TITLE PAGE

Information Type: ViiV Healthcare Epidemiology Study Protocol

Title:	Abacavir Usage Patterns and Trends in Hypersensitivity Reactions (HSR) in the EuroSIDA cohort

Compound Number:	GI265235
Development Phase	IV
Effective Date:	DD-MM-YYYY
Subject:	Abacavir, hypersensitivity reaction, HSR

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LIST OF ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
AEs	adverse events
AIDS	Acquired Immune Deficiency Syndrome
cART	combination antiretroviral therapy
CVD	cardiovascular disease
DTG	dolutegravir
FDA	Food and Drug Administration
FU	follow up
HIV	human immunodeficiency virus
HSR	hypersensitivity reaction
INSTI	integrase strand transfer inhibitor
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
PI	protease inhibitor

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1. RESPONSIBLE PARTIES: SPONSOR INFORMATION PAGE

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name**:** [redacted]

Investigator Signature Date

Investigator Name: [redacted]

Investigator Signature Date

2. ABSTRACT

Abacavir (ABC) sulphate, a carbocyclic 2'-deoxyguanosine nucleoside analogue, was approved by the Food and Drug Administration (FDA) in December 1998, for the treatment of adults and children with human immunodeficiency virus (HIV) infection. Originally marketed as Ziagen®, abacavir has since been co-formulated with two other nucleoside reverse transcriptase inhibitors, zidovudine and lamivudine (3TC), approved as Trizivir®, followed by co-formulations with lamivudine, approved as Kivexa® and with lamivudine and dolutegravir (DTG), approved as Triumeq®. Individuals carrying the HLA-B*5701 gene are have an increased risk of ABC hypersensitivity reaction (HSR), and most guidelines now recommend screening for HLA-B*5701 before initiating an ABC containing regimen.

Objectives:

1. To describe the proportion of individuals on combination antiretroviral therapy (cART) receiving an ABC-based cART regimen per year from 1/1/2009 to 1/4 2016, describe the type of drugs used with ABC and identify factors associated with starting ABC-based cART.

2. To describe the cumulative frequency, incidence and factors associated with ABC discontinuation, due to any reason and due to HSR among persons starting ABC after 1/1/2009 as part of a cART regimen.

This will be a retrospective analysis of prospectively collected data from the EuroSIDA cohort study which consists of data from over 22,000 HIV infected patients in 35 European countries plus Israel and Argentina.

3. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
<1>	<Date>	<Text>	<Text>	<Text>
<2>	<Date>	<Text>	<Text>	<Text>
<n>	<Date>	<Text>	<Text>	<Text>

4. MILESTONES

Milestone	Planned date
Protocol draft	5-January-2017
Registration on the EU PAS register	23-Feb-2016
Start of data analysis	24-Feb-2016
Draft report of study results	15-May-2017
Final report of study results	31-May-2017
Abstract draft	15-Jun-2017
Manuscript draft	31-Oct-2017

5. BACKGROUND AND RATIONALE

5.1. Background

Between 5-8% of patients initiating ABC may experience a HSR which in a minority of cases is fatal (1). Individuals carrying the HLA-B*5701 gene have an increased risk of ABC HSR, and most guidelines now recommend screening for HLA-B*5701 before initiating an ABC containing regimen (2–4). A previous EuroSIDA analysis, carried out in 2008, estimated an annual incidence of HSR related ABC discontinuation events of 22.1 per 100 person years, and found some evidence that this was lower among individuals starting ABC after 2005 compared to individuals who initiated ABC between 1999-2000 (5).

5.2. Rationale

It is of interest to describe prescribing patterns of ABC over time, as these are likely to have changed considerably due to a greater availability of different HIV drugs and changing treatment guidelines. In addition, as HLA-B*5701 screening is likely to have grown more common over time, it is also important to investigate whether this has been reflected by a further decline in the incidence of HSR in more recent calendar years.

