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

Ashley Roen[1], Kamilla Laut[2], Annegret Pelchen-Matthews[1], Elena Borodulina[3], Luis Caldeira[4], Amanda Clarke[5], Bonaventura Clotet[6], Antonella d'Arminio Monforte[7], Gerd Fätkenheuer[8], Jose M. Gatell Artigas[9], Igor Karpov[10], Anastasiia Kuznetsova[11], Galina Kyselyova[12], Iwona Mozer-Lisewska[13], Fiona Mulcahy[14], Leigh Ragone[15], Alexandra Scherrer[16], Vilma Uzdaviniene[17], Linos Vandekerckhove[18], Vani Vannappagari[15], Lars Ostergaard[19], Amanda Mocroft[1] on behalf of the EuroSIDA study*

1 University College London, London, UK

2 University of Copenhagen, Copenhagen, Denmark

3 Samara State Medical University, Samara, Russia

4 Hospital Santa Maria, Lisbon, Portugal

5 Royal Sussex County Hospital, Brighton, UK

6 Hospital Universitari Germans Trias i Pujol, Barcelona, Spain

7 Ospedale San Paulo, Milan, Italy

8 University Hospital Cologne, Cologne, Germany

9 Hospital Clinic, Barcelona, Spain

10 Belarus State Medical University, Minsk, Belarus

11 Kharkov State Medical University, Khrakov, Ukraine

12 Crimean Republican AIDS centre, Simferopol, Ukraine

13 Poznan University of Medical Sciences, Poznań, Poland

14 St. James' Hospital, Dublin, Ireland

15 ViiV Healthcare, RTP, North Carolina, USA

16 University Hospital Zürich, Zürich, Switzerland

17 Vilnius University Hospital Santariskiu Klinikos, Vilnius, Lithuania

18 University Ziekenhuis Gent, Gent, Belgium

19 Aarhus universitetshospital, Skejby, Denmark

**Study group listed in appendix*

Correspondence to: Ashley Roen. University College London, London UK. a.roen@ucl.ac.uk

Funding: EuroSIDA was supported by the European Union's Seventh Framework Programme for research, technological development and demonstration under EuroCoord grant agreement n˚ 260694. Current support includes unrestricted grants by Bristol-Myers Squibb, Gilead, GlaxoSmithKline LLC, Janssen R&D, Merck and Co. Inc., Pfizer Inc. The participation of centres from Switzerland was supported by The Swiss National Science Foundation (Grant 108787). The study is also supported by a grant [grant number DNRF126] from the Danish National Research Foundation. This analysis was funded by ViiV Healthcare.

Word Count: abstract (222), main text (2,243)

Tables (2), Figures (2)

Abstract

Objective: 5-8% of HIV-positive individuals initiating abacavir (ABC) experience potentially fatal hypersensitivity reactions (HSR).

Methods: We calculated the proportion of EuroSIDA individuals receiving ABC-based cART among those receiving cART after 1/1/2009. Poisson regression was used to identify demographic, and current clinical and laboratory factors associated with ABC utilization and discontinuation.

Results: Between 2009-2016, of 10,076 individuals receiving cART, 3,472 (34%) had ever received ABC-based cART. Temporal trends of ABC utilization were also heterogeneous, 28% in 2009, dropping to 26% in 2010 and increasing to 31% in 2016, and varied across region and time. Poisson models showed lower ABC utilization in older individuals, those with higher CD4 cell-counts, higher cART lines, and prior AIDS. Higher ABC utilization was associated with higher HIV-RNA, poor renal function, and was more common in Central-East and Eastern Europe and lowest during 2014. During 779 PYFU in 2,139 individuals starting ABC after 1/1/2009, 113 discontinued ABC within 6 weeks of initiation for any reason (IR =14.5 (12.1, 17.5) per 100-person-year follow-up), 13 due to reported HSR (IR =0.3 (0.1, 1.0)) and 35 due to reported HSR/any toxicity (IR = 4.5 (3.2, 6.3)). There were no factors significantly associated with ABC discontinuation due to reported HSR/any toxicity.

Conclusion: ABC remains commonly used across Europe and the incidence of discontinuation due to reported HSR was low in our study population.

Introduction

In the absence of genetic screening, hypersensitivity reaction (HSR) presents in approximately 5-8% of persons living with HIV (PLHIV) initiating abacavir [1,2](ABC). HSR can vary in severity and clinical manifestation indicative of multiorgan involvement and includes fever, skin rash, constitutional, gastrointestinal tract and respiratory symptoms [1-5]. In rare cases, HSR is fatal[6,7]. Risk of ABC HSR is high for patients who test positive for the HLA-B*5701 allele[1,8,9]; however, ABC HSRs have been reported at a lower frequency in patients who do not carry this allele and therefore risk for HSR can be reduced by HLA B*5701 screening.[1,3] ABC should never be initiated in patients with a positive HLA-B*5701 status, and ABC re-challenge among those previously experiencing HSR is contraindicated, as acute onset of potentially fatal symptoms have been reported[2,10-12].

ABC remains a commonly used drug throughout Europe and is recommended as a part of first line therapy by national and international guidelines[13,14]; it is therefore important to continually examine safety of ABC over time. A previous 2008 report using data from EuroSIDA, a longitudinal cohort collaboration across 35 countries across Europe plus Israel and Argentina[15], showed the HSR incidence within 3 months of starting ABC of 22.1 (18.7, 25.4) per 100 person-years follow-up with a decreasing trend for ABC discontinuation due to HSR over time[16]. HSR due to ABC typically presents within 6 weeks of therapy initiation[4,17], and presentation of HSR later than 8 weeks after ABC initiation is almost always due to other causes[18].

