Poster 96

7th European HIV Drug Resistance workshop, 25-27 March 2009, Stockholm, Sweden

Rules-Based HIV-1 Genotypic Resistance Interpretation Systems Predict 8-week and 24-week Virological Antiretroviral Treatment Outcome and Benefit from Drug Potency Weighting

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BACKGROUND

Genotypic antiretroviral resistance testing is an integral part of the current monitoring of HIV-1 infected patients. While the use of novel, totally data-driven systems is being explored with encouraging results, interpretation of HIV-1 genotypic drug resistance in clinical practice still relies on rules-based expert algorithms.

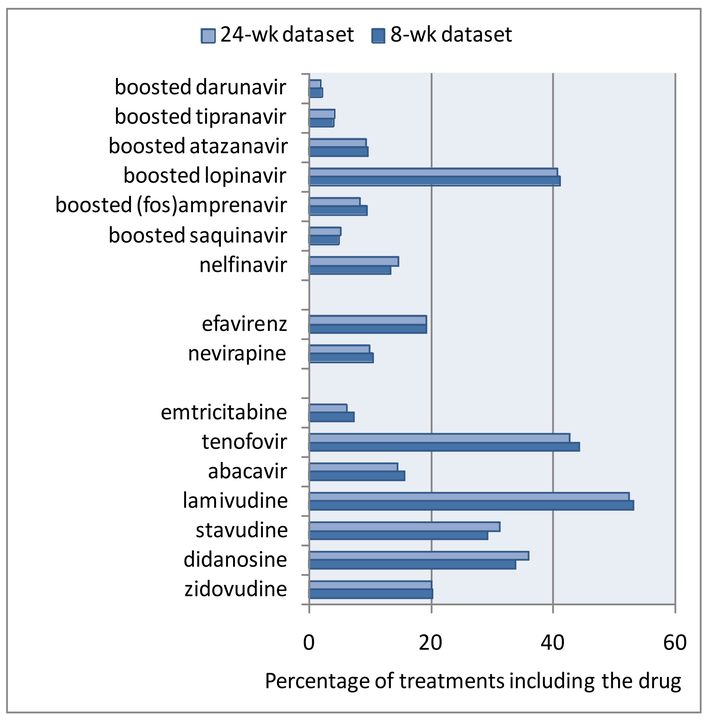
To be used with confidence, a genotypic interpretation system (GIS) must be periodically validated to ensure its reliability along with algorithm updates and changes in treatment strategies. In this work, a large dataset of HIV-1 genotypes coupled with short and medium-term virological treatment response data was used to test the performance of four recently updated GISs available over the internet as lists of interpretation rules or full-fledged programs.

METHODS

The HIV-1 GISs HIVdb 5.0.0, ANRS 17, Rega 7.1.1 and AntiRetroScan 2.0 were tested for their accuracy in predicting response to highly active antiretroviral therapy using 8-week (n = 765) and 24-week (n = 634) follow-up standardized treatment change episodes (TCEs) extracted from the ARCA (www.hivarca.net) database. Short-term treatment outcome was dichotomized into success and failure based on achievement and failure to achieve an undetectable viral load or at least a 2-log decrease in viral load at 8 (4-12) weeks. Medium-term success and failure were defined as achieving and not achieving an undetectable viral load at week 24 (16-32). A genotypic sensitivity score (GSS) was derived for each genotype-treatment pair for the different GISs and tested as a predictor of virological treatment outcome by univariate and multivariate logistic regression as well as by receiver operating characteristic curve (ROC) analysis. Since the Rega and AntiRetroScan systems have recently implemented drug potency weighting factors, these algorithms were additionally tested without weights to check whether this approach actually improves their performance.

RESULTS

Distribution of NRTIs, NNRTIs and PIs in the 8-week and 24-week treatment response datasets. Only treatments made of drugs considered by all the four algorithms were selected for analysis. Virological outcomes of first-line therapy on drug-naïve patients were excluded in order to build a more challenging dataset.



