

Original article

Incidence of abacavir hypersensitivity reactions in EuroSIDA

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Background: The aim of the study was to investigate the incidence of abacavir-related hypersensitivity reaction (HSR) and associated deaths in EuroSIDA HIV-1-infected patients. **Methods:** Poisson regression models were developed to compare incidence of abacavir discontinuation according to the line of therapy within which abacavir was received, geographical regions, calendar time and drug formulation (abacavir/lamivudine combination tablet versus abacavir as a single drug or abacavir/zidovudine/lamivudine combination).

Results: Of 3,278 patients that started abacavir, 2,101 (64.1%) discontinued. Of these, 167 (5.1%) discontinued abacavir within 3 months due to HSR with an incidence of 22.1 (95% confidence interval [CI] 18.7–25.4) per 100 person-years of follow-up. After adjustment for gender, prior AIDS, hepatitis C serostatus, baseline CD4⁺ T-cell count, region and calendar time, HSR incidence

was significantly higher in those starting abacavir in a first-line regimen compared with second-line (incidence rate ratio [IRR] 2.04 [95% CI 1.24–3.38]; $P=0.005$). There was no significant difference between regions. HSR incidence from 2005 onwards was significantly lower compared with 1999–2000 (IRR 0.54 [95% CI 0.32–0.92]; $P=0.024$). There was a lower observed incidence in patients starting abacavir/lamivudine compared with other formulations (IRR 0.33 [95% CI 0.13–0.88]; $P=0.027$), however, available data were limited.

Conclusions: Incidence of abacavir-related HSR is higher in patients starting abacavir in first-line therapy, which could indicate increased over-diagnosis. HSR incidence has decreased in recent years, which might reflect the wider availability of genetic screening and improved awareness of symptoms. There were no reported deaths due to abacavir HSR.

Introduction

Hypersensitivity reaction (HSR) occurs in approximately 4–8% of patients starting abacavir generally within 6 weeks of initiation [1–5]. It is characterized by fever, rash, neurological, gastrointestinal, musculoskeletal and respiratory symptoms [1,4–6] and if the drug is not discontinued immediately there is a risk of death [3,6,7]. Potentially fatal symptoms may reoccur within hours if the drug is restarted [8,9]. However, as patients are advised to stop immediately if symptoms arise, reported incidence of fatal HSR is fortunately rare. A recent study reported no HSR-related deaths in over 11,500 patients exposed

to either Ziagen® (abacavir as a single tablet) or Trizivir® (abacavir, lamivudine and zidovudine) [10]. This study also found no differences in the frequency of abacavir HSR between patients starting either formulation.

The genetic allele HLA-B*5701 has been found to be strongly associated with abacavir-related HSR and is more prevalent in Caucasian individuals, which could account for differences in observed rates of HSR between ethnic groups [11–15]. In particular, the presence of HLA-B*5701, HLA-DR7 and HLA-DQ3 was found to have a positive predictive value of 100% and absence of

this combination had a negative predictive value of 97% [16]. Prospective genetic screening for HLA-B*5701 prior to prescribing abacavir has been shown to dramatically reduce the incidence of abacavir-related HSR, but is not widely available to all patients [11,14,15,17–21]. In clinical practice, diagnosis of HSR can be difficult as it includes a combination of non-specific symptoms. Patients who exhibit symptoms consistent with HSR may be given a skin patch test to immunologically confirm whether or not they are a true HSR case [19,21]. Recent findings from the PREDICT-1 study provided evidence that the presence of HLA-B*5701 was a necessary condition for abacavir HSR and that withholding the drug from these patients would eliminate the reaction [15]. The findings also highlighted the problem of clinical over-diagnosis of HSR that results from physicians not being able to risk missing any potential true cases of HSR. Further factors that have been linked to an increased risk of HSR include female gender, higher CD8⁺ T-cell counts at initiation of abacavir and abacavir use during primary HIV infection [22–24]. Factors linked to a decreased risk include previous treatment experience and more advanced disease [22,25].

EuroSIDA collects prospective longitudinal data from a large, heterogeneous population in centres across Europe, which provides the opportunity to compare incidence of abacavir-related HSR across different patient subsets. The objective of these analyses was to investigate the incidence of abacavir discontinuation, particularly as a result of HSR, according to the line of therapy within which abacavir was received (first, second, third or subsequent regimens), geographical region, calendar time and coformulation of abacavir (as part of the combination tablet, Kivexa[®] [abacavir/lamivudine] or as part of either the combination tablet Trizivir[®] or as Ziagen[®]). The incidence of HSR within these patient subsets has not previously been evaluated in a large cohort study and is important to identify patients most at risk and to monitor trends. The rate of death associated with abacavir HSR was also determined.

Methods

Patients

The EuroSIDA study is a prospective, observational cohort of 14,310 HIV-1-infected patients in 93 centres across Europe, Israel and Argentina. The study has been described in detail previously [26]. In brief, patients were enrolled into seven cohorts from May 1994 onwards and median follow-up time was to January 2007. Information is collected on a standardized data collection form every 6 months, including all CD4⁺ T-cell counts and viral loads measured since the last follow-up and starting and stopping dates of all antiretroviral drugs.

