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Abacavir hypersensitivity reaction in EuroSIDA

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INTRODUCTION

- 4 to 8% of patients starting abacavir (ABC) experience a severe allergic hypersensitivity reaction (HSR) as a side effect, typically within 3 months.
- In 2004, a combination drug, Kivexa, comprising ABC and lamivudine (3TC) became available in Europe. It is unclear as to whether or not incidence of ABC HSR remains similar in those taking Kivexa compared to other use of ABC.

OBJECTIVES

To compare the incidence of reported ABC HSR:

- Between regions of Europe.
- Between time periods of starting ABC, including before and after the launch of Kivexa.

METHODS

- Collection of reasons for discontinuation of antiretroviral therapy (ART) were implemented in EuroSIDA in 1999, therefore only patients starting ABC/Trizivir/Kivexa after 1/99 with prospective follow-up were included.
- Incidence of ABC HSR was defined as discontinuation of ABC within 3 months of initiation with HSR as specified reason for discontinuation.
- Incidence was assessed using a person-year analysis and incidence rate ratios were analysed using Poisson regression models.
- Follow-up time was from starting ABC to the earliest of the last follow-up visit, death, discontinuation of ABC or 3 months after starting ABC.
- Multivariable models were developed including factors significant in univariable analyses ($p<0.1$). Factors tested were concurrent use of specific antiretroviral drugs, whether or not patients were ART-naïve, gender, ethnicity, CD_4 count, CD_4 nadir, viral load and prior AIDS diagnosis.
- EuroSIDA centres were divided into 4 geographical regions: South, Central, North and East (detailed in Figure 1 footnote).
- Temporal changes were explored before/after the median date of starting ABC (6/01) and before/after the launch of Kivexa (1/04)

RESULTS

- A total of 2635 EuroSIDA patients started ABC with a total of 605 person-years of follow-up (PYF) (during 3 month window after starting ABC).
- 153 (6%) discontinued ABC due to HSR within 3 months, on average 3.1 weeks (95% CI: 2.0-4.3) after initiation. Patient characteristics according to whether or not ABC HSR was reported are displayed in Table 1.
- Incidence of ABC HSR was 25.3, 95% CI: (21.3-29.3) cases/100 PYF within first 3 months. Table 2 displays incidence rates according to region and time periods.
- Factors significantly associated with reported ABC HSR were found to be concurrent use of nevirapine, being ART-naïve before starting ABC, lower baseline CD_4 count and no prior AIDS diagnosis.

Regional differences in incidence of HSR

- Unadjusted analysis of incidence of ABC HSR showed no significant difference between regions, global p-value=0.127.
- A multivariable model containing factors significantly associated with ABC HSR (above) plus region and time period before/after 6/01 also showed no significant difference in incidence of HSR between regions, incidence rate ratios (IRRs) (compared to North), South: 1.61, (1.06-2.44), Central: 1.32, (0.87-2.00) and East: 1.16, (0.58-2.31), global p-value=0.157.
  See Figure 1.

Incidence of HSR before/after median date of starting ABC

- Unadjusted analysis showed no significant difference in incidence between periods, IRR for second time period compared to first: 1.03, 95% CI: (0.75-1.41), p=0.871.
- In the same multivariable model as above, there was still no significant difference, IRR: 1.05, 95% CI: (0.75-1.47), p=0.792. See Figure 1.

Incidence of HSR before/after launch of Kivexa

- Unadjusted analysis showed a significantly lower incidence in the period after the launch of Kivexa compared to before, IRR: 0.56, 95% CI: (0.33-0.93), p=0.026.
- After adjustment for use of nevirapine, whether or not ART-naïve, baseline CD_4 count, prior AIDS diagnosis and region, the difference remained significant, IRR: 0.57, 95% CI: (0.34-0.97), p=0.037.