Crude and adjusted odds ratios for virological success depending on the different genotypic sensitivity scores (GSSs). Odds ratio values are per unit increase of each GSS.

GSS	8-week dataset[a]		24-week dataset[a]	
	Crude OR (95% CI)	Adjusted OR[b] (95% CI)	Crude OR (95% CI)	Adjusted OR[c] (95% CI)
HIVdb	**2.39 (2.01 – 2.85)**	**2.15 (1.77 – 2.61)**	**2.21 (1.83 – 2.67)**	**2.02 (1.62 – 2.52)**
AntiRetroScan	**2.49 (2.10 – 2.95)**	**2.26 (1.88 – 2.73)**	**2.52 (2.09 – 3.06)**	**2.31 (1.86 – 2.86)**
ANRS	**2.31 (1.93 – 2.75)**	**2.13 (1.76 – 2.59)**	**2.25 (1.85 – 2.73)**	**2.12 (1.70 – 2.66)**
Rega	**2.29 (1.93 – 2.71)**	**2.06 (1.71 – 2.46)**	**2.28 (1.88 – 2.76)**	**2.09 (1.67 – 2.60)**

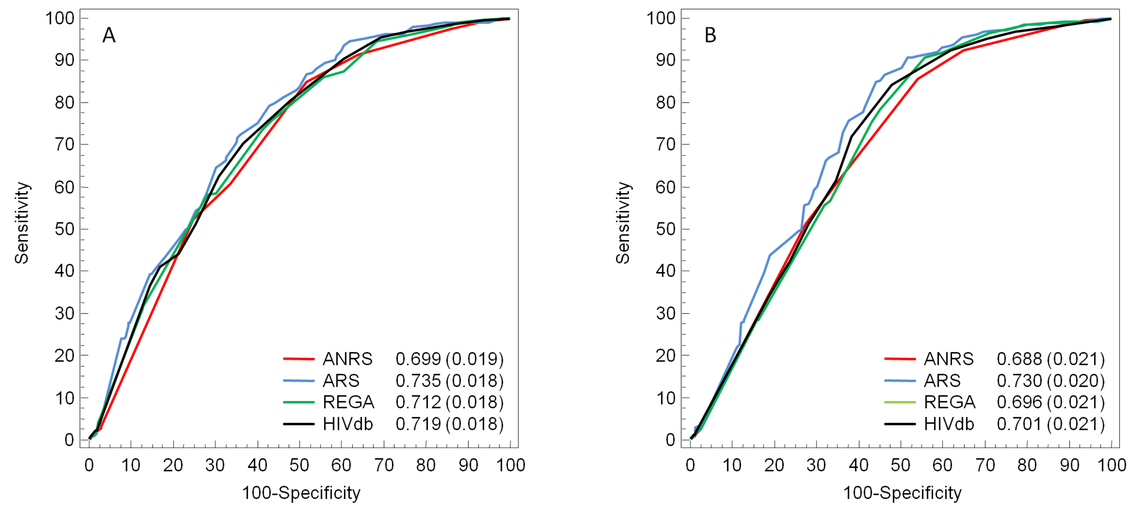
[a]All P values < .0001.

[b]Additional significant predictors of success include older age (all GSSs) and undergoing a protease inhibitor-based treatment switch (HIVdb). Additional significant predictors of failure include a larger number of previously used protease inhibitors (all GSSs) and a higher baseline viral load (AntiRetroScan).

[c]Additional significant predictors of success include older age and undergoing a protease inhibitor-based treatment switch (all GSSs). Additional significant predictors of failure include a higher baseline viral load and a larger number of previously used protease inhibitors (all GSSs).

RESULTS — *continued*

Receiver Operating Characteristic curves for the four genotypic sensitivity scores as predictors of treatment success at 8 (A) and 24 (B) weeks. The inserts show the values of the area under the curve with its standard error in parentheses. ARS, AntiRetroScan.



