	2,136 (38.1)	1,651 (38.6)	485 (36.3)	2 (40.0)	1 (100.0)	0 (0.0)	333 (36.3)	149 (36.2)

			Discontinued					
	Overall	**Did not discontinue**	**Total**	**HSR**	**Hepato-toxicity**	**Severe skin rash (Not HSR)**	**Other**	**Unknown**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Unknown	201 (3.6)	103 (2.4)	98 (7.3)	1 (20.0)	0 (0.0)	0 (0.0)	51 (5.6)	46 (11.2)
Date of baseline[10]								
Median date (IQR)	FEB16 (APR15,MAR17)	APR16 (MAY15,JUN17)	SEP15 (DEC14,JUN16)	NOV15 (FEB15,NOV16)	DEC16 (DEC16,DEC16)		DEC15 (APR15,OCT16)	DEC14 (JUN14,JUL15)

[1] Date of discontinuation in those who stopped DTG, RAL or EVG, or last clinic visit in those who did not
[2] After the 16 Jan 2014
[3] Note that switching between DTG regimens A, B and E, or between EVG/RAL regimens C and D, was allowed within an episode. The integrase inhibitor treatment group here is reported as at the start of the episode.
[4] DTG with ABC
[5] DTG without ABC
[6] EVG/RAL with ABC
[7] EVG/RAL without ABC
[8] DTG mono- and 2-drug therapy

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

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

Table 9: Clinical characteristics at time of discontinuation[1] for individuals using DTG, RAL, and EVG[2].

			Discontinued					
	Overall	Did not discontinue	Total	HSR	Hepato-toxicity	Severe skin rash (Not HSR)	Other	Unknown
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
All								
	5,608 (100)	4,272 (100)	1,336 (100)	5 (100)	1 (100)	0 (0.0)	918 (100)	412 (100)
Prior AIDS[3]								
Yes	1,580 (28.2)	1,209 (28.3)	371 (27.8)	2 (40.0)	1 (100)	0 (0.0)	260 (28.3)	108 (26.2)
No	4,028 (71.8)	3,063 (71.7)	965 (72.2)	3 (60.0)	0 (0.0)	0 (0.0)	658 (71.7)	304 (73.8)
Prior non-AIDS[4]								
Yes	983 (17.5)	769 (18.0)	214 (16.0)	2 (40.0)	0 (0.0)	0 (0.0)	149 (16.2)	63 (15.3)
No	4,625 (82.5)	3,503 (82.0)	1,122 (84.0)	3 (60.0)	1 (100)	0 (0.0)	769 (83.8)	349 (84.7)
Diabetes[5]								
Yes	475 (8.5)	374 (8.8)	101 (7.6)	0 (0.0)	0 (0.0)	0 (0.0)	71 (7.7)	30 (7.3)
No	5,133 (91.5)	3,898 (91.2)	1,235 (92.4)	5 (100)	1 (100)	0 (0.0)	847 (92.3)	382 (92.7)
Hypertension[6]								
Yes	3,972 (70.8)	3,060 (71.6)	912 (68.3)	3 (60.0)	1 (100)	0 (0.0)	649 (70.7)	259 (62.9)
No	1,490 (26.6)	1,131 (26.5)	359 (26.9)	1 (20.0)	0 (0.0)	0 (0.0)	242 (26.4)	116 (28.2)
Unknown	146 (2.6)	81 (1.9)	65 (4.9)	1 (20.0)	0 (0.0)	0 (0.0)	27 (2.9)	37 (9.0)
Anaemia[7]								
Severe anaemia/ mild anaemia	612 (10.9)	454 (10.6)	158 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)	100 (10.9)	58 (14.1)
Normal	2,246 (40.0)	1,665 (39.0)	581 (43.5)	2 (40.0)	0 (0.0)	0 (0.0)	398 (43.4)	181 (43.9)

			Discontinued					
	Overall	Did not discontinue	Total	HSR	Hepato-toxicity	Severe skin rash (Not HSR)	Other	Unknown
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Unknown	2,750 (49.0)	2,153 (50.4)	597 (44.7)	3 (60.0)	1 (100)	0 (0.0)	420 (45.8)	173 (42.0)
Prior HCV diagnosis[8]								
Yes	2,468 (44.0)	1,863 (43.6)	605 (45.3)	3 (60.0)	0 (0.0)	0 (0.0)	429 (46.7)	173 (42.0)
No	2,679 (47.8)	2,088 (48.9)	591 (44.2)	2 (40.0)	1 (100)	0 (0.0)	409 (44.6)	179 (43.4)
Unknown	461 (8.2)	321 (7.5)	140 (10.5)	0 (0.0)	0 (0.0)	0 (0.0)	80 (8.7)	60 (14.6)
Prior HBV diagnosis[9]								
Yes	283 (5.0)	216 (5.1)	67 (5.0)	1 (20.0)	0 (0.0)	0 (0.0)	54 (5.9)	12 (2.9)
No	5,080 (90.6)	3,885 (90.9)	1,195 (89.4)	4 (80.0)	1 (100)	0 (0.0)	836 (91.1)	354 (85.9)
Unknown	245 (4.4)	171 (4.0)	74 (5.5)	0 (0.0)	0 (0.0)	0 (0.0)	28 (3.1)	46 (11.2)
HIV viral load (copies/mL)[10]								
< 400	4,680 (83.5)	3,647 (85.4)	1,033 (77.3)	3 (60.0)	1 (100)	0 (0.0)	686 (74.7)	343 (83.3)
≥ 400	163 (2.9)	81 (1.9)	82 (6.1)	0 (0.0)	0 (0.0)	0 (0.0)	59 (6.4)	23 (5.6)
Unknown	765 (13.6)	544 (12.7)	221 (16.5)	2 (40.0)	0 (0.0)	0 (0.0)	173 (18.8)	46 (11.2)
Peak HIV viral load (copies/mL)[11]								
< 400	726 (12.9)	538 (12.6)	188 (14.1)	0 (0.0)	0 (0.0)	0 (0.0)	132 (14.4)	56 (13.6)
≥ 400	4,875 (86.9)	3,734 (87.4)	1,141 (85.4)	5 (100)	1 (100)	0 (0.0)	783 (85.3)	352 (85.4)
Unknown	7 (0.1)	0 (0.0)	7 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)	4 (1.0)
CD4 count (cells/mm³)[10]								
<200	226 (4.0)	160 (3.7)	66 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)	52 (5.7)	14 (3.4)
200 - 349	415 (7.4)	315 (7.4)	100 (7.5)	1 (20.0)	0 (0.0)	0 (0.0)	76 (8.3)	23 (5.6)
350 – 499	732 (13.1)	579 (13.6)	153 (11.5)	0 (0.0)	0 (0.0)	0 (0.0)	107 (11.7)	46 (11.2)

			Discontinued					
	Overall	Did not discontinue	Total	HSR	Hepato-toxicity	Severe skin rash (Not HSR)	Other	Unknown
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
≥500	2,923 (52.1)	2,328 (54.5)	595 (44.5)	0 (0.0)	1 (100)	0 (0.0)	402 (43.8)	192 (46.6)
Unknown	1,312 (23.4)	890 (20.8)	422 (31.6)	4 (80.0)	0 (0.0)	0 (0.0)	281 (30.6)	137 (33.3)
CD4 count nadir(cells/mm³) [12]								
<200	3,320 (59.2)	2,528 (59.2)	792 (59.3)	3 (60.0)	1 (100)	0 (0.0)	556 (60.6)	232 (56.3)
200 - 349	1,577 (28.1)	1,217 (28.5)	360 (26.9)	2 (40.0)	0 (0.0)	0 (0.0)	244 (26.6)	114 (27.7)
350 - 499	451 (8.0)	340 (8.0)	111 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	78 (8.5)	33 (8.0)
≥500	232 (4.1)	171 (4.0)	61 (4.6)	0 (0.0)	0 (0.0)	0 (0.0)	35 (3.8)	26 (6.3)
Unknown	28 (0.5)	16 (0.4)	12 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.5)	7 (1.7)
eGFR (ml/min/1.73m²) [13]								
<60	692 (12.3)	534 (12.5)	158 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)	113 (12.3)	45 (10.9)
≥60	4,894 (87.3)	3,734 (87.4)	1,160 (86.8)	4 (80.0)	1 (100)	0 (0.0)	803 (87.5)	352 (85.4)
Unknown	22 (0.4)	4 (0.1)	18 (1.3)	1 (20.0)	0 (0.0)	0 (0.0)	2 (0.2)	15 (3.6)
ALT (U/L)								
<40	3,771 (67.2)	3,012 (70.5)	759 (56.8)	2 (40.0)	0 (0.0)	0 (0.0)	529 (57.6)	228 (55.3)
≥40	1,080 (19.3)	821 (19.2)	259 (19.4)	0 (0.0)	0 (0.0)	0 (0.0)	156 (17.0)	103 (25.0)
Unknown	757 (13.5)	439 (10.3)	318 (23.8)	3 (60.0)	1 (100)	0 (0.0)	233 (25.4)	81 (19.7)
AST (U/L)								
<40	3,336 (59.5)	2,700 (63.2)	636 (47.6)	2 (40.0)	0 (0.0)	0 (0.0)	436 (47.5)	198 (48.1)
≥40	712 (12.7)	531 (12.4)	181 (13.5)	0 (0.0)	0 (0.0)	0 (0.0)	104 (11.3)	77 (18.7)
Unknown	1,560 (27.8)	1,041 (24.4)	519 (38.8)	3 (60.0)	1 (100)	0 (0.0)	378 (41.2)	137 (33.3)
Proportion of follow-up time in EuroSIDA with immunosuppression (defined as a CD4 count <200/cells mm3) [14]								

			Discontinued					
	Overall	Did not discontinue	Total	HSR	Hepato-toxicity	Severe skin rash (Not HSR)	Other	Unknown
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
<20%	4,638 (82.7)	3,557 (83.3)	1,081 (80.9)	2 (40.0)	1 (100)	0 (0.0)	751 (81.8)	327 (79.4)
≥20%	942 (16.8)	699 (16.4)	243 (18.2)	3 (60.0)	0 (0.0)	0 (0.0)	162 (17.6)	78 (18.9)
Unknown	28 (0.5)	16 (0.4)	12 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.5)	7 (1.7)
Proportion of follow-up time in EuroSIDA with uncontrolled viremia (HIV RNA VL > 400 copies/ml)[15]								
<20%	3,833 (68.3)	2,983 (69.8)	850 (63.6)	2 (40.0)	1 (100)	0 (0.0)	604 (65.8)	243 (59.0)
≥20%	1,768 (31.5)	1,289 (30.2)	479 (35.9)	3 (60.0)	0 (0.0)	0 (0.0)	311 (33.9)	165 (40.0)
Unknown	7 (0.1)	0 (0.0)	7 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)	4 (1.0)

[1] Date of discontinuation in those who stopped DTG, RAL or EVG, 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(4)
[4] Non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, NADM(5)
[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: Haemoglobin < 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 viremia 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 the time of discontinuation[1] for individuals using DTG, RAL, and EVG[2].

			Discontinued					
	Overall	**Did not discontinue**	**Total**	**HSR**	**Hepatotoxicity**	**Severe skin rash (Not HSR)**	**Other**	**Unknown**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
All								
	5,608 (100)	4,272 (100)	1,336 (100)	5 (100)	1 (100)	0 (0.0)	918 (100)	412 (100)
Treatment naïve at baseline[3]								
Yes	168 (3.0)	130 (3.0)	38 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	27 (2.9)	11 (2.7)
Integrase inhibitor naïve at baseline[3]								
Yes	3,851 (68.7)	2,993 (70.1)	858 (64.2)	2 (40.0)	1 (100)	0 (0.0)	588 (64.1)	267 (64.8)
Current regimen includes PI								
Yes	2,411 (43.0)	1,963 (46.0)	448 (33.5)	2 (40.0)	0 (0.0)	0 (0.0)	295 (32.1)	151 (36.7)
Current regimen includes NNRTI								
Yes	1,560 (27.8)	1,249 (29.2)	311 (23.3)	0 (0.0)	0 (0.0)	0 (0.0)	215 (23.4)	96 (23.3)
Current regimen includes NRTI								
Yes	4,899 (87.4)	4,023 (94.2)	876 (65.6)	2 (40.0)	0 (0.0)	0 (0.0)	591 (64.4)	283 (68.7)
Prior exposure to PI								
Yes	4,531 (80.8)	3,446 (80.7)	1,085 (81.2)	4 (80.0)	0 (0.0)	0 (0.0)	745 (81.2)	336 (81.6)
Prior exposure to NNRTI								
Yes	3,787 (67.5)	2,853 (66.8)	934 (69.9)	5 (100)	1 (100)	0 (0.0)	644 (70.2)	284 (68.9)
Prior exposure to NRTI								
Yes	5,601 (99.9)	4,266 (99.9)	1,335 (99.9)	5 (100)	1 (100)	0 (0.0)	917 (99.9)	412 (100)

			Discontinued					
	Overall	**Did not discontinue**	**Total**	**HSR**	**Hepatotoxicity**	**Severe skin rash (Not HSR)**	**Other**	**Unknown**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Prior exposure to DTG at baseline[3]								
Yes	453 (8.1)	311 (7.3)	142 (10.6)	1 (20.0)	0 (0.0)	0 (0.0)	104 (11.3)	37 (9.0)
Prior exposure to EVG at baseline[3]								
Yes	259 (4.6)	165 (3.9)	94 (7.0)	0 (0.0)	0 (0.0)	0 (0.0)	68 (7.4)	26 (6.3)
Prior exposure to RAL at baseline[3]								
Yes	1,333 (23.8)	983 (23.0)	350 (26.2)	3 (60.0)	0 (0.0)	0 (0.0)	236 (25.7)	111 (26.9)
Number of ARVs previously exposed to								
Median years [IQR]	8.0 (6.0,11.0)	8.0 (6.0,11.0)	9.0 (6.0,12.0)	11.0 (8.0,14.0)	6.0 (6.0,6.0)		9.0 (6.0,11.0)	9.0 (6.0,12.0)
Years since first use of any ARV (years)[4]								
Median years [IQR]	17.4 (10.2,21.8)	17.5 (10.4,22.0)	17.1 (9.3,20.9)	20.9 (13.8,22.5)	9.6 (9.6,9.6)		17.7 (10.1,21.3)	15.7 (8.5,19.9)

[1] Date of discontinuation in those who stopped DTG, RAL or EVG, or last clinic visit in those who did not
[2] After the 16 Jan 2014

[3] Baseline was defined as the date of starting the DTG (or other integrase inhibitor).

[4] 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.

Notes

HSR:
There were five discontinuations due to HSR.
- One person received DTG at 50 mg once daily for 43 days.
- One person received DTG at 50 mg once daily once daily for 40 days.
- One person received RAL at 400 mg twice daily for 79 days.
- One person received EVG as Genvoya (150 mg EVG) once daily for 216 days.
- One person received EVG as Genvoya (150 mg EVG) once daily for 7 days.

Hepatotoxicity:
There was one discontinuation due to Hepatotoxicity.
- This individual received DTG as TRIUMEQ (50 mg DTG) once daily for 115 days (overall, they received DTG with ABC+3TC for 233 days).

Severe skin rash (not HSR):
There were no discontinuations due to severe skin rash (not HSR).

Table 11:

Drug	Dosage	Total	Discontinuation									
			HSR		Hepato-toxicity		Severe skin rash (Not HSR)		Other		Unknown	
			n	%	n	%	n	%	n	%	n	%
DTG												
	50 mg x 1 daily	3	2	0.3	1	0.1						
	50 mg x 2 daily	-										
	Unknown	721										
EVG												
	150 mg x 1 daily	2	2	0.7								
	Unknown	295										
RAL												
	400 mg x 2 daily	1	1	0.3								
	Unknown	314										
Total		1336	5	0.4	1	0.1			918	68.7	412	30.8

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

10.4 Comparisons of the characteristics of individuals according to treatment regimen.

Unadjusted and adjusted odds ratios for starting different treatment regimens are presented in **Table 12** to **Table 14**.

A comparison of the characteristics of those starting cART (≥3 ARVs) with DTG (with or without ABC, i.e. groups A and B) vs EVG/RAL (with or without ABC, i.e. groups C and D) is shown in **Table 12**[6]. Individuals of non-white ethnicity, or who were living in South and Argentina, East Central or East Europe (relative to West Central Europe) were less likely to start DTG (A and B) than RAL/EVG (C and D). Individuals with unknown BMI were more likely to start DTG than RAL/EVG, while those with unknown smoking status, or individuals who were treatment-naïve at baseline were less likely to start DTG (A and B) than RAL/EVG (C and D).

In a comparison between persons who started DTG with ABC compared to without ABC (treatment group A vs B) (**Table 13**)[6], individuals on cART (≥3 ARVs) who started DTG with ABC compared to without ABC (treatment group A vs B) were more likely to be from South Europe and Argentina (relative to West Central Europe), and more likely to be treatment-naïve at baseline. Individuals with unknown BMI, current smokers or those who had unknown smoking status were less likely to be on DTG with ABC (A) than DTG without ABC (B). (**Table 13**).

Individuals on cART (≥3 ARVs) who started RAL or EVG with ABC compared to without ABC (C vs D) were more likely to have acquired HIV through IDU transmission mode (relative to through sex between men) and more likely to be from the South and Argentina or from East Central or East Europe compared to West Central Europe (**Table 14**)**.**

[6] Individuals from Group E (DTG mono- and 2-drug therapy) were not included in this comparison.

