Initiatives for developing and comparing genotype interpretation systems: An updated analysis of validation of existing rules-based algorithm for abacavir and ddI evaluated on virologic response

D Costagliola[1], A Cozzi-Lepri[2], KL Assoumou[1], B Cheng[3], on behalf of the Standardization and Clinical Relevance of HIV Drug Resistance Testing Project from the Forum for Collaborative HIV Research

1 INSERM U 720 and University Pierre et Marie Curie, Paris, France, 2 Royal Free and University College Medical School, London, UK, 3 Forum for Collaborative Research, The George Washington University, Washington, USA

Objective

- The Forum for Collaborative HIV Research initiated a study to investigate the relationship between baseline genotype interpreted by different algorithms and virologic outcome for ddI and abacavir.
- Here, we update analyses reported last year using larger datasets which now include patients previously treated with the drug in question and using updated algorithms, where available.

Inclusion criteria

- Drug experienced people starting a new regimen including the drug under consideration 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
- Patients were eligible whether they were or not previously exposed to the drug under study

Interpretation systems evaluated

- For both ddI and abacavir
  - ANRS V13, Detroit Medical Center-3 (DMC-3), Stanford HIV RT and PR Sequence Database (HIVDB-1.4.4), Rega 6.4, Sao Paulo 4.0, Bayer V10.0
- For abacavir
  - CHL 4.4, Retrogram 1.6 and Quest

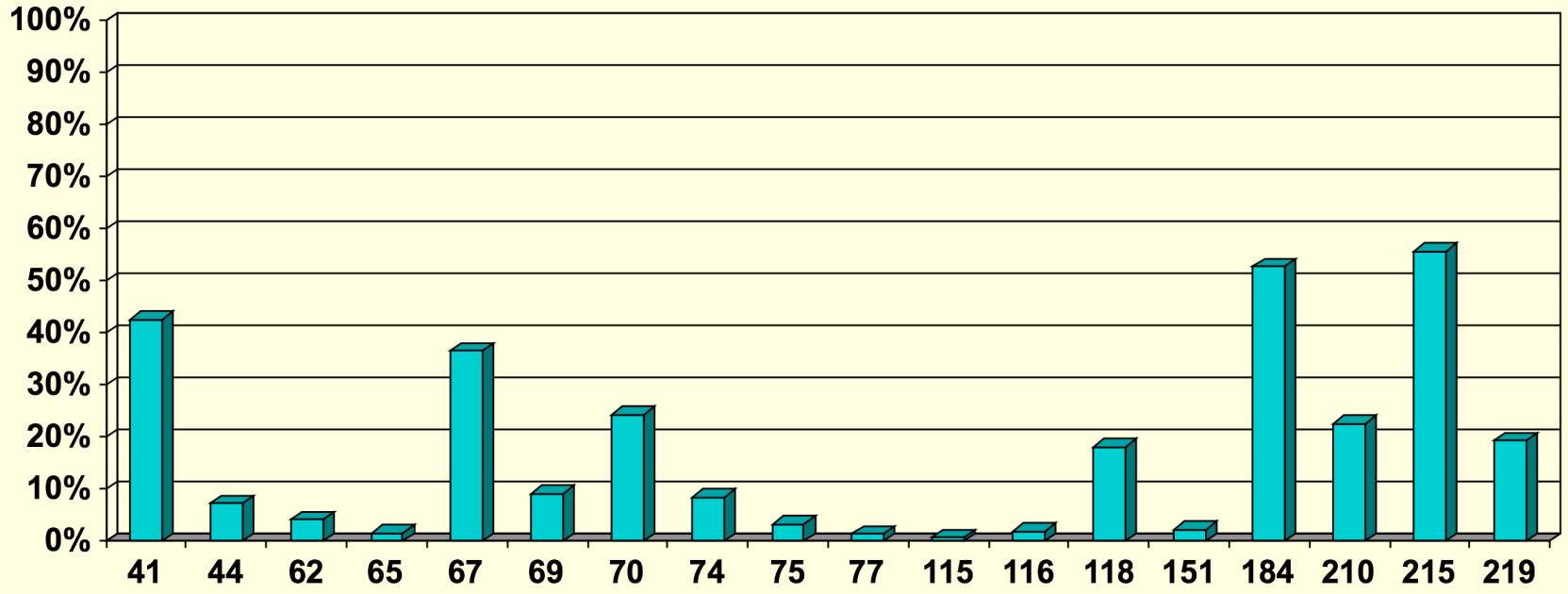
Analysis plan

- 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)