The forms (available at www.cphiv.dk) provide a list of reasons for discontinuation of antiretroviral drugs from which sites are asked to indicate the most appropriate reason (with one reason chosen per drug stopped) on the basis of the physician's assessment. EuroSIDA also requests that all deaths are recorded on the forms with the cause of death selected from a list provided. To ensure correct patient selection and to verify that accurate data is supplied, members of the coordinating office visit all centres to check the information provided against case notes for all patients with clinical events and 10% of randomly selected patients per year.

Patients were included in the analyses if they initiated abacavir as Ziagen[®], Trizivir[®] or Kivexa[®] for the first time during prospective follow-up after 1 January 1999 (the date at which EuroSIDA started collecting data on reasons for discontinuation of therapy).

Statistical methods

Patient characteristics were compared using χ^2 tests and Fisher's exact tests for categorical data and Kruskal–Wallis tests for continuous data. Only the first abacavir discontinuation with a corresponding reason was considered and baseline was defined as the date that the drug was first started. Incidence of abacavir discontinuation was assessed using a person-year analysis with person-years of follow-up (PYFU) measured from the date of starting abacavir to the earliest of the last follow-up visit, death or until abacavir was discontinued for any reason. The incidence of abacavir HSR was assessed in the 3 months after initiating abacavir treatment with follow-up time to the earliest of 3 months, death or abacavir discontinuation. No standardized guidelines were used to define HSR and cases of HSR were not reviewed centrally. Diagnosis was based on physician assessment.

Univariable Poisson regression models were used to identify factors that could potentially affect incidence of HSR-related discontinuation within 3 months of starting abacavir. Factors investigated were gender, HIV exposure group, ethnicity, prior AIDS diagnosis, hepatitis B/C coinfection serostatus, CD4⁺ T-cell count, nadir CD4⁺ T-cell count and viral load at date of starting abacavir (baseline), whether or not patients were previously antiretroviral-naïve, age and concurrent use of other drugs that may cause HSR. The potential interactions between hepatitis C status and both HIV exposure groups and nevirapine use were also investigated. A multivariable Poisson regression model was then developed adjusting for the factors found to be significant (P -value <0.1) in the univariable models. The model also included factors such as whether patients started abacavir as part of a first-line regimen (containing at least one protease inhibitor [PI], non-nucleoside reverse transcriptase inhibitor [NNRTI] or abacavir), second regimen (containing a new PI, a new NNRTI or abacavir

and started at least 1 month after initiation of the first), third or subsequent regimen; other factors included were the geographical region of EuroSIDA the patients were seen in (categorized into South, Central West, North and East, as described in a previous analysis [27]) and calendar time of starting abacavir, which was divided into two-year periods (1999–2000, 2001–2002, 2003–2004 and 2005 onwards). A further factor considered in a separate model was whether a patient started abacavir for the first time as part of the coformulation Kivexa® or whether they started abacavir as the single drug Ziagen® or as part of Trizivir®. As Kivexa® was first introduced in January 2004, only patients who started abacavir after this time were included in this particular analysis.

All tests were two-sided and a *P*-value of <0.05 was taken to be statistically significant. SAS software version 9.1 (SAS Institute, Cary, NC, USA) was used for all analyses.

Results

Patient numbers

A total of 3,278 (22.9%) patients fulfilled the inclusion criteria with a median follow-up time of 1.4 years (range 0.0–8.5) and a total follow-up time of 6,803 person-years. Among the patients who started abacavir, there were 2,101 (64.1%) discontinuations, of which 193 (9.2%) were associated with HSR. As expected from the literature, HSR was experienced very soon after starting abacavir with a median time to HSR-related discontinuation of 1 month (interquartile range [IQR] 0.3–1.2). A further 344 (16.4%) patients discontinued due to treatment failure with a median time on abacavir treatment of 16 months (IQR 8.4–29.0). Other reasons for discontinuation reported by 317 (15.1%) patients included clinical fat abnormalities, dyslipidaemia, toxicities and structured treatment interruption. A further 285 (13.5%) patients had other causes, not specified in the list. Finally, 607 (28.9%) had the reason for discontinuation as patient or physician's choice and 357 (17.0%) had an unknown reason. As the median times to discontinuation for these groups were over a year (13.0 months [IQR 4.2–32.5] and 18.0 months [IQR 5.3–40.6], respectively), it is unlikely that these patients experienced HSR.

Patient characteristics at date of abacavir initiation

Table 1 shows a comparison of the patient characteristics at date of abacavir initiation between 1,177 patients who continued on abacavir therapy in the available follow-up time, 193 patients who discontinued abacavir due to HSR and 1,908 patients who discontinued due to a reason not reported as HSR. Patients who continued abacavir throughout their follow-up time started treatment most recently, followed by those who discontinued due to HSR and then those who discontinued for

another reason (medians June 2004, June 2001 and January 2001, respectively, *P*<0.001). Patients who discontinued abacavir were more likely to be intravenous drug users (*P*<0.001) than those who continued on the drug, had lower baseline CD4⁺ T-cell counts (*P*<0.001) and higher baseline viral loads (*P*<0.001). A higher percentage of patients who discontinued abacavir due to HSR were Caucasian (95.3%, *P*=0.011), hepatitis C positive (28.0%, *P*<0.001), antiretroviral-naïve (5.7%, *P*=0.007) and were less likely to start abacavir in a triple nucleoside reverse transcriptase inhibitor (NRTI) regimen (11.9%, *P*<0.001). They were also more likely to have started nevirapine at the same time as abacavir (7.8%, *P*=0.042). There were similar percentages of patients across the three groups starting other drugs that have been linked to HSR, that is, efavirenz, amprenavir and cotrimoxazole.

