Poster #91

XVI International HIV Drug Resistance Workshop

Association between Resistance and CD4 Count Change in Patients on ART with Ongoing Viraemia

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BACKGROUND

Among patients with ongoing viraemia (i.e. two consecutive viral loads › 500 copies/mL) CD4 count changes are more favourable in patients receiving antiretroviral therapy (ART) compared to patients with comparable viral loads who are not on ART.

This could be because the presence of resistance mutations may cause a virus to have a reduced capacity for inducing CD4 count declines.

We hypothesized that in patients on ART with a given viral load or a given amount of suppression from their pre-ART viral load levels, differences in the rates of CD4 count decline may relate to differences between the resistance mutations that are present. If such an effect does exist we wanted to ascertain whether it is specific to the class of ARTs affected by the mutations or whether it can be attributed to individual mutations specifically.

A reduction in viral fitness associated with viruses containing resistance mutations has been shown previously, but this reduced fitness may act entirely through a reduction in the viral load. In this comparison we aimed to address whether resistance mutations are associated with CD4 count declines *for a given viral load or extent of viral suppression from the pre-ART level*

OBJECTIVES

We studied viraemic patients on ART to assess whether resistance mutations were associated with CD4 count changes, independent of viral load levels.

METHODS

Combined data from the following sources were analysed:

- UK Collaborative Group on HIV Drug Resistance
- UK CHIC
- EuroSIDA

We identified all patients with pairs of consecutive viral loads (both › 500 cps/mL), 8 to 26 weeks apart who: i) had a CD4 count measurement available at each time-point (+/- 1 week); ii) were receiving the same ART for at least 4 months prior to the first viral load measurement AND up to the second viral load measurement; and iii) had a resistance test in the interval or 4 weeks either side of it.

We fit standard linear regression models on the CD4 count change over time for these patients

RESULTS

We included 1912 patients with 3220 paired measurements (Figure 1)

The median (IQR) length of the interval was 13 (10 to 17) weeks

The median (IQR) CD4 count at the start of the episode was 274 (168 to 410) cells/μL and there was a median change of -7 (-50 to 38) cells/μL during the interval

The median (IQR) viral load at the start of the episode was 3.93 (3.39 to 4.54) $\log_{10}$ cps/ml with a median increase of 0.08 (-0.19 to 0.40) $\log_{10}$ cps/ml during the interval

Overall, 52% of patients had primary PI mutations, 46% had NNRTI mutations and 84% had NRTI mutations (IAS-USA 2006).

Mean monthly CD4 count changes according to resistance mutations and drugs used are shown in Table 1.

Patients on NNRTIs had more favourable CD4 count changes if they did not have NNRTI-specific mutations present. Conversely patients receiving PIs or PI/rs have more favourable CD4 count slopes if they had PI-specific mutations present.

After adjustments for confounders there was little evidence for a difference in the CD4 count change according to which IAS-USA mutations were present (Table 1). Adjusted mean (95% CI) CD4 count changes were: -1.33 (-7.25 to 4.59); -2.36 (-9.48 to 4.75); -5.89 (-10.13 to -1.64); and -1.17 (-9.21 to 6.86) cells/μL/month for patients on PI/rs with PI-mutations, on PI/rs without PI-mutations, on NNRTIs with NNRTI-mutations and on NNRTIs without NNRTI-mutations, respectively.

All NNRTI-specific mutations were associated with greater CD4 count declines, but only two reached borderline significance. In separate models the presence of K103N and Y181C were associated with a mean (95% CI) 2.96 (-0.16, 6.09) and a 4.48 (0.74, 8.23) cells/μL greater CD4 count reduction per month compared to patients without either mutation, respectively.

No PI or NRTI mutation alone was associated with the CD4 count change (Table 2).

Data from PLATO showed an association between the extent of viral load reduction from the pre-ART value with the CD4 count slopes. We repeated the above analysis on 1062 CD4 count pairs for which the viral load reduction from the pre-ART value was known and saw the same patterns as described above.

SENSITIVITY ANALYSIS

Viral load changes within the interval are likely to influence CD4 count slopes so we repeated the analysis on patients with minimal viral load changes (i.e. ‹0.25 $\log_{10}$ cps/ml). We also adjusted the main analysis for viral load changes in the interval to quantify the effect of these changes on our estimates.

We restricted the analysis to patients with a viral load ›10000 cps/ml during the interval because the effect of specific mutations may be stronger in this virologically failing population.

We restricted the analysis to patients with a genotypic sensitivity score (GSS)›2, but with at least one IAS-USA mutation present, to investigate the effect of mutations in adherent patients who had limited benefit from the ARTs they were receiving.

We restricted the analysis to patients with a GSS‹1 to see whether clearer differences can be seen in patients with limited treatment options available.

We restricted the analysis to patients whose resistance test was taken within the viral load interval to eliminate the possibility of reverse causality between mutation development and CD4 count slopes.

All of the above methods provided results consistent with what we have shown in the main analysis

DISCUSSION POINTS/CONCLUSIONS

We did not identify any clear differences in CD4 count slopes for a given viral load (or for a given viral load change from the pre-ART value) according to the presence of resistance.