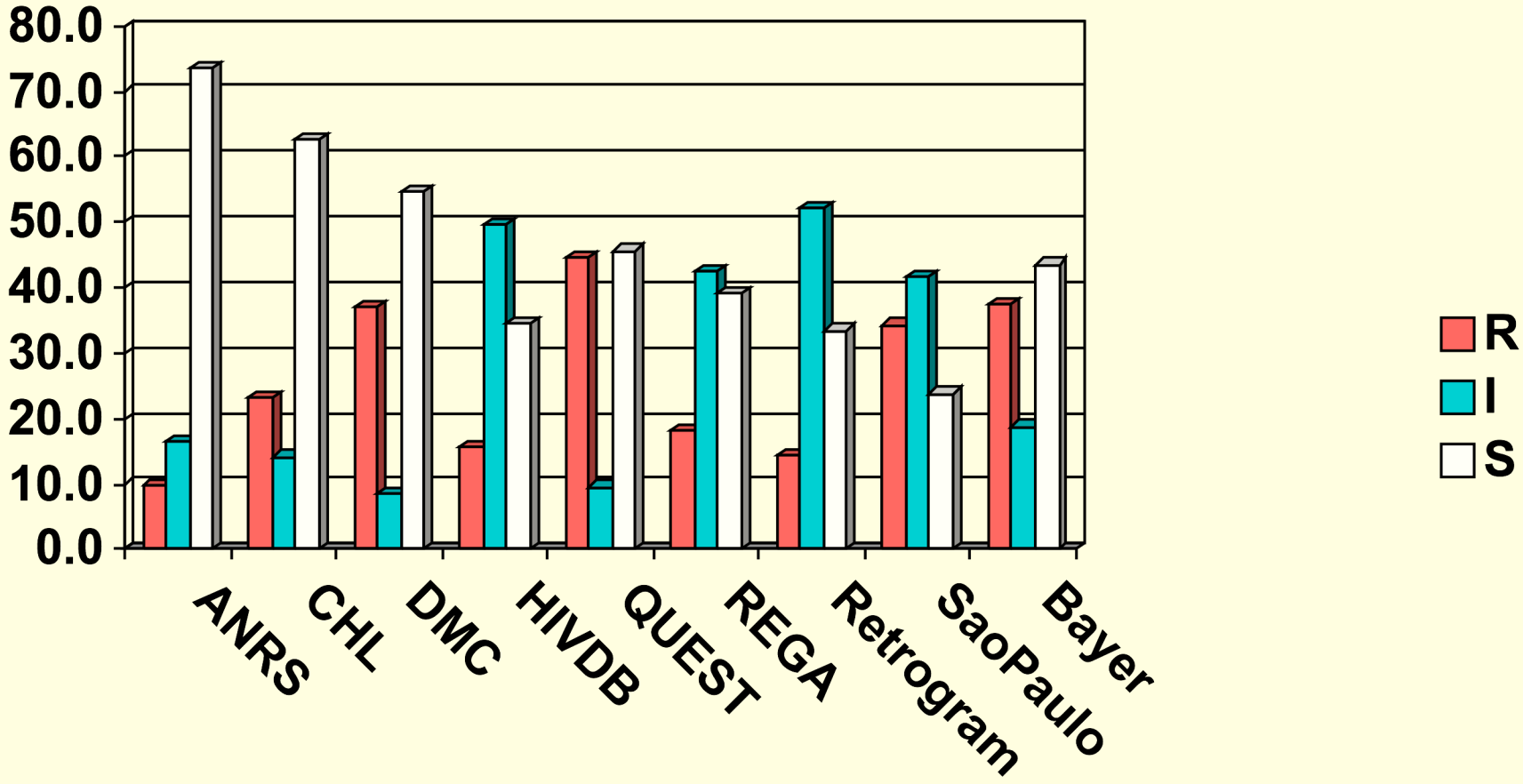
Data Sources

- 17 sources
  - Aquitaine cohort, France;
  - Adult AIDS Clinical Trials Group, USA;
  - ARCA, Italy;
  - British Columbia Cohort , Canada;
  - CNA GSK Trials
  - EuroSIDA, Europe;
  - I.Co.N.A., Italy;
  - IDIBAPS Barcelona Hospital Clinic cohort, Spain;
  - Jaguar trial BMS France;
  - Narval ANRS 88, France;
  - National Institute of Allergy and Infectious Disease (NIAID), USA;
  - Ramon Y Cajal Madrid Hospital, Spain;