6. RESEARCH QUESTION AND OBJECTIVE(S)

This analysis seeks to describe changes in ABC treatment utilization and ABC hypersensitivity reactions (HSR) over time. The specific objectives of the analyses are to:

1. Describe treatment utilization patterns of Abacavir (ABC) between 1/1/2009 and 1/4/2016 by:

    a. Calculating the proportion of individuals on cART including ABC at the mid-point of each calendar year. Among those on ABC at the midpoint of the year, persons will be grouped as:

        i. Individuals who started ABC from ARV naïve
        ii. Individuals who switched to ABC for the first time that year
        iii. Individuals re-starting ABC that year
        iv. Individuals maintained on ABC.

    b. Describe ART drugs prescribed with ABC and the use of different ABC formulations (Ziagen®, Kivexa®, Trivizir®, Triumeq®) among individuals on cART who receive ABC during a given calendar year according to categories1a:i-iv as outlined above.

    c. Among the sub-group of individuals who switch to an ABC regimen from a non-ABC based cART regimen, the reasons for stopping the previous regimen will be summarised as well as key parameters at the time of stopping the previous regimen.

    d. Identify factors associated with ABC initiation.

2. Describe the cumulative frequency, incidence and factors associated with ABC discontinuation due to any reason and due to hypersensitivity reactions (HSR) among persons initiating ABC as part of a cART regimen after 1/1/2009.

    a. Describe reasons for ABC discontinuation.

    b. Estimate cumulative probabilities of ABC discontinuation due to:

        i. Any reason
        ii. HSR
        iii. All other reasons separately, as listed in protocol section 8.3.2, given that a discontinuation in the relevant category occurred

    c. Estimate the incidence rate of ABC discontinuation due to categories 2b:i-ii as outlined above.

    d. Compare key characteristics of individuals who initiate ABC and consequently:

i. Remain on ABC
ii. Discontinue ABC due to HSR
iii. Discontinue ABC due to any other reason

e. Identify factors associated with ABC discontinuation due to any reason and ABC discontinuation due to HSR among individuals receiving ABC.

For objectives [1a-c] as well as [2b-c], the results will be presented overall as well as stratified according to:

iv. Calendar year
v. Geographical region
vi. Calendar year and geographical region

Depending on numbers, objective 2b will be conducted separately for the first initiation of ABC and for those with prior ABC exposure. The number of individuals who re-start ABC following ABC related HSR will also be presented.

7. RESEARCH METHODS

7.1. Study Design

This is a retrospective analysis of prospectively collected data obtained from the EuroSIDA clinical cohort study. The study design builds on and expands previous work by Bannister et al investigating the incidence of and risk factors for ABC HSR between 1999 and 2008 (1). In order to provide information that is complimentary to Bannister et al, this analysis will only include individuals who receive or initiate ABC after 1/1/2009.

The analysis will use data captured routinely as part of the ongoing EuroSIDA study activities and will not require any additional data collection. The study is non-interventional, and whether to initiate or discontinue ABC for a given patient will be decided by the treating physicians, taking treatment history, patient characteristics and local clinical guidelines into account. ABC dosage, formulation and regimen composition will also be fully determined by treating physicians.

The study objectives are described in section 7. Objective [1a-c] and [2a-c] are descriptive in nature and do not have any comparator groups. Objective [2d] compares demographic and clinical characteristics of individuals who initiate ABC and consequently:

(i) Remain on ABC
(ii) Discontinue ABC due to HSR
(iii) Discontinue ABC due to any other reason.

Objective [1d] and [2e] identifies factors associated with ABC initiation [1d] and discontinuation due to HSR [2e]. These analyses compare the incidence of ABC initiation and discontinuation according to a number of demographic and clinical characteristics,

which are described in detail in section 8.3.3. The end-point for analysis [1d] will be initiation of ABC. The end-point for analysis [2e] will be the discontinuation of ABC due to HSR. The measures of effect for both [1d] and [2e] will be raw incidence rates, unadjusted rate ratios and adjusted rate ratios.

7.2. Study Population and Setting

Description of the EuroSIDA cohort

This analysis will include individuals from the EuroSIDA cohort study. EuroSIDA is a prospective observational cohort study that was initiated in 1994, and currently holds data on more than 22,000 people living with HIV followed in 100 hospitals in 35 European countries, Israel and Argentina. The main objective of the study is to describe the long-term clinical prognosis of people living with HIV and HIV/Hepatitis C co-infection in Europe and to assess the impact of antiretroviral drugs on the long-term prognosis for these individuals.