The objectives of this study were twofold. First, to describe the proportion of individuals across Europe on combination antiretroviral therapy (cART) receiving an ABC based regimen from 1/1/2009 to 1/4/2016 and the factors associated with ABC initiation. Second, we sought to describe the cumulative frequency, incidence and factors associated with ABC discontinuation due to reported HSR or due to reported HSR/any toxicity among those starting ABC after 1/1/2009 as part of a cART regimen.

Methods

Study Population

EuroSIDA is a longitudinal observational cohort study that was initiated in 1994, and has been previously described[15]. The data collected includes start and stop dates for each antiretroviral drug used, reasons for discontinuing an antiretroviral drug and clinical events. Further details on data collected can be found at www.cphiv.dk.

Individuals from the EuroSIDA cohort over the age of 16 at enrolment receiving cART (at least 3 drugs from any class, excluding ritonavir) after 1/1/2009 were included in the ABC utilisation over time analysis. All persons starting ABC based cART after 1/1/2009 were eligible for inclusion for analyses of reported HSR related discontinuation.

Statistical Methods

Among those receiving cART and under active follow-up, the proportion of individuals who received ABC at the midpoint of each calendar year (July 1st) from 1/1/2009 onwards and by geographical region was summarised using descriptive statistics. Active follow-up was defined as having a first visit date before and last visit date after the midpoint of the year.

Factors associated with ABC utilization were investigated using Poisson regression with generalised estimating equations (GEE) to control for the inclusion of repeated exposuresand events. Baseline was defined as 1/1/2009 or enrolment into EuroSIDA, whichever occurred later. Individuals off ABC contributed follow-up (FU) until ABC initiation, the 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. Factors that were significantly associated with ABC initiation ($p<0.1$) in univariate analyses were included in multivariable models. Factors investigated were gender, age, ethnicity, HIV transmission risk group, region of care, calendar year, CD4 cell count, nadir CD4 cell count, HIV-RNA, line of cART regimen, Hepatitis B and C status, previous AIDS diagnosis, Framingham 10 year elevated cardiovascular disease (CVD) risk[19], chronic kidney disease (CKD), and Data on Adverse Drugs(D.A.D) CKD risk[20,21]. Line of cART regimen captured the extent of previous antiretroviral treatment and treatment failure and was defined as a change in at least 2 ARV drugs accompanied by an HIV-RNA > 500 copies/ml, or more than 6 months off treatment before starting a new therapy. CKD was defined as 2 consecutive eGFRs < 60 more than three months apart using the CKD EPI formula[22].

For the second objective, analysing reported HSR related discontinuation, 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 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 later. This was an on-treatment analysis where individuals contributed follow-up until 6 weeks after ABC initiation, ABC discontinuation due to any cause, death or their last visit date, whichever occurred first. The primary outcome was discontinuation due to reported HSR. We also analyzed a composite outcome of discontinuation due to reported HSR or any toxicity, as well as investigating all reasons for discontinuation to account for underreporting and potentially undiagnosed HSR cases.

Factors associated with reported HSR or any toxicity related discontinuation were identified in a multivariable Poisson Regression Model using GEE to adjust for repeated events; those that were significant ($p<0.1$) in univariable analyses were included in multivariable models.

Results

Baseline Characteristics

Among 10,076 individuals in EuroSIDA receiving cART between 1/1 2009 and 4/1 2016, 3472 (34%; 95% CI (34-35)) had ever received ABC during follow-up (Table 1). 74% were male and 27% were female with HIV risk-group of sex between men (MSM) (40%), injection drug users (IDU) (22%) sex between men and women (MSW) (31%) or other/unknown (7%). The highest proportion received care in Southern Europe (28%) followed by Western Europe (25%), Northern Europe (22%), Central-East Europe (14%), and Eastern Europe (12%). Median baseline age was 45 years (IQR: 37, 52). In general, demographic characteristics among 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. Baseline HIV-RNA values among those initiating ABC were slightly higher compared to those not exposed to ABC, and there was also a higher prevalence of AIDS among those initiating ABC.

ABC utilization and factors associated with starting ABC

ABC utilization significantly varied over time, starting at 28% in 2009, dropping to 26% in 2010 and increasing to 31% in 2016. (p-heterogeneity from univariate analysis = <0.001) Figure 1. There was a significant interaction with region and time where ABC utilization in Northern Europe decreased, Southern and Eastern Europe increased and Western and Central-East Europe remained relatively consistent with time (p-interaction < 0.001).

Using multivariable Poisson regression, factors associated with lower rates of ABC utilization were older age (IRR = 0.73 (0.59, 0.90) for highest age quintile, >58 compared to the lowest, 18-41), higher CD4 cell counts (IRR = 0.68 (0.56, 0.82) for CD4 > 500 compared to CD4 < 200 cells/mm^3), and those exposed to more cART treatment regimens (IRR = 0.55 (0.46, 0.66) for 4^{th}+ line compared to first line regimens), and having a previous AIDS diagnosis (IRR = 0.9 (0.8, 1.0) compared to those without a previous AIDS diagnosis). Higher ABC utilization 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 CKD risk scores (IRR = 1.18 (1.01, 1.38) for those at high risk compared to low risk). There was heterogeneity in ABC utilization among region; those in Central-East and Eastern Europe were more likely to initiate ABC compared to Southern Europe; IRR = 1.58 (1.35, 1.84) and 1.71 (1.42,

2.05). Persons under follow-up in 2014 were less likely to start ABC compared to those under follow-up in 2009 (IRR = 0.69 (0.57, 0.85)) Figure 2.