  - Swiss HIV Cohort Study, Switzerland;
  - Stanford HIV Database, USA;
  - Catholic University Sacro Cuore (UCSC), Italy;
  - UK National Resistance Database , UK
  - US Military HIV Research program, USA.
- Abacavir N=1,230
  - VL 4.3 (3.8-5.0), mean change in VL: -1.6 $\log_{10}$ copies/ml
- ddI N=1,455
  - VL 4.3 (3.7-4.9), mean change in VL: -1.3 $\log_{10}$ copies/ml

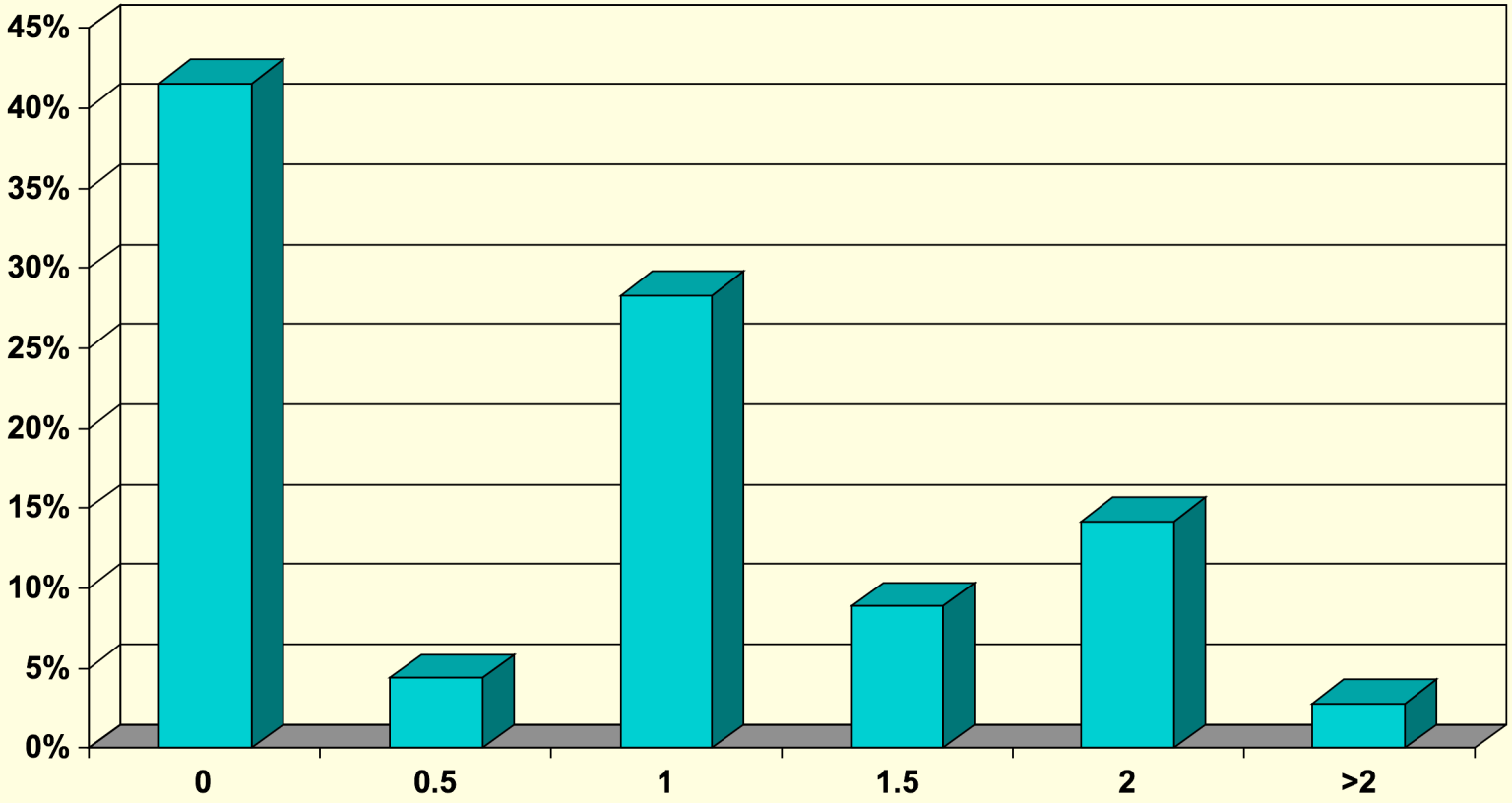
Prevalence of IAS NRTI mutations at baseline in the abacavir dataset