CONCLUSIONS

- Within this heterogeneous population, HSR within 3 months of starting ABC was reported in 6% of patients.
- There were no significant differences in incidence of reported ABC HSR between regions of Europe or between time periods defined before/after the median date of starting ABC (6/01).
- The incidence did appear to decrease in patients starting ABC in the period 1/04 onwards, coinciding with the launch of Kivexa. However, limited data are available for the use of Kivexa and analyses of this drug remain preliminary. This decrease may reflect physicians' growing skills and awareness of HSR, resulting in avoidance of this drug for patients most at risk of HSR.

Table 1

Characteristics at initiation of ABC

		HSR within 3 months	No HSR within 3 months	p
All, n (%)		153 (6)	2482 (94)	-
Male		114 (75)	1937 (78)	0.307
MSM exposure		65 (42)	1165 (47)	0.276
White ethnicity		135 (88)	2092 (84)	0.190
ART-naïve		11 (7)	64 (3)	0.003
Region	South	46 (30)	599 (24)	0.124
	Central	50 (33)	804 (32)	-
	North	44 (29)	920 (37)	-
	East	13 (9)	159 (6)	-
Date started ABC, median		May 01	Mar 01	0.654
Baseline CD_4 count (cells/mm^3)		300	340	0.414
Baseline viral load (log_{10}cps/mL)		3.5	3.1	0.119

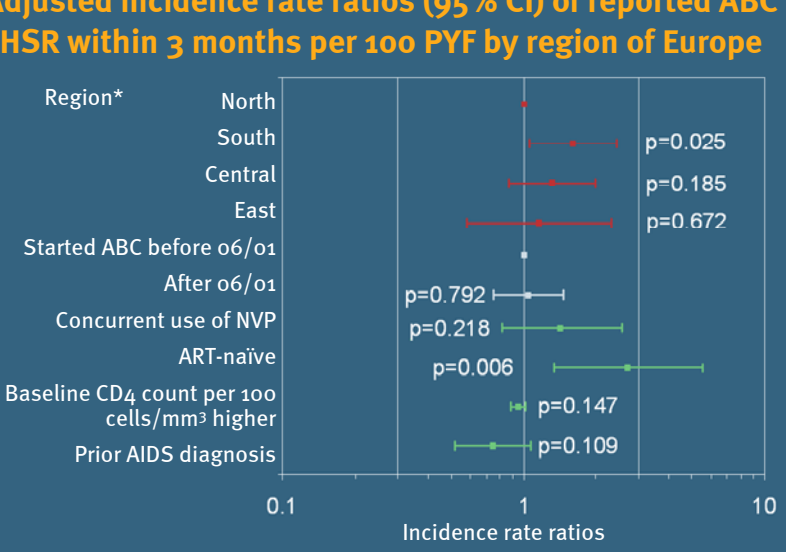
Table 2

Incidence rates of reported HSR within 3 months of starting ABC

		No. started ABC	Discontinued ABC due to HSR, n (%)	Person years of follow up (PYF)	Incidence per 100 PYF (95% CI)
All, n (%)		2635	153 (6)	605	25.3 (21.3-29.3)
Region	South	645	46 (7)	148	31.0 (22.1-40.0)
	Central	854	50 (6)	192	26.0 (18.8-33.2)
	North	964	44 (5)	224	19.6 (13.8-25.4)
	East	172	13 (8)	40	32.6 (14.9-50.3)
Started ABC before 6/01 (median)		1389	80 (6)	320	25.0 (19.5-30.5)
After 6/01		1246	73 (6)	285	25.7 (19.8-31.5)
Started ABC before 1/04 (launch of Kivexa)		2170	137 (6)	500	27.4 (22.8-32.0)
After 1/04		465	16 (3)	105	15.2 (8.7-24.7)

Figure 1

Adjusted incidence rate ratios (95% CI) of reported ABC HSR within 3 months per 100 PYF by region of Europe



*North (Denmark, Ireland, N Germany, Netherlands, Norway, Sweden, UK, Finland), South (Argentina, Greece, Israel, Italy, Portugal, Spain, Serbia and Montenegro, Croatia), Central (Austria, Belgium, France, S Germany, Luxembourg and Switzerland), East (Belarus, Russia, Ukraine, Poland, Hungary, Romania, Slovakia, Czech Republic, Bulgaria, Estonia, Latvia and Lithuania)

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