Incidence of abacavir discontinuation and abacavir-related HSR

The incidence of abacavir discontinuation for any reason (including HSR) was 30.9 (95% confidence interval [CI] 29.6–32.2) per 100 PYFU and for HSR specifically the incidence was 2.8 (95% CI 2.4–3.2) per 100 PYFU. To avoid including patients who may have been misclassified as experiencing HSR, 167 patients (86.5% of the 193 reported to have discontinued abacavir due to HSR) who discontinued abacavir due to HSR within the first 3 months of abacavir treatment were investigated further. This accounted for 5.1% of all patients starting the drug. The incidence of abacavir discontinuation due to HSR within 3 months was 22.1 (95% CI 18.7–25.4) per 100 PYFU during 757 PYFU.

Incidence according to the line of therapy within which abacavir was received

A total of 252 (7.7%) patients started abacavir as part of a first-line regimen, 952 (29.0%) started it as part of a second regimen, 1,081 (33.0%) as part of a third and 993 (30.3%) as part of a fourth or subsequent regimen (Table 2). The highest incidence of abacavir discontinuation for any reason was in those who started abacavir as part of a fourth/subsequent regimen (*P*=0.002). Incidence of HSR-related discontinuation within the first 3 months was highest in those who started abacavir as part of a first-line regimen (*P*=0.002).

Incidence according to EuroSIDA region

A total of 929 (28.3%) patients were from the South region, 938 (28.6%) were from the Central West, 1,164 (35.5%) were from the North and 247 (7.5%) were from the East (Figure 1). Overall there was no significant difference in incidence of discontinuation due to any reason and incidence of discontinuation due to HSR between regions (*P*=0.797 and *P*=0.114,

respectively), however, the North region appeared to have a lower incidence of HSR-related discontinuation than the other regions.

Incidence according to date of initiation of abacavir
A total of 1,245 (38.0%) patients started abacavir between 1999 and 2000, 863 (26.3%) between 2001 and 2002, 450 (13.7%) between 2003 and 2004 and 720 (22.0%) from 2005 onwards (Figure 2). Incidence of

abacavir discontinuation for any reason was similar over 1999–2000 and 2001–2002 followed by a slight increase during 2003–2004 and a drop from 2005 onwards, giving an overall significant difference ($P=0.014$). Incidence of abacavir discontinuation due to HSR within the first 3 months of abacavir treatment remained similar over the years until 2005 onwards when a sharp decrease to 11.4 cases per 100 PYFU during 166 PYFU was observed, giving an overall significant difference ($P=0.004$).

Table 1. Patient characteristics at start of abacavir therapy according to continuation of abacavir therapy, discontinuation of abacavir due to hypersensitivity reaction or discontinuation of abacavir due to another reason