Level of resistance to abacavir according to system



Number of active drugs in regimen besides abacavir



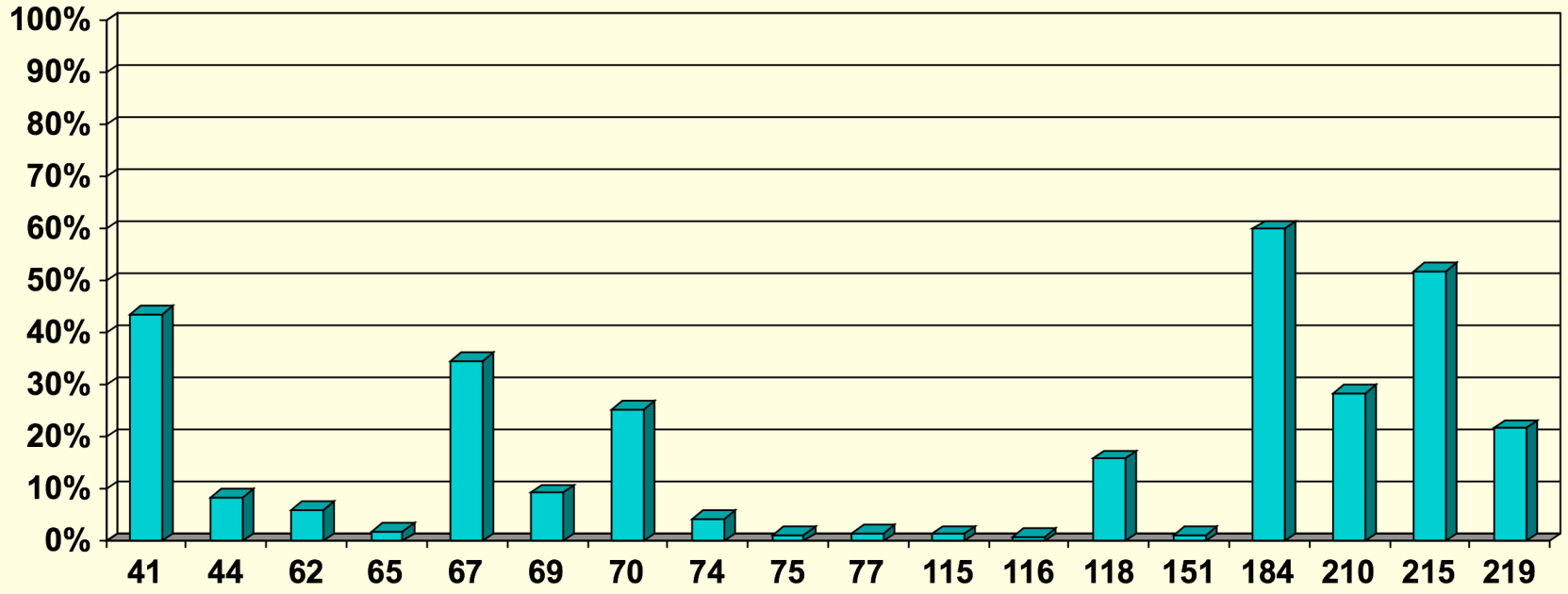
Using the ANRS system

Evaluation of interpretation systems for abacavir

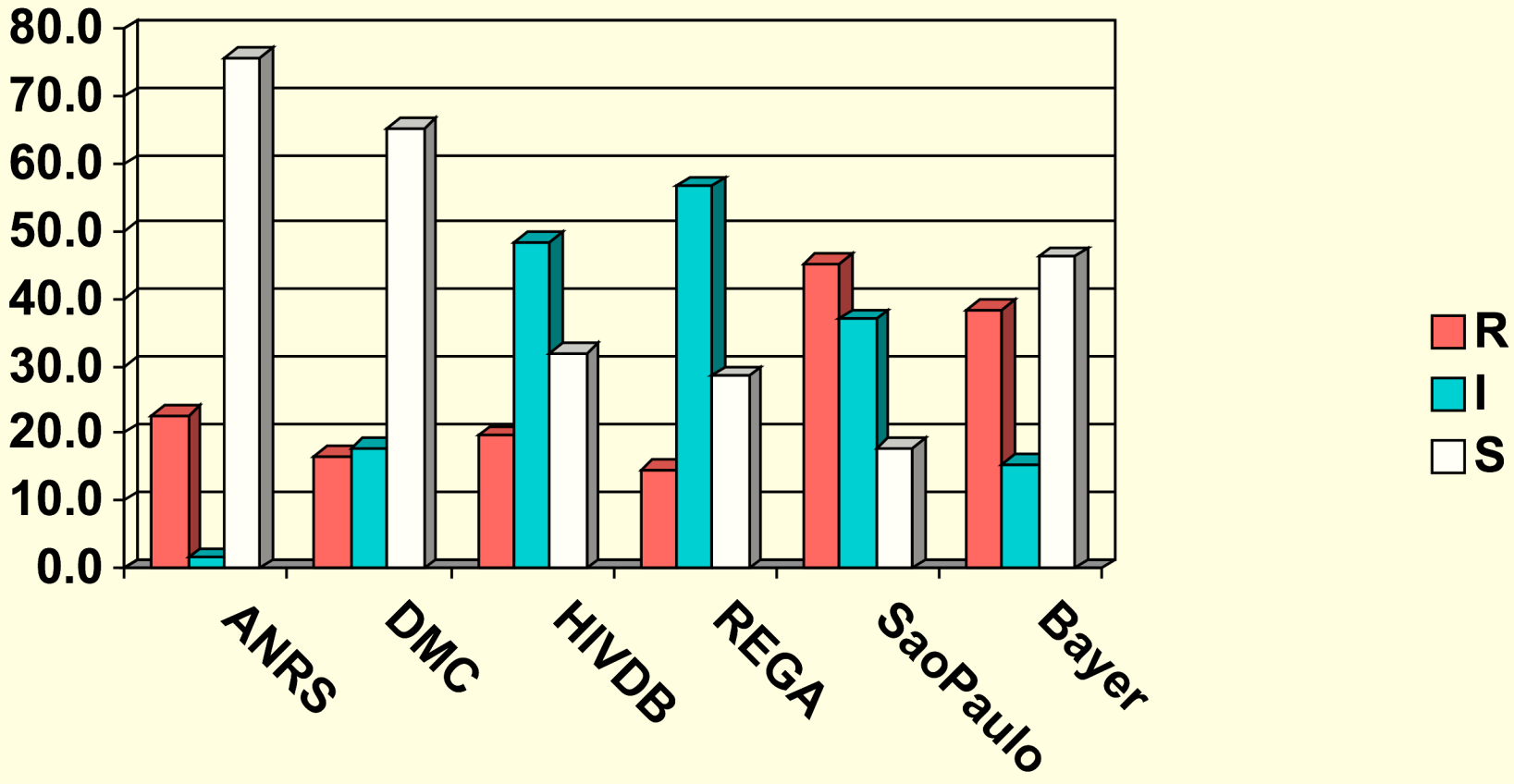
	R	I Mean change in VL relative to R* (Crude change)	S Mean change in VL relative to R* (Crude change)	P value I/R and S/R
ANRS	0.00 (-0.41)	**+0.47** **(-1.38)**	**+0.64** **(-1.68)**	0.001/0.0001
CHL	0.00 (-1.06)	+0.46 (-1.72)	+0.41 (-1.70)	0.0001/0.0001
DMC	0.00 (-1.21)	+0.45 (-1.73)	+0.37 (-1.69)	0.0001/0.0005
HIVDB	0.00 (-0.69)	**+0.45** **(-1.56)**	**+0.73** **(-1.85)**	0.0001/0.0001
QUEST	0.00 (-1.40)	+0.07 (-1.35)	+0.31 (-1.73)	0.55/0.0001
REGA	0.00 (-0.76)	+0.52 (-1.66)	+0.61 (-1.75)	0.0001/0.0001
RetroGram	0.00 (-1.21)	+0.15 (-1.56)	+0.29 (-1.76)	0.14/0.008
SaoPaulo	0.00 (-1.38)	**+0.16** **(-1.61)**	**+0.39** **(-1.83)**	0.05/0.0001
Bayer	0.00 (-1.35)	**+0.21** **(-1.45)**	**+0.42** **(-1.76)**	0.03/0.0001

