4th European HIV Drug Resistance Workshop

Poster No. 57

The ability of four genotypic resistance algorithms to predict HIV-RNA responses to boosted PI-containing regimens after 4 and 12 weeks follow-up

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BACKGROUND

- Genotyping provides lists of mutations that are translated into a sensitivity score for each antiretroviral (ARV) using an available interpretation system (IS)
- ARVs are usually assigned a score of 1 if the virus is deemed to be sensitive to that ARV, 0.5 for intermediate resistance and 0 for full resistance.
- These scores are then summed to generate an overall genotypic sensitivity score (GSS)
- Limited information is available on the prognostic value of each IS for patients receiving a ritonavir boosted protease inhibitor (PI/r)

OBJECTIVES

- To investigate:
  - Concordance between predicted PI/r resistance levels using four genotypic interpretation systems (IS)
  - The relationship between the predicted level of sensitivity to the randomised PI/r and virological response at week 4 and at week 12
- To assign a genotypic sensitivity score (GSS) to the rest of the regimen and explore the relationship between this GSS and virological response

DATA

We used combined data from three, international, 48-week, multi-centre trials (MaxCmin1, MaxCmin2, COLATE)

- MaxCmin1: Safety and efficacy of indinavir/r (800/100 mg bid) *vs.* saquinavir/r (1000/100 mg bid)
- MaxCmin2: Safety and efficacy of lopinavir/r (400/100 mg bid) *vs.* saquinavir/r (1000/100 mg bid)
- COLATE: Patients failing a lamivudine (3TC) containing regimen either continued or discontinued 3TC while starting a new cART regimen – we used a sub-group of these patients who initiated a PI/r containing regimen

METHODS

- Reverse transcriptase and protease mutations were identified for all patients with baseline viral load >500 cps/ml
- Each set of mutations was run through the following ISs to obtain a score relating to whether a patient was sensitive, intermediate or resistant to each ARV:
  - **REGA**: Sept. 2005, version 6.4
  - **ANRS**: July 2005, version 13
  - **Detroit Medical Center**: Oct. 2004
  - **Stanford University**: June 2005
- Stanford did not have algorithms available for PI/rs
- Concordance between PI/r resistance levels was evaluated using kappa statistics
- Factors associated with HIV-RNA change were identified through censored regression analysis

RESULTS

- Baseline HIV-1 genotypic resistance tests were available for 368 patients [89 (24%) indinavir/r; 126 (34%) lopinavir/r; and 153 (42%) saquinavir/r]
- At baseline, 9 (10%), 3 (2%) and 6 (4%) patients had full resistance and 74 (83%), 110 (87%) and 142 (93%) were sensitive to IDV/r, LPV/r and SQV/r, respectively (illustrated using the REGA IS – Figure 1).
- Overall, 241 (65%) patients were susceptible to ≥2 ARVs other than the PI/r

Concordance

- All ISs predicted high levels of sensitivity to the PI/rs combined
- Slightly more patients had intermediate or full sensitivity to their PI/r according to the DMC compared to the other ISs
- When we looked at concordance between ISs for each PI/r individually we found that kappas ranged from 0.37 (REGA-DMC) to 0.72 (REGA-Stanford) for IDV/r; 0.46 (ANRS-DMC) to 0.93 (REGA-ANRS) for LPV/r; and 0.39 (ANRS- Stanford) to 0.70 (REGA-Stanford) for SQV/r (Figure 2). Where large kappas relate to good agreement and small kappas to poor agreement
- Overall ISs were concordant on the level of resistance to the PI/r for 296 (80%) patients. This increased to 89% when DMC was removed

Virological response

Median (IQR) baseline viral load was 4.7 (3.9 to 5.2) $\log_{10}$ cps/ml.

