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Relating Protease Inhibitor Resistance at Time of Virological Failure with Drug Exposure

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BACKGROUND

- Many patients with virological failure to boosted protease inhibitor (PI/r) regimens do not have viral resistance to PIs.
- A potential explanation for the absence of viral resistance after PI treatment failure may be non-adherence.

OBJECTIVES

- The goal of this analysis was to investigate the association between adherence and the presence of PI resistance in patients enrolled in the EuroSIDA study experiencing virological failure to a PI/r-based regimen.

METHODS

- EuroSIDA is a prospective pan-European cohort study that includes more than 16,000 HIV-infected patients from 32 European countries, Israel and Argentina.
- Patients were included if they had experienced virological failure to PI/r, defined as a viral load >1000 copies/mL after ≥ 4 months continuous exposure to a PI/r and if they had a plasma sample available within 1 month of the estimated virologic failure date.
- Samples were analysed for PI levels by a validated reversed-phase HPLC method; an undetectable PI level was defined as below the PI-specific lower limit of detection.
- Patients were considered non-adherent if they had undetectable PI levels.
- For those with no previous PI failure, genotypic sequencing was carried out retrospectively on the identified sample.
- PI resistance was defined as the presence of ≥ 1 major PI mutation (IAS-USA).
- Logistic regression was used to assess risk factors for an undetectable PI level and for detection of PI resistance at virological failure using exact methods for small datasets. Potential confounding factors investigated included demographics, CD4 count and viral load at the time of starting the PI/r-based regimen (defined as baseline) and previous treatment. For **table 2** the model strategy was to select the best 3-covariates model using the score selection in SAS. All bivariable models were explored for **table 3** and adjusted estimates were reported if markedly different from crude.

RESULTS

- Eighty-five patients were included. PI/r regimens were started in Sept 2002 (median) with virological failure occurring a median time of 17 months later.
- At time of starting the PI/r, 57% of the patients were ARV-naïve, median CD4 count was 217 cells/mm^3 (IQR:109-321) and median VL was 4.8 $\log_{10}$ copies/mL (IQR:3.3-5.2).
- Forty-three patients (51%) had an undetectable PI level at time of virologic failure. Demographics (**table 1**), ARV history and history of previous virologic failure (data not shown) were similar in patients with and without detectable PI levels.
- Injecting drug use was associated with a greater risk of an undetectable PI level (adjusted odds ratio (OR): 5.01; 95% CI: 1.08- 23.34; p=0.04), **table 2**.
- Forty-four (52%) of the 85 patients had no history of previous PI failure and were successfully tested for resistance. Five out of these 44 patients (11.4%) had PI resistance detected. Mutations detected were: M46I (n=4), V82T (n=2), T74P (n=2), I84V (n=4) and L90M (n=4).
- Those with undetectable PI levels appeared to be less likely to have PI resistance (0% of 24 patients, 95% CI: 0-14%) than those with detectable levels (25% of 20, 9-49%), univariable OR: 0.14; p=0.07. Adjusted ORs from bivariable models are given in **table 3**.

CONCLUSIONS

- Patients infected with HIV by injecting drug use were more likely to have undetectable PI levels at the moment of virological failure.
- Resistance to protease inhibitors was not detectable in the majority of patients at the moment of virological failure.
- The prevalence of PI resistance tended to be lower in patients with undetectable PI levels compared to those who had detectable PI levels.
- The lack of detection of mutations in people with undetectable drug levels may not mean that such mutations are completely absent; it is possible that viruses with resistance may have been reduced to represent only a small (and hence undetectable) minority of the total viral population and were out-competed by viruses without resistance.
- Small sample size limits the possibility to perform full adjustment for confounding and therefore the strength of the conclusions of this study.

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Table 1
Patient characteristics at time of starting PI/r regimen according to detectable/undetectable PI plasma concentration at PI/r failure

	PI Levels		p-value
	Detectable N=42	Undetectable N=43	
Male, n(%)	32 (76%)	31 (72%)	0.67
White etnicity, n(%)	38 (91%)	38 (88%)	1.00
HIV transmission, n(%)			0.16
Homosexual contacts	17 (41%)	14 (32%)	
IDU	4 (10%)	12 (28%)	
Heterosexual contacts	18 (43%)	13 (30%)	
Other	3 (7%)	1 (2%)	
Viral load at starting PI/r, copies /mL, n(%)			0.19
<500	4 (10%)	6 (14%)	
500-10,000	10 (24%)	6 (14%)	
>10,000	19 (45%)	27 (63%)	
Missing	9 (21%)	4 (9%)	
Hep B co-infection, n(%)	2 (5%)	1 (2%)	0.54
Hep C co-infection, n(%)	4 (10%)	9 (21%)	0.26
Previous AIDS, n(%)	10 (24%)	16 (37%)	0.18
Age in Years			
Median (IQR)	36 (32-47)	36 (31-41)	0.65
Time of enrolment			
Median (IQR)	Jan02 (Mar99-Feb04)	Oct01 (Mar97-Nov03)	0.32
Time of starting PI/r			
Median (IQR)	Apr02 (Jan01-Sep04)	Nov02 (Aug00-Oct04)	0.73
Time since HIV diagnosis, Months			
Median(IQR)	59 (12-135)	87 (37-139)	0.30

Table 2
Univariable and multivariable OR of having undetectable PI levels at failure from fitting a logistic regression analysis

Factors	Univariable OR (95% CI) p-value	Multivariable OR (95% CI) p-value
HIV transmission		
Homosexual contacts	1.00	1.00
IDU	3.64 (0.96-13.84) p=0.06	5.01 (1.08-23.34) p=0.04
Heterosexual contacts	0.88 (0.32-2.40) p=0.80	1.02 (0.34-3.03) p=0.98
AIDS before starting PI/r		
No	1.00	1.00
Yes	1.90 (0.74-4.86) p=0.18	2.47 (0.80- 7.66) P=0.12
Viral load at starting PI/r		
<500	1.00	1.00
500-10,000	0.40 (0.08-2.02) p=0.27	0.26 (0.04-1.56) p=0.14
>10,000	0.95 (0.24-3.82) p=0.94	0.95 (0.22-4.09) p=0.94

Table 3
Univariable and multivariable ORs of detecting PI resistance at failure associated with undetectable PI levels from fitting a logistic regression analysis

	OR	95% CI	p-value
Univariable	0.14	0.0-1.16	0.07
After adjusting for HBV+	0.19	0.0-1.81	0.15
After adjusting for age	0.32	0.0-1.86	0.22
After adjusting for CD4 at starting PI/r	0.18	0.0-1.54	0.12
After adjusting for duration of HIV infection	0.52	0.0-2.11	0.36
After adjusting for No. of drugs received before PI/r	0.17	0.0-1.41	0.11

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