Characteristic	Total	Continuation of abacavir	Discontinuation due to HSR	Discontinuation due to other reason	P-value
All patients, <i>n</i> (%)	3,278 (100.0)	1,177 (35.9)	193 (5.9)	1,908 (58.2)	–
Male gender, <i>n</i> (%)	2,539 (77.5)	937 (79.6)	141 (73.1)	1,461 (76.6)	0.047
HIV exposure					
Male homosexual intercourse, <i>n</i> (%)	1,507 (46.0)	591 (50.2)	80 (41.5)	836 (43.8)	<0.001
Heterosexual intercourse, <i>n</i> (%)	861 (26.3)	306 (26.0)	48 (24.9)	507 (26.6)	–
Intravenous drug use, <i>n</i> (%)	672 (20.5)	192 (16.3)	51 (26.4)	429 (22.5)	–
Other, <i>n</i> (%)	238 (7.3)	88 (7.5)	14 (7.3)	136 (7.1)	–
White ethnicity, <i>n</i> (%)	3,026 (92.3)	1,066 (90.5)	184 (95.3)	1,776 (93.1)	0.011
Previous AIDS	1,197 (36.5)	412 (35.0)	59 (30.6)	726 (38.1)	0.049
Hepatitis B status					
Negative, <i>n</i> (%)	2,561 (78.1)	976 (82.9)	143 (74.1)	1,442 (75.6)	<0.001
Positive, <i>n</i> (%)	206 (6.3)	58 (4.9)	14 (7.0)	134 (7.0)	–
Unknown, <i>n</i> (%)	511 (15.6)	143 (12.2)	36 (18.7)	332 (17.4)	–
Hepatitis C status					
Negative, <i>n</i> (%)	1,950 (59.5)	785 (66.7)	103 (53.4)	1,062 (59.5)	<0.001
Positive, <i>n</i> (%)	717 (21.9)	228 (19.4)	54 (28.0)	435 (22.8)	–
Unknown, <i>n</i> (%)	611 (18.6)	164 (13.9)	36 (18.7)	411 (21.5)	–
Type of regimen					
Single PI plus ≥ 2 NRTIs, <i>n</i> (%)	281 (8.6)	92 (7.8)	21 (10.9)	168 (8.8)	<0.001
Ritonavir-boosted PI plus ≥ 2 NRTIs, <i>n</i> (%)	687 (21.0)	326 (27.7)	39 (20.2)	322 (16.9)	–
Single NNRTI plus ≥ 2 NRTIs, <i>n</i> (%)	917 (28.0)	392 (33.3)	51 (26.4)	474 (24.8)	–
Triple NRTI, <i>n</i> (%)	722 (22.0)	182 (15.5)	23 (11.9)	517 (27.1)	–
Other, <i>n</i> (%)	671 (20.5)	185 (15.7)	59 (30.6)	427 (22.4)	–
Concurrent use of drugs that may cause HSR					
Nevirapine, <i>n</i> (%)	183 (5.6)	51 (4.3)	15 (7.8)	117 (6.1)	0.042
Efavirenz, <i>n</i> (%)	511 (15.6)	165 (14.0)	33 (17.1)	313 (16.4)	0.173
Amprenavir, <i>n</i> (%)	108 (3.3)	32 (2.7)	3 (1.6)	73 (3.8)	0.093
Cotrimoxazole, <i>n</i> (%)	42 (1.3)	14 (1.2)	3 (1.6)	25 (1.3)	0.903
Antiretroviral-naïve at start of abacavir, <i>n</i> (%)	96 (2.9)	42 (3.6)	11 (5.7)	43 (2.3)	0.007
Median date of abacavir start (IQR)	Oct 01 (Apr 00–Jun 04)	Jun 04 (Jul 01–Feb 06)	Jun 01 (Jan 00–Feb 06)	Jan 01 (Jan 00–Sep 02)	<0.001
Median age, years (IQR)	41 (37–48)	42 (37–49)	41 (37–48)	41 (36–48)	0.005
Median CD4 ⁺ T-cell count (IQR)					
At baseline, cells/mm ³ *	357 (211–544)	394 (239–586)	327 (226–480)	336 (190–520)	<0.001
At nadir, cells/mm ³ †	127 (50–215)	134 (51–218)	136 (63–200)	121 (46–214)	0.114
Median viral load (IQR)					
At baseline, log ₁₀ copies/ml†	2.8 (1.7–4.4)	2.1 (1.7–4.0)	3.1 (1.7–4.4)	3.3 (1.7–4.6)	<0.001

Median CD4⁺ T-cell counts and viral loads were based on measurements from *3,138 patients, †3,276 patients or ‡3,090 patients. P-values were obtained from χ^2 , Fisher's exact and Kruskal–Wallis tests. HSR, hypersensitivity reaction; IQR, interquartile range; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Incidence according to use of Kivexa®

A total of 928 (28.3%) previously abacavir-naïve patients started abacavir in January 2004 onwards, the date when the coformulation drug Kivexa® was first introduced into clinical practice. Of these 928 patients, 342 (36.9%) started Kivexa®. Overall, 305 (32.9%) patients discontinued abacavir, of which 27 (8.9%) discontinuations occurred within 3 months and were associated with HSR. Incidence of discontinuation due to any reason was significantly higher ($P<0.001$) in the non-Kivexa® group (38.6 [95% CI 33.9–43.3] cases per 100 PYFU during 676 PYFU) compared with the Kivexa® group (13.1 [95% CI 9.3–17.0] cases per 100 PYFU during 335 PYFU). There was also a significant difference ($P=0.036$) in incidence of discontinuation due to HSR within 3 months (16.2 [95% CI 9.4–23.0] cases per 100 PYFU during 136 PYFU) in the non-Kivexa® group compared with the Kivexa® group (6.3 [95% CI 2.0–14.6] cases per 100 PYFU during 80 PYFU).

Multivariable incidence rate ratios

In univariable models, female gender, positive hepatitis C coinfection serostatus, lack of prior AIDS diagnosis and a lower baseline CD4⁺ T-cell count were significantly associated with incidence of abacavir discontinuation due to HSR within 3 months of treatment. The concurrent use of drugs such as nevirapine, efavirenz, amprenavir and cotrimoxazole that can cause HSR, started at the same time as abacavir, were investigated to check that symptoms arising from one of these drugs had not been misdiagnosed as abacavir HSR. However, none were found to be significantly associated with HSR-related abacavir discontinuation. Ethnicity was also found to be unassociated with HSR-related abacavir discontinuation. However, the HSR incidence rate was

lower in those with non-white ethnicity compared with those with white ethnicity, as expected from the literature, with an incidence rate ratio (IRR) of 0.66 (95% CI 0.34–1.30; $P=0.230$). A multivariable model was then developed that contained the above factors significantly associated with HSR in univariable analyses, as well as whether abacavir was a component of a first, second, third or subsequent regimen, geographical region and calendar time when abacavir was started. Figure 3 displays the adjusted IRRs and 95% CIs from this model.

The multivariable model provided evidence that the incidence of abacavir discontinuation due to HSR among patients starting abacavir as part of a first-line regimen was twice that observed among those starting abacavir in a second-line regimen (IRR 2.04 [95% CI 1.24–3.38]; $P=0.005$). Incidence of HSR was similar across regions, although it was lowest in the North. There was also evidence that among patients starting abacavir from 2005 onwards, the incidence of HSR-related discontinuation was almost half that observed among patients starting abacavir between 1999 and 2000 (IRR 0.54 [95% CI 0.32–0.92]; $P=0.024$).