Discontinuation of ABC

Among 2,139 individuals initiating ABC after 1/1/2009, contributing 778 person years of follow-up, 113 (5.3%) individuals discontinued ABC within 6 weeks of ABC initiation, an incidence rate of 14.51 (12.07, 17.45) per 100 person-years follow-up. The most common single reason for discontinuation within the first 6 weeks was unknown, followed by the patient's wish/decision, then other causes. 13 individuals (0.6%) discontinued due to reported HSR (IR =1.67 (0.97, 2.87)) and 35 (4.6%) discontinued due to reported HSR or any toxicity, IRR = 4.49 (3.23, 6.26) per 100 person-years follow-up, Table 2.

As only 13 persons discontinued due to reported HSR, we could not formally investigate factors associated with reported HSR related discontinuation. Expanding the endpoint to discontinuation due to reported HSR or any toxicity did not identify any factors associated with discontinuation. The strongest factor associated with discontinuation for reported HSR/any toxicity was nadir CD4 cell count, where those with a nadir CD4 cell count of 350-500 cells/mm^3 were at the highest risk of discontinuing due to reported HSR/any toxicity (IRR = 1.60 (0.59, 4.37) compared to those with CD4 <200 cells/mm^3, p-heterogeneity = 0.078). This analysis had limited power as there were few events (n=35).

Seven individuals died within 6 weeks of initiating ABC, all with advanced HIV disease and other comorbidities. HSR was not reported among these individuals and was unlikely the cause of these deaths.

Discussion

Despite the risk of HSR, ABC remains a commonly used ARV drug across Europe in EuroSIDA. Among individuals initiating ABC based cART after 2009, there were very few discontinuations within 6 weeks of ABC initiation, and discontinuation rates due to reported hypersensitivity reactions were 0.3 (0.1, 1.0) per 100 person-years follow-up. There were 7 deaths within 6 weeks of starting ABC, but these were likely due to causes unrelated to ABC HSR reactions.

ABC utilization was lower among individuals exposed to more treatment regimens and had previous ABC exposure. Because there is evidence to suggest ABC re-challenge should be avoided[5,12,23], it is possible this result is due to lower ABC prescription rates among those already exposed to ABC. Unexpectedly, higher ABC utilization was associated with CKD and higher DAD CKD risk scores, though this could be attributed to confounding by indication. Use of tenofovir has been linked to kidney disease[24] and individuals on tenofovir with decreasing renal function are likely to discontinue tenofovir[25] and be switched to ABC[26], a drug with no reported adverse effect on renal function. Changes over time and within regions in use of abacavir likely reflects marketing and availability of abacavirt.

Overall, the rate of discontinuation of ABC in the first 6 weeks after starting ABC was low, which is similar to Phase II clinical trials[27,28], but slightly lower than previous EuroSIDA findings[16], although the previous EuroSIDA report had a much larger window to observe reported HSR cases (3 months vs. 6 weeks in our study). The rate of stopping due to reported HSR or the composite endpoint of reported HSR or any toxicity was also low, which could indicate the effectiveness of screening for HLA B*5701, better patient care and a greater understanding of HSR among treating physicians. Screening uptake for the HLA B*5701 allele has likely avoided many HSR reactions in recent years. EuroSIDA does not collect genetic screening information, thus it is unknown which individuals were tested for HLA B*5701, or whether the frequency of testing varied between regions and/or over calendar time.

It is possible that we found low rates of discontinuation due to using a 6-week window from ABC initiation, but it is well established that this is when HSR is most likely to occur[18]. Even so, compared to early cART, where discontinuation rates at 3 months have reported between 10-15%[29,30], discontinuation due to ABC was low, indicating the effectiveness of screening for HLA B*5701, improved patient management, improved ARV regimens, reduction in toxicities, and improved adherence[31]. We found no factors significantly associated with ABC

discontinuation due to reported HSR/any toxicity, though this might partly be due to low power as few patients discontinued.

Along with lack of data on HLA B*5701 screening, there are other limitations to our study. Most notably, the symptoms of HSR can be difficult to distinguish from other adverse events in the population, possibly leading to over or underreporting of discontinuation due to reported HSR. EuroSIDA also only collects one reason for discontinuing a drug, so if HSR and another simultaneous reason for discontinuation occurred, HSR may have not been reported as the reason for discontinuation in our data. We have investigated underreporting by using a composite outcome of reported HSR or any toxicity, with consistent results. Finally, the validity of our models depends on the assumption that we appropriately adjusted for confounding; it is however possible that our models have residual confounding by indication. 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.

This study also has several strengths including the use of a large dataset from a heterogeneous population, and including data from Eastern Europe. In addition, EuroSIDA covers the period 1994-2016 with consistent records of all ARV use and reasons for stopping, allowing for comparisons of temporal trends of ABC utilization and subsequent HSR. There has also been consistency in the way ARVs were collected and the subsequent reasons for stopping over our study duration.

In summary, ABC remains a commonly used drug throughout Europe, and the incidence of reported hypersensitivity reaction among those on ABC is low, likely attributable to screening for HLA B*5701, improved patient care and a greater understanding and awareness of HSR.

