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

Z Fox1, A Cozzi-Lepri2, B Catolet3, E Kjaer4, AH Phillips5 and JD Lundgren for the EuroSIDA study group

1Copenhagen HIV Programme, University of Copenhagen; 2Faculty of Health Sciences, Denmark; 3Royal Free and University College Medical School, UK; 4Hospital Garmen Tías; 5Pujol, 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/r) and in their abilities to predict virological response

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>500

RESULTS
- A total of 3445 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 9.3% - 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 0.2%, 1.0% 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 4,275 (76.7%) PI-experienced patients: kappas ranged from 0.26 (ANRS- vs Stanford) to 0.57 (REGA- 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 2,372 patients who had subtype information
- Overall, 88.3% 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 TPV/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/r. The GISs can then be refined and concordance between them will consequently improve

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Concordance between GISs - Kappas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>REGA</td>
</tr>
<tr>
<td>TPV/r</td>
<td>0.46</td>
</tr>
<tr>
<td>DRV/r</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Figures:
- Figure 1: Concordance between GISs - Kappas
- Figure 2: Baseline sensitivity to the TPV/r according to each GIS
- Figure 3: Baseline sensitivity to the DRV/r according to each GIS

References: