Poster No. P3.4/02

EACS 2007

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

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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

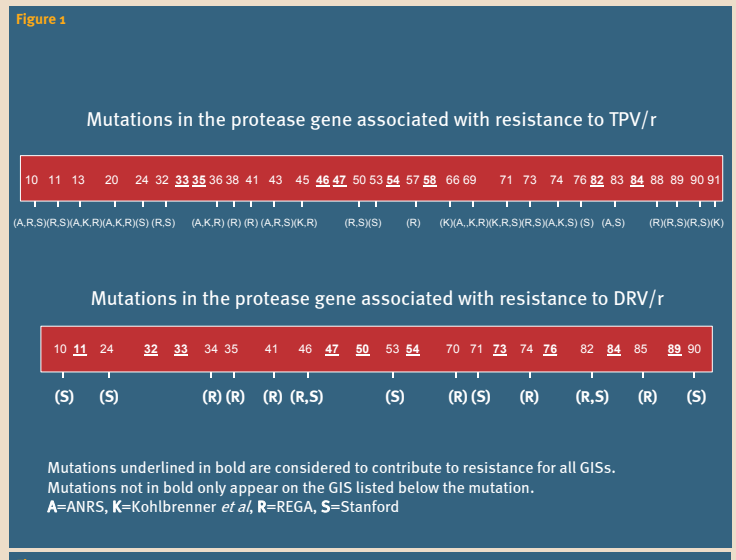

Figure 2

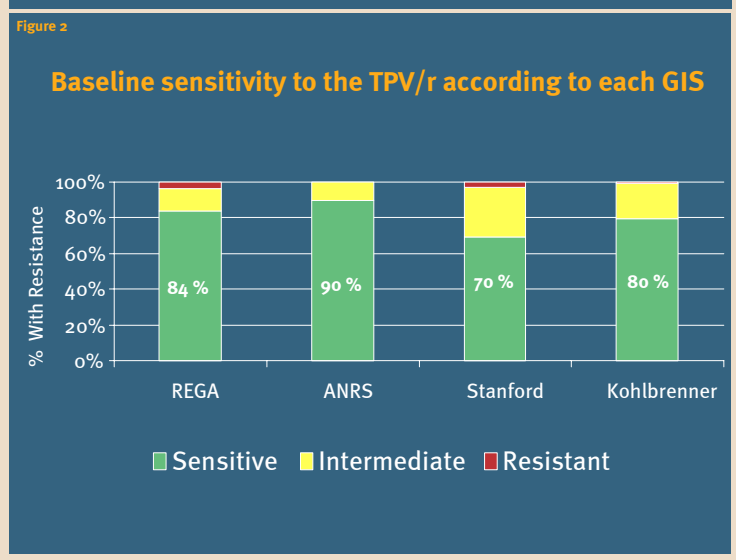

Figure 3

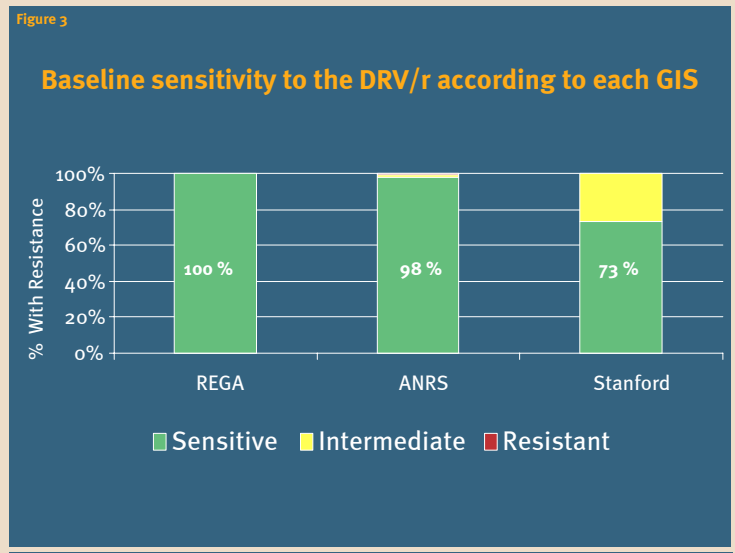

Table 1

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

ACKNOWLEDGEMENTS:

The EuroSIDA Study Group
The multicentre study group on EuroSIDA (national coordinators in parenthesis).