In EuroSIDA, annual data collection is performed directly by treating clinicians using the online REDCAP system. The data collected includes start and stop dates for each antiretroviral drug used, reasons for discontinuing an antiretroviral drug and clinical events, including both AIDS (using the 1993 clinical definition of AIDS from the Centers for Disease Control and Prevention) and non-AIDS events. A detailed description of the data collected can be found below in Table 1.

Table 1. Data collected in EuroSIDA [2016 update]

Available for all patients	
Demographics and basic clinical information	Date of birth
	Date first seen at department
	Date of first positive HIV1-Ab test
	Gender
	Mode of infection (HIV)
	Mode of infection (HCV)
	Country of origin
	Weight
	Height
	Blood Pressure
	Smoking Status
Laboratory Values	ALT
	AST
	Platelets
	Serum creatinine
	Total cholesterol
	HDL
	HbA1c
	CD4
	HIV-RNA
	HBsAg

	Anti-HCV IgG
Medical treatment	ART: start and stop dates, reason for discontinuation
	Treatment related to risk of CVD: antihypertensives, antidiabetics, antiplatelets lipid lowering medication
Clinical events	Opportunistic infections
	Cardiovascular events, end stage renal and liver disease
	AIDS and non-AIDS malignancies
	Cause of death
Plasma samples	Continuous collection for most patients
Available for HIV/HCV co-infected patients	
	Alcohol abuse
	Active injecting drug use
	Opioid maintenance therapy
	Haemoglobin
	Bilirubin
	INR
	Albumin
	HCV genotype and subtype
	HCV-RNA
	Fibroscan
	CT/ultrasound of abdomen
Available for HIV/HCV infected patients treated against HCV	
	Treatment against HCV, start and stop dates
	Discontinuation of HCV drug before scheduled end and reason for discontinuation
	Adherence to HCV drug
	Adverse events to anti-HCV treatment
Available for patients that discontinue treatment with an integrase inhibitor containing regimen due to liver toxicity, HSR or rash	
	Type of HSR
	Drug dosage priod to discontinuation, including frequency of administration
	Symptoms at discontinuation
	Liver parameters if hepatotoxicity

EuroSIDA is an observational cohort study which collects data that reflects routine clinical care in different countries in Europe. Treatment allocations are not randomised or influenced by the coordinating staff in anyway, which means that treatment decisions can be influenced by prognostic factors. This can lead to imbalances in the underlying risk factor distribution between groups receiving different treatments (confounding by indication). Although EuroSIDA collects data on a range of prognostic markers, we cannot rule out that there are differences between treatment groups that we cannot control for in the analyses. In addition, the people enrolled in EuroSIDA are by definition those that are linked to and retained in care. They may differ in significant ways from individuals who do not access or enter into the care system, which can reduce the generalizability of the findings. Results generated by analysing the EuroSIDA cohort

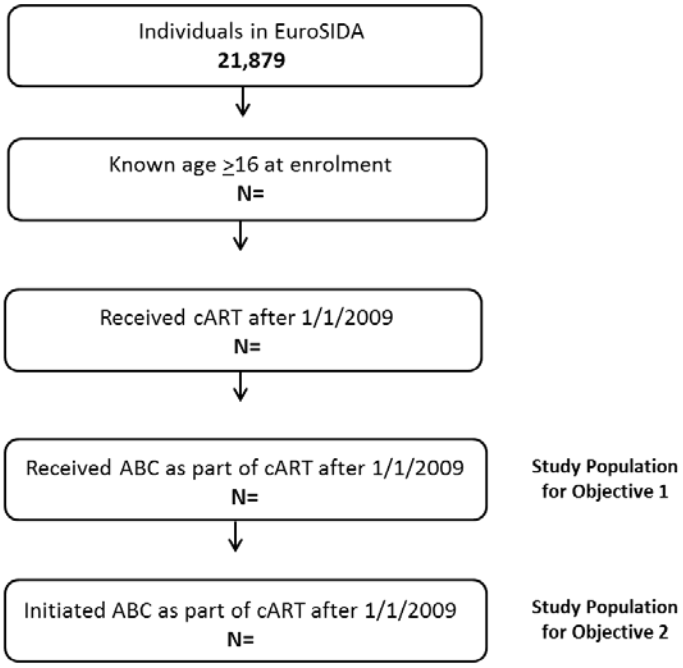
should be interpreted with the knowledge of these limitations and potential for inherent biases in mind. Nonetheless, EuroSIDA is in a unique position to compare and describe treatment patterns due to the standardised nature of the data collection and the inclusion of countries for which there are no national cohorts or surveillance structures. EuroSIDA does not collect data on HLA-B*5701 status.