A multivariable model was developed containing the same variables as before, but adjusting for the abacavir start date instead of the time period and with the addition of whether patients received Kivexa® or Ziagen®/Trizivir®. After adjustment, there was evidence of a significantly lower incidence of abacavir discontinuation due to HSR within 3 months in those starting Kivexa® compared with those starting Ziagen®/Trizivir® (IRR 0.33 [95% CI 0.13–0.88]; $P=0.027$).

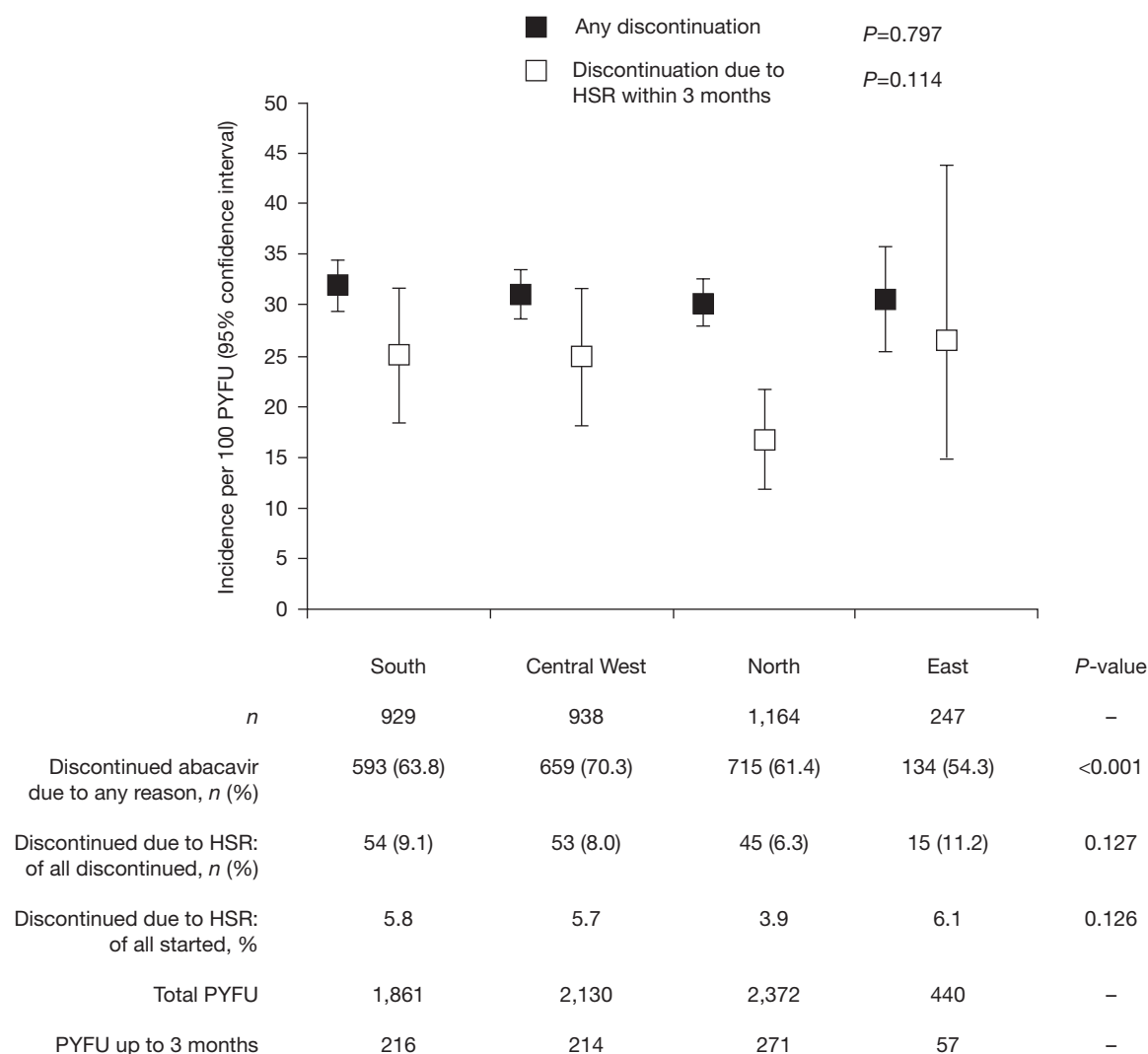
Rate of death associated with abacavir HSR

There were no fatal cases of HSR registered (defined as patients who discontinued abacavir therapy due to HSR and died within 1 month of discontinuation). A

Table 2. Abacavir discontinuation due to any reason or due to hypersensitivity reaction within 3 months according to the line of therapy within which abacavir was received

