The ability of four genotypic resistance algorithms to predict HIV-RNA response 4-24 weeks after initiating a boosted PI containing regimen

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BACKGROUND

- Genotypic interpretation systems (GIS) are used to translate lists of mutations into a sensitivity score for each antiretroviral (ARV)

- ARVs are usually assigned a sensitivity 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 summed to generate an overall genotypic sensitivity score (GSS) for the regimen

- Ritonavir has been used to boost levels of other protease inhibitors (PIs) since the late 1990s

- There is limited information available on the prognostic value of GISs for patients receiving ritonavir-boosted protease inhibitors (PI/r)

OBJECTIVES

- To compare PI/r resistance levels using four GISs and relate these levels to viral load reductions from PI/r initiation (baseline) to the first viral load measurement between 4 and 24 weeks

- To assign a GSS to the rest of the regimen (i.e. excluding the PI/r) and explore the relationship between this GSS and virological response

DATA

- EuroSIDA is a prospective, observational cohort of 11,928 HIV-1 infected patients from 83 centres across 28 European countries, Israel and Argentina

- EuroSIDA patients who started a single PI/r were included in the analysis if they had genotyping performed on plasma samples (viral load >500 cps/ml) in the year prior to starting the PI/r

METHODS

- Each sequence of mutations was run through the following GISs:

  - **REGA**: Dec. 2004, version 6.4
  - **ANRS**: Sept. 2005, version 13
  - **Detroit Medical Center (DMC):** Oct. 2004
  - **Stanford University:** May 2006, version 4.2.0

- Neither DMC or Stanford had interpretations for all of the PI/rs investigated in this study so the interpretations for the unboosted PI were used instead

- Concordance between PI/r resistance levels was evaluated using kappa statistics

- Factors associated with viral load change were identified through censored regression analysis

RESULTS

- Baseline HIV-1 genotypic resistance tests were available for 376 patients [55 indinavir/r (15%), 231 lopinavir/r (61%), 33 saquinavir/r (9%), 28 amprenavir/r (7%) and 29 atazanavir/r (8%)]

- Every GIS predicted high levels of sensitivity to the PI/r received at baseline

- Using REGA 68 (18%) patients had a virus with intermediate or full resistance to the PI/r they received [10 (18%), 44 (19%), 3 (9%), 9 (32%) and 2 (7%) patients had a virus with resistance/intermediate resistance to indinavir/r, lopinavir/r, saquinavir/r, amprenavir/r and atazanavir/r respectively]

- More patients were deemed to have a virus with resistance/intermediate resistance to the PI/r received using either the DMC or Stanford GIS (Figure 1)

- There were 197 (52%) patients overall who had a virus that was susceptible to ≥ 2 Non-PI ARVs using the REGA GIS. Similar numbers were found using the other GISs (data not shown)

Concordance

- Kappa statistics to evaluate concordance ranged from 0.48 to 0.79 for indinavir/r; 0.34 to 0.77 for lopinavir/r; 0.30 to 0.57 for saquinavir/r; 0.01 to 0.38 for amprenavir/r; and 0.31 to 1.00 for atazanavir/r (Table 1)

Virological response

- Median (IQR) baseline viral load was 4.0 (3.2 to 4.9) $\log_{10}$ cps/ml

- After a median (IQR) 13 (9 to 17) weeks from the start of the PI/r-containing regimen this was reduced by a mean 1.8 (95% CI: 1.7 to 1.9) $\log_{10}$ cps/ml

- Mean viral load reductions were 1.3 (0.8 to 1.8), 1.4 (1.0 to 1.8) and 1.9 (1.8 to 2.1) $\log_{10}$ cps/ml for viruses that were resistant, intermediate resistant and sensitive to the PI/r using the REGA GIS

- After adjustments for baseline viral load, the time between baseline and follow-up viral load values and also for the time between baseline resistance test and the date of PI/r initiation all GISs showed significantly greater reductions as sensitivity to the PI/r increased (p<0.01 in all cases) in a censored regression analysis that takes into account the partial observation of reduction

- Using Stanford, patients sensitive to the PI/r had a 0.84 greater $\log_{10}$ reduction from baseline compared to patients with full resistance

- The GSS to the rest of the regimen (i.e. all ARVs excluding the PI/r) was not a predictor of response (Figure 2)

- We also restricted the analysis to the 301 (80%) PI-experienced patients. This group experienced smaller HIV-RNA reductions but with more noticeable differences between PI/r resistance levels

Figure 1

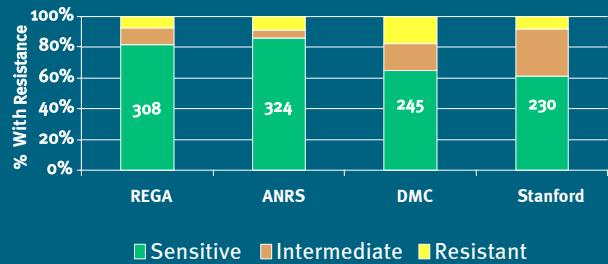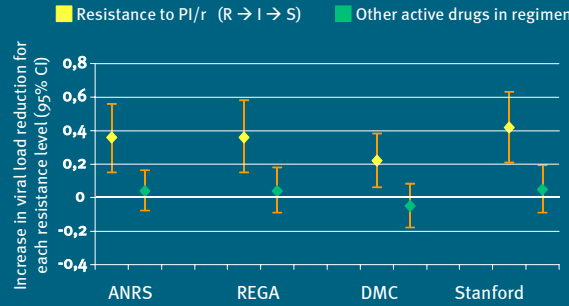**Baseline sensitivity to the PI/rs combined according to each GIS**

(Bar chart — % With Resistance by GIS: REGA 308, ANRS 324, DMC 245, Stanford 230; categories: Sensitive, Intermediate, Resistant)

Table 1

Concordance between ISs - Kappas

		REGA	DMC	Stanford
IDV/r	ANRS	0.65	0.48	0.68
	REGA	-	0.67	0.79
	DMC	-	-	0.52
LPV/r	ANRS	0.77	0.36	0.34
	REGA	-	0.50	0.48
	DMC	-	-	0.65
SQV/r	ANRS	0.57	0.31	0.30
	REGA	-	0.35	0.45
	DMC	-	-	0.47
AMP/r	ANRS	0.18	0.17	0.08
	REGA	-	0.06	0.01
	DMC	-	-	0.38
ATZ/r	ANRS	1.00	0.31	0.35
	REGA	-	0.31	0.35
	DMC	-	-	0.92

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 yellow the lowest

Figure 2

Differences in HIV-RNA reductions from baseline to weeks 4-24

(Plot — Increase in viral load reduction for each resistance level (95% CI) for ANRS, REGA, DMC, Stanford; Resistance to PI/r (R → I → S), Other active drugs in regimen)

Analyses are adjusted for the PI/r used, baseline HIV-RNA, time between baseline and follow-up HIV-RNA and time between baseline resistance test and date of PI/r initiation

SUMMARY AND CONCLUSIONS

- Overall concordance between GISs was moderate

- The highest concordance was between REGA and ANRS for lopinavir/r, saquinavir/r and atazanavir/r

- The lowest concordance between predicted resistance levels existed for amprenavir/r

- Viral load reductions of >1 $\log_{10}$ cps/ml were still seen for patients with a virus deemed fully resistant according to each GIS. This suggests that either PI/rs exert antiviral effects in the presence of resistance or that the nucleoside backbone actively reduces viral load despite PI/r resistance

- GISs need further refinement so there is better agreement between them and they capture the magnitude of viral load changes observed when using ritonavir boosted PIs more accurately