*adjusted for VL and number of active drugs using ANRS rules
Positive estimates from the model indicate a larger difference in reduction in log viral load

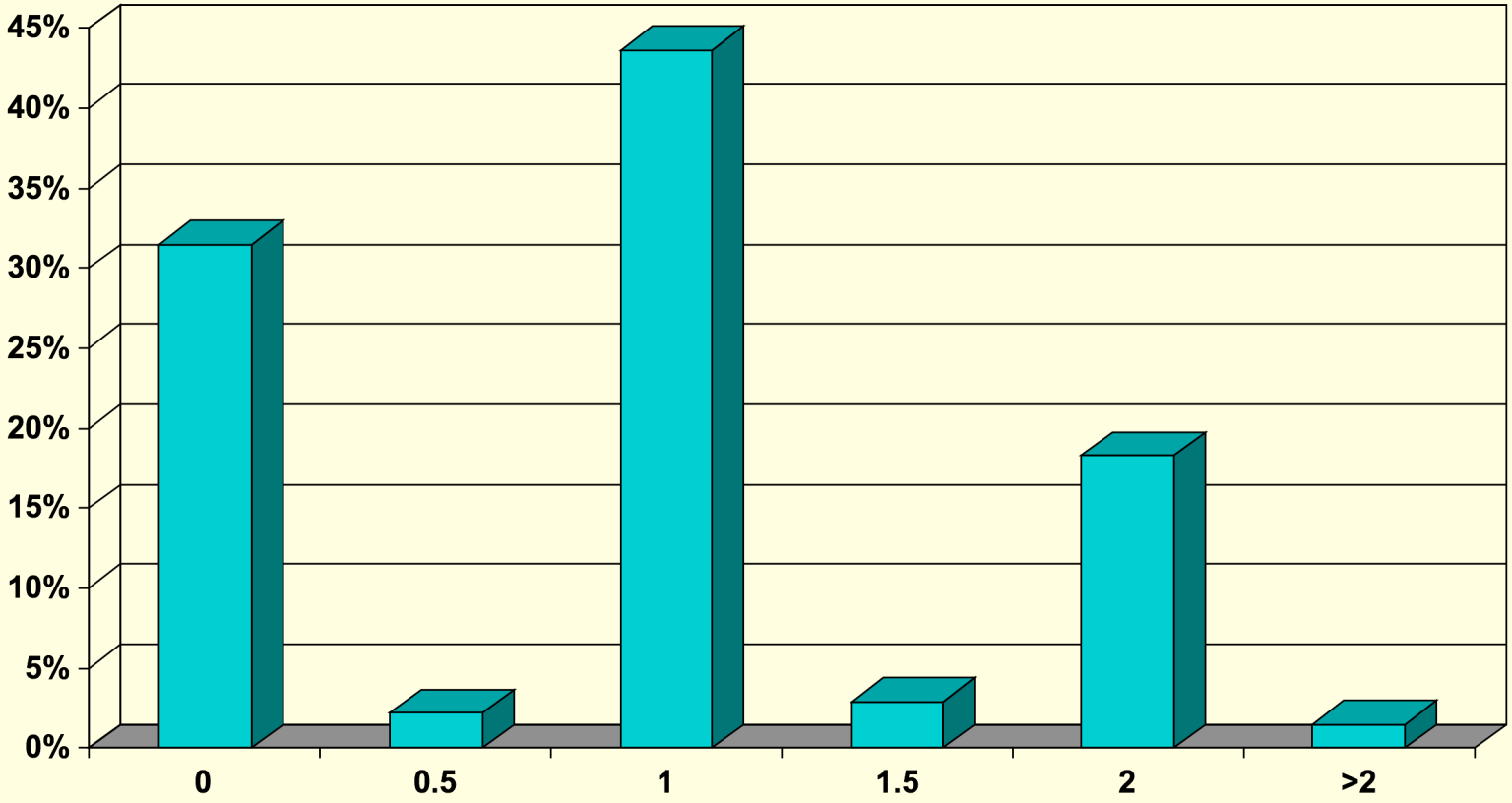
Prevalence of IAS NRTI mutations at baseline in the ddI dataset