Table 12: Comparison of characteristics of those starting[1] DTG (with or without ABC) vs EVG/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	0.94 (0.69,1.29)	0.701	0.92 (0.67,1.27)	0.628
36 - 40 years	reference		reference	
41 - 50 years	1.18 (0.94,1.48)	0.143	1.02 (0.81,1.30)	0.839
51 + years	1.48 (1.19,1.83)	<.001	1.12 (0.89,1.41)	0.351
Gender				
Male	reference		reference	
Female	0.99 (0.86,1.14)	0.904	1.12 (0.95,1.32)	0.180
Race				
White	reference		reference	
Other or Missing	0.97 (0.83,1.14)	0.701	0.67 (0.56,0.81)	<.001
HIV exposure group				
MSM	reference		reference	
IDU	0.71 (0.61,0.82)	<.001	0.88 (0.74,1.05)	0.161
Heterosexual	0.89 (0.76,1.04)	0.130	0.93 (0.77,1.13)	0.476
Other/Missing	1.04 (0.82,1.32)	0.759	1.06 (0.82,1.36)	0.668
Region of Europe[7]				
South and Argentina	0.48 (0.41,0.56)	<.001	0.48 (0.41,0.57)	<.001
North	1.00 (0.84,1.20)	0.962	1.13 (0.94,1.36)	0.210
West Central	reference		reference	
East Central	0.43 (0.35,0.52)	<.001	0.43 (0.35,0.52)	<.001
East	0.44 (0.32,0.60)	<.001	0.45 (0.32,0.63)	<.001
Body mass index (BMI)				
<18	0.86 (0.52,1.44)	0.573	0.79 (0.46,1.34)	0.375
18 - 25	reference		reference	
>25	1.11 (0.92,1.33)	0.288	1.09 (0.90,1.33)	0.372
Unknown	1.22 (1.05,1.41)	0.007	1.24 (1.06,1.45)	0.008

	Unadjusted		Adjusted	
Variable	**OR**	**P**	**OR[6]**	**P**
Smoking status				
Current	0.86 (0.74,0.99)	0.042	0.92 (0.78,1.08)	0.293
Never	reference		reference	
Former	0.87 (0.72,1.05)	0.138	0.86 (0.71,1.05)	0.139
Unknown	0.53 (0.43,0.65)	<.001	0.50 (0.40,0.63)	<.001
Treatment naïve at baseline				
Yes	0.53 (0.39,0.72)	<.001	0.68 (0.49,0.94)	0.020
No	reference		reference	

[1] After the 16 Jan 2014.

[2] DTG with ABC

[3] DTG without ABC

[4] EVG/RAL with ABC

[5] EVG/RAL without ABC

[6] Models adjusted for all variables shown in the table

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

Note: Individuals in treatment group E (DTG mono- and 2-drug therapy) were not included in the models.

Table 13: Comparison of characteristics of those starting[1] DTG with ABC vs DTG without ABC: Treatment groups A[2] vs B[3] only (excluding those on EVG or RAL: C[4] and D[5], or those on DTG mono- and 2-drug therapy: E[6])

	Unadjusted		Adjusted	
Variable	**OR**	**P**	**OR[7]**	**P**
Age (years)				
≤ 35 years	1.04 (0.68,1.60)	0.848	0.98 (0.63,1.54)	0.940
36 - 40 years	reference		reference	
41 - 50 years	0.88 (0.65,1.20)	0.424	0.93 (0.68,1.27)	0.648
51 + years	0.82 (0.62,1.09)	0.180	0.88 (0.65,1.19)	0.421
Gender				
Male	reference		reference	
Female	1.13 (0.95,1.34)	0.168	1.21 (0.98,1.49)	0.075
Race				
White	reference		reference	
Other or Missing	0.87 (0.72,1.07)	0.187	1.00 (0.80,1.25)	0.992
HIV exposure group				
MSM	reference		reference	
IDU	1.04 (0.86,1.26)	0.693	0.96 (0.77,1.20)	0.726
Heterosexual	0.92 (0.76,1.11)	0.382	0.80 (0.64,1.01)	0.062
Other/Missing	1.02 (0.76,1.36)	0.904	1.02 (0.76,1.37)	0.898
Region of Europe[7]				
South and Argentina	2.04 (1.65,2.52)	<.001	1.98 (1.59,2.47)	<.001
North	1.09 (0.90,1.32)	0.396	1.09 (0.89,1.33)	0.423
West Central	reference		reference	
East Central	1.31 (1.01,1.69)	0.040	1.20 (0.91,1.58)	0.197
East	1.35 (0.87,2.10)	0.185	1.28 (0.81,2.03)	0.295
Body mass index (BMI)				
<18	0.88 (0.44,1.76)	0.715	0.88 (0.44,1.78)	0.727
18 - 25	reference		reference	
>25	0.79 (0.62,1.00)	0.049	0.79 (0.62,1.01)	0.055
Unknown	0.69 (0.57,0.83)	<.001	0.75 (0.61,0.91)	0.004

	Unadjusted		Adjusted	
Variable	**OR**	**P**	**OR[7]**	**P**
Smoking status				
Current	0.85 (0.71,1.01)	0.072	0.81 (0.67,0.98)	0.033
Never	reference		reference	
Former	0.84 (0.67,1.06)	0.152	0.83 (0.65,1.06)	0.130
Unknown	0.74 (0.56,0.98)	0.033	0.72 (0.53,0.97)	0.032
Treatment naïve at baseline				
Yes	2.09 (1.26,3.47)	0.004	2.09 (1.23,3.55)	0.006
No	reference		reference	

[1] After the 16 Jan 2014.

[2] DTG with ABC

[3] DTG without ABC

[4] EVG/RAL with ABC

[5] EVG/RAL without ABC

[6] DTG mono- and 2-drug therapy

[7] Models adjusted for all variables shown in table

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

NOTE: Variables had to have 5 or more individuals receiving each drug to be included in the model. Levels of variables with <5 people receiving each drug were combined if this seemed appropriate. For this table, BMI <18 and 18 – 25 were combined due to low numbers of individuals in treatment group C.

Table 14: Comparison of characteristics of those starting[1] EVG/RAL with ABC vs EVG/RAL without ABC: C[4] vs D[5] (excluding those on DTG: A[2], B[3] and E[6])

	Unadjusted		Adjusted	
Variable	**OR**	**P**	**OR[7]**	**P**
Age (years)				
≤ 35 years	0.91 (0.51,1.61)	0.741	0.92 (0.50,1.70)	0.792
36 - 40 years	reference		reference	
41 - 50 years	0.58 (0.37,0.89)	0.013	0.87 (0.54,1.41)	0.570
51 + years	0.52 (0.35,0.79)	0.002	0.99 (0.61,1.60)	0.959
Gender				
Male	reference		reference	
Female	1.45 (1.08,1.95)	0.013	1.12 (0.78,1.59)	0.550
Race				
White	reference		reference	
Other or Missing	0.56 (0.37,0.85)	0.006	1.05 (0.65,1.68)	0.851
HIV exposure group				
MSM	reference		reference	
IDU	2.66 (1.85,3.82)	<.001	1.81 (1.21,2.71)	0.004
Heterosexual	1.95 (1.32,2.89)	<.001	1.40 (0.88,2.23)	0.150
Other/Missing	1.87 (1.05,3.34)	0.035	1.56 (0.85,2.86)	0.147
Region of Europe[7]				
South and Argentina	2.46 (1.58,3.81)	<.001	2.28 (1.49,3.50)	<.001
North	0.88 (0.49,1.60)	0.675	0.94 (0.51,1.71)	0.833
West Central	reference		reference	
East Central	3.19 (2.01,5.07)	<.001	3.04 (1.91,4.85)	<.001
East	14.02 (7.97,24.66)	<.001	12.25 (6.66,22.55)	<.001
Body mass index (BMI)				
<18, 18 - 25	reference		reference	
>25	0.93 (0.63,1.37)	0.714	0.96 (0.64,1.45)	0.850
Unknown	0.69 (0.51,0.95)	0.021	0.80 (0.57,1.12)	0.187

	Unadjusted		Adjusted	
Variable	**OR**	**P**	**OR[7]**	**P**
Smoking status				
Current	1.01 (0.73,1.40)	0.930	0.79 (0.55,1.12)	0.186
Never	reference		reference	
Former	0.82 (0.52,1.27)	0.365	0.67 (0.41,1.09)	0.104
Unknown	0.83 (0.53,1.29)	0.410	0.90 (0.54,1.50)	0.689
Treatment naïve at baseline				
Yes	0.93 (0.50,1.74)	0.825	0.74 (0.38,1.45)	0.378
No	reference		reference	

[1] After the 16 Jan 2014.

[2] DTG with ABC

[3] DTG without ABC

[4] EVG/RAL with ABC

[5] EVG/RAL without ABC

[6] DTG mono- and 2-drug therapy

[7] Models adjusted for all variables shown in table

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

10.5 Incidence of discontinuations of DTG or other Integrase Inhibitors

10.5.1 Kaplan-Meier plots of discontinuations of DTG or other integrase inhibitors

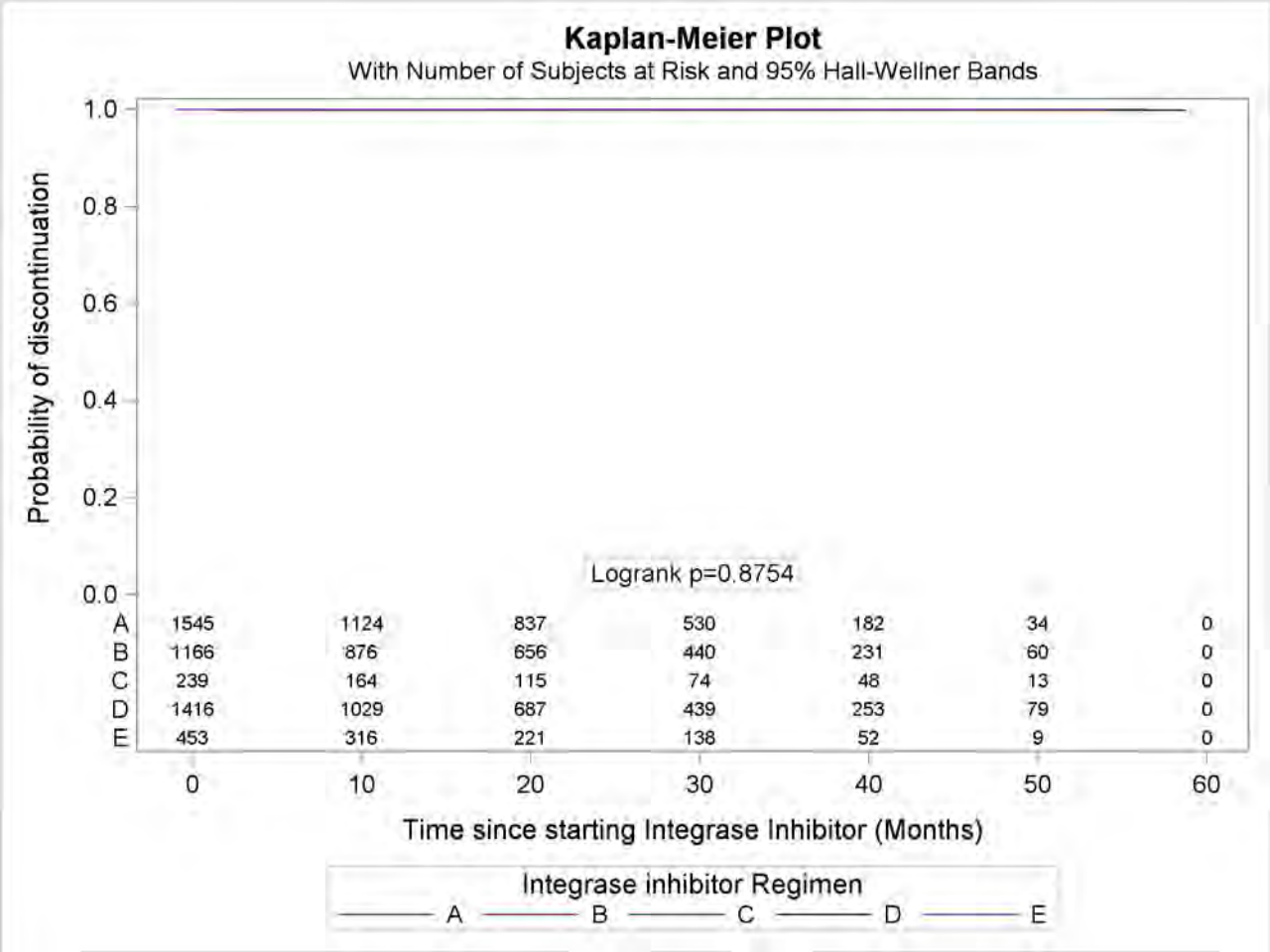
The incidence of discontinuations of DTG or other Integrase inhibitors for first INSTI episodes, stratified by treatment group, are shown in the Kaplan-Meier-plot in Figure 2.

The incidence of discontinuations of DTG or other Integrase inhibitors due to possible or definite HSR, stratified by first INST episode, are shown in the Kaplan-Meier-plot in Figure 3.

Figure 2: Time to event Kaplan-Meier (KM) estimates of discontinuation by first INSTI treatment episode (A[1], B[2], C[3], D[4] and E[5]).

[1] Group A: DTG with ABC
[2] Group B: DTG without ABC
[3] Group C: EVG/RAL with ABC
[4] Group D: EVG/RAL without ABC
[5] Group E: DTG mono- and 2-drug therapy

Figure 3: Time to event Kaplan-Meier (KM) estimates of discontinuation due to HSR by first treatment episode (A[1], B[2], C[3], D[4] and E[5]).



Note: This plot shows discontinuation according to the first treatment group, and therefore includes only four cases of HSR (one in Group A, one in Group B and two in Group D, as in **Table 1A**)

10.5.2 Incidence rates for discontinuations of DTG or other Integrase Inhibitors according to Treatment Group

The incidence rates for discontinuations by reason for discontinuation and treatment group (discontinuation of cART including DTG, groups A and B combined, discontinuation of cART including other integrase inhibitors (RAL or EVG), groups C and D combined, or of DTG as mono- or dual therapy, group E) are shown in the **SUMMARY TABLE 15**.

The rate of discontinuation in individuals treated with DTG cART (treatment group A and B combined) was 11.5 (95% CI: 10.7, 12.5)/100 PYFU (653 discontinuations over 5662 PYFU) and the rate of discontinuation in those with DTG on mono- or 2-drug therapy (E) was 8.7 (95% CI 6.9, 10.9)/100 PYFU (71 discontinuations over 820 PYFU).

The rate of discontinuation in the RAL/EVG-treated group (C and D) combined was 17.3 (95%CI: 16.0, 18.8)/100 PYFU (612 discontinuations over 3531 PYFU) (**SUMMARY Table 15**).

There were too few events within the treatment groups of interest for independent analysis according to reason of discontinuation (i.e. HSR or hepatotoxicity), therefore **Tables 16-21** are not presented[7]. **Tables 22** and **23** summarising discontinuations for “other causes” and **Tables 24** and **25** for “unknown causes” are included below (these are based on the numbers of events and PYFU estimates as shown in the **SUMMARY Table 15**).

[7] Tables were planned to be presented once 30 events or more have occurred in treatment groups A and B combined and C and D combined.

Table 16 and Table 17 were planned to summarise discontinuations due to HSR
Table 18 and Table 19 were planned to summarise discontinuations due to hepatotoxicity
Table 20 and Table 21 were planned to summarise discontinuations due to severe rash.

SUMMARY TABLE: Crude incidence rates of discontinuation[1] by reason for discontinuation as reported on the HSR CRF

Reason for discontinuation	Treatment group	Events	PYFU*	Incidence rate per 100 PYFU [95% CI][2]
All causes	Overall	1336	10013	13.3 (12.6,14.1)
	A[3] and B[4]	653	5662	11.5 (10.7,12.5)
	C[5] and D[6]	612	3531	17.3 (16.0,18.8)
	E[7]	71	820.3	8.7 (6.9,10.9)
HSR	Overall	5	10013	0.05 (0.02,0.12)
	A[3] and B[4]	2	5662	0.04 (0.00,0.13)
	C[5] and D[6]	3	3531	0.09 (0.02,0.25)
	E[7]	0	820.3	0 (0.00,0.45)
Hepatotoxicity	Overall	1	10013	0.01 (0.00,0.06)
	A[3] and B[4]	1	5662	0.02 (0.00,0.10)
	C[5] and D[6]	0	3531	0 (0.00,0.10)
	E[7]	0	820.3	0 (0.00,0.45)
Severe skin rash (Not HSR)	Overall	0	10013	0 (0.00,0.04)
	A[3] and B[4]	0	5662	0 (0.00,0.07)
	C[5] and D[6]	0	3531	0 (0.00,0.10)
	E[7]	0	820.3	0 (0.00,0.45)
Other causes	Overall	918	10013	9.2 (8.6,9.8)
	A[3] and B[4]	458	5662	8.1 (7.4,8.9)
	C[5] and D[6]	405	3531	11.5 (10.4,12.6)
	E[7]	55	820.3	6.7 (5.1,8.7)
Unknown	Overall	412	10013	4.1 (3.7,4.5)
	A[3] and B[4]	192	5662	3.4 (2.9,3.9)
	C[5] and D[6]	204	3531	5.8 (5.0,6.6)
	E[7]	16	820.3	2.0 (1.1,3.2)

[1] Multiple events per person included
[2] Exact confidence intervals were calculated for all categories with 20 events or less
[3] DTG with ABC
[4] DTG without ABC
[5] EVG/RAL with ABC
[6] EVG/RAL without ABC
[7] DTG mono- and 2-drug therapy
* This refers to the time spent on all integrase inhibitor regimens after 16 January 2014.

Note: For computational reasons person-years of follow-up (PYFU) were estimated by month of drug-use and are rounded and therefore differ slightly from the precise estimates shown in **Table 1B**. This represents a 0.2% difference in PYFU due to rounding. Using this computational approximation, 4 discontinuation events were switched from Group E to Groups A and B combined compared to **Table 1B**, but this has a negligible effect on the incidence rates for discontinuation reported.