Argentina: (M Losso), A Duran, Hospital JM Ramos Mejia, Buenos Aires; **Austria**: (N Vetter) Pulmonologisches Zentrum der Stadt Wien, Vienna; **Belarus**: (I Karpov), A Vassilenko, Belarus State Medical University, Minsk, VM Mitsura, Gomel State Medical University, Gomel; O Suetnov, Regional AIDS Centre, Svetlogorsk.; **Belgium**: (N Clumeck) S De Wit, B Poll, Saint-Pierre Hospital, Brussels; R Colebunders, Institute of Tropical Medicine, Antwerp ; **Bulgaria**: K Kostov, Infectious Diseases Hospital, Sofia. Croatia: I Begovac, University Hospital of Infectious Diseases, Zagreb; **Czech Republic**: (E Machala) H Rozsypal, Faculty Hospital Bulovka, Prague; D Sedlacek, Charles University Hospital, Plzen; **Denmark**: (J Nielsen) J Lundgren, T Benfield, O Kirk, Hvidovre Hospital, Copenhagen; J Gerstoft, T Katzenstein, A-B E Hansen, P Skinhøj, Rigshospitalet, Copenhagen; C Pedersen, Odense University Hospital, Odense, L Oestergaard, Skejby Hospital, Aarhus; **Estonia**: (K Zilmer) West-Tallinn Central Hospital, Tallinn, Jelena Smidt, Nakkusosakond Siseklinik, Kohtla-Järve; **Finland**: (M Ristola), Helsinki University Central Hospital, Helsinki; **France**: (C Katlama) Hôpital de la Pitié-Salpêtière, Paris; J-P Viard, Hôpital Necker-Enfants Malades, Paris; P-M Girard, Hospital Saint-Antoine, Paris; JM Livrozet, Hôpital Edouard Herriot, Lyon; P Vanhems, University Claude Bernard, Lyon; C Pradier, Hôpital de l'Archet, Nice; F Dabis, Unité INSERM, Bordeaux..**Germany**: (J Rockstroh) Universitäts Klinik Bonn; R Schmidt, Medizinische Hochschule Hannover; J van Lunzen, O Degen, University Medical Center Hamburg-Eppendorf, Infectious Diseases Unit, Hamburg; HJ Stellbrink, IPM Study Center, Hamburg; S Staszewski. JW Goethe University Hospital, Frankfurt; J Bogner, Medizinische Poliklinik, Munich; G. Fätkenheuer, Universität Köln, Cologne; **Greece**: (J Kosmidis) P Gargalianos, G Xylomenos, J Perdios, Athens General Hospital; G Panos, A Filandras, E Karabatsaki, 1st IKA Hospital; H Sambattakou, Ippokration Genereal Hospital, Athens; **Hungary** (D Banhegyi) Szent László Hospital, Budapest.

