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*

Report #1

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

June 2017

Contacts: PPD

HIV Epidemiology and Biostatistics Group, Research Department of Infection and Population Health, University College London Medical School, Royal Free Campus, Rowland Hill St, London, NW3 2PF, UK.

Tel: PPD
Fax: PPD

TABLE OF CONTENTS

PAGE

1. CONTENT

1.1. List of Results Tables

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

Table 1a: % on ABC over time overall and according to individuals who started ABC from naïve, switched to ABC for the first time that year, individuals re-starting ABC that year, and individuals maintained on ABC

Table 1b: % on ABC by region. Note: this cannot be broken down into ABC groups as this is a time dependent measure.

Table 2a: Type of cART and all individual drugs prescribed with ABC overall and according to those initiating ABC for the first time or not by year (years 2013-2016 in following table). Note: type of cART cannot be assessed overall as this is a time dependent measure.

Table 3a: Reasons for stopping previous ARV regimen in those switching to ABC and starting ABC as a part of a cART regimen within 7 days of stopping one or more previous drugs.

Table 3b: Reasons for stopping previous ARV regimen in those switching to ABC and starting ABC as a part of a cART regimen within 7 days of stopping one or more previous drugs by calendar year

Table 3c: Reasons for stopping previous ARV regimen in those switching to ABC and starting ABC as a part of a cART regimen within 7 days of stopping one or more previous drugs by region

Table 4a: Laboratory and clinical parameters among those starting ABC as a part of a cART regimen within 7 days of stopping one or more previous drugs. Data for all variables was used from up to two months before the date of stopping the previous treatment.

Table 4b: Laboratory and clinical parameters among those starting ABC as a part of a cART regimen within 7 days of stopping one or more previous drugs by year Data for all variables was used from up to two months before the date of stopping the previous treatment.

Table 4c: Laboratory and clinical parameters among those starting ABC as a part of a cART regimen within 7 days of stopping one or more previous drugs by region. Data for all variables was used from up to two months before the date of stopping the previous treatment.

Table 5a: Factors associated with ABC initiation

Table 5b: A sensitivity analysis: factors associated with ABC initiation among those initiating ABC for the first time

Table 5c: A sensitivity analysis: Factors associated with ABC initiation among those re-initiating ABC

Table 7a: Reasons for ABC discontinuation among those discontinuing within 6 weeks of ABC initiation

Table 7b: A sensitivity analysis: Reasons for ABC discontinuation among those discontinuing within 4 weeks of after ABC initiation

Table 7c: A sensitivity analysis: Reasons for discontinuation among those discontinuing within 6 weeks of ABC initiation. Individuals were assumed to stay on ABC for 4 weeks after their stop date. The following are reasons for stopping other drugs between ABC initiation and 6 weeks post ABC initiation.

Table 8a: Incidence rate of ABC discontinuation by reason for stopping treatment. Individuals were censored at 6 weeks after ABC initiation, ABC discontinuation or death. Note: only displaying rates containing 30 or more individuals discontinuing for that reason.

Table 8b: A sensitivity analysis: Incidence rate of ABC discontinuation by reason for stopping treatment. Individuals were censored at 4 weeks after ABC initiation, ABC discontinuation or death. Note: only displaying rates containing 30 or more individuals discontinuing for that reason.

Table 8c: A sensitivity analysis: Incidence rate of ABC discontinuation by reason for stopping treatment among those exposed to ABC for the first time after 1/1/2009. Individuals were censored at 6 weeks after ABC initiation, ABC discontinuation or death. Note: only displaying rates containing 30 or more individuals discontinuing for that reason.

Table 9a: Baseline characteristics of individuals who initiate ABC and remain on ABC, discontinue due to HSR and discontinue due to any other reason over the first two ABC exposures

Table 9b: A sensitivity analysis: Baseline characteristics of individuals who initiate ABC and remain on ABC, discontinue due to HSR or any toxicity and discontinue due to any other reason over the first two ABC exposures

Table 10: Factors associated with time from ABC initiation to discontinuation due to HSR or any toxicity. Individuals were censored at 6 weeks after ABC initiation, ABC discontinuation or death. Note: this was the only outcome with >30 events and could be analysed in a statistical model

1.2. List of Figures

Figure 1: Flowchart of the participant selection

Figure 1a i: % on ABC overall by year

Figure 1a ii: % starting ABC from naïve by year

Figure 1a iii: % starting ABC for the first time by year

Figure 1a iv: % re-starting ABC by year

Figure 1a v: % maintained on ABC by year

Figure 1b: % on ABC by region. Note: this cannot be broken down into ABC groups as this is a time dependent measure.

Figure 2b: All individual drugs prescribed with ABC by Region. Note: type of cART and stratification by individual's initiation ABC for the first time could not be included as these are time dependent measures.

Figure 2c i: Type of cART and all individual drugs prescribed with ABC according to those initiating ABC for the first time or not by region in 2009

Figure 2c ii: Type of cART and all individual drugs prescribed with ABC according to those initiating ABC for the first time or not by region in 2010

Figure 2c iii: Type of cART and all individual drugs prescribed with ABC according to those initiating ABC for the first time or not by region in 2011

Figure 2c iv: Type of cART and all individual drugs prescribed with ABC according to those initiating ABC for the first time or not by region in 2012

Figure 2c v: Type of cART and all individual drugs prescribed with ABC according to those initiating ABC for the first time or not by region in 2013

Figure 2c vi: Type of cART and all individual drugs prescribed with ABC according to those initiating ABC for the first time or not by region in 2014

Figure 2c vii: Type of cART and all individual drugs prescribed with ABC according to those initiating ABC for the first time or not by region in 2015

Figure 2c viii: Type of cART and all individual drugs prescribed with ABC according to those initiating ABC for the first time or not by region in 2016

Figure 3a. Kaplan-Meier failure estimates of time to from ABC initiation to ABC discontinuation due to any reason in the first exposure to ABC. Individuals were censored at 6 weeks after ABC initiation, ABC discontinuation or death. Note: only displaying figures containing 30 or more individuals discontinuing for that reason.

Figure 3b. A sensitivity analysis: Kaplan-Meier failure estimates of time to from ABC initiation to ABC discontinuation due to any reason in the first exposure to ABC. Individuals were censored at 4 weeks after ABC initiation, ABC discontinuation or death. Note: only displaying figures containing 30 or more individuals discontinuing for that reason

1.3. 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

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 was 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. BACKGROUND AND RATIONALE

3.1. 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).

3.2. 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.

4. RESEARCH QUESTION AND OBJECTIVE(S)

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

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

    a. Calculate 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 were 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 categories a: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 were 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, given that a discontinuation in the relevant category occurred

    c. Estimate the incidence rate of ABC discontinuation due to categories 2 b: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 were presented overall as well as stratified according to:

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

Objective 2b was 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 was also presented.

5. RESEARCH METHODS

5.1. Study Design

This was 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 only included individuals who receive or initiate ABC after 1/1/2009.

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

The study objectives are described in section 5.8. 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] sought to identify factors associated with ABC initiation [1d] and discontinuation due to HSR [2e]. These analyses compared the incidence of ABC initiation and discontinuation according to a number of demographic and clinical characteristics. The end-point for analysis [1d] was initiation of ABC. The end-point for analysis [2e] was the discontinuation of ABC due to HSR. The measures of effect for both [1d] and [2e] was raw incidence rates, unadjusted rate ratios and adjusted rate ratios.

5.2. Study Population and Setting

Description of the EuroSIDA cohort

This analysis included 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 was 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 was 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 a.

Table a. 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
	Treatment related to risk of CVD: antihypertensives, antidiabetics, antiplatelets lipid lowering medication
Clinical events	Opportunistic infections
	Cardiovascular events, end stage renal and liver
	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 were 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

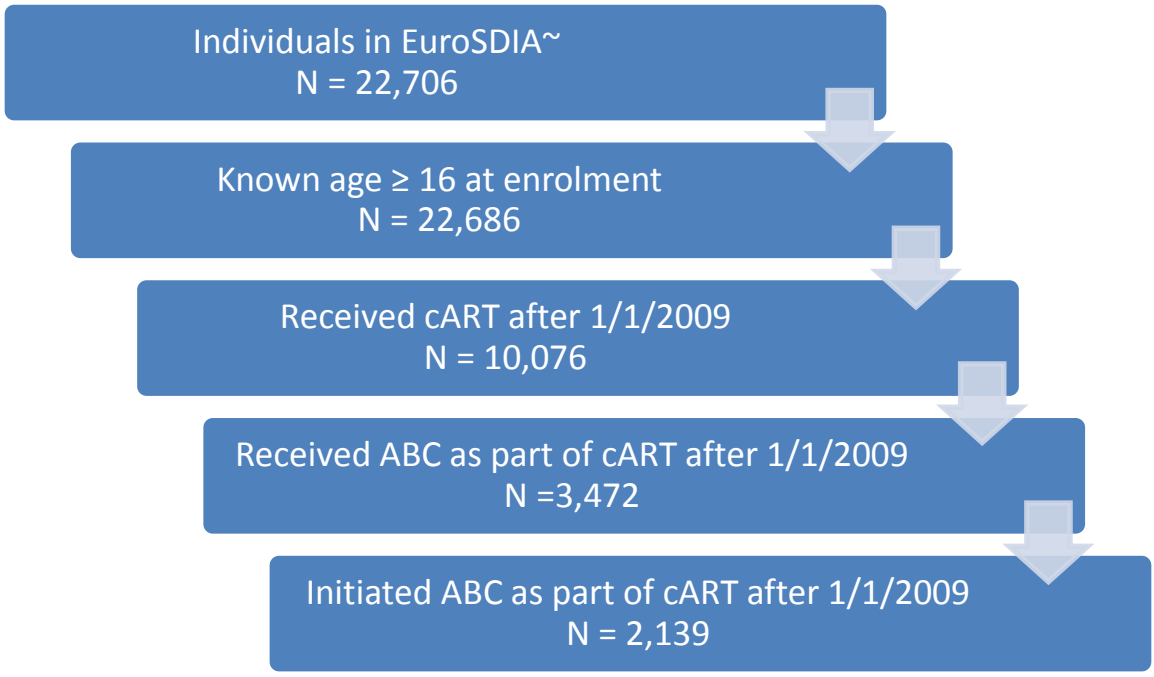
cannot rule out that there are differences between treatment groups that we cannot control for in the analyses. In addition, the people enrolled in EuroSIDA are by definition those that are linked to and retained in care. They may differ in significant ways from individuals who do not access or enter 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 were be eligible for inclusion (Objective 1). Objective 2 further required all individuals to have initiated ABC after 1/1/2009. Drug exposure prior to EuroSIDA enrolment cannot be assessed, and was not be considered for the inclusion criteria.

Figure 1. Flowchart of the participant selection



5.3. Variables

5.3.1. Exposure definitions

Identifying HSR cases

Utilising the available data elements collected in the 6-monthly EuroSIDA follow-up data collection, the potential cases were 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 were be described per calendar year and geographical region. EuroSIDA has developed standard categorisations of geographical regions which were used in this analysis, as detailed in Table b below. Events were described per region per year where possible.

Table b. 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	

5.3.2. Outcome definitions

The outcome for Objective 1 was be receipt of ABC. ABC information was provided by the treating physician, and collected in EuroSIDA in four possible ways. ABC treatment could 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 c.

Table c. 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 was ABC discontinuation. Stop dates of ABC were provided by the treating physician, with an option of indicating the reason for stopping the drug. Only one reason per drug was collected. Possible reasons are shown in Table d below.

Table d. Reasons for discontinuation collected in

Discontinuation	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 was 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) was not counted as a discontinuation. ABC discontinuation due to HSR was 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), were presumed to be due to HSR (representing a worst-case scenario) was conducted.

5.3.3. 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 presented a detailed overview of the characteristics of patients starting and not starting ABC to assess bias, and adjusted 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 were be evaluated for objective 1 and 2 can be seen in Table e below.

Table e. Factors to evaluate for their association with ABC

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

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	
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.*

5.4. Data sources

Data used for this analysis will come from the existing EuroSIDA cohort study, and no additional data collection was undertaken. 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).

5.5. Data management

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

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

5.5.2. Timings of Assessment during follow-up

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

5.6. Data analysis

The primary objectives of this analysis were 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.

5.7. Statistical Analysis

The proportion of individuals who received ABC on the 1/7 (1st of July) of each calendar year from 1/1/2009 onwards were described graphically, using everyone receiving cART and under active follow-up (FU) at the same date as the denominator. Active FU was defined as 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 were 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 could move from one group to another over time. The type of cART (triple NRTI, NNRTI, PI, INSTI, Other) and individual drugs prescribed with ABC were also described, as well as the use of different ABC formulations (Ziagen, Trivizir, Kivexa and Triumeq). These descriptions were stratified, comparing those initiating ABC for the first time or not. All treatment utilisation descriptions were 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) were summarised. We described HIV RNA, CD4, ALT, Framingham risk score, the DAD CKD risk score, FIB-4, APRI, haemoglobin and creatinine levels 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 was 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) were 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 was defined as the 1/1/2009 or enrolment into EuroSIDA, whichever occurred latest. Individuals with prior ABC exposure were included. It was likely that some patients who were on older ABC containing regimens may be using newer options such as Triumeq in their cART regimen and it is important to capture such potential re-exposures.

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

5.7.1. Objective 2

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

Baseline characteristics were compared among individuals remaining on ABC throughout their FU, discontinued 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 were 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 were conducted separately for the first or repeated exposure to ABC. Factors associated with HSR-related discontinuation were identified in a multivariable Poisson Regression Model using GEE to adjust for repeated events. Factors investigated for their association with ABC initiation are shown in Table e; those that were significant ($p<0.1$) in univariable analyses were 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) was conducted. We also conducted 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 was also conducted.

5.7.2. General considerations for data analyses

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

Not all variables within EuroSIDA were 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 chose to include a missing category for where data are missing in order to maximise the number of individuals that could be included.

5.8. 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.

5.9. Limitations of the research methods

This study has a number of 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 was 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 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 was complemented by site monitoring visits by EuroSIDA coordinating center staff. Nonetheless, it is

possible that ART drugs were 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.

6. RESULTS

6.1. Executive Summary

Between January 1, 2009 and April 1, 2016, 10,076 individuals in EuroSIDA received cART, of which 3,472 (34%) individuals received an ABC- based cART regimen. South Europe had the lowest proportion on ABC (30%) followed by Central Europe (33%), Central-East Europe (37%), and North-West Europe (38%) and East Europe (38%), **Table 1b**. In general, ABC use remained fairly constant over time starting at 28% in 2009, dropping to 26% in 2010 and increasing to 31% in 2016, **Table 1a**. This pattern over time remained similar across regions.

NNRTI regimens were the most common cART type followed by PI, triple NRTI and INSTI, although this did change over time with INSTI becoming much more utilized in 2015 and 2016, **Table 2a**. Overall, 88% of individuals were prescribed lamivudine with ABC, making this the most common drug prescribed with ABC. Lamivudine remained the most common drug prescribed with ABC over time and among all regions, **Table 2a/b**.

In multivariable Poisson models, several factors were associated with ABC initiation. Lower rates of ABC initiation were found among older individuals, Central and North-West Europe (compared to Southern Europe), higher CD4 cell counts, higher lines of therapy, and previous AIDS diagnosis. Higher rates of ABC initiation were found among Central-East and Eastern Europe (compared to Southern Europe), higher HIV-RNA, CKD, and higher DAD risk scores. There was also heterogeneity associated with ABC initiation over time with ABC initiation being the lowest in 2014, **Table 5a**.

Hypersensitivity reaction or any other toxicity was the most common reason for discontinuing ABC among those discontinuing 6 weeks after ABC initiation (n = 35, IR = 4.5 (95% CI 3.2, 6.3) per 100-person years follow-up. There were no factors significantly associated with HSR or any toxicity in univariable Poisson models, **Table 10**.

6.2. ***Objective 1***

Table 1 summarizes the patient population. Among 10,076 individuals in EuroSIDA receiving cART Between January 1, 2009 and April 1, 2016, 74% were male and 27% were female with HIV risk-group of MSM (40%), IDU (22%) MSW (31%) or other/unknown (7%). The highest proportion received care in Southern Europe (28%) followed by Central Europe (25%), North-West Europe (22%), Central-East Europe (14%), and East Europe (12%). Median baseline age, defined as 1/1/2009 or enrolment into EuroSIDA, was 44.77. (37.43, 51.52). In general, those exposed to ABC were similar to those not exposed, apart from baseline age, with those receiving ABC slightly older than those not receiving ABC.

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

	No ABC		ABC		Total	
	No.	**%**	**No.**	**%**	**No.**	**%**
Gender						
Female	4926	75	2482	72	7408	74
Male	1678	25	990	29	2668	27
Region						
South Europe	1962	30	857	25	2819	28
Central Europe	1672	25	806	23	2478	25
North-West Europe	1348	20	839	24	2187	22
Central-East Europe	897	14	533	15	1430	14
East Europe	725	11	437	13	1162	12
Ethnicity						
White	5,773	87	3,054	88	8,827	88
Black	361	6	202	6	563	6
Asian	108	2	55	2	163	2
OTH/NK	362	6	161	5	523	5
HIV-Risk group						
MSM	2,701	41	1,353	39	4,054	40
IDU	1,438	22	760	22	2,198	22
MSW	2,012	31	1,126	32	3,138	31
OTH/NK	453	7	233	7	686	7
Calendar year*						
2009	4,499	68	2,521	73	7,020	70
2010	358	5	149	4	507	5
2011	229	4	131	4	360	4
2012	319	5	123	4	442	4
2013	366	6	180	5	546	5
2014	304	5	87	3	391	4
2015	408	6	215	6	623	6
2016	121	2	66	2	187	2
Entry Age - median	44.55	(36.99, 51.21)	51.21	(38.32, 51.93)	44.77	(37.43, 51.52)

(IQR)

Baseline is defined as entry to the study which is 1/1/2009 or enrolment into EuroSIDA, whichever occurred latest.

% are column percentages

* calendar year of first ABC initiation

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

Abbreviations: MSM - sex between men; IDU - injection drug use; MSW - sex between men and women; OTH/NK - other, unknown; IQR – interquartile range.

Table 1a presents the number of individuals receiving cART and a cART containing ABC overall, and stratified by region of care. Individuals receiving ABC were classified into four categories, namely: 1. Starting ABC from naïve, 2. Switching to ABC for the first time (not naïve), 3. Restarting ABC, and 4. Maintained on ABC. For example, in 2009, 6418 individuals were receiving cART, of which 1818 (28%) were on a regimen containing ABC. The overall results are summarized in Figures 1a i-v which shows changes in ABC utilization over time. There was a significant trend for higher ABC utilization over time overall (p-trend = 0.001), among those restarting ABC (p-trend = 0.022), and maintained on ABC (p-trend = 0.001). There was no significant difference in first ABC use over time.