For comparison, exact discontinuation rates based on Table 1B are shown below:

	Precise PYFU from start and end dates (as Table 1B)			**Estimated PYFU by month of drug use**		
Treatment group	**Events[1]**	**PYFU**	**Incidence rate per 100 PYFU**	**Events[2]**	**PYFU**	**Incidence rate per 100 PYFU**
Overall	1336	9990	13.4	1336	10013	13.3 (12.6,14.1)
A[3] and B[4]	649	5637	11.5	653	5662	11.5 (10.7,12.5)
C[5] and D[6]	612	3521	17.4	612	3531	17.3 (16.0,18.8)
E[7]	75	832	9.0	71	820.3	8.7 (6.9,10.9)
All DTG discontinuations	724	6469	11.2	724	6483	11.2 (10.4,12.0)

[1] Events categorized by treatment group at the start of the integrase inhibitor treatment episode

[2] Events categorized by treatment group at discontinuation

[3] DTG with ABC

[4] DTG without ABC

[5] EVG/RAL with ABC

[6] EVG/RAL without ABC

[7] DTG mono- and 2-drug therapy

Note: There were no treatment switches in the individuals with HSR or hepatotoxicity events, and incidence rate estimates are not affected.

For the analyses summarising discontinuation for "other causes" in **Table 22** and **Table 23** and for "unknown causes" in **Table 24** and **Table 25** we used the numbers of events and PYFU estimates by month of treatment, as shown in the **SUMMARY TABLE** (**Table 15**).

Table 22: 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	**Events**	**PYFU***	**Incidence rate 100 PYFU [95% CI]**
Integrase inhibitor Regimen			
A[2] and B[3]	458	5662.4	8.1 (7.4,8.9)
C[4] and D[5]	405	3530.6	11.5 (10.4,12.6)
E[6]	55	820.3	6.7 (5.1,8.7)
Demographic			
Age (years)			
≤ 35 years	45	453.2	9.9 (7.4,13.3)
36 - 40 years	63	686.8	9.2 (7.2,11.7)
41 - 50 years	234	2823.8	8.3 (7.3,9.4)
51 + years	576	6049.7	9.5 (8.8,10.3)
Gender			
Male	671	7402.3	9.1 (8.4,9.8)
Female	247	2611.0	9.5 (8.4,10.7)
Race			
White	741	8132.9	9.1 (8.5,9.8)
Other/Unknown	177	1880.4	9.4 (8.1,10.9)
HIV exposure group			
MSM	363	3883.7	9.3 (8.4,10.4)
IDU	274	2699.8	10.1 (9.0,11.4)
Heterosexual	210	2591.5	8.1 (7.1,9.3)
Other/Unknown	71	838.3	8.5 (6.7,10.7)
Region of Europe[7]			
South and Argentina	208	2627.5	7.9 (6.9,9.1)
North	229	2314.2	9.9 (8.7,11.3)
West Central	366	3573.0	10.2 (9.2,11.3)
East Central	92	1312.9	7.0 (5.7,8.6)
East	23	185.8	12.4 (8.2,18.6)

	Discontinued due to other causes		
Level	**Events**	**PYFU***	**Incidence rate 100 PYFU [95% CI]**
Body mass index (BMI)			
<18	15	124.2	12.1 (7.3,20.0)
18 - 25	179	2293.3	7.8 (6.7,9.0)
>25	132	1851.0	7.1 (6.0,8.5)
Unknown	592	5744.7	10.3 (9.5,11.2)
Smoking status			
Current	350	3919.8	8.9 (8.0,9.9)
Former	184	1765.6	10.4 (9.0,12.0)
Never	329	3727.3	8.8 (7.9,9.8)
Unknown	55	600.7	9.2 (7.0,11.9)
Clinical history			
Prior AIDS[8]			
Yes	260	2776.0	9.4 (8.3,10.6)
No	658	7237.3	9.1 (8.4,9.8)
Prior non-AIDS[9]			
Yes	147	1631.3	9.0 (7.7,10.6)
No	771	8382.0	9.2 (8.6,9.9)
Diabetes[10]			
Yes	70	842.9	8.3 (6.6,10.5)
No	848	9170.4	9.2 (8.6,9.9)
Hypertension[11]			
Yes	643	6760.2	9.5 (8.8,10.3)
No	245	2828.5	8.7 (7.6,9.8)
Unknown	30	424.6	7.1 (4.9,10.1)
Anaemia[12]			
Severe anaemia/ mild anaemia	80	844.3	9.5 (7.6,11.8)
Normal	297	3674.4	8.1 (7.2,9.1)
Unknown	541	5494.6	9.8 (9.1,10.7)

	Discontinued due to other causes		
Level	**Events**	**PYFU***	**Incidence rate 100 PYFU [95% CI]**
Prior HCV diagnosis[13]			
Yes	429	4349.1	9.9 (9.0,10.8)
No	409	4836.7	8.5 (7.7,9.3)
Unknown	80	827.6	9.7 (7.8,12.0)
Prior HBV diagnosis[14]			
Yes	55	466.6	11.8 (9.1,15.4)
No	833	9033.6	9.2 (8.6,9.9)
Unknown	30	513.2	5.8 (4.1,8.4)
HIV viral load (copies/mL)[15]			
< 400	662	7876.7	8.4 (7.8,9.1)
≥ 400	51	212.2	24.0 (18.3,31.6)
Unknown	205	1924.5	10.7 (9.3,12.2)
Peak HIV viral load (copies/mL)[16]			
< 400	131	1287.1	10.2 (8.6,12.1)
≥ 400	783	8678.6	9.0 (8.4,9.7)
Unknown	4	47.7	8.4 (3.1,22.4)
CD4 count (cells/mm^3)[15]			
<200	50	321.2	15.6 (11.8,20.5)
200 - 349	66	726.5	9.1 (7.1,11.6)
350 - 499	98	1164.5	8.4 (6.9,10.3)
≥ 500	377	4535.1	8.3 (7.5,9.2)
Unknown	327	3266.0	10.0 (9.0,11.2)
CD4 count nadir(cells/mm^3) [17]			
<200	556	5885.5	9.4 (8.7,10.3)
200 - 349	244	2856.0	8.5 (7.5,9.7)
350 - 499	78	810.6	9.6 (7.7,12.0)
≥ 500	35	424.2	8.2 (5.9,11.5)
Unknown	5	37.0	13.5 (5.6,32.5)
eGFR (ml/min/1.73m^2) [18]			
<60	113	1090.1	10.4 (8.6,12.5)
≥ 60	803	8818.9	9.1 (8.5,9.8)

	Discontinued due to other causes		
Level	**Events**	**PYFU***	**Incidence rate 100 PYFU [95% CI]**
Unknown	2	104.3	1.9 (0.5,7.7)
ALT (U/L)			
<40	488	5413.4	9.0 (8.2,9.9)
≥ 40	158	1946.5	8.1 (6.9,9.5)
Unknown	272	2653.4	10.3 (9.1,11.5)
AST (U/L)			
<40	416	4918.0	8.5 (7.7,9.3)
≥ 40	103	1225.9	8.4 (6.9,10.2)
Unknown	399	3869.4	10.3 (9.3,11.4)
Proportion of follow-up time in EuroSIDA with immunosuppression (defined as a CD4 count <200/cells mm3)[19]			
<20%	750	8145.6	9.2 (8.6,9.9)
≥ 20%	163	1830.7	8.9 (7.6,10.4)
Unknown	5	37.0	13.5 (5.6,32.5)
Proportion of follow-up time in EuroSIDA with uncontrolled viremia (HIV RNA VL > 400 copies/ml)[20]			
<20%	602	6655.1	9.0 (8.4,9.8)
≥ 20%	312	3310.6	9.4 (8.4,10.5)
Unknown	4	47.7	8.4 (3.1,22.4)
ARV history			
Treatment naïve at baseline			
Yes	27	385.7	7.0 (4.8,10.2)
No	891	9627.6	9.3 (8.7,9.9)
Integrase inhibitor naïve at baseline			
Yes	588	7183.7	8.2 (7.5,8.9)
No	330	2829.7	11.7 (10.5,13.0)
Current regimen includes PI			
Yes	401	4863.1	8.2 (7.5,9.1)
No	517	5150.2	10.0 (9.2,10.9)
Current regimen includes NNRTI			
Yes	291	2971.2	9.8 (8.7,11.0)

	Discontinued due to other causes		
Level	**Events**	**PYFU***	**Incidence rate 100 PYFU [95% CI]**
No	627	7042.2	8.9 (8.2,9.6)
Current regimen includes NRTI			
Yes	871	9475.1	9.2 (8.6,9.8)
No	47	538.2	8.7 (6.6,11.6)
Prior exposure to PI			
Yes	745	8067.5	9.2 (8.6,9.9)
No	173	1945.8	8.9 (7.7,10.3)
Prior exposure to NNRTI			
Yes	643	6573.6	9.8 (9.1,10.6)
No	275	3439.8	8.0 (7.1,9.0)
Prior exposure to NRTI			
Yes	917	9994.8	9.2 (8.6,9.8)
No	1	18.5	5.4 (0.8,38.4)
Prior exposure to DTG			
Yes	104	530.2	19.6 (16.2,23.8)
No	814	9483.2	8.6 (8.0,9.2)
Prior exposure to EVG			
Yes	68	302.6	22.5 (17.7,28.5)
No	850	9710.7	8.8 (8.2,9.4)
Prior exposure to RAL			
Yes	236	2316.3	10.2 (9.0,11.6)
No	682	7697.0	8.9 (8.2,9.6)
Number of ARVs previously exposed to			
1 - lowest quintile	174	2302.0	7.6 (6.5,8.8)
2	187	2203.5	8.5 (7.4,9.8)
3	179	1741.7	10.3 (8.9,11.9)
4	219	1985.2	11.0 (9.7,12.6)
5 - highest quintile	159	1780.9	8.9 (7.6,10.4)
Years since first use of any ARV (years)[20]			
1 - lowest quintile	150	2002.5	7.5 (6.4,8.8)
2	186	2002.3	9.3 (8.0,10.7)

	Discontinued due to other causes		
Level	Events	PYFU*	Incidence rate 100 PYFU [95% CI]
3	159	2002.9	7.9 (6.8,9.3)
4	214	2000.7	10.7 (9.4,12.2)
5 - highest quintile	209	2004.8	10.4 (9.1,11.9)

[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] EVG/RAL with ABC
[5] EVG/RAL without ABC
[6] DTG mono- and 2-drug therapy
[7] Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; West Central: Austria, Belgium, France, Germany, Luxembourg, Switzerland; North: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovenia; East: Belarus, Estonia, Georgia, Latvia, Lithuania, Russia, Ukraine
[8] Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition(4)
[9] Non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, NADM(5)
[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: Haemoglobin <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 viremia 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

*This refers to the time spent on all integrase inhibitor regimens after 16 January 2014

Table 23: 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)

NOTE: The following variables were excluded due to insufficient numbers: Prior HBV diagnosis, peak HIV viral load, proportion of follow-up time in EuroSIDA with uncontrolled viremia, treatment naïve at baseline, current regimen includes NRTI, prior exposure to NRTI.

The following variables were not considered due to collinearity with other variables: Nadir CD4 count, proportion of follow-up time in EuroSIDA with immunosuppression, current regimen includes PI, current regimen includes NNRTI, previous exposure to RAL, DTG, EVG and years since first use of any ARV.

Due to low numbers of treatment-naïve patients included, models presented in this report are not adjusted for treatment-naïve and are instead adjusted for INSTI naïve.

	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]	1.42 (1.24,1.62)	<.001	1.49 (1.30,1.72)	<.001
E[7]	0.83 (0.63,1.10)	0.188	0.78 (0.58,1.03)	0.082
Demographic				
Age (years)				
≤ 35 years	1.08 (0.74,1.59)	0.688		
36 - 40 years	reference			
41 - 50 years	0.90 (0.69,1.19)	0.469		
51 + years	1.04 (0.80,1.34)	0.777		
Gender				
Male	reference			
Female	1.04 (0.90,1.21)	0.568		
Race				
White	reference			
Other/Unknown	1.03 (0.88,1.22)	0.698		
HIV exposure group				
MSM	reference		reference	

	Discontinued due to other causes			
Variable	**Unadjusted IRR**	**P**	**Adjusted IRR[2]**	**P**
IDU	1.09 (0.93,1.27)	0.305	1.02 (0.83,1.25)	0.867
Heterosexual	0.87 (0.73,1.03)	0.100	0.83 (0.69,1.00)	0.055
Other/Unknown	0.91 (0.70,1.17)	0.451	0.82 (0.63,1.07)	0.151
Region of Europe[8]				
South and Argentina	0.77 (0.65,0.92)	0.003	0.71 (0.59,0.85)	<.001
North	0.97 (0.82,1.14)	0.685	0.82 (0.65,1.04)	0.101
West Central	reference		reference	
East Central	0.68 (0.55,0.86)	<.001	0.61 (0.48,0.78)	<.001
East	1.21 (0.80,1.82)	0.363	1.01 (0.68,1.50)	0.954
Body mass index (BMI)				
<18	1.55 (0.92,2.60)	0.100	1.57 (0.96,2.59)	0.075
18 - 25	reference		reference	
>25	0.91 (0.73,1.14)	0.431	0.97 (0.76,1.23)	0.786
Unknown	1.32 (1.12,1.56)	0.001	1.31 (1.10,1.57)	0.002
Smoking status				
	1.01 (0.87,1.18)	0.881	0.91 (0.76,1.08)	0.287
Former	1.18 (0.99,1.41)	0.072	1.12 (0.91,1.36)	0.282
Never	reference		reference	
Unknown	1.04 (0.78,1.37)	0.797	0.97 (0.70,1.33)	0.848
Clinical history				
Prior AIDS[9]				
Yes	1.03 (0.89,1.19)	0.686		
No	reference			
Prior non-AIDS[10]				
Yes	0.98 (0.82,1.17)	0.821		
No	reference			
Diabetes[11]				
Yes	0.90 (0.70,1.15)	0.386		
No	reference			
Hypertension[12]				
Yes	1.10 (0.95,1.27)	0.213		

	Discontinued due to other causes			
Variable	**Unadjusted IRR**	**P**	**Adjusted IRR[2]**	**P**
No	reference			
Unknown	0.82 (0.56,1.19)	0.285		
Anaemia[13]				
Severe anaemia/ mild anaemia	1.17 (0.91,1.50)	0.209	1.06 (0.83,1.36)	0.644
Normal	reference		reference	
Unknown	1.22 (1.06,1.40)	0.006	1.25 (1.04,1.50)	0.017
Prior HCV diagnosis[14]				
Yes	1.17 (1.02,1.34)	0.026	1.20 (1.00,1.45)	0.056
No	reference		reference	
Unknown	1.14 (0.90,1.45)	0.269	1.09 (0.84,1.41)	0.520
HIV viral load (copies/mL)[15]				
< 400	0.35 (0.26,0.46)	<.001	0.37 (0.27,0.50)	<.001
≥ 400	reference		reference	
Unknown	0.44 (0.33,0.60)	<.001	0.45 (0.32,0.64)	<.001
CD4 count (cells/mm³)[15]				
< 200	1.87 (1.40,2.50)	<.001	1.48 (1.06,2.08)	0.022
200 - 349	1.09 (0.84,1.42)	0.504	1.00 (0.76,1.30)	0.975
350 - 499	1.01 (0.81,1.26)	0.914	0.97 (0.76,1.23)	0.784
≥ 500	reference		reference	
Unknown	1.20 (1.04,1.40)	0.014	1.02 (0.85,1.22)	0.864
eGFR (ml/min/1.73m²) [16]				
<60	1.14 (0.94,1.38)	0.195	1.07 (0.86,1.33)	0.517
≥ 60	reference		reference	
Unknown	0.21 (0.05,0.83)	0.026	0.13 (0.03,0.54)	0.005
ALT (U/L)				
<40	1.11 (0.93,1.33)	0.253	1.08 (0.87,1.33)	0.492
≥ 40	reference		reference	
Unknown	1.26 (1.04,1.54)	0.019	0.97 (0.71,1.32)	0.837
AST (U/L)				
<40	1.01 (0.81,1.25)	0.951	1.01 (0.78,1.31)	0.921
≥ 40	reference		reference	

	Discontinued due to other causes			
Variable	**Unadjusted IRR**	**P**	**Adjusted IRR[2]**	**P**
Unknown	1.23 (0.99,1.52)	0.064	1.18 (0.85,1.64)	0.319
ARV history				
Integrase inhibitor naïve at baseline				
Yes	0.70 (0.61,0.80)	<.001	0.75 (0.64,0.87)	<.001
No	reference		reference	
Prior exposure to PI				
Yes	1.04 (0.88,1.23)	0.654		
No	reference			
Prior exposure to NNRTI				
Yes	1.22 (1.06,1.41)	0.005	1.15 (0.96,1.36)	0.125
No	reference		reference	
Number of ARVs previously exposed to				
1 - lowest quintile	reference		reference	
2	1.12 (0.91,1.38)	0.269	1.12 (0.89,1.39)	0.331
3	1.36 (1.10,1.67)	0.004	1.31 (1.03,1.66)	0.029
4	1.46 (1.20,1.78)	<.001	1.33 (1.05,1.70)	0.020
5 - highest quintile	1.18 (0.95,1.47)	0.130	0.98 (0.74,1.29)	0.879

[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 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, race, BMI, HIV viral load, eGFR, Integrase inhibitor naïve at baseline and number of ARVs previously exposed to
[3] DTG with ABC
[4] DTG without ABC
[5] EVG/RAL with ABC
[6] EVG/RAL without ABC
[7] DTG mono- and 2-drug therapy
[8] Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; West Central: Austria, Belgium, France, Germany, Luxembourg, Switzerland; North: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and

Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovenia; East: Belarus, Estonia, Georgia, Latvia, Lithuania, Russia, Ukraine

[9] Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition(4)

[10] Non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, NADM(5)