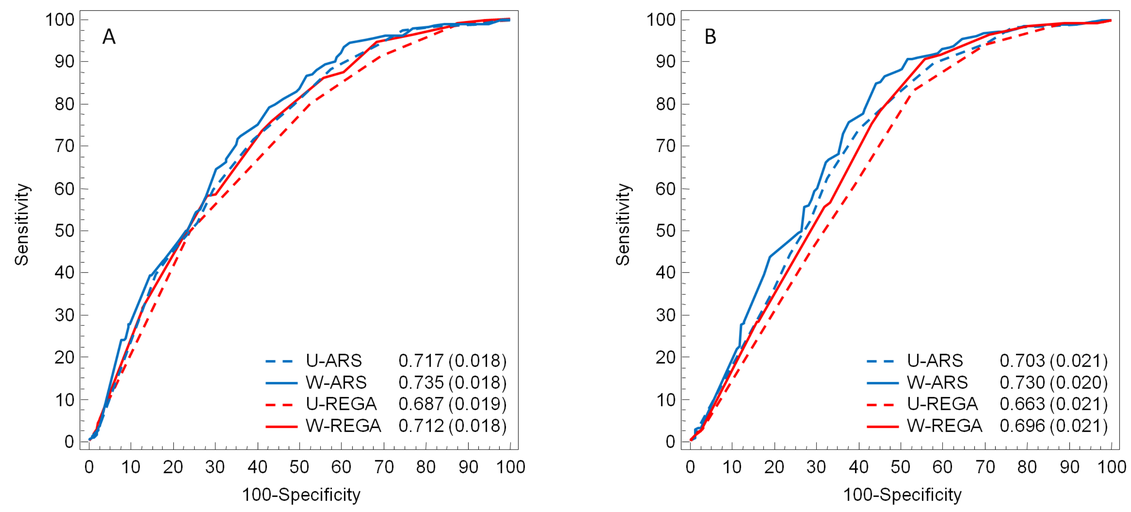
Significant differences at week 8: P = .001 for ARS vs. ANRS; P = .016 for ARS vs. Rega; P = .045 for ARS vs. HIVdb; P = .048 for HIVdb vs. ANRS.

Significant differences at week 24: P < .001 for ARS vs. ANRS; P = .003 for ARS vs. HIVdb; P = .004 for ARS vs. Rega.

The apparently higher accuracy of AntiRetroScan with respect to the other GISs is entirely driven by a better performance with PI-based treatments

GSS	8-week AUC (standard error)		24-week AUC (standard error)	
	NNRTI-based	PI-based	NNRTI-based	PI-based
HIVdb	**0.730 (0.033)**	**0.692 (0.021)**	**0.722 (0.038)**	**0.684 (0.023)**
AntiRetroScan	**0.732 (0.033)**	**0.728 (0.020)**	**0.744 (0.037)**	**0.724 (0.022)**
ANRS	**0.737 (0.033)**	**0.713 (0.021)**	**0.753 (0.037)**	**0.695 (0.023)**
Rega	**0.727 (0.033)**	**0.705 (0.021)**	**0.730 (0.038)**	**0.687 (0.023)**

Receiver Operating Characteristic curves for the drug potency unweighted (U) and weighted (W) Rega and AntiRetroScan (ARS) genotypic sensitivity scores as predictors of treatment success at 8 (A) and 24 (B) weeks. The inserts show the values of the area under the curve with its standard error in parentheses.



Significant differences between weighted and unweighted algorithm at week 8: P = .001 for ARS; P < .001 for Rega.

Significant differences between weighted and unweighted algorithm at week 24: P < .001 for ARS; P < .001 for Rega.

CONCLUSIONS

- Currently available GISs are valuable tools for assisting antiretroviral treatment choices in clinical practice.
- The GISs appear to be amenable to further improvement with the inclusion and/or refinement of drug potency weighting factors.
- The overall accuracy of the GISs in pretreated patients remains below 80%, likely due to patient related variables currently not considered.