Study population

Inclusion Criteria

Individuals from the EuroSIDA cohort over the age of 16 at enrolment receiving cART (at least 3 drugs from any class, excluding ritonavir) at some point after 1/1/2009 will be eligible for inclusion (Objective 1). Objective 2 will further require all individuals to have initiated ABC after 1/1/2009. Drug exposure prior to EuroSIDA enrolment cannot be assessed, and will not be considered for the inclusion criteria.

Figure 1. Proposed flowchart of the participant selection



7.3. Variables

7.3.1. Exposure definitions

Identifying HSR cases

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

A potential case of ABC HSR is one in which ABC is discontinued due to Hypersensitivity / anaphylactic reaction / allergic reaction / drug allergy related to ABC.

Case Definition for HSR: A case ABC HSR is one in which conditions in ***A*** or ***B*** are fulfilled.

A. Hypersensitivity / anaphylactic reaction / allergic reaction / drug allergy to ABC is reported.

   OR

B. Two or more events are reported from two or more of the following groups of signs/symptoms:
   a. rash
   b. fever
   c. gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain)
   d. constitutional symptoms (lethargy, fatigue, malaise, myalgia, arthralgia, general ill feeling)
   e. respiratory symptoms (dyspnoea, sore throat, cough, chest X-ray changes, predominantly infiltrates, which can be localised).
   f. eosinophilia
   g. hepatic dysfunction as indicated by liver chemistry tests (LCT) will include the following, with a focus on alanine aminotransferase elevations and total bilirubin elevations:
      i. ALT elevations (ALT is also called serum glutamic pyruvic transaminase (SGPT))
      ii. AST elevations (AST is also called serum glutamic oxaloacetic transaminase (SGOT))
      iii. Alkaline phosphatase (ALP) elevations
      iv. Total bilirubin elevations
      v. Albumin

Key outcomes for Objective 1 and 2 will be described per calendar year and geographical region. EuroSIDA has developed standard categorisations of geographical regions which will be used in this analysis, as detailed in Table 2 below. Events will be described per per year where possible, if numbers do not permit this, time-trends will be described by grouping calendar year into periods of two years (09/10, 11/12, 13/14, 15/16/17).

Table 2. EuroSIDA contributing countries and geographical regions

Southern Europe	Central Western Europe	Northern Europe	Central Eastern Europe	Eastern Europe
Spain	France	United Kingdom	Poland	Estonia
Portugal	Belgium	Ireland	Czech Republic	Latvia
Italy	Luxembourg	Netherlands	Slovakia	Lithuania
Greece	Switzerland	Denmark	Hungary	Belarus
Israel	Austria	Sweden	Romania	Ukraine
Argentina	Germany	Norway	Serbia	Russia
		Finland	Bulgaria	
			Croatia	

7.3.2. Outcome definitions

The outcome for Objective 1 will be receipt of ABC. ABC information is provided by the treating physician, and is collected in EuroSIDA in four possible ways. ABC treatment can either be listed as an individual drug, or, through the clinician entering free text into the CRF, as part of one of 3 combination tablets: Kivexa, Triumeq or Trizivir. Each drug combination is given a unique drug code. The drug codes used to determine ABC use are outlined in Table 3.

Table 3. Drug codes used to identify Abacavir

Drug code	Drug
1	Abacavir (ABC)
1003	Kivexa (3TC/ABC)
2319	Triumeq (3TC/ABC/DTG)
14	Trizivir (AZT/3TC/ABC)

The outcome for Objective 2 will be ABC discontinuation. Stop dates of ABC are provided by the treating physician, with an option of indicating the reason for stopping the drug. Only one reason per drug is collected. Possible reasons are shown in Table 4 below.

