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Detection of Resistance Mutations and CD4 Slopes in Individuals Experiencing Sustained Virological Failure

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INTRODUCTION

Several HIV- drug resistance mutations have been shown to affect viral fitness in vitro, and their presence may result in clinical benefit for patients kept on a virologically failing regimen due to an exhaustion of drug options.

AIM

To quantify the effect of resistance mutations on CD4 slopes in patients undergoing episodes of viral failure.

PATIENTS AND METHODS

- The data used come from EuroSIDA and the UK Collaborative HIV Cohort (UK CHIC) study. EuroSIDA contains data on >18,000 individuals from 34 European countries, Israel and Argentina; UK CHIC contains data on >45,000 individuals attending HIV clinics in the UK, whose records are linked to the UK HIV Drug Resistance Database.

- Patients were included in this analysis if they had at least one episode of sustained virological failure ($\geq$3 consecutive RNA measurements >500 copies/ml on ART) with at least 3 CD4 measurements and a resistance test during the episode.

- Mutations were identified using the IAS-USA[1] list, and were presumed to be present from detection until the end of an episode.

- Linear mixed models with a random intercept and slope were used to estimate CD4 slopes.

- Individual mutations with a population prevalence of >10% were tested for their association with CD4 slope.
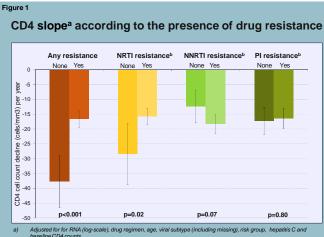
RESULTS

- 2731 patients experiencing a median of 1 (range 1-4) episodes were included. Baseline characteristics can be seen in **Table 1**.

- Overall, CD4 counts declined by 17.1 (-19.7; -14.5) cells per year; this decline was less marked when viral suppression was higher (current HIV RNA more than 1.5 log below the setpoint; p=0.01).

- In multivariable models adjusting for viral load, CD4 decline was slower during episodes with detected resistance (21.0 cells/year less, 95%CI=11.7-30.3) compared to episodes without detected resistance, p<0.001; **Figure 1**).

- Among those with more than 1 resistance mutation, there was only weak evidence that class-specific mutations had any effect on the CD4 slope (**Figure 1**).

- The effects of individual mutations were explored, but none were significantly associated with the CD4 slope (**Table 2-3**).
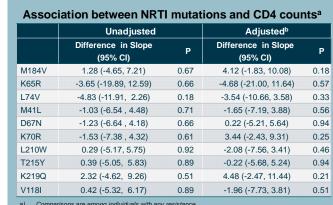
CONCLUSIONS

In our study population, presence of resistance mutations was associated with less steep CD4 declines. This may be due to a biological effect of resistance on CD4 slopes, or other unmeasured factors such as poor adherence among individuals without resistance. Among individuals with detected drug resistance, we found no evidence suggesting that the presence of individual mutations was associated with beneficial CD4 slope changes.

1. Victoria A. Johnson, MD; Vincent Calvez, MD, PhD; Huldrych F. Günthard, MD; Roger Paredes, MD, PhD; Deenan Pillay, MD, PhD; Robert W. Shafer, MD; Annemarie Wensing, MD, PhD; Douglas D. Richman, MD. Update of the Drug Resistance Mutations in HIV-1: March 2013. *Top. Antivir. Med.* **21**, 6–14 (2013)

Table 1

Baseline Characteristics

		N	%
Total		2731	100
Gender	Male	2179	79.8
Ethnicity	White	2003	73.3
Infection Mode	MSM	1541	56.4
	IDU	272	1.0
	Heterosexual	754	27.6
Age	Median, IQR	39	35, 45
CD4 (cells/mm3)	Median, IQR	260	146, 394
HIV RNA (cp/ml)	Median, IQR	14100	3660, 66189
For each episode:		**N**	**%**
Duration of episode	Median, IQR	15	9, 27
GSS	Median, IQR	1	0, 2
Any resistance		2778	88.4
NRTI		2466	78.5
NNRTI		1952	62.1
PI		1520	48.4

Figure 1

CD4 slope[a] according to the presence of drug resistance

a) Adjusted for RNA (log-scale), drug regimen, age, viral subtype (including missing), risk group, hepatitis C and baseline CD4 counts.
b) Comparisons are among individuals with any resistance.

Table 2

Association between NRTI mutations and CD4 counts[a]

	Unadjusted		Adjusted[b]	
	Difference in Slope (95% CI)	P	Difference in Slope (95% CI)	P
M184V	1.28 (-4.65, 7.21)	0.67	4.12 (-1.83, 10.08)	0.18
K65R	-3.65 (-19.89, 12.59)	0.66	-4.68 (-21.00, 11.64)	0.57
L74V	-4.83 (-11.91, 2.26)	0.18	-3.54 (-10.66, 3.58)	0.33
M41L	-1.03 (-6.54, 4.48)	0.71	-1.65 (-7.19, 3.88)	0.56
D67N	-1.23 (-6.64, 4.18)	0.66	0.22 (-5.21, 5.64)	0.94
K70R	-1.53 (-7.38, 4.32)	0.61	3.44 (-2.43, 9.31)	0.25
L210W	0.29 (-5.17, 5.75)	0.92	-2.08 (-7.56, 3.41)	0.46
T215Y	0.39 (-5.05, 5.83)	0.89	-0.22 (-5.68, 5.24)	0.94
K219Q	2.32 (-4.62, 9.26)	0.51	4.48 (-2.47, 11.44)	0.21
V118I	0.42 (-5.32, 6.17)	0.89	-1.96 (-7.73, 3.81)	0.51

a) Comparisons are among individuals with any resistance.
b) Models adjusted for RNA (log-scale), drug regimen, age, viral subtype (including missing), risk group, hepatitis C and baseline CD4 counts.

Table 3

Association between NNRTI/PI mutations and CD4 counts[a]

	Unadjusted		Adjusted[b]	
	Difference in Slope (95% CI)	P	Difference in Slope (95% CI)	P
NNRTI mutations				
K103N	-0.78 (-6.50, 4.94)	0.79	-1.41 (-7.15, 4.33)	0.64
Y181C	0.85 (-5.53, 7.22)	0.79	1.05 (-5.35, 7.44)	0.75
G190A	-0.79 (-7.68, 6.10)	0.82	-1.32 (-8.22, 5.58)	0.71
PI mutations				
M46I	-0.83 (-6.81, 5.15)	0.79	-1.07 (-7.06, 4.93)	0.73
V82A	2.05 (-3.87, 7.97)	0.50	2.28 (-3.66, 8.21)	0.45
L90M	-2.74 (-8.23, 2.75)	0.33	-3.77 (-9.28, 1.74)	0.18

a) Comparisons are among individuals with any resistance.
b) Models adjusted for RNA (log-scale), drug regimen, age, viral subtype (including missing), risk group, hepatitis C and baseline CD4 counts.

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