Table 1: Baseline characteristics of all participants, split by ABC use (total *vs.* no ABC *vs*. ever *ABC*) in the EuroSIDA cohort from 1/1/2009 to 4/1/2016

	Total		No ABC		ABC		
	No.	%	No.	%	No.	%	p-value
Gender							
Female	7408	74	4926	75	2482	72	0.001
Male	2668	27	1678	25	990	29	
Region of care in Europe							
South	2819	28	1962	30	857	25	<0.001
West	2478	25	1672	25	806	23	
North	2187	22	1348	20	839	24	
Central-East	1430	14	897	14	533	15	
East	1162	12	725	11	437	13	
Ethnicity							
White	8,827	88	5,773	87	3,054	88	0.291
Black	563	6	361	6	202	6	
Asian	163	2	108	2	55	2	
OTH/NK	523	5	362	6	161	5	
HIV-Risk group							
MSM	4,054	40	2,701	41	1,353	39	0.171
IDU	2,198	22	1,438	22	760	22	
MSW	3,138	31	2,012	31	1,126	32	
OTH/NK	686	7	453	7	233	7	
Calendar year*ł	2009	(2009, 2011)	2009	(2009, 2011)	2011	(2009, 2010)	0.001
Baseline Age ł	45	(37, 52)	45	(37, 51)	51	(38, 52)	0.001
Baseline HIV-RNA ł	49	(39, 74)	49	(39, 71)	71	(33, 90)	<0.001
Baseline CD4 cell count ł	490	(337, 688)	488	(340, 679)	679	(333, 709)	0.385
CKD							
No	7,354	84	5,597	85	1,757	51	<0.001
Yes	172	2	106	2	66	2	
missing	1,232	14	901	14	1,649	47	
AIDS							
No	6,848	68	4,559	69	2,289	66	0.001
Yes	3,228	32	2,045	31	1,183	34	
cART line							
1st	5,859	58	3,815	58	2,044	59	<0.001
2nd	2,043	20	1,307	20	736	21	
3rd	964	10	611	9	353	10	
4th+	1,210	12	871	13	339	10	

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

% are column percentages

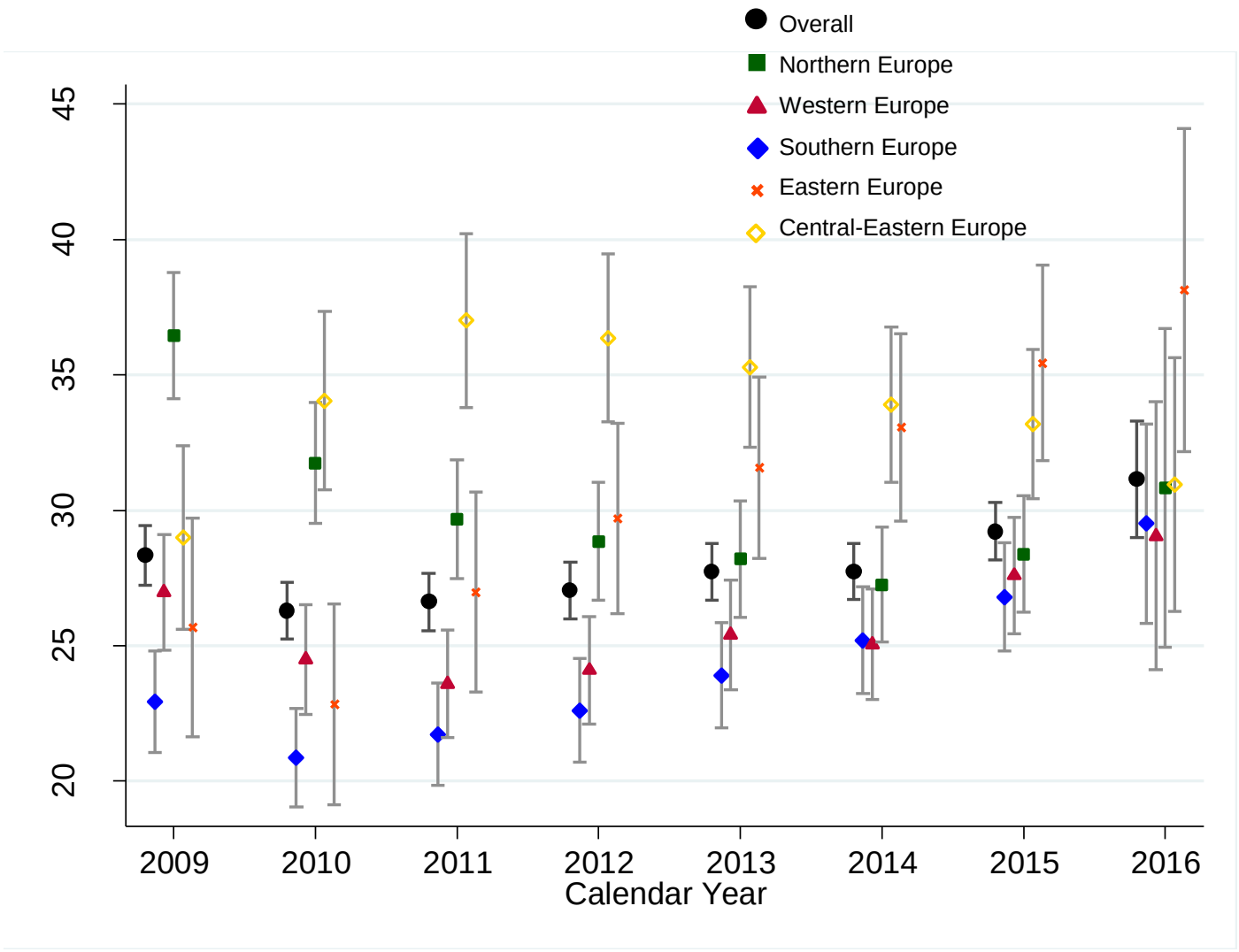
* calendar year for the first ABC utilization date in the follow-up period