The median (IQR) decrease in viral load from baseline was:

- 1.8 (1.2 to 2.3) $\log_{10}$ cps/ml to **week 4**
- 2.3 (1.4 to 3.0) $\log_{10}$ cps/ml to **week 12**

Similar viral load reductions were seen for all of the PI/rs studied at both time-points

- Reductions in viral load between baseline and week 4 were associated with PI/r resistance levels ($p<0.10$ for all ISs), but not the number of other active drugs in the regimen in unadjusted analysis
- Reductions in viral load between baseline and week 12 were associated with both the PI/r resistance levels ($p<0.0001$ for all ISs) and the number of other active drugs in the regimen ($p<0.01$ for all ISs) in unadjusted analysis
- After adjustments, none of the ISs predicted viral load reductions to week 4 when looking at resistance to PI/r or the number of other active drugs in each patient's regimen at baseline (Figure 3)
- In multivariable analysis only DMC and Stanford showed significantly greater reductions as sensitivity to PI/r increased (Figure 4)
- Using Stanford, patients sensitive to the PI/r had a 0.82 greater $\log_{10}$ reduction between baseline and week 12 compared to patients with full resistance
- The number of other active drugs in the regimen did not predict response further

SUMMARY AND CONCLUSIONS

- Concordance between ISs was moderate
- Virological outcomes are used to test the clinical value of the ISs
- In our study baseline resistance to the PI/r did not show a difference in viral load responses until week 12
- A consensus needs to be reached on when we would expect resistance to impact on viral load response
- This study included patients with high levels of viral sensitivity, limiting our ability to assess the association with viral load response
- At week 12, the level of baseline resistance to the PI/r predicted a 0.8 log cps/ml difference between sensitive and resistant viruses after adjustments for baseline viral load, the number of other active drugs, gender and PI-naivity
- A surprising 1.3 log cps/ml reduction in viral load was still seen for patients with a fully resistant virus
- Potency of the PI/rs may be such that viral benefit is seen even in the presence of resistance
- ISs need to be improved so that they capture the magnitude of these viral load changes more accurately for PI/rs

ACKNOWLEDGEMENTS:

N Clumeck, K Kabeya, J Gerstoft, L Mathiesen, C Pedersen, C Katlama, P Dellamonica, F D Goebel, S Staszewski, G Panos, F Mulcahy, A d'Arminio Montforte, J N Bruun, A Horban, B Clotet, K Gyllensten, D Churchill, B Gazzard, C Leen, B Peters, M Johnson, M Youle, J Benetucci, P Cahn, I Cassetti, A Duran, A Rieger, H Nielsen, N Obel, J Lunzen, A Stoehr, G Carosi, A Lazzarin, S Geest, F Antunes, J Gatell, J.-P. Chave, A Telenti, P Vernazza, B Peters, J Lederman, A Castagna, A Hill, W Belloso, S Ivalo, D Pugliese, D Garone, A Krolewiecki, A Casiro, R Bologna, M. Losso, J Toibaro, B Vago, K Kabeya, C Cooper, S Dufresne, R Lalonde, S Walmsley, J Arnaiz, A Blaxhult, L Flamholc, M Gisslén, J Bingham, M Nelson, J Weber, G Scullard, I Brar, V Bouzi, A Brutus D T Jayaweera, M Mogyoros, B M Rodwick, D Stein, A Wiznia, R Schwartz, M G Vandenberg-Wolf, E Tedaldi, A Babiker, F Raffi, A N. Phillips, P Reiss, J D Lundgren, U B Dragsted, J Kjær, K B Jensen, A Fau Greve, A. Cozzi-Lepri, A Mocroft, A Phillips, C Sabin, C Smith, D Puradiredja, E Harris, F Lampe, L Bansi, S Shah, T Hill, W Bannister