Number of patients who started abacavir	Discontinued abacavir due to any reason, <i>n</i> (%)	Discontinued abacavir due to HSR in 3 months		Any discontinuation incidence per 100 PYFU (95% CI)	Total PYFU	Discontinuation due to HSR in 3 months	
		Of all those who discontinued, <i>n</i> (%)	Of all those started abacavir, %			incidence per 100 PYFU (95% CI)	PYFU up to 3 months
Overall <i>n</i> =3,278	2,101 (64.1)	167 (7.9)	5.1	30.9 (29.6–32.2)	6,803	22.1 (18.7–25.4)	757
As first-line therapy <i>n</i> =252	171 (67.9)	27 (15.8)	10.7	32.3 (27.5–37.2)	529	48.8 (30.4–67.2)	55
As second-line therapy <i>n</i> =952	585 (61.5)	44 (7.5)	4.6	27.4 (25.1–29.6)	2,138	19.9 (14.0–25.7)	222
As third-line therapy <i>n</i> =1,081	714 (66.1)	52 (7.3)	4.8	31.5 (29.2–33.8)	2,266	21.0 (15.3–26.7)	248
As fourth-line therapy or later <i>n</i> =993	631 (63.5)	44 (7.0)	4.4	33.7 (31.1–36.4)	1,870	19.0 (13.4–24.6)	232
<i>P</i> -value	0.095*	0.001*	<0.001*	0.002†	–	0.002†	–

P-values obtained from * χ^2 tests and †univariable Poisson regression models. CI, confidence interval; HSR, hypersensitivity reaction; PYFU, person-years of follow-up.

Figure 1. Abacavir discontinuation due to any reason or due to hypersensitivity reaction within 3 months according to EuroSIDA region

HSR, hypersensitivity reaction; PYFU, person-years of follow-up.

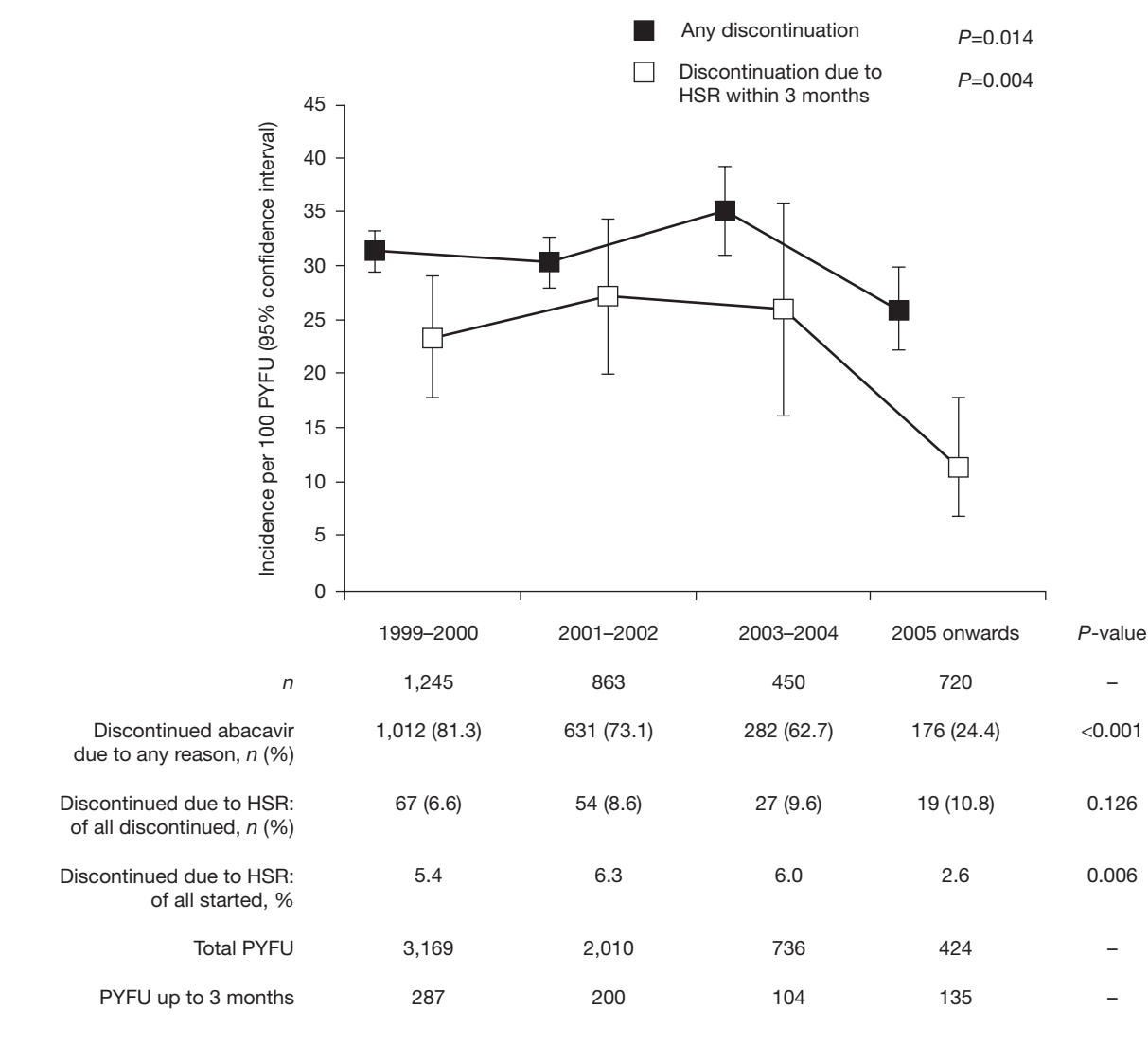
total of 111 (3.4%) patients died on abacavir therapy or within 1 month of a non-HSR related discontinuation. Of these, 55 had specific non-HSR-related causes of death recorded and of the remaining 56 patients, 33 had a previous AIDS diagnosis and 36 had received at least two or three PI/NNRTI-containing regimens prior to the abacavir regimen. Among these 111 patients, 15 died within 3 months of starting abacavir. The investigators classified 13 of these 15 deaths as due to specific and mainly AIDS-related causes rather than as a result of HSR. Non-AIDS-related causes of death included myocardial infarction and complications in hepatitis infection. The two remaining patients had unknown

causes of death, but both died with low CD4⁺ T-cell counts of 106 cells/mm³ and 120 cells/mm³.