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

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

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

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

[15] Within 6 months prior to date

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

Table 24: Crude incidence rates[1] of discontinuation due to unknown causes

	Discontinued due to unknown causes		
Level	**Events**	**PYFU**	**Incidence rate 100 PYFU [95% CI]**
Integrase inhibitor Regimen			
A[2] and B[3]	192	5662.4	3.4 (2.9,3.9)
C[4] and D[5]	204	3530.6	5.8 (5.0,6.6)
E[6]	16	820.3	2.0 (1.2,3.2)
Demographic			
Age (years)			
≤ 35 years	15	453.2	3.3 (2.0,5.5)
36 - 40 years	41	686.8	6.0 (4.4,8.1)
41 - 50 years	97	2823.8	3.4 (2.8,4.2)
51 + years	259	6049.7	4.3 (3.8,4.8)
Gender			
Male	301	7402.3	4.1 (3.6,4.6)
Female	111	2611.0	4.3 (3.5,5.1)
Race			
White	320	8132.9	3.9 (3.5,4.4)
Other/Unknown	92	1880.4	4.9 (4.0,6.0)
HIV exposure group			
MSM	183	3883.7	4.7 (4.1,5.4)
IDU	109	2699.8	4.0 (3.3,4.9)
Heterosexual	93	2591.5	3.6 (2.9,4.4)
Other/Unknown	27	838.3	3.2 (2.2,4.7)
Region of Europe[7]			
South and Argentina	65	2627.5	2.5 (1.9,3.2)
North	137	2314.2	5.9 (5.0,7.0)
West Central	185	3573.0	5.2 (4.5,6.0)
East Central	23	1312.9	1.8 (1.2,2.6)
East	2	185.8	1.1 (0.3,4.3)

	Discontinued due to unknown causes		
Level	**Events**	**PYFU**	**Incidence rate 100 PYFU [95% CI]**
Body mass index (BMI)			
<18	8	124.2	6.4 (3.2,12.9)
18 - 25	101	2293.3	4.4 (3.6,5.4)
>25	61	1851.0	3.3 (2.6,4.2)
Unknown	242	5744.7	4.2 (3.7,4.8)
Smoking status			
Current	162	3919.8	4.1 (3.5,4.8)
Former	55	1765.6	3.1 (2.4,4.1)
Never	147	3727.3	3.9 (3.4,4.6)
Unknown	48	600.7	8.0 (6.0,10.6)
Clinical history			
Prior AIDS[8]			
Yes	108	2776.0	3.9 (3.2,4.7)
No	304	7237.3	4.2 (3.8,4.7)
Prior non-AIDS[9]			
Yes	62	1631.3	3.8 (3.0,4.9)
No	350	8382.0	4.2 (3.8,4.6)
Diabetes[10]			
Yes	29	842.9	3.4 (2.4,5.0)
No	383	9170.4	4.2 (3.8,4.6)
Hypertension[11]			
Yes	256	6760.2	3.8 (3.4,4.3)
No	116	2828.5	4.1 (3.4,4.9)
Unknown	40	424.6	9.4 (6.9,12.8)
Anaemia[12]			
Severe anaemia/ mild anaemia	53	844.3	6.3 (4.8,8.2)
Normal	180	3674.4	4.9 (4.2,5.7)
Unknown	179	5494.6	3.3 (2.8,3.8)

	Discontinued due to unknown causes		
Level	**Events**	**PYFU**	**Incidence rate 100 PYFU [95% CI]**
Prior HCV diagnosis[13]			
Yes	171	4349.1	3.9 (3.4,4.6)
No	179	4836.7	3.7 (3.2,4.3)
Unknown	62	827.6	7.5 (5.8,9.6)
Prior HBV diagnosis[14]			
Yes	12	466.6	2.6 (1.5,4.5)
No	351	9033.6	3.9 (3.5,4.3)
Unknown	49	513.2	9.5 (7.2,12.6)
HIV viral load (copies/mL)[15]			
< 400	326	7876.7	4.1 (3.7,4.6)
≥ 400	26	212.2	12.3 (8.3,18.0)
Unknown	60	1924.5	3.1 (2.4,4.0)
Peak HIV viral load (copies/mL)[16]			
< 400	56	1287.1	4.4 (3.3,5.7)
≥ 400	352	8678.6	4.1 (3.7,4.5)
Unknown	4	47.7	8.4 (3.1,22.4)
CD4 count (cells/mm^3)[15]			
<200	15	321.2	4.7 (2.8,7.7)
200 - 349	23	726.5	3.2 (2.1,4.8)
350 - 499	41	1164.5	3.5 (2.6,4.8)
≥ 500	185	4535.1	4.1 (3.5,4.7)
Unknown	148	3266.0	4.5 (3.9,5.3)
CD4 count nadir(cells/mm^3)[17]			
<200	232	5885.5	3.9 (3.5,4.5)
200 - 349	114	2856.0	4.0 (3.3,4.8)
350 - 499	33	810.6	4.1 (2.9,5.7)
≥ 500	26	424.2	6.1 (4.2,9.0)
Unknown	7	37.0	18.9 (9.0,39.7)
eGFR (ml/min/1.73m^2)[18]			
<60	43	1090.1	3.9 (2.9,5.3)
≥ 60	351	8818.9	4.0 (3.6,4.4)

	Discontinued due to unknown causes		
Level	**Events**	**PYFU**	**Incidence rate 100 PYFU [95% CI]**
Unknown	18	104.3	17.3 (10.9,27.4)
ALT (U/L)			
<40	214	5413.4	4.0 (3.5,4.5)
≥ 40	98	1946.5	5.0 (4.1,6.1)
Unknown	100	2653.4	3.8 (3.1,4.6)
AST (U/L)			
<40	192	4918.0	3.9 (3.4,4.5)
≥ 40	67	1225.9	5.5 (4.3,6.9)
Unknown	153	3869.4	4.0 (3.4,4.6)
Proportion of follow-up time in EuroSIDA with immunosuppression (defined as a CD4 count <200/cells mm3)[19]			
<20%	327	8145.6	4.0 (3.6,4.5)
≥ 20%	78	1830.7	4.3 (3.4,5.3)
Unknown	7	37.0	18.9 (9.0,39.7)
Proportion of follow-up time in EuroSIDA with uncontrolled viremia (HIV RNA VL > 400 copies/ml)[20]			
<20%	242	6655.1	3.6 (3.2,4.1)
≥ 20%	166	3310.6	5.0 (4.3,5.8)
Unknown	4	47.7	8.4 (3.1,22.4)
ARV history			
Treatment naïve at baseline			
Yes	11	385.7	2.9 (1.6,5.1)
No	401	9627.6	4.2 (3.8,4.6)
Integrase inhibitor naïve at baseline			
Yes	267	7183.7	3.7 (3.3,4.2)
No	145	2829.7	5.1 (4.4,6.0)
Current regimen includes PI			
Yes	194	4863.1	4.0 (3.5,4.6)
No	218	5150.2	4.2 (3.7,4.8)
Current regimen includes NNRTI			
Yes	114	2971.2	3.8 (3.2,4.6)

	Discontinued due to unknown causes		
Level	**Events**	**PYFU**	**Incidence rate 100 PYFU [95% CI]**
No	298	7042.2	4.2 (3.8,4.7)
Current regimen includes NRTI			
Yes	402	9475.1	4.2 (3.8,4.7)
No	10	538.2	1.9 (1.0,3.5)
Prior exposure to PI			
Yes	336	8067.5	4.2 (3.7,4.6)
No	76	1945.8	3.9 (3.1,4.9)
Prior exposure to NNRTI			
Yes	282	6573.6	4.3 (3.8,4.8)
No	130	3439.8	3.8 (3.2,4.5)
Prior exposure to NRTI			
Yes	412	9994.8	4.1 (3.7,4.5)
No	0	18.5	0.0 (0.0,0.0)
Prior exposure to DTG			
Yes	37	530.2	7.0 (5.1,9.6)
No	375	9483.2	4.0 (3.6,4.4)
Prior exposure to EVG			
Yes	26	302.6	8.6 (5.9,12.6)
No	386	9710.7	4.0 (3.6,4.4)
Prior exposure to RAL			
Yes	111	2316.3	4.8 (4.0,5.8)
No	301	7697.0	3.9 (3.5,4.4)
Number of ARVs previously exposed to			
1 - lowest quintile	89	2302.0	3.9 (3.1,4.8)
2	71	2203.5	3.2 (2.6,4.1)
3	73	1741.7	4.2 (3.3,5.3)
4	95	1985.2	4.8 (3.9,5.9)
5 - highest quintile	84	1780.9	4.7 (3.8,5.8)
Years since first use of any ARV (years)[21]			
1 - lowest quintile	93	2002.5	4.6 (3.8,5.7)
2	87	2002.3	4.3 (3.5,5.4)

	Discontinued due to unknown causes		
Level	**Events**	**PYFU**	**Incidence rate 100 PYFU [95% CI]**
3	93	2002.9	4.6 (3.8,5.7)
4	71	2000.7	3.5 (2.8,4.5)
5 - highest quintile	68	2004.8	3.4 (2.7,4.3)

[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] EVG/RAL with ABC
[5] EVG/RAL without ABC
[6] DTG mono- and 2-drug therapy
[7] Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; West Central: Austria, Belgium, France, Germany, Luxembourg, Switzerland; North: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovenia; East: Belarus, Estonia, Georgia, Latvia, Lithuania, Russia, Ukraine
[8] Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition(4)
[9] Non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, NADM(5)
[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: Haemoglobin <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 viremia 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

*This refers to the time spent on all integrase inhibitor regimens after 16 January 2014

Table 25: Adjusted incidence rate ratios[1] of discontinuation due to unknown causes

NOTE: The following variables were excluded due to insufficient numbers: Prior HBV diagnosis, peak HIV viral load, Proportion of follow-up time in EuroSIDA with uncontrolled viremia, proportion of follow-up time in EuroSIDA with immunosuppression, treatment naïve at baseline, current regimen includes NRTI, prior exposure to NRTI, and prior exposure to DTG, prior exposure to EVG.

The following variables were not considered due to collinearity with other variables: Nadir CD4, current regimen includes PI, current regimen includes NNRTI, previous exposure to RAL and years since first use of any ARV.

Due to low numbers of treatment naïve patients included, models presented in this report are not adjusted for treatment naïve and are instead adjusted for INSTI naïve.

	Discontinued due to unknown causes			
Variable	**Unadjusted IRR**	**P**	**Adjusted IRR[2]**	**P**
Integrase inhibitor Regimen				
A[3] and B[4]	reference		reference	
C[5] and D[6]	1.70 (1.39,2.09)	<.001	1.95 (1.58,2.40)	<.001
E[7]	0.58 (0.34,0.96)	0.036	0.61 (0.35,1.07)	0.085
Demographic				
Age (years)				
≤ 35 years	0.55 (0.30,1.01)	0.055	0.50 (0.27,0.92)	0.026
36 - 40 years	reference		reference	
41 - 50 years	0.58 (0.40,0.83)	0.003	0.53 (0.36,0.78)	0.001
51 + years	0.72 (0.51,1.00)	0.053	0.71 (0.49,1.03)	0.072
Gender				
Male	reference			
Female	1.05 (0.84,1.31)	0.697		
Race				
White	reference		reference	
Other/Unknown	1.24 (0.98,1.58)	0.073	0.95 (0.71,1.28)	0.741
HIV exposure group				
MSM	reference		reference	
IDU	0.86 (0.67,1.09)	0.214	0.93 (0.68,1.28)	0.659
Heterosexual	0.76 (0.59,0.98)	0.037	0.86 (0.65,1.15)	0.319

	Discontinued due to unknown causes			
Variable	**Unadjusted IRR**	**P**	**Adjusted IRR[2]**	**P**
Other/Unknown	0.68 (0.45,1.04)	0.073	0.69 (0.45,1.07)	0.098
Region of Europe[8]				
South and Argentina	0.48 (0.36,0.64)	<.001	0.40 (0.29,0.54)	<.001
North	1.14 (0.91,1.44)	0.252	1.33 (0.99,1.79)	0.055
West Central	reference		reference	
East Central and East	0.32 (0.21,0.49)	<.001	0.28 (0.17,0.45)	<.001
Body mass index (BMI)				
<18	1.46 (0.71,3.03)	0.306	1.29 (0.56,2.97)	0.544
18 - 25	reference		reference	
>25	0.75 (0.54,1.03)	0.076	0.84 (0.60,1.17)	0.308
Unknown	0.96 (0.76,1.21)	0.711	0.78 (0.61,1.01)	0.055
Smoking status				
Current	1.05 (0.83,1.32)	0.688	1.02 (0.78,1.32)	0.906
Former	0.79 (0.58,1.08)	0.141	0.84 (0.60,1.18)	0.312
Never	reference		reference	
Unknown	2.03 (1.45,2.83)	<.001	0.99 (0.64,1.53)	0.970
Clinical history				
Prior AIDS[9]				
Yes	0.93 (0.74,1.16)	0.505		
No	reference			
Prior non-AIDS[10]				
Yes	0.91 (0.69,1.20)	0.505		
No	reference			
Diabetes[11]				
Yes	0.82 (0.56,1.21)	0.328		
No	reference			
Hypertension[12]				
Yes	0.92 (0.74,1.15)	0.485	0.80 (0.63,1.03)	0.084
No	reference		reference	
Unknown	2.30 (1.58,3.33)	<.001	2.09 (1.33,3.26)	0.001

	Discontinued due to unknown causes			
Variable	**Unadjusted IRR**	**P**	**Adjusted IRR[2]**	**P**
Anaemia[13]				
Severe anaemia/mild anaemia	1.28 (0.94,1.75)	0.119	1.21 (0.87,1.68)	0.264
Normal	reference		reference	
Unknown	0.67 (0.54,0.82)	<.001	0.53 (0.40,0.70)	<.001
Prior HCV diagnosis[14]				
Yes	1.06 (0.86,1.32)	0.581	0.84 (0.63,1.12)	0.239
No	reference		reference	
Unknown	2.02 (1.50,2.73)	<.001	1.61 (1.13,2.29)	0.008
HIV viral load (copies/mL)[15]				
< 400	0.34 (0.23,0.51)	<.001	0.33 (0.20,0.56)	<.001
≥ 40	reference		reference	
Unknown	0.25 (0.16,0.41)	<.001	0.26 (0.15,0.46)	<.001
CD4 count (cells/mm³)[15]				
<200	1.14 (0.67,1.95)	0.619		
200 - 349	0.78 (0.50,1.20)	0.257		
350 - 499	0.86 (0.61,1.21)	0.398		
≥ 500	reference			
Unknown	1.11 (0.89,1.38)	0.341		
eGFR (ml/min/1.73m²) [16]				
<60	0.99 (0.72,1.37)	0.957	0.95 (0.66,1.36)	0.772
≥ 60	reference		reference	
Unknown	4.33 (2.68,7.01)	<.001	3.15 (1.61,6.17)	<.001
ALT (U/L)				
<40	0.79 (0.62,1.00)	0.050	0.80 (0.58,1.09)	0.158
≥ 40	reference		reference	
Unknown	0.75 (0.57,0.99)	0.043	1.25 (0.80,1.93)	0.325
AST (U/L)				
<40	0.71 (0.54,0.95)	0.019	0.89 (0.62,1.29)	0.539
≥ 40	reference		reference	
Unknown	0.72 (0.54,0.97)	0.028	0.80 (0.51,1.24)	0.318

	Discontinued due to unknown causes			
Variable	**Unadjusted IRR**	**P**	**Adjusted IRR[2]**	**P**
ARV history				
Integrase inhibitor naïve at baseline				
Yes	0.73 (0.59,0.89)	0.002	0.80 (0.64,0.99)	0.044
No	reference		reference	
Prior exposure to PI				
Yes	1.07 (0.83,1.38)	0.621		
No	reference			
Prior exposure to NNRTI				
Yes	1.14 (0.92,1.40)	0.242		
No	reference			
Number of ARVs previously exposed to				
1 - lowest quintile	reference			
2	0.83 (0.61,1.15)	0.262		
3	1.08 (0.79,1.49)	0.617		
4	1.24 (0.92,1.66)	0.158		
5 - highest quintile	1.22 (0.90,1.66)	0.204		

[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 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, HIV exposure group, region of Europe, smoking status, hypertension, prior HCV, HIV viral load, eGFR, Integrase inhibitor naïve at baseline, prior exposure to NNRTI, number of ARVs previously exposed to
[3] DTG with ABC
[4] DTG without ABC
[5] EVG/RAL with ABC
[6] EVG/RAL without ABC
[7] DTG mono- and 2-drug therapy
[8] Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; West Central: Austria, Belgium, France, Germany, Luxembourg, Switzerland; North: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovenia; East: Belarus, Estonia, Georgia, Latvia, Lithuania, Russia, Ukraine

[9] Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition(4)
[10] Non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, NADM(5)
[11] Prior diabetes defined as: Prior diagnosis of diabetes mellitus, or taking oral antidiabetic agents or insulin
[12] Hypertension defined as: SBP ≥140 mmHg, DBP ≥90 mmHg or taking angiotensin-converting enzyme inhibitors/antihypertensive agents
[13] Severe/mild anaemia defined as: Haemoglobin <14 and <12 in males and females respectively
[14] Prior Hepatitis C Virus (HCV) defined as: Prior HCV antibody test Positive (Yes), Negative (No) or no test or inconclusive (Unknown)
[15] Within 6 months prior to date
[16] Estimated glomerular filtration rate (eGFR) calculated using: CKD-EPI

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

		Total	A[1]	B[2]	C[3]	D[4]	E[5]
All discontinuations (N)		**6**	**2**	**1**	**0**	**3**	**0**
HSR		5	1	1	0	3	0
Hepatotoxicity		1	1	0	0	0	0
Severe Skin Rash (not		0	0	0	0	0	0
Reported Symptoms (N)							
Fever							
	Yes	1	0	1	0	0	0
	No	5	2	0	0	3	0
	Unknown	0	0	0	0	0	0
Eosinophilia							
	Yes	0	0	0	0	0	0
	No	4	2	0	0	2	0
	Unknown	2	0	1	0	1	0
Skin rash							
	Yes	3	1	0	0	2	0
	Severe	*1*	*0*	*0*	*0*	*1*	*0*
	Moderate	*0*	*0*	*0*	*0*	*0*	*0*
	Mild	*2*	*1*	*0*	*0*	*1*	*0*
	No	3	1	1	0	1	0
	Unknown	0	0	0	0	0	0
Gastro-intestinal							
	Yes	4	1	1	0	2	0
	Nausea	3	1	1	0	1	0
	Vomiting	1	0	0	0	1	0
	Diarrhoea	0	0	0	0	0	0
	No	2	1	0	0	1	0
	Unknown	0	0	0	0	0	0
Respiratory							
	Yes	1	1	0	0	0	0
	Dyspnoea	1	1	0	0	0	0
	Sore throat	0	0	0	0	0	0
	Cough	0	0	0	0	0	0
	Chest x-ray changes	0	0	0	0	0	0
	No	5	1	1	0	3	0
	Unknown	0	0	0	0	0	0
Elevated ALT							
	>5xULN	1	1	0	0	0	0
Elevated Bilirubin							
	>2xULN	0	0	0	0	0	0

[1] DTG with ABC
[2] DTG without ABC
[3] EVG/RAL with ABC
[4] EVG/RAL without ABC
[5] DTG mono- and 2-drug therapy

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

Treatment group	Total N	≥1 ALT or Bilirubin test during follow-up N (% of total)	At least 1 test elevated[1] N (% of tested)
A[2]	1545	1372 (88.8)	45 (3.3)
B[3]	1166	1063 (91.2)	39 (3.7)
C[4]	239	211 (88.3)	10 (4.7)
D[5]	1416	1251 (88.3)	40 (3.2)
E[6]	453	403 (89.0)	9 (2.2)
Total	4819	4300 (89.2)	143 (3.3)

[1] Defined as liver chemistry test elevations of either alanine aminotransferase (ALT) test >5xULN (ULN=40) or ALT test >3x ULN and bilirubin >2xULN (ULN=1.2 mg/dL); see section 8.3.2.2 and reference(2).