Level of resistance to ddI according to system



Number of active drugs in regimen besides ddI



Using the ANRS system

Evaluation of interpretation systems for ddI

	R	I Mean change in VL relative to R* (Crude change)	S Mean change in VL relative to R* (Crude change)	P value I/R and S/R
ANRS	0.00 (-0.98)	+0.33 (-1.31)	+0.34 (-1.35)	0.18/<0.0001
DMC	0.00 (-0.93)	0.00 (-1.01)	+0.34 (-1.36)	0.96/<0.0001
HIVDB	0.00 (-0.94)	**+0.22** **(-1.19)**	**+0.37** **(-1.45)**	0.0032/<0.0001
REGA	0.00 (-1.04)	+0.09 (-1.23)	+0.15 (-1.31)	0.27/0.10
SaoPaulo	0.00 (-1.04)	+0.25 (-1.35)	+0.27 (-1.42)	0.0001/0.0005
Bayer	0.00 (-0.98)	+0.30 (-1.31)	+0.33 (-1.39)	0.0004/<0.0001

*adjusted for VL and number of active drugs using ANRS rules
Positive estimates from the model indicate a larger difference in reduction in log viral load

Conclusion

- Several of the systems performed well for abacavir. For ddI, several systems had trouble discriminating between either I and S or I and R, while discriminating well between R and S.
- Power to discriminate among R, S and I improved in comparison to previous analyses reflecting the expansion of the database.
- There remains substantial discordance between interpretation systems (even those performing well) for both abacavir and ddI.
- These results show that with a large enough dataset and adequate distribution of resistance levels, the performance of interpretations systems for identifying abacavir and ddI resistance can be evaluated.

Acknowledgments

- To all data providers
- To all interpretation system providers

Project Structure

- Chairs: D. Kuritzkes and V. Miller
- Sub-group planning committee chairs:
  - Genotypic algorithms: Françoise Brun-Vezinet and Andrew Zolopa
  - Phenotypic cut-offs: Richard Haubrich and Joe Eron
  - Technology and standardization: Lisa Demeter and Rob Schuurman
  - Analysis: Victor DeGruttola, Dominique Costagliola and Andrew Phillips