Table 1a: % on ABC over time overall and according to individuals who started ABC from naïve, switched to ABC for the first time that year, individuals re-starting ABC that year, and individuals maintained on ABC

		Overall		Southern Europe		Central Europe		North West Europe		Central East Europe		East Europe	
Year	Category	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
2009	Overall	1818/6418	28	445/1940	23	452/1676	27	604/1657	36	201/693	29	116/452	26
	ABC from naïve	38/6418	1	3/1940	0	6/1676	0	8/1657	0	14/693	2	7/452	2
	Switched to ABC	130/6418	2	27/1940	1	16/1676	1	24/1657	1	30/693	4	33/452	7
	Restarting ABC	43/6418	1	9/1940	0	12/1676	1	12/1657	1	5/693	1	5/452	1
	Maintained on ABC	1607/6418	25	406/1940	21	418/1676	25	560/1657	34	152/693	22	71/452	16
2010	Overall	1747/6644	26	402/1927	21	427/1744	24	533/1679	32	272/799	34	113/495	23
	ABC from naïve	30/6644	0	1/1927	0	1/1744	0	1/1679	0	21/799	3	6/495	1
	Switched to ABC	109/6644	2	10/1927	1	15/1744	1	18/1679	1	51/799	6	15/495	3
	Restarting ABC	47/6644	1	12/1927	1	11/1744	1	16/1679	1	7/799	1	1/495	0
	Maintained on ABC	1561/6644	23	379/1927	20	400/1744	23	498/1679	30	193/799	24	91/495	18
2011	Overall	1783/6700	27	401/1846	22	415/1760	24	495/1668	30	322/870	37	150/556	27
	ABC from naïve	40/6700	1	6/1846	0	0/1760	0	1/1668	0	10/870	1	23/556	4

	Switched to ABC	134/6700	2	39/1846	2	12/1760	1	9/1668	1	44/870	5	30/556	5
	Restarting ABC	46/6700	1	10/1846	1	14/1760	1	8/1668	0	11/870	1	3/556	1
	Maintained on ABC	1563/6700	23	346/1846	19	389/1760	22	477/1668	29	257/870	30	94/556	17
2012	Overall	1853/6854	27	414/1831	23	431/1789	24	479/1660	29	336/924	36	193/650	30
	ABC from naïve	33/6854	0	6/1831	0	2/1789	0	2/1660	0	5/924	1	18/650	3
	Switched to ABC	129/6854	2	32/1831	2	27/1789	2	12/1660	1	19/924	2	39/650	6
	Restarting ABC	51/6854	1	16/1831	1	14/1789	1	13/1660	1	5/924	1	3/650	0
	Maintained on ABC	1640/6854	24	360/1831	20	388/1789	22	452/1660	27	307/924	33	133/650	20
2013	Overall	1965/7088	28	446/1866	24	452/1780	25	478/1695	28	355/1006	35	234/741	32
	ABC from naïve	38/7088	1	9/1866	0	1/1780	0	0/1695	0	8/1006	1	20/741	3
	Switched to ABC	147/7088	2	47/1866	3	31/1780	2	14/1695	1	21/1006	2	34/741	5
	Restarting ABC	48/7088	1	8/1866	0	18/1780	1	9/1695	1	7/1006	1	6/741	1
	Maintained on ABC	1732/7088	24	382/1866	20	402/1780	23	455/1695	27	319/1006	32	174/741	23
2014	Overall	1962/7073	28	473/1877	25	434/1733	25	463/1699	27	356/1050	34	236/714	33
	ABC from naïve	19/7073	0	7/1877	0	1/1733	0	0/1699	0	3/1050	0	8/714	1
	Switched to ABC	80/7073	1	30/1877	2	13/1733	1	8/1699	0	12/1050	1	17/714	2
	Restarting ABC	48/7073	1	13/1877	1	13/1733	1	12/1699	1	5/1050	0	5/714	1
	Maintained on ABC	1815/7073	26	423/1877	23	407/1733	23	443/1699	26	336/1050	32	206/714	29
2015	Overall	2061/7053	29	508/1896	27	457/1656	28	480/1691	28	375/1130	33	241/680	35
	ABC from naïve	32/7053	0	7/1896	0	3/1656	0	1/1691	0	3/1130	0	18/680	3
	Switched to ABC	144/7053	2	43/1896	2	37/1656	2	25/1691	1	20/1130	2	19/680	3
	Restarting ABC	76/7053	1	19/1896	1	22/1656	1	19/1691	1	10/1130	1	6/680	1
	Maintained on ABC	1809/7053	26	439/1896	23	395/1656	24	435/1691	26	342/1130	30	198/680	29
2016	Overall	559/1795	31	175/593	30	95/327	29	74/240	31	117/378	31	98/257	38
	ABC from naïve	9/1795	1	3/593	1	0/327	0	0/240	0	2/378	1	4/257	2
	Switched to ABC	54/1795	3	25/593	4	7/327	2	6/240	3	7/378	2	9/257	4
	Restarting ABC	17/1795	1	8/593	1	5/327	2	2/240	1	2/378	1	0/257	0
	Maintained on ABC	479/1795	27	139/593	23	83/327	25	66/240	28	106/378	28	85/257	33

*95% confidence intervals are suppressed to conserve space. To calculate the confidence interval, use the following formula: $p \pm 1.96 * (p(1-p)/\sqrt{n})$, where p is the proportion and n is the sample size

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

Figure 1a i: % on ABC overall by year

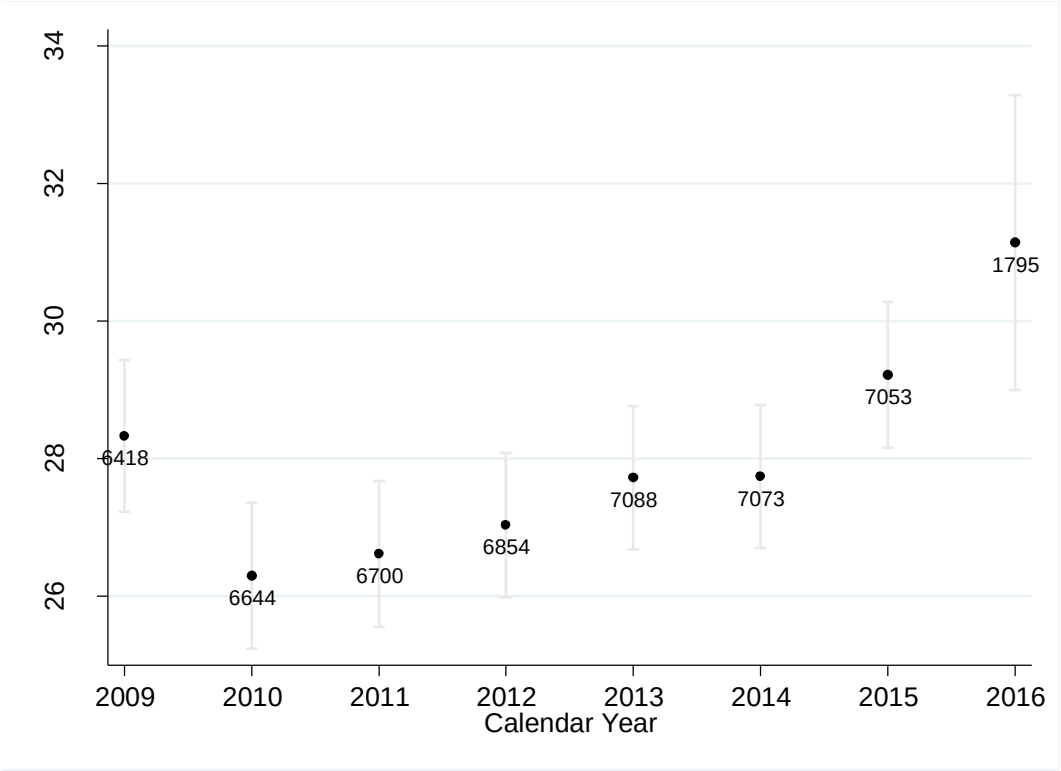


Figure 1a ii: % starting ABC from naïve by year

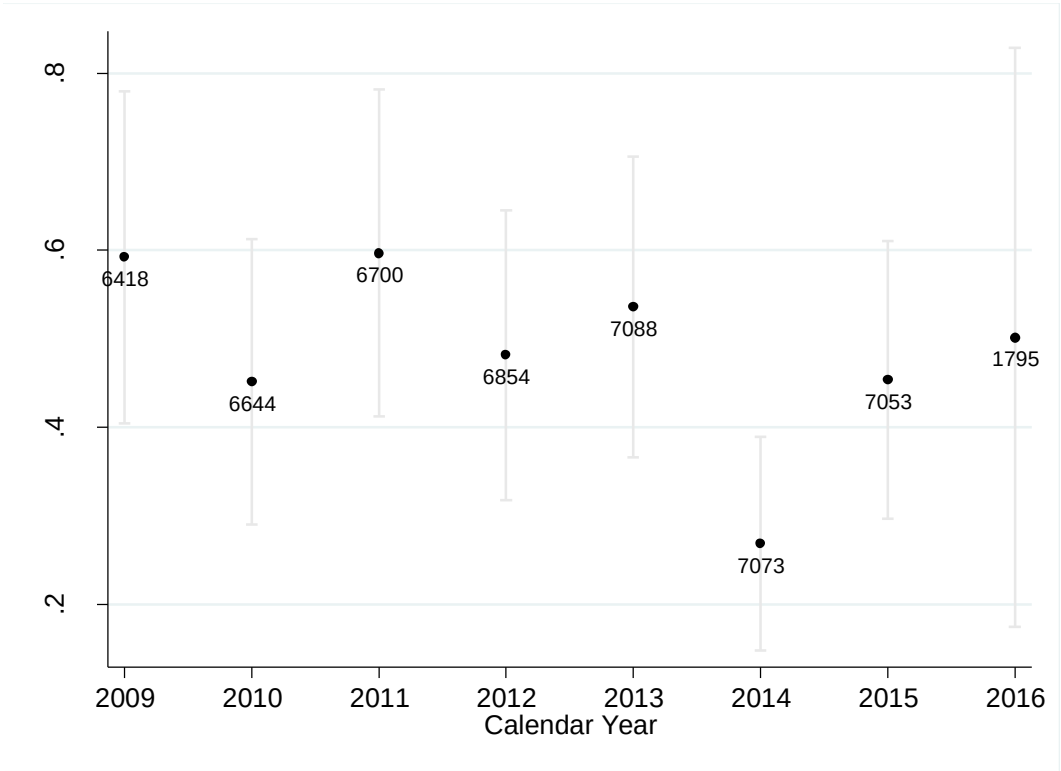


Figure 1a iii: % starting ABC for the first time by year

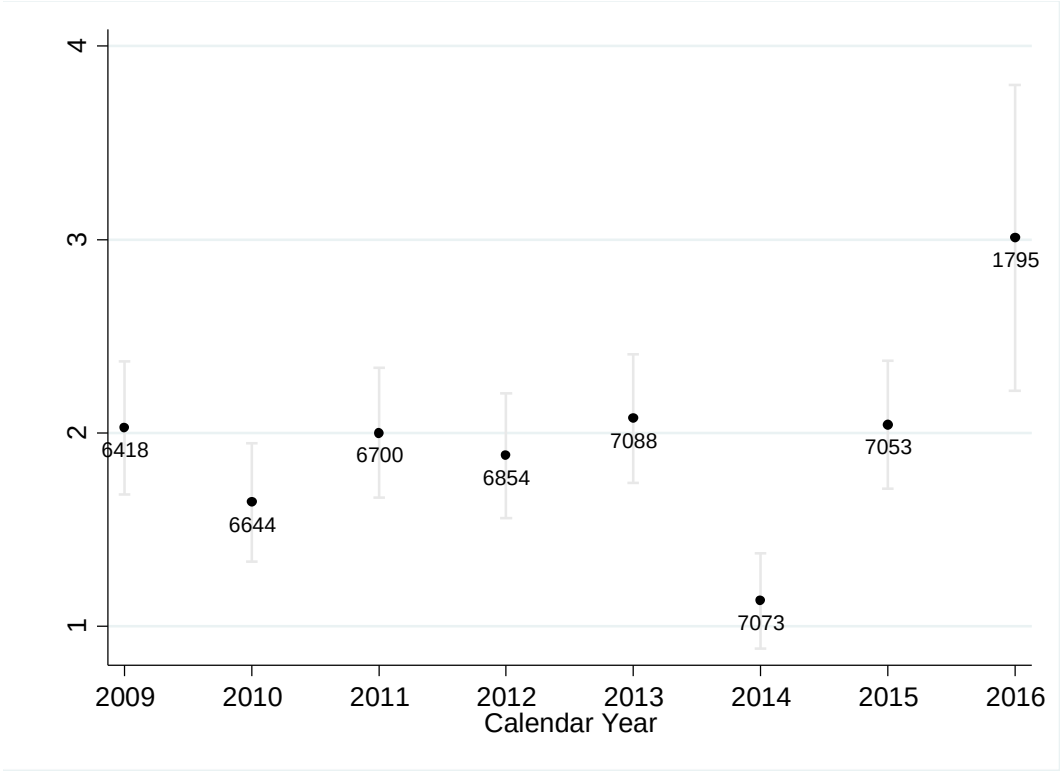


Figure 1a iv: % re-starting ABC by year

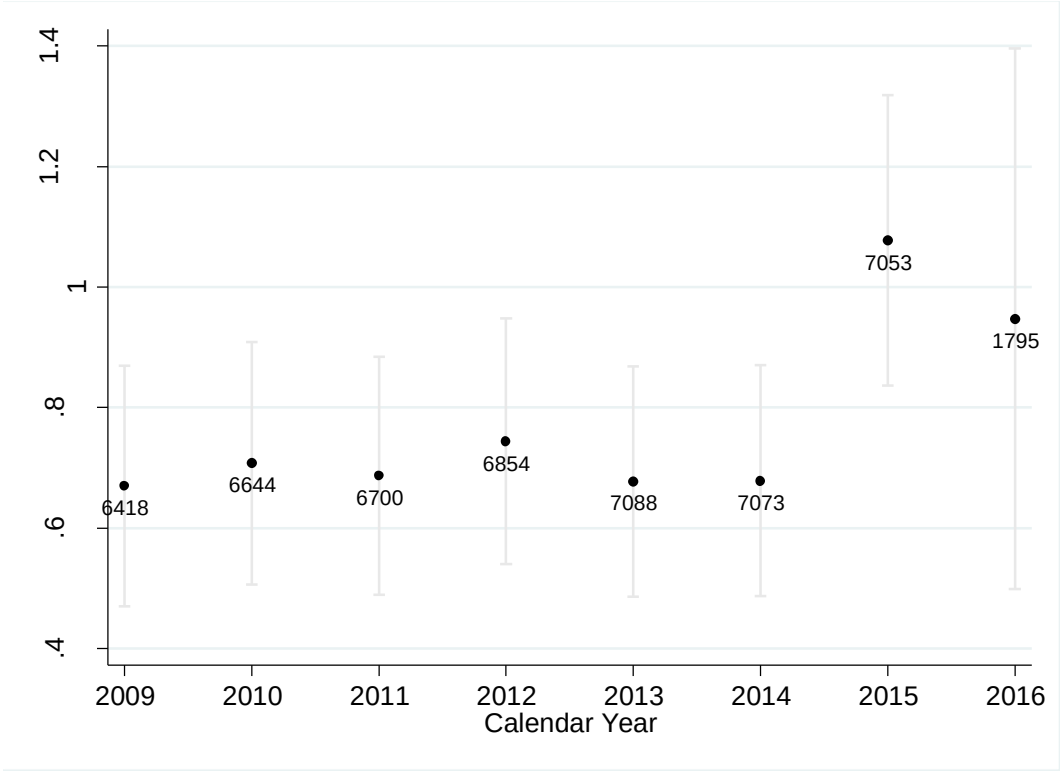


Figure 1a v: % maintained on ABC by year

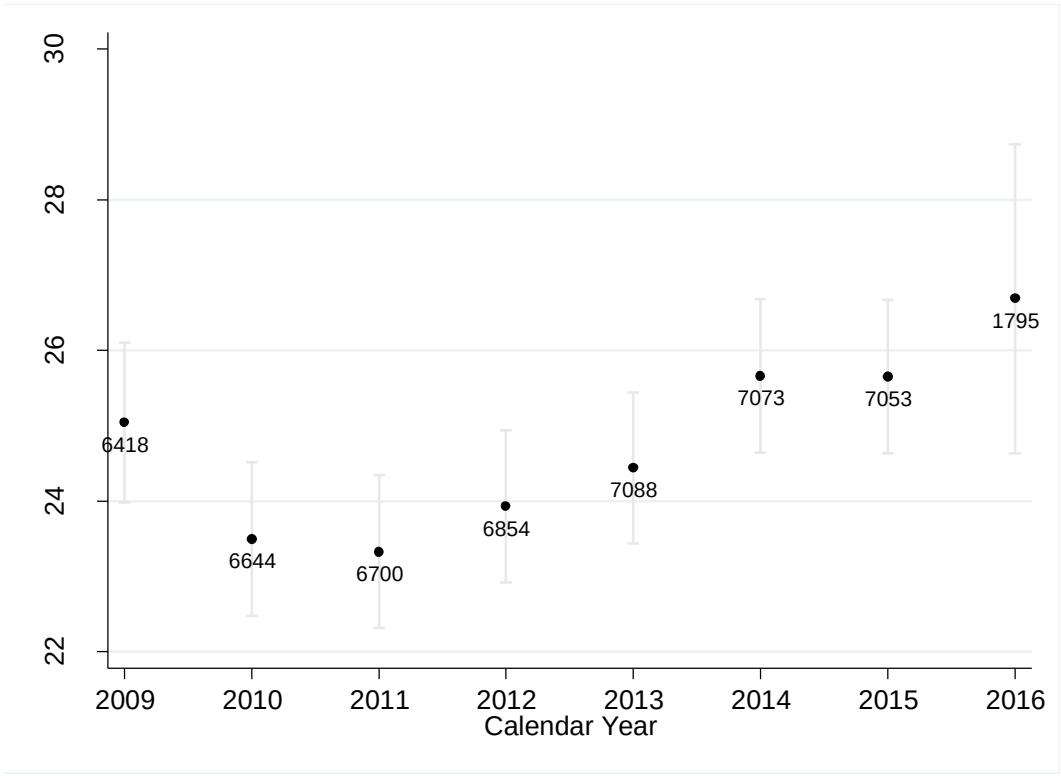


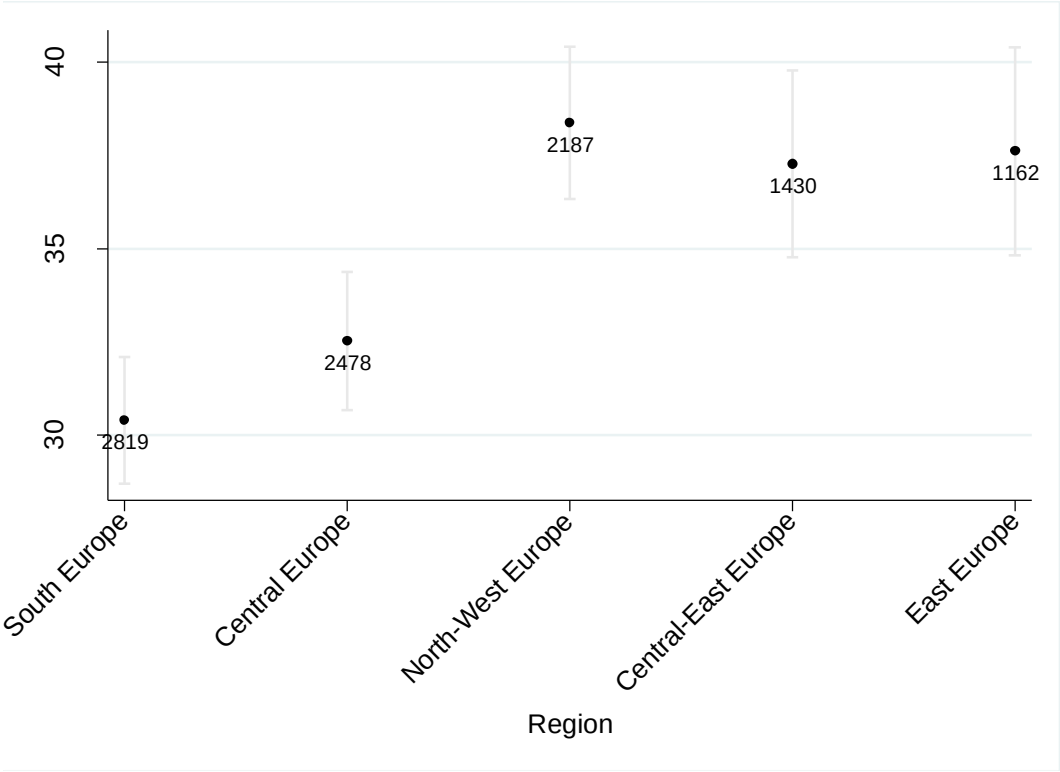
Table 1b presents the number of individuals receiving cART and a cART containing ABC stratified by region of care. There was significant heterogeneity in ABC utilization among region of care (p-heterogeneity < 0.001), with North-West and Eastern Europe having the highest percent of individuals receiving ABC containing regimens (38%), and Southern Europe with the lowest percent of individuals receiving ABC containing regimens (30%). Figure 1b represents this graphically.