Although there is an indication that patients on NNRTIs have greater CD4 count declines if NNRTI mutations are present and patients on PIs have smaller CD4 count declines if PI mutations are present these differences are not as clear after adjustments. This is consistent with the high fitness of K103N mutants that has been reported by others.

The presence of mutations may have affected the CD4 count prior to the interval covered by the pair. This makes it hard to quantify the relationship between CD4 counts, viral load levels and mutations.

This analysis has limited power so further analyses using a larger number of patients is still required.

Figure 1

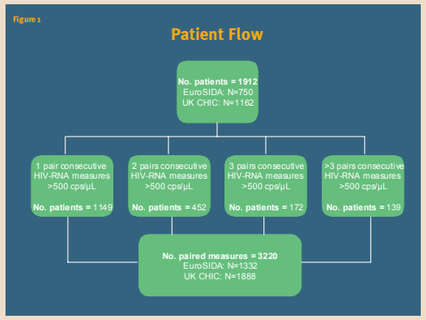

Table 1

Mean CD4 count change according to class-specific mutations and ARTs used

Mutation category (IAS-USA)	Number (%) (N=3220)	Mean CD4 count change (per month; 95% CI)	Difference in mean CD4 count change per month (95% CI) relative to group 1**
On PI/r, PI mutations* (group 1)	426 (13.2%)	-0.4 (-3.7, 2.9)	Ref
On PI/r, no PI mutations*	184 (5.7%)	-3.7 (-8.8, 1.4)	-1.6 (-8.8, 5.6)
On PI, PI mutations*	704 (21.9%)	1.1 (-1.5, 3.8)	1.4 (-3.2, 6.0)
On PI, no PI mutations*	292 (9.1%)	-1.7 (-6.8, 3.3)	0.3 (-6.1, 6.6)
On NNRTI, NNRTI mutations*	698 (21.7%)	-5.2 (-8.1, 2.3)	-4.6 (-9.3, 0.1)
On NNRTI, no NNRTI mutations*	142 (4.4%)	-3.2 (-10.4, 4.0)	-0.4 (-8.5, 7.7)
On PI & NNRTI, mutations to both*	278 (8.6%)	-3.7 (-7.7, 0.2)	-3.5 (-9.3, 2.3)
On PI & NNRTI, mutsto 1 class or no muts*	113 (3.5%)	-5.5 (-11.5, 0.4)	-3.0 (-11.5, 5.5)
On NRTIs only, NRTI mutations	326 (10.1%)	-3.4 (-8.7, 1.9)	-3.0 (-8.5, 2.6)
On NRTIs only, no NRTI mutations	57 (1.8%)	1.5 (-7.6, 10.5)	5.0 (-6.6, 16.5)

*These groups can also include NRTI mutations
**Adjusted for the time between the start of the interval and the resistance test, the genotypic sensitivity score (according to the Stanford interpretation system) and the viral load at the start of the interval

Table 2

Mean CD4 count change according to specific mutations

Specific IAS-USA mutations (occurring in ›5% of the population)		CD4 cell count change associated with each mutation (95% CI)*	P-value
PI mutations	M46I/L	1.86 (-1.38, 5.10)	0.26
	V82A/F/L/T/S	0.99 (-2.29, 4.58)	0.55
	I84V	-0.43 (-4.49, 3.64)	0.84
	L90M	-0.53 (-3.64, 2.57)	0.74
NNRTI mutations	K103N	-2.96 (-6.09, 0.16)	0.06
	Y181C	-4.48 (-8.23, -0.74)	0.02
	G190A	-1.93 (-5.98, 2.12)	0.35
NRTI mutations	M41L	-0.32 (-3.33, 2.69)	0.84
	D67N	-0.18 (-3.19, 2.83)	0.91
	K70R	-1.21 (-4.36, 1.94)	0.45
	L74V	-1.45 (-6.05, 3.16)	0.54
	M184V	0.16 (-2.80, 3.11)	0.92
	L210W	0.78 (-2.40, 3.96)	0.63
	T215Y	0.73 (-2.22, 3.68)	0.63
	T215F	-2.08 (-6.13, 1.96)	0.31
	K219Q/E	-1.04 (-4.37, 2.28)	0.54

*Adjustments are for the same variables as in Table 1

ACKNOWLEDGEMENTS

The EuroSIDA Study Group
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Mazzotta, A Gabbuti, Ospedale S Maria Annunziata, Firenze; Vullo, M Lichtner, University di Roma la Sapienza, Rome; A Chirianni, E Montesarchio, Presidio Ospedaliero AD, Cotugno, Monaldi Hospital, Napoli; Antonucci, F Iacomi, Narcisi, Zaccarelli, Istituto Nazionale Malattie Infettive Lazzaro Spallanzani, Rome; A Lazzarin, R Finazzi, Ospedale San Raffaele, Milan; A D'Arminio Monforte, Osp. L. 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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 were the primary sponsors of the study. Unrestricted grants were also provided 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..

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