ł values are median (IQR)

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

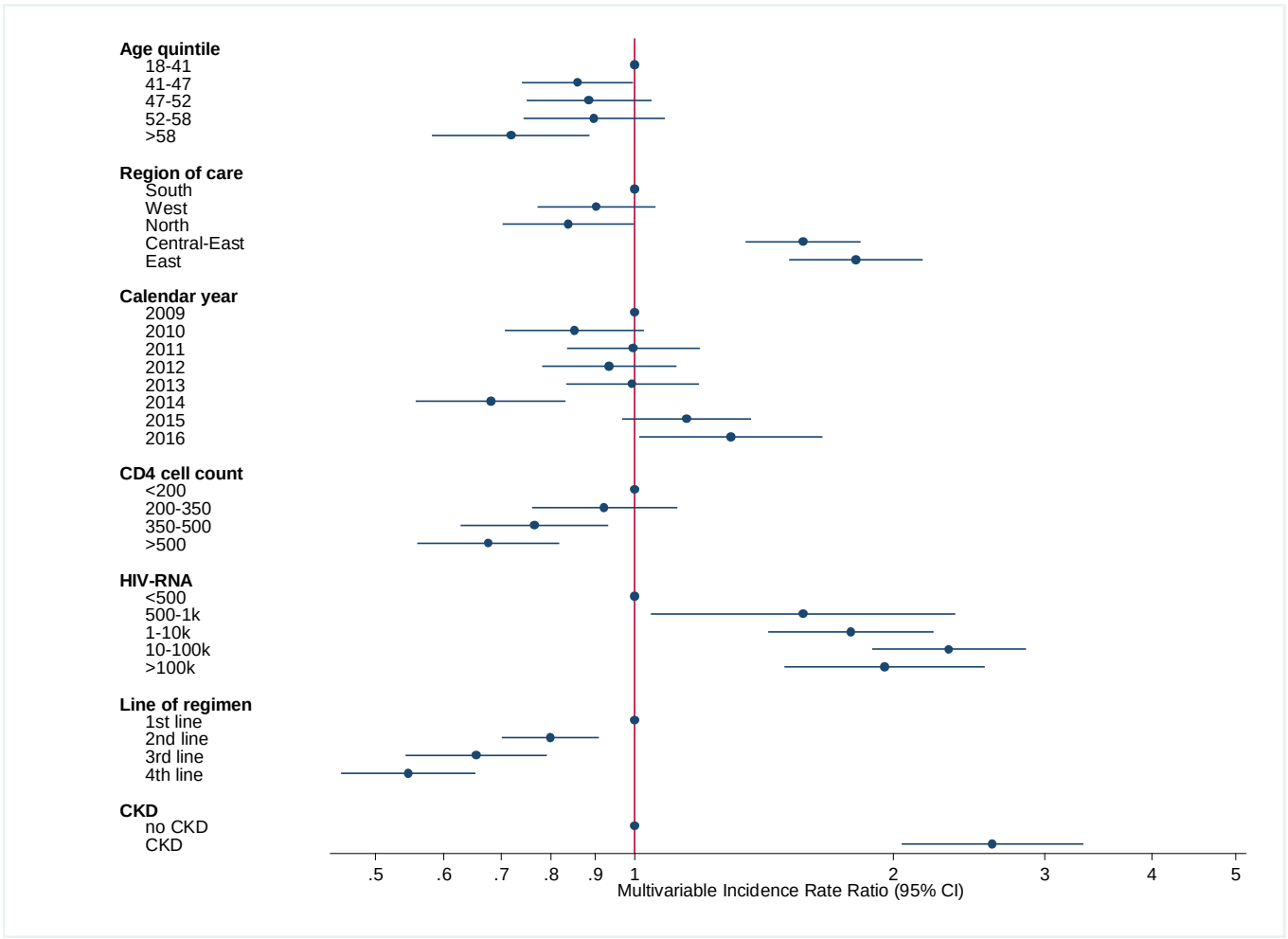
Abbreviations: MSM - sex between men; IDU - injection drug use; MSW - sex between men and women; OTH/NK - other, unknown; IQR – interquartile range.

Figure 1: Percent prescribed abacavir at the midpoint of each year overall by year and region in the EuroSIDA cohort from 2009 -2016



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

Figure 2: Multivariable incidence rate ratios for ABC utilization in the EuroSIDA cohort from 1/1/2009 to 4/1/2016



All clinical and laboratory variables are time updated; CKD = Chronic kidney Disease defined as 2 consecutive eGFRs < 60 more than 3 months apart using the CKD EPI formula; Other variables in the model include Gender, Framingham CVD 10 year elevated risk, HCV, and HBV status, DAD CKD risk score and previous AIDS diagnosis.

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

Table 2. Reasons and incidence rates for ABC discontinuation by reason for stopping treatment in the EuroSIDA cohort from 1/1/2009 to 4/1/2016. Individuals were censored at 6 weeks after ABC initiation, ABC discontinuation or death, whichever came first.