Table 1b: % on ABC by region. Note: this cannot be broken down into ABC groups as this is a time dependent measure.

Region	n/N	%	95% CI
South Europe	857/2819	30	(29, 32)
Central Europe	806/2478	33	(31, 34)
North-West Europe	839/2187	38	(36, 40)
Central-East Europe	533/1430	37	(35, 40)
East Europe	437/1162	38	(35, 40)

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

Figure 1b: % on ABC by region. Note: this cannot be broken down into ABC groups as this is a time dependent measure.



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

Tables 2 a-c i-viii present the type of cART and all individuals drugs prescribed with ABC according to weather it is the individuals first ABC or not. Table 2a stratifies individual by year, Table 2b stratified individuals by region and table 2c i-viii stratified individuals by year and region. cART type and first ABC exposure are time dependent measures so are only described when stratified by year.

cART type significantly varied by year (chi-squared $p < 0.001$), with proportion of individuals on 3N, NNRTI, PI decreasing over time and INSTIs increasing over time. Type of cART also significantly varied by country (chi-squared $p < 0.001$) with Eastern Europe prescribing the highest proportion of individuals on 3Ns (43%), Central Europe prescribing the highest proportion of individuals on NNRTIs (40%), North-West Europe prescribing the highest proportion of PIs (37%) and Central Europe prescribing the highest proportion of individuals on INSTIs (20%).

Overall, Lamivudine (87%), Kivexa (50%), Ziagen(43%) and ritonavir (31%) were the most common drugs prescribed in combination with ABC. Overall, the proportion of individuals prescribed Lamivudine and Kivexa with ABC significantly increased over time (p-trend < 0.001), whereas the proportion of individuals prescribed Ziagen with other ABC decreased over time (p-trend < 0.001). The proportion of individuals receiving Lamivudine with their first ABC increased over time (p-trend = 0.05), but did not change significantly for Kivexa. The proportion of individuals receiving Ziagen or Ritonavir with their first ABC decreased over time (p-trend <0.001 and 0.02, respectively).

Lamivudine, Kivexa, Ziagen, and Ritonavir prescribed with ABC also varied by region (p-heterogenity < 0.001 for all drugs) with central Europe prescribing Lamivudine with ABC to 94% of individuals compared to Central Europe only prescribing 86% of individuals Lamivudine with ABC (p-heterogeneity < 0.001). Eastern Europe prescribed the highest proportion of individuals Ziagen with ABC (58%) compared to only 28% of individuals in Central Europe. North-West Europe prescribed 40% of individuals ritonavir with ABC compared to only 16% in Eastern Europe. (Table 2a).

Table 2a: Type of cART and all individual drugs prescribed with ABC overall and according to those initiating ABC for the first time or not by year (years 2013-2016 in following table). Note: type of cART cannot be assessed overall as this is a time dependent measure.

	Overall		2009				2010				2011				2012			
			1st ABC		Other		1st ABC		Other		1st ABC		Other		1st ABC		Other	
Drug	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
cART type																		
3N			31	23	503	24	32	29	474	22	29	22	448	20	24	19	443	19
NNRTI			58	43	726	34	37	34	727	34	61	46	754	34	59	46	800	35
PI			41	31	666	31	32	29	685	32	38	28	738	34	38	29	787	34
INSTI			1	1	101	5	6	6	131	6	4	3	139	6	7	5	171	7
Other			3	2	119	6	2	2	117	5	2	1	108	5	1	1	107	5
lamivudine	3,067	88	106	82	1,337	79	100	92	1,335	82	120	90	1,375	83	117	91	1,467	85
kivexa	1,919	55	74	57	639	38	75	69	700	43	89	66	789	48	88	68	907	53
ziagen	1,383	40	55	42	930	55	32	29	837	51	45	34	770	47	42	33	739	43
ritonavir	1,148	33	33	25	540	32	34	31	535	33	30	22	562	34	30	23	585	34
efavirenz	761	22	40	31	398	24	20	18	377	23	34	25	368	22	33	26	366	21
atazanavir	704	20	27	21	389	23	19	17	378	23	23	17	361	22	19	15	378	22
kaletra	586	17	32	25	285	17	29	27	253	15	27	20	237	14	24	19	234	14
darunavir	549	16	9	7	115	7	8	7	162	10	9	7	215	13	13	10	250	15
nevirapine	509	15	19	15	259	15	17	16	244	15	28	21	249	15	26	20	273	16
tenofovir	460	13	8	6	307	18	8	7	270	16	9	7	251	15	5	4	241	14
dolutegravir	417	12	0	0	1	0	0	0	1	0	0	0	1	0	0	0	1	0
raltegravir	391	11	2	2	105	6	6	6	130	8	5	4	133	8	7	5	160	9
zidovudine	297	9	4	3	220	13	6	6	171	10	1	1	143	9	3	2	118	7
triumeq	257	7	0	0	1	0	0	0	1	0	0	0	1	0	0	0	1	0
trizivir	206	6	2	2	168	10	2	2	141	9	1	1	121	7	1	1	98	6
didanosine	160	5	15	12	111	7	6	6	78	5	4	3	53	3	11	9	42	2
emtricitabine	126	4	1	1	51	3	0	0	48	3	5	4	49	3	3	2	52	3
etravirine	121	3	0	0	35	2	4	4	40	2	1	1	54	3	0	0	56	3
amprenavir	110	3	2	2	66	4	2	2	61	4	5	4	57	3	4	3	50	3

rilpivirine	79	2	0	0	0	0	0	0	0	0	0	0	0	0	1	1	2	0
saquinavir hard	78	2	2	2	60	4	4	4	42	3	2	1	41	2	2	2	35	2
maraviroc	38	1	1	1	9	1	0	0	12	1	1	1	16	1	0	0	17	1
stavudine	30	1	2	2	23	1	1	1	16	1	0	0	12	1	0	0	12	1
nelfinavir	19	1	1	1	12	1	1	1	12	1	2	1	12	1	1	1	13	1
cobicistat	17	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
tipranavir	15	0	1	1	13	1	1	1	9	1	0	0	8	0	0	0	5	0
saquinavir	14	0	0	0	7	0	2	2	6	0	0	0	6	0	0	0	6	0
indinavir	14	0	0	0	10	1	1	1	7	0	0	0	7	0	0	0	6	0
enfurvitide	13	0	0	0	12	1	0	0	9	1	0	0	5	0	0	0	3	0
saquinavir soft	9	0	1	1	6	0	0	0	4	0	2	1	1	0	0	0	2	0
zalcitabine	9	0	0	0	6	0	0	0	5	0	0	0	5	0	0	0	6	0
elvitegravir	8	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
pbt	5	0	0	0	1	0	0	0	2	0	0	0	2	0	0	0	2	0
ART unspecified	2	0	0	0	2	0	0	0	2	0	0	0	2	0	0	0	2	0
delivirdine	2	0	0	0	2	0	0	0	2	0	0	0	2	0	0	0	2	0
NRTI unspecified	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

% are column percentages

Table 2a continued: Type of cART and all individual drugs prescribed with ABC according to those initiating ABC for the first time or not by year

	2013				2014				2015				2016			
	1st ABC		Other		1st ABC		Other		1st ABC		Other		1st ABC		Other	
Drug	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
cART type																
3N	28	19	453	18	9	11	473	18	12	8	453	16	6	5.8	465	16
NNRTI	66	44	863	35	33	41	926	35	45	31	947	34	15	15	943	32
PI	38	25	825	34	22	28	827	32	18	12	789	28	6	5.8	749	25
INSTI	14	9	210	9	14	18	279	11	66	46	498	18	76	74	716	24
Other	4	3	110	4	2	3	110	4	4	3	106	4	0	0	111	4
lamivudine	141	96	1,568	86	79	99	1,647	88	142	99	1,733	90	54	100	461	91
kivexa	106	72	1,026	56	69	86	1,131	60	90	63	1,172	61	19	35	274	54
ziagen	39	27	725	40	11	14	690	37	17	12	645	34	6	11	161	32
ritonavir	34	23	604	33	21	26	585	31	19	13	529	28	3	6	108	21
efavirenz	34	23	376	21	15	19	368	20	27	19	312	16	5	9	88	17
atazanavir	21	14	358	20	14	18	314	17	11	8	274	14	4	7	48	10
kaletra	20	14	242	13	9	11	241	13	11	8	213	11	1	2	52	10
nevirapine	15	10	294	16	6	8	310	16	12	8	294	15	1	2	73	14
darunavir	26	18	291	16	15	19	300	16	14	10	293	15	3	6	44	9
dolutegravir	6	4	233	13	0	0	221	12	12	8	195	10	1	2	53	10
tenofovir	0	0	3	0	3	4	41	2	55	38	252	13	33	61	132	26
zidovudine	14	10	189	10	11	14	209	11	11	8	193	10	5	9	48	10
raltegravir	8	5	109	6	2	3	92	5	2	1	74	4	1	2	22	4
triumeq	0	0	1	0	0	0	4	0	37	26	128	7	29	54	96	19
trizivir	3	2	90	5	1	1	76	4	0	0	58	3	0	0	11	2
didanosine	0	0	39	2	1	1	31	2	0	0	13	1	0	0	3	1

emtricitabine	3	2	53	3	0	0	52	3	13	9	53	3	1	2	17	3
amprenavir	7	5	57	3	1	1	66	4	3	2	53	3	0	0	9	2
etravirine	4	3	50	3	2	3	43	2	2	1	37	2	1	2	8	2
saquinavir hard	2	1	16	1	3	4	41	2	6	4	68	4	0	0	16	3
stavudine	1	1	32	2	0	0	29	2	0	0	22	1	0	0	3	1
rilpivirine	0	0	18	1	1	1	20	1	0	0	20	1	0	0	4	1
nelfinavir	2	1	7	0	1	1	8	0	0	0	7	0	0	0	1	0
maraviroc	0	0	11	1	0	0	9	0	0	0	8	0	0	0	2	0
indinavir	0	0	2	0	0	0	2	0	1	1	5	0	2	4	8	2
combicistat	0	0	2	0	0	0	2	0	0	0	0	0	0	0	0	0
tipranavir	0	0	6	0	1	1	5	0	0	0	3	0	0	0	0	0
saquinavir soft	1	1	4	0	0	0	5	0	1	1	4	0	0	0	0	0
enfurvitide	0	0	3	0	0	0	2	0	0	0	0	0	0	0	0	0
saquinavir	0	0	2	0	0	0	2	0	0	0	2	0	0	0	0	0
zalcitabine	0	0	4	0	0	0	2	0	1	1	2	0	0	0	1	0
elvitegravir	0	0	2	0	0	0	2	0	0	0	4	0	0	0	3	1
pbt	0	0	1	0	0	0	2	0	0	0	2	0	0	0	0	0
delivirdine	0	0	2	0	0	0	2	0	0	0	0	0	0	0	0	0
ART unspecified	0	0	2	0	0	0	2	0	0	0	0	0	0	0	0	0
NRTI unspecified	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0

% are column percentages

Figure 2b: All individual drugs prescribed with ABC by Region. Note: type of cART and stratification by individual's initiation ABC for the first time could not be included as these are time dependent measures.

	South Europe		Central Europe		North West Europe		Central East Europe		East Europe	
Drug	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
lamivudine	748	87	695	86	735	88	500	94	389	89
kivexa	457	53	431	53	474	56	379	71	178	41
ziagen	375	44	319	40	287	34	150	28	252	58
ritonavir	258	30	305	38	338	40	175	33	72	16
efavirenz	146	17	122	15	208	25	146	27	139	32
atazanavir	190	22	162	20	243	29	70	13	39	9
kaletra	105	12	85	11	113	13	131	25	152	35
darunavir	97	11	181	22	153	18	76	14	42	10
nevirapine	164	19	127	16	126	15	72	14	20	5
tenofovir	119	14	141	17	132	16	47	9	21	5
dolutegravir	99	12	155	19	127	15	35	7	1	0
raltegravir	103	12	143	18	89	11	38	7	18	4
zidovudine	69	8	101	13	45	5	29	5	53	12
triumeq	55	6	86	11	93	11	23	4	0	0
trizivir	34	4	87	11	53	6	16	3	16	4
didanosine	46	5	24	3	29	3	13	2	48	11
emtricitabine	41	5	29	4	31	4	17	3	8	2
etravirine	38	4	41	5	23	3	13	2	6	1
amprenavir	33	4	28	3	9	1	24	5	16	4
rilpivirine	41	5	9	1	11	1	10	2	8	2
saquinavir hard	12	1	17	2	20	2	24	5	5	1

maraviroc	7	1	22	3	7	1	2	0	0	0
stavudine	11	1	6	1	3	0	1	0	9	2
nelfinavir	5	1	5	1	3	0	4	1	2	0
cobicistat	5	1	5	1	5	1	2	0	0	0
tipranavir	7	1	4	0	1	0	3	1	0	0
indinavir	3	0	2	0	2	0	7	1	0	0
saquinavir	1	0	0	0	5	1	6	1	2	0
enfurvitide	3	0	3	0	2	0	1	0	4	1
zalcitabine	2	0	4	0	1	0	2	0	0	0
saquinavir soft	3	0	2	0	3	0	1	0	0	0
elvitegravir	3	0	1	0	3	0	1	0	0	0
pbt	3	0	0	0	0	0	1	0	1	0
ART unspecified	0	0	2	0	0	0	0	0	0	0
delivirdine	0	0	0	0	2	0	0	0	0	0
NRTI unspecified	1	0	0	0	0	0	0	0	0	0

*% are column percentages

Figure 2c i: Type of cART and all individual drugs prescribed with ABC according to those initiating ABC for the first time or not by region in 2009

	Southern Europe				Central Europe				North West Europe				Central East Europe				East Europe			
	1st ABC		Other		1st ABC		Other		1st ABC		Other		1st ABC		Other		1st ABC		Other	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
cART type																				
3N	3	11	88	21	4	25	89	20	5	21	91	16	5	17	52	30	13	39	37	45
NNRTI	11	41	144	34	3	19	128	29	14	58	243	42	16	53	55	32	12	36	28	34
PI	12	44	150	36	8	50	151	35	4	17	195	34	9	30	54	32	7	21	13	16
INSTI	0	0	25	6	1	6	38	9	0	0	31	5	0	0	4	2	0	0	0	0
Other	1	4	11	3	0	0	30	7	1	4	20	3	0	0	6	4	1	3	5	6
Drugs																				
lamivudine	21	78	321	77	12	75	345	79	23	96	475	82	29	97	138	81	21	64	58	70
kivexa	13	48	132	32	12	75	161	37	23	96	278	48	21	70	53	31	5	15	15	18
ziagen	14	52	267	64	5	31	239	55	1	4	243	42	8	27	116	68	27	82	65	78
ritonavir	10	37	122	29	5	31	159	36	5	21	199	34	8	27	47	27	5	15	13	16
efavirenz	5	19	84	20	2	13	81	19	11	46	170	29	12	40	38	22	10	30	25	30
atazanavir	9	33	99	24	7	44	96	22	4	17	169	29	3	10	19	11	4	12	6	7
kaletra	3	11	65	16	6	38	59	14	6	25	88	15	5	17	49	29	12	36	24	29
darunavir	1	4	20	5	0	0	55	13	0	0	24	4	5	17	7	4	3	9	9	11
nevirapine	7	26	68	16	1	6	68	16	4	17	96	17	4	13	23	13	3	9	4	5
tenofovir	2	7	73	17	3	19	106	24	2	8	108	19	1	3	20	12	0	0	0	0
dolutegravir	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
raltegravir	0	0	26	6	1	6	42	10	0	0	33	6	1	3	4	2	0	0	0	0
zidovudine	0	0	60	14	0	0	87	20	0	0	39	7	1	3	20	12	3	9	14	17
triumeq	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
trizivir	0	0	30	7	0	0	73	17	0	0	49	8	1	3	12	7	1	3	4	5
didanosine	5	19	34	8	0	0	22	5	0	0	28	5	0	0	12	7	10	30	15	18

emtricitabine	0	0	14	3	1	6	12	3	0	0	16	3	0	0	9	5	0	0	0	0
etravirine	0	0	7	2	0	0	15	3	0	0	10	2	0	0	2	1	0	0	1	1
amprenavir	2	7	24	6	0	0	22	5	0	0	9	2	0	0	11	6	0	0	0	0
rilpivirine	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
saquinavir hard	1	4	10	2	1	6	14	3	0	0	19	3	0	0	15	9	0	0	2	2
maraviroc	0	0	1	0	0	0	6	1	0	0	1	0	1	3	1	1	0	0	0	0
stavudine	0	0	10	2	0	0	4	1	0	0	2	0	0	0	1	1	2	6	6	7
nelfinavir	0	0	5	1	0	0	4	1	0	0	1	0	0	0	2	1	1	3	0	0
cobicistat	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
tipranavir	0	0	7	2	0	0	4	1	0	0	1	0	1	3	1	1	0	0	0	0
indinavir	0	0	3	1	0	0	1	0	0	0	2	0	0	0	4	2	0	0	0	0
saquinavir	0	0	1	0	0	0	0	0	0	0	4	1	0	0	2	1	0	0	0	0
enfurvitide	0	0	3	1	0	0	3	1	0	0	2	0	0	0	1	1	0	0	3	4
zalcitabine	0	0	2	0	0	0	2	0	0	0	1	0	0	0	1	1	0	0	0	0
saquinavir soft	0	0	1	0	0	0	2	0	1	4	2	0	0	0	1	1	0	0	0	0
elvitegravir	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
pbt	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ART unspecified	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0
delivirdine	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0
NRTI unspecified	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

% are column percentages

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

Figure 2c ii: Type of cART and all individual drugs prescribed with ABC according to those initiating ABC for the first time or not by region in 2010

	Southern Europe				Central Europe				North West Europe				Central East Europe				East Europe			
	1st ABC		Other		1st ABC		Other		1st ABC		Other		1st ABC		Other		1st ABC		Other	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
cART type																				
3N	2	20	71	18	3	20	79	19	4	22	68	13	13	25	56	25	10	67	41	42
NNRTI	4	40	129	33	3	20	117	28	5	28	207	40	22	43	86	39	3	20	34	35
PI	4	40	151	39	6	40	146	35	5	28	184	36	16	31	62	28	1	7	17	17
INSTI	0	0	29	7	3	20	45	11	3	17	38	7	0	0	10	5	0	0	0	0
Other	0	0	12	3	0	0	25	6	1	6	18	4	0	0	7	3	1	7	6	6
Drugs																				
lamivudine	8	80	297	76	13	87	333	81	17	94	433	84	51	100	195	88	11	73	77	79
kivexa	5	50	128	33	9	60	160	39	14	78	277	54	44	86	113	51	3	20	22	22
ziagen	5	50	247	63	5	33	212	51	4	22	196	38	7	14	109	49	11	73	73	74
ritonavir	4	40	126	32	6	40	148	36	7	39	186	36	15	29	58	26	2	13	17	17
efavirenz	1	10	73	19	3	20	72	17	3	17	141	27	11	22	62	28	2	13	29	30
atazanavir	2	20	103	26	4	27	94	23	4	22	150	29	8	16	23	10	1	7	8	8
kaletra	2	20	54	14	3	20	46	11	5	28	69	13	13	25	53	24	6	40	31	32
darunavir	1	10	26	7	4	27	60	15	3	17	48	9	0	0	16	7	0	0	12	12
nevirapine	1	10	62	16	1	7	63	15	2	11	84	16	11	22	31	14	2	13	4	4
tenofovir	1	10	68	17	4	27	90	22	1	6	88	17	0	0	22	10	2	13	2	2
dolutegravir	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
raltegravir	0	0	31	8	3	20	49	12	3	17	39	8	0	0	11	5	0	0	0	0
zidovudine	0	0	44	11	1	7	79	19	1	6	27	5	0	0	9	4	4	27	12	12
triumeq	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
trizivir	0	0	26	7	1	7	71	17	0	0	33	6	0	0	8	4	1	7	3	3
didanosine	2	20	30	8	0	0	16	4	1	6	13	3	0	0	9	4	3	20	10	10

emtricitabine	0	0	18	5	0	0	6	1	0	0	17	3	0	0	7	3	0	0	0	0
etravirine	2	20	7	2	0	0	15	4	2	11	12	2	0	0	3	1	0	0	3	3
amprenavir	1	10	23	6	0	0	17	4	0	0	7	1	1	2	14	6	0	0	0	0
rilpivirine	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
saquinavir hard	0	0	6	2	0	0	12	3	0	0	14	3	3	6	8	4	1	7	2	2
maraviroc	0	0	4	1	0	0	5	1	0	0	1	0	0	0	2	1	0	0	0	0
stavudine	0	0	8	2	0	0	4	1	1	6	1	0	0	0	0	0	0	0	3	3
nelfinavir	0	0	4	1	0	0	4	1	1	6	1	0	0	0	3	1	0	0	0	0
cobicistat	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
tipranavir	0	0	5	1	0	0	3	1	0	0	0	0	1	2	1	0	0	0	0	0
indinavir	0	0	3	1	0	0	0	0	0	0	1	0	1	2	3	1	0	0	0	0
saquinavir	0	0	0	0	0	0	0	0	0	0	4	1	2	4	2	1	0	0	0	0
enfurvitide	0	0	2	1	0	0	2	0	0	0	1	0	0	0	0	0	0	0	4	4
zalcitabine	0	0	2	1	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0	0
saquinavir soft	0	0	1	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0	0
elvitegravir	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
pbt	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
ART unspecified	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0
delivirdine	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0
NRTI unspecified	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