Table 4. Reasons for discontinuation collected in EuroSIDA

Discontinuation code	Reason
1.	Treatment Failure
2.	Abnormal Fat Redistribution
3.	Concern of cardiovascular disease, including dyslipidaemia
3. 1	*Dyslipidaemia*
3.2	*Cardiovascular disease*
4.	Hypersensitivity Reaction
5.	Toxicity, predominantly abdomen/GI tract
5.1	*Toxicity - GI tract*
5.2	*Toxicity – Liver*
5.3	*Toxicity – Pancreas*
6.	Toxicity, predominantly CNS
7.	Toxicity, predominantly kidneys
8.	Toxicity, predominantly endocrine

8.1	*Diabetes*
9	Haematological toxicity
10	Hyperlactataemia/lactic acidosis
90	Toxicity, any other
91	Patient's choice
92	Physician's choice
93	Structured Treatment interruption
94	Other, not specified
99	Unknown

ABC discontinuation will be defined as a stop of ABC, irrespective of whether or what reason for discontinuation is recorded. Changes in the ABC formulation (eg a switch from Kivexa to Triumeq or a change in the dosage of ABC) will not be counted as a discontinuation. ABC discontinuation due to HSR will be defined as a stop of ABC with a reason for discontinuation indicated as discontinuation code 4: "Hypersensitivity reactions".

Sensitivity analyses, where all discontinuations of ABC occurring within the first 3 months and reported to be due to any toxicity (codes: 2,3, 3.1, 3.2, 4, 5, 5.1, 5.2, 5.3, 6, 7, 8, 8.1, 9, 10, 90), patient choice (codes: 91) and physicians choice (codes: 92) are presumed to be due to HSR (representing a worst-case scenario) will be conducted.

7.3.3. Confounders and effect modifiers

Confounding by indication in observational data is a significant issue. This arises whereby persons are chosen to start a treatment for reasons that are either unknown or unmeasured within the study, and which cannot therefore be adjusted for as confounders in analyses. The statistical analysis will present a detailed overview of the characteristics of patients starting and not starting ABC to assess bias, and adjust for confounders and effect modifiers wherever possible. However, results from observational studies should always be interpreted with caution due to the potential for confounding. EuroSIDA does not have data on HLA B*5701 status.

Risk factors that will be evaluated for objective 1 and 2 can be seen in Table 5 below.

Table 5. Factors to evaluate for their association with ABC initiation/discontinuation

Demographics	
Gender	Male/Female
Age	Grouped into quintiles and evaluated for linearity, if appropriate included as a continuous variable per 10 years
Ethnicity	White/Non-white
HIV risk group[1]	MSM/PWID/Heterosexual/Other
Geographical Region	Southern/Central Western/Northern/Central Eastern/Eastern
Calendar Year	Evaluated for linearity, if appropriate included as a continuous variable per year. If not linear, split into groups of two years.
HIV-related factors	
CD4 count (time-updated)	Grouped into <200/200-350/350-500/>500 and evaluated for linearity, if appropriate included as a continuous variable per 100 cells/mm3

VL (time-updated)	Grouped into <500/500-1000/1000-10000/10000-100,000/>100,000 and evaluated for linearity, if appropriate included as a continuous variable per 1 log10 copies/ml
CD4 nadir	Grouped into <200/200-350/350-500/>500 and evaluated for linearity, if appropriate included as a continuous variable per 100 cells/mm3
Line of ABC regimen [2]	1st line/2nd line/3rd line/4th or higher line
Prior AIDS diagnosis	Yes/No
Non-HIV related clinical factors	
Framingham CV Risk	High/Low/Unknown risk. High risk will be defined as a predicted 10-year Framingham risk of 20% or higher (REF).
Kidney Function	CKD; CKD will be defined as 2 consecutive (> 3 months apart) eGFR < 60 using the CKD-EPI formula. Patients will also be classified using the DAD CKD risk equation (2) , low, moderate and high risk of CKD over the next 5 years.
Hepatitis B antigen status	Yes/No/Unknown
Hepatitis C antibody status	Yes/No/Unknown

1. *MSM=Men who have Sex with Men, PWID=Person who Injects Drugs*
2. *Only evaluated for objective 2 – factors associated with ABC discontinuation.*

7.4. Data sources

As outlined in Section 8.2, data used for this analysis will come from the existing EuroSIDA cohort study, and no additional data collection will be undertaken. The exposures and outcomes will be defined as specified in section 8.3. The quality assurance processes in place for assuring study validity follow the EuroSIDA and Copenhagen HIV Programme SOP (http://www.cphiv.dk/Studies/EuroSIDA/Study-documents).