Reason for stopping treatment as reported to EuroSIDA	Failures	Rate	95% CI
Any Reason	113	14.51	(12.07, 17.45)
HSR or any toxicity	35	4.49	(3.23, 6.26)
Any toxicity	22	2.82	(1.86, 4.29)
Unknown	21	2.70	(1.76, 4.14)
Patient's wish/decision	20	2.57	(1.66, 3.98)
Other causes	17	2.18	(1.36, 3.51)
Physician's decision	16	2.05	(1.26, 3.35)
Toxicity - GI tract	16	2.05	(1.26, 3.35)
HSR	13	1.67	(0.97, 2.87)
Toxicity – Liver	2	0.26	(0.06, 1.03)
Toxicity, predominantly CNS	2	0.26	(0.06, 1.03)
Toxicity, predominantly kidneys	2	0.26	(0.06, 1.03)
Treatment Failure	1	0.13	(0.02, 0.91)
Concern of cardiovascular disease, including dyslipidaemia	1	0.13	(0.02, 0.91)
Other Toxicity	1	0.13	(0.02, 0.91)
Non-compliance	1	0.13	(0.02, 0.91)

*Total person years follow-up = 778; Rate = per 100 person years

References:

1. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med.* 2008;358(6):568-579.
2. Hewitt RG. Abacavir hypersensitivity reaction. *Clin Infect Dis.* 2002;34(8):1137-1142.
3. Rauch A, Nolan D, Thurnheer C, et al. Refining abacavir hypersensitivity diagnoses using a structured clinical assessment and genetic testing in the Swiss HIV Cohort Study. *Antivir Ther.* 2008;13(8):1019-1028.
4. Chaponda M, Pirmohamed M. Hypersensitivity reactions to HIV therapy. *Br J Clin Pharmacol.* 2011;71(5):659-671.
5. Clay PG. The abacavir hypersensitivity reaction: a review. *Clin Ther.* 2002;24(10):1502-1514.
6. Calmy A, Hirschel B, Cooper DA, Carr A. Clinical update: adverse effects of antiretroviral therapy. *Lancet.* 2007;370(9581):12-14.
7. de la Rosa R, Harris M, Uyeda L, Goodison K, Keown P, Montaner JS. Life-threatening reaction after first ever dose of abacavir in an HIV-1-infected patient. *AIDS.* 2004;18(3):578-579.
8. Martin AM, Nolan D, Gaudieri S, et al. Predisposition to abacavir hypersensitivity conferred by HLA-B*5701 and a haplotypic Hsp70-Hom variant. *Proc Natl Acad Sci U S A.* 2004;101(12):4180-4185.
9. Hetherington S, Hughes AR, Mosteller M, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. *Lancet.* 2002;359(9312):1121-1122.
10. Temesgen Z, Beri G. HIV and drug allergy. *Immunol Allergy Clin North Am.* 2004;24(3):521-531, viii.
11. Walensky RP, Goldberg JH, Daily JP. Anaphylaxis after rechallenge with abacavir. *AIDS.* 1999;13(8):999-1000.
12. Frissen PH, de Vries J, Weigel HM, Brinkman K. Severe anaphylactic shock after rechallenge with abacavir without preceding hypersensitivity. *AIDS.* 2001;15(2):289.
13. Churchill D, Waters L, Ahmed N, et al. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015. *HIV Med.* 2016;17 Suppl 4:s2-s104.
14. Battegay ML, Jens; Ryom, Lene European AIDS Clinical Society Guidelines for treatment of HIV-positive adults in Europe. 2017. Accessed July 20, 2017.
15. Mocroft A, Ledergerber B, Katlama C, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet.* 2003;362(9377):22-29.
16. Bannister WP, Friis-Moller N, Mocroft A, et al. Incidence of abacavir hypersensitivity reactions in euroSIDA. *Antivir Ther.* 2008;13(5):687-696.
17. Hetherington S, McGuirk S, Powell G, et al. Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir. *Clin Ther.* 2001;23(10):1603-1614.
18. Carr A, Cooper DA. Adverse effects of antiretroviral therapy. *Lancet.* 2000;356(9239):1423-1430.
19. Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation.* 1998;97(18):1837-1847.
20. Mocroft A, Lundgren J, Ross M, et al. A clinically useful risk-score for chronic kidney disease in HIV infection. *J Int AIDS Soc.* 2014;17(4 Suppl 3):19514.
21. Mocroft A, Lundgren JD, Ross M, et al. Development and validation of a risk score for chronic kidney disease in HIV infection using prospective cohort data from the D:A:D study. *PLoS Med.* 2015;12(3):e1001809.
22. Mocroft A, Ryom L, Reiss P, et al. A comparison of estimated glomerular filtration rates using Cockcroft-Gault and the Chronic Kidney Disease Epidemiology Collaboration estimating equations in HIV infection. *HIV Med.* 2014;15(3):144-152.
23. Escaut L, Liotier JY, Albengres E, Cheminot N, Vittecoq D. Abacavir rechallenge has to be avoided in case of hypersensitivity reaction. *AIDS.* 1999;13(11):1419-1420.
24. Scherzer R, Estrella M, Li Y, et al. Association of tenofovir exposure with kidney disease risk in HIV infection. *AIDS.* 2012;26(7):867-875.
25. Ryom L, Mocroft A, Kirk O, et al. Predictors of advanced chronic kidney disease and end-stage renal disease in HIV-positive persons. *AIDS.* 2014;28(2):187-199.
26. Guillemi SA, Ling SH, Dahlby JS, et al. Effects of a switch from tenofovir- to abacavir-based antiretroviral therapy, with or without atazanavir, on renal function. *J Int AIDS Soc.* 2016;19(1):20995.
27. Saag MS, Sonnerborg A, Torres RA, et al. Antiretroviral effect and safety of abacavir alone and in combination with zidovudine in HIV-infected adults. Abacavir Phase 2 Clinical Team. *AIDS.* 1998;12(16):F203-209.