CHIP COPENHAGEN HIV PROGRAMME

Figure 1

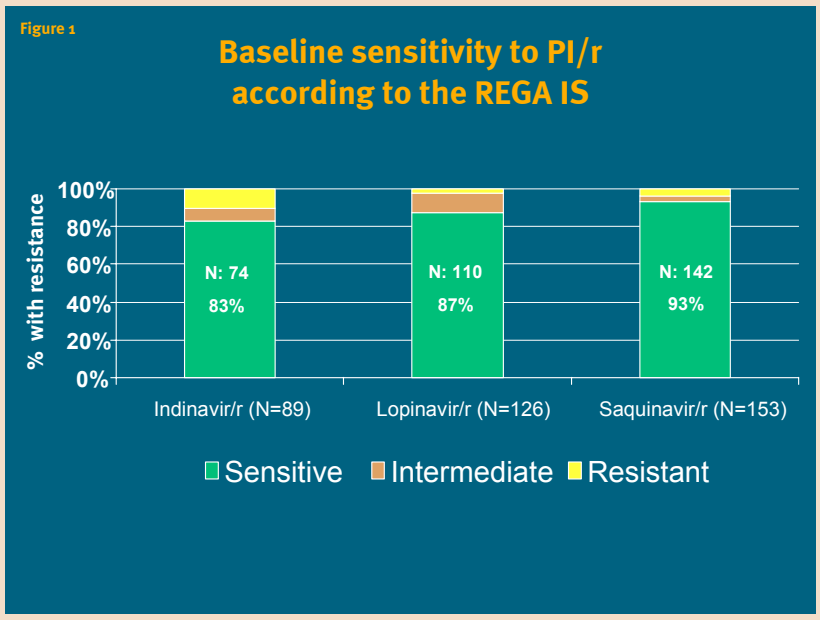


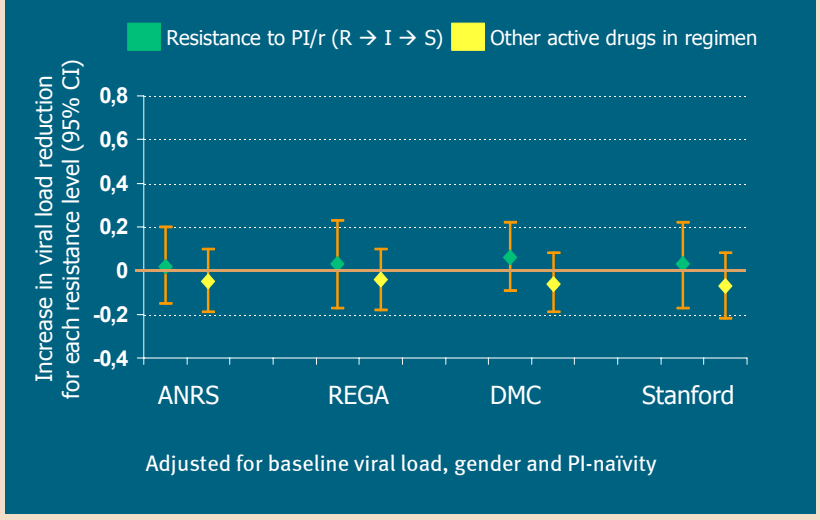
Figure 2

Concordance between ISs - Kappas

		REGA	DMC	Stanford
IDV/r	ANRS	0.68	0.43	0.67
	REGA	-	0.37	0.72
	DMC	-	-	0.49
LPV/r	ANRS	0.93	0.46	0.57
	REGA	-	0.54	0.64
	DMC	-	-	0.66
SQV/r	ANRS	0.51	0.42	0.39
	REGA	-	0.56	0.70
	DMC	-	-	0.60

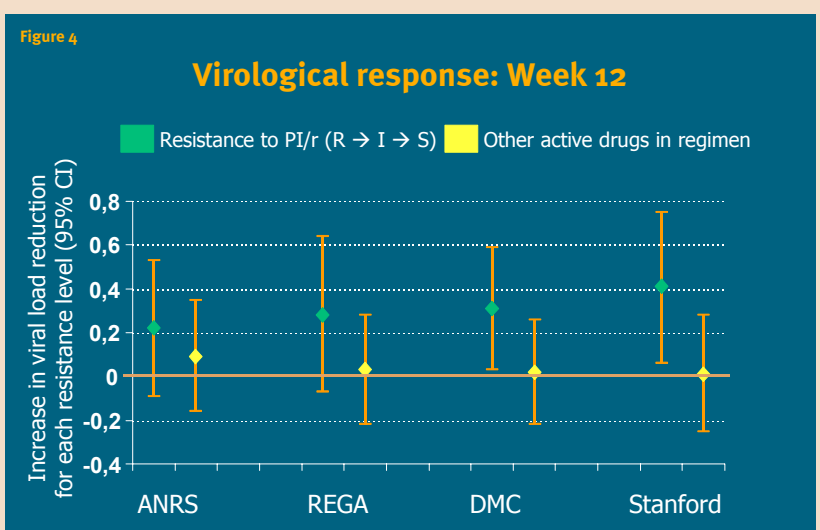
For 296 (80%) patients, ISs were concordant on the level of resistance to the PI/r combined

Figure 3



Adjusted for baseline viral load, gender and PI-naïvity

Figure 4



Adjusted for baseline viral load, gender and PI-naïvity

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