[2] DTG with ABC
[3] DTG without ABC
[4] EVG/RAL with ABC
[5] EVG/RAL without ABC
[6] Mono- or 2-drug therapy with DTG

10.6 Breakdown of the DTG-based ARV regimens taken by individuals in Group E.

There were 453 individuals who started a regimen in treatment group E (Patients that started other DTG based ARV regimens including DTG as monotherapy or two-drug regimens).

A breakdown of the regimens used by this group of individuals is shown in **SUPPLEMENTARY TABLE 3**.

Of the 453 individuals in Group E, 49 (10.8%) were on DTG monotherapy and 394 (87.0%) were on a standard 2-drug regimen with DTG. A further 10 individuals (2.2%) reported regimens of DTG with ETR, NVP or ZDV.

The 49 episodes of DTG monotherapy reflect prescribing practices in Europe. Most individuals on DTG monotherapy are from South Europe (55%) and West Central Europe (33%). DTG monotherapy was mostly used early in the study (median start date 28 October 2015).

The most common 2-drug regimen was DTG + DRV/r or DRV/c (150 individuals, 33.1%), followed by DTG + RPV (92 individuals, 20.3%), DTG + 3TC (88 individuals, 19.4%), DTG + FTC (23 individuals, 5.1%) and DTG + ATV or ATV/r (21 individuals, 4.6%). Of the remaining individuals, eight were taking DTG with TDF, six were on DTG with the CCR5 inhibitor MVC, four were taking DTG with LPV/r and two were on DTG with EFV.

SUPPLEMENTARY TABLE 3. ARV regimens in use by individuals in Group E (any other DTG based ARV regimen [including DTG as monotherapy or two-drug regimens]).

Regimen	N	%
All in Group E	**453**	**100**
DTG monotherapy	49	10.8
DTG dual therapy (2DR)	**394**	**87.0**
of which		
with darunavir (DRV/r or DRV/c)	150	33.1
with rilpivirine (RPV)	92	20.3
with lamivudine (3TC)	88	19.4
with emtricitabine (FTC)	23	5.1
with atazanavir (ATV or ATV/r)	21	4.6
with tenofovir disoproxil fumarate (TDF)	8	1.8
with maraviroc (MVC)	6	1.3
with lopinavir (LPV/r)	4	0.9
with efavirenz (EFV)	2	0.4
Other dual (2DR) regimens[1]	**10**	**2.2**
which contain DTG and		
etravirine (ETR)	4	0.9
nevirapine (NVP)	4	0.9
zidovudine (ZDV)	2	0.4

[1] Because of possible errors in the ARV record, some DTG-containing regimens are non-standard and queries are constantly raised with the sites which means these ARV regimens may change at next download. The data presented is according to the closed version of the database used to generate the final study report.

10.7 Sensitivity analyses

Results of sensitivity analysis were to be included when 30 events or more have occurred in treatment groups A and B combined and C and D combined. The planned sensitivity analyses were:

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

The following tables were planned to be provided:

Table S1 – S6: As Table 16 – 21, but including DEFINITIVE events only: Since fewer than 30 events accumulated during the 5-year study period, these tables are not presented.

2. 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 were 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 analysis, if patients have switched from one treatment group to another, the event was assumed to have occurred in the first treatment group.

The following tables were planned to be provided:

Table S7 – S16: As Table 16 – 25 but including results from first treatment group only. Only the tables where more than 30 events accumulated during the 5-year study period are shown, namely:

- **Table S13**, showing crude incidence rates 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.
- **Table S14**, showing adjusted incidence rate ratios 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
- **Table S15**, showing crude incidence rates of discontinuation due to unknown 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.
- **Table S16**, showing adjusted incidence rate ratios of discontinuation due to unknown 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.

Results of the sensitivity analyses were generally consistent with the main analyses. The discontinuation rates for the first treatment episode only (**Tables S13** and **S15**) were overall around 10% lower than discontinuation rates for all treatment episodes (compared to **Tables 22** and **24**, respectively), except that for the first INSTI treatment episodes very few individuals had a prior exposure to DTG or EVG (see also **Table 10** and **APPENDIX Table 10** reporting prior ART history for all treatment episodes (**table 10**) or first episodes only (**APPENDIX Table 10**). Higher rates of discontinuation for "other reasons" (**Table S13**) or "unknown" (**Table S14**) were reported in the category "prior exposure to DTG", but these were based on low numbers of discontinuations. The unadjusted and adjusted incidence rate ratios for discontinuations due to "other reasons" or "unknown" reasons were also consistent (compare **Tables S14** and **S16** for "other reasons" or "unknown" with **Tables 23** and **25** for all episodes), although there were some small differences in the variables selected in the multivariable models.

Table S17 – S22: As Table 16 – 21 but allowing 4 additional weeks of follow-up after discontinuation. Since fewer than 30 events accumulated during the 5-year study period, these tables are not presented.

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 episode only.

	Discontinued due to other causes		
Level	**Events**	**PYFU***	**Incidence rate 100 PYFU [95% CI]**
Integrase inhibitor Regimen			
A[2] and B[3]	379	5213.9	7.3 (6.6,8.0)
C[4] and D[5]	318	3073.3	10.3 (9.3,11.5)
E[6]	47	771.3	6.1 (4.6,8.1)
Demographic			
Age (years)			
≤ 35 years	38	420.6	9.0 (6.6,12.4)
36 - 40 years	50	633.2	7.9 (6.0,10.4)
41 - 50 years	195	2586.5	7.5 (6.6,8.7)
51 + years	461	5418.3	8.5 (7.8,9.3)
Gender			
Male	547	6726.9	8.1 (7.5,8.8)
Female	197	2331.7	8.4 (7.3,9.7)
Race			
White	600	7385.0	8.1 (7.5,8.8)
Other/Unknown	144	1673.6	8.6 (7.3,10.1)
HIV exposure group			
MSM	292	3514.2	8.3 (7.4,9.3)
IDU	220	2404.8	9.1 (8.0,10.4)
Heterosexual	172	2379.9	7.2 (6.2,8.4)
Other/Unknown	60	759.7	7.9 (6.1,10.2)
Region of Europe[7]			
South and Argentina	179	2431.5	7.4 (6.4,8.5)
North	166	2042.2	8.1 (7.0,9.5)
West Central	293	3188.7	9.2 (8.2,10.3)
East Central	84	1225.3	6.9 (5.5,8.5)

	Discontinued due to other causes		
Level	**Events**	**PYFU***	**Incidence rate 100 PYFU [95% CI]**
East	22	170.9	12.9 (8.5,19.5)
Body mass index (BMI)			
<18	12	110.6	10.9 (6.2,19.1)
18 - 25	152	2097.6	7.2 (6.2,8.5)
>25	105	1699.8	6.2 (5.1,7.5)
Unknown	475	5150.6	9.2 (8.4,10.1)
Smoking status			
Current	277	3521.4	7.9 (7.0,8.8)
Former	146	1613.8	9.0 (7.7,10.6)
Never	276	3366.2	8.2 (7.3,9.2)
Unknown	45	557.2	8.1 (6.0,10.8)
Clinical history			
Prior AIDS[8]			
Yes	205	2492.7	8.2 (7.2,9.4)
No	539	6565.9	8.2 (7.5,8.9)
Prior non-AIDS[9]			
Yes	118	1435.6	8.2 (6.9,9.8)
No	626	7623.0	8.2 (7.6,8.9)
Diabetes[10]			
Yes	58	768.0	7.6 (5.8,9.8)
No	686	8290.6	8.3 (7.7,8.9)
Hypertension[11]			
Yes	513	6122.4	8.4 (7.7,9.1)
No	203	2538.8	8.0 (7.0,9.2)
Unknown	28	397.3	7.0 (4.9,10.2)
Anaemia[12]			
Severe anaemia/ mild anaemia	63	744.6	8.5 (6.6,10.8)
Normal	243	3366.6	7.2 (6.4,8.2)
Unknown	438	4947.4	8.9 (8.1,9.7)

	Discontinued due to other causes		
Level	**Events**	**PYFU***	**Incidence rate 100 PYFU [95% CI]**
Prior HCV diagnosis[13]			
Yes	348	3886.8	9.0 (8.1,9.9)
No	335	4434.1	7.6 (6.8,8.4)
Unknown	61	737.7	8.3 (6.4,10.6)
Prior HBV diagnosis[14]			
Yes	44	429.4	10.2 (7.6,13.8)
No	674	8166.3	8.3 (7.7,8.9)
Unknown	26	462.8	5.6 (3.8,8.3)
HIV viral load (copies/mL)[15]			
< 400	526	7112.9	7.4 (6.8,8.1)
≥ 400	40	179.7	22.3 (16.3,30.4)
Unknown	178	1766.0	10.1 (8.7,11.7)
Peak HIV viral load (copies/mL)[16]			
< 400	106	1152.5	9.2 (7.6,11.1)
≥ 400	634	7859.7	8.1 (7.5,8.7)
Unknown	4	46.3	8.6 (3.2,23.0)
CD4 count (cells/mm^3)[15]			
<200	31	277.3	11.2 (7.9,15.9)
200 - 349	56	663.4	8.4 (6.5,11.0)
350 - 499	74	1042.8	7.1 (5.7,8.9)
≥ 500	312	4119.9	7.6 (6.8,8.5)
Unknown	271	2955.2	9.2 (8.1,10.3)
CD4 count nadir(cells/mm^3) [17]			
<200	443	5325.6	8.3 (7.6,9.1)
200 - 349	201	2602.7	7.7 (6.7,8.9)
350 - 499	65	732.7	8.9 (7.0,11.3)
≥ 500	31	364.2	8.5 (6.0,12.1)
Unknown	4	33.5	11.9 (4.5,31.8)
eGFR (ml/min/1.73m^2) [18]			
<60	89	964.4	9.2 (7.5,11.4)
≥ 60	653	7992.5	8.2 (7.6,8.8)

	Discontinued due to other causes		
Level	**Events**	**PYFU***	**Incidence rate 100 PYFU [95% CI]**
Unknown	2	101.7	2.0 (0.5,7.9)
ALT (U/L)			
<40	389	4842.5	8.0 (7.3,8.9)
≥ 40	122	1777.0	6.9 (5.7,8.2)
Unknown	233	2439.1	9.6 (8.4,10.9)
AST (U/L)			
<40	338	4440.3	7.6 (6.8,8.5)
≥ 40	76	1114.2	6.8 (5.4,8.5)
Unknown	330	3504.2	9.4 (8.5,10.5)
Proportion of follow-up time in EuroSIDA with immunosuppression (defined as a CD4 count <200/cells mm3)[19]			
<20%	616	7361.4	8.4 (7.7,9.1)
≥ 20%	124	1663.7	7.5 (6.3,8.9)
Unknown	4	33.5	11.9 (4.5,31.8)
Proportion of follow-up time in EuroSIDA with uncontrolled viremia (HIV RNA VL > 400 copies/ml)[20]			
<20%	492	6003.3	8.2 (7.5,9.0)
≥ 20%	248	3008.9	8.2 (7.3,9.3)
Unknown	4	46.3	8.6 (3.2,23.0)
ARV history			
Treatment naïve at baseline			
Yes	27	385.7	7.0 (4.8,10.2)
No	717	8672.8	8.3 (7.7,8.9)
Integrase inhibitor naïve at baseline			
Yes	588	7183.7	8.2 (7.5,8.9)
No	156	1874.9	8.3 (7.1,9.7)
Current regimen includes PI			
Yes	333	4511.5	7.4 (6.6,8.2)
No	411	4547.1	9.0 (8.2,10.0)
Current regimen includes NNRTI			
Yes	251	2794.6	9.0 (7.9,10.2)

	Discontinued due to other causes		
Level	**Events**	**PYFU***	**Incidence rate 100 PYFU [95% CI]**
No	493	6264.0	7.9 (7.2,8.6)
Current regimen includes NRTI			
Yes	704	8555.1	8.2 (7.6,8.9)
No	40	503.5	7.9 (5.8,10.8)
Prior exposure to PI			
Yes	591	7266.9	8.1 (7.5,8.8)
No	153	1791.7	8.5 (7.3,10.0)
Prior exposure to NNRTI			
Yes	513	5918.6	8.7 (7.9,9.5)
No	231	3140.0	7.4 (6.5,8.4)
Prior exposure to NRTI			
Yes	743	9040.6	8.2 (7.6,8.8)
No	1	18.0	5.6 (0.8,39.4)
Prior exposure to DTG			
Yes	4	7.2	55.2 (20.7,147.0)
No	740	9051.3	8.2 (7.6,8.8)
Prior exposure to EVG			
Yes	5	34.6	14.5 (6.0,34.7)
No	739	9024.0	8.2 (7.6,8.8)
Prior exposure to RAL			
Yes	150	1845.6	8.1 (6.9,9.5)
No	594	7213.0	8.2 (7.6,8.9)
Number of ARVs previously exposed to			
1 - lowest quintile	158	2164.7	7.3 (6.2,8.5)
2	160	2008.5	8.0 (6.8,9.3)
3	136	1546.2	8.8 (7.4,10.4)
4	168	1769.1	9.5 (8.2,11.0)
5 - highest quintile	122	1570.1	7.8 (6.5,9.3)
Years since first use of any ARV (years)[21]			
1 - lowest quintile	130	1843.7	7.1 (5.9,8.4)
2	152	1807.8	8.4 (7.2,9.9)

	Discontinued due to other causes		
Level	**Events**	**PYFU***	**Incidence rate 100 PYFU [95% CI]**
3	127	1847.1	6.9 (5.8,8.2)
4	173	1790.7	9.7 (8.3,11.2)
5 - highest quintile	162	1769.2	9.2 (7.8,10.7)

[1] Although 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, this table shows result for the first INSTI exposure only.
[2] DTG with ABC
[3] DTG without ABC
[4] EVG/RAL with ABC
[5] EVG/RAL without ABC
[6] DTG mono- and 2-drug therapy
[7] Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; West Central: Austria, Belgium, France, Germany, Luxembourg, Switzerland; North: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovenia; East: Belarus, Estonia, Georgia, Latvia, Lithuania, Russia, Ukraine
[8] Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition(4)
[9] Non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, NADM(5)
[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: Haemoglobin <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 viremia 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

* This refers to the time spent on the **first** integrase inhibitor regimen after 16 January 2014

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 episode only.

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).

The following variables were excluded: Prior HBV diagnosis, peak HIV viral load, Proportion of follow-up time in EuroSIDA with uncontrolled viremia, treatment naïve at baseline, current regimen includes NRTI, prior exposure to NRTI, prior exposure to DTG.

The following variables were not considered due to collinearity with other variables: nadir CD4, proportion of follow-up time in EuroSIDA with immunosuppression, current regimen includes PI, current regimen includes NNRTI, prior exposure to EVG, prior exposure to RAL, years since first use of any ARV.