28. Staszewski S, Katlama C, Harrer T, et al. A dose-ranging study to evaluate the safety and efficacy of abacavir alone or in combination with zidovudine and lamivudine in antiretroviral treatment-naive subjects. *AIDS.* 1998;12(16):F197-202.
29. Di Biagio A, Cozzi-Lepri A, Prinapori R, et al. Discontinuation of Initial Antiretroviral Therapy in Clinical Practice: Moving Toward Individualized Therapy. *J Acquir Immune Defic Syndr.* 2016;71(3):263-271.
30. Elzi L, Marzolini C, Furrer H, et al. Treatment modification in human immunodeficiency virus-infected individuals starting combination antiretroviral therapy between 2005 and 2008. *Arch Intern Med.* 2010;170(1):57-65.
31. Yuan Y, L'Italien G, Mukherjee J, Iloeje UH. Determinants of discontinuation of initial highly active antiretroviral therapy regimens in a US HIV-infected patient cohort. *HIV Med.* 2006;7(3):156-162.

Appendix

The EuroSIDA Study Group

The multi-centre study group, EuroSIDA (national coordinators in parenthesis).Argentina: (M Losso), M Kundro, Hospital JM Ramos Mejia, Buenos Aires. Austria: (B Schmied), Pulmologisches Zentrum der Stadt Wien, Vienna; R Zangerle, Medical University Innsbruck, Innsbruck. Belarus: (I Karpov), A Vassilenko, Belarus State Medical University, Minsk, VM Mitsura, Gomel State Medical University, Gomel; D Paduto, Regional AIDS Centre, Svetlogorsk. Belgium: (N Clumeck), S De Wit, M Delforge, Saint-Pierre Hospital, Brussels; E Florence, Institute of Tropical Medicine, Antwerp; L Vandekerckhove, University Ziekenhuis Gent, Gent. Bosnia-Herzegovina: (V Hadziosmanovic), Klinicki Centar Univerziteta Sarajevo, Sarajevo. Croatia: (J Begovac), University Hospital of Infectious Diseases, Zagreb. Czech Republic: (L Machala), D Jilich, Faculty Hospital Bulovka, Prague; D Sedlacek, Charles University Hospital, Plzen. Denmark: G Kronborg,T Benfield, Hvidovre Hospital, Copenhagen; J Gerstoft, T Katzenstein, Rigshospitalet, Copenhagen; NF Møller, C Pedersen, Odense University Hospital, Odense; L Ostergaard, Skejby Hospital, Aarhus, L Wiese, Roskilde Hospital, Roskilde; L N Nielsen, Hillerod Hospital, Hillerod. Estonia: (K Zilmer), West-Tallinn Central Hospital, Tallinn; Jelena Smidt, Nakkusosakond Siseklinik, Kohtla-Järve. Finland: (M Ristola), I Aho, Helsinki University Central Hospital, Helsinki. France: (J-P Viard), Hôtel-Dieu, Paris; P-M Girard, Hospital Saint-Antoine, Paris; C Pradier, E Fontas, Hôpital de l'Archet, Nice; C Duvivier, Hôpital Necker-Enfants Malades, Paris. Germany: (J Rockstroh), Universitäts Klinik Bonn; G Behrens, Medizinische Hochschule Hannover; O Degen, University Medical Center Hamburg-Eppendorf, Infectious Diseases Unit, Hamburg; HJ Stellbrink, IPM Study Center, Hamburg; C Stefan, JW Goethe University Hospital, Frankfurt; J Bogner, Medizinische Poliklinik, Munich; G. Fätkenheuer, Universität Köln, Cologne. Georgia: (N Chkhartishvili) Infectious Diseases, AIDS & Clinical Immunology Research Center, Tbilisi. Greece: (P Gargalianos), G Xylomenos, K Armenis, Athens General Hospital "G Gennimatas"; H Sambatakou, Ippokration General Hospital, Athens. Hungary: (J Szlávik), Szent Lásló Hospital, Budapest. Iceland: (M Gottfredsson), Landspitali University Hospital, Reykjavik. Ireland: (F Mulcahy), St. James's Hospital, Dublin. Israel: (I Yust), D Turner, M Burke, Ichilov Hospital, Tel Aviv; E Shahar, G Hassoun, Rambam Medical Center, Haifa; H Elinav, M Haouzi, Hadassah University Hospital, Jerusalem; D Elbirt, ZM Sthoeger, AIDS Center (Neve Or), Jerusalem. Italy: (A D'Arminio Monforte), Istituto Di Clinica Malattie Infettive e Tropicale, Milan; R Esposito, I Mazeu, C Mussini, Università Modena, Modena; F Mazzotta, A Gabbuti, Ospedale S Maria Annunziata, Firenze; V Vullo, M Lichtner, University di Roma la Sapienza, Rome; M Zaccarelli, A Antinori, R Acinapura, M Plazzi, Istituto Nazionale Malattie Infettive Lazzaro Spallanzani, Rome; A Lazzarin, A Castagna, N Gianotti, Ospedale San Raffaele, Milan; M Galli, A Ridolfo, Osp. L. Sacco, Milan. Latvia: (B Rozentale), Infectology Centre of Latvia, Riga. Lithuania: (V Uzdaviniene) Vilnius University Hospital Santaros Klinikos, Vilnius; R Matulionyte, Centro poliklinika, Vilnius, Vilnius University Hospital Santaros Klinikos, Vilnius. Luxembourg: (T Staub), R Hemmer, Centre Hospitalier, Luxembourg. Netherlands: (P Reiss), Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam. Norway: (DH Reikvam), A Maeland, J Bruun, Ullevål Hospital, Oslo. Poland: (B Knysz), J Gasiorowski, M Inglot, Medical University, Wroclaw; A Horban, E Bakowska, Centrum Diagnostyki i Terapii AIDS, Warsaw; R Flisiak, A Grzeszczuk, Medical University, Bialystok; M Parczewski, K Maciejewska, B Aksak-Was, Medical Univesity, Szczecin; M Beniowski, E Mularska, Osrodek Diagnostyki i Terapii AIDS, Chorzow; T Smiatacz, M Gensing, Medical University, Gdansk; E Jablonowska, E Malolepsza, K Wojcik, Wojewodzki Szpital Specjalistyczny, Lodz; I Mozer-Lisewska, Poznan University of Medical Sciences, Poznan. Portugal: (L Caldeira), Hospital Santa Maria, Lisbon; K Mansinho, Hospital de Egas Moniz, Lisbon; F Maltez, Hospital Curry Cabral, Lisbon. Romania: (R Radoi), C Oprea, Spitalul Clinic de Boli Infectioase si Tropicale: Dr. Victor Babes, Bucuresti. Russia: (A Panteleev), O Panteleev, St Petersburg AIDS Centre, St Peterburg; A Yakovlev, Medical Academy Botkin Hospital, St Petersburg; T Trofimora, Novgorod Centre for AIDS, Novgorod, I Khromova, Centre for HIV/AIDS & and Infectious Diseases, Kaliningrad; E Kuzovatova, Nizhny Novgorod Scientific and Research Institute of Epidemiology and Microbiology named after Academician I.N. Blokhina, Nizhny Novogrod; E Borodulina, E Vdoushkina, Samara State Medical University, Samara. Serbia: (D Jevtovic), The Institute for Infectious and Tropical Diseases, Belgrade. Slovenia: (J Tomazic), University Clinical Centre Ljubljana, Ljubljana. Spain: (JM Gatell), JM Miró, Hospital Clinic Universitari de Barcelona, Barcelona; S Moreno, J. M. Rodriguez, Hospital Ramon y Cajal, Madrid; B Clotet, A Jou, R Paredes, C Tural, J Puig, I Bravo, Hospital Germans Trias i Pujol, Badalona; P Domingo, M Gutierrez, G Mateo, MA Sambeat, Hospital Sant Pau, Barcelona; JM Laporte, Hospital Universitario de Alava, Vitoria-Gasteiz. Sweden: (K Falconer), A Thalme, A Sonnerborg, Karolinska University Hospital, Stockholm; A Blaxhult, Venhälsan-Sodersjukhuset, Stockholm; L Flamholc, Malmö University Hospital, Malmö. Switzerland: (A Scherrer), R Weber, University Hospital Zurich; M Cavassini, University Hospital Lausanne; A Calmy, University Hospital Geneva; H Furrer, University Hospital Bern; M Battegay, University Hospital Basel; P Schmid, Cantonal Hospital St. Gallen. Ukraine: A Kuznetsova, Kharkov State Medical University, Kharkov; G Kyselyova, Crimean Republican AIDS centre, Simferopol; M