Ireland: (F Mulcahy) St. James's Hospital, Dublin; **Israel**: (I Yust) D Turner, M Burke, Ichilov Hospital, Tel Aviv; S Pollack, G Hassoun, Rambam Medical Center, Haifa;S Maayan, Hadassah University Hospital, Jerusalem; **Italy**: (A Chiesi) Istituto Superiore di Sanità, Rome; R Esposito, I Mazeu, C Mussini, Università Modena, Modena; C Arici, Ospedale Riuniti, Bergamo; R Pristera, Ospedale Generale Regionale, Bolzano; F Mazzotta, A Gabbuti, Ospedale S Maria Annunziata, Firenze; V Vullo, M Lichtner, University di Roma la Sapienza, Rome; A Chirianni, E Montesarchio, M Gargiulo, Presidio Ospedaliero AD Cotugno, Monaldi Hospital, Napoli; G Antonucci, F Iacomi, P Narciso, C Viassi, M Zaccarelli, Istituto Nazionale Malattie Infettive Lazzaro Spallanzani, Rome; A Lazzarin, R Finazzi, Ospedale San Raffaele, Milan; M Galli, A Ridolfo, Osp. L. Sacco, Milan; A d'Arminio Monforte, Istituto Di Clinica Malattie Infettive e Tropicale, Milan; **Latvia**: (B Rozentale) P Aldins, Infectology Centre of Latvia, Riga; **Lithuania**: (S Chaplinskas) Lithuanian AIDS Centre, Vilnius; **Luxembourg**: (R Hemmel), T Staub, Centre Hospitalier, Luxembourg; **Netherlands**: (P Reiss) Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam; **Norway**: (J Bruun) A Maeland, V Ormaasen, Ullevål Hospital, Oslo; **Poland**: (B Knysz) J Gasiorowski, Medical University, Wroclaw; A Horban, Centrum Diagnostyki i Terapii AIDS, Warsaw; D Prokopowicz, A Wiercinska-Drapalo, Medical University, Bialystok; A Boron-Kaczmarska, M Pynka, Medical Unevsity, Szczecin; M Beniowski, E Mularska, Osrodek Diagnostyki i Terapii AIDS, Chorzow; H Trocha, Medical Unversity, Gdansk; **Portugal**: (F Antunes) E Valadas, Hospital Santa Maria, Lisbon; K Mansinho, Hospital de Egas Moniz, Lisbon; F Maltez, Hospital Curry Cabral, Lisbon; **Romania**: (D Duiculescu) Spitalul de Boli Infectioase si Tropicale: Dr. Victor Babes, Bucarest; **Russia**: (A Rakhmanova), Medical Academy Botkin Hospital, St Petersburg; E Vinogradova, St Petersburg AIDS Centre, St Peterburg; S Buzunova, Novgorod Centre for AIDS, Novgorod; **Serbia**: (D Jevtovic), The Institute for Infectious and Tropical Diseases, Belgrade; **Slovakia**: (M Mokráš) D Staneková, Dérer Hospital, Bratislava; **Spain**: (J González-Lahuz) V Soriano, J. Martín-Carbonero, P Labarga, Hospital Carlos III, Madrid; B Clotet, A Jou, J Conejero, C Tural, Hospital Germans Trias i Pujol, Badalona; JM Gatell, JM Miró, Hospital Clinic i Provincial, Barcelona; P Domingo, M Gutierrez, G Mateo, MA Sambeat, Hospital Sant Pau, Barcelona; **Sweden**: (A Karlsson), Karolinska University Hospital, Stockholm; PO Persson, Karolinska University Hospital, Huddinge; L Flamholc, Malmö University Hospital, Malmö; **Switzerland**: (B Ledergerber) R Weber, University Hospital, Zürich; P Francioli, M Cavassini, Centre Hospitalier Universitaire Vaudois, Lausanne; B Hirschel, E Boffi, Hospital Cantonal Universitaire de Geneve, Geneve; H Furrer, Inselspital Bern, Bern; M Battegay, L Elzi, University Hospital Basel; **Ukraine**: (E Kravchenko) N Chentsova, Kiev Centre for AIDS, Kiev; **United KIngdom**: (S Barton) St. Stephen's Clinic, Chelsea and Westminster Hospital, London; AM Johnson, D Mercey, Royal Free and University College London Medical School, London (University College Campus); A Phillips, MA Johnson, A Mocroft, Royal Free and University College Medical School, London (Royal Free Campus); M Murphy, Medical College of Saint Bartholomew's Hospital, London; J Weber, G Scullard, Imperial College School of Medicine at St. Mary's, London; M Fisher, Royal Sussex County Hospital, Brighton; R Brettle, Western General Hospital, Edinburgh.

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Statement of Funding: Primary support for EuroSIDA is provided by 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. Current support also includes unrestricted grants 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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