	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]	1.42 (1.23,1.65)	<.001	1.47 (1.27,1.72)	<.001
E[7]	0.84 (0.62,1.13)	0.252	0.81 (0.60,1.10)	0.181
Demographic				
Age (years)				
≤ 35 years	1.14 (0.75,1.75)	0.533		
36 - 40 years	reference			
41 - 50 years	0.95 (0.70,1.30)	0.766		
51 + years	1.08 (0.81,1.44)	0.611		
Gender				
Male	reference			
Female	1.04 (0.88,1.22)	0.643		
Race				
White	reference			
Other/Unknown	1.06 (0.88,1.27)	0.534		

	Discontinued due to other causes			
Variable	**Unadjusted IRR**	**P**	**Adjusted IRR[2]**	**P**
HIV exposure group				
MSM	reference			
IDU	1.10 (0.93,1.31)	0.278		
Heterosexual	0.87 (0.72,1.05)	0.143		
Other/Unknown	0.95 (0.72,1.26)	0.722		
Region of Europe[8]				
South and Argentina	0.80 (0.67,0.96)	0.019	0.70 (0.58,0.86)	<.001
North	0.88 (0.73,1.07)	0.207	0.73 (0.57,0.92)	0.009
West Central	reference		reference	
East Central	0.75 (0.59,0.95)	0.016	0.63 (0.49,0.81)	<.001
East	1.40 (0.92,2.14)	0.117	1.09 (0.70,1.69)	0.714
Body mass index (BMI)				
<18	1.50 (0.84,2.66)	0.167	1.51 (0.85,2.67)	0.162
18 - 25	reference		reference	
>25	0.85 (0.67,1.09)	0.207	0.91 (0.71,1.16)	0.431
Unknown	1.27 (1.06,1.53)	0.010	1.28 (1.06,1.55)	0.010
Smoking status				
Current	0.96 (0.81,1.13)	0.624		
Former	1.10 (0.90,1.35)	0.334		
Never	reference			
Unknown	0.99 (0.73,1.34)	0.923		
Clinical history				
Prior AIDS[9]				
Yes	1.00 (0.85,1.18)	0.982		
No	reference			
Prior non-AIDS[10]				
Yes	1.00 (0.82,1.22)	0.993		
No	reference			
Diabetes[11]				
Yes	0.91 (0.70,1.19)	0.500		
No	reference			

	Discontinued due to other causes			
Variable	**Unadjusted IRR**	**P**	**Adjusted IRR[2]**	**P**
Hypertension[12]				
Yes	1.05 (0.89,1.23)	0.570		
No	reference			
Unknown	0.88 (0.60,1.30)	0.524		
Anaemia[13]				
Severe anaemia/ mild anaemia	1.17 (0.89,1.55)	0.263	1.10 (0.83,1.47)	0.506
Normal	reference		reference	
Unknown	1.23 (1.05,1.43)	0.010	1.24 (1.02,1.52)	0.033
Prior HCV diagnosis[14]				
Yes	1.19 (1.02,1.38)	0.026	1.25 (1.07,1.47)	0.006
No	reference		reference	
Unknown	1.09 (0.84,1.43)	0.507	1.07 (0.81,1.40)	0.634
HIV viral load (copies/mL)[15]				
< 400	0.33 (0.24,0.45)	<.001	0.33 (0.24,0.45)	<.001
≥ 400	reference		reference	
Unknown	0.45 (0.32,0.63)	<.001	0.41 (0.28,0.60)	<.001
CD4 count (cells/mm^3)[15]				
< 200	1.48 (1.03,2.11)	0.034	1.13 (0.80,1.61)	0.487
200 - 349	1.11 (0.84,1.48)	0.451	1.00 (0.75,1.34)	0.990
350 - 499	0.94 (0.73,1.21)	0.615	0.90 (0.70,1.17)	0.429
≥ 500	reference		reference	
Unknown	1.21 (1.03,1.43)	0.021	1.00 (0.82,1.22)	0.972
eGFR (ml/min/1.73m^2) [16]				
<60	1.13 (0.91,1.41)	0.277	1.13 (0.90,1.42)	0.293
≥ 60	reference		reference	
Unknown	0.24 (0.06,0.95)	0.042	0.14 (0.03,0.53)	0.004
ALT (U/L)				
<40	1.17 (0.95,1.43)	0.130	1.10 (0.87,1.40)	0.419
≥ 40	reference		reference	
Unknown	1.39 (1.12,1.73)	0.003	0.93 (0.66,1.32)	0.699

	Discontinued due to other causes			
Variable	**Unadjusted IRR**	**P**	**Adjusted IRR[2]**	**P**
AST (U/L)				
<40	1.12 (0.87,1.43)	0.388	1.10 (0.82,1.47)	0.532
≥ 40	reference		reference	
Unknown	1.38 (1.08,1.77)	0.011	1.39 (0.96,2.01)	0.082
Integrase inhibitor naïve at baseline				
Yes	0.98 (0.82,1.17)	0.855		
No	reference			
Prior exposure to PI				
Yes	0.95 (0.80,1.14)	0.590		
No	reference			
Prior exposure to NNRTI				
Yes	1.18 (1.01,1.37)	0.037	1.15 (0.95,1.38)	0.150
No	reference		reference	
Number of ARVs previously exposed to				
1 - lowest quintile	reference		reference	
2	1.09 (0.88,1.36)	0.430	1.09 (0.86,1.38)	0.466
3	1.21 (0.96,1.51)	0.107	1.19 (0.93,1.53)	0.173
4	1.30 (1.05,1.61)	0.017	1.24 (0.96,1.60)	0.098
5 - highest quintile	1.06 (0.84,1.35)	0.602	1.00 (0.76,1.33)	0.979

[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 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, HIV exposure group, HIV viral load, eGFR, and number of ARVs previously exposed to
[3] DTG with ABC
[4] DTG without ABC
[5] EVG/RAL with ABC
[6] EVG/RAL without ABC
[7] Mono- or 2-drug therapy with DTG
[8] Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; West Central: Austria, Belgium, France, Germany, Luxembourg, Switzerland; North: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovenia; East: Belarus, Estonia, Georgia, Latvia, Lithuania, Russia, Ukraine

[9] Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition(4).
[10] Non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, NADM(5)
[11] Prior diabetes defined as: Prior diagnosis of diabetes mellitus, or taking oral antidiabetic agents or insulin
[12] Hypertension defined as: SBP >= 140 mmHg, DBP >= 90 mmHg or taking angiotensin-converting enzyme inhibitors/antihypertensive agents
[13] Severe/mild anaemia defined as: Haemoglobin < 14 and <12 in males and females respectively.
[14] Prior Hepatitis C Virus (HCV) defined as: Prior HCV antibody test Positive (Yes), Negative (No) or no test or inconclusive (Unknown).
[15] Within 6 months prior to date
[16] Estimated glomerular filtration rate (eGFR) calculated using: CKD-EPI

Table S15: Crude incidence rates[1] of discontinuation due to unknown 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 episode only.

	Discontinued due to unknown causes		
Level	**Events**	**PYFU***	**Incidence rate 100 PYFU [95% CI]**
Integrase inhibitor Regimen			
A[2] and B[3]	168	5213.9	3.2 (2.8,3.7)
C[4] and D[5]	170	3073.3	5.5 (4.8,6.4)
E[6]	14	771.3	1.8 (1.1,3.1)
Demographic			
Age (years)			
≤ 35 years	14	420.6	3.3 (2.0,5.6)
36 - 40 years	38	633.2	6.0 (4.4,8.2)
41 - 50 years	79	2586.5	3.1 (2.4,3.8)
51 + years	221	5418.3	4.1 (3.6,4.7)
Gender			
Male	255	6726.9	3.8 (3.4,4.3)
Female	97	2331.7	4.2 (3.4,5.1)
Race			
White	279	7385.0	3.8 (3.4,4.2)
Other/Unknown	73	1673.6	4.4 (3.5,5.5)
HIV exposure group			
MSM	146	3514.2	4.2 (3.5,4.9)
IDU	98	2404.8	4.1 (3.3,5.0)
Heterosexual	86	2379.9	3.6 (2.9,4.5)
Other/Unknown	22	759.7	2.9 (1.9,4.4)
Region of Europe[7]			
South and Argentina	61	2431.5	2.5 (2.0,3.2)
North	112	2042.2	5.5 (4.6,6.6)
West Central	155	3188.7	4.9 (4.2,5.7)
East Central	22	1225.3	1.8 (1.2,2.7)

	Discontinued due to unknown causes		
Level	**Events**	**PYFU***	**Incidence rate 100 PYFU [95% CI]**
East	2	170.9	1.2 (0.3,4.7)
Body mass index (BMI)			
<18	6	110.6	5.4 (2.4,12.1)
18 - 25	88	2097.6	4.2 (3.4,5.2)
>25	55	1699.8	3.2 (2.5,4.2)
Unknown	203	5150.6	3.9 (3.4,4.5)
Smoking status			
Current	138	3521.4	3.9 (3.3,4.6)
Former	46	1613.8	2.9 (2.1,3.8)
Never	121	3366.2	3.6 (3.0,4.3)
Unknown	47	557.2	8.4 (6.3,11.2)
Clinical history			
Prior AIDS[8]			
Yes	94	2492.7	3.8 (3.1,4.6)
No	258	6565.9	3.9 (3.5,4.4)
Prior non-AIDS[9]			
Yes	53	1435.6	3.7 (2.8,4.8)
No	299	7623.0	3.9 (3.5,4.4)
Diabetes[10]			
Yes	25	768.0	3.3 (2.2,4.8)
No	327	8290.6	3.9 (3.5,4.4)
Hypertension[11]			
Yes	207	6122.4	3.4 (3.0,3.9)
No	105	2538.8	4.1 (3.4,5.0)
Unknown	40	397.3	10.1 (7.4,13.7)
Anaemia[12]			
Severe anaemia/ mild anaemia	42	744.6	5.6 (4.2,7.6)
Normal	153	3366.6	4.5 (3.9,5.3)
Unknown	157	4947.4	3.2 (2.7,3.7)

	Discontinued due to unknown causes		
Level	**Events**	**PYFU***	**Incidence rate 100 PYFU [95% CI]**
Prior HCV diagnosis[13]			
Yes	147	3886.8	3.8 (3.2,4.4)
No	156	4434.1	3.5 (3.0,4.1)
Unknown	49	737.7	6.6 (5.0,8.8)
Prior HBV diagnosis[14]			
Yes	11	429.4	2.6 (1.4,4.6)
No	301	8166.3	3.7 (3.3,4.1)
Unknown	40	462.8	8.6 (6.3,11.8)
HIV viral load (copies/mL)[15]			
< 400	278	7112.9	3.9 (3.5,4.4)
≥ 400	18	179.7	10.0 (6.3,15.9)
Unknown	56	1766.0	3.2 (2.4,4.1)
Peak HIV viral load (copies/mL)[16]			
< 400	44	1152.5	3.8 (2.8,5.1)
≥ 400	304	7859.7	3.9 (3.5,4.3)
Unknown	4	46.3	8.6 (3.2,23.0)
CD4 count (cells/mm^3)[15]			
<200	15	277.3	5.4 (3.3,9.0)
200 - 349	22	663.4	3.3 (2.2,5.0)
350 - 499	35	1042.8	3.4 (2.4,4.7)
≥ 500	158	4119.9	3.8 (3.3,4.5)
Unknown	122	2955.2	4.1 (3.5,4.9)
CD4 count nadir(cells/mm^3)[17]			
<200	202	5325.6	3.8 (3.3,4.4)
200 - 349	100	2602.7	3.8 (3.2,4.7)
350 - 499	26	732.7	3.5 (2.4,5.2)
≥ 500	20	364.2	5.5 (3.5,8.5)
Unknown	4	33.5	11.9 (4.5,31.8)
eGFR (ml/min/1.73m^2)[18]			
<60	34	964.4	3.5 (2.5,4.9)
≥60	300	7992.5	3.8 (3.4,4.2)

	Discontinued due to unknown causes		
Level	**Events**	**PYFU***	**Incidence rate 100 PYFU [95% CI]**
Unknown	18	101.7	17.7 (11.2,28.1)
ALT (U/L)			
<40	176	4842.5	3.6 (3.1,4.2)
≥ 40	83	1777.0	4.7 (3.8,5.8)
Unknown	93	2439.1	3.8 (3.1,4.7)
AST (U/L)			
<40	158	4440.3	3.6 (3.0,4.2)
≥ 40	58	1114.2	5.2 (4.0,6.7)
Unknown	136	3504.2	3.9 (3.3,4.6)
Proportion of follow-up time in EuroSIDA with immunosuppression (defined as a CD4 count <200/cells mm3)[19]			
<20%	277	7361.4	3.8 (3.3,4.2)
≥ 20%	71	1663.7	4.3 (3.4,5.4)
Unknown	4	33.5	11.9 (4.5,31.8)
Proportion of follow-up time in EuroSIDA with uncontrolled viremia (HIV RNA VL > 400 copies/ml)[20]			
<20%	204	6003.3	3.4 (3.0,3.9)
≥ 20%	144	3008.9	4.8 (4.1,5.6)
Unknown	4	46.3	8.6 (3.2,23.0)
ARV history			
Treatment naïve at baseline			
Yes	11	385.7	2.9 (1.6,5.1)
No	341	8672.8	3.9 (3.5,4.4)
Integrase inhibitor naïve at baseline			
Yes	267	7183.7	3.7 (3.3,4.2)
No	85	1874.9	4.5 (3.7,5.6)
Current regimen includes PI			
Yes	175	4511.5	3.9 (3.3,4.5)
No	177	4547.1	3.9 (3.4,4.5)
Current regimen includes NNRTI			
Yes	102	2794.6	3.6 (3.0,4.4)

	Discontinued due to unknown causes		
Level	**Events**	**PYFU***	**Incidence rate 100 PYFU [95% CI]**
No	250	6264.0	4.0 (3.5,4.5)
Current regimen includes NRTI			
Yes	342	8555.1	4.0 (3.6,4.4)
No	10	503.5	2.0 (1.1,3.7)
Prior exposure to PI			
Yes	286	7266.9	3.9 (3.5,4.4)
No	66	1791.7	3.7 (2.9,4.7)
Prior exposure to NNRTI			
Yes	237	5918.6	4.0 (3.5,4.5)
No	115	3140.0	3.7 (3.1,4.4)
Prior exposure to NRTI			
Yes	352	9040.6	3.9 (3.5,4.3)
No	0	18.0	0.0 (0.0,0.0)
Prior exposure to DTG			
Yes	1	7.2	13.8 (1.9,97.9)
No	351	9051.3	3.9 (3.5,4.3)
Prior exposure to EVG			
Yes	9	34.6	26.0 (13.5,50.0)
No	343	9024.0	3.8 (3.4,4.2)
Prior exposure to RAL			
Yes	79	1845.6	4.3 (3.4,5.3)
No	273	7213.0	3.8 (3.4,4.3)
Number of ARVs previously exposed to			
1 - lowest quintile	79	2164.7	3.6 (2.9,4.5)
2	63	2008.5	3.1 (2.5,4.0)
3	59	1546.2	3.8 (3.0,4.9)
4	80	1769.1	4.5 (3.6,5.6)
5 - highest quintile	71	1570.1	4.5 (3.6,5.7)
Years since first use of any ARV (years)[21]			
1 - lowest quintile	80	1843.7	4.3 (3.5,5.4)
2	73	1807.8	4.0 (3.2,5.1)

	Discontinued due to unknown causes		
Level	**Events**	**PYFU***	**Incidence rate 100 PYFU [95% CI]**
3	83	1847.1	4.5 (3.6,5.6)
4	61	1790.7	3.4 (2.7,4.4)
5 - highest quintile	55	1769.2	3.1 (2.4,4.0)

[1] Although 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, this table shows result for the first INSTI exposure only.
[2] DTG with ABC
[3] DTG without ABC
[4] EVG/RAL with ABC
[5] EVG/RAL without ABC
[6] DTG mono- and 2-drug therapy
[7] Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; West Central: Austria, Belgium, France, Germany, Luxembourg, Switzerland; North: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovenia; East: Belarus, Estonia, Georgia, Latvia, Lithuania, Russia, Ukraine
[8] Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition(4)
[9] Non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, NADM(5)
[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: Haemoglobin <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 viremia 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

* This refers to the time spent on the **first** integrase inhibitor regimen after 16 January 2014

Table S16: Adjusted incidence rate ratios[1] of discontinuation due to unknown 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 episode only.

NOTE: Variables included in this model were consistent with those in table 24 (variables had to have 5 or more events within each category to be included in the model in table 24).

Levels of variables with <5 people receiving each drug were combined if this seemed appropriate (Here i.e. the regions East and East Central were combined).

The following variables were excluded: Prior HBV diagnosis, current HIV viral load, peak HIV viral load, CD4 nadir, proportion of follow-up time in EuroSIDA with uncontrolled viremia, proportion of follow-up time in EuroSIDA with immunosuppression, treatment naïve at baseline, current regimen includes NRTI, prior exposure to NRTI, prior exposure to DTG, prior exposure to EVG.

The following variables were not considered due to collinearity with other variables: nadir CD4, current regimen includes PI, current regimen includes NNRTI prior exposure to RAL, years since first use of any ARV.