Sluzhynska, Lviv Regional HIV/AIDS Prevention and Control CTR, Lviv. United Kingdom: (B Gazzard), St. Stephen's Clinic, Chelsea and Westminster Hospital, London; AM Johnson, E Simons, S Edwards, Mortimer Market Centre, London; A Phillips, MA Johnson, A Mocroft, Royal Free and University College Medical School, London (Royal Free Campus); C Orkin, Royal London Hospital, London; J Weber, G Scullard, Imperial College School of Medicine at St. Mary's, London; A Clarke, Royal Sussex County Hospital, Brighton; C Leen, Western General Hospital, Edinburgh.

The following centers have previously contributed data to EuroSIDA: Infectious Diseases Hospital, Sofia, Bulgaria. Hôpital de la Croix Rousse, Lyon, France. Hôpital de la Pitié-Salpétière, Paris, France. Unité INSERM, Bordeaux, France. Hôpital Edouard Herriot, Lyon, France. Bernhard Nocht Institut für Tropenmedizin, Hamburg, Germany. 1st I.K.A Hospital of Athens, Athens, Greece. Ospedale Riuniti, Divisione Malattie Infettive, Bergamo, Italy. Ospedale di Bolzano, Divisione Malattie Infettive, Bolzano, Italy. Ospedale Cotugno, III Divisione Malattie Infettive, Napoli, Italy. Dérer Hospital, Bratislava, Slovakia. Hospital Carlos III, Departamento de Enfermedades Infecciosas, Madrid, Spain. Kiev Centre for AIDS, Kiev, Ukraine. Luhansk State Medical University, Luhansk, Ukraine. Odessa Region AIDS Center, Odessa, Ukraine.

EuroSIDA Steering Committee: J Gatell, B Gazzard, A Horban, I Karpov, M Losso, A d'Arminio Monforte, C Pedersen, M Ristola, A Phillips, P Reiss, J Lundgren, J Rockstroh, A Scherrer, I Aho, LD Rasmussen, V Svedhem, G Wandeler, C Pradier, N Chkhartishvili, R Matulionyte, C Oprea, JD Kowalska, J Begovac, J Miro, G Guaraldi, R Paredes; Chair: J Rockstroh; Study Co-leads: A Mocroft, O Kirk

EuroSIDA staff: Coordinating Centre Staff: O Kirk, L Peters, A Bojesen, D Raben, D Kristensen, K Laut, JF Larsen, D Podlekareva, B Nykjær; Statistical Staff: A Mocroft, A Phillips, A Cozzi-Lepri, L Shepherd, S Amele, A Pelchen-Matthews