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Zoe Fox
Department of Primary Care and Population Sciences,
Royal Free and UC Medical School,
Tel: +44 (0) 20 7830 2859
E-mail: z.fox@pcps.ucl.ac.uk

Concordance between genotypic interpretation systems for predicting resistance to tipranavir/r and darunavir/r: results from the EuroSIDA study

Z Fox[1,2], A Cozzi-Lepri[2], B Clotet[3], J Kjaer[1], AN Phillips[2] and JD Lundgren[1] for the EuroSIDA study group

[1]Copenhagen HIV Programme, University of Copenhagen, Faculty of Health Sciences, Denmark; [2]Royal Free and University College Medical School, UK; [3]Hospital Germans Trias i Pujol, Spain

BACKGROUND

- Genotypic interpretation systems (GIS) are used to translate lists of mutations into a sensitivity score for each antiretroviral drug (ARV)
- These sensitivity scores are usually separated into three categories according to how sensitive a patient's virus is to each ARV: 1) sensitive to the ARV, 2) intermediate resistance to the ARV; and 3) full resistance to the ARV
- We have previously shown a difference between GISs in their abilities to ascribe resistance levels to ritonavir-boosted protease inhibitors (PI/rs) and in their abilities to predict virological response
  [Z Fox *et al,* AIDS 2007 Oct 1;21(15):2033-2042]
- Tipranavir (TPV/r) and darunavir (DRV/r) are two PI/rs that have recently entered the market so resistance development to these drugs is only currently emerging
- There are limited data available on the levels of concordance between ascribed levels of resistance to TPV/r and to DRV/r using each GIS

DATA

- Resistance data for this study come from EuroSIDA
- EuroSIDA is a prospective, observational cohort of over 14,200 HIV-1 infected patients from 93 centres across 31 European countries, plus Israel and Argentina
- EuroSIDA patients with HIV-RNA>1000 cps/ml were included in this analysis if they had genotyping performed on their plasma samples and their viral sequence contained at least one protease mutation (any mutation, not specifically a major mutation)

METHODS

- GISs containing 3 levels of resistance were selected for comparison
- Each sequence of mutations was run through the following GISs to generate a three-level resistance score to each PI/r:
  - REGA: version 7.1
  - ANRS: version 2006
  - Stanford University: version 4.2.9
  - Kohlbrenner *et al*: 2004 (XIII International HIV drug resistance workshop – TPV/r only)
- Differences between these GISs on which mutations are considered to contribute to resistance are outlined in figure 1
- Concordance between predicted resistance levels to TPV/r and to DRV/r were evaluated using kappa statistics
- Since we are comparing the resistance levels generated with each GIS we combined PI-naïve patients and PI-experienced patients in order to increase numbers.
- Subgroup analysis was performed in PI-experienced patients and within each subtype if N>100

RESULTS

- A total of 3045 EuroSIDA patients had 5442 isolates
- Every GIS predicted high levels of sensitivity to TPV/r and DRV/r at baseline
  - The proportion of isolates harbouring full/intermediate resistance to TPV/r ranged from 9.9% - ANRS to 30.5% - Stanford (figure 2)
  - GISs predicted lower levels of full/intermediate resistance to DRV/r: 0.1% - REGA to 26.9% - Stanford (figure 3)
- There were 6.6% of isolates with full/intermediate resistance to TPV/r and 0.1% to DRV/r using every GIS that we compared
- Overall 0.1%, 1.5% and 26.3% of patients were considered to have isolates containing mutations that are cross-resistant to both TPV/r and DRV/r using REGA, ANRS and Stanford, respectively

Concordance

- Kappas ranged from 0.28 (ANRS-*vs*-Stanford) to 0.57 (REGA-*vs*-Stanford) for TPV/r; and from 0.00 (REGA-*vs*-Stanford) to 0.10 (ANRS-*vs*-Stanford) for DRV/r (table 1)

Concordance for PI-experienced patients:

- Similar kappas were seen in the 4175 (76.7%) PI-experienced patients: kappas ranged from 0.26 (ANRS-*vs*-Stanford) to 0.57 (ANRS-*vs*-Kohlbrenner) for TPV/r; and from 0.00 (REGA-*vs*-Stanford) to 0.09 (ANRS-*vs*-Stanford) for DRV/r