Discussion

In this cohort of 3,278 HIV-1-infected patients who started abacavir across Europe, the incidence rate of abacavir discontinuation for any reason (including HSR) was 30.9 (95% CI 29.6–32.2) per 100 PYFU. In line with the 4–8% incidence found in other studies [1–5], the incidence of abacavir discontinuation due to HSR within 3 months was 22.1 (18.7–25.4) per 100 PYFU and this occurred in 5.1% of patients who

Figure 2. Abacavir discontinuation due to any reason or due to hypersensitivity reaction within 3 months according to date of initiation of abacavir



HSR, hypersensitivity reaction; PYFU, person-years of follow-up.

started the abacavir treatment. This analysis assessed the incidence of HSR across different patient subsets in a heterogeneous population from centres all across Europe with a standardized data collection and checking system, as well as investigating the factors associated with abacavir-related HSR, which is important to identify patients with the highest risk.

One of the main findings was that the adjusted HSR incidence rate was found to be twice as high when abacavir was started as part of a first-line regimen compared with a second-line regimen. This supports research that showed a 42% decreased risk in patients with prior

treatment experience [25]. Patients starting therapy for the first time might be more likely to be clinically diagnosed with suspected HSR, however, this might not reflect the incidence of true HSR cases. New patients could be more likely to report all symptoms experienced due to anxiety about starting treatment, whereas more experienced patients might not mention the more minor symptoms. This could result in physicians misdiagnosing HSR more often in patients starting first-line therapy to ensure that no true HSR cases are missed.

It is well-established that the HLA-B*5701 allele is associated with long-term non-progression of HIV

[28–30] and is linked to abacavir-related HSR in many studies [11–15]. Therefore, patients with this allele may be under-represented in the groups starting abacavir in second-, third- and fourth-line therapy, which could explain the increased incidence in the group starting a first-line regimen. It is more often found in Caucasian patients than in non-Caucasians [12–14], however, no significant association between white ethnicity and risk of HSR was found in this analysis and so ethnicity was ruled out as a potential confounder. This could be due to limited data as there were few non-Caucasians who discontinued due to HSR in this study (9 patients, 4.7%).

There was no evidence of a significant regional difference in abacavir discontinuation due to HSR within the first 3 months in this analysis. The frequency of HLA-B*5701 is known to vary across different populations and differences in frequency have been found across Europe [31]. Therefore, a possible explanation for this finding is that in areas of low prevalence of the allele, there could be more cases of clinical over-diagnosis of suspected HSR resulting in an overall similar incidence of abacavir HSR between regions.

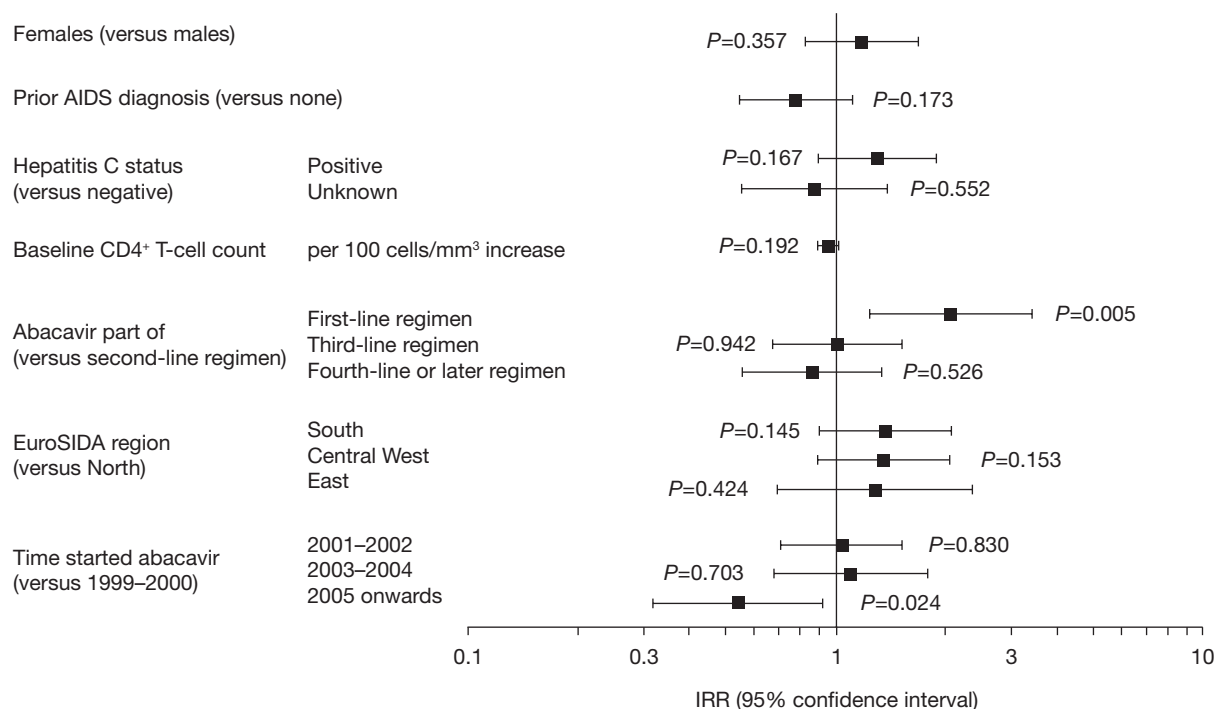
A significantly higher incidence rate of HSR was found in earlier years compared with 2005 onwards. A reason