% are column percentages

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

Figure 2c iii: Type of cART and all individual drugs prescribed with ABC according to those initiating ABC for the first time or not by region in 2011

	Southern Europe				Central Europe				North West Europe				Central East Europe				East Europe			
	1st ABC		Other		1st ABC		Other		1st ABC		Other		1st ABC		Other		1st ABC		Other	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
cART type																				
3N	3	8	49	14	1	8	62	15	1	11	49	10	7	16	67	24	17	57	53	44
NNRTI	23	59	127	35	4	33	115	29	3	33	195	40	23	52	110	40	8	27	41	34
PI	13	33	150	41	5	42	154	38	5	56	190	39	12	27	86	31	3	10	20	17
INSTI	0	0	27	7	1	8	50	12	0	0	36	7	1	2	9	3	2	7	2	2
Other	0	0	9	2	1	8	22	5	0	0	16	3	1	2	6	2	0	0	4	3
Drugs																				
lamivudine	37	95	282	78	12	100	329	82	9	100	414	85	43	98	255	92	19	63	95	79
kivexa	21	54	128	35	9	75	171	42	9	100	276	57	42	95	174	63	8	27	40	33
ziagen	18	46	217	60	3	25	200	50	0	0	173	36	2	5	103	37	22	73	77	64
ritonavir	7	18	120	33	4	33	159	39	3	33	183	38	12	27	79	28	4	13	21	18
efavirenz	7	18	65	18	2	17	61	15	2	22	131	27	16	36	75	27	7	23	36	30
atazanavir	9	23	100	28	4	33	85	21	4	44	138	28	6	14	31	11	0	0	7	6
kaletra	4	10	41	11	0	0	37	9	2	22	53	11	7	16	70	25	14	47	36	30
darunavir	1	3	32	9	3	25	84	21	0	0	63	13	4	9	23	8	1	3	13	11
nevirapine	15	38	62	17	3	25	67	17	1	11	79	16	8	18	37	13	1	3	4	3
tenofovir	1	3	66	18	0	0	83	21	0	0	78	16	1	2	18	6	7	23	6	5
dolutegravir	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
raltegravir	0	0	28	8	2	17	55	14	0	0	38	8	1	2	10	4	2	7	2	2
zidovudine	0	0	31	9	1	8	65	16	0	0	22	5	0	0	7	3	0	0	18	15
triumeq	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
trizivir	0	0	21	6	1	8	59	15	0	0	30	6	0	0	8	3	0	0	3	3
didanosine	0	0	16	4	0	0	12	3	0	0	5	1	0	0	8	3	4	13	12	10

emtricitabine	2	5	18	5	0	0	10	2	0	0	13	3	0	0	6	2	3	10	2	2
etravirine	1	3	9	2	0	0	20	5	0	0	15	3	0	0	7	3	0	0	3	3
amprenavir	1	3	20	6	0	0	13	3	0	0	5	1	1	2	16	6	3	10	3	3
rilpivirine	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
saquinavir hard	1	3	4	1	0	0	11	3	0	0	11	2	1	2	12	4	0	0	3	3
maraviroc	0	0	5	1	1	8	6	1	0	0	3	1	0	0	2	1	0	0	0	0
stavudine	0	0	4	1	0	0	4	1	0	0	3	1	0	0	0	0	0	0	1	1
nelfinavir	0	0	2	1	0	0	5	1	1	11	2	0	1	2	3	1	0	0	0	0
cobicistat	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
tipranavir	0	0	4	1	0	0	2	0	0	0	0	0	0	0	2	1	0	0	0	0
indinavir	0	0	1	0	0	0	0	0	0	0	1	0	0	0	5	2	0	0	0	0
saquinavir	0	0	0	0	0	0	0	0	0	0	3	1	0	0	3	1	0	0	0	0
enfurvitide	0	0	1	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	2	2
zalcitabine	0	0	2	1	0	0	2	0	0	0	1	0	0	0	0	0	0	0	0	0
saquinavir soft	2	5	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
elvitegravir	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
pbt	0	0	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ART unspecified	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0
delivirdine	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0
NRTI unspecified	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

% are column percentages

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

Figure 2c iv: Type of cART and all individual drugs prescribed with ABC according to those initiating ABC for the first time or not by region in 2012

	Southern Europe				Central Europe				North West Europe				Central East Europe				East Europe			
	1st ABC		Other		1st ABC		Other		1st ABC		Other		1st ABC		Other		1st ABC		Other	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
cART type																				
3N	3	9	45	12	2	7	55	14	0	0	30	6	3	16	67	21	16	41	71	46
NNRTI	18	56	140	37	13	48	116	29	6	50	179	38	11	58	132	42	11	28	47	31
PI	7	22	162	42	11	41	149	37	6	50	195	42	4	21	101	32	10	26	27	18
INSTI	4	13	28	7	0	0	64	16	0	0	43	9	1	5	12	4	2	5	6	4
Other	0	0	7	2	1	4	20	5	0	0	20	4	0	0	5	2	0	0	3	2
Drugs																				
lamivudine	31	97	314	82	26	96	334	83	12	100	403	86	19	100	293	92	29	74	123	80
kivexa	24	75	166	43	24	89	187	46	9	75	278	60	19	100	216	68	12	31	60	39
ziagen	9	28	206	54	4	15	185	46	3	25	160	34	0	0	99	31	26	67	89	58
ritonavir	6	19	124	32	11	41	154	38	3	25	190	41	3	16	93	29	7	18	24	16
efavirenz	8	25	59	15	5	19	60	15	2	17	118	25	9	47	86	27	9	23	43	28
atazanavir	3	9	112	29	6	22	83	21	4	33	134	29	1	5	38	12	5	13	11	7
kaletra	5	16	40	10	1	4	34	8	0	0	36	8	3	16	72	23	15	38	52	34
darunavir	3	9	32	8	5	19	88	22	2	17	83	18	2	11	33	10	1	3	14	9
nevirapine	10	31	78	20	9	33	70	17	3	25	79	17	2	11	42	13	2	5	4	3
tenofovir	2	6	61	16	2	7	78	19	1	8	69	15	0	0	20	6	0	0	13	8
dolutegravir	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
raltegravir	4	13	29	8	0	0	68	17	0	0	44	9	1	5	13	4	2	5	6	4
zidovudine	1	3	23	6	0	0	56	14	0	0	16	3	0	0	6	2	2	5	17	11
triumeq	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
trizivir	0	0	13	3	0	0	51	13	0	0	22	5	0	0	7	2	1	3	5	3
didanosine	0	0	9	2	0	0	11	3	0	0	2	0	1	5	8	3	10	26	12	8

emtricitabine	2	6	19	5	1	4	11	3	0	0	13	3	0	0	5	2	0	0	4	3
etravirine	0	0	10	3	0	0	17	4	0	0	15	3	0	0	11	3	0	0	3	2
amprenavir	0	0	20	5	0	0	6	1	0	0	4	1	1	5	14	4	3	8	6	4
rilpivirine	0	0	0	0	0	0	1	0	1	8	1	0	0	0	0	0	0	0	0	0
saquinavir hard	0	0	4	1	1	4	10	2	0	0	6	1	0	0	12	4	1	3	3	2
maraviroc	0	0	4	1	0	0	8	2	0	0	3	1	0	0	2	1	0	0	0	0
stavudine	0	0	4	1	0	0	4	1	0	0	3	1	0	0	0	0	0	0	1	1
nelfinavir	0	0	2	1	0	0	5	1	0	0	3	1	0	0	3	1	1	3	0	0
cobicistat	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
tipranavir	0	0	3	1	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0
indinavir	0	0	1	0	0	0	0	0	0	0	1	0	0	0	4	1	0	0	0	0
saquinavir	0	0	0	0	0	0	0	0	0	0	3	1	0	0	3	1	0	0	0	0
enfurvitide	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	1
zalcitabine	0	0	2	1	0	0	3	1	0	0	1	0	0	0	0	0	0	0	0	0
saquinavir soft	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
elvitegravir	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
pbt	0	0	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ART unspecified	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0
delivirdine	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0
NRTI unspecified	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

% are column percentages

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

Figure 2c v: Type of cART and all individual drugs prescribed with ABC according to those initiating ABC for the first time or not by region in 2013

	Southern Europe				Central Europe				North West Europe				Central East Europe				East Europe			
	1st ABC		Other		1st ABC		Other		1st ABC		Other		1st ABC		Other		1st ABC		Other	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
cART type																				
3N	2	4	42	11	4	13	49	12	2	14	25	5	6	29	70	21	14	41	84	42
NNRTI	33	70	157	39	8	26	125	30	4	29	173	37	9	43	141	42	11	32	63	32
PI	8	17	152	38	11	35	156	37	4	29	195	42	5	24	104	31	8	24	41	21
INSTI	3	6	39	10	5	16	72	17	4	29	51	11	1	5	16	5	1	3	8	4
Other	1	2	9	2	3	10	19	5	0	0	20	4	0	0	3	1	0	0	4	2
Drugs																				
lamivudine	46	98	334	84	29	94	359	85	12	86	405	87	21	100	309	93	33	97	161	81
kivexa	35	74	196	49	27	87	229	54	12	86	282	61	21	100	235	70	11	32	84	42
ziagen	13	28	202	51	4	13	164	39	2	14	156	34	0	0	95	28	20	59	108	54
ritonavir	8	17	124	31	14	45	159	38	4	29	191	41	5	24	96	29	3	9	34	17
efavirenz	14	30	65	16	3	10	56	13	1	7	106	23	9	43	92	28	7	21	57	29
atazanavir	4	9	100	25	8	26	84	20	2	14	123	27	2	10	36	11	5	15	15	8
kaletra	1	2	43	11	4	13	28	7	1	7	31	7	5	24	73	22	9	26	67	34
darunavir	3	6	40	10	5	16	96	23	3	21	98	21	2	10	42	13	2	6	18	9
nevirapine	15	32	85	21	6	19	77	18	2	14	80	17	0	0	44	13	3	9	5	3
tenofovir	2	4	57	14	2	6	73	17	1	7	65	14	1	5	25	7	0	0	13	7
dolutegravir	0	0	0	0	0	0	2	0	0	0	1	0	0	0	0	0	0	0	0	0
raltegravir	3	6	40	10	5	16	75	18	4	29	49	11	1	5	17	5	1	3	8	4
zidovudine	2	4	21	5	1	3	52	12	0	0	13	3	0	0	5	1	5	15	18	9
triumeq	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
trizivir	0	0	10	3	0	0	47	11	0	0	18	4	0	0	7	2	3	9	8	4
didanosine	0	0	6	2	0	0	8	2	0	0	2	0	0	0	4	1	0	0	19	10

emtricitabine	1	2	18	5	1	3	13	3	1	7	15	3	0	0	4	1	0	0	3	2
etravirine	4	9	12	3	2	6	19	5	0	0	14	3	0	0	9	3	1	3	3	2
amprenavir	2	4	16	4	1	3	7	2	0	0	3	1	0	0	14	4	1	3	10	5
rilpivirine	1	2	3	1	0	0	4	1	1	7	7	2	0	0	1	0	0	0	1	1
saquinavir hard	0	0	3	1	0	0	9	2	0	0	5	1	1	5	10	3	0	0	5	3
maraviroc	0	0	5	1	0	0	9	2	0	0	2	0	0	0	2	1	0	0	0	0
stavudine	0	0	2	1	1	3	3	1	0	0	1	0	0	0	0	0	1	3	1	1
nelfinavir	0	0	1	0	0	0	4	1	0	0	3	1	0	0	2	1	0	0	1	1
cobicistat	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0
tipranavir	0	0	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
indinavir	0	0	0	0	1	3	0	0	0	0	0	0	0	0	4	1	0	0	0	0
saquinavir	0	0	0	0	0	0	0	0	0	0	3	1	0	0	3	1	0	0	0	0
enfurvitide	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	1
zalcitabine	0	0	1	0	0	0	2	0	0	0	1	0	0	0	0	0	0	0	0	0
saquinavir soft	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
elvitegravir	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0
pbt	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ART unspecified	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0
delivirdine	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0
NRTI unspecified	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

% are column percentages

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

Figure 2c vi: Type of cART and all individual drugs prescribed with ABC according to those initiating ABC for the first time or not by region in 2014

	Southern Europe				Central Europe				North West Europe				Central East Europe				East Europe			
	1st ABC		Other		1st ABC		Other		1st ABC		Other		1st ABC		Other		1st ABC		Other	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
cART type																				
3N	1	3	42	9	0	0	46	11	0	0	23	5	2	17	69	20	6	35	95	43
NNRTI	17	57	194	44	5	38	120	29	1	13	165	36	5	42	151	44	5	29	68	31
PI	6	20	150	34	3	23	143	34	4	50	176	39	3	25	101	29	6	35	46	21
INSTI	5	17	49	11	4	31	90	21	3	38	74	16	2	17	21	6	0	0	7	3
Other	1	3	8	2	1	8	22	5	0	0	17	4	0	0	2	1	0	0	3	1
Drugs																				
lamivudine	29	97	382	86	13	100	362	86	8	100	399	88	12	100	322	94	17	100	182	83
kivexa	27	90	243	55	13	100	250	59	8	100	282	62	12	100	254	74	9	53	102	47
ziagen	4	13	200	45	0	0	145	34	0	0	148	33	0	0	86	25	7	41	111	51
ritonavir	6	20	127	29	4	31	155	37	3	38	172	38	3	25	93	27	5	29	38	17
efavirenz	5	17	70	16	1	8	54	13	1	13	95	21	4	33	95	28	4	24	54	25
atazanavir	4	13	95	21	2	15	70	17	3	38	102	22	2	17	32	9	3	18	15	7
kaletra	2	7	39	9	0	0	26	6	0	0	26	6	2	17	73	21	5	29	77	35
darunavir	3	10	46	10	2	15	93	22	1	13	103	23	0	0	47	14	0	0	21	10
nevirapine	10	33	97	22	4	31	75	18	0	0	77	17	1	8	42	12	0	0	9	4
tenofovir	0	0	56	13	0	0	70	17	0	0	60	13	0	0	23	7	0	0	12	5
dolutegravir	1	3	3	1	2	15	19	5	0	0	18	4	0	0	1	0	0	0	0	0
raltegravir	4	13	48	11	2	15	78	19	3	38	55	12	2	17	21	6	0	0	7	3
zidovudine	1	3	16	4	0	0	44	10	0	0	10	2	0	0	3	1	1	6	19	9
triumeq	0	0	0	0	0	0	3	1	0	0	1	0	0	0	0	0	0	0	0	0
trizivir	0	0	8	2	0	0	42	10	0	0	16	4	0	0	3	1	1	6	7	3
didanosine	1	3	6	1	0	0	4	1	0	0	2	0	0	0	2	1	0	0	17	8

emtricitabine	0	0	20	5	0	0	13	3	0	0	14	3	0	0	2	1	0	0	3	1
etravirine	1	3	20	5	0	0	20	5	0	0	13	3	0	0	9	3	0	0	4	2
amprenavir	0	0	16	4	0	0	7	2	0	0	1	0	1	8	9	3	1	6	10	5
rilpivirine	2	7	16	4	0	0	5	1	0	0	10	2	0	0	7	2	1	6	3	1
saquinavir hard	0	0	3	1	0	0	9	2	0	0	3	1	0	0	10	3	0	0	4	2
maraviroc	0	0	5	1	1	8	12	3	0	0	1	0	0	0	2	1	0	0	0	0
stavudine	1	3	1	0	0	0	4	1	0	0	1	0	0	0	0	0	0	0	2	1
nelfinavir	0	0	1	0	0	0	3	1	0	0	3	1	0	0	1	0	0	0	1	0
cobicistat	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0
tipranavir	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
indinavir	0	0	0	0	0	0	1	0	0	0	0	0	0	0	4	1	0	0	0	0
saquinavir	0	0	0	0	0	0	0	0	0	0	1	0	0	0	3	1	1	6	1	0
enfurvitide	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
zalcitabine	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0
saquinavir soft	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
elvitegravir	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0
pbt	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ART unspecified	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0
delivirdine	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0
NRTI unspecified	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

% are column percentages

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

Figure 2c vii: Type of cART and all individual drugs prescribed with ABC according to those initiating ABC for the first time or not by region in 2015

	Southern Europe				Central Europe				North West Europe				Central East Europe				East Europe			
	1st ABC		Other		1st ABC		Other		1st ABC		Other		1st ABC		Other		1st ABC		Other	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
cART type																				
3N	1	2	30	6	1	3	29	7	1	4	17	4	4	20	63	18	5	26	96	43
NNRTI	21	49	202	43	4	11	104	25	4	16	145	32	3	15	144	41	13	68	65	29
PI	5	12	130	28	4	11	109	26	1	4	152	33	6	30	106	30	1	5	49	22
INSTI	15	35	94	20	26	70	165	39	19	76	127	28	6	30	39	11	0	0	10	5
Other	1	2	9	2	2	5	13	3	0	0	14	3	1	5	3	1	0	0	2	1
Drugs																				
lamivudine	43	100	415	89	36	97	375	89	25	100	407	89	20	100	330	93	18	95	206	93
kivexa	37	86	284	61	21	57	250	60	8	32	276	61	18	90	258	73	6	32	104	47
ziagen	2	5	184	40	1	3	125	30	0	0	137	30	1	5	85	24	13	68	114	51
ritonavir	5	12	111	24	6	16	123	29	1	4	153	34	7	35	102	29	0	0	40	18
efavirenz	8	19	62	13	2	5	32	8	2	8	79	17	2	10	90	25	13	68	49	22
atazanavir	3	7	86	18	2	5	51	12	2	8	89	20	3	15	31	9	1	5	17	8
kaletra	1	2	30	6	1	3	17	4	1	4	19	4	4	20	68	19	4	21	79	36
darunavir	4	9	42	9	5	14	78	19	0	0	92	20	3	15	56	16	0	0	26	12
nevirapine	8	19	99	21	3	8	72	17	1	4	73	16	2	10	39	11	0	0	10	5
tenofovir	4	9	52	11	0	0	53	13	3	12	51	11	4	20	27	8	1	5	12	5
dolutegravir	9	21	36	8	23	62	106	25	19	76	93	20	4	20	16	5	0	0	1	0
raltegravir	6	14	58	12	3	8	68	16	0	0	35	8	2	10	23	6	0	0	9	4
zidovudine	0	0	13	3	0	0	31	7	0	0	9	2	1	5	3	1	1	5	18	8
triumeq	4	9	7	2	15	41	47	11	17	68	65	14	1	5	9	3	0	0	0	0
trizivir	0	0	7	2	0	0	30	7	0	0	12	3	0	0	4	1	0	0	5	2
didanosine	0	0	5	1	0	0	4	1	0	0	2	0	0	0	2	1	0	0	0	0

emtricitabine	4	9	17	4	2	5	12	3	3	12	15	3	3	15	6	2	1	5	3	1
etravirine	1	2	21	5	1	3	14	3	1	4	8	2	0	0	9	3	0	0	1	0
amprenavir	0	0	10	2	1	3	8	2	0	0	1	0	1	5	13	4	0	0	5	2
rilpivirine	6	14	34	7	0	0	8	2	0	0	9	2	0	0	9	3	0	0	8	4
saquinavir hard	0	0	2	0	0	0	8	2	0	0	2	0	0	0	8	2	0	0	2	1
maraviroc	0	0	4	1	0	0	11	3	0	0	3	1	0	0	2	1	0	0	0	0
stavudine	0	0	1	0	0	0	4	1	0	0	1	0	0	0	0	0	0	0	1	0
nelfinavir	0	0	1	0	0	0	2	0	0	0	3	1	0	0	0	0	0	0	2	1
cobicistat	0	0	0	0	1	3	2	0	0	0	2	0	0	0	1	0	0	0	0	0
tipranavir	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
indinavir	0	0	0	0	0	0	1	0	0	0	0	0	1	5	3	1	0	0	0	0
saquinavir	0	0	0	0	0	0	0	0	0	0	1	0	0	0	2	1	0	0	0	0
enfurvitide	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
zalcitabine	0	0	0	0	0	0	2	0	0	0	0	0	1	5	0	0	0	0	0	0
saquinavir soft	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
elvitegravir	0	0	1	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0	0
pbt	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
ART unspecified	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
delivirdine	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NRTI unspecified	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