7.5. Study size

Based on the currently available data, we anticipate that approximately 14,000 persons received cART and had active FU after 1/1/2009. Approximately 4,500 individuals received ABC and 1,900 initiated ABC as part cART for the first time after 1/1/2009.

These numbers are an estimate and may change with updates to the data available and with changes in inclusion and exclusion criterion

7.6. Data management

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

7.6.1. Data handling conventions

Data handing follows the HICDEP - HIV Collaboration Data Exchange Protocol for data submitted electronically (http://www.hicdep.org/). Data submitted on paper based forms are handled according to above mentioned standard operating procedures (SOPs) (http://www.cphiv.dk/Studies/EuroSIDA/Study-documents).

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

7.6.2. Timings of Assessment during follow-up

Data collection in EuroSIDA is done annually through the online REDCAP system, and the frequency of measurements reflects the standard of clinical care in each contributing country.

7.7. Data analysis

The primary objectives of this analysis are to:

1. Describe the use of ABC as part of cART over time, evaluate reasons for switching to an ABC containing regimen and identify factors associated with starting ABC.

2. Describe the cumulative probability and incidence of ABC discontinuations and to identify risk factors for discontinuing ABC due to HSR.

Statistical Analysis

Objective 1

The proportion of individuals who receive ABC on the 1/7 (1st of July) of each calendar year from 1/1/2009 onwards will be described graphically, using everyone receiving cART and under active follow-up (FU) at the same date as the denominator. Active FU will be defined having a first visit date before the 1/7 and a last visit date after the 1/7. Among those on ABC at the midpoint of the year, persons will be further described as (i) individuals who started ABC from ARV naive (ii) individuals who switched to ABC for the first time that year (iii) individuals re-starting ABC that year and (iv) individuals maintained on ABC. Individuals can move from one group to another over time.The type of cART (triple NRTI, NNRTI, PI, INSTI, Other) and individual drugs prescribed with ABC will also be described, as will the use of different ABC formulations (Ziagen, Trivizir, Kivexa and Triumeq). These descriptions will be stratified, comparing those

initiating ABC for the first time or not. All treatment utilisation descriptions will be done per calendar year, per geographical region and per year and region.

Among those who started ABC as part of a cART regimen within 7 days of stopping one or more previous drugs, the reasons for stopping the previous drug(s) will be summarised. HIV RNA, CD4, ALT, Framingham risk score, the DAD CKD risk score, FIB-4, APRI, haemoglobin and creatinine levels will be described at the time of stopping previous cART regimen (using data from up to two months before the date of stopping) the in order to give information on why the previous regimen was stopped. This will be described per year and region.

Factors associated with ABC initiation (either a switch to ABC or starting ABC from naïve/a gap in the ART treatment history) will be investigated using a Poisson model with generalised estimating equations (GEE) to control for the inclusion of repeated exposure periods and/events. For this part of the analysis, baseline will be defined as the 1/1/2009 or enrolment into EuroSIDA, whichever occurs latest. Individuals with prior ABC exposure will be included. It is likely that some patients who were on older ABC containing regimens may now be using newer options such as Triumeq in their cART regimen and it is important to capture such potential re-exposures.

Individuals will contribute follow up (FU) time until they start ABC,, their last EuroSIDA visit date or death, whichever occurs first. If an individual stops ABC they will be allowed to re-enter the analysis, and once again considered eligible for starting ABC. The outcome will be starting ABC, either as an add-on drug or as part of a new cART regimen. Factors to be investigated for their association with ABC initiation are shown in Table 4 section 8.3.3; those that are significant ($p<0.1$) in univariate analyses will be included in multivariate models. Sensitivity analyses will investigate the consistency of the results depending on whether it was the first initiation of ABC or whether persons had previously been exposed.