for this could be that more clinics are using prospective genetic screening, which has been shown to effectively reduce the incidence of HSR by preventing the prescription of abacavir to those at high risk [11,14,15,17–21]. Also, as HSR symptoms are now better-documented, it could be more recognizable and therefore correctly identified more frequently, reducing the chance of over-diagnosis. If symptoms were misclassified as HSR in earlier years, this could explain the decrease in recent years.

A decreased incidence of abacavir discontinuation due to HSR within 3 months was observed in patients starting Kivexa® compared with those starting Ziagen® or Trizivir®. All known, measured variables that could potentially confound the results were investigated but a difference remained after adjustment. This could be due to the relatively small number of person-years available for the Kivexa® group and the small number of events during this time. Therefore, these results should be treated with caution.

Severe abacavir-related HSRs, which can lead to death, are rare but have been reported in a few case studies [7–9]. In this analysis, there were no reports of patients who discontinued abacavir due to HSR and then died within 1 month. Patients who died on abacavir therapy

Figure 3. Multivariable incidence rate ratios and 95% confidence intervals of abacavir discontinuation due to hypersensitivity reaction within 3 months



HSR, hypersensitivity reaction; IRR, incidence rate ratios; PYFU, person-years of follow-up.

or within 1 month after stopping mostly had advanced disease with known non-HSR causes of death. This suggests that any patients with severe reactions to abacavir were taken off the drug promptly to prevent fatality.

The main potential limitation of these analyses is that there could be bias in the reporting of reasons of discontinuation. The definition of HSR is unclear as it includes a combination of clinical symptoms. The incidences reported in this analysis are therefore made on the basis of a practical 'real life' approach to the diagnosis of HSR and could possibly reflect clinical diagnosis rather than true HSR. Examination of the data did not show any major differences in reported HSR between centres, suggesting that reporting bias across centres was minimal (results not shown). Furthermore, the EuroSIDA follow-up forms only collect one reason for discontinuation per drug and some patients may experience more than one toxicity, which could mean that HSR is not always reported. The forms also allow 'patient's wish' and 'physician's decision' as reasons for discontinuation, which could result in misclassification of HSR.

Another limitation is that EuroSIDA does not collect information on genetic screening. Thus, it is unknown if patients were tested for HLA-B*5701 and prescribed abacavir according to results. There is also no information on CD8⁺ T-cell count so it was not possible to look at any association between this and HSR. Although it is assumed in this study that all deaths are recorded on the follow-up forms, it is possible that some were missed. Causes of death could also be misclassified or coded differently in different centres. The introduction of the CoDe ('Coding of Death in HIV') project in cohort studies (details at www.cphiv.dk) has helped to standardize the approach to collecting and reviewing causes of death.

In summary, incidence of abacavir discontinuation due to HSR appears to be higher in patients starting abacavir as part of first-line therapy, which might be explained by increased clinical over-diagnosis. Incidence of abacavir HSR has decreased in recent years, suggesting that prospective genetic screening, improved patient care and awareness of the symptoms of HSR may have prevented the use of this drug for high-risk patients. There appears to be a similar rate of abacavir discontinuation due to HSR across Europe. Patients starting the coformulation drug Kivexa[®] which was introduced in January 2004, appear to have a decreased risk to those starting Ziagen[®] or Trizivir[®]; however, limited data are available for the use of Kivexa[®] and so results remain preliminary. There were no reported deaths due to abacavir HSR in this analysis.

Acknowledgements

Primary funding support for EuroSIDA is provided by the European Commission BIOMED 1 (CT94-1637),

BIOMED 2 (CT97-2713), the 5th Framework (QLK2-2000-00773) and the 6th Framework (LSHP-CT-2006-018632) programs. Current funding support also includes unrestricted grants by Bristol-Myers Squibb, GlaxoSmithKline, Roche, Gilead, Pfizer, Merck and Co., Tibotec and Boehringer-Ingelheim. The participation of centres from Switzerland was supported by a grant from the Swiss Federal Office for Education and Science.

Disclosure statement

The authors declare no conflicts of interest.

Additional file

The additional file 'The EuroSIDA Study Group', which lists the members of the EuroSIDA study group, can be accessed via the Volume 13 Issue 5 contents page for *Antiviral Therapy*, which can be found at www.intmedpress.com (by clicking on 'Antiviral Therapy' then 'Journal PDFs').

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Accepted for publication 29 April 2008