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Genotypic resistance profile before initiation of combination antiretroviral therapy and association with virological and immunological outcome in EuroSIDA

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INTRODUCTION

- Resistance of HIV-1 to antiretroviral (ARV) drugs is associated with virological failure in patients undergoing treatment and limits subsequent therapy options
- Current European guidelines recommend the clinical use of resistance testing in ARV-naïve patients for those newly diagnosed with acute/recent HIV infection and for chronically infected patients starting therapy if the suspicion of resistance is high or the prevalence of resistance in the population exceeds 10%

OBJECTIVES

- To describe the change in prevalence of transmitted drug resistance (TDR) in EuroSIDA over calendar time
- To compare virological and immunological response to combination antiretroviral therapy (cART) in those with TDR to those without

METHODS

- Patients were included who had genotypic resistance test results available before starting any ARV therapy
- Sequence data were obtained by retrospectively performing a genotypic test on stored plasma samples in one of the central EuroSIDA laboratories or from clinical site reports
- For patients with multiple test results, the results closest to seroconversion were taken
- Logistic regression was used to analyse virological and immunological response at the first measurements 6-12 months after starting cART
- cART was defined as ≥ 3 drugs including a PI/NNRTI/ABC

RESULTS

- 561 patients had resistance test results available before starting ARV, of which 305 started cART.
- 18% had ≥ 1 NRTI, NNRTI or major PI resistance mutation according to IAS-USA October/November 2005 (Table 1) (12% of those who started cART).
- Over calendar time, the percentage of patients under follow-up who had NRTI, NNRTI or major PI resistance increased from 13% in 1996 to 36% in 2003-05, p=0.032 after adjustment for demographics, CD4 cell count and viral load at time of resistance test (Figure 1).

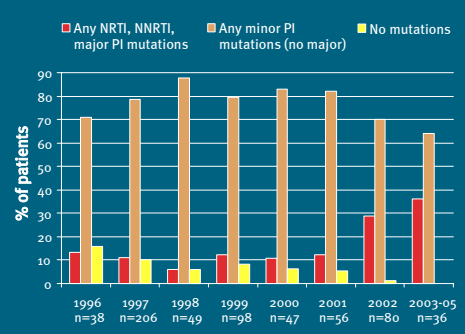
Table 1

Resistance profiles in ARV-naive patients

IAS-USA mutation	ARV-naïve	ARV-naïve and start cART
All, n (%)	561 (100.0)	305 (100.0)
Any NRTI, NNRTI, major PI	102 (18.2)	37 (12.1)
Any NRTI	85 (15.2)	27 (8.9)
M41L	30 (5.3)	7 (2.3)
D67N	20 (3.6)	3 (1.0)
K70R	17 (3.0)	10 (3.3)
L210W	32 (5.7)	6 (2.0)
T215Y/F	15 (2.7)	3 (1.0)
K219Q/E	27 (4.8)	4 (1.3)
Any NNRTI	11 (2.0)	4 (1.3)
Any major PI	29 (5.2)	9 (3.0)
Any minor PI	513 (91.4)	279 (91.5)

Figure 1

Resistance profiles in ARV-naive patients over calendar time



- Of 305 patients who started cART from ARV-naïve, 90% were sensitive to all of the drugs started ('active' group), with resistance interpreted using Rega algorithm, v6.4 (Table 2)
- 10% started a regimen with full or intermediate resistance to at least one drug ('resistant' group)
- Less patients started boosted PI regimens and more started single NNRTIs in the 'active' group (p<0.001). Patients also started cART later (p<0.001) in this group
- 270 patients with viral loads >500 copies/mL at time of starting cART were included in the virological response analysis. Counting missing values at 6-12 months after starting cART as virological failures, 75% achieved virological suppression (<=500 copies/mL) of 248 patients in the 'active' group, 50% of 22 in the 'resistant' group (Figure 2)
- Of 296 patients with baseline CD4 counts who were included in the immunological response analysis, 48% achieved a 100 cell/mm³ increase in CD4 count 6-12 months after cART of 267 in the 'active' group and 41% of 29 in the 'resistant' group.
- After adjustment for type of regimen, region, risk group, hepatitis B/C status, gender, race, prior AIDS diagnosis, year started cART, age, CD4 count, viral load and date of HIV diagnosis, there was no significant difference in virological response, OR: 0.47, 95% CI: (0.15-1.43), p=0.183 (Figure 3).
- There was also no significant difference in immunological response, adjusted OR: 0.64, 95% CI: (0.26-1.62), p=0.349.

CONCLUSIONS

- The relatively high prevalence of TDR observed in ARV-naïve EuroSIDA patients (18%) is due to a surprising upswing of TDR in 2002-2005, which may be due to an increase in selection bias.
- After adjustment for baseline viral load, CD4 count and demographics, there was a non-significant trend towards a worse virological and immunological response to cART in patients starting treatment with resistance to one or more drugs, however additional data are needed to increase power before a firm conclusion can be drawn.

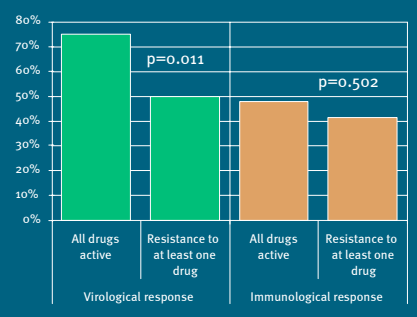
Table 2

Characteristics at start of cART regimen

	All drugs active	Resistance to at least one drug	p
All, n (%)	274 (90)	31 (10)	-
Male	209 (76)	28 (90)	0.075
MSM exposure	142 (52)	21 (68)	0.191
Previous AIDS diagnosis	32 (12)	4 (13)	0.217
cART regimen (incl >=2 NRTIs)			<0.001
Single PI	122 (45)	15 (48)	-
RTV-boosted PI	27 (10)	11 (36)	-
Single NNRTI	76 (28)	2 (7)	-
Other	49 (17)	3 (9)	-
Date started cART, median	Dec 99	Sep 97	<.001
Baseline CD4 count (cells/mm³)	249	246	0.836
Baseline viral load (log_{10}cps/mL)	4.9	5.0	0.678

Figure 2

% with virological[1] and immunological[2] response 6-12 months after starting cART

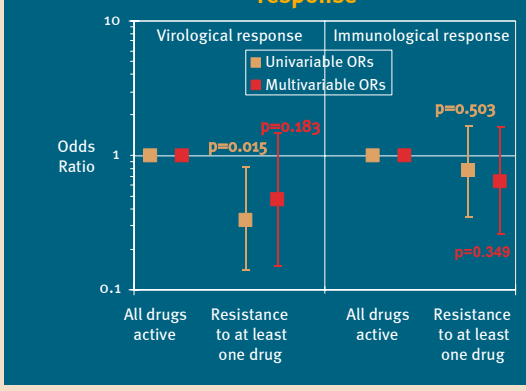


[1]Virological response: <500 copies/mL at first measurement 6-12 months after cART

[2]Immunological response: at least 100 cells/mm³ CD4 cell increase 6-12 months after cART

Figure 3

Odds ratios of virological[1] and immunological[2] response



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