Objective 2

For this analysis, individuals will be included if they initiate ABC as part of cART after 1/1/2009. Individuals with prior ABC exposure will be included, and individuals who start ABC more than once after the 1/1/2009 can contribute multiple exposure periods. Baseline will be defined as the start of an ABC-containing regimen, 1/1/2009 or recruitment to EuroSIDA, whichever occurs last. This will be an on-treatment analysis, and for the analysis of time to discontinuation for any reason individuals will contribute FU until ABC discontinuation, death or their last visit date, whichever comes first. For the analysis of time to discontinuation due to HSR, individuals will contribute FU until 6 weeks after ABC initiation, ABC discontinuation or death, whichever comes first. Cumulative frequencies of time to discontinuation for any reason and due to HSR will be calculated using survival methods and displayed in KM plots, stratified according to whether it is the first or a repeated exposure to ABC. This will ensure that only one record per individual is included in each KM plot The rate of ABC discontinuation due to any reason and due to HSR will be displayed in plots stratified by calendar year and region, and presented with 95% CI corrected for repeated events

We will compare baseline characteristics among those individuals who remain on ABC throughout their FU, discontinue due to any reason (not HSR) and discontinue due to HSR using chi-squared tests/Fisher's exact test and Kruskal-Wallis tests as appropriate. Characteristics, including HIV RNA, CD4, ALT, Framingham risk score, the DAD CKD risk score, FIB-4, APRI, haemoglobin and creatinine levels will be described at the time of ABC discontinuation (using data from up to two months before the date of stopping), among those who discontinued ABC. These descriptions will be conducted separately for the first or repeated exposure to ABC. Factors associated with HSR-related discontinuation will be identified in a multivariable Poisson Regression Model using GEE to adjust for repeated events. Factors to be investigated for their association with ABC initiation are shown in Table 4 section 8.3.3; those that are significant ($p<0.1$) in univariable analyses will be included in multivariable models.

Sensitivity analyses, where all discontinuations of ABC occurring within the first 6 weeks and reported to be due to any toxicity are presumed to be due to HSR (representing a worst-case scenario) will be conducted. We will also conduct a time-lag analysis, where individuals are assumed to stay on ABC for 4 weeks after their stop date. Finally, a sensitivity analysis where only individuals who start ABC for the first time after 1/1/2009 are included will be conducted.

7.7.1. Essential analysis

The following analyses will be conducted to address the primary aims:

Objective 1

Table 1. Baseline characteristics of all participants, split by ABC use (ever *vs.* not)

Figure 1a-c. % on ABC over time, per region and over time per region according to the groups laid out in 1a:i-iv.

Figure 2a-d. Type of cART and all individual drugs prescribed with ABC according to categories 1a: i-iv, overall, per calendar year, per region and per region and calendar year.

Table 3. Reasons for switching to ABC

Table 4. Laboratory and clinical parameters at stop of regimen prior to ABC switch

Table 5. Factors associated with ABC initiation

Objective 2

Table 7. Reasons for ABC discontinuation

Figure 3a-x. Time to ABC discontinuation due to any reason, HSR and all other reasons.

Table 8. Incidence rate of ABC discontinuation due to any reason, HSR and all other reasons.

Table 9. Compare baseline characteristics of individuals who initiate ABC and remain on ABC, discontinue due to HSR and discontinue due to any other reason.

Table 10. Factors associated with ABC discontinuation due to HSR.

7.7.2. Exploratory analysis

Sensitivity analysis 1: All discontinuations of ABC occurring with the first 6 weeks months reported to be due to any toxicity will be considered to be due to HSR. Analyses Table 8-9 will be repeated.

Sensitivity analysis 2: Individuals will be censored 4 weeks after ABC discontinuation. Analyses Figure 3a-x and Table 8-10 will be repeated.

Sensitivity analysis 3: Only the 1st ABC exposure period after 1/1/2009 will be considered. Figure 3a-x and Table 8-10 will be repeated.

Sensitivity analysis 4: If numbers permit, the analyses will be stratified according to EU countries (Spain, Portugal, Italy, Greece, France, Belgium, Luxembourg, Austria, Germany, the UK, Ireland, the Netherlands, Denmark, Sweden, Finland, Poland, Czech Republic, Slovakia, Hungary, Romania, Bulgaria, Croatia, Estonia, Latvia, Lithuania) and non EU countries (Israel, Argentina, Switzerland, Norway, Serbia, Belarus, Ukraine, Russia). Figure 3a-x and Table 8-10 will be repeated.

