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CORRELATION OF RESISTANCE ALGORITHMS FOR TIPRANAVIR SUSCEPTIBILITY WITH RESPONSE TO TIPRANAVIR CONTAINING REGIMENS IN THE RESIST TRIALS

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BACKGROUND

A variety of resistance algorithms are available to interpret resistance to the new PI tipranavir (TPV). We compared the performance of three genotypic algorithm-based scores to phenotypic resistance based scores (derived from vircoTYPE-HIV-1) in predicting response to TPV containing regimens in the multi-experienced patient population participating in the RESIST studies.

METHODS

- The resistance call for TPV by each interpretation system analyzed (Stanford (version 4.2.6), TPV mutation score developed by Boehringer Ingelheim (VM Kohlbrenner et al., 13th International HIV Drug Resistance Workshop, Tenerife, Spain), PI mutation list presented in the US Product Label, and vircoType (version 4.0.01)) was correlated with the clinical outcome data from the RESIST studies. The TPV mutation score by Boehringer Ingelheim involved the following PI mutations: 10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D, 84V. The mutation list by the US product label involves any mutation at the following positions: 30, 32, 36, 46, 47, 48, 50, 53, 54, 82, 84, 88 or 90.
- In order to standardize the interpretation of backbone activity to compare only the prediction of TPV, the activity of the drugs used in combination with TPV was scored by a continuous phenotypic sensitivity score (cPSS) calculated as the sum of the activities of each drug in the backbone (1 if FC < vircoTYPE clinical cutoff 1 (CC01), 0 if FC > CC02, linear interpolation between 1 and 0 if FC between clinical cut-offs). The resistance interpretation for TPV by each of the interpretation systems was combined with the activity of the backbone in one model predicting clinical outcome.
- A responder was defined as a patient having reached a 1 log drop in viral load or below the detection limit of the viral load test kit at 8 and/or 24 weeks. Patients dropping out before the 24 week evaluation were considered non-responders.
- The association of baseline sensitivity scores with virologic outcome to the TPV containing regimens was evaluated using 4 metrics
 - Baseline sensitivity scores, calculated as the sum of the TPV call by the respective algorithm and the cPSS of the backbone by vircoTYPE, were correlated with viral load drop at weeks 8 and 24 using Spearman correlation. Drop-outs at week 24 were treated as missing for this analysis.
 - Baseline sensitivity scores were correlated with response rate at weeks 8 and 24 using logistic regression accuracy (area under the ROC curve) and odds ratio based on a logistic regression model including the cPSS of the backbone and the resistance call of TPV by the respective algorithm. This resulted in 4 similar models differing only in the TPV interpretation:

Model 1:

Clinical outcome = TPV Call by vircoTYPE + cPSS of backbone by vircoTYPE

Model 2:

Clinical outcome = TPV Call by US Product Label + cPSS of backbone by vircoTYPE

Model 3:

Clinical outcome = TPV Call by Stanford + cPSS of backbone by vircoTYPE

Model 4:

Clinical outcome = TPV Call by Boehringer Ingelheim + cPSS of backbone by vircoTYPE

- Additionally, the proportion of patients correctly classified as responders or non-responders was evaluated using a logistic regression model including the cPSS of the backbone and the resistance call of TPV by the respective algorithm.

RESULTS

Of the interpretation methodologies evaluated, the TPV resistance call based on vircoTYPE predicted FC was most strongly associated with virologic response at week 8 and at week 24 (Table 1).

Table 1: Area under the ROC curve, odds ratio of being a responder in the sensitive class as compared to the resistant class and Spearman correlation coefficient for each of the algorithms included in the analysis at week 8 (a) and week 24 (b) (N=743).

A WEEK 8				B WEEK 24			
	Area under the ROC	Odds Ratio Estimates for TPV call	Correlation		Area under the ROC	Odds Ratio Estimates for TPV call	Correlation
vircoTYPE	71%	6.8	-0.303	vircoTYPE	72.3%	6.3	-0.315
Boehringer Ingelheim mutation score	64.5%	3.4	-0.150	Boehringer Ingelheim mutation score	68%	4.7	-0.178
Stanford	64.0%	2.6	-0.112	Stanford	67.2%	2.6	-0.131
US Product Label mutation list	63.9%	1.7	-0.078	US Product Label mutation list	67.1%	1.8	-0.093

Figure 1: Receiver-Operator Characteristic curves for the interpretation algorithms included in the evaluation at week 8 (a) and week 24 (b). Number of patients correctly assigned, calculated as the Area under the ROC curve multiplied by the number of subjects (743) at week 8 ranged from 474 (US Product Label mutation list) to 527 (vircoType), and at week 24: 498 (US Product Label mutation list) to 537 (vircoType).