% are column percentages

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

Figure 2c viii: Type of cART and all individual drugs prescribed with ABC according to those initiating ABC for the first time or not by region in 2016

	Southern Europe				Central Europe				North West Europe				Central East Europe				East Europe			
	1st ABC		Other		1st ABC		Other		1st ABC		Other		1st ABC		Other		1st ABC		Other	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
cART type																				
3N	1	4	6	4	2	29	12	14	0	0	16	24	1	14	34	31	4	44	31	35
NNRTI	1	4	48	32	0	0	17	19	0	0	19	28	2	29	27	25	2	22	16	18
PI	1	4	30	20	5	71	57	65	6	100	24	35	4	57	31	28	1	11	3	3
INSTI	22	88	66	44	0	0	1	1	0	0	6	9	0	0	1	1	0	0	2	2
Other	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Drugs																				
lamivudine	25	100	139	93	7	100	81	92	6	100	61	90	7	100	101	92	9	100	79	89
kivexa	7	28	90	60	3	43	41	47	1	17	38	56	4	57	70	64	4	44	35	39
ziagen	0	0	46	31	0	0	19	22	1	17	19	28	0	0	26	24	5	56	51	57
ritonavir	0	0	23	15	0	0	21	24	0	0	26	38	2	29	27	25	1	11	11	12
efavirenz	0	0	22	15	0	0	7	8	0	0	11	16	1	14	23	21	4	44	25	28
atazanavir	1	4	21	14	0	0	4	5	0	0	9	13	2	29	7	6	1	11	7	8
kaletra	0	0	6	4	0	0	0	0	0	0	1	1	0	0	18	16	1	11	27	30
darunavir	0	0	9	6	0	0	19	22	0	0	20	29	0	0	18	16	1	11	7	8
nevirapine	1	4	18	12	2	29	5	6	0	0	9	13	0	0	7	6	0	0	5	6
tenofovir	1	4	17	11	0	0	13	15	0	0	4	6	0	0	12	11	0	0	7	8
dolutegravir	21	84	47	31	4	57	44	50	5	83	21	31	3	43	20	18	0	0	0	0
raltegravir	1	4	17	11	1	14	14	16	1	17	4	6	1	14	10	9	1	11	3	3
zidovudine	0	0	3	2	0	0	5	6	0	0	2	3	0	0	2	2	1	11	10	11
triumeq	18	72	33	22	4	57	34	39	4	67	15	22	3	43	14	13	0	0	0	0
trizivir	0	0	1	1	0	0	4	5	0	0	2	3	0	0	1	1	0	0	3	3
didanosine	0	0	0	0	0	0	1	1	0	0	0	0	0	0	2	2	0	0	0	0

emtricitabine	1	4	6	4	0	0	4	5	0	0	1	1	0	0	4	4	0	0	2	2
etravirine	0	0	1	1	0	0	1	1	0	0	4	6	0	0	2	2	0	0	1	1
amprenavir	0	0	3	2	1	14	1	1	0	0	0	0	0	0	3	3	0	0	1	1
rilpivirine	0	0	11	7	0	0	0	0	0	0	0	0	0	0	3	3	0	0	2	2
saquinavir hard	0	0	0	0	0	0	2	2	0	0	0	0	0	0	1	1	0	0	0	0
maraviroc	0	0	0	0	0	0	1	1	0	0	3	4	0	0	0	0	0	0	0	0
stavudine	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0
nelfinavir	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	1	1
cobicistat	2	8	3	2	0	0	2	2	0	0	1	1	0	0	2	2	0	0	0	0
tipranavir	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
indinavir	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
saquinavir	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
enfurvitide	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
zalcitabine	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0
saquinavir soft	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
elvitegravir	0	0	2	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0
pbt	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ART unspecified	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
delivirdine	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NRTI unspecified	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

% are column percentages

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

Table 3 a (overall) b (stratified by region) c (stratified by year) describe the reasons for stopping an ARV treatment among those switching to ABC within 7 days of stopping the previous treatment. Overall, the physician's decision was the most common reason for stopping the previous ARV regimen. 2 individuals stopped due to Hypersensitivity reaction. Reason for stopping treatment did not significantly vary by year, but varied by region (chi squared $p < 0.001$). Southern Europe had slightly higher proportion of individuals stopping ARV for an unknown reason, those in Central Europe had slightly higher proportion of individuals stopping ARV for kidney toxicities, those in Central East Europe had a higher proportion stopping ARV due to the individuals' choice and Eastern Europe had a slightly higher proportion of individuals stopping ARV for other reasons.

Table 3a. Reasons for stopping previous ARV regimen in those switching to ABC and starting ABC as a part of a cART regimen within 7 days of stopping one or more previous drugs.

Reason for Stopping Treatment	No.	%
Any Reason	207	100
Physician's decision	60	29
Patient's wish/decision	25	12.1
Unknown	25	12.1
Other causes	23	11.1
Toxicity, predominantly from kidneys	23	11.1
Haematological toxicity	13	6.3
Abnormal fat redistribution	12	5.8
Treatment failure	6	2.9
Other Toxicity	4	1.9
Toxicity, predominantly from nervous system	4	1.9
Dyslipidaemia	3	1.4
Toxicity - Liver	3	1.4
Hypersensitivity reaction	2	1
Non-compliance	2	1
Structured Treatment Interruption (STI)	1	0.5
Toxicity, predominantly from endocrine system	1	0.5

Table 3b. Reasons for stopping previous ARV regimen in those switching to ABC and starting ABC as a part of a cART regimen within 7 days of stopping one or more previous drugs by calendar year

	Calendar Year															
	2009		2010		2011		2012		2013		2014		2015		2016	
Reason for Stopping Treatment	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Any Reason	41	100	21	100	48	100	27	100	29	100	15	100	23	100	3	100
Physician's decision	15	37	7	33	11	23	6	22	7	24	8	53	6	26	0	0
Unknown	5	12	4	19	2	4	2	7	3	10	4	27	5	22	0	0
Patient's wish/decision	2	5	2	10	9	19	4	15	5	17	1	7	1	4	1	33
Other causes	6	15	3	14	7	15	2	7	2	7	0	0	3	13	0	0
Toxicity, predominantly from kidneys	1	2	2	10	4	8	4	15	8	28	1	7	2	9	1	33
Haematological toxicity	3	7	1	5	2	4	4	15	0	0	1	7	2	9	0	0
Abnormal fat redistribution	3	7	1	5	3	6	3	11	1	3	0	0	1	4	0	0
Treatment Failure	1	2	0	0	4	8	0	0	1	3	0	0	0	0	0	0
Toxicity, predominantly from nervous system	2	5	0	0	0	0	1	4	1	3	0	0	0	0	0	0
Other Toxicity	1	2	0	0	2	4	1	4	0	0	0	0	0	0	0	0
Toxicity - Liver	2	5	0	0	0	0	0	0	0	0	0	0	1	4	0	0
Dyslipidaemia	0	0	1	5	2	4	0	0	0	0	0	0	0	0	0	0
Hypersensitivity reaction	0	0	0	0	0	0	0	0	1	3	0	0	0	0	1	33
Non-compliance	0	0	0	0	1	2	0	0	0	0	0	0	1	4	0	0
Structured Treatment Interruption (STI)	0	0	0	0	0	0	0	0	0	0	0	0	1	4	0	0
Toxicity, predominantly from endocrine system	0	0	0	0	1	2	0	0	0	0	0	0	0	0	0	0

Table 3c. Reasons for stopping previous ARV regimen in those switching to ABC and starting ABC as a part of a cART regimen within 7 days of stopping one or more previous drugs by region

	Region									
	South Europe		Central Europe		North-West Europe		Central-East Europe		East Europe	
Reason for Stopping Treatment	No.	%	No.	%	No.	%	No.	%	No.	%
Any Reason	21	100	45	100	17	100	72	100	52	100
Physician's decision	7	33	11	24	3	18	26	36	13	25
Unknown	1	5	2	4	1	6	19	26	2	4
Patient's wish/decision	4	19	11	24	3	18	5	7	2	4
Other causes	2	10	3	7	2	12	3	4	13	25
Toxicity, predominantly from kidneys	3	14	14	31	2	12	3	4	1	2
Haematological toxicity	1	5	0	0	0	0	7	10	5	10
Abnormal fat redistribution	1	5	3	7	0	0	5	7	3	6
Treatment Failure	0	0	1	2	1	6	0	0	4	8
Toxicity, predominantly from nervous system	0	0	0	0	0	0	0	0	4	8
Other Toxicity	1	5	0	0	2	12	1	1	0	0
Toxicity - Liver	0	0	0	0	1	6	0	0	2	4
Dyslipidaemia	0	0	0	0	0	0	3	4	0	0
Hypersensitivity reaction	0	0	0	0	1	6	0	0	1	2
Non-compliance	0	0	0	0	0	0	0	0	2	4
Structured Treatment Interruption (STI)	0	0	0	0	1	6	0	0	0	0
Toxicity, predominantly from endocrine system	1	5	0	0	0	0	0	0	0	0

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

Table 4 a (overall) b (stratified by year) c (stratified by region) describe the clinical parameters among those switching to ABC. Data for all variable was used from up to two months before the date of stopping the previous treatment. Overall, individuals had low HIV-RNA values (median (IQR) = 39.0 (19, 49)) and high CD4 cell counts (517.0 (370, 726)). There were no significant changes in any laboratory and clinical parameter by year. Among region, there was heterogeneity in median HIV-RNA (p-heterogeneity = 0.03), with individuals in Eastern Europe having higher HIV-RNA values than other countries, ALT (p-heterogeneity = 0.03), with individuals in Central East Europe having slightly lower values than other countries, CRE(p-heterogeneity < 0.001), with Central Europe having the lowest values compared to all other regions, HAEM (p-heterogeneity = 0.02), with individuals in North-West Europe having lower values compared to all other regions, Framingham 10 year risk score (p-heterogeneity = 0.01) and DAD CKD risk scores (p-heterogeneity < 0.001), with individuals in Central Europe having the highest values compared to other regions.

Table 4a. Laboratory and clinical parameters among those starting ABC

as a part of a cART regimen within 7 days of stopping one or more previous drugs. Data for all variables was used from up to two months before the date of stopping the previous treatment regimen.

Laboratory measurement	**Median**	**IQR**	**N**
HIV-RNA (cp/ml)	39.0	(19, 49)	107
CD4 (/mm^3)	517.0	(370, 726)	127
ALT (IU/L)	25.5	(18, 41)	84
Creatinine (umol/l)	0.8	(0.7, 1.0)	131
Haemoglobin (mg/dl)	14.4	(13.3, 15.4)	89
FIB-4	0.9	(0.7, 1.4)	77
APRI	0.3	(0.2, 0.4)	77
Framingham Risk Score	0.0	(0.0, 0.1)	44
DAD CKD Risk Score	3.0	(-1.0, 9.0)	176

Table 4b. Laboratory and clinical parameters among those starting ABC as a part of a cART regimen within 7 days of stopping one or more previous drugs by year Data for all variables was used from up to two months before the date of stopping the previous treatment.

	year	Median	IQR	N
HIV-RNA (cp/ml)	2009	39.0	(39.0, 40.0)	14
CD4 (/mm^3)		470.0	(349.0, 615.0)	17
ALT (IU/L)		51.0	(15.5, 60.5)	8
Creatinine (umol/l)		0.8	(0.7, 0.9)	18
Haemoglobin (mg/dl)		13.9	(5.4, 95.0)	10
FIB-4		0.6	(0.4, 1.3)	8
APRI		0.2	(0.1, 0.4)	8
Framingham Risk Score		0.0	(0.0, 0.0)	2
DAD CKD Risk Score		0.5	(-2.0, 4.0)	34
HIV-RNA (cp/ml)	2010	39.0	(39.0, 49.0)	17
CD4 (/mm^3)		457.0	(279.0, 514.0)	19
ALT (IU/L)		22.0	(20.0, 26.0)	9
Creatinine (umol/l)		0.9	(0.7, 1.0)	16
Haemoglobin (mg/dl)		15.6	(15.1, 127.0)	9
FIB-4		0.9	(0.8, 0.9)	9
APRI		0.3	(0.2, 0.3)	9
Framingham Risk Score		0.1	(0.0, 0.1)	6
DAD CKD Risk Score		1.0	(-1.0, 5.0)	19
HIV-RNA (cp/ml)	2011	19.0	(19.0, 39.0)	26
CD4 (/mm^3)		640.0	(463.0, 902.0)	33
ALT (IU/L)		25.5	(18.0, 33.5)	28
Creatinine (umol/l)		0.8	(0.7, 0.9)	36
Haemoglobin (mg/dl)		14.6	(13.8, 15.9)	29
FIB-4		0.8	(0.6, 1.4)	27
APRI		0.2	(0.2, 0.4)	27
Framingham Risk Score		0.0	(0.0, 0.1)	17
DAD CKD Risk Score		1.0	(-2.0, 6.0)	45
HIV-RNA (cp/ml)	2012	39.0	(19.0, 40.0)	15
CD4 (/mm^3)		526.0	(380.0, 740.0)	21
ALT (IU/L)		23.0	(20.0, 43.0)	13
Creatinine (umol/l)		0.9	(0.7, 1.2)	21
Haemoglobin (mg/dl)		14.1	(13.0, 14.8)	14
FIB-4		0.9	(0.8, 1.8)	11
APRI		0.3	(0.2, 0.5)	11
Framingham Risk Score		0.0	(0.0, 0.1)	8
DAD CKD Risk Score		3.0	(-1.0, 13.0)	23
HIV-RNA (cp/ml)	2013	39.0	(19.0, 49.0)	13
CD4 (/mm^3)		508.0	(395.0, 665.0)	15
ALT (IU/L)		19.0	(14.0, 33.0)	10
Creatinine (umol/l)		1.0	(0.8, 1.2)	16

Haemoglobin (mg/dl)		14.0	(13.0, 14.8)	10
FIB-4		1.2	(0.8, 1.4)	8
APRI		0.3	(0.2, 0.5)	8
Framingham Risk Score		0.0	(0.0, 0.1)	4
DAD CKD Risk Score		8.5	(-1.0, 16.0)	22
HIV-RNA (cp/ml)	2014	39.5	(29.0, 11847.5)	4
CD4 (/mm^3)		337.5	(306.0, 486.0)	6
ALT (IU/L)		38.0	(20.0, 39.0)	5
Creatinine (umol/l)		1.0	(0.7, 1.1)	7
Haemoglobin (mg/dl)		14.4	(10.3, 14.9)	5
FIB-4		1.4	(0.9, 1.6)	5
APRI		0.3	(0.3, 0.5)	5
Framingham Risk Score		0.1	(0.0, 0.1)	3
DAD CKD Risk Score		5.0	(2.5, 7.0)	12
HIV-RNA (cp/ml)	2015	39.0	(39.0, 239.0)	15
CD4 (/mm^3)		573.0	(395.0, 715.0)	13
ALT (IU/L)		26.5	(20.0, 35.0)	10
Creatinine (umol/l)		0.8	(0.7, 0.9)	16
Haemoglobin (mg/dl)		15.0	(13.5, 15.8)	11
FIB-4		1.1	(1.0, 1.8)	8
APRI		0.3	(0.2, 0.5)	8
Framingham Risk Score		0.1	(0.1, 0.2)	4
DAD CKD Risk Score		4.0	(0.0, 7.0)	18
HIV-RNA (cp/ml)	2016	36.0	(19.0, 5750.0)	3
CD4 (/mm^3)		561.0	(166.0, 1080.0)	3
ALT (IU/L)		30.0	(30.0, 30.0)	1
Creatinine (umol/l)		0.9	(0.9, 0.9)	1
Haemoglobin (mg/dl)		12.1	(12.1, 12.1)	1
FIB-4		1.1	(1.1, 1.1)	1
APRI		0.5	(0.5, 0.5)	1
Framingham Risk Score		.	(., .)	0
DAD CKD Risk Score		10.0	(0.0, 14.0)	3

Table 4c. Laboratory and clinical parameters among those starting ABC as a part of a cART regimen within 7 days of stopping one or more previous drugs by region. Data for all variables was used from up to two months before the date of stopping the previous treatment.

	Region	Median	IQR	N
HIV-RNA (cp/ml)	South Europe	36.0	(19.0, 39.0)	14
CD4 (/mm^3)		567.0	(463.0, 760.0)	18
ALT (IU/L)		37.0	(23.0, 50.0)	12
Creatinine (umol/l)		0.8	(0.8, 0.9)	18
Haemoglobin (mg/dl)		14.9	(12.4, 16.1)	12
FIB-4		1.5	(1.0, 3.6)	12
APRI		0.3	(0.3, 0.6)	12
Framingham Risk Score		0.1	(0.0, 0.1)	5
DAD CKD Risk Score		3.0	(0.0, 9.0)	19
HIV-RNA (cp/ml)	Central Europe	26.0	(19.0, 39.0)	25
CD4 (/mm^3)		611.0	(486.0, 780.0)	26
ALT (IU/L)		32.5	(20.0, 53.0)	10
Creatinine (umol/l)		1.0	(0.9, 1.3)	26
Haemoglobin (mg/dl)		15.4	(13.9, 16.0)	12
FIB-4		1.3	(0.8, 1.8)	10
APRI		0.2	(0.0, 0.3)	10
Framingham Risk Score		0.1	(0.1, 0.2)	5
DAD CKD Risk Score		8.5	(0.0, 15.5)	36
HIV-RNA (cp/ml)	North-West Europe	39.0	(39.0, 199.0)	13
CD4 (/mm^3)		450.0	(323.0, 700.0)	11
ALT (IU/L)		27.6	(24.0, 63.0)	7
Creatinine (umol/l)		1.0	(0.8, 1.2)	13
Haemoglobin (mg/dl)		6.3	(0.9, 13.8)	8
FIB-4		1.3	(0.9, 1.4)	6
APRI		0.3	(0.2, 0.3)	6
Framingham Risk Score		.	.	0
DAD CKD Risk Score		7.0	(0.0, 17.0)	14
HIV-RNA (cp/ml)	Central-East Europe	39.0	(19.0, 42.0)	37
CD4 (/mm^3)		514.0	(416.0, 747.0)	49
ALT (IU/L)		20.0	(16.0, 27.5)	40
Creatinine (umol/l)		0.8	(0.7, 0.9)	49
Haemoglobin (mg/dl)		14.8	(14.1, 15.7)	41
FIB-4		0.8	(0.6, 1.0)	39
APRI		0.2	(0.2, 0.3)	39
Framingham Risk Score		0.0	(0.0, 0.1)	33
DAD CKD Risk Score		0.0	(-2.0, 5.0)	66
HIV-RNA (cp/ml)	East Europe	214.5	(39.0, 1200.0)	18

CD4 (/mm^3)	349.0	(193.0, 604.0)	23
ALT (IU/L)	28.4	(21.0, 54.5)	15
Creatinine (umol/l)	0.7	(0.7, 0.9)	25
Haemoglobin (mg/dl)	13.5	(12.6, 13.9)	16
FIB-4	1.0	(0.7, 1.4)	10
APRI	0.4	(0.3, 0.9)	10
Framingham Risk Score	0.1	(0.1, 0.1)	1
DAD CKD Risk Score	2.0	(0.0, 5.0)	41

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

Table 5 a (overall) b (among those initiating ABC for the first time) c (among those re-initiating ABC) describes the factors associated with ABC initiation using Poisson models with generalised estimating equations to control for the inclusion of repeated exposure periods/events. Individuals with prior exposure to ABC exposure were included in the model as it is likely that some patients who were on older ABC containing regimens may now be using new options such as Triumeq in the cART regimen and it is important to capture such potential re-exposures. Factors investigated were gender, age, ethnicity, HIV transmission risk group, region, calendar year of follow-up, CD4 cell count, nadir CD4 cell count, HIV-RNA, line of regimen, HCV status, HBV status, AIDS diagnosis, Framingham CVD 10 year elevated risk, CKD, and the DAD CKD risk score. All variables were investigated univariately for statistical significance (Model 1). Factors that were significant ($p < 0.1$) were included in the multivariate model (Model 2).