7.7.3. General considerations for data analyses

Confounding will be taken into account through covariate adjustment. There will be no sub-group analyses, and as all analyses are pre-specified we are not seeking to control formally for multiple testing.

Not all variables within EuroSIDA are complete for all persons, and missing data is rarely missing at random from observational cohort studies. Data may be categorized, including a category for missing, persons may be completely excluded with missing data, or imputation can be used. None of these approaches are unbiased, and in this analysis we have chosen to include a missing category for where data are missing in order to maximise the number of individuals that could be included.

7.8. Quality control and Quality Assurance

Quality control follows the EuroSIDA SOP, EuroSIDA QA checks for data transfer (http://www.cphiv.dk/Studies/EuroSIDA/Study-documents) as well as the Copenhagen HIV Programme Quality Management Plan and related SOPs.

7.9. Limitations of the research methods

The proposed study has a number of potential limitations. Firstly, as EuroSIDA relies on routinely collected data from participating clinics, the results may not be generalizable to the wider population of individuals living with HIV in Europe. Nonetheless, the standardized data collection allows for comparisons across regions which may not be possible using nationally available data. EuroSIDA does not collect data on HLA-B*5701 status, which is a limitation of this analysis. As with any cohort study, loss to follow-up (LTFU) may introduce bias, particularly if those individuals who are LTFU are more likely to experience the event of interest, in this case discontinuation of ABC according to HSR. However, the relatively short FU period considered for this analysis (3 months) should help minimize the impact any LTFU may have had on the results. The accuracy of the data collection is also of paramount importance when studying specific treatment combinations. EuroSIDA has a rigorous QA process in place, and this is complemented by site monitoring visits by EuroSIDA coordinating center staff. Nonetheless, it is possible that ART drugs are entered incorrectly either by clinicians or at the data entry stage. And finally, as mentioned previously we cannot rule out the possibility of confounding by indication, as treatments in EuroSIDA are not randomized. All findings should be critically evaluated keeping these possible limitations in mind.

8. PROTECTION OF HUMAN SUBJECTS

8.1. Ethical approval and subject consent

Participating studies have existing national and/or local ethical approval, and obtain informed subject consent where required within these approvals.

8.2. Subject confidentiality

This analysis will use previously collected, anonymized electronic medical record data. No identifying information will be provided.

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves retrospective analysis of previously collected data in an aggregate manner. There is no potential to collect serious and non-serious adverse events (AEs), pregnancy exposures, or incidents related to any ViiV Healthcare product during the conduct of this research, as the minimum criteria needed to report AEs, pregnancy exposures, and incidents are not present in the data source. Specifically, the data are insufficient to establish attribution between a potential safety event and an individual patient using a ViiV Healthcare product.

Therefore, a study specific pharmacovigilance plan will not be developed.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

10.1. Target Audience

The target audience includes healthcare providers, regulatory and health authorities. The study results will be made available externally through peer reviewed manuscript and conference presentation.

10.2. Study reporting and publications

Final Study results will be included in safety and regulatory reports as appropriate. Results will also be submitted as an abstract to a congress and for publication in peer reviewed journal.

11. REFERENCES

1. Mallal S, Phillips E, Carosi G, Molina J-M, Workman C, Tomažič J, et al. HLA-B*5701 Screening for Hypersensitivity to Abacavir. N Engl J Med. 2008 Feb 7;358(6):568–79.

2. European AIDS Clinical Society (EACS). European AIDS Clinical Society Guidelines Version 7.0. European AIDS Clinical Society (EACS); 2013.

3. Asboe, D, on behalf of the BHIVA Guidelines Subcommittee. BHIVA guidelines for the routine investigation and monitoring of adult HIV-1 infected individuals 2011.

4. Postmarket Drug Safety Information for Patients and Providers - Information for Healthcare Professionals: Abacavir (marketed as Ziagen) and Abacavir-Containing Medications [Internet]. [cited 2016 Jul 8]. Available from: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm123927.htm

5. Bannister WP, Friis-Møller N, Mocroft A, Viard J-P, van Lunzen J, Kirk O, et al. Incidence of abacavir hypersensitivity reactions in euroSIDA. Antivir Ther. 2008;13(5):687–96.