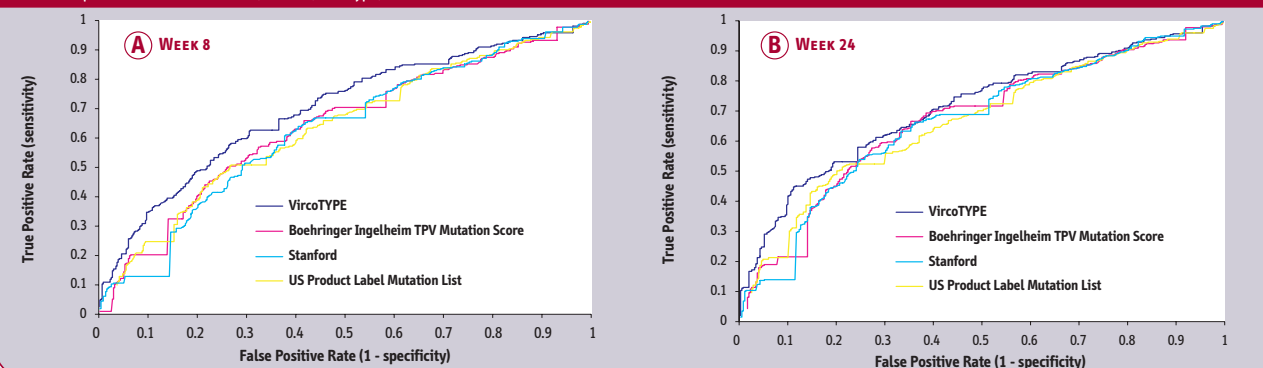


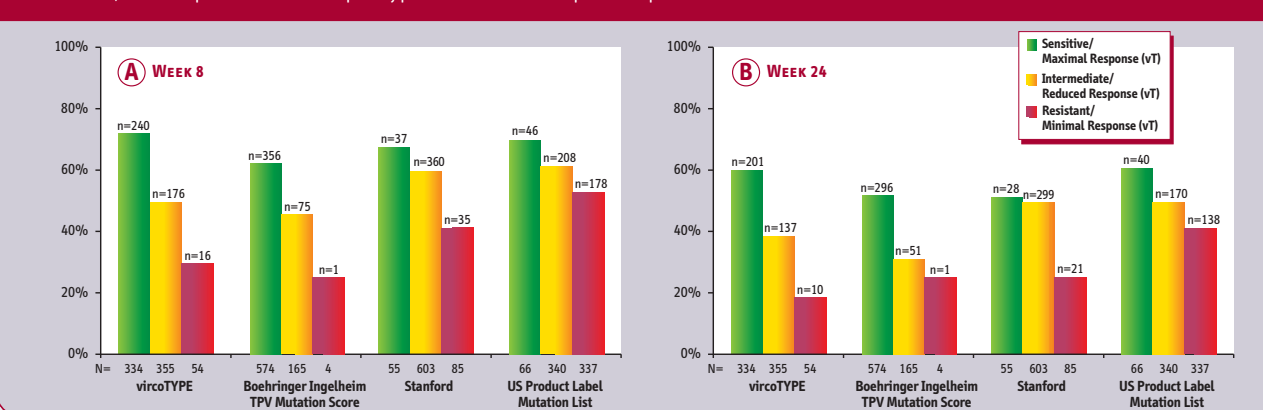
Table 2: Observed response at week 8 and week 24 versus predicted response derived from the logistic regression model (S: Success/ F: Failure).

A WEEK 8				B WEEK 24			
Observed Response	Predicted Response			Observed Response	Predicted Response		
	S	F	Total		S	F	Total
S	345	87	432	S	237	195	432
	(46.4%)	(11.7%)			(31.9%)	(26.2%)	
F	159	152	311	F	81	230	311
	(21.4%)	(20.5%)			(10.9%)	(31.0%)	
Total	504	239	743	Total	318	425	743

C STANFORD				D US PRODUCT LABEL MUTATION LIST			
Observed Response	Predicted Response			Observed Response	Predicted Response		
	S	F	Total		S	F	Total
S	351	81	432	S	351	81	432
	(47.2%)	(10.9%)			(47.2%)	(10.9%)	
F	205	106	311	F	197	114	311
	(27.5%)	(14.3%)			(26.5%)	(15.3%)	
Total	556	187	743	Total	548	195	743

A WEEK 8				B WEEK 24			
Observed Response	Predicted Response			Observed Response	Predicted Response		
	S	F	Total		S	F	Total
S	237	195	432	S	200	232	432
	(31.9%)	(26.2%)			(26.9%)	(31.2%)	
F	81	230	311	F	90	221	311
	(10.9%)	(31.0%)			(12.1%)	(29.7%)	
Total	318	425	743	Total	290	453	743

Figure 2: Distribution of patients who responded to treatment at week 8 and 24 according to baseline TPV call (n: number of responders and N: the total number of observations in each resistance class). vircoTYPE prediction of TPV susceptibility provides a more distinct separation of patients across the resistance continuum.



DISCUSSION

There are currently several different methods for interpreting resistance to antiretroviral agents. With the development of new generation Protease Inhibitors, it has become apparent that a higher number of mutations and mutation interactions play a role in decreasing susceptibility to the drug. We have analyzed the accuracy of different methods in interpreting resistance to the new PI tipranavir. In order to highlight the contribution of the tipranavir call to the response prediction, background regimen activity was scored by a consistent approach which used a cPSS calculation based on the vircoTYPE analysis.

CONCLUSIONS

- The use of a cPSS based on resistance interpretation by vircoTYPE for predicting response to antiretroviral regimens containing TPV in multi-experienced patients provided the best accuracy and correlation with treatment response.
- This was observed when performing the comparisons either at week 8 or week 24 after treatment initiation.
- All differences observed are due to TPV resistance interpretation based on the different methodologies utilized since background regimen activity was assessed in a consistent way.
- While vircoTYPE CCOs are based on week 8 outcome data, the good correlation with virologic response persisted through 24 weeks which is a more relevant timepoint for achieving a sustained and durable treatment response.
- The better performance of a predicted phenotype approach could be due to the ability of this method to factor complex mutational profiles in its resistance interpretation and more accurately predict expected activity of drugs against viruses with varying degrees of drug resistance. Among the genotypic algorithms evaluated, the Boehringer Ingelheim TPV mutation score provided the best performance.