	Discontinued due to unknown causes			
Variable	**Unadjusted IRR**	**P**	**Adjusted IRR[2]**	**P**
Integrase inhibitor Regimen				
A[3] and B[4]	reference		reference	
C[5] and D[6]	1.72 (1.38,2.14)	<.001	1.98 (1.58,2.49)	<.001
E[7]	0.56 (0.32,0.98)	0.042	0.61 (0.35,1.07)	0.087
Demographic				
	.	.	.	
Age (years)				
≤ 35 years	0.55 (0.30,1.04)	0.064	0.48 (0.25,0.93)	0.030
36 - 40 years	reference		reference	
41 - 50 years	0.51 (0.34,0.75)	<.001	0.48 (0.32,0.71)	<.001
51 + years	0.68 (0.48,0.97)	0.032	0.71 (0.49,1.04)	0.082
Gender				
Male	reference			
Female	1.10 (0.86,1.40)	0.449		
Race				
White	reference			

	Discontinued due to unknown causes			
Variable	**Unadjusted IRR**	**P**	**Adjusted IRR[2]**	**P**
Other/Unknown	1.15 (0.89,1.50)	0.287		
HIV exposure group				
MSM	reference			
IDU	0.98 (0.75,1.28)	0.885		
Heterosexual	0.87 (0.66,1.14)	0.316		
Other/Unknown	0.70 (0.44,1.10)	0.125		
Region of Europe[8]				
South and Argentina	0.52 (0.38,0.70)	<.001	0.38 (0.28,0.52)	<.001
North	1.13 (0.88,1.45)	0.348	1.26 (0.93,1.71)	0.138
West Central	reference		reference	
East Central and East	0.35 (0.23,0.55)	<.001	0.30 (0.19,0.47)	<.001
Body mass index (BMI)				
<18	1.29 (0.56,2.98)	0.546		
18 - 25	reference			
>25	0.77 (0.55,1.08)	0.134		
Unknown	0.94 (0.73,1.21)	0.629		
Smoking status				
Current	1.09 (0.85,1.40)	0.497	1.12 (0.86,1.45)	0.419
Former	0.79 (0.56,1.12)	0.187	0.88 (0.62,1.25)	0.470
Never	reference		reference	
Unknown	2.35 (1.66,3.32)	<.001	1.07 (0.69,1.66)	0.751
Clinical history				
	.	.	.	
Prior AIDS[9]				
Yes	0.96 (0.75,1.22)	0.739		
No	reference			
Prior non-AIDS[10]				
Yes	0.94 (0.70,1.27)	0.692		
No	reference			
Diabetes[11]				
Yes	0.83 (0.54,1.25)	0.368		
No	reference			

	Discontinued due to unknown causes			
Variable	**Unadjusted IRR**	**P**	**Adjusted IRR[2]**	**P**
Hypertension[12]				
Yes	0.82 (0.64,1.04)	0.099	0.69 (0.53,0.89)	0.004
No	reference		reference	
Unknown	2.43 (1.67,3.55)	<.001	2.03 (1.28,3.22)	0.003
Anaemia[13]				
Severe anaemia/ mild anaemia	1.24 (0.88,1.76)	0.223	1.21 (0.85,1.72)	0.286
Normal	reference		reference	
Unknown	0.70 (0.56,0.87)	0.002	0.56 (0.42,0.75)	<.001
Prior HCV diagnosis[14]				
Yes	1.07 (0.85,1.35)	0.539	0.78 (0.61,1.01)	0.062
No	reference		reference	
Unknown	1.89 (1.36,2.63)	<.001	1.42 (1.00,2.03)	0.051
HIV viral load (copies/mL)[15]				
< 400	0.39 (0.24,0.63)	<.001	0.40 (0.23,0.67)	<.001
³ 400	reference		reference	
Unknown	0.32 (0.19,0.54)	<.001	0.31 (0.17,0.56)	<.001
CD4 count (cells/mm³)[15]				
<200	1.41 (0.82,2.41)	0.209		
200 - 349	0.86 (0.55,1.36)	0.528		
350 - 499	0.88 (0.61,1.27)	0.479		
≥ 500	reference			
Unknown	1.08 (0.85,1.36)	0.541		
eGFR (ml/min/1.73m²) [16]				
<60	0.94 (0.65,1.35)	0.734	0.94 (0.65,1.37)	0.752
≥ 60	reference		reference	
Unknown	4.72 (2.91,7.65)	<.001	2.77 (1.38,5.56)	0.004
ALT (U/L)				
<40	0.78 (0.60,1.01)	0.062	0.79 (0.58,1.09)	0.158
≥ 40	reference		reference	
Unknown	0.82 (0.61,1.10)	0.181	1.29 (0.82,2.02)	0.276

	Discontinued due to unknown causes			
Variable	**Unadjusted IRR**	**P**	**Adjusted IRR[2]**	**P**
AST (U/L)				
<40	0.68 (0.50,0.93)	0.014	0.85 (0.59,1.24)	0.402
≥ 40	reference		reference	
Unknown	0.75 (0.55,1.02)	0.063	0.78 (0.51,1.20)	0.263
Integrase inhibitor naïve at baseline				
Yes	0.82 (0.64,1.05)	0.121		
No	reference			
Prior exposure to PI				
Yes	1.07 (0.81,1.41)	0.636		
No	reference			
Prior exposure to NNRTI				
Yes	1.09 (0.87,1.37)	0.442		
No	reference			
Number of ARVs previously exposed to				
1 - lowest quintile	reference			
2	0.86 (0.61,1.21)	0.381		
3	1.05 (0.74,1.48)	0.799		
4	1.24 (0.90,1.70)	0.187		
5 - highest quintile	1.24 (0.89,1.72)	0.202		

[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 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, region of Europe, smoking status, hypertension, prior HCV, eGFR, prior exposure to NNRTI and number of ARVs previously exposed to.
[3] DTG with ABC
[4] DTG without ABC
[5] EVG/RAL with ABC
[6] EVG/RAL without ABC
[7] Mono- or 2-drug therapy with DTG
[8] Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; West Central: Austria, Belgium, France, Germany, Luxembourg, Switzerland; North: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovenia; East: Belarus, Estonia, Georgia, Latvia, Lithuania, Russia, Ukraine

[9] Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition(4)
[10] Non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, NADM(5)
[11] Prior diabetes defined as: Prior diagnosis of diabetes mellitus, or taking oral antidiabetic agents or insulin
[12] Hypertension defined as: SBP >= 140 mmHg, DBP >= 90 mmHg or taking angiotensin-converting enzyme inhibitors/antihypertensive agents
[13] Severe/mild anaemia defined as: Haemoglobin < 14 and <12 in males and females respectively
[14] Prior Hepatitis C Virus (HCV) defined as: Prior HCV antibody test Positive (Yes), Negative (No) or no test or inconclusive (Unknown).
[15] Within 6 months prior to date
[16] Estimated glomerular filtration rate (eGFR) calculated using: CKD-EPI

10.8 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.

There were no other adverse events identified.

11 DISCUSSION

11.1 Interpretations of Results

This is the final report from a five year-long prospective cohort study concerning a category 3 post-authorisation safety non-interventional study. The study aimed to monitor hypersensitivity reactions, hepatotoxicity and severe skin rash among all patients discontinuing treatment with DTG or other integrase inhibitor (RAL or EVG).

The study collected almost 10,000 person-years of follow-up (PYFU) of INSTI use in the EuroSIDA cohort. Use of INSTIs increased in recent years.

Of the almost 10,000 PYFU of INSTI use, approximately 65% were with DTG-containing regimens, and 35% with other INSTIs (RAL or EVG). The total follow-up times on DTG were similar for regimens that contained ABC (treatment group A, which accumulated 3100 PYFU) and regimens without ABC (groups B and E together, accounting for 3369 PYFU); other integrase inhibitors (RAL and EVG) were mainly used without ABC (group D, 3037 PYFU).

We recorded 1336 discontinuations of DTG or other integrase inhibitors in 4819 persons, with a rate of discontinuation of 13.3 (95% CI 12.6, 14.1) discontinuations/100 PYFU overall. Rates of discontinuation were lower for DTG (11.2, 95% CI 10.4, 12.0 discontinuations/100 PYFU for groups A, B and E combined) than for other integrase inhibitors (RAL and EVG, 17.3, 95% CI 16.0, 18.8 discontinuations/100 PYFU for groups C and D, see the **SUMMARY TABLE, Table 15**). For individuals on DTG, the discontinuation rate was higher in those on 3-drug regimens (group A and B combined 11.5, CI 10.7, 12.5/100 PYFU) than for users of DTG in monotherapy or 2-drug regimens (Group E, 8.7, CI 6.9, 10.9/100 PYFU). This is also apparent in the Kaplan-Meier plot showing the probability of discontinuation of INSTIs for Groups A to E (**Figure 2A**).

During the 5-year observation period, the rate of reporting of events of HSR, hepatotoxicity and severe skin reactions was low, in keeping with estimates from clinical trials that suggested HSRs for DTG were seen in <1% of patients treated (see e.g. Curtis et al. 2014 (7)). In the present study we noted 5 cases of HSR, of which two were among individuals taking DTG (one with ABC, group A, and one without ABC in Group B),

and three in individuals on other integrase inhibitors (without ABC, in group D: one individual on RAL and two individuals who were taking EVG).

Characteristics of the five individuals with HSR and the case of hepatotoxicity are shown in **Tables 8 – 10**. Individuals who experienced HSR were older (4/5 or 80% were >50 years old), 60% were men and 80% of white ethnicity. Of the HSR cases, 40% were in South Europe and Argentina, 40% in North Europe and one in West Central Europe, while the hepatotoxicity event occurred in a woman in East Europe (**Table 8**). Of the individuals with HSR, 40% had a prior AIDS-defining condition, 40% experienced a prior non-AIDS clinical event, 60% were co-infected with HCV and one individual (20%) with HBV (**Table 9**). All individuals had a CD4 cell count nadir <350 cells/µl, including 3 individuals (60%) with CD4 nadir <200 cells/µl; 60% of the individuals with HSR spent ≥20% of FU time with immunosuppression (<200 cells/µl) and 60% spent ≥20% of FU time with uncontrolled viremia (HIV RNA VL > 400 copies/ml). All individuals who experienced HSR had previously taken ARVs (**Table 10**). Three individuals had a prior exposure to INSTIs (two individuals had previously been exposed to RAL, and one had a previous exposure to DTG), and two individuals (40%) were INSTI naïve. All individuals had previously taken NRTIs or NNRTIs, and 80% had previously been exposed to Protease inhibitors. Individuals with HSR had been exposed to more ARV drugs than those in the cohort overall (median 11 ARVs previously exposed to, IQR 8, 14) and had been taking ARVs for longer (median 20.9 years (IQR 13.8, 22.5 years)). The HSR events occurred a median of 43 days (range 7 to 216 days) after starting the INSTI-containing treatment regimen (see **Table 11**).

The incidence of HSR and hepatotoxicity was low, precluding detailed analyses; per protocol, detailed analyses were planned where the number of events exceeded 30. Nevertheless we can estimate the rate of HSRs overall (0.05; 95% CI 0.02, 0.12 events/100 PYFU; equivalent to 1 case per 2000 years of INSTI exposure) and the upper 95% confidence intervals for HSR among individuals on DTG (0.11/100 PYFU for groups A, B and E combined, or 0.13/100 PYFU for groups A and B only) or using other integrase inhibitors (0.25 events/100 PYFU overall for groups C and D combined). The estimated upper 95% CI for hepatotoxicity was 0.06 events/100 PYFU. There were no cases of severe skin rash during 10,000 PYFU, giving an estimated upper 95% CI for this outcome of 0.04 events/100 PYFU.

We also noted altogether 918 discontinuations of INSTIs due to other causes (i.e. not HSR, hepatotoxicity or unknown reasons) reported on the case review forms (CRFs), accounting for 68.7% of the 1336 discontinuations, or 16.4% of all 5608 INSTI use episodes. The rate of discontinuations due to other causes was highest in group C and D (other INSTIs, 11.5, CI 10.4, 12.6 events/100 PFU), followed by group A and B combined (DTG-containing regimens, 8.1, CI 7.4, 8.9/100 PYFU) and was lowest in Group E (DTG in a monotherapy or 2-drug regimen, 6.7, CI 5.1, 8.7/100 PYFU). Accordingly, the adjusted IRR (aIRR) for discontinuation due to other causes was almost 50% higher for Group C and D compared to group A and B combined (aIRR 1.49, 95% CI 1.30, 1.72, P < 0.001, **Table 22**). Discontinuations due to other causes were lower in South and East Central Europe compared to West Central Europe (aIRR for South 0.71 (0.59, 0.85), and for East Central Europe 0.61 (0.48, 0.78), P <0.001 for both). Discontinuations due to other causes were also significantly lower in individuals with controlled HIV viral load

(<400 copies/ml, aIRR 0.37 (0.27, 0.50), P <0.001), higher in persons with <200 CD4 T cells/µl (aIRR 1.48 (1.06, 2.08), P = 0.022) and lower in those who were INSTI-naïve at baseline (aIRR 0.75 (0.64, 0.87), P <0.001).

11.2 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 may 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 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 was not adequately powered to compare antiretroviral naïve to experience within treatment groups A-E described above.

It was important to capture all discontinuations due to HSR, hepatotoxicity and serious skin rash. To this end, an independent adjudication committee was established at the start of the study to review and validate potential discontinuations due adverse events and to ensure minimization of misclassification. This process was performed for all discontinuations of integrase inhibitors due to hypersensitivity, hepatotoxicity, and severe skin rash, and for individuals where the ART stopping reason was reported as “other causes” or “unknown”, as described in section 8.3.2.4 “Verification and adjudication of discontinuations to ensure accurate identification of hypersensitivity, hepatotoxicity and severe skin rash”. In addition, as part of quality assurance for this study report all EuroSIDA data on INSTI discontinuations were thoroughly checked and further queries were raised with the sites to ensure coding for discontinuation reason was updated. Furthermore, this study report contains detailed information on those who discontinued for “other causes” or “unknown” reasons in Tables 8-10 for all INSTI episodes to allow comparisons to be made; similar listings for first INSTI episode are shown in APPENDIX tables 8-10.

Because the study focuses on discontinuations of integrase inhibitors, there was a concern that the protocol may only capture the most severe cases and may not include milder or more transient cases of drug induced liver injury (DILI) which would not lead to discontinuation. To estimate the frequency of hepatotoxicity that may not lead to INSTI discontinuation liver function was assessed as the incidence of cases of combined alanine aminotransferase (ALT) and total bilirubin liver chemistry test (see **SUPPLEMENTARY TABLE 2**). Liver function test data were available for 4300 of the 4819 individuals in the

study and overall combined ALT and bilirubin elevations were found in 3.3% of those tested.

12 CONCLUSIONS

The frequency of discontinuation due to HSR, hepatotoxicity and severe skin rash in users of integrase inhibitors was low, 0.1%, 0.02% and 0.0%, respectively, despite an increasing number of persons exposed to cART containing DTG (n=2711) or RAL or EVG (n=1655). Exposure to DTG as mono- or dual therapy was limited (n=453), therefore power in this group was limited and the data should be interpreted with caution.

13 REFERENCES

1. Laut K, Kirk O, Rockstroh J, Phillips A, Ledergerber B, Gatell J, et al. The EuroSIDA study: 25 years of scientific achievements. HIV Med. 2019.
2. European Association for the Study of the Liver. Electronic address eee, Clinical Practice Guideline Panel C, Panel m, representative EGB. EASL Clinical Practice Guidelines: Drug-induced liver injury. J Hepatol. 2019;70(6):1222-61.
3. Bannister WP, Friis-Moller N, Mocroft A, Viard JP, van Lunzen J, Kirk O, et al. Incidence of abacavir hypersensitivity reactions in euroSIDA. Antivir Ther. 2008;13(5):687-96.
4. Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep. 1992;41(RR-17):1-19.
5. Mocroft A, Reiss P, Gasiorowski J, Ledergerber B, Kowalska J, Chiesi A, et al. Serious Fatal and Nonfatal Non-AIDS-Defining Illnesses in Europe. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2010;55(2):262-70.
6. Johnson VA, Calvez V, Gunthard HF, Paredes R, Pillay D, Shafer RW, et al. Update of the drug resistance mutations in HIV-1: March 2013. Top Antivir Med. 2013;21(1):6-14.
7. Curtis L, Nichols G, Stainsby C, Lim J, Aylott A, Wynne B, et al. Dolutegravir: clinical and laboratory safety in integrase inhibitor-naive patients. HIV Clin Trials. 2014;15(5):199-208.

14 APPENDICES

Appendix 1, showing characteristics of individuals at the time of the FIRST INSTI discontinuation

APPENDIX Tables 8 – 10 show the characteristics of participants at the time of discontinuation of their **first** INSTI regimen for comparison with the tables in the previous interim reports. Note that one HSR event in Group D, which occurred in the individual's second INSTI episode, is therefore not included.

APPENDIX Table 8: Demographic characteristics at time of first discontinuation[1] of new users[2] of DTG, RAL, and EVG.

			Discontinued					
	Overall	**Did not discontinue**	**Total**	**HSR**	**Hepatotoxicity**	**Severe skin rash (Not HSR)**	**Other**	**Unknown**
All								
	4,819 (100.0)	3,718 (100.0)	1,101 (100.0)	4 (100.0)	1 (100.0)	0 (0.0)	744 (100.0)	352 (100.0)
Integrase inhibitor Regimen[3]								
A[4]	1,545 (32.1)	1,254 (33.7)	291 (26.4)	1 (25.0)	1 (100.0)	0 (0.0)	191 (25.7)	98 (27.8)
B[5]	1,166 (24.2)	911 (24.5)	255 (23.2)	1 (25.0)	0 (0.0)	0 (0.0)	184 (24.7)	70 (19.9)
C[6]	239 (5.0)	161 (4.3)	78 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	51 (6.9)	27 (7.7)
D[7]	1,416 (29.4)	1,004 (27.0)	412 (37.4)	2 (50.0)	0 (0.0)	0 (0.0)	267 (35.9)	143 (40.6)
E[8]	453 (9.4)	388 (10.4)	65 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	51 (6.9)	14 (4.0)
Age (years)								
≤ 35 years	197 (4.1)	145 (3.9)	52 (4.7)	0 (0.0)	0 (0.0)	0 (0.0)	38 (5.1)	14 (4.0)
36 - 40 years	303 (6.3)	216 (5.8)	87 (7.9)	0 (0.0)	0 (0.0)	0 (0.0)	49 (6.6)	38 (10.8)
41 - 50 years	1,254 (26.0)	980 (26.4)	274 (24.9)	1 (25.0)	0 (0.0)	0 (0.0)	195 (26.2)	78 (22.2)
51 + years	3,065 (63.6)	2,377 (63.9)	688 (62.5)	3 (75.0)	1 (100.0)	0 (0.0)	462 (62.1)	222 (63.1)
Gender								
Male	3,555 (73.8)	2,751 (74.0)	804 (73.0)	2 (50.0)	0 (0.0)	0 (0.0)	547 (73.5)	255 (72.4)
Female	1,264 (26.2)	967 (26.0)	297 (27.0)	2 (50.0)	1 (100.0)	0 (0.0)	197 (26.5)	97 (27.6)
Race								
White	3,959 (82.2)	3,076 (82.7)	883 (80.2)	3 (75.0)	1 (100.0)	0 (0.0)	600 (80.6)	279 (79.3)
Other or Missing	860 (17.8)	642 (17.3)	218 (19.8)	1 (25.0)	0 (0.0)	0 (0.0)	144 (19.4)	73 (20.7)