Overall and after adjustment, factors associated with lower rates of ABC initiation were older age (IRR = 0.73 (0.59, 0.90) for highest age quintile compared to the lowest), higher CD4 cell counts (IRR = 0.68 (0.56, 0.82) for CD4 > 500 compared to CD4 < 200 cells/mm^3), higher lines of ABC regimen (IRR = 0.55 (0.46, 0.66) for line 4+ compared to first line), and having a previous AIDS diagnosis (IRR = 0.9 (0.8, 1.0) compared to those without a previous AIDS diagnosis). Higher ABC initiation rates were associated with higher HIV-RNA copies/ml (IRR =1.92 (1.47, 2.51) for HIV-RNA > 100k compared to <500 copies/ml), CKD (IRR = 2.62 (2.06, 3.34) compared to those without CKD), and higher DAD CDK risk scores (IRR = 1.18 (1.01, 1.38) for those at high risk compared to low risk). There was heterogeneity in ABC initiation among region (those in Central East and Eastern Europe more likely to initiate ABC compared to other countries; IRR = 1.58 (1.35, 1.84) and 1.71 (1.42, 2.05), compared to South Europe respectively), calendar year, with 2014 having the lowest ABC initiation rates (IRR = 0.69 (0.57, 0.85) compared to 2009).

Similar trends were seen in the sensitivity analysis. Among those initiating ABC for the first time, adjusted initiation rates were highest in Central East and Eastern Europe (IRR = 1.68 (1.42, 1.99) and 2.02 (1.65, 2.48) compared to South Europe, receptively), and 2014 had the lowest rates of first ABC initiation (IRR = 0.57 (0.45, 0.72) compared to 2009). Region was not statistically different among those re-initiating ABC in univariate models so was not included in the adjusted model. There was significant heterogeneity in ABC re-initiation rates and calendar year with re-initiation increasing in later years, IRR = 1.47 (0.85, 2.54) in 2016 compared to 2009.

Table 5a. Factors associated with ABC initiation

	Model 1			Model 2		
	IRR	**95% CI**	**p-value**	**IRR**	**95% CI**	**p-value**
Gender						
Female	1.00			1.00		
Male	0.72	[0.65 , 0.80]	< 0.001	0.90	[0.79 , 1.02]	0.106
Age Quintile						
1	1.00			1.00		
2	0.59	[0.51 , 0.68]		0.86	[0.74 , 1.00]	

3	0.53	[0.46 , 0.62]		0.89	[0.76 , 1.06]	
4	0.52	[0.45 , 0.60]		0.91	[0.75 , 1.10]	
5	0.46	[0.39 , 0.53]	< 0.001*	0.73	[0.59 , 0.90]	0.0282*
Ethnicity						
White	1.00			1.00		
Black	0.90	[0.72 , 1.12]		1.22	[0.96 , 1.55]	
Asian	0.57	[0.35 , 0.93]		0.83	[0.52 , 1.33]	
NK	0.71	[0.54 , 0.93]	0.0084*	1.01	[0.77 , 1.34]	0.3278*
HIV-Risk group						
MSM	1.00			1.00		
IDU	1.72	[1.51 , 1.96]		1.21	[1.03 , 1.41]	
MSW	1.46	[1.29 , 1.65]		1.09	[0.94 , 1.27]	
OTH/NK	1.35	[1.10 , 1.66]	< 0.001*	1.15	[0.93 , 1.42]	0.1262*
Region						
South Europe	1.00			1.00		
Central Europe	0.82	[0.71 , 0.96]		0.85	[0.72 , 1.00]	
North-West Europe	0.77	[0.65 , 0.90]		0.81	[0.68 , 0.96]	
Central-East Europe	1.83	[1.57 , 2.12]		1.58	[1.35 , 1.84]	
East Europe	2.58	[2.23 , 2.98]	< 0.001*	1.71	[1.42 , 2.05]	< 0.001*
Calendar year						
2009	1.00			1.00		
2010	0.84	[0.69 , 1.01]		0.86	[0.71 , 1.03]	
2011	0.97	[0.81 , 1.15]		1.00	[0.84 , 1.20]	
2012	0.92	[0.77 , 1.10]		0.94	[0.79 , 1.13]	
2013	0.98	[0.83 , 1.17]		1.00	[0.84 , 1.20]	
2014	0.65	[0.54 , 0.80]		0.69	[0.57 , 0.85]	
2015	1.11	[0.94 , 1.32]		1.15	[0.97 , 1.37]	
2016	1.36	[1.07 , 1.74]	< 0.001*	1.29	[1.01 , 1.64]	< 0.001*
CD4 cell count						
<200	1.00			1.00		
200-350	0.80	[0.66 , 0.97]		0.93	[0.77 , 1.13]	
350-500	0.60	[0.49 , 0.72]		0.77	[0.63 , 0.94]	
>500	0.48	[0.40 , 0.57]		0.68	[0.56 , 0.82]	
missing	0.57	[0.46 , 0.72]	< 0.001*	0.60	[0.43 , 0.84]	< 0.001*
Nadir CD4 cell count						
<200	1.00					
200-350	1.14	[1.02 , 1.28]				
350-500	1.17	[0.98 , 1.39]				
>500	1.05	[0.81 , 1.35]				
missing	1.05	[0.88 , 1.25]	0.174*			
HIV-RNA						
<500	1.00			1.00		
500-1k	1.93	[1.30 , 2.88]		1.54	[1.02 , 2.31]	
1k-10k	2.39	[1.93 , 2.97]		1.77	[1.42 , 2.21]	

10k-100k	3.13	[2.57 , 3.80]		2.30	[1.87 , 2.83]	
>100k	3.12	[2.43 , 4.00]		1.92	[1.47 , 2.51]	
missing	1.47	[1.27 , 1.71]	< 0.001*	1.47	[1.19 , 1.80]	< 0.001*
Line of ABC regimen						
1	1.00			1.00		
2	0.79	[0.69 , 0.89]		0.81	[0.71 , 0.92]	
3	0.63	[0.52 , 0.75]		0.66	[0.55 , 0.80]	
4+	0.52	[0.44 , 0.62]	< 0.001*	0.55	[0.46 , 0.66]	< 0.001*
HCV status						
-	1.00			1.00		
+	1.53	[1.27 , 1.85]		0.99	[0.81 , 1.22]	
missing	0.82	[0.72 , 0.93]	< 0.001*	0.71	[0.59 , 0.84]	0.0001*
HBV status						
-	1.00			1.00		
+	0.56	[0.46 , 0.68]		0.85	[0.69 , 1.04]	
missing	0.56	[0.48 , 0.65]	< 0.001*	1.05	[0.85 , 1.29]	0.0672*
Previous AIDS diagnosis						
No	b			1.00		
Yes	0.85	[0.76 , 0.95]	0.0036	0.90	[0.80 , 1.00]	< 0.001
Framingham 10 year elevated risk						
Low (≤20%)	1.00			1.00		
High (>20%)	0.75	[0.62 , 0.92]		0.92	[0.74 , 1.14]	
missing	0.91	[0.82 , 1.01]	0.0123*	0.78	[0.70 , 0.88]	< 0.001*
CKD						
No	1.00			1.00		
Yes	2.11	[1.68 , 2.65]		2.62	[2.06 , 3.34]	
missing	1.26	[1.10 , 1.45]	< 0.001*	0.80	[0.58 , 1.12]	< 0.001*
DAD CKD risk						
low	1.00			1.00		
medium	0.77	[0.67 , 0.89]		0.91	[0.77 , 1.07]	
high	0.91	[0.80 , 1.03]		1.18	[1.01 , 1.38]	
missing	1.08	[0.93 , 1.24]	< 0.001*	1.44	[0.99 , 2.11]	0.0011*

Global p-values by Wald test or test for heterogenity(*)
Model 1: Each factor included in separate model.
Model 2: Any factor with p<0.10 in unadjusted analysis included in a single model.
IRR: incidence rate ratio; CI: confidence interval; MSM - sex between men; IDU - injection drug use; MSW - sex between men and women; OTH/NK - other, unknown;
line of therapy: change in 2 drugs with HIV-RNA > 500 copies/ml or more than 6 months lag between treatment regimens.
Age quintiles are as follows: 1 – 18-41; 2 – 41-47; 3 – 47-52; 4 – 52-58; 5 – >58.
CKD defined as 2 consecutive eGFRs >60 more than 3 months apart using the CKD EPI formula.
Framingham CVD 10 year elevated risk defined as risk of 20% or higher.
Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition
Prior Hepatitis C Virus (HCV) defined as: Prior HCV antibody test Positive (Yes), Negative (No) or no test or inconclusive (Unknown)
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).
Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; North: Austria, Belgium, France, Germany, Luxembourg, Central: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia; East: Belarus, Estonia, Latvia, Lithuania, Russian Federation, Ukraine.

Table 5b. A sensitivity analysis: factors associated with ABC initiation among those initiating ABC for the first time

	Model 1			Model 2		
	IRR	95% CI	p-value	IRR	95% CI	p-value
Gender						
Female	1.00			1.00		
Male	0.68	[0.61 , 0.77]	< 0.001	0.92	[0.79 , 1.06]	0.235
Age Quintile						
1	1.00			1.00		
2	0.50	[0.42 , 0.58]		0.82	[0.70 , 0.97]	
3	0.45	[0.38 , 0.53]		0.91	[0.75 , 1.10]	
4	0.38	[0.32 , 0.46]		0.85	[0.68 , 1.06]	
5	0.33	[0.28 , 0.40]	< 0.001*	0.67	[0.52 , 0.86]	0.0156*
Ethnicity						
White	1.00			1.00		
Black	0.80	[0.61 , 1.04]		1.32	[0.99 , 1.77]	
Asian	0.61	[0.35 , 1.04]		1.03	[0.61 , 1.73]	
NK	0.60	[0.43 , 0.83]	0.0022*	1.09	[0.77 , 1.54]	0.2882*
HIV-Risk group						
MSM	1.00			1.00		
IDU	1.75	[1.50 , 2.03]		1.13	[0.94 , 1.36]	
MSW	1.57	[1.36 , 1.81]		1.10	[0.92 , 1.31]	
OTH/NK	1.36	[1.07 , 1.73]	< 0.001*	1.14	[0.89 , 1.47]	0.5465*
Region						
South Europe	1.00			1.00		
Central Europe	0.67	[0.55 , 0.80]		0.70	[0.58 , 0.85]	
North-West Europe	0.60	[0.49 , 0.73]		0.63	[0.51 , 0.79]	
Central-East Europe	2.03	[1.72 , 2.40]		1.68	[1.42 , 1.99]	
East Europe	3.10	[2.65 , 3.64]	< 0.001*	2.02	[1.65 , 2.48]	< 0.001*
Calendar year						
2009	1.00			1.00		
2010	0.79	[0.63 , 0.97]		0.81	[0.66 , 1.01]	
2011	0.95	[0.77 , 1.16]		0.98	[0.80 , 1.21]	
2012	0.87	[0.70 , 1.07]		0.89	[0.72 , 1.10]	
2013	0.97	[0.79 , 1.18]		0.97	[0.79 , 1.19]	
2014	0.54	[0.42 , 0.68]		0.57	[0.45 , 0.72]	
2015	0.97	[0.79 , 1.18]		0.98	[0.80 , 1.20]	
2016	1.34	[1.01 , 1.77]	< 0.001*	1.21	[0.92 , 1.61]	< 0.001*
CD4 cell count						
<200	1.00			1.00		
200-350	0.83	[0.66 , 1.04]		0.85	[0.68 , 1.08]	
350-500	0.61	[0.49 , 0.77]		0.66	[0.52 , 0.84]	
>500	0.51	[0.41 , 0.62]		0.59	[0.46 , 0.75]	

missing	0.55	[0.42 , 0.72]	< 0.001*	0.00	[0.00 , 0.00]	< 0.001*
Nadir CD4 cell count						
<200	1.00			1.00		
200-350	1.33	[1.17 , 1.52]		1.27	[1.10 , 1.47]	
350-500	1.36	[1.11 , 1.65]		1.44	[1.16 , 1.79]	
>500	1.31	[1.00 , 1.72]		1.46	[1.09 , 1.96]	
missing	1.05	[0.85 , 1.30]	< 0.001*	13512.32	[6905.07 , 26441.84]	< 0.001*
HIV-RNA						
<500	1.00			1.00		
500-1k	1.91	[1.18 , 3.08]		1.46	[0.90 , 2.37]	
1k-10k	2.61	[2.03 , 3.34]		1.71	[1.33 , 2.20]	
10k-100k	3.22	[2.56 , 4.05]		2.09	[1.65 , 2.65]	
>100k	3.46	[2.60 , 4.60]		1.82	[1.35 , 2.45]	< 0.001*
missing	1.52	[1.27 , 1.81]	< 0.001*			
Line of ABC regimen						
1	1.00			1.00		
2	0.66	[0.56 , 0.76]		0.70	[0.61 , 0.82]	
3	0.40	[0.31 , 0.51]		0.46	[0.36 , 0.59]	
4+	0.21	[0.15 , 0.27]	< 0.001*	0.25	[0.19 , 0.33]	< 0.001*
HCV status						
-	1.00			1.00		
+	1.48	[1.20 , 1.83]		0.91	[0.72 , 1.14]	
missing	0.74	[0.64 , 0.85]	< 0.001*	0.69	[0.56 , 0.85]	0.0016*
HBV status						
-	1.00			1.00		
+	0.47	[0.38 , 0.59]		0.78	[0.62 , 0.99]	
missing	0.45	[0.38 , 0.53]	< 0.001*	0.93	[0.73 , 1.17]	0.0939*
Previous AIDS diagnosis						
No	1.00			1.00		
Yes	0.73	[0.64 , 0.83]	< 0.001*	0.87	[0.76 , 1.00]	0.042
Framingham 10 year elevated risk						
Low (≤20%)	1.00			1.00		
High (>20%)	0.60	[0.47 , 0.77]		0.80	[0.61 , 1.04]	
missing	0.86	[0.76 , 0.97]	< 0.001*	0.74	[0.64 , 0.84]	< 0.001*
CKD						
No	1.00			1.00		
Yes	1.86	[1.40 , 2.48]		2.74	[2.03 , 3.70]	
missing	1.33	[1.14 , 1.55]	< 0.001*	0.82	[0.55 , 1.22]	< 0.001*
DAD CKD risk						
low	1.00			1.00		
medium	0.70	[0.59 , 0.82]		0.96	[0.79 , 1.16]	
high	0.74	[0.64 , 0.85]		1.20	[1.00 , 1.44]	

missing	0.98	[0.84 , 1.16]	< 0.001*	1.46	[0.92 , 2.30]	0.0256*

Global p-values by Wald test or test for heterogenity(*)
Model 1: Each factor included in separate model.
Model 2: Any factor with p<0.10 in unadjusted analysis included in a single model.
IRR: incidence rate ratio; CI: confidence interval; MSM - sex between men; IDU - injection drug use; MSW - sex between men and women; OTH/NK - other, unknown;
line of therapy: change in 2 drugs with HIV-RNA > 500 copies/ml or more than 6 months lag between treatment regimens.
Age quintiles are as follows: 1 – 18-41; 2 – 41-47; 3 – 47-52; 4 – 52-58; 5 – >58.
CKD defined as 2 consecutive eGFRs >60 more than 3 months apart using the CKD EPI formula.
Framingham CVD 10 year elevated risk defined as risk of 20% or higher.
Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition
Prior Hepatitis C Virus (HCV) defined as: Prior HCV antibody test Positive (Yes), Negative (No) or no test or inconclusive (Unknown)
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).
Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; North: Austria, Belgium, France, Germany, Luxembourg, Central: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia; East: Belarus, Estonia, Latvia, Lithuania, Russian Federation, Ukraine.