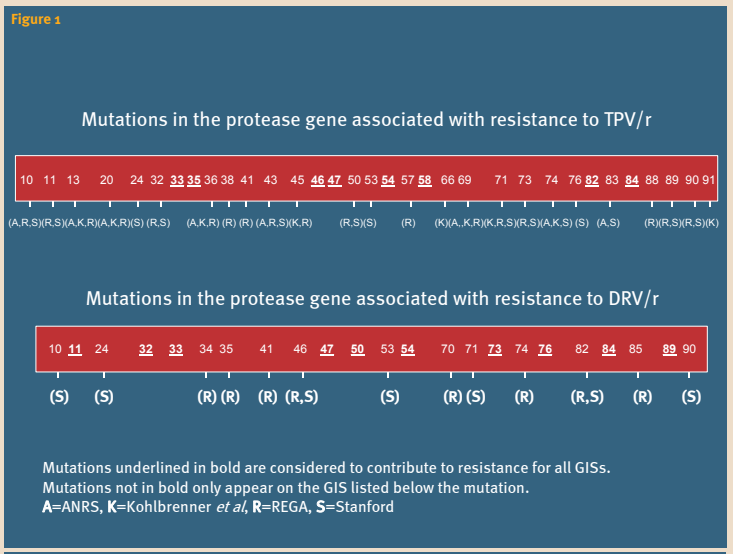
Concordance according to subtype

- There were 2727 patients who had subtype information
- Overall, 88.5% of isolates were from patients infected with subtype-B HIV, 3.6% from subtype A and 2.6% from subtype C. All other resistance tests were performed on viruses assigned a different subtype
- For TPV/r kappas ranged from 0.06 (Kohlbrenner-*vs*-REGA) to 0.56 (REGA-*vs*-Stanford) for subtype-A; from 0.26 (ANRS-*vs*-Stanford) to 0.58 (Kohlbrenner-*vs*-REGA) for subtype-B; and from 0.28 (Kohlbrenner-*vs*-REGA) to 0.72 (Kohlbrenner-*vs*-ANRS) for subtype-C
- Not enough isolates harboured DRV mutations to perform within subtype comparisons for DRV/r

CONCLUSIONS

- Concordance between GISs was fair-to-moderate for determining resistance to TPV/r
- Concordance between ascribed resistance levels was poor for DRV/r
- The predictive ability of GISs varied by subtype
- The observed variability between GISs in predicting susceptibility to TVP/r and DRV/r makes treatment decisions difficult
- Ascribed resistance levels still need to be related to viral load changes in patients receiving these PI/rs. The GISs can then be refined and concordance between them will consequently improve

Figure 1



Mutations underlined in bold are considered to contribute to resistance for all GISs.
Mutations not in bold only appear on the GIS listed below the mutation.
A=ANRS, **K**=Kohlbrenner *et al*, **R**=REGA, **S**=Stanford

Figure 2

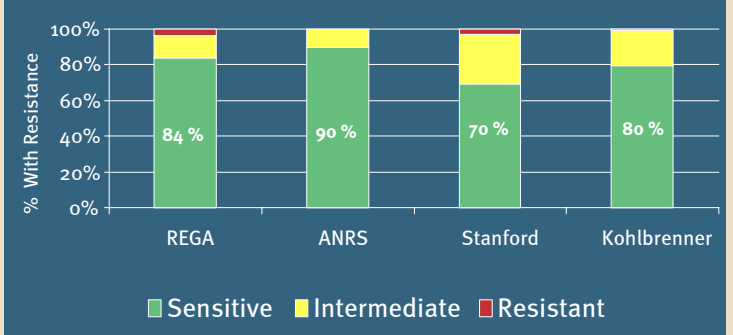


Figure 3

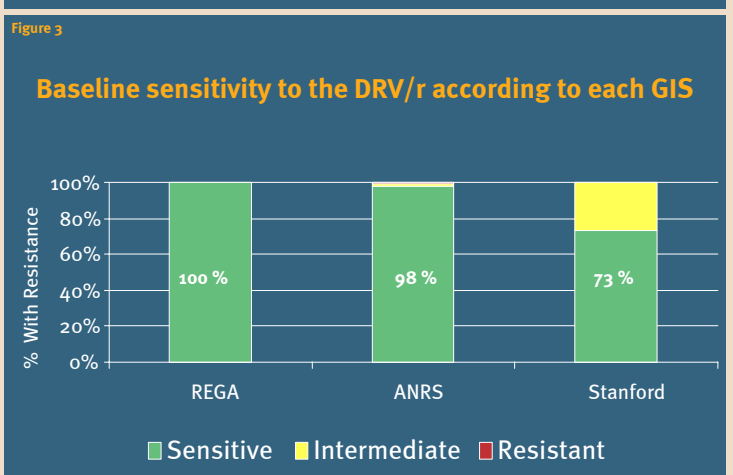


Table 1

Concordance between GISs - Kappas

		REGA	Stanford	Kohlbrenner
TPV/r	ANRS	0.40	0.28	0.55
	REGA	-	0.57	0.52
	Stanford	-	-	0.46
DRV/r	ANRS	0.05	0.10	-
	REGA	-	0.00	-
	Stanford	-	-	-

Agreement:
Poor κ≤0.2
Fair 0.21≤κ≤0.40
Moderate 0.41≤κ≤0.60
Good 0.61≤κ≤0.80
Very Good κ>0.80

For each PI/r green represents the highest agreement and pink the lowest

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