			Discontinued					
	Overall	**Did not discontinue**	**Total**	**HSR**	**Hepatotoxicity**	**Severe skin rash (Not HSR)**	**Other**	**Unknown**
HIV exposure group								
MSM	1,818 (37.7)	1,378 (37.1)	440 (40.0)	2 (50.0)	0 (0.0)	0 (0.0)	292 (39.2)	146 (41.5)
IDU	1,337 (27.7)	1,019 (27.4)	318 (28.9)	0 (0.0)	0 (0.0)	0 (0.0)	220 (29.6)	98 (27.8)
Heterosexual	1,274 (26.4)	1,014 (27.3)	260 (23.6)	1 (25.0)	1 (100.0)	0 (0.0)	172 (23.1)	86 (24.4)
Other/Missing	390 (8.1)	307 (8.3)	83 (7.5)	1 (25.0)	0 (0.0)	0 (0.0)	60 (8.1)	22 (6.3)
Region of Europe[9]								
South and Argentina	1,267 (26.3)	1,026 (27.6)	241 (21.9)	1 (25.0)	0 (0.0)	0 (0.0)	179 (24.1)	61 (17.3)
North	1,070 (22.2)	790 (21.2)	280 (25.4)	2 (50.0)	0 (0.0)	0 (0.0)	166 (22.3)	112 (31.8)
West Central	1,620 (33.6)	1,171 (31.5)	449 (40.8)	1 (25.0)	0 (0.0)	0 (0.0)	293 (39.4)	155 (44.0)
East Central	686 (14.2)	580 (15.6)	106 (9.6)	0 (0.0)	0 (0.0)	0 (0.0)	84 (11.3)	22 (6.3)
East	176 (3.7)	151 (4.1)	25 (2.3)	0 (0.0)	1 (100.0)	0 (0.0)	22 (3.0)	2 (0.6)
Body mass index (BMI)								
<18	67 (1.4)	50 (1.3)	17 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	11 (1.5)	6 (1.7)
18 - 25	1,185 (24.6)	921 (24.8)	264 (24.0)	1 (25.0)	0 (0.0)	0 (0.0)	172 (23.1)	91 (25.9)
>25	993 (20.6)	823 (22.1)	170 (15.4)	2 (50.0)	1 (100.0)	0 (0.0)	110 (14.8)	57 (16.2)
unknown	2,574 (53.4)	1,924 (51.7)	650 (59.0)	1 (25.0)	0 (0.0)	0 (0.0)	451 (60.6)	198 (56.3)
Smoking status								
Current	1,991 (41.3)	1,550 (41.7)	441 (40.1)	2 (50.0)	0 (0.0)	0 (0.0)	303 (40.7)	136 (38.6)
Former	810 (16.8)	642 (17.3)	168 (15.3)	0 (0.0)	0 (0.0)	0 (0.0)	120 (16.1)	48 (13.6)
Never	1,842 (38.2)	1,437 (38.6)	405 (36.8)	1 (25.0)	1 (100.0)	0 (0.0)	280 (37.6)	123 (34.9)
Unknown	176 (3.7)	89 (2.4)	87 (7.9)	1 (25.0)	0 (0.0)	0 (0.0)	41 (5.5)	45 (12.8)

			Discontinued					
	Overall	**Did not discontinue**	**Total**	**HSR**	**Hepatotoxicity**	**Severe skin rash (Not HSR)**	**Other**	**Unknown**
Date of baseline[10]								
Median date (IQR)	DEC15 (FEB15,FEB17)	FEB16 (APR15,APR17)	JUN15 (OCT14,APR16)	JUN15 (SEP14,OCT16)	DEC16 (DEC16,DEC16)		OCT15 (FEB15,AUG16)	NOV14 (MAY14,MAY15)

[1] Date of discontinuation in those who stopped DTG, RAL or EVG, or last clinic visit in those who did not
[2] After the 16 Jan 2014
[3] Note that switching between DTG regimens A, B and E, or between EVG/RAL regimens C and D, was allowed within an episode. The integrase inhibitor treatment group here is reported according as at the start of the episode.
[4] DTG with AB
[5] DTG without ABC
[6] EVG/RAL with ABC
[7] EVG/RAL without ABC
[8] DTG mono- and 2-drug therapy

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

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

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

			Discontinued					
	Overall	**Did not discontinue**	**Total**	**HSR**	**Hepatotoxicity**	**Severe skin rash (Not HSR)**	**Other**	**Unknown**
All								
	4,819 (100)	3,718 (100)	1,101 (100)	4 (100)	1 (100)	0 (0.0)	744 (100)	352 (100)
Prior AIDS[3]								
Yes	1,335 (27.7)	1,032 (27.8)	303 (27.5)	2 (50.0)	1 (100)	0 (0.0)	206 (27.7)	94 (26.7)
No	3,484 (72.3)	2,686 (72.2)	798 (72.5)	2 (50.0)	0 (0.0)	0 (0.0)	538 (72.3)	258 (73.3)
Prior non-AIDS[4]								
Yes	825 (17.1)	650 (17.5)	175 (15.9)	1 (25.0)	0 (0.0)	0 (0.0)	120 (16.1)	54 (15.3)
No	3,994 (82.9)	3,068 (82.5)	926 (84.1)	3 (75.0)	1 (100)	0 (0.0)	624 (83.9)	298 (84.7)
Diabetes[5]								
Yes	410 (8.5)	325 (8.7)	85 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	59 (7.9)	26 (7.4)
No	4,409 (91.5)	3,393 (91.3)	1,016 (92.3)	4 (100)	1 (100)	0 (0.0)	685 (92.1)	326 (92.6)
Hypertension[6]								
Yes	3,395 (70.5)	2,664 (71.7)	731 (66.4)	3 (75.0)	1 (100)	0 (0.0)	518 (69.6)	209 (59.4)
No	1,294 (26.9)	986 (26.5)	308 (28.0)	1 (25.0)	0 (0.0)	0 (0.0)	201 (27.0)	106 (30.1)
Unknown	130 (2.7)	68 (1.8)	62 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	25 (3.4)	37 (10.5)
Anaemia[7]								
Severe anaemia/ mild anaemia	511 (10.6)	384 (10.3)	127 (11.5)	0 (0.0)	0 (0.0)	0 (0.0)	81 (10.9)	46 (13.1)
Normal	1,964 (40.8)	1,474 (39.6)	490 (44.5)	1 (25.0)	0 (0.0)	0 (0.0)	331 (44.5)	158 (44.9)

			Discontinued					
	Overall	Did not discontinue	Total	HSR	Hepatotoxicity	Severe skin rash (Not HSR)	Other	Unknown
Unknown	2,344 (48.6)	1,860 (50.0)	484 (44.0)	3 (75.0)	1 (100)	0 (0.0)	332 (44.6)	148 (42.0)
Prior HCV diagnosis[8]								
Yes	2,097 (43.5)	1,597 (43.0)	500 (45.4)	3 (75.0)	0 (0.0)	0 (0.0)	348 (46.8)	149 (42.3)
No	2,341 (48.6)	1,848 (49.7)	493 (44.8)	1 (25.0)	1 (100)	0 (0.0)	335 (45.0)	156 (44.3)
Unknown	381 (7.9)	273 (7.3)	108 (9.8)	0 (0.0)	0 (0.0)	0 (0.0)	61 (8.2)	47 (13.4)
Prior HBV diagnosis[9]								
Yes	240 (5.0)	184 (4.9)	56 (5.1)	1 (25.0)	0 (0.0)	0 (0.0)	44 (5.9)	11 (3.1)
No	4,369 (90.7)	3,385 (91.0)	984 (89.4)	3 (75.0)	1 (100)	0 (0.0)	676 (90.9)	304 (86.4)
Unknown	210 (4.4)	149 (4.0)	61 (5.5)	0 (0.0)	0 (0.0)	0 (0.0)	24 (3.2)	37 (10.5)
HIV viral load (copies/mL)[10]								
< 400	4,024 (83.5)	3,180 (85.5)	844 (76.7)	2 (50.0)	1 (100)	0 (0.0)	550 (73.9)	291 (82.7)
≥ 400	128 (2.7)	65 (1.7)	63 (5.7)	0 (0.0)	0 (0.0)	0 (0.0)	46 (6.2)	17 (4.8)
Unknown	667 (13.8)	473 (12.7)	194 (17.6)	2 (50.0)	0 (0.0)	0 (0.0)	148 (19.9)	44 (12.5)
Peak HIV viral load (copies/mL)[11]								
< 400	612 (12.7)	461 (12.4)	151 (13.7)	0 (0.0)	0 (0.0)	0 (0.0)	107 (14.4)	44 (12.5)
≥ 400	4,200 (87.2)	3,257 (87.6)	943 (85.6)	4 (100)	1 (100)	0 (0.0)	634 (85.2)	304 (86.4)
Unknown	7 (0.1)	0 (0.0)	7 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.4)	4 (1.1)
CD4 count (cells/mm³)[10]								
<200	181 (3.8)	134 (3.6)	47 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	33 (4.4)	14 (4.0)
200 - 349	359 (7.4)	272 (7.3)	87 (7.9)	1 (25.0)	0 (0.0)	0 (0.0)	64 (8.6)	22 (6.3)
350 - 499	617 (12.8)	495 (13.3)	122 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	83 (11.2)	39 (11.1)
≥ 500	2,556 (53.0)	2,055 (55.3)	501 (45.5)	0 (0.0)	1 (100)	0 (0.0)	337 (45.3)	163 (46.3)

			Discontinued					
	Overall	Did not discontinue	Total	HSR	Hepatotoxicity	Severe skin rash (Not HSR)	Other	Unknown
Unknown	1,106 (23.0)	762 (20.5)	344 (31.2)	3 (75.0)	0 (0.0)	0 (0.0)	227 (30.5)	114 (32.4)
CD4 count nadir(cells/mm³) [12]								
<200	2,839 (58.9)	2,190 (58.9)	649 (58.9)	3 (75.0)	1 (100)	0 (0.0)	443 (59.5)	202 (57.4)
200 - 349	1,376 (28.6)	1,074 (28.9)	302 (27.4)	1 (25.0)	0 (0.0)	0 (0.0)	201 (27.0)	100 (28.4)
350 - 499	388 (8.1)	297 (8.0)	91 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	65 (8.7)	26 (7.4)
≥ 500	193 (4.0)	142 (3.8)	51 (4.6)	0 (0.0)	0 (0.0)	0 (0.0)	31 (4.2)	20 (5.7)
Unknown	23 (0.5)	15 (0.4)	8 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.5)	4 (1.1)
eGFR (ml/min/1.73m²) [13]								
<60	592 (12.3)	467 (12.6)	125 (11.4)	0 (0.0)	0 (0.0)	0 (0.0)	89 (12.0)	36 (10.2)
≥ 60	4,205 (87.3)	3,247 (87.3)	958 (87.0)	3 (75.0)	1 (100)	0 (0.0)	653 (87.8)	301 (85.5)
Unknown	22 (0.5)	4 (0.1)	18 (1.6)	1 (25.0)	0 (0.0)	0 (0.0)	2 (0.3)	15 (4.3)
ALT (U/L)								
<40	3,211 (66.6)	2,598 (69.9)	613 (55.7)	1 (25.0)	0 (0.0)	0 (0.0)	425 (57.1)	187 (53.1)
≥ 40	941 (19.5)	733 (19.7)	208 (18.9)	0 (0.0)	0 (0.0)	0 (0.0)	119 (16.0)	89 (25.3)
Unknown	667 (13.8)	387 (10.4)	280 (25.4)	3 (75.0)	1 (100)	0 (0.0)	200 (26.9)	76 (21.6)
AST (U/L)								
<40	2,880 (59.8)	2,361 (63.5)	519 (47.1)	1 (25.0)	0 (0.0)	0 (0.0)	354 (47.6)	164 (46.6)
≥ 40	602 (12.5)	458 (12.3)	144 (13.1)	0 (0.0)	0 (0.0)	0 (0.0)	78 (10.5)	66 (18.8)
Unknown	1,337 (27.7)	899 (24.2)	438 (39.8)	3 (75.0)	1 (100)	0 (0.0)	312 (41.9)	122 (34.7)
Proportion of follow-up time in EuroSIDA with immunosuppression (defined as a CD4 count <200/cells mm3)[14]								
<20%	3,994 (82.9)	3,099 (83.4)	895 (81.3)	1 (25.0)	1 (100)	0 (0.0)	616 (82.8)	277 (78.7)
≥ 20%	802 (16.6)	604 (16.2)	198 (18.0)	3 (75.0)	0 (0.0)	0 (0.0)	124 (16.7)	71 (20.2)

			Discontinued					
	Overall	**Did not discontinue**	**Total**	**HSR**	**Hepatotoxicity**	**Severe skin rash (Not HSR)**	**Other**	**Unknown**
Unknown	23 (0.5)	15 (0.4)	8 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.5)	4 (1.1)
Proportion of follow-up time in EuroSIDA with uncontrolled viremia (HIV RNA VL > 400 copies/ml)[15]								
<20%	3,313 (68.7)	2,612 (70.3)	701 (63.7)	2 (50.0)	1 (100)	0 (0.0)	494 (66.4)	204 (58.0)
≥ 20%	1,499 (31.1)	1,106 (29.7)	393 (35.7)	2 (50.0)	0 (0.0)	0 (0.0)	247 (33.2)	144 (40.9)
Unknown	7 (0.1)	0 (0.0)	7 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.4)	4 (1.1)

[1] Date of first discontinuation in those who stopped DTG, RAL or EVG, 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(4)
[4] Non-AIDS defining events include cardiovascular, end-stage renal disease, liver failure and pancreatitis, NADM(5)
[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: Haemoglobin < 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 viremia 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

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

			Discontinued					
	Overall	**Did not discontinue**	**Total**	**HSR**	**Hepatotoxicity**	**Severe skin rash (Not HSR)**	**Other**	**Unknown**
All								
	4,819 (100)	3,718 (100)	1,101 (100)	4 (100)	1 (100)	0 (0.0)	744 (100)	352 (100)
Treatment naïve at baseline[3]								
Yes	168 (3.5)	130 (3.5)	38 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)	27 (3.6)	11 (3.1)
Integrase inhibitor naïve at baseline[3]								
Yes	3,851 (79.9)	2,993 (80.5)	858 (77.9)	2 (50.0)	1 (100)	0 (0.0)	588 (79.0)	267 (75.9)
Current regimen includes PI								
Yes	2,159 (44.8)	1,776 (47.8)	383 (34.8)	1 (25.0)	0 (0.0)	0 (0.0)	244 (32.8)	138 (39.2)
Current regimen includes NNRTI								
Yes	1,415 (29.4)	1,147 (30.8)	268 (24.3)	0 (0.0)	0 (0.0)	0 (0.0)	185 (24.9)	83 (23.6)
Current regimen includes NRTI								
Yes	4,231 (87.8)	3,489 (93.8)	742 (67.4)	2 (50.0)	0 (0.0)	0 (0.0)	493 (66.3)	247 (70.2)
Prior exposure to PI								
Yes	3,860 (80.1)	2,980 (80.2)	880 (79.9)	3 (75.0)	0 (0.0)	0 (0.0)	591 (79.4)	286 (81.3)
Prior exposure to NNRTI								
Yes	3,236 (67.2)	2,478 (66.6)	758 (68.8)	4 (100)	1 (100)	0 (0.0)	514 (69.1)	239 (67.9)
Prior exposure to NRTI								
Yes	4,813 (99.9)	3,713 (99.9)	1,100 (99.9)	4 (100)	1 (100)	0 (0.0)	743 (99.9)	352 (100)
Prior exposure to DTG at baseline[3]								
Yes	7 (0.1)	2 (0.1)	5 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.5)	1 (0.3)

			Discontinued					
	Overall	**Did not discontinue**	**Total**	**HSR**	**Hepatotoxicity**	**Severe skin rash (Not HSR)**	**Other**	**Unknown**
Prior exposure to EVG at baseline[3]								
Yes	25 (0.5)	11 (0.3)	14 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.7)	9 (2.6)
Prior exposure to RAL at baseline[3]								
Yes	946 (19.6)	715 (19.2)	231 (21.0)	2 (50.0)	0 (0.0)	0 (0.0)	150 (20.2)	79 (22.4)
Number of ARVs previously exposed to								
Median years (IQR)	8.0 (6.0,11.0)	8.0 (6.0,11.0)	8.0 (6.0,11.0)	11.0 (6.0,14.5)	6.0 (6.0,6.0)		8.0 (6.0,11.0)	9.0 (6.0,12.0)
Years since first use of any ARV (years)[4]								
Median years (IQR)	17.3 (10.0,21.8)	17.4 (10.4,22.0)	16.8 (9.2,20.8)	17.3 (10.8,23.4)	9.6 (9.6,9.6)		17.3 (9.6,21.1)	15.7 (8.4,19.8)

[1] Date of first discontinuation in those who stopped DTG, RAL or EVG, or last clinic visit in those who did not.
[2] After the 16 Jan 2014.
[3] Baseline was defined as the date of starting the DTG (or other integrase inhibitor).
[4] Cumulative years since starting at least one ARV prior to date

15 ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Date	Title
1		29 November 2019	The EuroSIDA study group
2	*[Number]*	*[Date]*	*[Text]*
...	*[Number]*	*[Date]*	*[Text]*

15.1 The EuroSIDA study group

(See also https://chip.dk/Studies/EuroSIDA/Study-group)

The multi-centre study group, EuroSIDA (national coordinators in parenthesis).

Argentina: PPD

Austria: PPD

Belarus: PPD

Belgium: PPD

Bosnia-Herzegovina: PPD

Croatia: PPD

Czech Republic: PPD

Denmark: PPD

Estonia: PPD

Finland: PPD

France: PPD

Germany: PPD

Georgia: (PPD

Greece: PPD

Hungary: PPD

Iceland: PPD

Ireland: PPD

Israel: PPD

Italy: PPD

Lithuania: PPD

Luxembourg: PPD

Netherlands: PPD

Norway: PPD

Poland: PPD

Portugal: PPD

Romania: PPD

Russia: PPD

PPD

Serbia: PPD

Slovenia: PPD

Spain: PPD

Sweden: PPD

Switzerland: PPD

Ukraine: PPD

United Kingdom: PPD

The following centers have previously contributed data to EuroSIDA:

PPD

EuroSIDA Steering Committee

Steering Committee: PPD

Chair: PPD
Co-Chair: PPD

Study lead: PPD

EuroSIDA staff

Coordinating Centre Staff: PPD

Statistical Staff: PPD