Table 5c. A sensitivity analysis: Factors associated with ABC initiation among those re-initiating ABC

	Model 1			Model 2		
	IRR	**95% CI**	**p-value**	**IRR**	**95% CI**	**p-value**
Gender						
Female	1.00			1.00		
Male	0.82	[0.66 , 1.03]	0.086	0.90	[0.70 , 1.16]	0.423
Age Quintile						
1	1.00					
2	1.21	[0.87 , 1.69]				
3	1.09	[0.78 , 1.54]				
4	1.39	[1.01 , 1.92]				
5	1.28	[0.92 , 1.77]	0.2872*			
Ethnicity						
White	1.00					
Black	1.21	[0.81 , 1.81]				
Asian	0.45	[0.14 , 1.42]				
NK	1.08	[0.69 , 1.69]	0.4045*			
HIV-Risk group						
MSM	1.00			1.00		
IDU	1.71	[1.33 , 2.21]		1.42	[1.07 , 1.90]	
MSW	1.17	[0.90 , 1.51]		1.06	[0.78 , 1.44]	
OTH/NK	1.34	[0.90 , 2.00]	0.0004*	1.24	[0.82 , 1.87]	0.0660*
Region						
South Europe	1.00					
Central Europe	1.29	[0.98 , 1.69]				
North-West Europe	1.27	[0.95 , 1.69]				
Central-East Europe	1.22	[0.86 , 1.71]				
East Europe	1.02	[0.69 , 1.53]	0.3234*			
Calendar year						
2009	1.00			1.00		

2010	1.01	[0.67 , 1.51]		1.01	[0.67 , 1.51]	
2011	1.01	[0.68 , 1.51]		1.05	[0.70 , 1.57]	
2012	1.07	[0.72 , 1.58]		1.12	[0.76 , 1.66]	
2013	0.99	[0.67 , 1.48]		1.07	[0.72 , 1.59]	
2014	1.02	[0.69 , 1.52]		1.11	[0.75 , 1.66]	
2015	1.62	[1.13 , 2.33]		1.82	[1.27 , 2.61]	
2016	1.42	[0.82 , 2.46]	0.0322*	1.47	[0.85 , 2.54]	0.0041*
CD4 cell count						
<200	1.00			1.00		
200-350	0.69	[0.48 , 1.00]		0.91	[0.61 , 1.35]	
350-500	0.52	[0.36 , 0.75]		0.76	[0.51 , 1.14]	
>500	0.36	[0.26 , 0.51]		0.59	[0.39 , 0.88]	
missing	0.59	[0.39 , 0.90]	< 0.001*	0.00	[0.00 , 0.00]	< 0.001*
Nadir CD4 cell count						
<200	1.00			1.00		
200-350	0.69	[0.54 , 0.89]		0.97	[0.74 , 1.27]	
350-500	0.73	[0.49 , 1.08]		1.17	[0.76 , 1.80]	
>500	0.41	[0.20 , 0.84]		0.74	[0.36 , 1.54]	
missing	1.05	[0.76 , 1.45]	0.0039*	2406.99	[748.90 , 7736.18]	< 0.001*
HIV-RNA						
<500	1.00			1.00		
500-1k	2.13	[0.96 , 4.72]		1.73	[0.76 , 3.92]	
1k-10k	2.00	[1.21 , 3.29]		1.74	[1.05 , 2.89]	
10k-100k	3.31	[2.19 , 5.03]		2.80	[1.79 , 4.36]	
>100k	2.55	[1.41 , 4.60]		2.00	[1.06 , 3.74]	
missing	1.38	[1.02 , 1.89]	< 0.001*	1.48	[0.92 , 2.38]	< 0.001*
Line of ABC regimen						
1	1.00			1.00		
2	1.56	[1.20 , 2.05]		1.44	[1.10 , 1.88]	
3	1.97	[1.45 , 2.69]		1.77	[1.30 , 2.43]	
4+		[1.83 , 3.08]	< 0.001*	1.90	[1.44 , 2.50]	< 0.001*

	2.37					
HCV status						
-	1.00			1.00		
+	1.93	[1.27 , 2.93]		1.29	[0.82 , 2.02]	
missing	1.17	[0.87 , 1.56]	0.0051*	0.76	[0.51 , 1.11]	0.0203*
HBV status						
-	1.00			1.00		
+	1.31	[0.76 , 2.25]		1.57	[0.90 , 2.71]	
missing	1.57	[0.99 , 2.51]	0.0989*	2.27	[1.32 , 3.89]	0.0083*
Previous AIDS diagnosis						
No	1.00			1.00		
Yes	1.30	[1.06 , 1.60]	0.013	1.12	[0.90 , 1.38]	0.309
Framingham 10 year elevated risk						
Low (≤20%)	1.00					
High (>20%)	1.32	[0.92 , 1.89]				
missing	1.11	[0.89 , 1.38]	0.30*			
CKD						
No	1.00			1.00		
Yes	3.08	[2.07 , 4.58]		2.50	[1.65 , 3.80]	
missing	1.11	[0.83 , 1.49]	< 0.001*	0.68	[0.38 , 1.25]	< 0.001*
DAD CKD risk						
low	1.00			1.00		
medium	1.13	[0.82 , 1.56]		0.94	[0.68 , 1.31]	
high	1.75	[1.33 , 2.30]		1.42	[1.06 , 1.89]	
missing	1.57	[1.13 , 2.18]	< 0.001*	1.55	[0.74 , 3.26]	0.0115*

Global p-values by Wald test or test for heterogeneity (*)
Model 1: Each factor included in separate model.
Model 2: Any factor with p<0.10 in unadjusted analysis included in a single model.
IRR: incidence rate ratio; CI: confidence interval; MSM - sex between men; IDU - injection drug use; MSW - sex between men and women; OTH/NK - other, unknown;
line of therapy: change in 2 drugs with HIV-RNA > 500 copies/ml or more than 6 months lag between treatment regimens.
Age quintiles are as follows: 1 – 18-41; 2 – 41-47; 3 – 47-52; 4 – 52-58; 5 – >58.
CKD defined as 2 consecutive eGFRs >60 more than 3 months apart using the CKD EPI formula.
Framingham CVD 10 year elevated risk defined as risk of 20% or higher.
Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition
Prior Hepatitis C Virus (HCV) defined as: Prior HCV antibody test Positive (Yes), Negative (No) or no test or inconclusive (Unknown)
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).
Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; North: Austria, Belgium, France, Germany, Luxembourg, Central: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia; East: Belarus, Estonia, Latvia, Lithuania, Russian Federation, Ukraine.

6.3. Objective 2

Table 7 a-c describe the reasons for ABC discontinuation. Tables 7 a, b describe the reasons for stopping among those stopping within 6 and 4 weeks, respectively, of ABC initiation. Overall, 113 (18.9% - Kaplan Meier estimate) individuals stopped for any reason and 35 (4.6% - Kaplan Meier estimate) stopped for Hypersensitivity reaction or any toxicity within 6 weeks of ABC initiation. 70 individuals stopped for any reason and 25 stopped for Hypersensitivity reaction or any toxicity within 4 weeks of ABC initiation.

Table 7 c describes the reasons for ABC discontinuation among those stopping within 6 weeks of ABC initiation with a time-lag analysis. Individuals were assumed to remain on ABC for 4 weeks after they were recorded to have discontinued. Reasons for stopping other regimens between 4-6 weeks after ABC initiation were considered attributable to ABC and are listed in this table. 15 individuals stopped other drugs for any reason during this period.

Table 7a. Reasons for ABC discontinuation among those discontinuing within 6 weeks of ABC initiation

	Number of times exposed to ABC													
	1		2		3		4		5		6		Total	
Reason for Stopping Treatment	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Any Reason	58	100	25	100	20	100	5	100	4	100	1	100	113	100
HSR or any toxicity	21	36.2	5	20	6	30	2	40	1	25	0	0	35	31
Unknown	13	22.4	3	12	5	25	0	0	0	0	0	0	21	18.6
Hypersensitivity reaction (skin eruption etc.)	11	19	2	8	0	0	0	0	0	0	0	0	13	11.5
Patient's wish/decision	8	13.8	7	28	5	25	0	0	0	0	0	0	20	17.7
Other causes	7	12.1	5	20	2	10	1	20	0	0	1	100	16	14.2
Toxicity - GI tract	7	12.1	2	8	5	25	2	40	0	0	0	0	16	14.2
Physician's decision	6	10.3	4	16	3	15	1	20	3	75	0	0	17	15
Toxicity - Liver	2	3.4	0	0	0	0	0	0	0	0	0	0	2	1.8
Toxicity, predominantly from nervous system	2	3.4	0	0	0	0	0	0	0	0	0	0	2	1.8
Non-compliance	1	1.7	0	0	0	0	0	0	0	0	0	0	1	0.9
Other Toxicity	1	1.7	0	0	0	0	0	0	0	0	0	0	1	0.9
Concern of cardiovascular disease	0	0	1	4	0	0	0	0	0	0	0	0	1	0.9
Toxicity, predominantly from kidneys	0	0	1	4	0	0	0	0	1	25	0	0	2	1.8
Treatment failure	0	0	0	0	0	0	1	20	0	0	0	0	1	0.9

Table 7b. A sensitivity analysis: Reasons for ABC discontinuation among those discontinuing within 4 weeks of ABC initiation

	Number of times exposed to ABC													
	1		2		3		4		5		6		Total	
Reason for Stopping Treatment	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Any Reason	40	100	11	100	13	100	3	100	2	100	1	100	70	100
Hypersensitivity reaction or any toxicity	17	29.3	1	4	4	20	2	40	1	25	0	0	25	22.1
Unknown	13	32.5	1	9.1	2	15.4	0	0	0	0	0	0	16	22.9
Hypersensitivity reaction (skin eruption etc.)	9	22.5	1	9.1	0	0	0	0	0	0	0	0	10	14.3
Toxicity - GI tract	6	15	0	0	4	30.8	2	66.7	0	0	0	0	12	17.1
Physician's decision	4	10	2	18.2	2	15.4	0	0	0	0	1	100	9	12.9
Patient's wish/decision	3	7.5	4	36.4	4	30.8	0	0	0	0	0	0	11	15.7
Other causes	3	7.5	2	18.2	1	7.7	0	0	1	50	0	0	7	10
Toxicity - Liver	1	2.5	0	0	0	0	0	0	0	0	0	0	1	1.4
Toxicity, predominantly from nervous system	1	2.5	0	0	0	0	0	0	0	0	0	0	1	1.4
Concern of cardiovascular disease	0	0	1	9.1	0	0	0	0	0	0	0	0	1	1.4
Toxicity, predominantly from kidneys	0	0	0	0	0	0	0	0	1	50	0	0	1	1.4
Treatment failure	0	0	0	0	0	0	1	33.3	0	0	0	0	1	1.4

Table 7c. A sensitivity analysis: Reasons for discontinuation among those discontinuing within 6 weeks of ABC initiation. Individuals were assumed to stay on ABC for 4 weeks after their stop date. The following are reasons for stopping other drugs between ABC initiation and 6 weeks post ABC initiation.

	Number of times exposed to ABC 1	
Reason for Stopping Treatment	**No.**	**%**
Any Reason	15	100
Physician's decision	5	33.3
Other causes	3	20
Patient's wish/decision	2	13.3
Structured Treatment Interruption (STI)	1	6.7
Toxicity - GI tract	1	6.7
Other Toxicity	1	6.7
Treatment failure	1	6.7
Unknown	1	6.7

Figure 3a. Kaplan-Meier failure estimates of time to from ABC initiation to ABC discontinuation due to any reason in the first exposure to ABC. Individuals were censored at 6 weeks after ABC initiation, ABC discontinuation or death. At 6 weeks, 4.1% (95% CI (3.2%, 5.3%)) discontinued. Note: only displaying figures containing 30 or more individuals discontinuing for that reason.

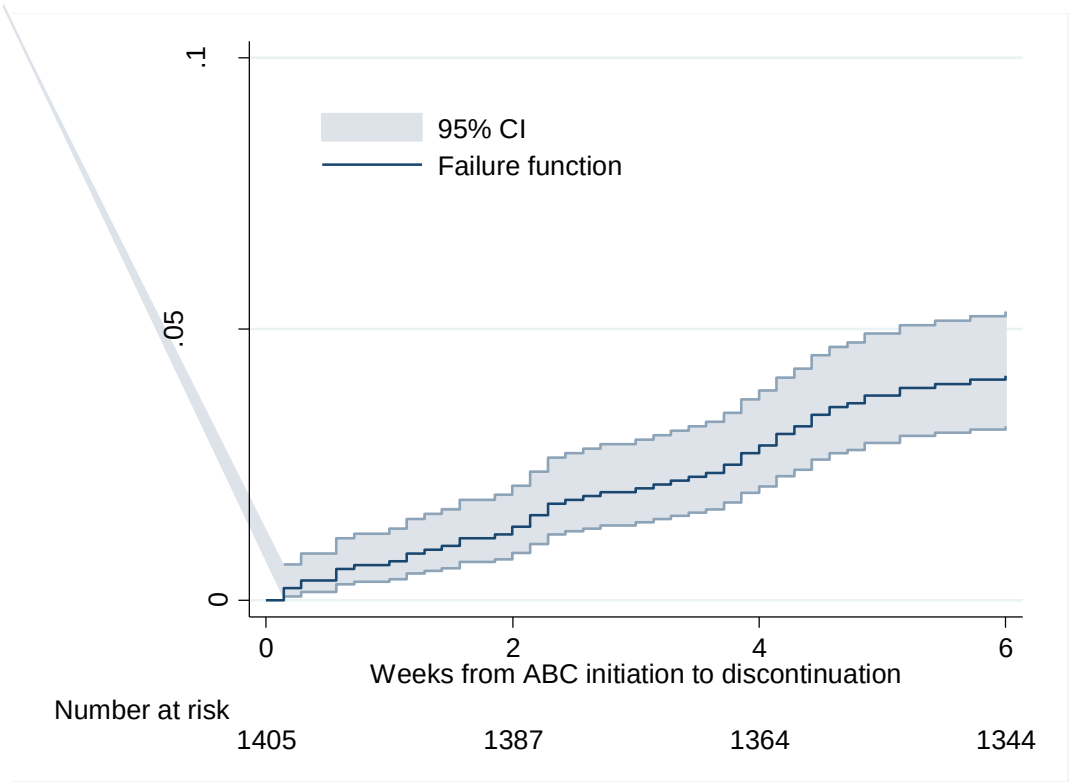


Figure 3b. A sensitivity analysis: Kaplan-Meier failure estimates of time to from ABC initiation to ABC discontinuation due to any reason in the first exposure to ABC. Individuals were censored at 4 weeks after ABC initiation, ABC discontinuation or death. At 4 weeks, 2.8% (2.1%, 3.8%) discontinued. Note: only displaying figures containing 30 or more individuals discontinuing for that reason.

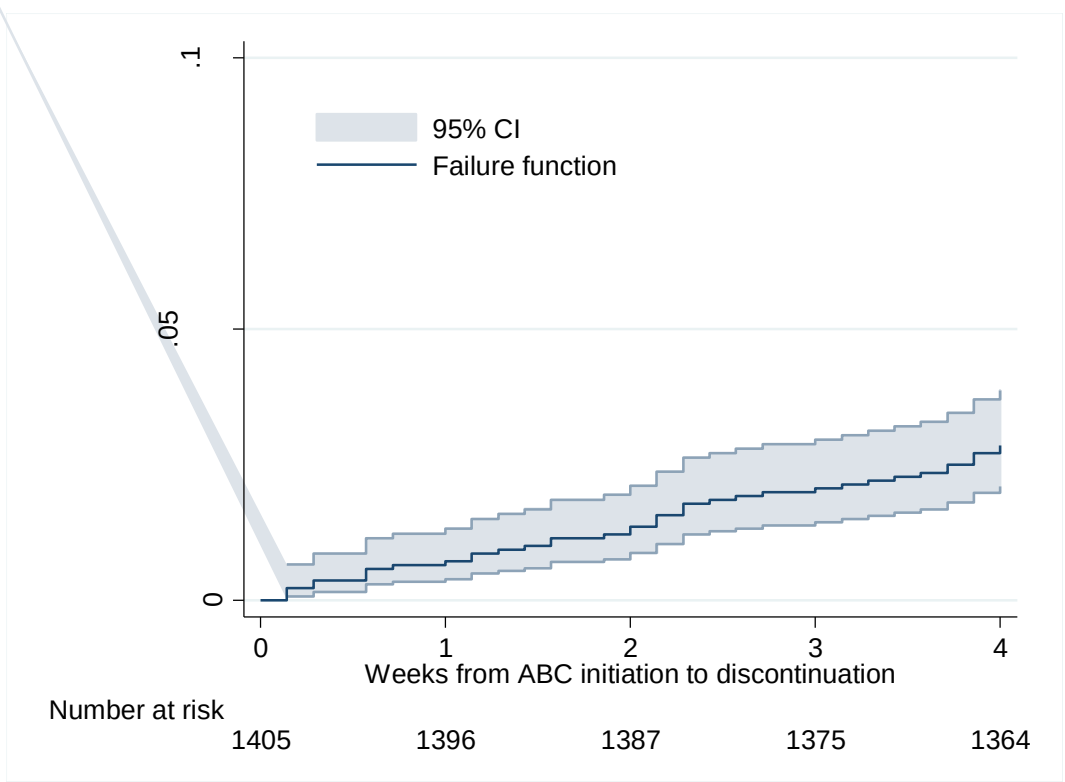


Table 8 a-c describe the incidence rate for each reason people discontinue ABC. Table 8 a censors individuals at 6 weeks after ABC initiation and Table 8 b censors individuals at 4 weeks after ABC initiation. Table 8 c includes only those who are exposed to ABC for the first time after 1/1/2009 and censors individuals 6 weeks after initiation. In 778 person years of follow-up, 113 individuals discontinued ABC within 6 weeks of ABC initiation, an incidence rate of 14.5 (12.1, 17.5) per 100 person years follow-up. 35 individuals discontinued due to HSR or any toxicity, IRR = 4.5 (1.0, 2.9) per 100 person years follow-up. In a sensitivity analysis censoring individuals 4 weeks after ABC initiation, 70 individuals discontinued ABC for any reason, an incidence rate of 10.0 (7.9, 12.7) per 100 person years follow-up. In a sensitivity analysis including individuals in their first ABC exposure censoring at 6 weeks after ABC initiation, 58 individuals discontinued ABC for any reason, an incidence rate of 36.7 (28.4, 47.5) per person year of follow-up.

Table 8a. Incidence rate of ABC discontinuation by reason for stopping treatment. Individuals were censored at 6 weeks after ABC initiation, ABC discontinuation or death. Note: only displaying rates containing 30 or more individuals discontinuing for that reason.

Reason for stopping treatment	Person-Time (years)	Failures	Rate*	95% CI
Any Reason	778.8	113	14.5	(12.1, 17.5)
HSR or any toxicity		35	4.5	(3.2, 6.3)
Unknown		21		
Patient's wish/decision		20		
Physician's decision		17		
Toxicity - GI tract		16		
Other causes		16		
HSR		13		
Toxicity – Liver		2		
Toxicity, predominantly CNS		2		
Toxicity, predominantly kidneys		2		
Treatment Failure		1		
Concern of cardiovascular disease, including dyslipidaemia		1		
Other Toxicity		1		
Non-compliance		1		

*per 100 person years

Table 8b. A sensitivity analysis: Incidence rate of ABC discontinuation by reason for stopping treatment. Individuals were censored at 4 weeks after ABC initiation, ABC discontinuation or death. Note: only displaying rates containing 30 or more individuals discontinuing for that reason.

Reason for stopping treatment	Person-Time (years)	Failures	Rate*	95% CI
Any Reason	699.5	70	10.0	(7.9, 12.7)
HSR or any toxicity		24		
Unknown		17		
Toxicity - GI tract		11		
Patient's wish/decision		11		
HSR		10		
Physician's decision		7		
Other causes		9		
Treatment Failure		1		
Concern of cardiovascular disease, including dyslipidaemia		1		
Toxicity – Liver		1		
Toxicity, predominantly CNS		1		
Toxicity, predominantly kidneys		1		

*per 100 person years

Table 8c. A sensitivity analysis: Incidence rate of ABC discontinuation by reason for stopping treatment among those exposed to ABC for the first time after 1/1/2009. Individuals were censored at 6 weeks after ABC initiation, ABC discontinuation or death. Note: only displaying rates containing 30 or more individuals discontinuing for that reason.

Reason for stopping treatment	Person-Time (years)	Failures	Rate*	95% CI
Any Reason	157.9	58	36.7	(28.4, 47.5)
HSR or any toxicity		21		
Unknown		14		
HSR		11		
Patient's wish/decision, not specified above		8		
Toxicity - GI tract		6		
Other causes, not specified above		8		
Physician's decision, not specified above		5		
Toxicity – Liver		2		
Toxicity, predominantly CNS		2		
Toxicity, not mentioned above		1		
Non-compliance		1		

*per 100 person years

Table 9a and b describe the patient population of those that initiate ABC, stratified by the number of times they have been exposed to ABC, if they remain on ABC, if they stop ABC due to HSR (HSR or any toxicity in Table 9b) or if they stop ABC for any other reason. The cell counts of those stopping ABC due to HSR or any other reason were largely too small to conduct formal statistical tests.

Table 9a. Baseline characteristics of individuals who initiate ABC and remain on ABC, discontinue due to HSR and discontinue due to any other reason over the first two ABC exposures. Note: only including p-values for cell counts of ≥ 5.

