Initiatives for developing and comparing genotype interpretation systems Step 1: External validation of existing rules-besed algorithm for abacavit and ddI evaluated on virologic response

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The Forum for Collaborative HIV Research is a coalition including government, industry, academia, advocy and foundations, with the mission to enhance and facilitate HIV research.

Objective

- The Forum for Collaborative HIV Research has set up an initiative to investigate the relationship of baseline genotype interpreted by different algorithms with virologic outcome for ddI and abacavir.
- An analysis plan was developed and investigators contributed data to create a large database.

Inclusion criteria

- Drug experienced people starting a new regimen including the drug under consideration (being used for the first time) were eligible for inclusion if
  - Virologically failed the previous regimen
  - <12 weeks before start of the new regimen while on the previous regimen
    - genotype resistance test
    - VL >500 copies/ml
  - VL measured between 4-12 weeks from the start
  - No changes in therapy
  - No evidence of inadequate adherence

Interpretation systems evaluated

- For both ddI and abacavir
  - ANRS V12, Detroit Medical Center-3 (DMC-3), Stanford HIV RT and PR Sequence Database-8 (HIVDB-8), Rega 6.3, Sao Paulo 4.0, VGI V10.0
- For abacavir
  - CHL 4.4, Retrogram 1.6

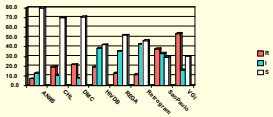
Analysis plan

- Change from baseline in viral load at 8 weeks (4-12 weeks), accounting for the censoring of VL measurements due to assay lower limits by use of a program designed for parametric survival analysis models (PROC LIFEREG in SAS, using the DIST=NORMAL option)
- For each interpretation system, a regression model was fitted with the following covariates:
  - Sensitivity (S, I, R with R as the base)
  - Baseline VL
  - Number of other drugs in the new regimen to which viruses are sensitive using either ANRS or Rega or HIVDB
- See analysis plan at (http://www.hivforum.org/analysis_collab.html)

Data Sources

- 9 sources
  - Adult AIDS Clinical Trials Group, USA;
  - British Columbia Cohort , Canada;
  - EuroSIDA , Europe;
  - I.Co.N.A , Italy;
  - Narval ANRS 88, France;
  - Swiss HIV Cohort Study, Switzerland;
  - Stanford HIV Database, USA;
  - Catholic University Sacro Cuore (UCSC), Italy;
  - UK National Resistance Database , UK
- Abacavir N=583
  - change in VL: -1.6 $\log_{10}$ copies/ml
- ddI N=400
  - change in VL: -1.8 $\log_{10}$ copies/ml

Results abacavir - I



Results abacavir - II

	R	I Meanchange in VL relative to R (95% CI)	S Meanchange in VL relative to R (95% CI)	P value I/R and S/R
ANRS	0.00	**+0.64** (+0.18;+1.11)	**+0.66** (+0.26;+1.05)	0.007/0.001
CHL	0.00	+0.19 (+0.33;+1.08)	+0.22 (-0.04;+0.48)	+0.001/0.10
DMC	0.00	+0.24 (+0.04;+0.90)	+0.20 (-0.08;+0.42)	0.03/0.19
HIVDB	0.00	+0.46 (+0.20;+0.76)	+0.07 (-0.21;+0.35)	+0.001/0.62
REGA	0.00	+0.56 (+0.25;+0.91)	+0.20 (-0.11;+0.53)	+0.001/0.20
RetroGram	0.00	+0.14 (-0.20;+0.48)	+0.06 (-0.40;+0.27)	0.42/0.71
SaoPaulo	0.00	+0.19 (-0.16;+0.37)	+0.09 (-0.47;+0.07)	0.45/0.15
VGI	0.00	+0.17 (+0.05;+0.68)	+0.07 (-0.26;+0.22)	0.02/0.88

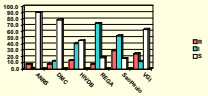
adjustedon VL and nb of activedrugs usingANRS rules

Impact of specific differences in mutations between interpretation systems

Among the 465 patients classified as 'S' by ANRS:

- if 'S' for ANRS and number of RT mutations=0(n=145)
  - ±thesarethose with the worst response possibly because of nonadherence
- if 'S' for ANRS and number of RT mutations >=1(N=170)
  - ± Mean numberof TAMS = 0.6; 6%with 184V
  - ± Thesehavebetter response than A more adherent= low resistance
- if 'S' for ANRS but 'I' for Rega and number of RT mutations >=1 (n=150)
  - ± Mean numberof TAMS = 2.5; 64% with 184V
  - ± Those have better response than R and are classified by Rega as intermediate resistance to abacavir
  - ± Indeed t he presence of >=3 TAMS or 184V+ >=1 TAM in Rega is a rule for intermediate resistance
  - ± In contrast, in ARNS the rule is to have 4 among 41, 67, 74, 184, 210 and 215 so 70 and 219 are not considered
- Our results seem to suggest that its better to leave 70 and 219 out of the rule for intermediate resistance and in general to give less weight to TAMS + 184

Results ddI - I

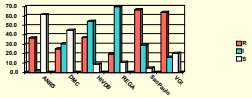


Results ddI - II

	R	I Meanchange in VL relative to R (95% CI)	S Meanchange in VL relative to R (95% CI)	P value I/R and S/R
ANRS	0.00	-0.05 (-1.16;+1.09)	+0.28 (-0.20;+0.77)	0.955/0.256
DMC	0.00	-0.11 (-0.68;+0.47)	+0.12 (-0.36;+0.61)	0.718/0.618
HIVDB	0.00	+0.02 (-0.39;+0.43)	-0.09 (-0.51;+0.33)	<0.915/0.665
REGA	0.00	+0.20 (-0.29;+0.68)	-0.07 (-0.62;+0.48)	0.425/0.816
SaoPaulo	0.00	+0.22 (-0.09;+0.52)	-0.12 (-0.53;+0.28)	0.171/0.550
VGI	0.00	+0.17 (-0.28;+0.62)	+0.02 (-0.30;+0.34)	0.456/0.890

adjustedon VL and nb of activedrugs usingANRS rules

Analysis in patients previously exposed and not exposed to ddI (Narval, n=300) - I



Analysis in patients previously exposed and not exposed to ddI (Narval, n=300) - II

	R	I Meanchange in VL relative to R (95% CI)	S Meanchange in VL relative to R (95% CI)	P value I/R and S/R
ANRS	0.00	-0.86 (-1.97;+0.21)	+0.36 (+0.03;+0.70)	0.114/0.035
DMC	0.00	**+0.08** (-0.34;+0.51)	**+0.45** (+0.04;+0.86)	0.702/0.032
HIVDB	0.00	+0.47 (+0.13;+0.80)	+0.44 (-0.17;+1.05)	0.007/0.161
REGA	0.00	+0.05 (-0.35;+0.45)	+0.39 (-0.20;+0.98)	0.810/0.197
SaoPaulo	0.00	+0.56 (+0.21;+0.91)	+0.52 (-0.24;+1.28)	0.002/0.180
VGI	0.00	+0.85 (+0.42;+1.28)	+0.43 (+0.02;+0.83)	<0.001/0.038

adjustedon VL and nb of activedrugs usingANRS rules

Conclusion

- Importance of external validation using virologic response as an outcome criteria of existing interpretation systems
- need for collaborative work
  - Importance of a large dataset and of the level of resistance in the dataset
  - Importance of developing innovative statistical approaches to improve the interpretation systems

Acknowledgments

- To all data providers
- To all interpretation system providers