	1st exposure							2nd exposure						
	Remain on ABC		Stop ABC for HSR		Stop ABC other			Remain on ABC		Stop ABC for HSR		Stop ABC other		
	N	%	N	%	N	%	p	N	%	N	%	N	%	p
Gender														
Female	466	34.6	5	45.5	15	31.9	0.70	188	32.2	0	0	8	34.8	
Male	882	65.4	6	54.5	32	68.1		395	67.8	2	100	15	65.2	
Region														
South Europe	327	24.3	4	36.4	11	23.4		160	27.4	0	0	3	13	
Central Europe	209	15.5	2	18.2	14	29.8		137	23.5	1	50	7	30.4	
North-West Europe	141	10.5	0	0	7	14.9		143	24.5	0	0	7	30.4	
Central-East Europe	309	22.9	0	0	5	10.6		83	14.2	1	50	3	13	
East Europe	362	26.9	5	45.5	10	21.3		60	10.3	0	0	3	13	
Ethnicity														
White	1232	91.4	9	81.8	43	91.5		518	88.9	1	50	21	91.3	
Black	67	5	0	0	2	4.3		36	6.2	0	0	1	4.3	
Asian	10	0.7	0	0	1	2.1		6	1	0	0	0	0	
OTH/NK	39	2.9	2	18.2	1	2.1		23	3.9	1	50	1	4.3	
HIV-Risk group														
MSM	416	30.9	2	18.2	14	29.8		200	34.3	0	0	7	30.4	
IDU	352	26.1	3	27.3	16	34		155	26.6	2	100	8	34.8	
MSW	487	36.1	4	36.4	12	25.5		192	32.9	0	0	5	21.7	

OTH/NK	93	6.9	2	18.2	5	10.6	36	6.2	0	0	3	13
Calendar year												
2009	147	10.9	1	9.1	4	8.5	57	9.8	0	0	3	13
2010	215	15.9	0	0	8	17	72	12.3	0	0	3	13
2011	205	15.2	3	27.3	2	4.3	76	13	2	100	4	17.4
2012	224	16.6	2	18.2	7	14.9	55	9.4	0	0	5	21.7
2013	174	12.9	0	0	10	21.3	80	13.7	0	0	2	8.7
2014	152	11.3	2	18.2	5	10.6	83	14.2	0	0	2	8.7
2015	228	16.9	3	27.3	10	21.3	159	27.3	0	0	4	17.4
2016	3	0.2	0	0	1	2.1	1	0.2	0	0	0	0
HIV-RNA												
<500	514	38.1	6	54.5	19	40.4	231	39.6	2	100	8	34.8
500-1k	17	1.3	0	0	0	0	6	1	0	0	0	0
1k-10k	32	2.4	0	0	1	2.1	15	2.6	0	0	0	0
10k-100k	31	2.3	0	0	3	6.4	26	4.5	0	0	2	8.7
>100k	26	1.9	1	9.1	0	0	6	1	0	0	2	8.7
missing	728	54	4	36.4	24	51.1	306	52.5	0	0	12	52.2
CD4 cell count												
<200	78	5.8	1	9.1	1	2.1	26	4.5	0	0	2	8.7
200-350	123	9.1	4	36.4	3	6.4	50	8.6	0	0	1	4.3
350-500	134	9.9	0	0	7	14.9	81	13.9	1	50	3	13
>500	300	22.3	3	27.3	9	19.1	135	23.2	1	50	4	17.4
missing	713	52.9	3	27.3	27	57.4	311	53.3	0	0	16	69.6
Nadir CD4 cell count												
<200	146	10.8	1	9.1	7	14.9	81	13.9	1	50	3	13
200-350	171	12.7	2	18.2	3	6.4	72	12.3	0	0	2	8.7
350-500	143	10.6	3	27.3	6	12.8	56	9.6	0	0	0	0
>500	175	13	2	18.2	4	8.5	63	10.8	1	50	2	8.7
missing	713	52.9	3	27.3	27	57.4	311	53.3	0	0	16	69.6
DAD risk												
low	191	14.2	2	18.2	7	14.9	39	6.7	0	0	1	4.3
medium	97	7.2	0	0	5	10.6	37	6.3	1	50	0	0
high	196	14.5	3	27.3	4	8.5	102	17.5	0	0	2	8.7
missing	864	64.1	6	54.5	31	66	405	69.5	1	50	20	87

Framingham 10 year elevated risk														
No	124	9.2	0	0	4	8.5		41	7	0	0	2	8.7	
Yes	33	2.4	0	0	0	0		14	2.4	0	0	0	0	
missing	1191	88.4	11	100	43	91.5		528	90.6	2	100	21	91.3	
Entry Age*	43.67	(35.03, 51.12)	33.62	(29.49, 52.72)	44.61	(33.82, 54.11)	0.24	48.89	(40.85, 55.83)	43.78	(35.81, 51.75)	51.06	(47.59, 54.58)	0.71
Laboratory measurements														
ALT*	31	(20, 47)	28.60	(21, 48.60)	27.60	(21, 46)	0.59	31	(21, 47)	62.50	(47, 78)	24	(23, 33)	0.63
Creatinine*	0.830	(0.700, 1)	0.705	(0.700, 0.750)	0.720	(0.630, 0.840)	0.65	0.859	(0.660, 1.050)	0.873	(0.816, 0.930)	0.940	(0.860, 0.990)	0.00
Haemoglobin*	14.10	(12.40, 15.10)	13.80	(12.70, 15.80)	13.60	(11, 14.85)	0.55	14	(11.30, 15.40)	7.795	(1.690, 13.90)	12.85	(6.790, 14.10)	0.00
FIB-4*	1.106	(0.757, 1.772)	0.872	(0.715, 1.097)	1.075	(0.741, 1.482)	0.47	1.240	(0.874, 1.914)	.	(., .)	1.259	(1.148, 1.388)	
APRI*	0.354	(0.227, 0.604)	0.293	(0.185, 0.441)	0.288	(0.218, 0.519)	0.19	0.353	(0.251, 0.539)	.	(., .)	0.286	(0.233, 1.055)	

Baseline is defined as ABC initiation date.

Laboratory measurements were taken from up to two months before ABC initiation. Abbreviations: MSM - sex between men; IDU - injection drug use; MSW - sex between men and women; OTH/NK - other, unknown;

*all measurements are median (IQR).

Framingham CVD 10 year elevated risk defined as risk of 20% or higher.

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

Table 9b. A sensitivity analysis: Baseline characteristics of individuals who initiate ABC and remain on ABC, discontinue due to HSR or any toxicity and discontinue due to any other reason over the first two ABC exposures. Note: only displaying p-values for cell counts ≥ 5.

	1st exposure							2nd exposure						
	Remain on ABC		Stop ABC for HSR		Stop ABC other			Remain on ABC		Stop ABC for HSR		Stop ABC other		
	N	%	N	%	N	%	p	N	%	N	%	N	%	p
Gender														
							0.9							
Female	466	34.6	7	33.3	13	35.1	7	188	32.2	1	20	7	35	
Male	882	65.4	14	66.7	24	64.9		395	67.8	4	80	13	65	
Region														
South Europe	327	24.3	7	33.3	8	21.6		160	27.4	0	0	3	15	
Central Europe	209	15.5	4	19	12	32.4		137	23.5	2	40	6	30	
North-West Europe	141	10.5	1	4.8	6	16.2		143	24.5	2	40	5	25	
Central-East Europe	309	22.9	3	14.3	2	5.4		83	14.2	1	20	3	15	
East Europe	362	26.9	6	28.6	9	24.3		60	10.3	0	0	3	15	
Ethnicity														
White	1232	91.4	18	85.7	34	91.9		518	88.9	3	60	19	95	
Black	67	5	1	4.8	1	2.7		36	6.2	1	20	0	0	
Asian	10	0.7	0	0	1	2.7		6	1	0	0	0	0	
OTH/NK	39	2.9	2	9.5	1	2.7		23	3.9	1	20	1	5	
HIV-Risk group														
MSM	416	30.9	7	33.3	9	24.3		200	34.3	1	20	6	30	
IDU	352	26.1	7	33.3	12	32.4		155	26.6	2	40	8	40	
MSW	487	36.1	4	19	12	32.4		192	32.9	1	20	4	20	
OTH/NK	93	6.9	3	14.3	4	10.8		36	6.2	1	20	2	10	
Calendar year														
2009	147	10.9	1	4.8	4	10.8		57	9.8	0	0	3	15	
2010	215	15.9	1	4.8	7	18.9		72	12.3	0	0	3	15	
2011	205	15.2	5	23.8	0	0		76	13	2	40	4	20	
2012	224	16.6	4	19	5	13.5		55	9.4	1	20	4	20	
2013	174	12.9	1	4.8	9	24.3		80	13.7	0	0	2	10	

2014	152	11.3	3	14.3	4	10.8	83	14.2	0	0	2	10	
2015	228	16.9	6	28.6	7	18.9	159	27.3	2	40	2	10	
2016	3	0.2	0	0	1	2.7	1	0.2	0	0	0	0	
HIV-RNA													
<500	514	38.1	12	57.1	13	35.1	231	39.6	4	80	5	25	
500-1k	17	1.3	0	0	0	0	6	1	0	0	0	0	
1k-10k	32	2.4	0	0	1	2.7	15	2.6	0	0	0	0	
10k-100k	31	2.3	1	4.8	2	5.4	19	3.3	1	20	0	0	
>100k	26	1.9	1	4.8	0	0	6	1	0	0	2	10	
missing	728	54	7	33.3	21	56.8	306	52.5	0	0	13	65	
CD4 cell count													
<200	78	5.8	1	4.8	1	2.7	26	4.5	0	0	2	10	
200-350	123	9.1	5	23.8	2	5.4	50	8.6	0	0	2	10	
350-500	134	9.9	3	14.3	4	10.8	61	10.5	1	20	0	0	
>500	300	22.3	6	28.6	6	16.2	135	23.2	2	40	3	15	
missing	713	52.9	6	28.6	24	64.9	311	53.3	2	40	13	65	
Nadir CD4 cell count													
<200	146	10.8	3	14.3	5	13.5	81	13.9	1	20	4	20	
200-350	171	12.7	3	14.3	2	5.4	72	12.3	0	0	2	10	
350-500	143	10.6	6	28.6	3	8.1	56	9.6	0	0	0	0	
>500	175	13	3	14.3	3	8.1	63	10.8	2	40	1	5	
missing	713	52.9	6	28.6	24	64.9	311	53.3	2	40	13	65	
DAD risk													
low	191	14.2	3	14.3	6	16.2	37	6.3	0	0	1	5	
medium	97	7.2	4	19	1	2.7	33	5.7	1	20	2	10	
high	199	14.8	5	23.8	2	5.4	101	17.3	0	0	1	5	
missing	861	63.9	9	42.9	28	75.7	412	70.7	4	80	16	80	
Framingham 10 year elevated risk													
No	123	9.1	1	4.8	3	8.1	42	7.2	1	20	1	5	
Yes	33	2.4	0	0	0	0	14	2.4	0	0	0	0	
missing	1192	88.4	20	95.2	34	91.9	527	90.4	4	80	19	95	
Entry Age*	43.67	(35.03, 51.12)	44.61	(31.55, 56.62)	38.60	(33.38, 50.83)	0.24	48.89	(40.85, 55.83)	52.39	(51.75, 66.64)	49.60	(46.19, 54.28)	0.47
Laboratory measurements													

			40.1			(16.50,	0.9	31.1		35.5	(19.50,	28.5		0.2
ALT*	31	(20, 47)	0	(22, 54.50)	26	35.50)	3	0	(21, 47)	0	62.50)	0	(23.50, 42)	0
	0.83		0.71	(0.680,	0.75	(0.630,	0.1	0.85	(0.660,	0.87	(0.643,	0.94	(0.860,	0.8
Creatinine*	0	(0.700, 1)	0	0.800)	0	0.980)	7	9	1.050)	3	1.175)	0	0.990)	7
	14.1	(12.40,	14.8	(13.25,	13.5		0.5		(11.30,	7.34	(1.285,	13.0	(12.70,	0.4
Haemoglobin*	0	15.10)	5	15.20)	0	(9.700, 14)	9	14	15.40)	5	13.45)	5	14.80)	4
	1.10	(0.757,	1.09	(0.872,	0.98	(0.708,	0.6	1.22	(0.874,	1.25	(1.259,	1.26	(1.060,	0.7
FIB-4*	6	1.772)	7	1.457)	1	1.507)	7	9	1.914)	9	1.259)	8	2.771)	0
	0.35	(0.227,	0.44	(0.293,	0.24	(0.209,	0.4	0.35	(0.252,	0.23	(0.233,	0.68	(0.286,	0.8
APRI*	4	0.604)	1	0.519)	7	0.301)	3	4	0.545)	3	0.233)	3	1.138)	6

Only including the first two exposures to ABC due to small number of individuals being exposed to ABC more than two times. Baseline is defined as ABC initiation date. Laboratory measurements were taken from up to two months before ABC initiation. Abbreviations: MSM - sex between men; IDU - injection drug use; MSW - sex between men and women; OTH/NK - other, unknown;

*all measurements are median (IQR).

Framingham CVD 10 year elevated risk defined as risk of 20% or higher.

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

Factors associated with discontinuation due to HSR alone could not be analysed in a statistical model as there were only 13 events. Discontinuation due to HSR or any toxicity, however, had 34 events and could be analysed in a statistical model. Table 10 presents the factors associated with ABC discontinuation due to HSR or any toxicity using Poisson models with generalised estimating equations to control for the inclusion of repeated exposure periods/events. Factors investigated were gender, age, ethnicity, HIV transmission risk group, region, calendar year of follow-up, CD4 cell count, nadir CD4 cell count, HIV-RNA, line of regimen, HCV status, HBV status, AIDS diagnosis, Framingham CVD 10 year elevated risk, CKD, and the DAD CKD risk score. All variables were investigated univariately for statistical significance. Because there were not multiple factors associated with discontinuation due to HSR or any toxicity, we did not utilize a multivariable model. The only factor significantly associated with discontinuation due to HSR was HCV status. There were no statistically significant factors associated with HSR or any toxicity. Note: calendar year does not include 2016 as this year of data collection only extended to April and there were too few events to analyse in this year.

Table 10. Factors associated with time from ABC initiation to discontinuation due to HSR or any toxicity. Individuals were censored at 6 weeks after ABC initiation, ABC discontinuation or death. Note: this was the only outcome with >30 events and could be analysed in a statistical model

	IRR	95% CI	p-value
Gender			
Female	1.00		
Male	0.87	[0.44 , 1.74]	0.698
Age Quintile			
1	1.00		
2	0.31	[0.09 , 1.08]	
3	0.27	[0.07 , 1.01]	
4	0.83	[0.32 , 2.16]	
5	1.04	[0.44 , 2.41]	0.1203*
Ethnicity			
White			
Black			
Asian			
NK			
HIV-Risk group			
MSM	1.00		
IDU	1.34	[0.55 , 3.25]	
MSW	0.91	[0.38 , 2.21]	
OTH/NK	1.95	[0.61 , 6.18]	0.5555*
Region			

South Europe	1.00		
Central Europe	1.52	[0.62 , 3.76]	
North-West Europe	0.74	[0.25 , 2.21]	
Central-East Europe	0.61	[0.19 , 1.96]	
East Europe	0.87	[0.31 , 2.42]	0.5115*
Calendar year			
2009	1.00		
2010	0.65	[0.11 , 3.90]	
2011	1.44	[0.39 , 5.29]	
2012	1.39	[0.38 , 5.10]	
2013	1.01	[0.23 , 4.44]	
2014	0.74	[0.15 , 3.55]	
2015	1.24	[0.35 , 4.35]	0.8526*
CD4 cell count			
<200	1.00		
200-350	2.45	[0.57 , 10.48]	
350-500	1.00	[0.18 , 5.52]	
>500	1.05	[0.24 , 4.59]	
missing	0.76	[0.20 , 2.91]	0.1423*
Nadir CD4 cell count			
<200	1.00		
200-350	0.37	[0.07 , 1.99]	
350-500	1.60	[0.59 , 4.37]	
>500	0.76	[0.22 , 2.60]	
missing	0.53	[0.22 , 1.32]	0.0780*
HIV-RNA			
<500			
500-1k			
1k-10k			
10k-100k			
>100k			
missing			
Line of ABC regimen			
1			
2			
3			
4+			
HCV status			
-	1.00		
+	1.44	[0.68 , 3.05]	
missing	2.50	[1.07 , 5.86]	0.1078*
HBV status			
-	1.00		
+	1.45	[0.70 , 3.03]	
missing	1.20	[0.42 , 3.43]	0.6038*
Previous AIDS diagnosis			

No	1.00		
Yes	0.59	[0.23 , 1.52]	0.276
Framingham 10 year elevated risk			
Low (≤20%)			
High (>20%)			
missing			
CKD			
No	1.00		
Yes	0.77	[0.05 , 11.64]	
missing	0.75	[0.38 , 1.49]	0.7014*
DAD CKD risk			
low	1.00		
medium	1.55	[0.47 , 5.09]	
high	0.57	[0.16 , 2.01]	
missing	0.65	[0.25 , 1.71]	0.2599*

Global p-values by Wald test or test for heterogenity(*)
IRR: incidence rate ratio; CI: confidence interval; MSM - sex between men; IDU - injection drug use; MSW - sex between men and women; OTH/NK - other, unknown;
line of therapy: change in 2 drugs with HIV-RNA > 500 copies/ml or more than 6 months lag between treatment regimens.
Age quintiles are as follows: 1 – 18-35; 2 – 35-43; 3 – 43-49; 4 – 49-55; 5 – >55.
CKD defined as 2 consecutive eGFRs >60 more than 3 months apart using the CKD EPI formula. s….
Framingham CVDFRAM 10 year elevated risk defined as risk of 20% or higher.?
Prior AIDS defined as: A prior diagnosis of AIDS-defining conditions listed in the 1993 CDC clinical definition
Prior Hepatitis C Virus (HCV) defined as: Prior HCV antibody test Positive (Yes), Negative (No) or no test or inconclusive (Unknown)
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).
Region of Europe includes South and Argentina: Argentina, Greece, Israel, Italy, Portugal, Spain; North: Austria, Belgium, France, Germany, Luxembourg, Central: Denmark, Finland, Iceland, Ireland, Netherlands, Norway, Sweden, United Kingdom; East Central: Bosnia and Herzegovina, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia; East: Belarus, Estonia, Latvia, Lithuania, Russian Federation, Ukraine.
Ethnicity, CD4 cell count, HIV-RNA, line of regimen, and Framingham 10 year elevated risk could not be analysed due to 0 cell counts.

7. PROTECTION OF HUMAN SUBJECTS

7.1. 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.

7.2. Subject confidentiality

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

8. 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.

9. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

9.1. 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.

9.2. 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.

10. 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.

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

Author(s):

1. PPD ViiV Healthcare
2. PPD EuroSIDA
3. PPD EuroSIDA
4. PPD ViiV Healthcare

TABLE OF CONTENTS

PAGE

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

Trademark Information

Trademarks of ViiV Healthcare and the GlaxoSmithKline group of companies
Ziagen®
Kivexa®
Trizivir®
Triumeq®

Trademarks not owned by ViiV Healthcare and the GlaxoSmithKline group of companies
[SAS]

1. RESPONSIBLE PARTIES: SPONSOR INFORMATION PAGE

MARKETING AUTHORISATION HOLDER

ViiV Healthcare UK Limited

Sponsor Legal Registered Address:

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

SPONSOR SIGNATORY:

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

INVESTIGATOR PROTOCOL AGREEMENT PAGE

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

Investigator Name**:** **Anna Schultze**

Investigator Signature Date

Investigator Name: **Amanda Mocroft**

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

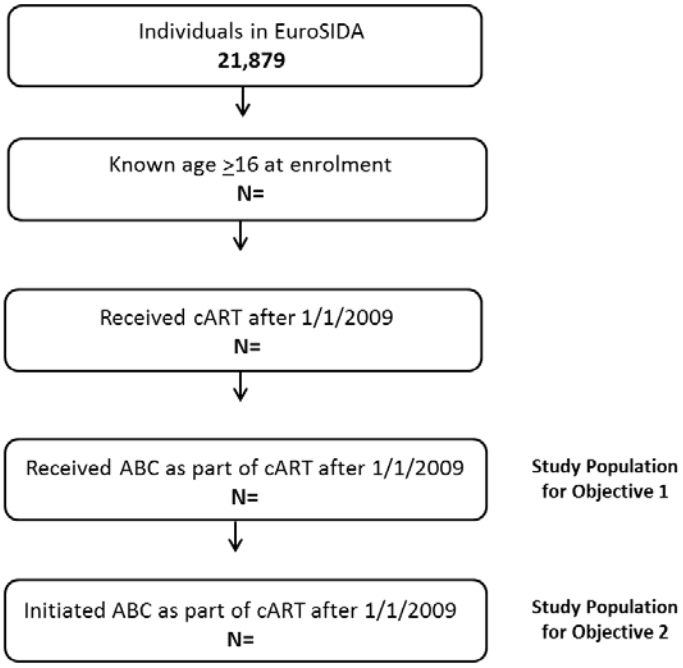
should be interpreted with the knowledge of these limitations and potential for inherent biases in mind. Nonetheless, EuroSIDA is in a unique position to compare and describe treatment patterns due to the standardised nature of the data collection and the inclusion of countries for which there are no 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.